The Bio-inspired Artificial Pancreas for Type 1 Diabetes Control in the Home – System Architecture and Preliminary Results

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Abbreviations: CGM (Continuous glucose monitoring); AP (Artificial Pancreas); BiAP (Bio-inspired Artificial Pancreas); PCB (Printed Circuit Board); ABC (Adaptive Bolus Calculator);

Key Words: type 1 diabetes; automatic insulin delivery; artificial pancreas; bio-inspired technology, low-power electronics.

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Figures and table count: 6 figures, 3 tables.

Funding Source: This project has received funding from the Wellcome Trust (100921/Z/13/Z).

Conflict-of-Interest Disclosure: None

Abstract

Background

Artificial pancreas technology has been proven to improve glucose and patient-centred outcomes for people with type 1 diabetes. Several approaches to implement the artificial pancreas have been described, clinically evaluated, and in one case, commercialised. However, none of these approaches has shown a clear superiority with respect to others. In addition, several challenges still need to be solved before achieving a fully-automated artificial pancreas that fulfils the users' expectations. We have introduced the Bio-inspired Artificial Pancreas (BiAP), a hybrid adaptive closed-loop control system based on beta-cell physiology and implemented directly in hardware to provide an embedded low-power solution in a dedicated handheld device. In coordination with the closed-loop controller, the BiAP system incorporates a novel adaptive bolus calculator which aims at improving post-prandial glycaemic control. This paper focuses on the latest developments of the BiAP system for its utilisation in the home environment.

Methods

The hardware and software architectures of the BiAP system designed to be used in the home environment are described. Then, the clinical trial design proposed to evaluate the BiAP system in an ambulatory setting is introduced. Finally, preliminary results corresponding to two participants enrolled in the trial are presented.

Results

Apart from minor technical issues, mainly due to wireless communications between devices, the BiAP system performed well (~88% of the time in closed-loop) during the clinical trials conducted so far.

Preliminary results show that the BiAP system might achieve comparable glycaemic outcomes to existing artificial pancreas systems (~73% time in target range 70-180 mg/dL).

Conclusion

The BiAP system is a viable platform to conduct ambulatory clinical trials and a potential solution for people with Type 1 diabetes to control their glucose control in a home environment.

1. Introduction

In the last two decades, technological progress in the field of diabetes management, especially in continuous glucose monitoring (CGM) [1], has enabled the development of automated insulin delivery systems, the so-called artificial pancreas (AP). The most common configuration of an AP consists of a CGM sensor and a subcutaneous infusion pump that delivers insulin at a rate decided by a computer program (control algorithm) [2, 3].

Clinical studies have shown that an AP can achieve greater time in glucose target than standard treatment in which a person makes insulin dosing decisions [4]. The commercialization of the first AP, the Medtronic 670G SmartGuard (Medtronic, CA, US) [5], occurred in 2018 and multiple further prototypes have been assessed [6]. At the time of writing this paper, 13 companies involved in AP programs were identified: Medtronic, Roche, Dexcom, Insulet, Bigfoot, Tandem, Kaleido, TypeZero, Inreda, Beta Bionics, Cellnovo, Medtrum, Lilly, and Diabeloop [7].

Many control algorithms have been described and clinically evaluated, including Model Predictive Control [8-12], Proportional Derivative Integral [13,14], Fuzzy Logic [15], and Bio-inspired [16]. However, none of these controllers have yet shown a clear superiority when compared to the others in a clinical setting [17][18].

Current limitations of subcutaneous insulin pharmacokinetics have limited the realisation of a fully-automated AP system able to control glucose levels at meal time. A practical solution to this problem is the hybrid AP system, in which mealtime insulin delivery is manually assisted by announcing the meals [19].

Physical exercise, together with meals, are probably the biggest challenges an artificial pancreas has to face [20]. When dealing with aerobic exercise, AP systems have to avoid hypoglycaemia during activity while previously administered insulin remains active. There is already clinical

evidence that by announcing exercise, an artificial pancreas can better cope with such perturbation by reducing the exercise-induced hypoglycaemia [21]. Another possible solution to address this challenge is the incorporation of glucagon delivery as counter regulatory action to insulin in a dual-hormone AP [22]. Although a dual-hormone AP has a potential benefit over its insulin-only counterpart, its development and commercialization has been delayed by the lack of a commercial stable glucagon solution [23].

Another challenge artificial pancreas systems face is the significant inter-day variability in insulin requirements that people with diabetes are subject to [24]. A solution to this problem is the inclusion of adaptive control mechanisms which automatically adjust the controller setting accordingly to the insulin requirements [25,26].

In this paper, we provide an overview of the Bio-inspired Artificial Pancreas (BiAP), a hybrid adaptive closed-loop control system based on a model of the beta-cell insulin secretion physiology which has been implemented in a dedicated low-power handheld device.

The first generation of the Bio-inspired Artificial Pancreas (BiAP Gen 1) was created in 2012. It consisted of a custom-made microcontroller-based handheld unit connected to a Medtronic Enlite sensor (Medtronic Diabetes, Northridge, CA, US), and an Accu-Chek Spirit Combo insulin pump (Roche, Basel, Switzerland) (Figure 1) [27]. The BiAP Gen 1 closed-loop control algorithm, implemented in the micro-controller, utilised a sub-cellular model of insulin secretion obtained from physiological data. This sub-cellular model of insulin release is able to replicate the majority of the experimental data, including biphasic insulin secretion, staircase modulation of insulin secretion, the potentiation effect of glucose, and kiss-and-run secretion by insulin granules [28]. Such model was then augmented by an insulin feedback term [29] and a predictive low-glucose suspend safety module to compensate for the mismatch between endogenous insulin secretion and subcutaneous insulin delivery.

A bihormonal version of the BiAP Gen 1 system, which include a proportional derivative controller for glucagon delivery, was also developed and evaluated [30].

BiAP Gen 1 was clinically tested in participants with type 1 diabetes during fasting conditions, overnight and following a standard meal (breakfast) challenge and the data showed good glycaemic control with minimal hypo- or hyperglycaemic excursions [31]. Following the feasibility studies, a 24-hour randomised control clinical trial demonstrated that the BiAP Gen 1 system significantly reduces hypoglycaemia compared to standard insulin pump therapy [32]. In a sub-study, we showed that participants using BiAP Gen 1 remained safe in the event that a meal is unannounced, or the carbohydrate content is underestimated [32].

The BiAP Gen 1 system was also evaluated in standard exercise studies with insulin-only closed-loop control, insulin and glucagon closed-loop control and standard open-loop insulin pump therapy. These demonstrated that the closed-loop controller is able to manage the challenge of prolonged aerobic exercise and suggested that the addition of glucagon does not impact on the risk of hypoglycaemia and hyperglycaemia with physical activity, immediately after physical activity or up to 16 hours after [33][34].

Figure 1. BiAP Gen 1 composed by a hand-held unit which communicated to a Medtronic Enlite Sensor, and an Accu-Chek Spirit Combo insulin pump.

In this manuscript, we present the latest developments of the BiAP system for its utilisation in the home environment. Finally, the design of the ambulatory clinical trial and some preliminary results are presented.

2. Methods

After proving that the BiAP system was safe and effective under different real-life scenarios (unannounced meals and exercise), the next logical step is to evaluate the system in an ambulatory environment. For this purpose, both the BiAP system hardware and software have been upgraded in order to improve the portability, usability and performance of system.

2.1. Handheld unit

The core hardware component of BiAP Gen 2 is the custom-made handheld unit (9x5cm) shown in Figure 2. The unit consists of a custom designed printed circuit board (PCB) contained within a 3D-printed box that has two main components, an embedded microchip that runs the bio-inspired closed-loop control algorithm (see Section 2.2), and a Nordic nRF52832 chip which handles the Bluetooth communication with the insulin pump, the glucose sensor, and a smartphone. The unit also includes an SD memory card in which the user settings are uploaded, and all input and output data are stored. A micro-USB port is available for battery charging and data transition. An OLED screen and three buttons allow the user to interface with the unit. User interaction includes starting and stopping the unit; paring the peripheral Bluetooth devices; basic data visualization, such as CGM measurement, glucose trend, delivered insulin, connectivity status, and historical glucose and insulin data. Users can choose to switch from closed-loop control model to open-loop mode (i.e., standard therapy), and vice versa, at their will, by selecting

the corresponding option in the BiAP unit menu.

The PCB also includes a buzzer which is used to alert the user about malfunctioning of the system (e.g. loss of wireless connectivity) and hypoglycemia. In the event of a device disconnection, the system automatically tries to reconnect the lost device for a predefined number of times, and if unsuccessful, then an audible alarm is triggered.

Further details about the BiAP hardware architecture, its power consumption, and hardware-in-the loop testing, have been published [35].

The BiAP Gen 2 system interfaces with the Tandem t:slim AP (Tandem Diabetes Care, San Diego, CA, US) insulin pump, and the Dexcom G6 glucose sensor (Dexcom, San Diego, CA, US) continuous glucose sensor.

The BiAP unit receives a glucose value from the Dexcom G6 transmitter every 5 minutes, calculates an insulin dose, which is subsequently sent to the insulin pump for delivery. In addition, the BiAP unit connects to a smartphone running Apple iOS (Apple, Cupertino, CA, US) and a dedicated app implementing an adaptive bolus calculator used to calculate the meal insulin dose (see Section 2.3). Finally, insulin, CGM, and meal data are uploaded through the phone to a MySQL database hosted in the cloud (Amazon Web Services) for remote monitoring purposes. The reason for including a smartphone is because the employed adaptive bolus calculator requires sending data to a server for the clinical supervision of its automatic adaptations. However, once the system has been validated, the adaptations can run locally on the BiAP unit and the phone can be eliminated. Figure 2 shows the BiAP Gen 2 architecture and the information flow between the different components.

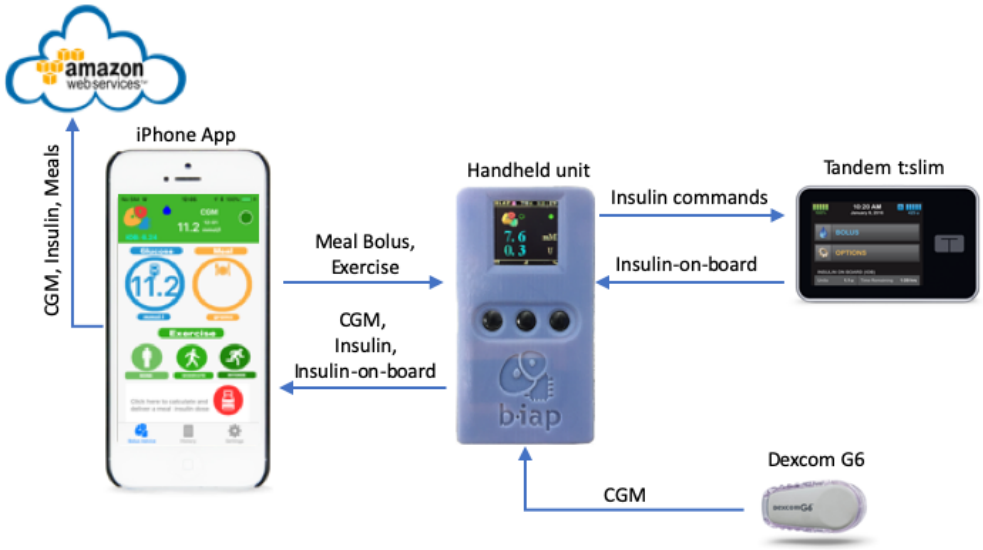


Figure 2. BiAP Gen 2 architecture and information flow.

2.2. Closed-loop control algorithm

The closed-loop glucose controller implemented in the microcontroller of BiAP Gen 2 has been previously described in [33]. In this updated version of the controller, the pancreatic insulin secretion model used in BiAP Gen 1 [16] has been replaced by the most recent model [36], with improved performance in simulation studies as well as reduced complexity which significantly speeds up the computations in the micro-controller, and consequently saves power. In particular, the computation time has been reduced from 60 seconds to less than 10 seconds.

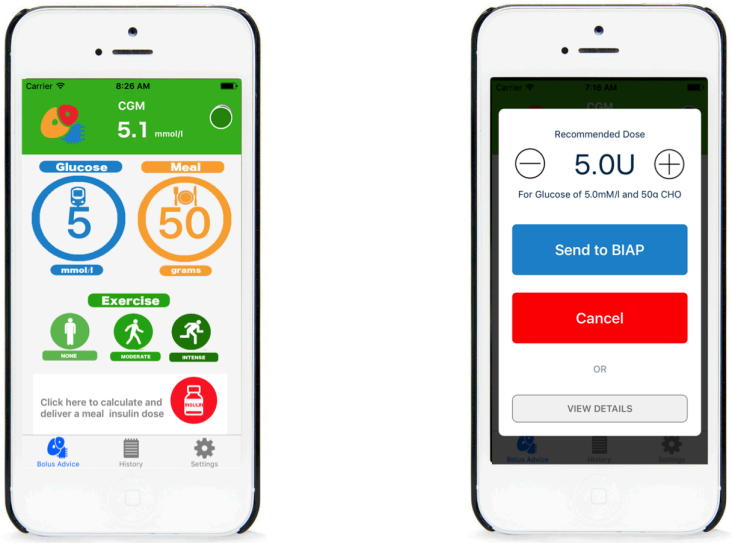
Appendix A provides a mathematical proof showing that the employed pancreatic insulin secretion model is equivalent to a Proportional Derivative controller with two low-pass filters. The low-pass filters can be thought of as human physiology smoothing out any abrupt transients in glucose, an inherent mechanism to remove noise from sensed glucose and provide smoother control. Finally, the tuning of the controller has been simplified so that only the insulin sensitivity factor (correction factor) and the user's basal insulin profile are needed.

2.3. Adaptive meal bolus calculator

BiAP Gen 2 is a hybrid AP system which implements a novel adaptive bolus calculator (ABC) which operates in coordination with the closed-loop controller [37].

There is significant evidence that good basal control (e.g., overnight control) is relatively easy to achieve independently to the employed control strategy [15, 31]. Therefore, the main improvement in glycaemic control can be achieved during the postprandial period, and potentially during and after exercise. Therefore, the inclusion of an adaptive bolus calculator that works in companionship with the closed-loop control law can potentially outperform existing hybrid closed-loop systems [37].

The ABC is implemented on an iOS app which also acts as a graphical user interface for the AP system. Screenshots of the app's graphical user interface are shown in Figure 3. CGM data are automatically transmitted from the BiAP unit to the phone. These readings can be overwritten by the user if considered inaccurate. Connectivity between the BiAP unit and the phone is indicated by a green indicator located the top-right corner of the screen (Figure 3A). In order to receive a meal insulin bolus recommendation, the user estimates the mealtime carbohydrate content and, if any, the planned physical exercise (none, moderate, intense). The suggested insulin dose can be modified by the user in the recommendation screen by using the +/- buttons (Figure 3B). Details about the calculation of the insulin dose recommendation can be obtained by clicking at the "View Details" button. Once accepted, the meal insulin dose is automatically transmitted to the BiAP unit for delivery. Insulin-on-board used by the ABC is obtained from the pump via the BiAP Unit. The iPhone app can also be used to visualize glucose and insulin historical data and a log of all the past entries.



(A) (B)

Figure 3. BiAP iPhone app graphical user interface. A) main screen for data input. B) Recommendation screen.

2.4. Exercise Announcement

BiAP Gen 2 exercise announcement strategy is based on knowledge acquired from previous in-clinic closed-loop trials involving exercise [31][32], and existing clinical guidelines [38]. In particular, at mealtime, if users plan to exercise after the meal, they can activate the exercise function available in the iPhone app. This will automatically reduce the recommended meal bolus by 30%. Then, before or during exercise, the user can additionally press the exercise button on the app which will reduce the insulin dose delivered by the closed-loop controller by 50% for 90 minutes. The BiAP will then beep and display an icon of an individual running on the main GUI screen to indicate that system is in exercise mode. Exercise mode can be stopped at any time within the app.

It is worth noting that glucose levels were not accounted for within the employed exercise announcement strategy, the reason being that, in previous clinical trials, we observed that actual

blood glucose levels can drop relatively quickly after the initiation of exercise (<30min), while CGM measurements are significantly lagging behind. Hence, adjusting insulin delivery based on glucose levels at exercise time might not always be a good strategy. Although the employed strategy for minimising exercise-induced hypoglycaemia might be suboptimal for very elevated blood glucose levels (e.g., >300 mg/dL), and a more elaborated strategy might be required, we opted for the more conservative approach. In the event of significant hyperglycaemia, participants were advised to check their blood ketones and take the corresponding correction actions to normalise glycemia (e.g. small correction bolus) before engaging with exercise.

2.5. Safety Layer

Safety is paramount in any insulin delivery system, hence the importance of a safety layer within an AP system [39]. In BiAP Gen 2, individualized constraints based on user-specific parameters (e.g. basal insulin) are applied to the insulin calculated by the closed-loop controller. In particular, the closed-loop controller is not allowed to deliver more than six times the basal insulin delivery within an hour. The iPhone ABC app has in-built constraints that limit the amount of carbohydrate that can be manually inputted. Hypoglycemia prevention strategies including basal insulin infusion reduction and suspension are employed for forecasted glucose concentrations below predefined thresholds. Glucose forecasting is carried out by means of a linear regression algorithm which accounts for current glucose levels and glucose rate of change. Glucose forecasting horizon is fixed to 20 minutes. A predictive low-blood insulin suspension algorithm reduces the basal insulin delivery by 50% if the forecasted glucose value falls below a predefined threshold (80 mg/dL) and suspends the basal insulin delivery if it falls below a second lower predefined threshold (70 mg/dL). To prevent rebound hyperglycaemia, the basal insulin suspension is limited to 90 minutes, after which time the insulin delivery is resumed to 50% for 30 minutes and after this period total suspension is activated again if the hypoglycaemic condition is satisfied. It is worth

noting that the closed-loop control algorithm does not deliver additional insulin while the low-blood insulin suspension algorithm is acting on the basal insulin delivery [40].

An alarm system for wireless communication disconnection between devices is in place. To reduce alarm fatigue, alarms due to communication problems are not triggered until 20 minutes of disconnection have elapsed. During this time, the system tries to reconnect. In addition to the glucose alarms provided by the Dexcom G6 mobile app, the BiAP unit has an additional hypoglycemia alarm.

In case of sensor or pump disconnection, insulin infusion reverts to a safe basal rate (70% of pre-programmed rates). The reason for not reverting to 100% of the basal insulin is to minimise the risk of a potential nocturnal hypoglycaemic event, since the low-glucose suspension mechanism is disabled during disconnection time.

Real-time remote monitoring of CGM, insulin and meal data is available through a web browser (Amazon Web Services). Finally, automatic alarms to the expert team, sent via email, are available.

2.6. Clinical Trial Design

The main objectives of the research study are to evaluate the safety, efficacy and cost-effectiveness of a BiAP Gen 2 with, and without, the addition of the adaptive bolus calculator (ABC) compared to gold-standard sensor-augmented pump therapy. Adaptations of the ABC are performed off-line every two weeks.

The study design consists of a 3-way crossover open label randomized controlled trial. The total duration of the study is 24 weeks with two weeks run-in period, six weeks per way and wash-out periods of two weeks. Figure 4 shows a graphical representation of the proposed study design. The study population are 20 adults with type 1 diabetes. Inclusion criteria were: adults over 18 years of age, T1D confirmed on the basis of clinical features and a fasting c-peptide <200 pmol/L; T1D for greater than 1 year; continuous subcutaneous insulin infusion for greater than 6 months;

HbA1c <10% (86mmol/mol); and compliance with sensor augmented pump therapy during run-in period. Exclusion criteria were: more than one episode of severe hypoglycaemia (defined as hypoglycaemia requiring 3rd party assistance) in the preceding year; hypoglycaemia unawareness; pregnant or planning pregnancy; breastfeeding; enrolled in other clinical trials; have active malignancy or under investigation for malignancy; severe visual impairment; reduced manual dexterity; ischaemic heart disease; anti-anginal medications (e.g., GTN); unable to participate due to other factors, as assessed by the clinical investigator.

The primary outcome from the studies is percentage time spent with a glucose concentration in the target range (3.9-10.0mmol/l). This outcome incorporates safety as it ensures participants do not have low or high glucose excursions and is the principal measure of efficacy for closed-loop insulin delivery systems in the scientific literature. Secondary outcomes include percentage time spent in euglycaemia (3.9-7.8mmol/l), percentage time spent in hypoglycaemia (<3mmol/l and <3.9mmol/l), percentage time spent in hyperglycaemia (>10mmol/l), mean venous blood and sensor glucose, glycaemic variability as measured by standard metrics, glycaemic risk as measured by low blood glucose index (LBGI) and high blood glucose index (HBGI), closed-loop error grid analysis, glucose area under the curve. All measures have been previously published and validated [41]. Quality of life, treatment satisfaction and device acceptability outcomes will be measured using mixed methods (questionnaires and semi-structured interviews).

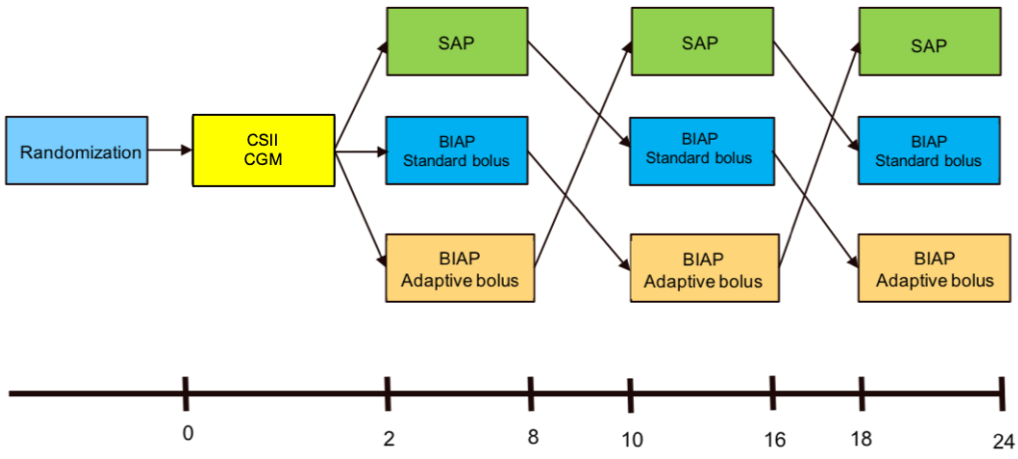


Figure 4. Clinical trial design for evaluation of BiAP Gen 2 in the home environment.

3. Results

At the time of writing this report, two participants, one allocated to the BiAP+Standard bolus arm (Participant #1) and the other one to the BiAP+ABC arm (Participant #2), had been in the trial for a duration of approximately two weeks (Participant #1: 11 days; Participant #2: 16 days). Since adaptation of the adaptive bolus calculator (ABC) are scheduled every two weeks, there was no time to perform any adaptation on the participant on the BiAP+ABC arm.

Preliminary glycaemic results corresponding to Participant #1 and Participant #2 are reported in Table 1. Glucose metrics are analysed per day and presented as media±IQR. In particular, we report percentage time in glucose target [70,180] mg/dl; percentage time below 54 mg/dl; percentage time below 70 mg/dl; and percentage time above 180 mg/dl. Figure 5 shows the CGM trace and insulin data for two selected days corresponding to Participants 1 and 2. Table 2 reports the average correction boluses administered per day and the average exercise announcements per day for each participant.

Table 1. Glycaemic outcomes corresponding to the two enrolled participants expressed as media±IQR.

Participant	Glucose mg/dL	%T in [70,180] mg/dl	%T < 54 mg/dl	%T < 70 mg/dl	%T > 180 mg/dl
# 1	154±[141, 168]	70±[57,83]	0.0±[0.0,0.0]	1.6±[0.0,1.6]	28±[16,41]
# 2	136±[122, 150]	77±[67,88]	0.0±[0.0,0.0]	5.1±[3.0,7.3]	22±[4,26]

Table 2. Average correction boluses administered per day and average exercise announcements per day for each of the two participants.

Participant	Correction boluses per day	Exercise announcements per day

# 1	1.3	0
# 2	2.7	0.3

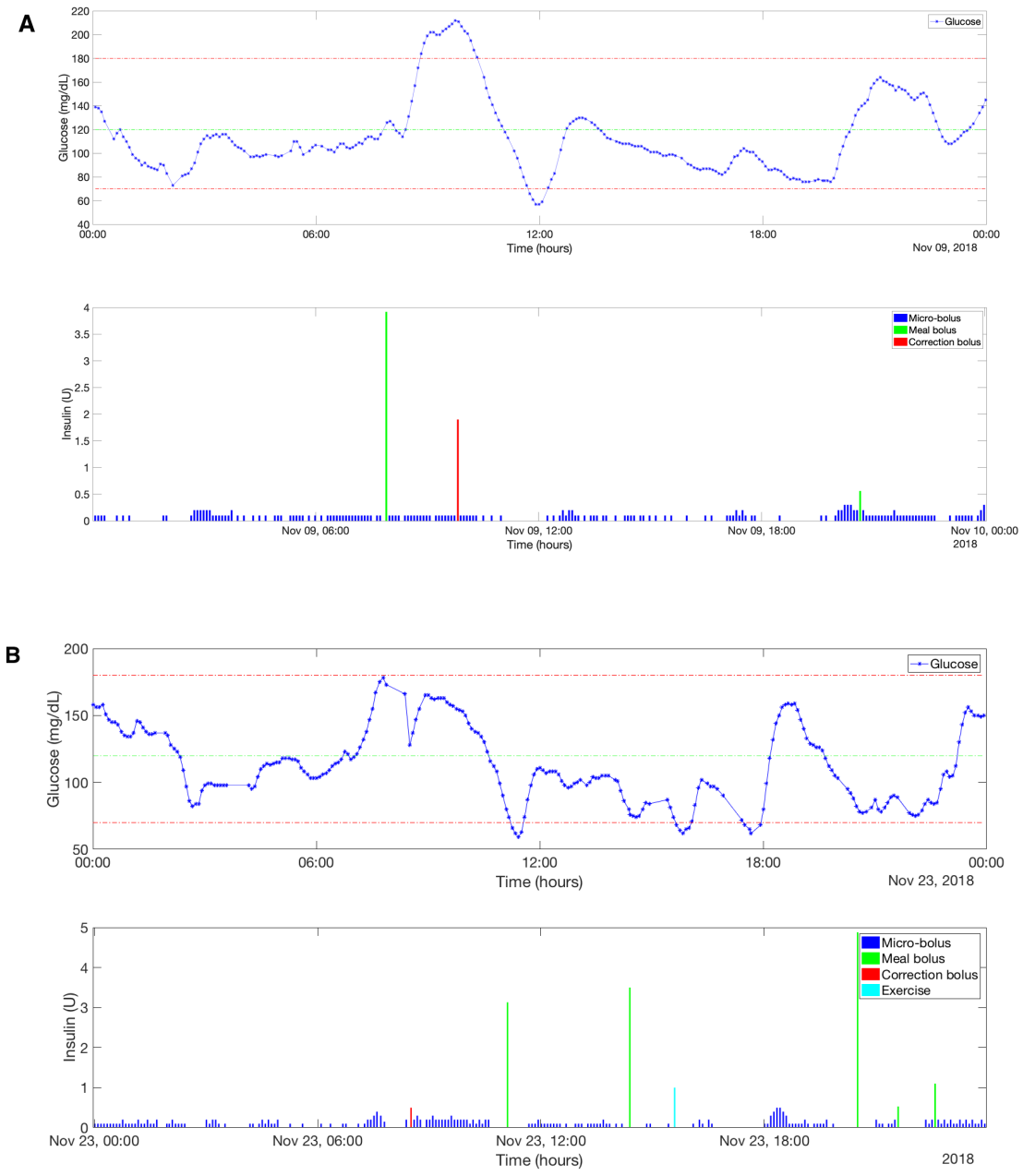


Figure 5. CGM and insulin data for a selected day corresponding to Participant 1 (A) and Participant 2 (B). In the lower graph, blue bars correspond to micro-boluses delivered by the

BiAP closed-loop controller, while green and red bars represent meal boluses and correction boluses, respectively. Cyan bar indicates the time the exercise was announced.

Regarding the device connectivity and safety measures, Table 3 reports the percentage time the CGM was connected to the BiAP; total number of pump disconnections; percentage time in closed-loop mode; the number of hypoglycaemia alarms; and the percentage of time the low-blood insulin suspension algorithm was active (i.e., partial suspension and total suspension) . There were no reported adverse events or serious adverse events during the study to date.

Table 3. Device connectivity metrics, hypoglycaemic alarms, and low-blood insulin suspension time

Participant	% Time CGM connected	Total number of pump disconnections per day	% Time in closed loop	No. of hypo alarms per day	% Time in partial suspension	% Time in total suspension
# 1	97.3	0.3	90.2	0.6	8.3	6.7
# 2	99.3	0.5	86	0.7	13.0	6.4

4. Discussion

Despite the limited amount of clinical data, preliminary results from the first two participants show that BiAP Gen 2 achieves comparable glycaemic outcomes to existing artificial pancreas systems in comparable conditions [5].

Concerning the device connectivity, the communication with the sensor was reliable (97.3% and 99.3% of the time connected). On the other hand, some disconnections were experienced with the communication to the pump. The Tandem t:slim insulin pump modified for AP clinical trials has a known issue arising from the Bluetooth chip which randomly disconnects and does not reconnect unless the Bluetooth on the pump is toggled off and on. This was also seen by other

groups using this pump [42,43]. The percentage time in closed-loop mode was comparable to the one achieved in other clinical trials [43].

When looking at the individual results, Participant 2 is more prone to administering correction boluses, and also does some physical exercise. In addition, Participant 2 spent less time in closed-loop mode. This might explain the slightly higher percentage of time spent in mild hypoglycaemia.

Regarding the usability of the system, carrying four devices (handled unit, phone, pump, and CGM) is not optimal, hence the plan for future generations of the system is to eliminate some of the devices. For instance, as a result of its low computational requirements, and its proven implementation on an embedded platform, the employed control algorithm can be easily integrated in the microcontroller of any insulin pump. Similarly, the adaptive bolus calculator could also be integrated within a pump like Tandem t:slim, which offers a graphical user interface sufficient for the required interaction.

5. Conclusions

The BiAP Gen 2 system is a viable artificial pancreas platform to conduct ambulatory clinical trials and a potentially solution for people with type 1 diabetes to achieve better glucose control in a home environment. However, additional clinical results are needed for validation.

Appendix A

This section mathematical proves that the employed pancreatic insulin secretion model within the BiAP Gen 2 system is equivalent to a Proportional Derivative controller with two low-pass filters.

The beta-cell insulin secretion model employed as the core of the BiAP controller is described by the equation

$$u(t) = SR(t) + SR_b, \quad (1)$$

where *SR* is the pancreatic insulin secretion (*SR*) above basal secretion, SR_b is the basal insulin secretion. As described in [36], the pancreatic insulin secretion (*SR*) above basal secretion (SR_b) is assumed proportional (*m*) to the amount *X* of readily releasable insulin in the beta-cells

$$SR(t) = m\,X(t). \qquad (2)$$

The change in the insulin amount in the ready releasable pool *X* results from the balance between the insulin secretion rate, the provision *Y* of insulin refilling the readily releasable pool, and recruitment of readily releasable insulin *XD*

$$\frac{dX(t)}{dt} = -mX(t) + Y(t) + X_D(t), \qquad X(0) = 0, \qquad (3)$$

where X_D is responsible for the first phase of secretion and is assumed to be proportional to the rate of increase of glucose via the constant parameter K_D and expressed as

$$X_D(t) = \begin{cases} K_D \frac{dG(t)}{dt}, & if\ \frac{dG(t)}{dt} > 0; \\ 0, & otherwise \end{cases} \qquad (4)$$

The provision *Y* generates the slower second phase and is controlled by glucose according to the equation

$$\frac{dY(t)}{dt} = -\alpha[Y(t) - \beta(G(t) - G_b)], \qquad Y(0) = 0, \qquad (5)$$

where G_b represents the basal value of glucose, and α and β are parameters.

By rewriting the error signal $\mathrm{G(t)} - G_b$ as $\mathrm{E(t)}$, and since Equations 1-5 is a system of linear differential equations with constant coefficients, we can perform a Laplace transformation which converts the system from differential equations in the time domain (t) to algebraic equations in a frequency domain (s).

Then, by using the differentiation rule, $\mathrm{df/dt}$ in the time domain becomes $\mathrm{s \cdot F(s) - f(0)}$ in the frequency domain. Taking advantage of the Laplace transformation we further transform $\mathrm{a \cdot f(t) + b \cdot g(t)}$ in the time domain to $\mathrm{a \cdot F(s) + b \cdot G(s)}$ in the frequency domain. With these transformations we can then rewrite Equation 1-5 system in the frequency domain such as

$$SR(s) = m \cdot X(s). \qquad (6)$$

$$s \cdot X(s) = -m \cdot X(s) + Y(s) + K_D \cdot s \cdot G(s), \qquad (7)$$

$$s \cdot Y(s) = -\alpha \cdot Y(s) + \alpha \cdot \beta \cdot E(s). \qquad (8)$$

By doing some algebraic manipulations, the system can be represented as follows

$$SR(s) = m \cdot \frac{1}{m+s} \cdot \big(Y(s) + K_D \cdot s \cdot G(s)\big) = \frac{m}{s+m}\left(\frac{\alpha \cdot \beta \cdot E(s)}{s+\alpha} + K_D \cdot s \cdot G(s)\right)$$

$$= \frac{m}{s+m} \cdot \frac{\alpha}{s+\alpha}\beta \cdot E(s) + \frac{m}{s+m}K_D \cdot s \cdot G(s). \qquad (9)$$

The insulin secretion rate is hence formed by a sum of a proportional term $\mathrm{E(s)}$ and a derivative term $\mathrm{s \cdot G(s)}$, which makes it equivalent to a Proportional Derivative (PD) controller. In addition, the factors multiplying these two terms act as filters. Hence, for small frequencies s, the factor $\frac{m}{s+m}$ becomes 1 and lets the signal pass through, while for large s it makes the factor go asymptotically to 0 and eventually lets nothing pass through. The same applies to $\frac{\alpha}{s+\alpha}$, but this factor only acts on the proportional term, whereas $\frac{m}{s+m}$ acts on both the proportional and derivative term. Therefore, the beta-cell insulin secretion model is equivalent to a PD controller with two filters. These two filters can be used to get rid of high frequency signals, such as glucose sensor noise. This can be particularly useful for the derivative term of the equation.

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