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Fully Automated Artificial Pancreas

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Abstract: Artificial pancreas technology, involving ‘‘closed-loop’’ controls with real-time blood glucose monitoring, has been increasing in reliability as its potential for clinical use and application grows. Prandial glucose regulation is a major challenge for the artificial pancreas using subcutaneous insulin (without a feed forward bolus) due to insulin’s slow absorption-peak (50–60 min). Intra peritoneal insulin, with a fast absorption peak (20–25 min), has been suggested as an alternative to address these limitations. An artificial pancreas using intra peritoneal insulin was designed and evaluated on 100 in silico subjects and compared with two designs using subcutaneous insulin with and without a feed forward bolus, following the three meal (40–70g-carbohydrates) evaluation protocol.

Keywords: Artificial, Closed, Pancreas, Automated, Diabetes.

I. INTRODUCTION

The artificial pancreas (AP), known as closed-loop control of blood glucose in diabetes, is a system combining a glucose sensor, a control algorithm, and an insulin infusion device. AP developments can be traced back 50 years to when the possibility for external blood glucose regulation was established by studies in individuals with type 1 diabetes using intravenous glucose measurement and infusion of insulin and glucose. After the pioneering work by Kadish in 1964, expectations for effectively closing the loop were inspired by the nearly simultaneous work of five teams reporting closed-loop control results between 1974 and 1978 [1]. Developing a closed-loop insulin delivery system has the potential to transform diabetes management and improve the lives of those living with the disease. Since JDRF (formerly the Juvenile Diabetes Research Foundation) launched the Artificial Pancreas Project in 2006, various studies have reported the feasibility of different closed-loop algorithms control blood glucose levels in patients with type 1 diabetes. Although much technical progress has been made, patients with type 1 diabetes carry a significant burden in the completion of day-to-day diabetes care tasks, and run the continual risk of hypoglycaemia and hyperglycaemia in their attempts to achieve optimal glucose control. Home care delivery is considered a key issue to enforce a better control on chronic diseases,1 delay the onset of their complications, and save any related cost.2 Unfortunately, until the past decade only few parameters could be collected in real time outside clinical settings mainly because of technical and connection-related limitations [2]. However, the recent progresses in the information and communication technologies (ICT), together with the appearance of new biosensor families made available through advances in miniaturization and nanotechnologies, 3 are deeply reshaping the way in which real-time surveillance of physiological parameters is accomplished.

That trend anticipates new scenarios for the development of monitoring devices that are no longer constrained at the bedside, and whose focus will be on data integration, yielding an improved and more timely detection of abnormal situations representing deviations off the normal course of a disease. The AP is a closed-loop system that aims to regulate glucose level in diabetes patients.6 It has 3 main components: a real-time continuous glucose monitoring (CGM) device acquiring blood glucose levels readings, a control algorithm that calculates the appropriate insulin dosage given those readings, and a continuous subcutaneous insulin infusion (CSII) pump delivering the computed insulin doses. Even if the AP development started about 50 years ago when the possibility of controlling blood glucose in Type 1 diabetes using intravenous glucose measurement along with the infusion of insulin and glucose was proven [4].

II. CLOSED-LOOP SYSTEM

The use of a closed-loop system that combines continuous glucose monitoring with automated algorithm driven insulin delivery can potentially improve glycaemic control. The control algorithm translates in real time information received from continuous glucose monitoring and computes the amount of insulin to be delivered subcutaneously by a pump. Such a system has been shown to be safe and efficacious in controlled overnight studies in adults with type 1 diabetes. Feasibility of daytime use of closed-loop insulin delivery has also been demonstrated in adolescents and pregnant women with type 1 diabetes. To our knowledge, no studies have evaluated closed-loop systems in type 2 diabetes. The closed-loop system may be of significant benefit in glycaemic management of such patients in the hospital but, to date, has only been evaluated in intensive care patients receiving intravenous insulin with intravenous or subcutaneous glucose measurements [5]. The aim of the present study was to evaluate the feasibility of 24 h of fully closed-loop glucose control in insulin-na ıve patients with type 2 diabetes through subcutaneous continuous glucose sensing and subcutaneous insulin delivery figure 1.Glycaemic Control
The primary and secondary outcome data. Closed loop insulin delivery increased the primary outcome of time in target plasma glucose range (3.9–8.0 mmol/L) from 24% (2–43%) during control to 40% (30–64%, P = 0.016). Time spent .8.0 mmol/L was lowered from 76% (57–98%) to 60% (36–70%, P = 0.016). Mean plasma glucose concentration was similar (9.7 6 1.4 vs. 9.4 6 1.9 mmol/L,

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P = 0.480), and there was no time spent, 3.9 mmol/L during either intervention. Plasma glucose SD, representing glucose variability, was higher during closed-loop delivery (1.8 6 0.4 vs. 2.2 6 0.7 mmol/L, P = 0.041

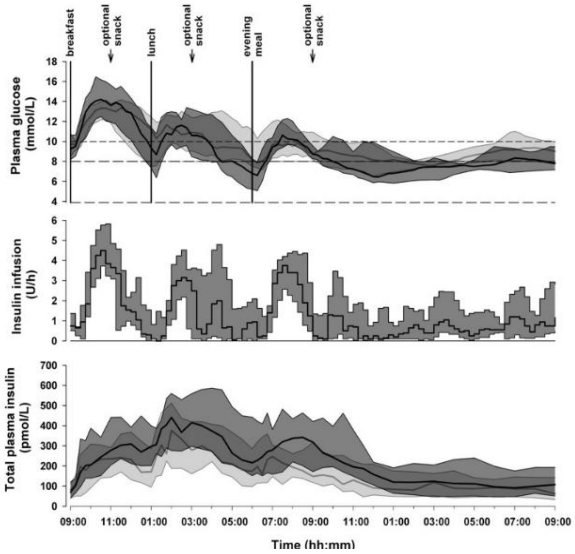

Figure 1: Time during 24 hours

III.LOW GLUCOSE PREDICTOR DESIGN

The pre-processing component of the LGP is used to filter the CGM data for prediction. This is motivated by the presence of noisy data, missed data points, or shifts due to calibration. These issues are addressed in the pre-processing section [4].

Sustainability and operability of a safety system is a key design principle. The ability to operate without the need for user input is a clear advantage of the HMS over other safety systems and control algorithms.As such, notification of calibration, physical activity, meals, or any other external prompt is not needed. The inherent calibration detection feature provides a smooth transition even when calibration is conducted. Calibration detection without announcement is achieved via the first component of the pre-processing section. In order to make a better and more accurate prediction, shifts introduced to the system, such as calibrations, must be detected so that the shift does not produce a nonphysiologic rate of change estimate. A shift in the signal is detected when the change in the raw signal is too large (absolute value > 4 mg/dl/min, considered to be nonphysiologic28) and then the next data point continues roughly the same trend as before the shift, but with an offset. When a shift is detected, the points after the shift can be considered more accurate, and the same offset can be applied to the points before the shift to reflect the true trend [7].

Results were generated for all subjects using the HMS, both with and without the pre-processing module (latter denoted HMSbasic). Overall, results are shown in Figure 5 and 66., the true positive ratio (TPR), or percentage of hypoglycaemic events that were predicted by the algorithm within 1 h prior to the event, is plotted versus the false positive ratio (FPR), the ratio of false positive alarms to the number of readings in the false positive region. Hypoglycaemia events were defined, in this study, when the unfiltered CGM data were under the hypo-glycaemia threshold (e.g., 70 mg/dl) for at least 10 min.37 The false positive region is defined as the sum of all segments not in hypoglycaemia (<70 mg/dl) or the hour preceding the onset of hypoglycemia.37 Only predictive alarms were assessed, not including any alarms that occurred during hypoglycaemia. Results with both the HMS and the HMS basic show an increase in both TPR and FPR as the PH increases, as would be expected. The most significant result of this study is the shifting of the points from HMS basic to HMS upward and to the left. This result suggests that the modifications of the data used in the pre-processing section cause more hypoglycaemia events to be detected with fewer false alarms figure 2.

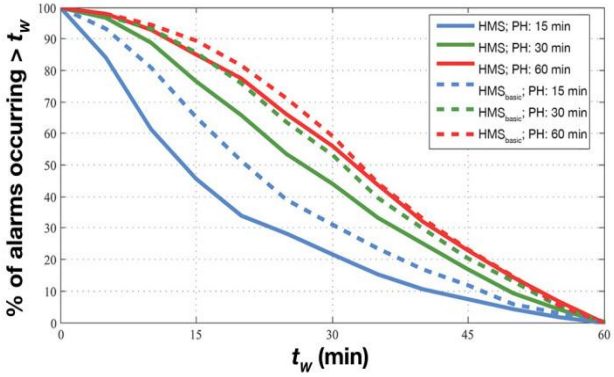

Figure 2: FPR (alarms /a day)

IV. SEMI-AUTOMATED ARTIFICIAL PANCREAS WITH TECHNO SPHERE INSULIN

Normal physiological insulin secretion at mealtime consists of two phases: the rapid rising cephalic first phase of insulin secretion and the prolonged second phase of insulin secretion. Thus, to reproduce the physiological insulin secretion pattern, an ideal AP needs to capture both phases. As depicted, the semi-automated AP with TI combines two insulin delivery methods (ultra-rapid-acting TI and CSII controlled by zone-MPC) to capture the two insulin secretion phases mentioned earlier demonstrates the design of the semi-automated AP with TI manual feed-forward TI action and feedback loop of CGM, CSII, and the control algorithm [3].Zone-MPC is a model predictive algorithm that was designed to control predicted output within a suitable range, or zone, of values, rather than to a set point of a single value. As discussed in the work of Grossman and coauthors, high-frequency measurement errors in glucose measurements and model–subject mismatches in the current AP make the use of a specific set point for BG regulation irrelevant or impractical [8]. Also, normoglycemia itself is defined as a zone. Thus defining the control objective as a zone is a natural strategy for the algorithm of an AP. The model of glucose/SC insulin interaction that is used in this study is presented by Van Heusden and coauthors. The model utilizes a priori knowledge of a subject (i.e., individual correction factor) to account for the inter subjective variability of insulin sensitivity and incorporates an

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adjustable safety factor to improve system robustness due to human errors in the estimation of the correction factor. The health monitoring system (HMS) developed by Harvey and coauthors and Dassau and coauthors is implemented in parallel to the control loop to provide a safety layer and further reduce hypoglycemia risk. It was designed to receive and process CGM data and make a prediction of glucose trends. The HMS automatically sends SMS and MMS (short and multimedia message services) to a predefined contact list to alert the receiver of imminent safety hazards [6].

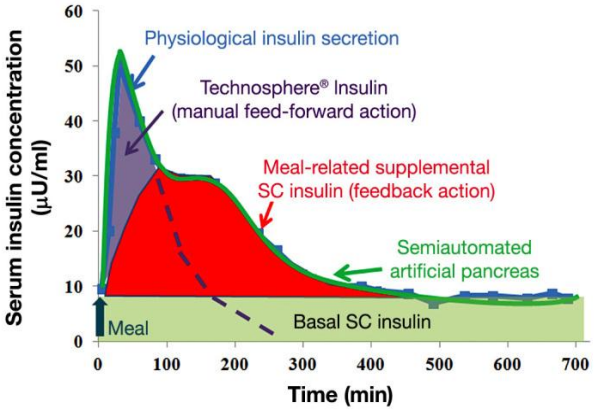

Figure 3: Time (min)

V. CLOSED-LOOP SYSTEM USING THE INTRAPERITONEAL ROUTE

The average BG profiles during the in silico evaluation illustrate that the average postprandial BG peak was lower by38 mg/dL in the IP–SC case than the SC–SC case. Also, after the meal, the IP–SC design brought average BG back into the clinically accepted region (70–180 mg/dL) significantly faster by 1.5–2 h than the SC–SC design , the p-value < 0.01 for the paired t-test) figure 4.

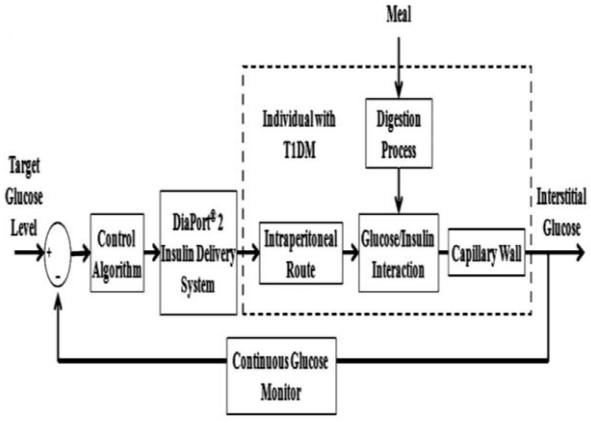

Figure 4: IP–SC design

Subcutaneous insulin delivery has been the basis of insulin therapy for people with T1DM since 1922. Although the SC delivery is minimally invasive and user-friendly, it exhibits inherent slow absorption characteristics as well as the risk of insulin depot in the SC space (i.e., insulin remains in the SC region instead of diffusing into the blood vessels) (Schaepelynck et al., 2011). In the development of a closed-loop AP, the insulin depot effect and slow absorption characteristics limits the controller's ability to achieve normoglycemia and introduces hypoglycemia risk [5]. Hence, the fast-absorbing IP route that delivers insulin into the abdominal cavity may provide a breakthrough method in an AP development. Since IP insulin is absorbed by the capillary bed in the.

Even though the possible benefit of pre-meal IP bolus was concleavable, IP–SC design with manual feed forward IP bolus was not considered in this work because of the possibility of the safety hazard from an inaccurate bolus calculation mentioned above. Additionally, because of the rapid absorption rate of IP insulin, the risk of overestimated IP bolus or delayed meal intake would be even bigger than the risk of SC case. This safety risk would nullify the possible benefit of pre-meal IP bolus. Furthermore, the time window for providing the standard hypoglycemia treatment (e.g., glucose tablet or fruit juice) to reverse the overdose might be too short figure 5.

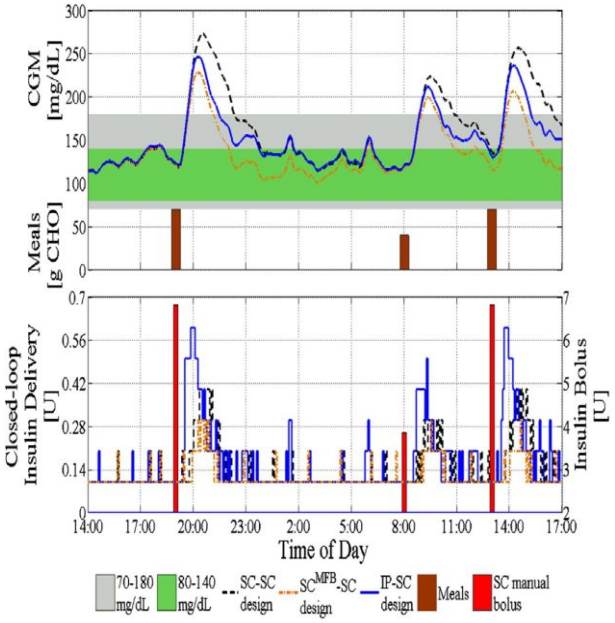

Figure 5: Evolutions the designs

VI. CONCLUSION

Overall, in vivo results were slightly different and inconsistent from our blood sampling study based sample readings. For example, our blood sampling study-based sample data with canine blood samples demonstrated a trend whereby the discrepancy between STG-22whole blood and reference [glucose] readings were reduced with increased [glucose] such that under severe hyperglycemia conditions, both readings were similar. He evaluation also showed that the IP–SC design without user interactions achieved similar BG regulation compared to the SCMFB–SC design that requires manual meal bolus injections. Hence, the fast action and rapid clearance of IP insulin reduced the burden of the user to maintain BG within the clinically accepted region by eliminating the actuation delay of the closed-loop system.

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