

ARTIFICIAL PANCREAS WITH CLOSED-LOOP CONTROL FOR TYPE 1 DIABETES: DESIGN, IMPLEMENTATION, AND EVALUATION

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ABSTRACT

A closed-loop controller of insulin supply, often known as an artificial pancreas, is used to treat type 1 diabetes. This research presents the status of closed-loop control systems and anticipated future developments while discussing the difficulties of automated glucose management using fuzzy model predictive Controller. By limiting or preventing short- and long-term impacts, these solutions lessen the daily strain of managing diabetes. This paper investigates the current literature on artificial pancreas and suggests a strategy to enhance its regulation. Contrarily, a closed loop system can deliver the proper dose and timing of insulin and glucose. The artificial pancreas' algorithm entails monitoring a patient's blood glucose levels using a glucose sensor before sending a signal to an insulin pump to alter basal insulin dosage in accordance with the desired level of insulin the patient requires. The noninvasive glucose sensor prototype's results point to a promising future for NIR technology in biomedicine, particularly in optical spectroscopy for continuous, real-time glucose monitoring. The outcomes of the non-invasive glucose sensor prototype show that NIR technology has promising applications in biomedicine, particularly in optical spectroscopy for continuous, real-time glucose monitoring.

KEYWORDS

Artificial pancreas, type 1 diabetes, infra-red spectroscopy, closed-loop insulin delivery.

INTRODUCTION

Diabetes was the ninth leading cause of mortality in 2021, it is the primary cause of blindness, heart attacks, strokes, renal failure and amputation of lower limbs, [1] and is responsible for around 1.5 million deaths annually. To prevent hyperglycemia and hypoglycemia, diabetic individuals receive insulin and glucose via an artificial pancreas. A pancreatic hormone called insulin reduces blood sugar by preventing the

synthesis of new sugar and encouraging the utilization of existing glucose. On the other hand, glucagon is released by the pancreatic alpha cells, which prompts the liver to release glucose that has been stored as glycogen. The second pump releases glucagon, which increases blood glucose levels by converting glycogen stores in the liver to glucose and releasing it into the bloodstream. Glucagon is secreted by the alpha cells of the pancreas. These two hormones strictly govern the amount of glucose in the blood in healthy humans. Fig. 1 shows the natural pancreas functions to maintain blood glucose levels in balance.

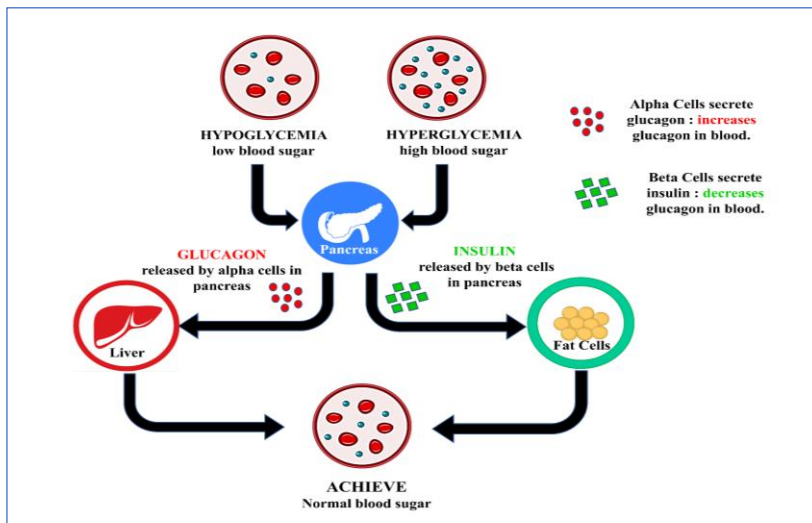


Fig. 1 Natural pancreas balances blood glucose.

Many studies have investigated the development of AP, in 1921 Frederick Banting, a physician and scientist, was one of the co-discoverers of insulin, a hormone that is essential for blood sugar regulation. Diabetes mellitus is caused by a lack of insulin activity, [2]. Millions of individuals throughout the world have been able to prolong their lives by decades. Kadish A, [3], in 1964 designed the first portable insulin pump. Albisser et. Al, [4] and Pfeiffer et. Al, [5], developed prototypes of an artificial pancreas that used intravascular sensing and administration in the 1970s. Bergman et al, [6], in 1979 presented a Model-predictive control (MPC) controllers, that are newer, bypass these constraints by employing a mathematical model of the person's metabolic system in their computations. Pickup et al., [7], in 1979 and Tamborlane et al., [8], demonstrated that continuous insulin infusion via the subcutaneous method was possible. Mastrototaro J. in 2000, [9], showed that real-time glucose monitoring allows patients to make rapid adjustments to insulin dosages, food consumption, and physical activity by analyzing glucose levels and trends and responding to low and high glucose alarms. Hovorka et al. in 2000, [10], used dual-hormone approaches and a multimodal MPC algorithm to determine in real time which patient model fits the available data the best and combines insulin delivery with glucagon therapy to prevent hypoglycemia. Renard E., in 2002, [11], made preliminary studies with intravascular enzymatic sensors that show their clinical acceptance and accuracy, as well as the potential for closed-loop insulin administration using implanted pumps. The Artificial Pancreas Consortium was created in 2006 as part of JDRF's Artificial Pancreas Project, a multimillion-dollar, multiyear project to develop automated blood glucose control solutions for diabetes patients. Steil A. et al. in 2006, [12], the US Food and Drug Administration (FDA) approved the T1D simulator developed by the Universities of Virginia (UVA) and Padova as a substitute for preclinical trials for

various insulin treatments, including closed-loop algorithms for AP, in 2008, [13]. The closed-loop study was the first to show that the subcutaneous-subcutaneous method could be used for completely automated blood glucose management in type 1 diabetics. Kovatchev et al., [14], in 2009 . The aggressiveness of the controller was tailored to the patient's body mass index, carbohydrate ratio, and insulin basal rate. Steven J et al., [15], in 2014 AP has demonstrated promising effects in first outpatient trials, according to the first outpatient research in clinical usage. Longer-term, free-living trials should reveal the relative merits of these approaches. The use of an artificial pancreas for automated glucose control is no longer a viable option. Xia Dai et al., [16], in 2018 performed a systematic review and meta-analysis concluding that AP may be considered an effective option for 24 hours use in T1DM patients. The artificial pancreas shown a number of benefits in maintaining and raising glucose levels when compared to its regulation. However, the extremely low number of patients investigated is a significant weakness in this study. Takuya Hinoue et al., [17], in 2021 submitted a case study. An artificial pancreas may benefit individuals with severe COVID-19 on extracorporeal membrane oxygenation, according to the research, the progression of AP is demonstrated in Fig. 2.

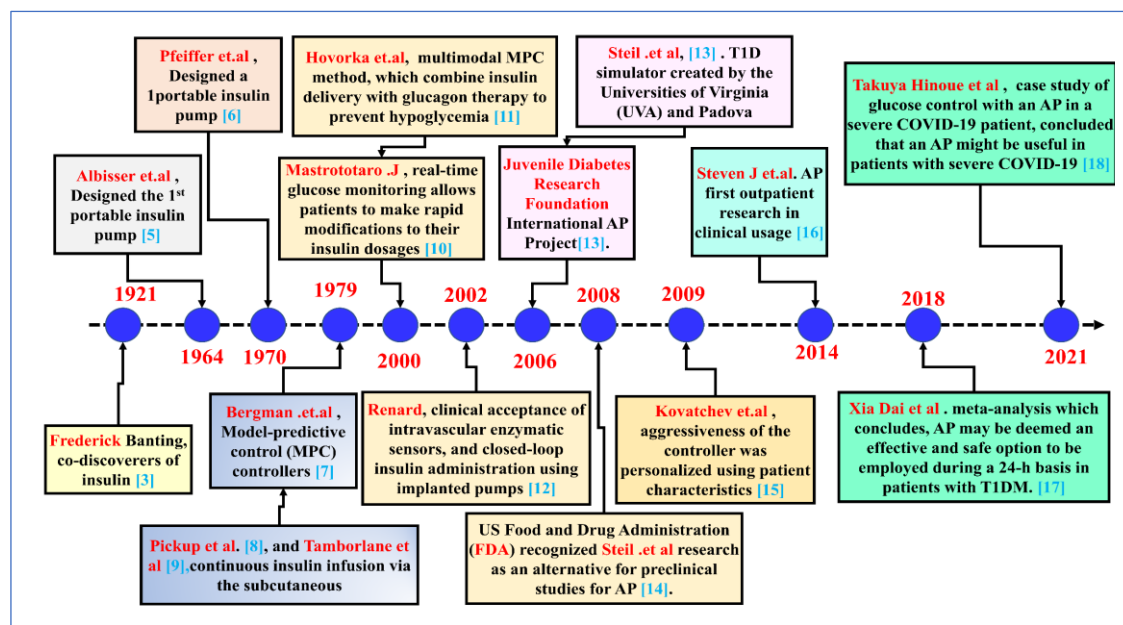


Fig. 2 The progression of AP.

The primary issues that a diabetic patient faces are listed below:

- Patients with type 1 diabetes are susceptible to problems with their eyes, kidneys, hearts, brains, feet, and nerves.
- Several insulin syringe or insulin pen injections every day.
- Elderly people may be unable to self-administer insulin, have trouble determining the proper quantity of insulin units needed, and have trouble monitoring their blood glucose levels.
- The primary problem with forgetting to measure is that it is impossible to continually indicate the glucose level when using a glucose meter because it must be used 2–5 times each day. The problem is constant indication.

- As a result of the excessively low blood glucose levels that occur when sleeping, hypoglycemic individuals may experience difficulties (when blood sugar levels fall below normal).

The reference values for blood sugar levels are provided in TABLE I, Fig. 3.

TABLE I Fasting and random blood sugar reference ranges, [18].

| mg/dl | Fasting | After Eating | 2-3 hours after Eating |
|------------------|-----------------|---------------|------------------------|
| Normal case | 80 up to 100 | 170 up to 200 | 120 up to 140 |
| Prediabetic case | 101 up to 230 | 190 up to 230 | 140 up to 160 |
| Diabetic case | reater than 126 | 220 up to 300 | greater than 200 |

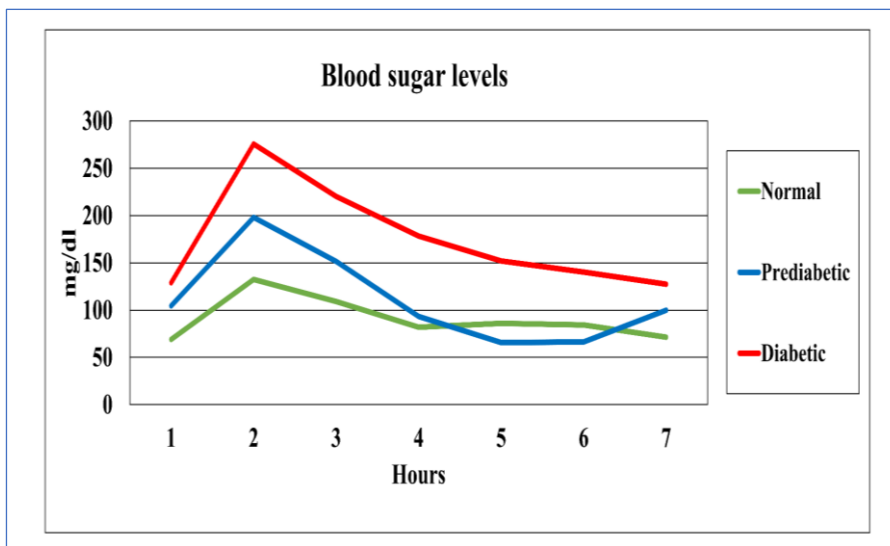


Fig. 3 Blood sugar levels.

The main objective of this study is the development, testing, and evaluation of a suggested smart closed-loop artificial pancreas system for the management of type 1 diabetes that can employ a glucose sensor to maintain blood glucose levels within a healthy range.

MATERIALS AND METHODS

The current study took into account a number of methods, such as the use of medical devices like an insulin pump that is controlled in a closed loop using real-time data from a continuous blood glucose sensor, the development of a biocompatible sheet of long-lasting encapsulated beta cells that can be surgically implanted to mimic an endocrine pancreas, and gene therapy.

A. Closed-loop artificial pancreas system

A closed-loop artificial pancreas device that controls blood glucose levels. Physiologic glycemic levels can be attained with this system for glucose monitoring, insulin dose estimation, and insulin delivery without the use of finger stick blood glucose tests, insulin injections, or hypoglycemia episodes. By simulating the endocrine function of a healthy pancreas.

Fig. 4 illustrates a Closed loop for AP where: GL_d is the desired glucose level, GL_s is the sensed glucose level, G_e is the glucose error signal = $GL_d - GL_s$, Pi_d is the predicted insulin delivery, DP represent dynamic physiology (eating, exercise, stress, and illness), and Ai_d is the actual glucose metabolism.

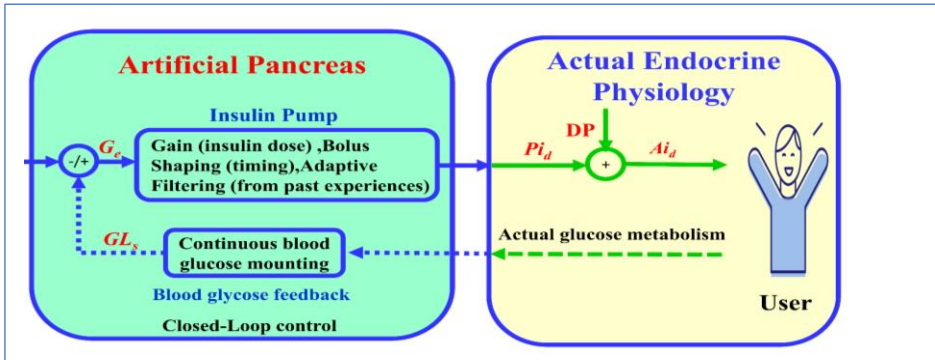


Fig. 4 Closed loop artificial pancreas.

Providing a blood glucose reading without requiring the user to place their finger inside the device every few minutes. Forecasting blood glucose levels for the near future benefits from monitoring blood sugar levels for rising and falling trends using a high blood sugar threshold to contrast predictions and readings of blood sugar. The user is subsequently informed that an immediate corrective bolus for the insulin pump is required. The forecasts and blood sugar levels are compared using a low blood sugar threshold. The user is then offered the choice of eating something or decreasing the basal insulin of the pump. Fig. 5 shows a multivariable artificial pancreas flowchart.

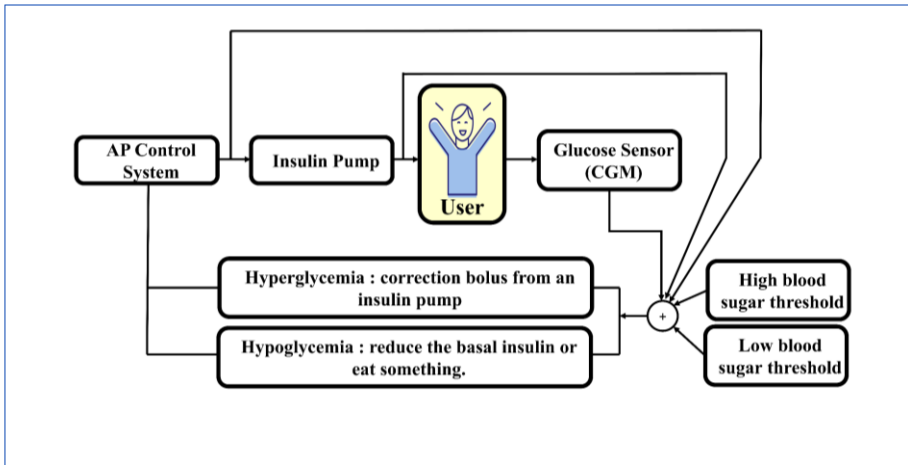


Fig. 5 Multivariable artificial pancreas flowchart.

B. Continuous Glucose Monitoring Sensor (CGM)

CGM sensors are small, portable devices that provide information on glucose trends as well as the ability to measure and visualize the Real-time glucose level practically constantly for several days. The therapy of Type 1 diabetes (T1D) has altered, improving glucose control, with the introduction of CGM sensors in conjunction with technologies for self-monitoring blood glucose. CGM sensors have also sped up the development of applications that require a continuous-time glucose signal, such as real-time predictive hypo/hyperglycemic alarms based on future glucose

concentration projections, automatic basal insulin attenuation techniques, and an artificial pancreas, [19]. A glucose sensor needs to be reliable over time. Because foreign body immune rejection can directly alter the readings or lower the level of glucose in the interstitial fluid, biocompatibility is one of the most important difficulties. This research involves the development and testing of a non-invasive wearable glucose monitoring device prototype. The technology uses optical spectroscopy to gauge the blood glucose levels of humans. The wavelength range for near infrared spectroscopy (NIR) is 750–2500 nm. The glucose molecule has the chemical formula $C_6H_{12}O_6$, which includes the bonds C-H, O-H, and C = O. Blood absorb NIR light due to the presence of these bonds. For finger tips and earlobes, NIR transmittance spectroscopy is an option, but because the NIR has very weak penetrating strength, reflection spectroscopy is used for forearms and cheeks.

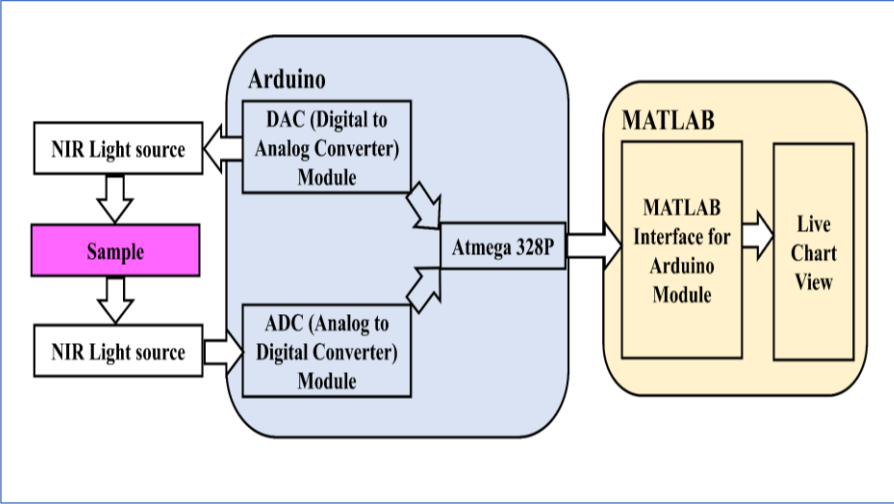


Fig. 6 Non-invasive glucose monitoring system block diagram.

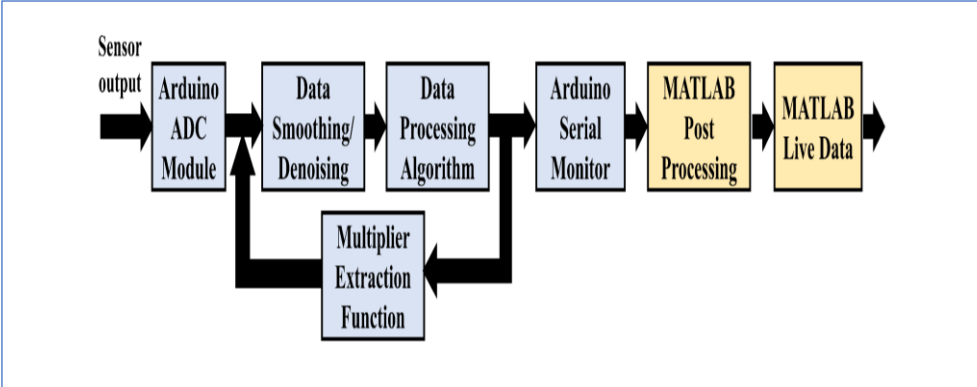


Fig. 7 Diagram of a data processing system.

The choice of a light with a wavelength of 940 nm was made since other researchers have previously utilized it in their investigations.

C. Electronic Parts

NIR Spectroscopy: A 940 nm infrared transmitter (emitter) and receiver (detector) are excellent for general-purpose IR systems, such as touch-free object detection and remote control. The emitter is powered up to 50mA with a current limiting resistor,

much like any other LED device. As seen in Fig. 6, an NPN transistor acting as the detector is biased by incoming IR light.

Microcontroller: The Arduino Uno microcontroller transfers the obtained blood glucose levels to the internal control algorithm in order to choose the appropriate insulin dosages and deliver them to the body by controlling the stepper motor. A simple Analog-to-Digital Converter (ADC) on any micro-controller can be used to get variable readings from the detector. Arduino Nano has been used because of its compact size and extensive availability, as seen in Fig. 7.

The incoming IR light biases the NPN transistor that serves as the detect. Variable readings from the detector can be obtained using a straightforward ADC on any micro-controller. Because of its small size and marketability, Arduino Nano has been employed. In order to transfer blood glucose readings wirelessly and to be compatible with all devices, the Bluetooth module (HC-05) has been employed. For powering the sensor, a small 400mAh lithium battery has been employed. The battery pins on the body's side can be used to recharge it, all the previous mention electronic parts are demonstrated in Fig. 8.

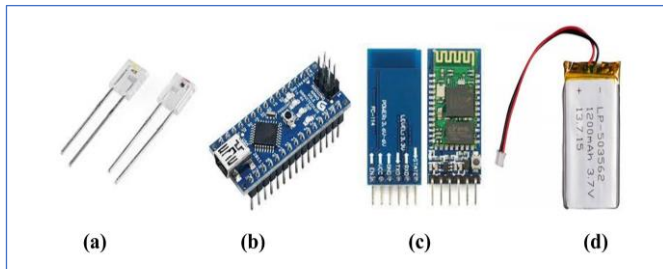


Fig. 8 (a) NIR transmitter & receiver, (b) Microcontroller, (c) Wireless Connectivity, and (d) battery.

Proteus software was used to model the pump circuit, and a suitable Printed circuit board (PCB) with a compact design was created, as shown in Fig. 9. Using a magnet on the moving portion and a hall-effect sensor that detects the proximity of the magnet at the end of the movement limit, a 5V stepper motor is used to drive a syringe. The syringe pump was built to include end-stop protection at the limit of the pump movement, as illustrated in Fig. 10.

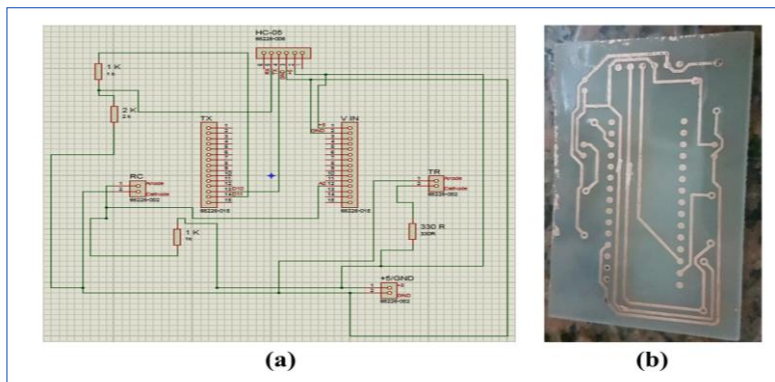


Fig. 9 (a) CGM schematic design, and (b) CGM using PCB.

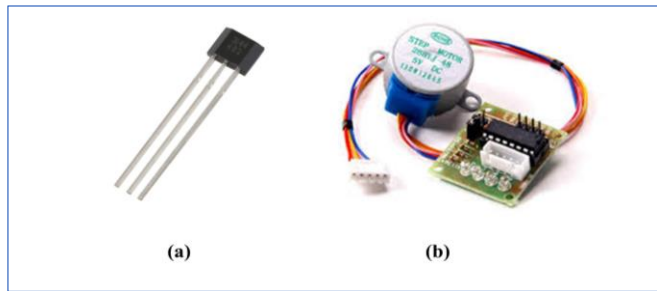


Fig. 10 A 5V stepper motor, (b) hall-effect sensor and magnet.

D. Insulin Syringe Pump

The Pump major component of the pumping station is its body. It houses the motor as well as the guiding and transmission systems. The body also houses the syringe's front end. The body's design allows for the installation of two hall sensors within its chassis. There is room on the body's side for the wires from the hall sensors. It was created in SolidWorks and produced on a Prusa i3 3D printer, as shown in Fig. 11.a.

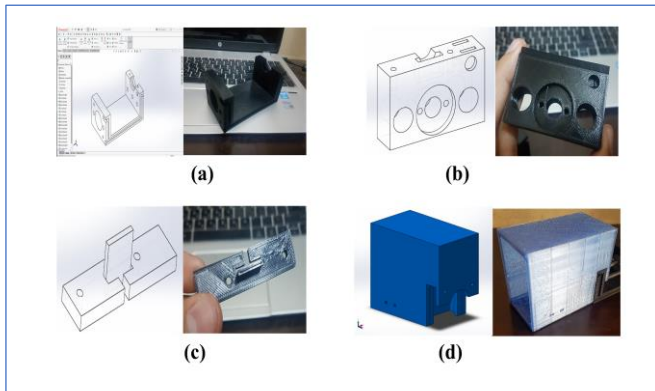


Fig. 11 Insulin Syringe Pump, (a) Pump body, (b) syringe carrier, (c) carrier cover, and (d) control box.

The syringe carrier job, in the system moving component, is to move the syringe back and forth. The magnet will be put into a small hole in the upper right corner of the object. One hole is for the nut screw, and there are two holes for copper bearings, Fig. 11. b.

Carrier Cover: The aim of the 3D-printed syringe fixation part is to fixate the back of the syringe to the syringe carrier element. These fixings components snugly tuck away into the void between the syringe and the pump. The width of the vertical walls is the only adjustment that needs to be made in order for these components to fit various syringes, as shown in Fig. 11. c.

Control Box: The microcontroller, motor driver, PCB, and battery are all contained within the electronics enclosure. There are two holes for the battery charging, as shown in Fig. 11. d.

E. Mechanical Parts

Lead Screw and Nut: A lead screw is a linkage used in a pump to convert the stepper motor's turning motion into linear motion that moves the plunger. The carrier for the

syringe is secured with the nut. The on-campus workshops' lathes were used to create the nut, as shown in Fig. 12. A.

Guide System: Two round rail-calibrated strengthened shafts and two oil-impregnated brass bearings make up the guidance system in operation, as shown in Fig. 12. b.

Coupler: It was created using SolidWorks and 3D printed to connect the motor shaft to the lead screw for the purpose of powering the stepper motor, Fig. 12. c, the measurements procedures illustrated in Fig. 12.

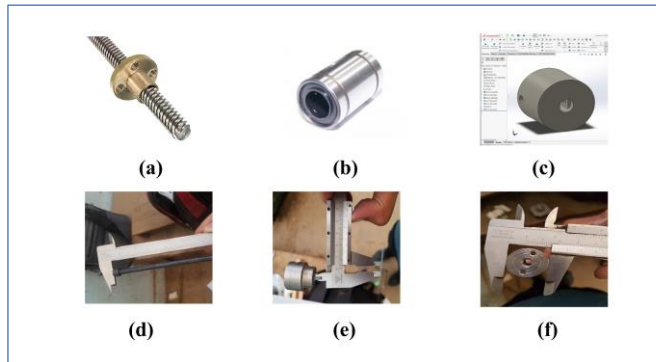


Fig. 12 Mechanical Parts, (a) Lead Screw and Nut, (b) Guide System, (c) Coupler, (d) Smooth rod, (e) , and (f) measurements procedures.

The proposed prototype of the Insulin Syringe Pump demonstrated in Fig. 13.

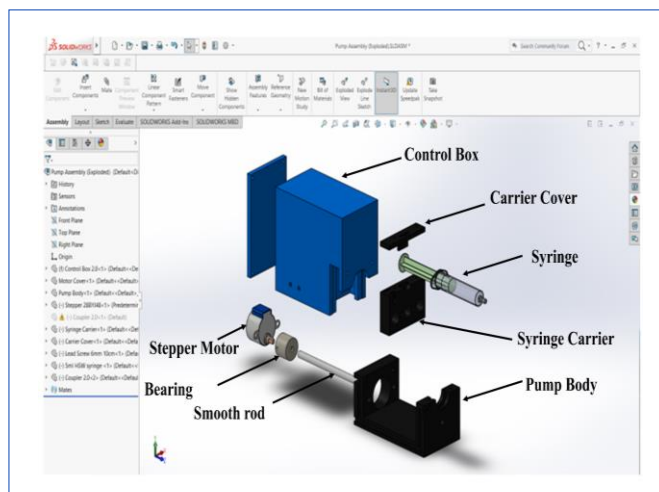


Fig. 13. Proposed Prototype.

F. Fuzzy Inference System

A fuzzy inference system, (FIS), has three essential stages, fuzzification, inference, and defuzzification. FIS has two inputs: BGL input and Pre-Meal level, with insulin units acting as the system's output demonstrates the use of fuzzy logic, [20, 21], as shown in Fig. 14.

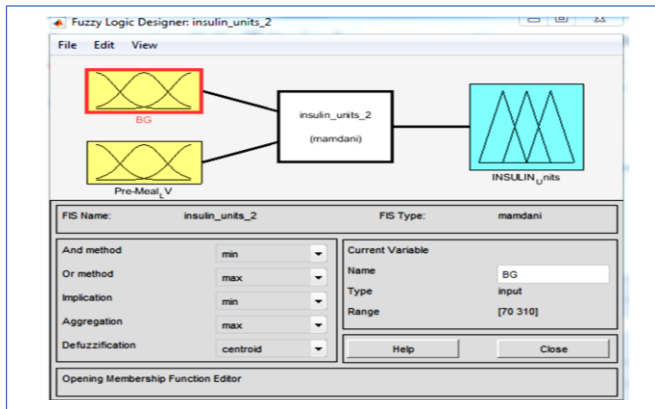


Fig. 14 The fuzzy logic system.

The Gaussian membership function is used as the input for blood glucose. BGL has a range of 70 to 310. It employs nine Gaussian functions, namely [70, 100, 130, 150 to 310], where Fig. 15 shows the membership function of BGL input.

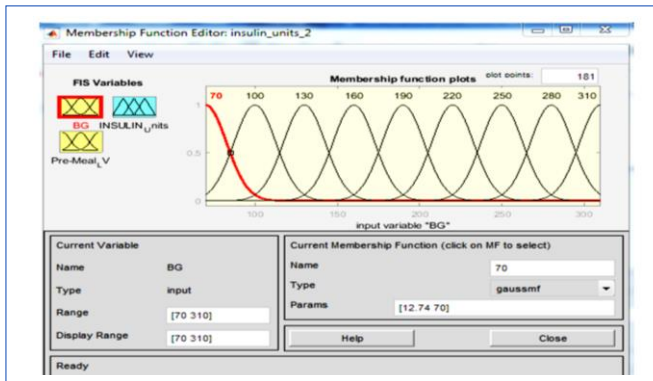


Fig. 15 The membership functions of blood glucose input.

The Pre-Meal level input that makes use of the triangle membership function, is the second input. It employs four triangle functions, [0 1 2 3], and has a range of 0 to 3, as shown in Fig. 16.

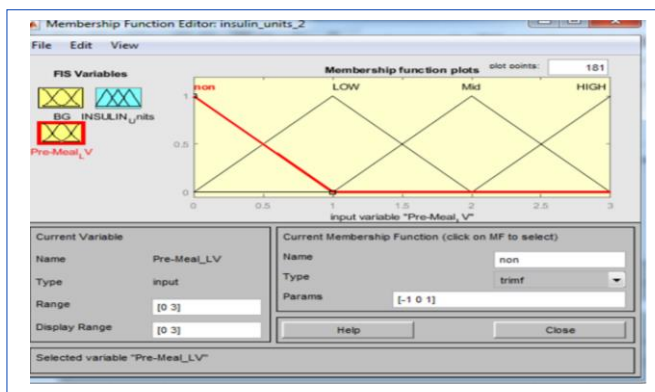


Fig. 16 The membership functions of Pre-Meal level input.

The inference is a modification of membership values by using fuzzy rules. Fuzzy rules use 36 rules, as illustrated in Fig. 17.

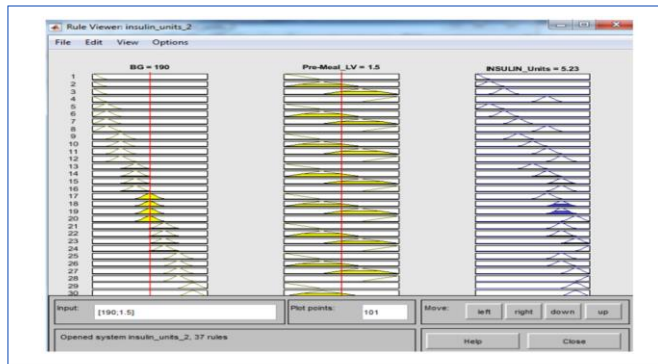


Fig. 17 The Fuzzy rules viewing.

The Gaussian membership function is used in the insulin unit output. Insulin units have a range of 0 to 7. There are nine Gaussian functions used in this: 0, 0.5, 1, 1.5, 2, 2.5, 4, 6, and 8. Fig. 18 shows the membership function of insulin unit output, and Fig. 19 show the rules and surface viewing.

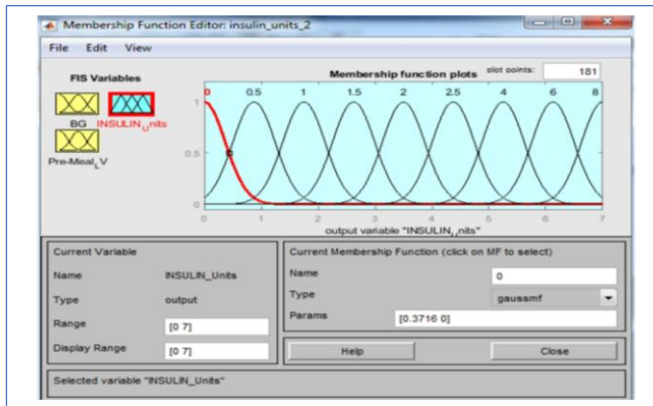


Fig. 18 The membership function of insulin unit output.

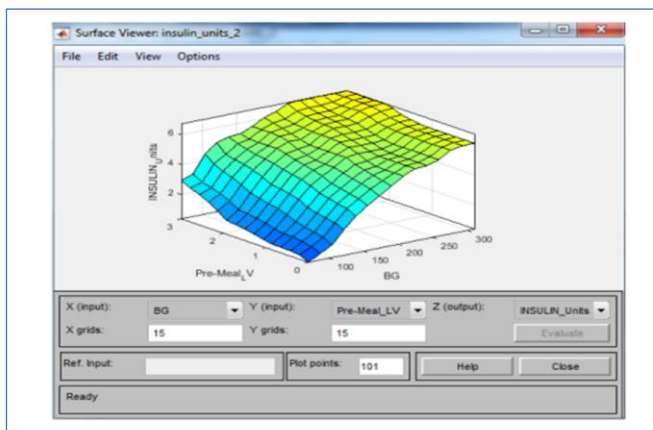


Fig. 19 The Fuzzy surface viewing.

G. Bolus shape and Dosing

Using an insulin pump, rapid-acting insulin can be continuously infused in place of basal-demand slow-acting insulin. A single type rapid-acting insulin is delivered by the insulin pump in two different ways:

- The forms and characteristics of boluses are shown in TABLE II . They are a bolus dose that is pumped to cover meals consumed or to treat an elevated blood glucose level.
- A continuous basal dose that pumps insulin required at bedtime and during meals at an adjusted basal rate.

TABLE II Bolus types and characteristic.

| Bolus Shape | Rate | Shape | Appropriate for |
|-------------|------|----------------------------|---|
| Standard | fast | spike , Fig. 20. a | eating high carb low protein low fat meals |
| Extended | slow | square, Fig. 20. b | high fat high protein meals, and patient with slow digestion |
| Combination | slow | spike - square, Fig. 20. c | high carb high fat meals |

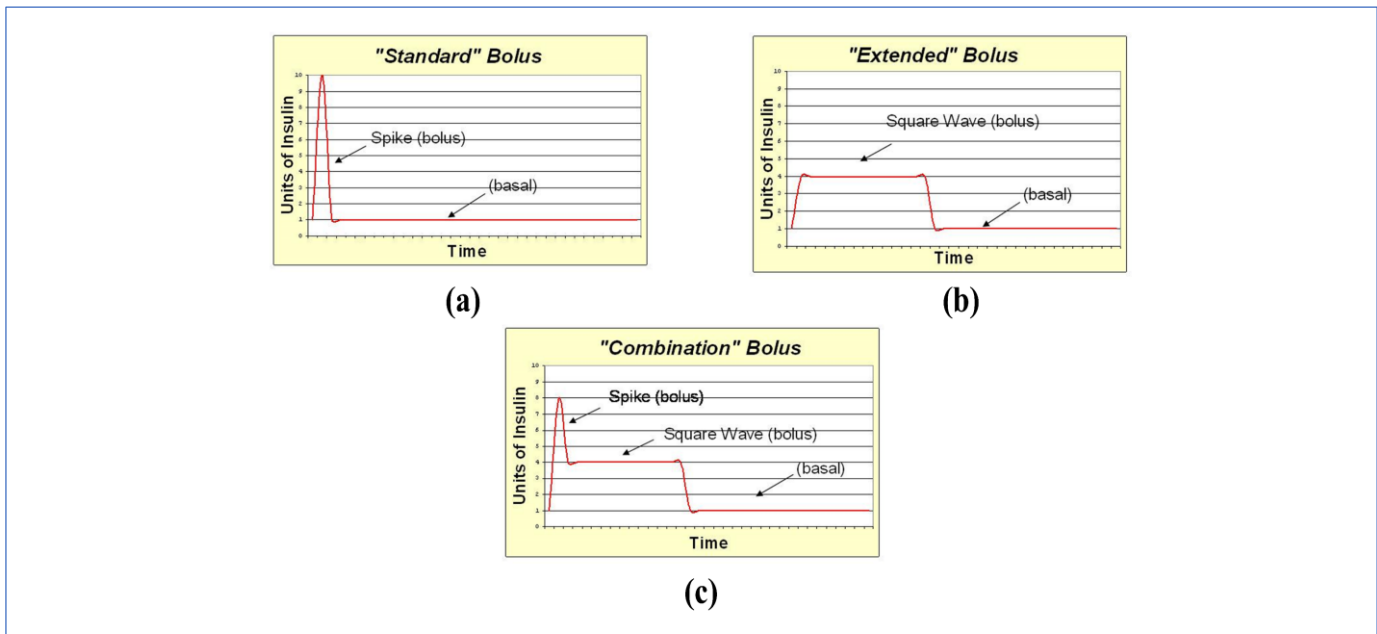


Fig. 20 Bolus shape (a) Standard, (b) Extended, and (c) Combination.

H. Blood Glucose Controller

PID controllers are frequently used as control loop feedback mechanisms in industrial control systems and other applications where continuously modulated control is needed. A PID controller, an insulin feed-back loop (IFL), and a PID controller make up the blood glucose controller. A proportional, integral, and derivative correction are then applied by a PID controller after continually calculating an error value $e(t)$ as the difference between a desired set point (SP) and a measured process variable (PV), as shown in Fig. 21.

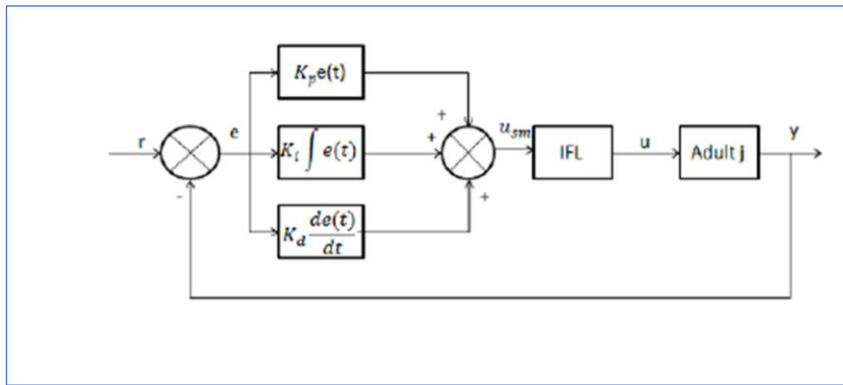


Fig. 21 Closed loop block schematic with PID controller.

The reference input is shown as (r) in the block diagram, and the error signal is shown as (e), which is created by deducting the reference input level from the patient's current blood glucose level. The PID controller block receives this error signal and uses it to detect the error and provide the necessary dose of insulin to the patient via the insulin feedback loop.

Three parameters that make up the PID controller each perform a separate action or function. The proportional controller parameter influences the system's output, which is dependent on the current error change. While the output of the system produced by the derivative parameter is dependent on the predicted error, the output of the system caused by the integral parameter is dependent on the historical error. By using all these control actions. PID is a successful method for performance control. To get the desired outcome from the system, these three parameters' values are altered. Proportional integral (PI), proportional derivative (PD), and proportional integral derivative refer to the combination of these three variables, as explained in equation (1).

$$u(t) = K_p e(t) + K_i \int_0^t e(t) dt + K_d \frac{de(t)}{dt} \quad (1)$$

Where $u(t)$ denotes the overall control function of PID controller and. K_p denote the present gain of the error, K_i denote the past error and K_d denote the future error.

I. Sample Preparations for In-Vitro and In-Vivo testing

A solution of glucose at a high concentration (DEXTROSE 25%) and its NIR spectra were examined in order to determine the pure element spectra. A 25 ml high precision measurement tube, an electric balance, and distilled water were all used. Solutions were created for in vitro experimentation.

Two levels of testing were done on the simulated system. The first step involved in-vitro testing, while the second stage involved in-vivo testing.

• In-Vitro testing:

Each of the three solutions had the same amount of glucose in it at all times. The glucose solutions had the following concentrations: 20 % glucose and 80 % distilled water; 40 % glucose and 60 % distilled water; 60 % glucose and 40 % distilled water; 80 % glucose and 20 % distilled water; 100 % glucose and 0 % distilled water; and 100 % glucose and 0 % distilled water.

• **In-Vivo testing:**

This research work was approved by unit of research ethics approval committee (UREAC), (PUA/04/2023/4/30/3/099) Faculty of Pharmacy, Pharos University in Alexandria in accordance with relevant guidelines and regulations. Moreover, an informed consent was obtained from participants involved in the study. Non-invasive glucose sensor measurements are used as test subjects for the accuracy and error rate. The test is conducted on the index volunteers finger because it is simple and practical to use and because NIR light has a propensity to pass through earlobes and the outer webbing of a human index finger. The implementation of the non-invasive glucose measurement finger tips test prototype system is shown (Fig. 22). Once the finger has been positioned in-between the NIR source and photodiode detection circuits. The spectroscopic process is started by the system. In this case, readings are gathered from a large number of volunteers (50 volunteers). In order to avoid interference, it is crucial to remember that when the finger is positioned between the source and the detector, the area in between is kept in the dark and shielded from outside (visible) light. This is done in order to ensure that the source and the detector do not interact with one another. The testing phase focused on evaluating the capabilities of the proposed system on a group of three participants. "PRECICHECK," a commercially available intrusive sensor, was utilized to evaluate the performance of the created device.

J. Mobile Application

A mobile application allows the patient to monitor his blood glucose levels and insulin doses. Android is popular because it is open source, offers a sophisticated set of software tools, and allows for flexible inter-process communication. It is also available on a wide range of smartphones and other devices.

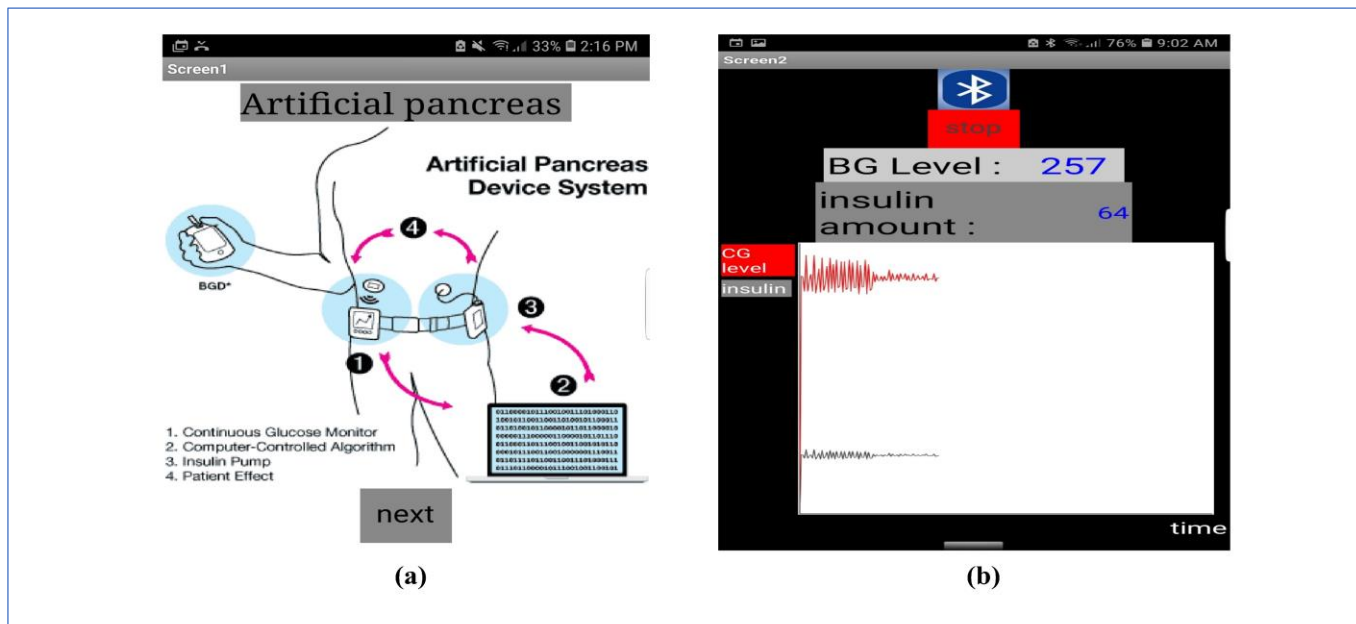


Fig. 22. Mobile application screens (a) Homepage, and (b) Display of insulin amount and blood glucose amount with the graph.

As shown in Fig. 22, the application consists of two screens. The first screen displays information about the project and has one button. When the button is pressed, the app moves to the second screen that display the blood glucose level and insulin amount, the second screen consist of:

- **Bluetooth Icon:** When it is pressed the application opens the list of paired Bluetooth devices. The user can select the “HC-05” module used in the CGM.
- **Start Button:** When you press this button and your Bluetooth isn't connected, the message "Please Connect to a Bluetooth Device First" appears. Readings will appear in the text label if Bluetooth is connected. When you press the button again, the reading will stop.
- **Two text labels:** Displays the blood glucose level and insulin units
- **Canvas:** Plots blood glucose and insulin levels
- **Exit Button:** Exit the application.

RESULTS AND DISCUSSION

A. Closed loop

To examine the effectiveness of feedback-controlled insulin infusion devices, the proposed model is first evaluated in open loop, then in closed loop without a controller, and finally, a controlled strategy is developed and put into operation using a PID controller. In this section, you will find the results of closed-loop analysis, open-loop analysis, as well as the impact of PID gains on closed-loop systems.

The step response using proportional controller shown in Fig. 23. a, The proportional controller, on the other hand, causes the system to respond more quickly when the rise time is slashed, and it also lowers the steady state inaccuracy. However, this controller increases the number of oscillations in the step response.

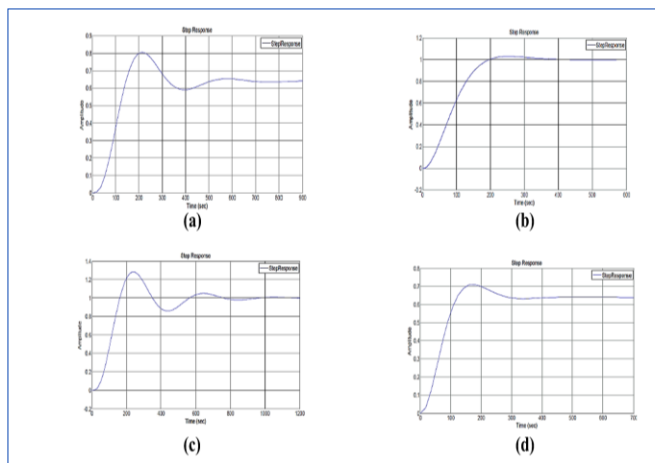


Fig. 23 Step response using (a) PC, (b) PDC, (c) PIC, and (d) PID controller.

The step response employing a proportional derivative controller is shown in Fig. 23.b. When the derivative controller increases the damping ratio, the step response obtained using a proportional derivative (PD) controller shows fewer oscillations and less overshoot. Since proportional action reduces system rising time and derivative action reduces system settling time, the proportional derivative controller sped up system response. However, steady state error persisted, thus integral action was required to get rid of it. The step response employing a proportional integral controller is shown

in Fig. 23. c. The installation of an integral controller eliminates the system's steady state inaccuracy, but the integral effect causes the overshoot to be introduced. The reaction takes longer to settle due to the absence of derivative action while taking less time to ascend due to proportional action. After examining the actions of various PID gains, it is discovered that all three actions-proportional, derivative, and integral-are required to provide the desired and ideal response. The step response employing a proportional derivative integral controller is shown in Fig. 23. d. The system possesses all the desirable qualities that may be used to create an automated insulin infusion system.

B. In-Vitro testing

The finding, which are displayed by averaging each set of readings, reveal a pattern indicating a relationship between the output voltage and the value of the solution concentration. The concentration increases proportionately to the (readout) output voltage. In MATLAB, the in-vitro results' regression analysis was carried out. Fig. 24 demonstrates the regression analysis results of the dataset after excluding outliers. The explanatory variable is believed to account for 95.77% of the variation in the response because the significant F value is less than 0.05 and the R square term is equal to 0.9577.

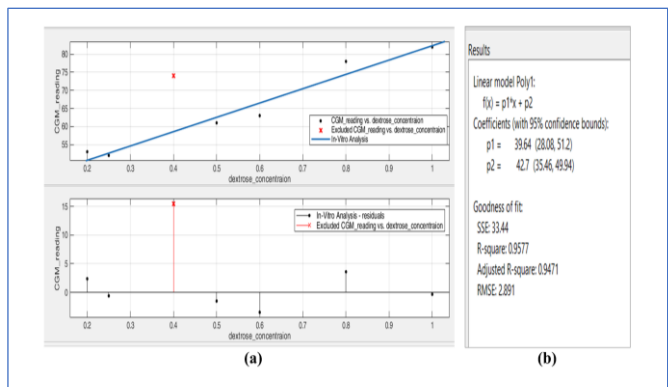


Fig. 24 In-vitro results (a) dataset regression (curve fitting), and (b) dataset analysis results.

C. In- Vivo testing

The test measurement data points obtained are within the allowed range, proving the built-in non-invasive glucose sensor's accuracy. During calibration, invasive and non-invasive data were obtained and compared in order to calculate the molar absorptivity coefficient. Members of the team and a diabetic patient took a number of actions. A 0.5 microliter sample size is all that is needed for the glucose meter to perform accurate and simple testing. Within 5 seconds, the test results are displayed. The benchmarking test results for suggested non-invasive sensors and commercial invasive sensors are shown in Fig. 25.

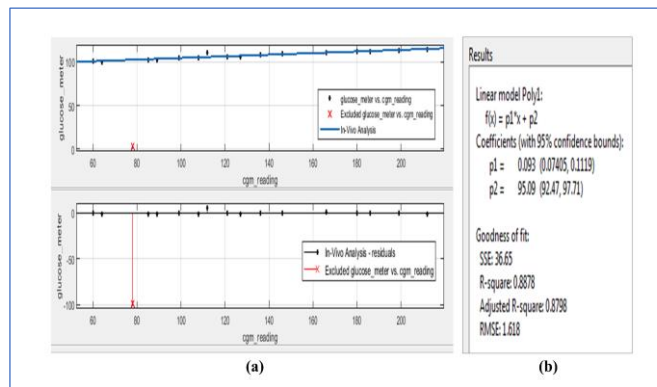


Fig. 25 In- Vivo results (a) dataset regression (curve fitting), and (b) regression analysis results of the dataset.

CONCLUSIONS

Our study successfully demonstrated the low production and upkeep costs and high in vitro accuracy of the suggested noninvasive glucose monitoring device. The research includes the design, implementation, and evaluation of the suggested system. Results from the suggested non-invasive glucose sensor prototype show how NIR technology has a lot of applications in the biomedical sector, particularly in optical spectroscopy for continuous real-time non-invasive glucose monitoring. A prospective use of the suggested experiment is the non-invasive continuous monitoring of glucose levels in humans using NIR spectroscopy.

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