ROBUST AND FAULT-TOLERANT STRATEGIES FOR CONTROLLING BLOOD GLUCOSE IN PATIENTS WITH TYPE 1 DIABETES

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Universitat
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Doctoral Thesis

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DOCTORAL THESIS

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ALEIX BENEYTO TANTIÑA

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Supervised by: Josep Vehí Casellas

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DOCTORAL THESIS

ROBUST AND FAULT-TOLERANT STRATEGIES FOR CONTROLLING BLOOD GLUCOSE IN PATIENTS WITH TYPE 1 DIABETES

A dissertation presented in partial fulfillment of the requirements for a doctoral degree from the University of Girona.

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To my parents, Jordi and Mercè, for their endless support and encouragement over the years.

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LIST OF PUBLICATIONS

This thesis is based on a compendium of the following publications:

1. **Aleix Beneyto** and Josep Vehí. Postprandial fuzzy adaptive strategy for a hybrid proportional derivative controller for the artificial pancreas, *Medical & Biological Engineering & Computing*, 56(11):1973-1986, **2018**.

2. **Aleix Beneyto**, Arthur Bertachi, Jorge Bondia and Josep Vehí. A new blood glucose control scheme for unannounced exercise in type 1 diabetic subjects, *IEEE Transactions on Control Systems Technology*, 28(2):593-600, **2018**.

3. **Aleix Beneyto**, Vicenç Puig, B. Wayne Bequette and Josep Vehí. A hybrid automata approach for monitoring the patient in the loop in artificial pancreas systems, *IEEE Journal of Biomedical and Health Informatics*, Submitted.

The research work leading to this thesis resulted in additional journal and conference publications, which are listed below and sorted by publication date.

Journals

4. Clara Viñals, **Aleix Beneyto**, Juan-Fernando Martín-SanJosé, Clara Furió-Novejarque, Arthur Bertachi, Jorge Bondia, Josep Vehí, Ignacio Conget and Marga Giménez. Artificial pancreas with carbohydrate suggestion performance for unannounced and announced exercise in Type 1 Diabetes, *The Journal of Clinical Endocrinology & Metabolism*, Accepted **2020**.

5. Arthur Bertachi, **Aleix Beneyto**, Charrise M. Ramkissoon, and Josep Vehí, Assessment of Mitigation Methods to Reduce the Risk of Hypoglycemia for Announced Exercise in a Uni-hormonal Artificial Pancreas, *Diabetes Technology & Therapeutics*, 20(4):285-295, **2018**.

6. Charrise M. Ramkissoon, Arthur Bertachi, **Aleix Beneyto**, Jorge Bondia, and Josep Vehí, Detection and Control of Unannounced Exercise in the Artificial Pancreas without Additional Physiological Signals: A Feasibility Study, *IEEE Journal of Biomedical and Health Informatics*, 1(1):1-1,2019.

7. Arthur Bertachi, Lyvia Biagi, **Aleix Beneyto**, and Josep Vehí. Dynamic Rule-Based Algorithm to Tune Insulin on Board Constraints for a Hybrid Artificial Pancreas System, *Journal of Healthcare Engineering*, 2020, vol. 2020.

Conferences

1. **Aleix Beneyto**, Arthur Bertachi and Josep Vehí, Coordinated Insulin and Carbohydrates Delivery to deal with Announced and Unannounced Exercise, In 17th Annual Diabetes Technology Meeting, Bethesda - USA, page A7, **2017**. (abstract).

2. **Aleix Beneyto** and Josep Vehí, Closed-loop blood glucose control using insulin and carbohydrates in front meals and exercise, In 20th World Congress of teh International Federation of Automatic Control, Toulouse - France, 50(1): 2058-2063, **2017**. (full-paper).

3. Charrise M. Ramkissoon, Arthur Bertachi, **Aleix Beneyto** and Josep Vehí, Insulin-Only Blood Glucose Control in Type 1 Diabetes during Unannounced Aerobic Exercise, In 18th Annual Diabetes Technology Meeting, Bethesda - USA,2018. (abstract).

4. Arthur Bertachi, Charrise M. Ramkissoon, **Aleix Beneyto** and Josep Vehí, Exercise-induced Hypoglycemia in Type 1 Diabetes: in-silico Comparison Between Announced and Unannounced Strategies in Closed-loop Control, In 12th IFAC Symposium on Dynamics and Control of Process Systems, including Biosystems (DYCOPS 2019), Florianópolis- Brazil, pages 1000-10052019. (full-paper).

5. Clara Viñals, **Aleix Beneyto**, Juan-Fernando Martín-SanJosé, Jorge Bondia, Josep Vehí, Ignacio Conget and Marga Giménez. Control de la glucemia durante el ejercicio físico anunciado y no anunciado utilizando un controlador multivariable en lazo cerrado con sugerencia automática de carbohidratos. In 31th Congreso Nacional de la Sociedad Española de Diabetes

6. Clara Viñals, **Aleix Beneyto**, Juan-Fernando Martín-SanJosé, Clara Furió-Novejarque, Arthur Bertachi, Jorge Bondia, Josep Vehí, Ignacio Conget and Marga Giménez, Automatic Control of Blood Glucose under Announced and Unannounced Exercise using a New Multivariable Closed Loop Controller with Automatic Carbohydrate Suggestion and

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ACRONYMS AND ABBREVIATIONS

The following acronyms and abbreviations can be found in this thesis.

Acronyms and abbreviations

AGP	Ambulatory Glucose Profile
AP	Artificial Pancreas
BG	Blood Glucose
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CIBERDEM	*Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas*
CL	Closed-Loop
COB	Carbohydrates On Board
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DM	Diabetes Mellitus
eSCAPE	Spanish Consortium on Artificial Pancreas and Diabetes Technology
FD	Fault Detection
FDA	Food and Drug Administration
HbA_{1c}	Glycated Hemoglobin
IDF	International Diabetes Federation
IDIBAPS	*Institut d'Investigacions Biomèdiques August Pi i Sunyer*
IIT	Intensive Insulin Therapy
IOB	Insulin On Board
jAP	Java Artificial Pancreas
LADA	Latent Autoimmune Diabetes in Adults
LGS	Low Glucose Suspend
MDI	Multiple Daily Injections
MEDERI	Medical Devices Research & Innovation Living Lab
MICELAB	Modeling, Identification & Control Engineering Laboratory
MODY	Maturity-Onset Diabetes of the Young
MPC	Model Predictive Control
OL	Open-Loop

PD	Proportional-Derivative
PID	Proportional-Integral-Derivative
PLGS	Predictive Low Glucose Suspend
PP	Postprandial Period
SAFE	Safety Auxiliary Feedback Element
SAP	Sensor-Augmented Pump
SMBG	Self-Monitoring of Blood Glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TIR	Time in Range
UdG	University of Girona - *Universitat de Girona*
UPV	Polytechnic University of Valencia - *Universitat Politècnica de València*

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Abstract

Diabetes Mellitus (DM) is a chronic metabolic condition characterized by raised levels of blood glucose (BG), which can lead to long-term health complications if not treated. The irreversible destruction of the insulin producing β-cells in the pancreas or an increased body resistance to insulin action lead to type 1 diabetes (T1D) and type 2 diabetes (T2D), respectively. In 2019 the total world adult population with DM in the range of 20-79 years was estimated in 463 million, number that is predicted to rise to 578 million by 2030.

Type 1 diabetes is a serious disease that must be monitored and controlled artificially by supplying exogenous insulin to the body. Intensive insulin therapy was demonstrated to alleviate DM symptoms and to reduce the risk of diabetes complications. It can be performed using multiple daily injections (MDI) or using a continuous subcutaneous insulin infusion (CSII). During the last decade, several technological advancements in BG sensing led to reliable continuous glucose monitors (CGM). The artificial pancreas (AP) is a closed-loop (CL) system that resulted from integrating an insulin pump with a CGM and uses a control algorithm to automate insulin infusion. Several control approaches have been explored and tested in simulation and in clinical trials, showing that AP systems have the potential to revolutionize T1D and T2D treatment. However, big disturbances such as meals and exercise, important delays in the measurements and control actions, and having the patient in the control loop pose major impediments for the success of AP systems.

In this work, a novel control approach is presented for an AP system aimed to be robust against patient variability, meals and exercise. To enhance safety, fault detection strategies are also developed as an integral part of the system. One of the hurdles of AP systems lies in the fact that the plant to control is also its operator, i.e. the patient is in the loop. This poses limitations on performance if the controller tuning and performance is not monitored and adapted if needed. A fuzzy adaptive system has been developed to supervise the control performance during postprandial periods, and to adapt the controller tuning if needed. Another disturbance that increases the risk of hypoglycemia is physical activity. To cope with this, a multivariable control algorithm has been developed, which uses insulin infusion and prompts rescue carbohydrates. The proposed approach was firstly tested in-silico simulations and validated later in an inpatient clinical study. The multivariable approach relies on patient compliance. For that reason, a fault detection (FD) mechanism that uses a bank of observers is developed to detect patient modes and potential faults.

All of the results obtained from the different experiments conducted using the presented approaches are promising. Specifically, the clinical trial results suggest that physical activity

can be done safely with an AP system. The obtained outcomes have the potential to contribute in the future AP development.

RESUMEN

La Diabetes Mellitus (DM) es una enfermedad metabólica crónica caracterizada por elevados niveles de glucosa en sangre, que pueden provocar complicaciones a largo plazo sin el tratamiento apropiado. La destrucción irreversible de las células β productoras de la insulina en el páncreas o un aumento de la resistencia a la acción de la insulina conduce respectivamente a la diabetes tipo 1 (T1D) o a la diabetes tipo 2 (T2D). En 2019 la población total adulta mundial con DM en el rango de 20-79 años fue estimada en 463 millones, número que se prevé que aumente hasta los 578 millones en 2030.

La T1D es una enfermedad seria que requiere monitorización y tiene que ser controlada de forma artificial, subministrando insulina exógena al cuerpo. La terapia intensiva de insulina demostró que podía mitigar los síntomas de la DM y reducir el riesgo de las complicaciones de la diabetes. Esta puede ser realizada mediante múltiples inyecciones diarias (MDI) o usando infusión subcutánea continua de insulina (CSII). Durante la última década, varios avances tecnológicos en la medición de glucosa en sangre han permitido obtener monitores continuos de glucosa (CGM) de confianza. El páncreas artificial (AP) es un sistema en lazo cerrado (CL) resultante de integrar una bomba de insulina con un CGM, y usa un algoritmo de control para automatizar la infusión de insulina. Varios enfoques de control han sido explorados y probados tanto en simulación como en ensayos clínicos, mostrando que los sistemas AP tienen el potencial para revolucionar el tratamiento de la T1D y la T2D. No obstante, grandes perturbaciones como las comidas o el ejercicio, el retardo en las medidas y en las acciones de control, y teniendo el paciente en el lazo de control imponen obstáculos importantes para el éxito de los sistemas AP.

En este trabajo se presenta un sistema de control nuevo para sistemas AP, diseñado para ser robusto en frente a variabilidad del paciente, a comidas y ejercicio. Para aumentar la seguridad del paciente, se diseñan también estrategias para la detección de fallos como una parte integral del sistema. Uno de los obstáculos de los sistemas AP radica en el hecho que la planta a controlar es muy variable en el tiempo. Esto pone limitaciones en el rendimiento si el ajuste del controlador y su rendimiento no se monitoriza y no se adapta si fuera necesario. Un sistema adaptativo difuso ha sido desarrollado para supervisar el rendimiento del controlador en periodos postprandiales, y para adaptar el ajuste del controlador si fuera necesario. Otra perturbación que incrementa el riesgo de hipoglucemia es la actividad física. Para hacer frente a esto un sistema multivariable de control ha sido desarrollado. Este sistema usa infusión de insulina y sugiere carbohidratos de rescate. El enfoque propuesto fue probado en simulaciones in silico y posteriormente validado en un ensayo clínico. El sistema de control multivariable

depende de la obediencia del paciente. Por esta razón, un sistema de detección de fallos que usa un banco de observadores ha sido desarrollado para detectar fallos del paciente.

Todos los resultados obtenidos de los diferentes experimentos realizados utilizando las propuestas de este trabajado son prometedores. En particular, los resultados del ensayo clínico sugieren que la actividad física se puede realizar de forma segura con un sistema AP. Los resultados tienen el potencial para contribuir en el futuro del desarrollo de sistemas AP.

RESUM

La Diabetis Mellitus (DM) és una malaltia metabòlica crònica, caracteritzada per elevats nivells de glucosa en sang que poden provocar complicacions a llarg termini sense el tractament apropiat. La destrucció irreversible de les cèl·lules β productores d'insulina al pàncrees o un augment de la resistència a l'acció de la insulina condueixen respectivament a la diabetis tipus 1 (T1D) o a la diabetis tipus 2 (T2D). El 2019 la població total adulta mundial amb DM dins el rang de 20-79 anys va ser estimada en 463 milions, xifra que es preveu que s'incrementi fins als 578 milions al 2030.

La T1D és una greu que requereix de monitorització i que ha de ser controlada de forma artificial subministrant insulina exògena. La teràpia intensiva d'insulina va demostrar que podia mitigar els símptomes de la DM i reduir el risc de les complicacions de la diabetis. Aquesta pot ser realitzada mitjançant múltiples injeccions diàries (MD) o utilitzant infusió continua subcutània d'insulina (CSII). Durant l'última dècada, varis avenços tecnològics en la mesura de glucosa en sang han aconseguit obtenir monitors continus de glucosa (CGM) de confiança. El pàncrees artificial (AP) és un sistema de llaç tancat (CL) resultant d'integrar una bomba d'insulina amb un CGM, i utilitza un sistema de control per automatitzar la infusió d'insulina. Varis enfocaments de control han estat explorats i provats tant en simulació com en assajos clínics, mostrant que els sistemes AP tenen el potencial per revolucionar el tractament de la T1D i la T2D. No obstant, grans pertorbacions com els menjars o l'exercici, el retard en les mesures i en les accions de control, y tenir el pacient dins el llaç de control imposen obstacles importants per l'èxit del AP.

En aquest treball es presenta un sistema de control nou per a sistemes AP, dissenyat per ser robust davant la variabilitat del pacient, a menjars i exercici. Per augmentar la seguretat del pacient, també es dissenyen estratègies de detecció de fallades com una part integral dels sistema. Un dels obstacles dels sistemes AP radica en el fet que la planta a controlar és molt variable en el temps. Això imposa restriccions sobre el rendiment si l'ajust del controlador y el seu rendiment no es monitoritzen i no s'adapten en cas que fos necessari. Un sistema adaptatiu difús ha estat desenvolupat per a supervisar el rendiment del controlador en períodes postprandials, i per ajustar el controlador si és necessari. Una altra pertorbació que incrementa el risc d'hipoglucèmia és l'activitat física. Per fer-ne front, un sistema multivariable de control ha estat desenvolupat. Aquest sistema utilitza la infusió d'insulina i suggereix carbohidrats de rescat. L'enfocament proposat ha estat provat en simulacions in silico i posteriorment validat en un assaig clínic. El sistema de control multivariable depèn de l'obediència del pacient. Per aquesta raó, un sistema de detecció de fallades que utilitza un banc d'observadors ha estat

desenvolupat per a detectar fallades del pacient.

Tots els resultats obtinguts dels diferents experiments realitzats utilitzant les propostes d'aquest treball són prometedors. En particular, els resultats de l'assaig clínic suggereixen que l'activitat física es pot realitzar de forma segura amb un sistema AP. Els resultats tenen el potencial per a contribuir en el futur del desenvolupament de sistemes AP.

CHAPTER 1

INTRODUCTION

This chapter presents a concise introductory background to diabetes mellitus (DM) in Section 1.1 and Section 1.2, where the reader is introduced to DM associated problems and current technologies aimed to overcome them. Then, Section 1.3 describes the context in which this work has been developed. Finally, the main objectives of the work are presented in Section 1.4, and Section 1.5 concludes with the organization of this document.

1.1 Diabetes Mellitus

DM is a chronic condition caused by a group of metabolic disorders characterized by raised levels of blood glucose (BG) (Ahmad, 2013). The cause of high glucose concentration, also known as hyperglycemia, lies in the fact that the body cannot produce or effectively use an hormone called insulin. Insulin is an essential hormone secreted by the β-cells in the pancreas, and is fundamental for the glucose, protein and fat metabolism. In healthy people, BG levels are appropriately regulated by complex metabolic feedback processes driven by the action of several

endocrine hormones produced in the pancreas, see figure 1.1. Insulin allows glucose uptake by tissue cells from the bloodstream to be used as energy, and also activates the glycogenesis process by which excessive glucose can be stored as glycogen in the liver. Glucagon is a hormone, also produced in the pancreas by the α-cells, that is also key to correctly regulate the glucose metabolism. The secretion of glucagon is stimulated by low BG and insulin levels, and triggers another metabolic process known as gluconeogenesys. This process results in the generation of glucose by breaking down previously stored glucose as glycogen. In people with DM the insulin signal flows from figure 1.1 are seriously severed, disabling glucose homeostasis. Over time, the production and effectivity of glucagon is also decreased. Therefore, people with DM cannot regulate properly BG levels because both pathways are severely injured or even broken (Greenbaum et al., 2002; Sayama et al., 2005; Atkinson et al., 2011).

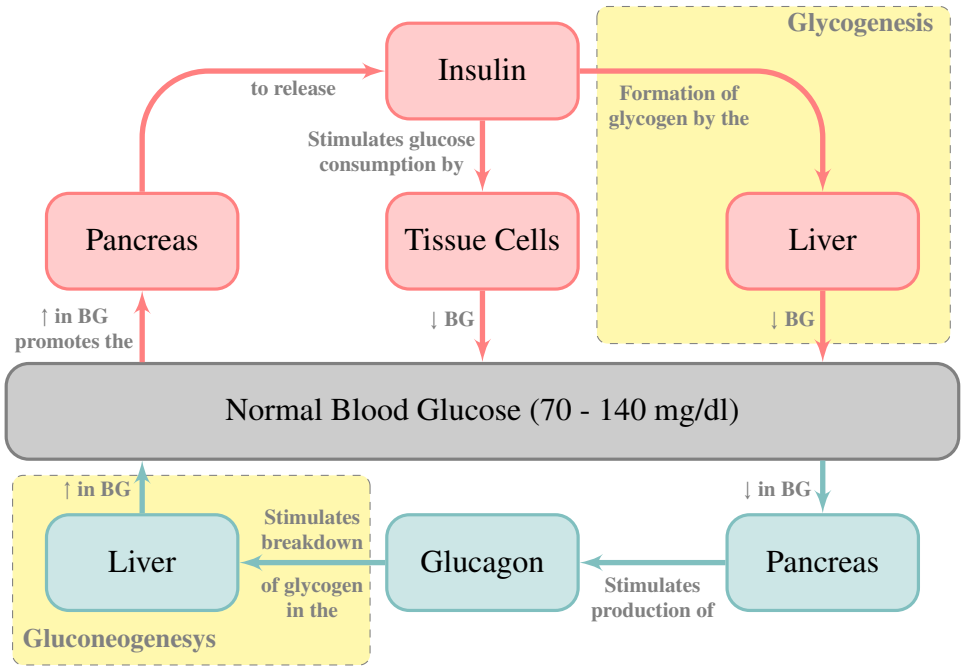

Figure 1.1: Homeostasis regulation of BG in healthy people. Red color depicts mechanisms triggered to lower BG, and blue color shows mechanisms that increase BG.

According to the International Diabetes Federation (IDF), 463 million of adults between 20-79 years are estimated to have one form of DM in 2019, with projections to rise to 578

million by 2030. This represents the 9.3% of the adult world population in that age group and has huge social and economical impacts. The global health care expenditure on DM in 2019 was estimated to be 760 billion US dollars. Table 1.1 shows the fact that DM is growing steadily in the countries with more incidence in the world. More importantly, figure 1.2 illustrates that DM is a worldwide pandemic with incidence in all countries.

	2019		2030	
Rank	Country	Number of people (milion)	Country	Number of people (milion)
1	China	116.4	China	140.5
2	India	77.0	India	101.0
2	United States	31.0	United States	34.4
4	Pakistan	19.4	Pakistan	26.2
5	Brazil	16.8	Brazil	21.5
6	Mexico	12.8	Mexico	17.2
7	Indonesia	10.7	Indonesia	13.7
8	Germany	9.5	Egypt	11.9
9	Egypt	8.9	Bangladesh	11.4
10	Bangladesh	8.4	Germany	10.1

Table 1.1: Top 10 counties with the highest number of adults (20-79 years) with diabetes in 2019 and estimated numbers for 2030 according to the (IDF, 2019) projection.

DM can be mainly classified into three groups, type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes. T1D is generally thought to be caused by an autoimmune reaction in which the body's immune system destroys the insulin producing β-cells of the pancreas. This results in a permanent insulin deficiency, leaving the body with little to none insulin production. Therefore, people with T1D need to exogenously supply insulin to the body to survive (Atkinson et al., 2014). Contrarily, T2D is caused by a combination of resistance to insulin action and insufficient insulin secretory response. It is commonly developed in older adults due to obesity and sedentary lifestyles (Chatterjee et al., 2017). Gestational diabetes is usually temporal and arises during pregnancy in women with insufficient insulin production. The diminished insulin secretory response is insufficient to regulate BG due to an increased insulin resistance caused by the production of other hormones by the placenta (American

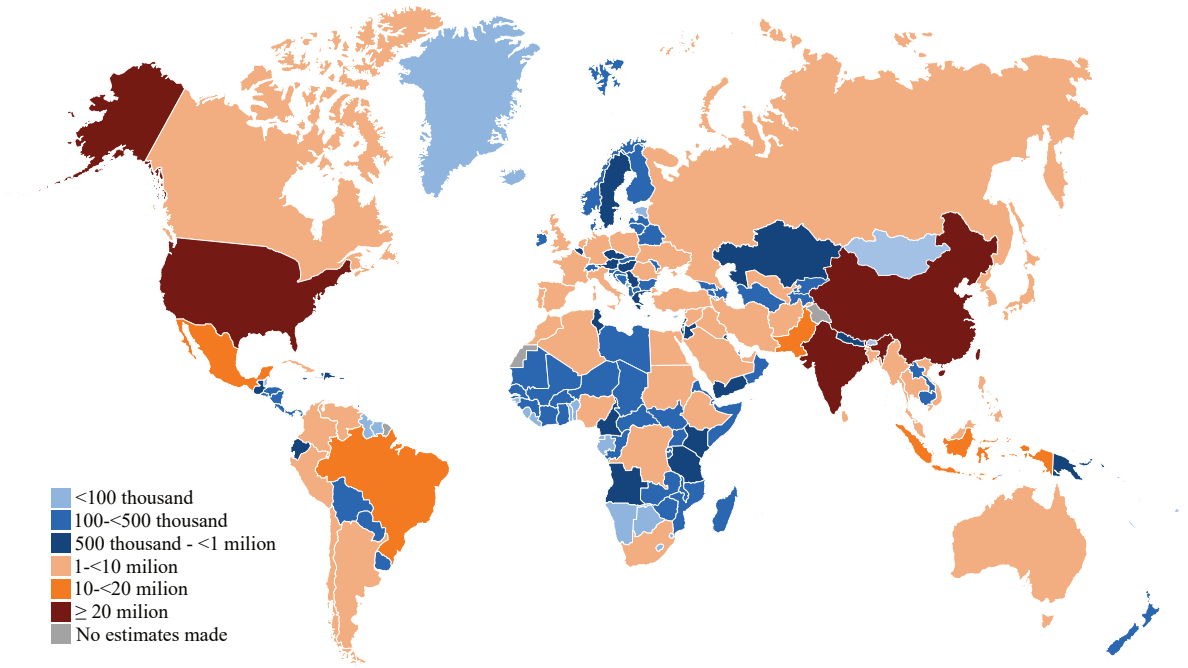

Figure 1.2: Estimated number of adults (20-79 years) with diabetes in 2019. Adapted from the (IDF, 2019)

Diabetes Association, 2004). Other types of DM exist, such as the Maturity-Onset Diabetes of the Young (MODY) and the Latent Autoimmune Diabetes in Adults (LADA) (American Diabetes Association et al., 2014; Canivell and Gomis, 2014). The MODY is described as a type of β-cell dysfunction caused by mutations in different genes. It is usually misclassified as T1D or T2D leading to suboptimal BG control (Thanabalasingham and Owen, 2011). The LADA is a specific form of DM that describe adult people that have a slowly progressive T1D, often not requiring insulin therapy initially (Fourlanos et al., 2005; Kumar and de Leiva, 2017).

This work is focused on T1D, which if left untreated will lead to the development of serious disabling, long-term and life-threatening complications, with severe mortality (Lind et al., 2014; Rawshani et al., 2017). Some of the complications include but are not limited to neuropathy, nephropathy, retinopathy, cardiovascular disease and death (IDF, 2019). The results from Diabetes Control and Complications Trial (DCCT) showed that controlling BG by exogenously injecting insulin was able to reduce diabetes related complications (DCCT, 1993).

The study also revealed that intense insulin therapy was associated with an increased incidence of low BG levels. Hypoglycemia or low BG levels is also a complication from DM and pose short term risks that can be severe, including seizures, comma and death (Shafiee et al., 2012).

People with T1D are encouraged to regularly check and keep track of their BG levels, because it is associated with better glucose control (Schütt et al., 2006). It is known that glycated hemoglobin (HbA_{1c}), a marker that reflects the average BG levels of the past 3 months, correlates with the frequency of BG measurements (Miller et al., 2015). However, better HbA_{1c} levels may also correlate with an increased hypoglycemia occurrence (Ziegler et al., 2011).

Self-monitoring of blood glucose (SMBG) refers to the home monitoring of BG for people with DM, and it is usually done by pricking a finger and taking a blood sample (Benjamin, 2002). Then, the blood sample is deposited on a test strip and an electronic device, called glucometer, returns the estimated BG levels. Glucometers offer accurate readings and enable people with diabetes to make daily decisions on insulin infusion. However, some of the disadvantages of SMBG are the need to prick fingers multiple times a day and that it does not give continuous readings (Boland et al., 2001; Klonoff, 2007; Erbach et al., 2016).

Continuous glucose monitoring (CGM) is a newer technology that estimates BG levels from glucose in the subcutaneous tissue (Klonoff et al., 2017). It is based on a small subcutaneous sensor that measures interstitial glucose. The main advantage of CGM devices over SMBG is the amount of readings they provide, CGM can provide BG estimates every five minutes in contrast with the few daily measurements of SMBG. Even though CGM showed great potential to overcome the limitations of glucometers, their BG estimations were traditionally not as accurate (Clarke et al., 2005; Kovatchev et al., 2008). This resulted in CGM's only being used as an adjunctive tool to glucometers, and insulin decisions were not allowed to be taken from CGM data (Rodbard, 2016). However, CGM technology has substantially evolved during the last years and in 2016 the Food and Drud Administration (FDA) approved the first non-adjunctive CGM for diabetes treatment decisions (Beck et al., 2020). This marked

a milestone for future CGM devices, since CGM measurements can now be used to make diabetes treatment decisions. The newest available CGM is the Dexcom G6, that comes factory calibrated and does not require people to prick their fingers (Shah et al., 2018). Currently, two types of CGM technology are available on the market, real-time CGM and intermittently scanned CGM. While real-time CGM provides constanat readings over time, intermittently scanned CGM require the user to purposely scan the sensor to download glucose information. Each of these types of CGM provide the same type of information and they should be adjuncted based on the patient needs (Edelman et al., 2018).

Treatments for T1D are based on exogenous insulin infusion. Traditionally, insulin has been administered through either conventional or intensive insulin therapy (IIT). Conventional therapy involved two or three injections of slow acting insulin per day and proper diet management. Contrarily, IIT requires more than three daily injections and require people with diabetes to take several BG readings every day. The DCCT showed that IIT improves BG control and has the potential to reduce long-term health complications (DCCT, 1993). However, it also showed that an intensive treatment also increases the risk of hypoglycemia. Hypoglycemia is not caused by DM, but is rather an effect of poorly adjusted insulin therapies. Moreover, severe cases of hypoglycemia can lead in the short-term to loss of consciousness, seizures, coma, and ultimately death (Zoungas et al., 2010). Therefore, there is a trade-off between the achievable performance without increasing too much the risk of low BG levels. IIT has become the standard of care for T1D due to its proven ability to reduce complications. Within IIT there are two common treatments on the market, multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII). Both approaches use a basal-bolus strategy for delivering insulin, are individualized for each patient characteristics and require people with diabetes to estimate carbohydrate (CHO) consumption (Brazeau et al., 2013). MDI therapies consist on using long-term insulin injections to simulate a basal insulin profile, and fast acting injections to cover postprandial periods (PP). Contrarily, CSII therapies use an insulin pump with fast

acting insulin, which allow more customization of the insulin therapy and have been showed to outperform MDI therapies (Hoogma et al., 2006). The integration of insulin pumps and CGM sensors resulted in the so-called sensor augmented pump (SAP) therapy, which has shown to improve glycemic control compared to MDI therapy (Bergenstal et al., 2010; Hermanides et al., 2011; Slover et al., 2012). A first step of closing the loop was made by the low glucose suspend (LGS) approach on SAP therapies. As the name suggests, LGS systems suspend insulin infusion if BG is lower than a given threshold and have been shown to enhance performance and safety in avoiding hypoglycemia (Danne et al., 2011; Ly et al., 2013). Predictive low glucose suspend (PLGS) systems became the next step after LGS systems, they use CGM readings to predict hypoglycemia and automatically suspend insulin infusion. PLGS systems have shown to be feasible, safer and offer better performance than LGS systems (Buckingham et al., 2013; Müller et al., 2019; Choudhary et al., 2016; Battelino et al., 2017; Forlenza et al., 2018; Abraham et al., 2018; Chen et al., 2019). Even though the advancements that T1D management has experienced, it is known that there is still room to improve the outcomes for T1D treatments (Miller et al., 2015).

Assessing the glycemic control of people with T1D is fundamental. It allows physicians to adjust the therapy if it is underperforming and to optimize it over time to ultimately delay or avoid long-term complications. The current gold standard metric, the HbA_{1c}, is known to be associated with how good glucose control is. However, it does not provide information on glycemic variability, BG daily patterns or even hyper- and hypoglycemia events. BG may substantially fluctuate even in well-controlled people, and these fluctuations may end up into hyperglycemia and hypoglycemia events, also associated with short and long-term health complications. With the rise of CGM technology and the increase of available data, newer metrics have been proposed for BG monitoring (Battelino et al., 2019; Ajjan et al., 2019; American Diabetes Association, 2020). Most of the newer metrics evaluate glycemic control based on time spent in different glycemic ranges (TIR), the definition of level 1 and level 2

hypoglycemia events and glycemic variability in terms of the coefficient of glucose variation (Agiostratidou et al., 2017). The aforementioned CGM metrics are usually included in the Ambulatory Glucose Profile (AGP). The AGP is a widely used report by clinicians and patients for glucose management (Johnson et al., 2019) and is recognised to facilitate therapy decisions (Forlenza et al., 2017; Carlson et al., 2017).

1.2 The Artificial Pancreas

The artificial pancreas (AP) is a technology that automates the regulation of BG concentration. From a control oriented point of view an AP is a closed-loop (CL) control system that aims to improve traditional diabetes treatment. AP systems date back to the 1960's with the first inpatient commercial device in 1977 (Cobelli et al., 2011). Compared to those early CL prototype systems, which were developed for in-hospital use and used intravenous sensing and delivery, current AP technology is small, portable, designed to be suitable for day to day use and are the next step to PLGS (Jackson and Castle, 2020).

The basic AP system is composed of a control algorithm, a CGM device and an insulin pump. The first commercially available AP system was the Medtronic Minimed 670G, which included the basic three elements of any AP (Saunders et al., 2019). However, AP systems are not limited to basic configurations and much more complex systems are under development (Bertachi, Ramkissoon, Bondia and Vehí, 2018; Ramli et al., 2019). Figure 1.3 shows an updated taxonomy of current AP configurations (Doyle et al., 2014). An AP configuration is obtained by selecting options from each of the elements shown in the figure. Solid lines are connections that exists in any AP configuration and snaked lines represent connections that may partly be present in some configurations. Grey color distinguishes specific features of a block, teal lines are information/action flows conducted during operation, and yellow color show physiological states of the system. AP systems must be first and foremost safe, for that reason not only control algorithms have to be developed, but also appropriate fault diagnosis

mechanisms to ensure a safe operation (Bequette, 2014; Ramkissoon et al., 2017).

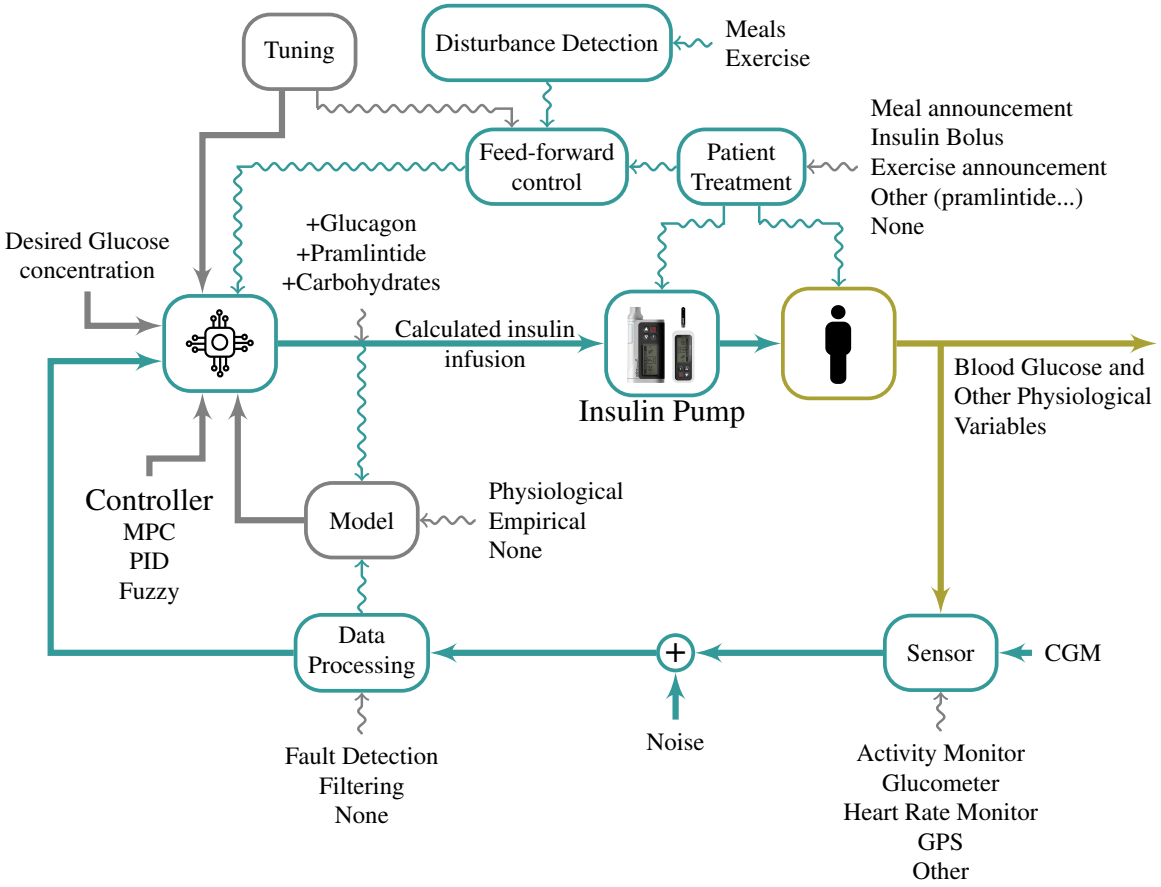

Figure 1.3: Updated taxonomy of the AP, adapted from (Doyle et al., 2014).

The disruptive element firstly introduced by AP technology was the embedded control algorithm within the strategy. AP systems are various and can be mainly classified into hybrid or fully CL systems depending on their level of automation. Hybrid AP systems rely on user input to counteract external disturbances, such as meals or exercise. Contrarily, fully CL systems can operate with minimal user interaction and do not require meal information. Hybrid systems are still very popular due to the existing limitations of AP systems, specially on postprandial periods. A primary challenge of BG control is related to the delays caused by the pharmacokinetic and pharmacodynamic behavior of current insulin analogues. The use of insulin infusion to counteract meals can lead to late posptrandial hypoglycemia as AP systems may overactuate as

a measure to mitigate high postprandial BG. This is caused by the implicit delays in the insulin action and in the subcutaneous route, where insulin is infused. Current fast acting insulin is not rapid enough to achieve optimal postprandial control (Gingras et al., 2018). The use of meal announcement as a feed-forward control approach in hybrid AP systems is intended to enhance the performance while mitigating the risk of late postprandial hypoglycemia. The use of a fully CL AP is aimed to reduce the patient burden of T1D managment at the cost of sacrificing performance when compared to hybrid solutions. Additionally, AP systems are usually categorized into uni-hormonal or bi-hormonal systems. Uni-hormonal systems are AP that only use insulin as a control action, whereas bi-hormonal systems use both insulin and glucagon as control actions (Ward et al., 2008; Van Bon et al., 2012; Taleb et al., 2017).

The feasibility and performance of several control algorithms for AP have been investigated extensively during the last decade. Specifically, most AP use either model predictive control (MPC) (Incremona et al., 2018; Boiroux et al., 2018; Gondhalekar et al., 2018; Abuin et al., 2020), proportional-integral-derivative (PID) (Steil et al., 2003; Marchetti et al., 2008; León-Vargas et al., 2013; Huyett et al., 2015; Beneyto et al., 2018) or fuzzy algorithms (Mauseth et al., 2013; Nimri and Phillip, 2014). There has been a lot of discussion comparing MPC and PID performance for BG regulation supporting the use of either algorithms (Bequette, 2013; Steil, 2013; Pinsker et al., 2016). Updated review on existing control algorithms for AP systems under development can be found elsewhere (Lunze et al., 2013; Tagougui et al., 2019).

Recently, additional modules have been incorporated into AP systems. This was motivated by the highly varying scenarios where AP have to work. Additionally, these systems are being managed by people, which are not experts on the system and may not behave as expected. Therefore, mechanisms to detect disturbances such as meals (Turksoy et al., 2015; Ramkissoon et al., 2018; Samadi et al., 2018; Sala-Mira et al., 2019) or exercise (Jacobs et al., 2015; DeBoer et al., 2017; Ramkissoon et al., 2019), insulin limiting techniques (Revert et al., 2013), fault detection mechanisms (Baysal et al., 2013; Del Favero et al., 2014; Meneghetti et al., 2018),

multivariable and adaptive systems (Cinar, 2017; Beneyto et al., 2018; Hajizadeh et al., 2018; Moscardó et al., 2019) and optimization strategies for the tunning of controllers (Toffanin et al., 2017; Shi et al., 2018; Beneyto and Vehi, 2018; Resalat et al., 2019; Bertachi et al., 2020) have been proposed.

AP systems have to undergo extensive testing before reaching the market. In silico simulations use a mathematical model of the glucose insulin system for testing control algorithms (Kovatchev et al., 2009). The use of in silico simulations rapidly increased after the FDA accepted a meal simulation model as a substitute to animal trials in the preclinical testing of CL strategies in 2013 (Dalla Man et al., 2007; Man et al., 2014; Visentin et al., 2018). Thus, most AP development included intensive in silico simulation of control strategies prior to clinical trials in humans. This was shortly followed by inpatient clinical trials, generally with a reduced number of subjects, to test the viability of the systems. Currently, the leading companies and research groups in the AP field have already gone beyond this point and are rapidly performing clinical outpatient trials to assess AP performance in free living conditions (Bekiari et al., 2018).

1.3 Research Context

The work presented in this thesis has been supported by the FPU15/00244 grant from the Spanish Government and has been developed in the Modeling, Identification & Control Engineering Laboratory (MICELAB) from the Universitat de Girona (UdG). The group is researching technologies for diabetes since 2004. It is a leading research group in technologies for diabetes and member of the Spanish Consortium on Artificial Pancreas and Diabetes Technology (eSCAPE). Since 2018 the consortium belongs to the prestigious center of excellence in diabetes *Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas* (CIBERDEM). The consortium integrates several multidisciplinary teams of engineers and physicians from the following institutions:

- MICELAB. This research group, led by professor Josep Vehí, was founded in 2000. Since 2005 the group is recognized and funded by the Government of Catalonia as "quality research group" (2017SGR1551). The group is characterized by having a solid theoretical basis in control engineering, artificial intelligence, machine learning, biomedical engineering, computer engineering and applied mathematics, with expertise in systems and control theory, modeling and control of biomedical systems, uncertain dynamical systems, robust and predictive control and decision support systems. Main research contributions to technologies for diabetes include the development of the AP, modeling and control in diabetes, including glucose prediction, uncertainty and intra-patient variability, optimization of insulin therapy, identifying patterns of CHO absorption and gastric emptying, calibration algorithms for CGM, fault detection (FD) in continuous monitors and insulin pumps and machine learning methods and its applications to diabetes.

- MEDERI Living Lab. The MEDERI Living Lab (Medical Devices Research & Innovation Living Lab) is a multidisciplinary research group aimed to create an innovative environment in the health technology sector. It was created in 2014 within the *Instituto Universitario de Automática e Informática Industrial* (Institute ai2) of the *Universitat Politècnica de València* (UPV).

- IDIBAPS. The IDIBAPS (*Institut d'Investigacions Biomèdiques August Pi i Sunyer*) is a biomedical research centre of excellence founded in 1996. It is a public consortium whose members are the Catalan Government, the *Hospital Clínic de Barcelona*, the Faculty of Medicine and Health Sciences at the University of Barcelona and the CSIC Institute of Biomedical Research of Barcelona.

The experiments, equipment and infrastructure resources used in this thesis have been partially funded by the following projects

- New strategies for postprandial glycemic control using insulin pump therapy in type 1

diabetes (ClosedLoop4Meals). Project funded by the *Ministerio de Ciencia e Innovación* (MICINN) (ref. DPI2010-20764-C02-02). The general objective of this project was the development of new efficient and safe strategies for postprandial glucose control in people with T1D, aiming at the relieve of the burden of hypoglycemia.

- New methods for an efficient and safe domiciliary artificial pancreas in type 1 diabetes (SAFE-AP). Project funded by the Ministerio de Economía y Competitividad (MINECO) (ref. DPI2013-46982-C2-2-R). The main objective of this project was the development of new methods and tools for efficiency and long-term safety of the AP at home.

- Solutions for the improvement of efficiency and safety of the artificial pancreas by fault tolerant multivariable control architectures (mSAFE-AP). Project funded by the Ministerio de Economía, Industria y Competitividad (MINECO) (ref. DPI2016-78831-C2-2-R). The overall objective of this project was the design of an efficient and safe artificial pancreas in normal free-living use, by means of new multivariable reconfigurable fault tolerant control architectures.

1.4 Thesis Objectives

With the background on AP technology and its current associated challenges alongside with the previous clinical trials conducted at eSCAPE, we can set the main goal of the thesis.

The goal of this thesis is to investigate and develop new robust strategies for AP systems to reject big and external disturbances. Additionally, the system must have fault tolerant tools to detect patient-in-the-loop behaviors.

The research objectives in this thesis can be further split into the following specific goals

- To assess current state of the art of multivariable control and fault-tolerant technologies for AP systems.

- Design a specific multivariable control system for AP, robust against patient variability, meals and exercise. To accomplish this objective, a control system that combines insulin infusion and CHO suggestions is presented. The robustness of this strategy against meals and heavy exercise is tested.

- To clinically test and validate the performance of the proposed AP against current open-loop (OL) therapies. To that aim an inpatient clinical trial was done at the Hospital Clínic de Barcelona in collaboration with the Universitat Politècnica de València.

- Design adaptive support systems for the tuning of the controller. Any AP system have tuning parameters that may negatively impact the system's performance if they are not correctly set. Most AP will be adjusted by physicians, with little to none engineering background. A fuzzy system is designed to help maintain proper tunings for few key parameters of the proposed AP system to alleviate tuning issues in real life.

- Design a FD algorithm to assess patient-in-the-loop behaviors. AP systems have the particularity that the patient is an active part of the control loop. With the developed system, the patient is responsible to follow the CHO recommendations made by the system. If the patient does not follow those recommendations, the system is under an actuator fault.

1.5 Thesis Structure

This document is organized as follows: Chapter 2 is constituted by a copy of the articles that allowed the presentation of this thesis as a compendium of publications. Chapter 3 presents a brief discussion on the main contributions of the articles that are part of this thesis. Finally, Chapter 4 presents the conclusions and future works. Two appendixes are included that include the article with clinical results and extended modules to the controller.

CHAPTER 2

ROBUST AND FAULT-TOLERANT STRATEGIES FOR CONTROLLING BLOOD GLUCOSE IN PATIENTS WITH TYPE 1 DIABETES

This chapter consists of four sections. Section 2.1 presents a paper which develops a methodology to adapt on real time the tuning of an AP to enhance safety and performance during postprandial periods. Section 2.2 consists of a paper in which a multivariable controller that uses insulin and CHO is designed. Section 2.3 presents a paper that introduces a FD methodology that considers the patient-in-the-loop modes and faults. Additional key results derived from this thesis are included in appendix A, which includes a clinical paper where the multivariable controller is tested against exercise.

- **2.1 Postprandial fuzzy adaptive strategy for a hybrid proportional derivative controller for the artificial pancreas**

- **2.2 A new blood glucose control scheme for unannounced exercise in type 1 diabetic subjects**

- **2.3 A hybrid automata approach for monitoring the patient in the loop in artificial pancreas systems**

2.1 Postprandial fuzzy adaptive strategy for a hybrid proportional derivative controller for the artificial pancreas

In this publication, we propose a novel adaptive strategy to automatically tune and keep tuned parameters of the Proportional-Derivative (PD) + Safety Auxiliary Feedback Element (SAFE) controller. The PD + SAFE algorithm was used in prior clinical trials during the ClosedLoop4Meals project (Rossetti et al., 2017). The goal is to optimize the performance of the control strategy during PP. The candidate's contribution for this publication consisted in the development, design and implementation of the fuzzy adaptive strategy, writing the manuscript, contributing to discussion, writing and editing the manuscript throughout the review rounds. During the development of the work, the candidate was assisted by Dr. Josep Vehí.

Title: Postprandial fuzzy adaptive strategy for a hybrid proportional derivative controller for the artificial pancreas

Authors: **Aleix Beneyto** and Josep Vehí

Journal: Medical & Biological Engineering & Computing

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DOI: https://doi.org/10.1007/s11517-018-1832-1

Quality index: JCR 2019 Computer Science, Interdisciplinary Applications, Impact factor: 2.022, Q3 (61/109)

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https://doi.org/10.1007/s11517-018-1832-1

ORIGINAL ARTICLE

Postprandial fuzzy adaptive strategy for a hybrid proportional derivative controller for the artificial pancreas

Aleix Beneyto [1] · Josep Vehi [1,2]

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Abstract
This paper presents a support fuzzy adaptive system for a hybrid proportional derivative controller that will refine its parameters during postprandial periods to enhance performance. Even though glucose controllers have improved over the last decade, tuning them and keeping them tuned are still major challenges. Changes in a patient's lifestyle, stress, exercise, or other activities may modify their blood glucose system, making it necessary to retune or change the insulin dosing algorithm. This paper presents a strategy to adjust the parameters of a proportional derivative controller using the so-called safety auxiliary feedback element loop for type 1 diabetic patients. The main parameters, such as the insulin on board limit and proportional gain are tuned using postprandial performance indexes and the information given by the controller itself. The adaptive and robust performance of the control algorithm was assessed "in silico" on a cohort of virtual patients under challenging realistic scenarios considering mixed meals, circadian variations, time-varying uncertainties, sensor errors, and other disturbances. The results showed that an adaptive strategy can significantly improve the performance of postprandial glucose control, individualizing the tuning by directly taking into account the intra-patient variability of type 1 patients.

Keywords Adaptive glucose control · Artificial pancreas · Fuzzy system · Sliding mode control

1 Introduction

Type 1 diabetes mellitus (T1DM) results from an autoimmune reaction that leads to the destruction of the pancreatic β cells in the islets of Langerhans, the place where insulin is produced. Thus, T1DM patients lose the capacity to produce insulin, leaving them in a chronic condition of concurrent hyperglycemia levels. The resulting excessive plasma glucose leads to long-term diseases, including microvascular and neurologic diseases [1]. The appropriate regulation of blood glucose concentration must be performed by infusing external insulin to maintain the glucose level within the euglycemic range (70–120 mg/dl). It has been proven that intensive insulin treatment that maintains the blood glucose level near normoglycemia significantly reduces diabetes complications [1].

Traditional treatments, such as multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) are currently used by T1DM patients to control their blood glucose. New hardware allows a patient to take more actions to maintain their glucose near normoglycemia. Insulin pumps can be programmed with different basal rates throughout the day. In addition, they can send alarms to the patient in the case of abnormal or dangerous glucose trends and can help the patient calculate the correct amount of bolus to administer [2, 3]. Likewise, the accuracy and reliability of continuous glucose monitoring (CGM) devices have increased since their first appearance. Thus, CGM devices can assist patients to take further corrective actions. However, incorrect ingested carbohydrate estimations, lifestyle changes, exercise, alcohol, stress, etc. can easily affect the patient treatment and lead to undesirable hypoglycemic events [1].

The artificial pancreas (AP) terminology encompasses a set of technological solutions that aim to overcome the drawbacks of conventional insulin therapies. The common AP includes a CGM sensor that reads the interstitial glucose and is connected to a closed-loop controller that computes the necessary

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insulin to administer through an insulin pump (actuator). Although these systems have shown promising results and easily have the capacity to surpass traditional therapies, the current CGM systems are not reliable enough, e.g., the rapid glucose drops caused by exercising usually remain undetected by CGM systems. This leads to decreased system performance. In addition, the subcutaneous route used by the majority of APs to administer insulin is affected by large and variable delays.

Regarding the closed-loop glucose control, the main research concern has been centered on developing reliable and robust controllers and ensuring safety under the current hardware limitations. Thus, a great variety of glucose control algorithms have appeared, from model predictive control (MPC) [4–10] and H_∞ [11, 12] to sliding mode control [13–16]. Simple linear control algorithms, such as proportional-integral-derivative (PID) techniques have also been proposed. The attractiveness of these approaches lies in the fact that PID techniques mimic the β cell response. Moreover, they represent a variety of control methods that are widely used in industry because they are reliable, with few parameters and easy tuning [2, 7, 15, 17–20]. Controllers based on fuzzy inference engines are also found in the literature [21–23]. Readers are referred to [24, 25] for the complete state of the art of AP control algorithms.

However, only a few of these approaches have been tested in clinical trials, mainly MPC and PID controllers. Furthermore, the majority of the reported clinical trials have focused on specific situations, such as postprandial control, exercise, alcohol consumption, or fasting conditions among others [26–28]. On top of this, the inter- and intra-patient variability also compromises the AP systems for real daily life. Recent AP research is moving to more adaptive strategies to deal with the time-varying changes of T1DM patients [29].

Concerning the postprandial response, the closed-loop controller of an AP has to be able to minimize the postprandial excursion and avoid late hypoglycemia due to excessive insulin infusion. Along this line, the implicit restrictions of the subcutaneous route impose the use of feedforward actions [19, 20, 30]. Semi-closed-loop control schemes with meal suggestions have shown superior performance and safety compared to fully closed-loop systems [20].

Independently of the used control algorithm, a trade-off between postprandial peak and late hypoglycemia risk is unavoidable. This is the point where the tuning of the controller should be taken into account. A more aggressive tuning will usually lower the postprandial peak but increase the hypoglycemia risk.

Mainly PID and MPC techniques have been used to deal with the postprandial period. For instance, the ePID-IFB algorithm uses plasma insulin feedback and pole placement to deal with delays in the subcutaneous route [18]. Regarding MPC algorithms, meal compensation, additional constraints, or model individualization have been used [27, 28]. In addition, insulin on board (IOB) constraints to overcome insulin stacking have been proposed in MPC strategies [4, 10]. Recently, a new safety scheme based on sliding mode reference conditioning (SMRC) has been designed to prevent hypoglycemia events and has shown promising performance during postprandial periods. This approach incorporates a new control layer that monitors the IOB and is called the safety auxiliary feedback element (SAFE) [14–16, 31].

Numerous AP control algorithms from the literature use static control parameters that cannot guarantee acceptable performances for all the situations that an AP is prone to face. Adaptive control can assist in tuning the parameters of the controller to maintain a tolerable performance level.

In this work, a fuzzy inference system was implemented, along with the hybrid proportional derivative (PD) control scheme developed at our research team [31]. This system will automatically update some parameters of the controller to safer values prior to meal disturbances. The results showed that providing the controller with adaptive parameter tuning could increase its performance.

2 Methods

2.1 Control algorithm: PD + SAFE loop

In this section, we briefly review the hybrid PD scheme with the SAFE layer shown in Fig. 1; the reader is referred to [14–16, 31] for further details. This control strategy is composed of two loops: an inner loop with the PD controller and outer loop with the SAFE layer. The inner PD control loop is composed of three insulin actions: (1) u_b represents the feedforward pre-meal bolus, (2) u_{basal} represents the constant insulin infusion due to the patient's daily basal profile, and 3) u_{PD} represents the PD control action. Then, the total insulin control action is as follows:

$$u_d(t) = k_p\left[e(t) + \tau_d \frac{dCGM(t)}{dt}\right] + u_{basal}(t) + u_b \tag{1}$$

with

$$u_b = \frac{\text{grams of CHO}}{I:CHO} + \int_{t}^{t+60\ min} u_{basal}\, dt + \frac{CGM(t) - G_d}{CF} \tag{2}$$

where k_p is the proportional gain, τ_d is the derivative time, I:CHO is the insulin to carbohydrates rate, CF is the correction factor, and G_d is the glucose target. Specifically, the proportional gain is tuned according to [18]:

$$k_p = \frac{60}{\tau_d}\frac{I_{TDD}}{1500} \tag{3}$$

where $I_{\text{TDD}}$is the total daily insulin dose.

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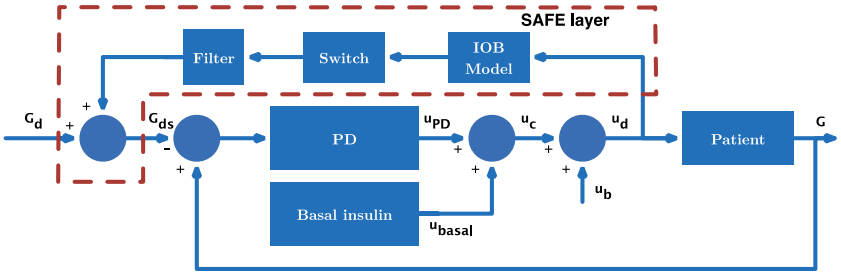


Fig. 1 Hybrid PD + SAFE algorithm

The control action is then computed as follows:

$$u_d = u_c + u_b = u_{\mathrm{PD}} + u_{basal} + u_b \tag{4}$$

where u_d is the total delivered insulin, u_c is the controller computed insulin, and G_{ds} is the filtered reference.

The main action of the outer SAFE loop, depicted in Fig. 2, is to guarantee that the IOB is bounded, i.e., $\mathrm{IOB} \in [0, \widehat{\mathrm{IOB}}]$. The SAFE layer will modify the predefined glucose reference G_d to a safety reference G_{ds} if the estimated IOB, i.e., $\widehat{\mathrm{IOB}}$, is about to violate the imposed constraint. This makes the controller robust prior to delays in the subcutaneous route. The idea is to stop the insulin infusion if $\widehat{\mathrm{IOB}}$ is close to $\overline{\mathrm{IOB}}$ and prevent stacking.

The IOB estimation can be computed using any available model from the literature [32]. The main SMRC technique is implemented within the switching action block from Fig. 2. The sliding surface [31] is defined as follows:

$$\sigma(t) = \widehat{\mathrm{IOB}} - \overline{\mathrm{IOB}} + \tau\left(\dot{\widehat{\mathrm{IOB}}} - \dot{\overline{\mathrm{IOB}}}\right) \tag{5}$$

where τ is a constant gain that regulates the sensibility of the reference conditioning prior to IOB changes. Then, the switching law follows:

$$\omega(t) = \begin{cases} \omega^{+} & if\ \sigma(t) > 0 \\ 0 & otherwise \end{cases} \tag{6}$$

Finally, the filter is defined as a low-pass first-order filter by the following:

$$\frac{d\omega_f(t)}{dt} = -\lambda\left(\omega_f(t) - \omega(t)\right) \tag{7}$$

where λ is the cutoff frequency and ω_f is the filtered switching signal. The background theory of the switching action and development of the sliding surfaces are based on invariance control. The full development can be found in [16].

2.2 Fuzzy adaptive strategy

In this section, we introduce a support strategy, which provides continuous adaptive tuning for the parameters of the control algorithm presented in Section 2. The dynamics of a T1DM patient are time-varying and thus require (1) robust controllers or (2) controllers that can be modified according to some performance index or heuristic to adapt to new situations in order to maintain acceptable performance. In this paper, we describe a fuzzy adaptive system that will automatically tune the PD + SAFE controller based on the expertise of engineers and physicians.

The attractiveness of fuzzy systems lies in the fact that they can seamlessly incorporate knowledge from physicians into the control algorithm, e.g., by setting rules or membership functions. Therefore, physicians can incorporate corrective actions into the controller when the patient's circumstances change, e.g., when the patient is ill or behaving abnormally.

The rest of this section introduces (A) the chosen adaptive parameters and (B) the characteristics of the fuzzy adaptation algorithm and how it works.

A. Selecting parameters to adapt

The first thing to decide is which parameters of the control algorithm are going to be adapted. In this sense, we differentiate the candidate parameters of the inner and outer loops in Tables 1 and 2.

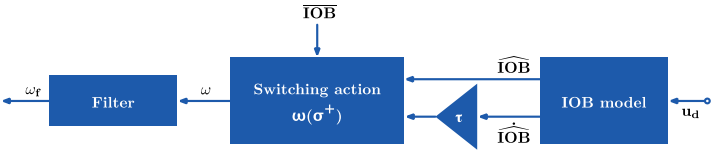
An optimal tuning of these parameters for a virtual cohort can be found in [14]. The main parameters of this optimal tuning are listed in Table 3.

Table 3 shows that only two out of the seven parameters are individualized, whereas the rest of the parameters have been adjusted based on a population analysis in [14].

We selected the proportional gain from the inner loop and the limit of the IOB from the outer loop as the parameters to adapt. The following are the underlying reasons for these choices.

1. The proportional gain is the main element that regulates the basal profile dosing from the inner PD algorithm.

Fig. 2 SAFE layer elements



2. The robustness of the SAFE layer is mainly guaranteed by the fact that once the sliding mode is on the surface $\sigma(t)$; it is insensitive to reference changes, measurement noise, and overestimated boluses [16]. The capacity to reach the sliding surface mainly depends on the choice of $\overline{IOB}$. If $\overline{IOB}$ is set too small, the SAFE layer will constantly actuate and suppress insulin, leaving the controller in the open loop. On the other hand, if $\overline{IOB}$ is too high, IÓB will not reach this limit, and the SAFE layer will not prevent hypoglycemia, leaving the closed-loop controller as a simple PD method.

Finally, the control algorithm will end up in a device operated by physicians and patients. Among the parameters of the controller, k_p and $\overline{IOB}$ are the most clinically relevant and easiest for physicians to understand.

B. Adaptation strategy

The adaptation strategy utilizes a fuzzy system, which includes a database of rules. This fuzzy system is used to improve and maintain the performance of the postprandial control. The adaptation algorithm will allow the controller to adapt and maintain acceptable performance despite changes in the behaviors of the patient.

Particularly, the algorithm monitors postprandial period data up to 480 min after a meal and stores it in a database. After four complete postprandial periods are recorded, the algorithm computes the input linguistic variables used to adapt the parameters. Then, the process is repeated when the next four postprandial periods are available. The fuzzy system only acts once every four postprandial periods, ensuring a gradual adaptation.

Figure 3 shows the implementation of the fuzzy inference engine with the PD + SAFE control strategy. It configures a new layer that takes real time information from the CGM and from the output of the switching law. Afterward, the system modifies two main blocks of the control scheme (the PD and switch). Thus, the presented system can adjust the controller based on patient needs, individualizing the tuning. Notice that this approach is applicable to any closed-loop controller that uses the SAFE law and a CGM. The only element to modify would be the database of rules according to the specific controller.

For this application, we use a Mamdani-style inference method. The fuzzy inference system is composed of three main parts: the linguistic variables, membership functions, and rules stored in a database. This section discusses the implementation of a new fuzzy inference engine for the hybrid PD strategy developed at MICElab. Appendix includes the complete description of the fuzzy system.

1) Monitoring input data

To correctly adapt k_p and $\overline{IOB}$, it is necessary to work with real time data. Thus, the system has to obtain data from two different locations of the scheme. The system only obtains data during postprandial periods, i.e., up to 480 min after a meal, because the aim of this approach is to correctly control them. Outside those time periods the system stops the acquisition and rests in standby.

Figure 3 shows that the fuzzy inference engine uses data from the CGM and the output of the switching law of the SAFE loop. These inputs were selected because (1) the CGM readings can be used as indicators of the overall performance of the controller and (2) the switch block provides information about how long the SAFE layer has been actuating.

Then, the data obtained during the four postprandial periods are stored and used to create a sliding window. The sliding window will be constantly updated online and reinitialized every four postprandial periods. In this work, four

Table 1 Eligible parameters of inner loop

Parameter	Specifications
k_p	Proportional gain [IU h^{-1} mg^{-1} dl^{-1}]
τ_d	Derivative weight [min]
G_d	Glucose reference [mg/dl]

Table 2 Eligible parameters of SAFE loop

Parameter	Specifications
ω^+	Upper bound of signal $\omega(t)$ [mg/dl]
τ	Controller gain [min]
$\overline{IOB}$	Limit of the IOB [IU]
λ	Cutoff frequency of the filter

Table 3 Optimal parameter values of hybrid PD strategy

Patient	G_d	k_p	τ_d	$\overline{\text{IOB}}$	ω^+	τ	λ
1	110	0.0122	60	6.1	350	10	0.1
2	110	0.0315	60	1.9	350	10	0.1
3	110	0.0147	60	5.7	350	10	0.1
4	110	0.0113	60	3.9	350	10	0.1
5	110	0.0122	60	7.8	350	10	0.1
6	110	0.0122	60	6.1	350	10	0.1
7	110	0.0147	60	3.8	350	10	0.1
8	110	0.0122	60	5.3	350	10	0.1
9	110	0.0099	60	8.9	350	10	0.1
10	110	0.0113	60	8.1	350	10	0.1

Values of optimal parameters for virtual patient cohort from [14]

postprandial periods are used based on the assumption that the adaptation must be smooth. It is not desirable that the adaptive strategy individually corrects each postprandial period because it could increase the probability of overfitting and instability. Furthermore, using these four postprandial periods the system is more robust against uncommon patient behavior.

Table 4 lists the monitored variables, and Figs. 4 and 5 graphically show a typical postprandial period with the monitored variables.

2) Linguistic variables

The input linguistic variables correspond to the means of the four postprandial periods from the variables of Table 3, e.g., the input linguistic variable for $G_{\min}$ is "meanGmean"

$$\text{mean\_Gmean} = \frac{\sum_{k-3}^{k} G_{min}}{4}, \quad if\ k = 4n \tag{8}$$

where k represents the current postprandial period, and n corresponds to the grouping of four postprandial periods and is initialized at one. Hence, the system obtains indicators of the postprandial performance of the last four meals. For example, if we are at the eighth postprandial period $n = 2$, meaning that we are waiting for the second group of postprandial periods to be completed, and as $k = 4n = 8$, we will compute the input linguistic variables and update $n = n + 1$.

The output linguistic variables are exactly the ones we want to adapt: k_p and $\overline{\text{IOB}}$. The domain of these variables is the allowed adaptation percentage.

3) Membership functions and linguistic terms

The linguistic variables have different membership functions but the same linguistic terms, producing an easy and understandable system. The linguistic terms for the five input linguistic variables are *Small*, *Normal*, and *High*. On the other hand, the linguistic terms for the output variables are *NoChange*, *IncreaseLittle*, *Increase*, *DecreaseLittle*, and *Decrease*. The complete set of membership functions for the input and output linguistic variables is attached in Appendix.

Notice, as previously stated, that the domain for the output variable is a percentage between −15 and 15% of the actual variable value. Hence, the maximum rate of parameter adaptation is limited. This adaptation range worked properly for our control approach and may vary depending on the controller used. With the PD + SAFE controller, higher ranges lead to heavy oscillations in the long run, while smaller ranges lead to poor performance. Here, the sensitivity of the controller should be considered when shaping the output membership functions to ensure that no risk of instability can happen.

The tuning of a fuzzy system mainly corresponds to the design of the fuzzy sets of the input/output linguistic variables. Particularly, for this application the fuzzy sets for the input linguistic variables can be directly defined from the common acceptable understanding of how a postprandial period should be. For example, when looking at the minimum level of glycaemia it is commonly accepted that between 70 and 100 mg/dl correspond to good performance. Hence, the fuzzy

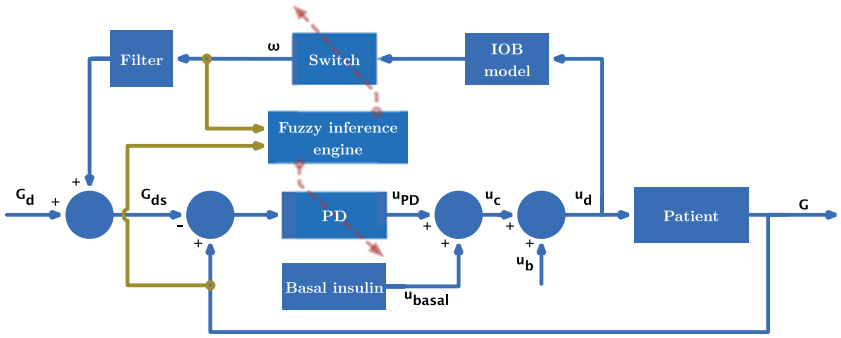


Fig. 3 Hybrid adaptive PD + SMRC and fuzzy inference engine

Table 4 Variables monitored for each postprandial period

Variable	Specifications
G_{min}	Minimum level of postprandial blood glucose (mg/dl)
Excursion	Difference between maximum glucose peak and initial level of glycaemia in the postprandial period (mg/dl)
T_{OFF}	Time of the postprandial period where the control algorithm is turned off due to the meal bolus (min)
#switch 0–4 h	Number of times that SMRC acts in the T_{OFF}–4-h period
#switch 4–8 h	Number of times that SMRC acts in the 4–8-h period.

sets involved with glycaemia were defined according to clinical criteria. The rest of the variables are focused on the actuation of the SAFE layer. For the PD + SAFE controller to work optimally, it must be a ratio between the time when the SAFE layer is actuating and when it is not. This ratio for optimum performance was assessed after analyzing the data obtained from the clinical trial NCT02100488 from clinicaltrials.gov, and used to shape the membership functions for T_{OFF} and #switch variables.

4) Rule database

The fuzzy system was initially created with a total of 15 rules. There are two groups with different rules. The first is used to exclusively improve the postprandial control of the PD + SAFE controller. However, it is necessary to consider safety rules, which are included in the second group. These heuristic auxiliary rules have the purpose of sending notifications to the patient and caregivers in the case of bad adaptation or degraded performance. The idea is that a marketable system must ensure the patient's safety. Thus, we already included a safety layer for a future real life application that could be implemented inside a smartphone with a support decision system. This should provide the patient and caregivers

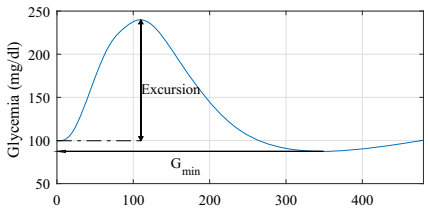


Fig. 4 Glycemic variables monitored by the fuzzy inference engine

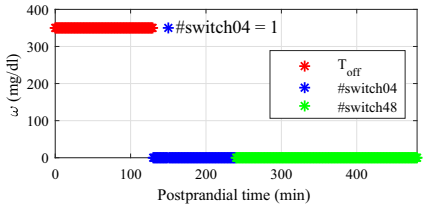


Fig. 5 SAFE related variables monitored by the fuzzy inference engine

with enough time to safely shut down the system or rapidly take corrective actions.

The whole first set of rules from the fuzzy system is described in Appendix A. The auxiliary rules were not included in the fuzzy engine, but were used as supervisory rules for the adaptation process, and hence for the fuzzy system. The implemented rules are as follows:

1. If meanG_{min} is Small for the last five postprandial periods, then shut down the fuzzy engine and notify the patient.
2. If the adjusted k_p is greater or lower than 50% of the initial k_p, then send a warning to the patient.
3. If Excursion is High for the last five postprandial periods, then send a warning to the patient.

5) Defuzzification method

The defuzzification process is used to convert the degrees of membership of the output variables within the possible linguistic terms into numerical outputs in the range of the output domain. Thus, in this particular case, the system gives a number between − 0.15 and 0.15.

Along the same line, the chosen defuzzification method is the modified center of area (mCoA), which is selected because it enables the system to span the full domain of the output linguistic terms. The mCoA is defined as

$$mCoA = \frac{\int f(x)\cdot x\, dx}{\int f(x) dx} \tag{9}$$

where *f(x)* represents the solution fuzzy set for the output variables and *x* the specific degree of membership. Testing scenario.

2.3 Testing scenario

The new adaptive control algorithm has been implemented within the UdG APsim platform for testing glucose controllers [33]. The whole strategy has been programmed with NI LabView® code and the fuzzy inference engine with the PID and fuzzy toolkit from NI LabView®.

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The PD + SAFE controller has already been tested in the clinical trial "Improving postprandial glycaemia by a new developed closed-loop control system (NCT02100488 from clinicaltrials.gov)" as part of the Closedloop4meals project. The objective of this trial was to show that closed-loop systems can have better performances than open-loop systems during the postprandial period. One of the issues that we found during the trial was a hindrance when tuning $\overline{\text{IOB}}$. Therefore, we will use the same "in silico" scenario used to validate the PD + SAFE controller to revalidate this controller using an adaptive strategy.

This scenario includes ten virtual patients from the FDA-approved UVa simulator [34]. Regarding the insulin therapy, each patient has its own basal profile $u_{\text{basal}}(t)$, with an attempt made to reflect a real basal profile for a T1DM patient [15].

The meals used in this trial have been selected from the mixed meal library [35]. Mixed meals are limited to those with close to 60 g of carbohydrates (CHO), and the intake is established at 12:00. This allows the control algorithm to ensure that the glycemic level is as close as possible to 90 mg/dl at 12:00 as a result of nighttime control. The rates of glucose absorption of the selected meals are displayed in Fig. 6.

Thus, the meal absorption model has been replaced by the mixed meals rate of appearance from the mixed-meal library. The scenario also includes subject specific circadian variability in insulin sensitivity depending on the basal requirements [15]. Finally, following [15], we also include sinusoidal variability to the insulin absorption.

3 Results

The original tuning [14] was taken as a starting point for the simulations. The k_p- and $\overline{\text{IOB}}$ -tuned parameters for each patient were randomly modified between − 50 and 50% of their original value. We repeated this procedure three times to obtain three starting misadjusted tunings for each patient. A total of 30 simulations were performed using the UdG APsim simulator and the PD + SAFE method with the fuzzy adaptive strategy.

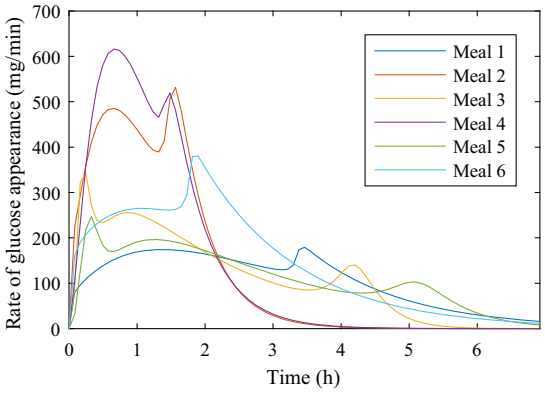

Fig. 6 Rate of glucose absorption of the mixed meals selected from [35]

First, we let the system adapt both parameters for all the cases with the initial misadjusted parameters. These adaptive simulations included a total of 101 meals (one meal per day) with the system adapting both k_p and $\overline{\text{IOB}}$ to safer ones. Notice that because we only consider one meal per day, the fuzzy engine requires a large number of simulation days to correctly adapt the parameters. In contrast, in a real setting where the patient eats many times a day, this would not be an issue. Figures 7 and 8 show example results of the adaptation mechanism.

After obtaining fine-tuned parameters from the fuzzy adaptive algorithm, we performed two more sets of simulations for validation purposes with the fuzzy inference engine deactivated. These simulations used the same scenario as the adaptive ones but restricted the number of meals to 18. This was done to match the validation analysis performed in NCT02100488. The first set used the original misadjusted parameters during the entire time, while the second set used the final tuned parameters.

A. Parameter adaptation

Figures 7 and 8 show how k_p and $\overline{\text{IOB}}$ start from three different misadjusted values. Then, for each group of four postprandial periods, the fuzzy engine adapts each of the parameters. When a sufficient number of postprandial periods have occurred, the parameters are optimized and converge to an optimal value regardless of the original tuning. The $\overline{\text{IOB}}$ presented a better adaptation and less oscillatory behavior than the k_p. Even though the parameters present small oscillations in some cases, the system is able to drive all the parameters to the same final one. This occurs with

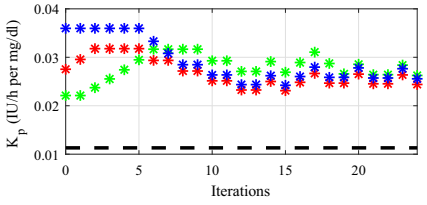

Fig. 7 Adaptation process of k_p for representative patient (patient 10) during adaptive simulations, where each iteration on horizontal axis corresponds to group of 4 postprandial periods. The black dashed line is the original tuning, the red, green and blue asterisk signals correspond to the first, second and third simulation respectively

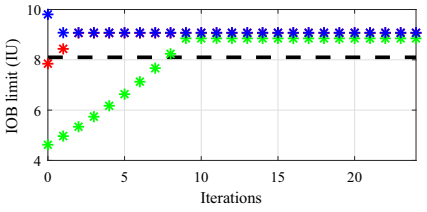

Fig. 8 Adaptation process of $\overline{IOB}$ for representative patient (patient 10) during adaptive simulations, where each iteration on horizontal axis corresponds to group of 4 postprandial periods. The black dashed line is the original tuning, the red, green and blue asterisk signals correspond to the first, second and third simulation respectively

all the simulated patients and suggests that the adaptation fuzzy engine works with the controller.

In this particular patient, it is demonstrated that the fuzzy inference engine adjusts $\overline{IOB}$ with more accuracy than k_p. Although $\overline{IOB}$ tends to achieve a unique value for the three simulations, k_p begins to stabilize at approximately the eleventh iteration. However, there is an obvious and visible variation in the end.

Figure 9 is attached to further analyze the behavior of the adaptive fuzzy system. The figure shows how much the parameters were adapted during the simulation. The convergence to a final parameter value was good for the $\overline{IOB}$, meaning that the system was able to find a stationary parameter value that optimizes the therapy. Contrarily, the k_p was more sensitive due to the variability of insulin sensitivity and carbohydrates absorption.

B. Tuned simulation versus original misadjusted simulation

To compare the adjusted and misadjusted simulations, we performed control variability grid analysis (CVGA) and

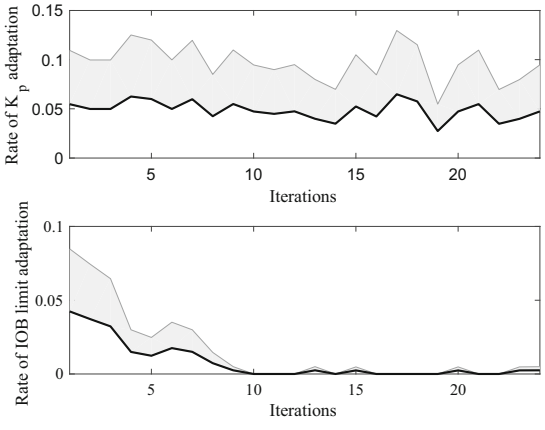

Fig. 9 Absolute value of parameter adaptation during the adaptive simulations. The black line is the MEAN and the gray line is the STD.

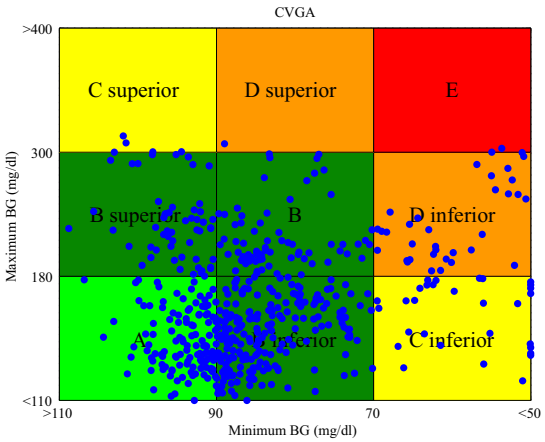

Fig. 10 CVGA results for misadjusted simulations

calculated some statistics. Figures 10 and 11 show the CVGA results for these simulations.

There is an obvious improvement in the postprandial control after the adaptive process. Moreover, an important reduction in hypoglycemic episodes has occurred, from 65 to 27, and most of the points of the CVGA have moved to the A and B zones.

The time with a value greater than 180 mg/dl has been reduced from 9.19 to 5.62%. Not only has the adaptive strategy been able to minimize the number of hypoglycemic events, but also a significant reduction in hyperglycemia exposure has occurred. This translates into lower excursions during postprandial periods, as listed in Table 5.

Please note that Fig. 10 shows what would have happened with the original controller. On the other hand, Fig. 11 shows what would have happened if we kept the fuzzy inference

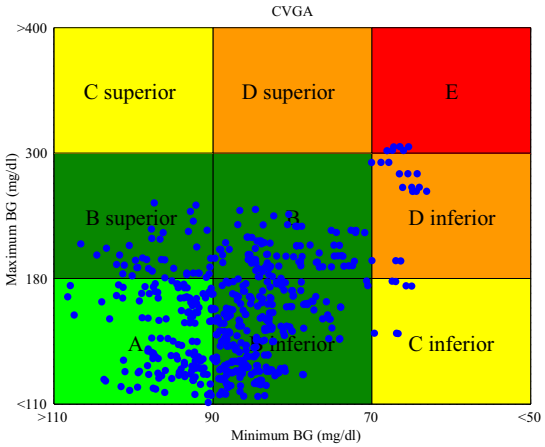

Fig. 11 CVGA results for adjusted simulations

Table 5 Results of "in silico" simulations

Parameters	Adjusted simulation	Misadjusted simulation
Time in range [70–180] mg/dl	93.75%	88.18%
Time above 180 mg/dl	5.62%	9.19%
Time below 70 mg/dl	0.63%	2.63%
N° hypoglycemia episodes	27	65
Mean duration of hypoglycemia episode (min)	60.6	105.3
Postprandial excursion (mg/dl)	37.4 ± 35.2	75.8 ± 43.3
Mean glycaemia (mg/dl)	120.6 ± 14.6	124.1 ± 22.1
Percentage of zones A and B	95%	87.03%
Percentage of zone C	1.3%	6.3%
Percentage of zone D	2.59%	6.3%
Percentage of zone E	1.11%	0.37%

engine activated for a prolonged period of time, i.e., after a month of normal life. Most of the points in the E and inferior D zones correspond to one particular patient from the cohort. This suggests that more parameters of the controller should be adapted to further improve the performance.

C. Qualitative analysis of the adaptive strategy improvements

In this section, qualitative measures will provide insights into the performance improvement. Firstly, recall that the system is designed to adapt postprandial periods. Figure 12 shows the aggregated postprandial blood glucose profiles of the whole cohort. It clearly outlines how the adaptation allowed for better control in the late postprandial period: the mean blood glucose and the variability were reduced without increasing the risk of hyperglycemia. Moreover, the risk of hypoglycemia is also reduced.

If we compare the mean curves from Fig. 12 and the membership functions of the glycemic input variables, we can verify that both the excursion and minimum glucose are within the normal case. That is the reason behind getting almost the same postprandial peak for both cases but not getting the same glycaemia level in the late period.

We can also analyze the adaptation of the SAFE layer inspecting the amount of time that it has been active during postprandial periods. The adapted system keeps the SAFE layer activated between 15 and 25% of the postprandial time. These values belong to the normal membership functions for the #switch04 and T_{OFF} input variables. For the misadjust system the SAFE layer was actuating mostly in these ranges too. However, notice that the fuzzy system has been able to drive all the points to a desired narrower range. Figure 13 shows the active time variation of the SAFE layer.

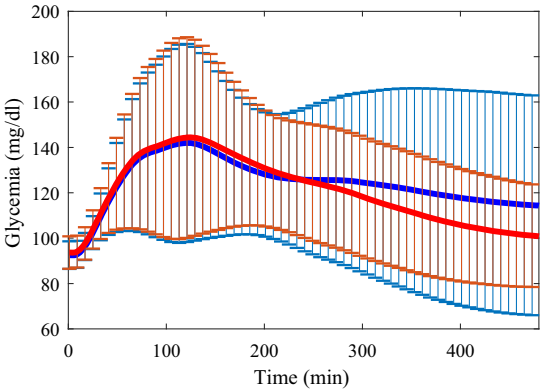

Fig. 12 Aggregated postprandial blood glucose profiles of the cohort as mean ± STD. The blue curve corresponds to the misadjusted case and the red curve to the adjusted case

4 Discussion

Recently, AP systems under research have started to include adaptive strategies to tune or optimize their controllers. It is not surprising that automatic systems aimed to control highly varying patients include adaptation mechanisms to improve

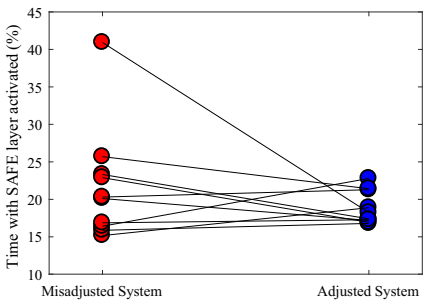

Fig. 13 Time percentage during postprandial periods that the SAFE layer is activated. Each point represents the mean value for each patient

performance. However, adaptive systems usually come at the price of a higher risk of instability. In most cases, stability cannot be analytically checked for highly complex systems under adaptive strategies. Therefore, one way to minimize the risks of instability is to develop a conservative adaptive system. This is the philosophy followed by our work. We used small adaptation gains, and we only allowed the system to adapt itself after a sufficient enough number of data was recorded. Although conservative, the adaptive system is capable to adapt enough the parameters and optimize the controller in a safe way. The resulting adaptive system keeps the controller well-tuned while ensuring safety.

We acknowledge that the design and validation procedures of this new fuzzy system have limitations. The scenario only included one meal per day, making the simulations not as realistic as they could have been if more meals were considered. Also, other type of disturbances, such as exercise or illness were not considered. The system has been tested with 10 "in silico" adult patients limiting the validity of the approach for a bigger cohort. To minimize this issue, we included high variability in the insulin sensitivity and absorption as done in [31]. This high variability makes our scenarios a very good test bench since they reproduce most of the expected situations in a real environment.

AP systems will inevitably have to deal with inter- and intra-patient variability. Therefore, they will also have to deal with day-to-day and patient-to-patient variability. In such a case, we can forecast that adapted parameters will show an oscillatory behavior. The results showed that even after a long simulation time k_p still had small variations. Then, adaptive systems should allow these kind of parameter variations even if the subject lifestyle has not changed. However, as a safety measure they should include an acceptable variation range.

Finally, we believe that adaptive systems should only be used by patients who are fit to use them. So, adaptive systems should undergo extensive "in silico" and clinical studies to prove stability and to define what subject profile is fit to use them.

5 Conclusions

A fuzzy inference engine for hybrid PD control with the SAFE algorithm was developed in NI LabView® code within the UdG APsim software. The implementation allows the control algorithm to gradually adapt its parameters to safer ones.

The system was tested based on the validation scenarios and procedures from a previous clinical trial (NCT02100488). The system was primarily designed to finely adapt two control parameters, i.e., k_p and $\bar{IOB}$, during the postprandial period in a meal announced scheme, with the objective of enhancing the glycemic control.

The results showed that the fuzzy inference engine contributes to a better postprandial glycemic control and improves the safety of the previously developed hybrid PD controller when using the SAFE layer with initially poor tunings.

The findings suggest that more complex adaptive systems based on some performance index rather than heuristic rules could be applied to refine the tunings of a given controller. Thus, individualizing the controller based on the patient's needs or lifestyle changes is a feasible and attractive approach for a commercial AP.

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Appendix

Overview of the fuzzy system

The presented fuzzy system is a multiple-input multiple-output (MIMO) system. Particularly, the system considers five input and two output variables as shown in Fig. 14.

The fuzzy inference engine is based on the Mamdani method. When using the Mamdani method the inference is performed in four stages: (1) fuzzification of the crisp inputs, (2) rule evaluation, (3) aggregation of the outputs, and (4) defuzzification of the output fuzzy set.

Prior to the description of the fuzzy system engine, let us make some definitions that will be used throughout the text.

Definition 1 The universe of discourse X is a collection of objects $\{x\}$ that can be discrete or continuous.

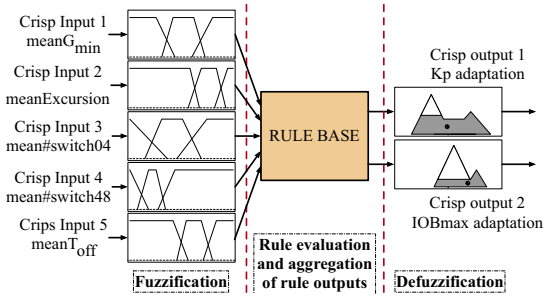

Fig. 14 Overview of the fuzzy system

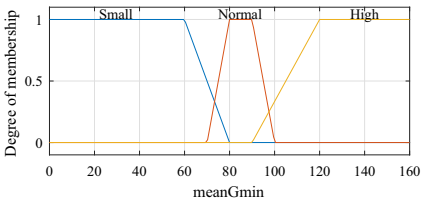

Fig. 15 Fuzzy sets for input linguistic variable meanG$_{min}$

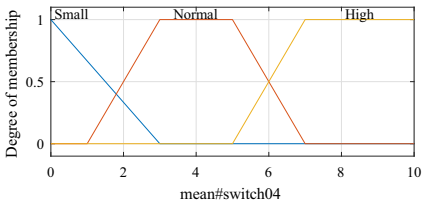

Fig. 17 Fuzzy sets for input linguistic variable mean_#switch04

Definition 2 Let X be the universe of discourse with elements $\{x\}$. Then, a fuzzy membership function is defined as

$$\mu_A(x) : X \rightarrow [0, 1] \tag{10}$$

where A is a fuzzy set, and if $\mu_A(x) = 1$ means that x is in A, $\mu_A(x) = 0$ means x is not in A and $0 < \mu_A(x) < 1$ means that x belongs to A up to a certain degree.

Definition 3 The degree of membership is the value that takes $\mu_A(x) \in [0, 1]$ given an object $\{x\}$ of the universe of discourse X.

Definition 4 The linguistic variable constitutes the range of possible values that can take the universe of discourse of that variable.

Definition 5 A fuzzy rule is a conditional statement of the form.

IF (antecedents), THEN (consequences).

where the antecedents and consequences are relations between linguistic variables and their fuzzy sets. The antecedents are referred to the input linguistic variables, and for the consequences the output linguistic variables.

Fuzzification

The fuzzification process starts by taking the input crisp linguistic variables and determining the degree of membership for their respective membership functions. Specifically, we consider five input linguistic variables: (1) meanGmin, (2) meanExcursion, (3) mean#switch04, (4) mean#switch48, and (5) meanToff. We designed three membership functions for each input variable. The membership functions are labeled by the linguistic terms *Small*, *Normal,* and *High*. The universes of discourse for all input variables are continuous and their elements belong to $\mathbb{R}_0^+$. Figures 15, 16, 17, 18, and 19 show the membership functions for the five input variables.

All of the designed membership functions are based on trapezoidal shapes with linear hedges defined as follows:

$$\mu_N(x|a,b,c,d) = \begin{cases} 0 & for\ x \leq a \\ \frac{x-a}{b-a} & for\ x \in [a,b] \\ 1 & for\ x \in [b,c] \\ \frac{d-x}{d-c} & for\ x \in [c,d] \\ 0 & for\ x \geq d \end{cases} \tag{11}$$

where the parameter set (a, b, c, d) define the domain of each sub-function of the piecewise trapezoidal membership function, e.g., the *Normal* membership function from Fig. 15 is defined by $\mu_{\text{Normal}}(x|\ 70,80,90,100)$.

We used trapezoidal shapes to lower the computational burden of more complex shapes, and also because they describe well enough the knowledge of the experts who participated in the system design.

The fuzzification process is performed by taking a specific crisp value of the input variables and evaluating the degree of membership. For example, for an input mean_Excursion = 70 mg/dl, the membership functions tell us that the particular excursion belongs 50% to *Small*, 50% to *Normal* and 0% to *High*. This process is performed for each input over all the membership

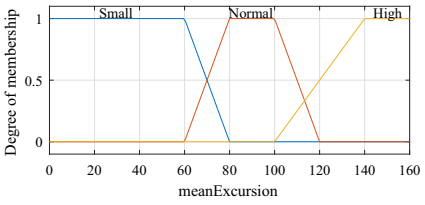

Fig. 16 Fuzzy sets for input linguistic variable meanExcursion

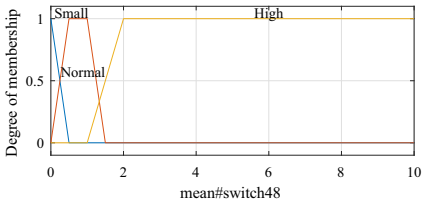

Fig. 18 Fuzzy sets for input linguistic variable mean#switch48

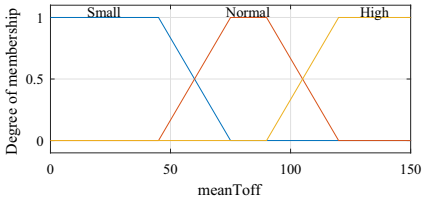

Fig. 19 Fuzzy sets for input linguistic variable mean_#T_{off}

functions. The output of the fuzzification process is the degree of membership of all the input variables to each of their fuzzy membership functions.

Rule evaluation

In this step, the rules stored at the rule database are used to apply the fuzzified inputs to the rule antecedents. The rule database of the system is composed by the following rules

1. IF meanG$_{min}$ is Small, THEN, IOBmax is Decrease.
2. IF meanG$_{min}$ is High AND meanExcursion is High, THEN, IOBmax is IncreaseLittle.
3. IF meanG$_{min}$ is High, THEN, k_p is IncreaseLittle.
4. IF meanT$_{OFF}$ is Small AND meanG$_{min}$ is Small, THEN, IOBmax is DecreaseLittle.
5. IF meanT$_{OFF}$ is High AND meanG$_{min}$ is High, THEN, IOBmax is IncreaseLittle.
6. IF meanSwitch04 is Small, THEN, k_p is IncreaseLittle.
7. IF meanSwitch04 is High, THEN, k_p is DecreaseLittle.
8. IF meanSwitch48 is High, THEN, k_p is Decrease.
9. IF meanSwitch48 is Small OR meanSwitch48 is Normal, THEN, k_p is NoChange.
10. IF meanG$_{min}$ is Normal AND meanExcursion is Normal, THEN IOBmax is NoChange AND k_p is NoChange.
11. IF meanT$_{OFF}$ is High, THEN, IOBmax is Increase.
12. IF meanT$_{OFF}$ is High AND meanG$_{min}$ is Normal, THEN, IOBmax is IncreaseLittle and k_p is NoChange.
13. IF meanT$_{OFF}$ is Small AND mean#switch04 is High, THEN IOBmax is Increase.

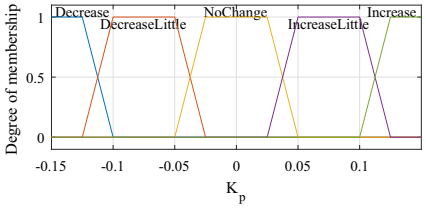

Fig. 20 Fuzzy sets for output linguistic variable k_p

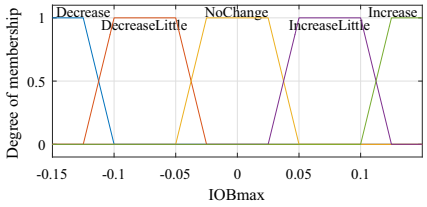

Fig. 21 Fuzzy sets for output linguistic variable IOBmax

14. IF meanT$_{OFF}$ is High AND mean#switch04 is Small, THEN IOBmax is Decrease.
15. IF meanExcursion is Normal OR meanExcursion is High, THEN, IOBmax is IncreaseLittle.

Both the antecedents and consequences can have multiple parts. These parts can use the fuzzy union (OR) and intersection (AND) operators. The union and intersection of two fuzzy sets A and B are defined as follows:

$$\mu_{A\cup B}(x) = \max[\mu_A(x), \mu_B(x)] \tag{12}$$

$$\mu_{A\cap B}(x) = \min[\mu_A(x), \mu_B(x)] \tag{13}$$

Using these operations, the system evaluates the antecedents of the rule to obtain the truth number. Then, this number is used to obtain the degree of membership of the output variables by applying the rule consequences.

For the output variables k_p and IOB$_{max}$, we designed identical membership functions as shown in Figs. 20 and 21.

By maintaining a sufficient overlap between adjacent membership functions, we tried to ensure a smooth response of the fuzzy system. Here, we clipped the consequent membership functions based on the degree of membership of the antecedent.

Aggregation of the outputs

Once all the rules have been evaluated, the clipped consequent sets are all combined into a single fuzzy set. The union operator is used to that aim. This generates an overall fuzzy output set.

Defuzzification

The defuzzification is a process that allows us to obtain a single value out of the overall fuzzy output set. In this application, the single value is contained in the universe of discourse of the output linguistic variables, i.e., [−0.15, 0.15]. The system uses the mCoA defined as follows:

$$mCoA = \frac{\int f(x)\cdot x\,dx}{\int f(x)dx} \tag{14}$$

where $f(x)$ represents the overall fuzzy output set and x belongs to the output domain. Therefore, the system takes the centroid of gravity of the overall fuzzy output. The x that corresponds to the centroid of gravity is taken as the output of the fuzzy inference engine.

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2.2 A new blood glucose control scheme for unannounced exercise in type 1 diabetic subjects

In this publication, we propose the first version of the multivariable AP system. The algorithm uses two coordinated feedback loops for insulin infusion and rescue CHO suggestion. The system is tested in-silico under challenging and realistic scenario settings. This control system has been tested in clinical trials and results are included in Appendix A. The candidate's contribution for this publication consisted in the development, design and implementation of the control scheme, the validation of the controller using in-silico simulations, writing the manuscript, contributing to discussion, writing and editing the manuscript throughout the review rounds. During the development of the work, the candidate worked with his colleague Arthur Bertachi. They were assisted by Dr. Jorge Bondia and Dr. Josep Vehí, who provided guidance in the design of the control system, contributed to discussion and reviewed the manuscript.

Title: A new blood glucose control scheme for unannounced exercise in type 1 diabetic subjects

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CHAPTER 2. ROBUST AND FAULT-TOLERANT STRATEGIES FOR CONTROLLING BLOOD GLUCOSE IN PATIENTS WITH TYPE 1 DIABETES

This article has been accepted for inclusion in a future issue of this journal. Content is final as presented, with the exception of pagination.

A New Blood Glucose Control Scheme for Unannounced Exercise in Type 1 Diabetic Subjects

Aleix Beneyto, Arthur Bertachi, Jorge Bondia, and Josep Vehi

***Abstract*— The artificial pancreas (AP) system or closed-loop blood glucose (BG) regulation is a technological advancement that aims to relieve diabetic subjects from their current decision-making burden while tightening their BG levels. However, large disturbances such as meals and exercise still pose great challenges to a fully closed-loop system. In this paper, the problem of BG regulation with unannounced physical activity for type 1 diabetic subjects is addressed. We use a coordinated control strategy with insulin infusion and extra carbohydrates (CHO) for hypoglycemia avoidance. The insulin algorithm is based on a proportional–derivative controller with insulin feedback and the so-called safety auxiliary feedback element (SAFE) layer, and the algorithm for CHO is based on a predictive, quantified proportional-derivative controller. The UVa/Padua simulator glucose-insulin model is modified to include the effects of physical activity and is used to test the new AP. We consider scenarios where the subject does not announce physical activity and with challenging meals. Then, we analyze the performance and robustness of the combined insulin and CHO recommender system and compare them to the insulin-only controller. The simulation results show that the new AP system is able to mitigate daily hypoglycemia episodes (0.9 versus 0.2, $p < 0.01$) and increase the time in range during day (91.5% versus 92.4%, $p < 0.01$) without increasing the time above 180 mg/dl (6.3% versus 6.4%, $p > 0.05$).**

***Index Terms*— Artificial pancreas, blood glucose (BG) control, carbohydrates (CHO), insulin, physical activity, proportional–derivative (PD), recursive least squares, sliding mode reference conditioning (SMRC), type 1 diabetes.**

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I. Introduction

DIABETES is a chronic metabolic condition in which blood glucose (BG) levels are not properly regulated. Type 1 diabetes mellitus (T1DM) is a form of diabetes characterized by an autoimmune reaction in which the insulin-producing β-cells of the pancreas are destroyed. Insulin is a key hormone that allows muscle tissue to use glucose for energy and the liver to store the excess of glucose as glycogen. People with T1DM suffer from an absolute deficiency of insulin, which develops to high BG levels or hyperglycemia. In addition, T1DM may also lead to impaired glucagon production, the counter-regulatory hormone to insulin.

People with T1DM have to administer exogenous insulin in order to keep BG levels in a safe range (70–180 mg/dl). Current therapy for T1DM can be divided into two approaches: multiple daily injections of insulin or insulin pump therapy. Multiple daily injections consist of measuring BG levels using a glucose meter and administer subcutaneously the insulin dose. Insulin pump therapy uses an insulin basal profile programmed into the pump to continuously administer insulin subcutaneously 24/7 with bolus doses to compensate meals.

The artificial pancreas (AP) is a system that integrates a continuous glucose monitor (CGM), a continuous subcutaneous insulin infusion pump, and a control algorithm. The controller uses the BG levels measured by the CGM to drive the insulin pump to maintain euglycemia, i.e., BG levels between 70 and 140 mg/dl in subjects with T1DM. Overall, the AP encompasses closed-loop system technology designed to be used by the people with T1DM.

Common AP technology can be classified in two categories: 1) fully closed-loop systems, where the subject is not a part of the control and 2) hybrid systems, where the system allows the subject to perform feed-forward actions to compensate known disturbances. Due to the delays in the subcutaneous route, hybrid systems with a feed-forward controller consisting of a premeal bolus usually perform better than fully closed-loop systems.

AP technology has been extensively tested both in-silico and in inpatient/outpatient clinical studies [1], and a large amount of control techniques have been developed and tested [2]. The most common controllers within AP systems can be classified as proportional–integral–derivative, model predictive control, or fuzzy control algorithms. These systems have been tested in daily life conditions. However, disturbances such as meals and physical activity are still a challenge.

Physical activity is a large and fast disturbance that brings AP systems to the limit. The metabolic effect of exercise may vary depending on the type of exercise [3]. For example,

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if a T1DM subject engages in an aerobic exercise session, e.g., cycling, then their BG levels will likely decrease and insulin sensitivity will be increased for the next 24–48 h. Conversely, high-intensity interval training may result in hyperglycemia (BG $>$ 180 mg/dl). In addition, the performance of AP systems is typically affected by the BG and insulin state at the onset of exercise and by when the subject exercises, e.g., the risk of hypoglycemia is considerably higher if the subject engages in aerobic physical exercise after a meal where a bolus has just been delivered. All these factors combined will typically drive the AP system to open loop, i.e., suspending the insulin infusion because the physical activity has driven the system to an uncontrollable state.

Regarding aerobic exercise, insulin-only controllers have shown poor performance, which is mainly due to the lack of a control action that counteracts the metabolic effect of exercise, i.e., a higher glucose uptake by muscles. The lasting effect of increased insulin sensitivity also increases the risk of postexercise hypoglycemia (BG $<$ 70 mg/dl) for at least 12 h [3]. A recent study [4] tested an insulin-only AP system against unannounced exercise to the control algorithm. The study showed that the closed-loop guaranteed more time in the euglycemia range and less insulin infusion compared to open-loop therapy. However, the time in the hypoglycemia range, which was their primary endpoint, was not met, and rescue carbohydrates (CHO) were still needed to avoid hypoglycemia. Insulin-only AP systems have been widely tested in response to exercise; see [5]–[7] for other recent studies.

In an attempt to solve this limitation of insulin-only controllers, several research groups have explored alternative control actions. The bihormonal AP appeared as a possible solution to minimize the risk of hypoglycemia by combining both insulin and glucagon hormones. Glucagon is a hormone secreted by the alpha cells in the pancreas that raises BG levels via glycogenolysis. Therefore, the administration of subcutaneous glucagon can potentially help minimize the risk of hypoglycemia in AP systems. The effectivity and safety of a bihormonal AP were clinically tested in [8]. A head-to-head comparison between insulin-only and bihormonal AP systems in front of physical activity showed that the bihormonal AP reduced the time in hypoglycemia along with the number of hypoglycemic events compared to the insulin-only AP [9].

Another strategy was recently presented in which an insulin-only controller was aided by suggesting CHO intakes to the subject if there was a risk of hypoglycemia [10]. In their strategy, an ARMAX model is used to predict BG levels 30 min ahead. Then, if below 70 mg/dl, the system classified in different phases the measured BG levels and BG trend. Finally, depending on the classification, the system suggested different fixed amounts of CHO ranging from 4 to 24 g. Their results showed that their system was able to prevent most hypoglycemic events by issuing rescue CHO consumption.

In this paper, we propose combining a previously developed [11] and clinically tested [12] insulin-only controller with a fast-acting CHO recommender system. The insulin-only controller is based on a proportional–derivative (PD) with insulin feedback (IFB) and a safety layer with insulin on board (IOB) constraints and sliding mode reference conditioning (SMRC). Meanwhile, CHO will be suggested by another feedback controller with a predictive PD, delivering fixed amounts of CHO that match commercially available products. The result will be a new control algorithm that mixes the insulin and CHO strategies in a coordinated way with the aim of maintaining BG in the euglycemic range even if measurable or unmeasurable disturbances appear. This constitutes a novel hybrid AP with an automatic insulin infusion algorithm and a reactive subject that will be asked to take CHO. The strategy is extensively tested in silico under realistic scenarios with a cohort of adult subjects.

II. Problem Statement

A. Models and Assumptions

1) Glucose-Insulin Model: In this paper, we use the UVa/Padova meal simulation model of T1DM subjects approved by the Food and Drug Administration [13]. We included circadian variability in the insulin sensitivity [11].

2) Exercise Model: At present, few exercise models are available [14]–[17]. In this paper, we use model C detailed in [16], which acts as a disturbance in the glucose uptake. This model increases the glucose uptake during and after an exercise session. Therefore, it is a disturbance model that may characterize aerobic exercise.

Model C from [16] was selected because it gave the highest fit in BG drops according to our clinical data. A Monte Carlo method was used to determine the values of the model parameter β_f and the coefficient of variation. The details of this procedure can be found in [18]. The fit model is able to accurately reproduce BG drops caused by aerobic exercise at 60% $\mathrm{VO}_{2\,\max}$ but is not able to model the lasting effect of exercise in insulin sensitivity.

III. Insulin Feedback Loop

The algorithm is composed of two loops: an inner loop with the PD controller with IFB and an outer loop with the safety auxiliary feedback element (SAFE) layer.

The inner control action is composed of three insulin signals: 1) u_b represents the feed-forward meal bolus; 2) u_{basal} is the insulin infusion due to the patient's daily basal profile; and 3) u_{PD} is the PD control action. Then, the total insulin control action is

$$u_c(t) = k_p\left[e_i(t) + \tau_d \frac{dCGM(t)}{dt}\right] + u_{\text{basal}}(t) + u_b \quad (1)$$

with u_b being a super bolus

$$u_b = \frac{M}{I2C} + \frac{\int_t^{t+60} u_{\text{basal}}dt}{60}M + \frac{\text{CGM}(t) - G_d}{\text{CF}} \quad (2)$$

where k_p is the proportional gain, τ_d is the derivative time, $I2C$ is the insulin to CHO ratio, CF is the correction factor, G_d is the predefined glucose reference, and M is the meal CHO content in grams. Specifically, the proportional gain is tuned according to [19]

$$k_p = \frac{60}{\tau_d}\frac{I_{\text{TDD}}}{1500} \quad (3)$$

where I_{TDD} is the subject's total daily insulin.

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The SAFE outer layer defines the conditions under which the reference G_d may be changed. The reference is changed to guarantee that the IOB is bounded, i.e., IOB $\in [0, \overline{\text{IOB}}]$, by ceasing insulin infusion. The SAFE layer will modify the reference G_d to a virtual reference G_{ds} if the estimated IOB, i.e., $\widehat{\text{IOB}}$, is about to violate the imposed constraint on the maximum allowed IOB, i.e., $\overline{\text{IOB}}$. This makes the controller robust to delays in the subcutaneous route.

The SAFE layer is composed of: 1) a model that estimates the IOB online; 2) an SMRC block; and 3) a low-pass first-order filter to smooth the reference adaptation.

We use an expanded form of the insulin absorption model [20] to account for basal and deviation IOB

$$\begin{aligned}
\frac{dc_1(t)}{dt} &= u_{\text{basal}}(t) - K_{\text{DIA}} C_1(t) \\
\frac{dc_2(t)}{dt} &= K_{\text{DIA}} \left(C_1(t) - C_2(t)\right) \\
\frac{d\Delta C_1(t)}{dt} &= u_d(t) - u_{\text{basal}}(t) - K_{\text{DIA}} \Delta C_1(t) \\
\frac{d\Delta C_2(t)}{dt} &= K_{\text{DIA}} \left(\Delta C_1(t) - \Delta C_2(t)\right) \\
\widehat{\text{IOB}}(t) &= C_1(t) + C_2(t) + \Delta C_1(t) + \Delta C_2(t) \qquad (4)
\end{aligned}$$

where $C_1(t)$ and $C_2(t)$ are the two compartments that account for the basal conditions, $\Delta C_1(t)$ and $\Delta C_2(t)$ are the two compartments that account for IOB deviations from basal conditions, $u_d(t)$ is the total insulin dose, and K_{DIA} is a subject-specific time constant that replicates the patient's duration of insulin action (DIA).

The idea behind the switching action block that includes SMRC is invariance control [21]. Basically, the set

$$\Sigma := \{x(t) | \text{IOB}(t) - \widehat{\text{IOB}}(t) \leq 0\} \qquad (5)$$

where $x(t)$ is the state of the system, which is invariant when using the following discontinuous signal:

$$\omega(t) = \begin{cases} \omega^+ & \text{if } \sigma(t) > 0 \\ 0 & \text{otherwise} \end{cases} \qquad (6)$$

with the sliding surface defined as

$$\sigma(t) = \widehat{\text{IOB}}(t) - \overline{IOB}(t) + \tau(\dot{\widehat{\text{IOB}}}(t) - \dot{\overline{\text{IOB}}}(t)). \qquad (7)$$

Finally, a low-pass first-order filter is defined to smooth the reference change

$$\frac{d\omega_f(t)}{dt} = -\lambda(\omega_f(t) - \omega(t)). \qquad (8)$$

The IFB is a mechanism that is widely used by AP systems to reproduce the β-cells response to plasma insulin concentration (PIC). Basically, the secretion of insulin is inhibited as the PIC increases. A straightforward way to replicate this effect in the control algorithm is to estimate the PIC ($\hat{I}_p$) online and then proportionally inhibit the insulin control action. Then, the new insulin dose computed by the controller becomes

$$u_d(t) = u_c(t) - \gamma\left(\hat{I}_p(t) - \hat{I}_p^{\text{ss}}\right) = u_c(t) - \gamma\,\delta\hat{I}_p^{\text{ss}} \qquad (9)$$

where $\hat{I}_p^{\text{ss}}$ refers to the PIC at steady state, i.e., plasma insulin due to the basal infusion and $\delta\hat{I}_p^{\text{ss}}$ represents PIC deviations from the basal infusion. Hence, the implemented IFB only accounts for deviations of plasma insulin from the basal one. To estimate the deviations of plasma insulin, we use the description of PIC from [20] and the deviation absorption rate from $\Delta C_2(t)$ compartment

$$\frac{d\delta\hat{I}_p^{\text{ss}}(t)}{dt} = \frac{\Delta C_2(t)}{t_{\text{max},I} V_I} - k_e \delta\hat{I}p^{\text{ss}} \qquad (10)$$

where $t_{max,I}$ is the time to maximum insulin absorption (min), k_e is the fractional elimination rate (min^{-1}), and V_I is the insulin distribution volume (L).

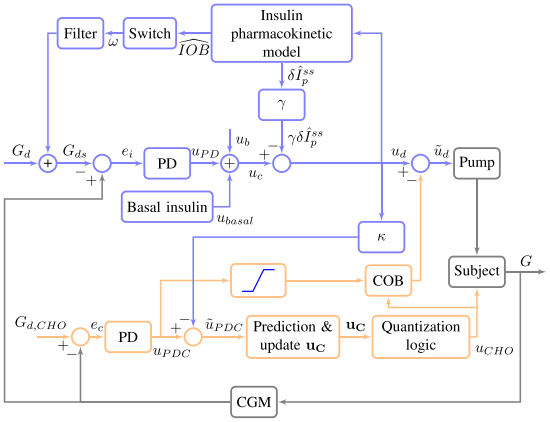

Fig. 1. PD + SAFE + IFB insulin controller in blue with the CHO controller in orange.

IV. Carbohydrate Recommender System

In this section, we introduce a novel approach to handle any type of disturbance that has a lowering effect on BG. The approach consists of a second feedback loop that will act as a recommender system. The CHO recommender system uses feedback signals to compute current control actions, inhibition signals to coordinate both loops, and past and predicted control actions to determine whether to recommend fixed amounts of 15 g of CHO.

The complete block diagram of the control strategy is presented in Fig. 1. Note the second negative feedback loop for the CHO controller that has been added to the previous insulin-only controller. Specifically, this negative feedback loop features: 1) a new PD controller; 2) an online recursive estimation in closed-loop for BG prediction; 3) a quantification of the CHO controller action; and 4) inhibition signals between both loops in both directions.

A. PD Controller for Carbohydrates

The CHO system was originally based on the insulin PD controller used in clinical trials [12]. The integral term has also been discarded because the aim of the CHO loop is not to closely regulate BG but rather to minimize the risk of hypoglycemia. A strong integral action would lead to too much error accumulation during low glucose periods and would

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trigger unnecessary CHO recommendations. Here, the CHO PD is defined as

$$u_{\mathrm{PDC}} = k_{\mathrm{pCHO}}\left[e_c(t) + \tau_{\mathrm{CHO}}\frac{\mathrm{dCGM}(t)}{dt}\right] \tag{11}$$

with

$$k_{\mathrm{pCHO}} = \alpha k_p \tag{12}$$

where k_p is the proportional gain of the insulin controller, α is a design gain parameter to adjust the CHO controller, and τ_{CHO} is the derivative time.

Therefore, the CHO PD controller computes control actions that require insulin extraction from the body, i.e., negative control actions. Later, these actions are transformed to the equivalent effect, i.e., BG increase, which a consumption of CHO would have.

B. Prediction Model

The BG levels of a T1DM subject can be represented as a function of past glucose and past input signals. For this purpose, an online adaptation of a linear time-invariant system can be used to express the patient's current and future BG concentrations. Particularly, we consider the family of linear time-invariant models $M(\theta)$ of the form

$$A(q)y(t) = \sum_{j=1}^{m} B_j(q)u_j(t) + C(q)e(t) \tag{13}$$

with

$$\begin{aligned} A(q) &= 1 + a_1 q^{-1} + \cdots + a_{n_a} q^{-n_a} \\ B_j(q) &= b_{1j} q^{-1} + \cdots + n_{n_b j} q^{-n_{bj}} \\ C(q) &= 1 + c_1 q^{-1} + \cdots + c_{n_c} q^{-n_c} \end{aligned} \tag{14}$$

where q^{-1} is the backward shifting operator. To estimate the model parameters, we use the recursive extended least squares algorithm [22]. The prediction capabilities for the family of models $M(\theta)$ were evaluated, and an autoregressive model of fourth order was selected to predict BG levels up to 20 min ahead of time. The complete procedure on the parameter estimation and prediction step can be found in [23].

Then, the system uses the predicted CHO control actions to build the following moving vector centered at the current time instant k

$$\begin{aligned} \mathbf{u_C}(k) = \big[&\tilde{u}_{\mathrm{PDC}}(k-3)\ \tilde{u}_{\mathrm{PDC}}(k-2)\ \tilde{u}_{\mathrm{PDC}}(k-1) \\ &\tilde{u}_{\mathrm{PDC}}(k)\ \hat{\tilde{u}}_{\mathrm{PDC}}(k+1|k)\ \hat{\tilde{u}}_{\mathrm{PDC}}(k+2|k) \\ &\ldots\ \hat{\tilde{u}}_{\mathrm{PDC}}(k+H_p|k)\big] \end{aligned} \tag{15}$$

where H_p is the prediction horizon in samples, $\tilde{u}_{\mathrm{PDC}}$ are the past and current CHO control action inhibited by the insulin loop, and $\hat{\tilde{u}}_{\mathrm{PDC}}$ are the predicted and inhibited CHO control actions.

C. Carbohydrates on Board

CHO on board (COB) is a concept similar to IOB. That is, the COB is the CHO that has been consumed but that still has not appeared in plasma. Here, the COB is used to estimate how many of the recommended CHO will still increase the BG concentration in the future. In this paper, we use the meal absorption model from [24], and glucose gels with 15 g of CHO are considered. Then, when the subject responds to a CHO recommendation, the input is $D(t) = 15$ g. In addition, we model $t_{\max} = 20$ min and $B = 0.9$. Then, the COB is defined as

$$\widehat{\mathrm{COB}}(t) = 1 - \frac{\int_{t^*}^{t} \frac{D(t^*)Bte^{-\frac{t}{\tau_{\max}}}}{t_{\max}^2}dt}{\mathrm{BD}(t^*)} \tag{16}$$

where t^* corresponds to the time instant when the subject has consumed the recommended CHO and $\widehat{\mathrm{COB}}(t)$ represents the percentage of remaining CHO.

D. Inhibition Signals From the Carbohydrate Loop

The COB is being used to inhibit the insulin control action u_d when the subject consumes fast-acting CHO recommended by the system. This allows the insulin controller to be coordinated with the CHO controller and not counteract the BG increase due to this specific type of CHO. Specifically, as shown in Fig. 1, there are two different COB inhibitions.

1) Direct Carbohydrates to Insulin Inhibition (COB_1): $\mathrm{COB}_1(k)$ is a virtual COB estimation computed from the positive CHO PD controller actions. It is used to continuously minimize the hypoglycemia risk if the prediction of hypoglycemia is high irrespective of whether CHO has been delivered.

2) Real Carbohydrates to Insulin Inhibition (COB_2): $\mathrm{COB}_2(k)$ is the COB estimation when there is a real CHO recommendation. Therefore, the inhibition of the insulin action is triggered because there is an actual consumption of CHO.

3) Insulin Control Action: The insulin control action $u_d(k)$ is therefore modified to $\tilde{u}_d(k)$ by the two COB signals

$$\tilde{u}_d(k) = \begin{cases} u_d(k) - \nu\mathrm{COB}_1(k) - \beta\mathrm{COB}_2(k), & \text{if } u_{\mathrm{PDC}} > 0 \\ u_d(k) - \beta\mathrm{COB}_2(k), & \text{otherwise} \end{cases} \tag{17}$$

where $\mathrm{COB}_1(k)$ and $\mathrm{COB}_2(k)$ are the COB estimations at time instant k and $\nu \in \mathbb{R}_0^+$ and $\beta \in \mathbb{R}_0^+$ are the gain parameters that adjust the insulin inhibition factor.

E. Inhibition Signal From the Insulin Loop

An inhibition signal from the insulin loop to the CHO loop is also considered to minimize the CHO recommendations. Thus, the CHO PD control action is modified to

$$\tilde{u}_{\mathrm{PDC}}(k) = u_{\mathrm{PDC}}(k) - \kappa u_d(k)$$

where κ is the inhibition gain.

F. Quantification of Carbohydrates

The CHO controller signal will be quantified according to 15 g of the glucose gels by using the following quantifier:

$$\delta(k) = \sigma(k) + 10\sum_{i=1}^{N} K\Gamma_i \mathbf{u_C}(i-1) \tag{18}$$

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where $\delta(k)$ is the quantified CHO controller action, $\sigma(k)$ accounts for the deficit or excess of CHO from past actions, K (CHO grams/insulin units (IU)) is a gain that allows transforming insulin control actions into the equivalent CHO control actions, N is the length of the vector $\mathbf{u_C}$, and $\mathbf{u_C}$ is a moving window of CHO controller actions. Then, CHO is suggested if

$$u_{\text{CHO}} = \begin{cases} 15, & \text{if } \delta(k) \geq T_{\text{CHO}} \\ 0, & \text{otherwise} \end{cases} \tag{19}$$

where T_{CHO} is a control design threshold, and the counter $\sigma(k)$ is updated as

$$\sigma(k) = \begin{cases} -\Delta(k), & \text{if } 0 \leq \Delta(k) < T_{\text{CHO}} \\ |\Delta(k)|, & \text{if } \Delta(k) < 0 \end{cases} \tag{20}$$

where $\Delta(k) = 15 - \delta(k)$.

G. Controller Tuning

Controller parameters were fixed to the same value except the proportional gain of both controllers, the $\overline{\text{IOB}}$ and the individualization gain K. These three varying parameters are used to individualize the AP tuning according to each individual needs. Specifically, the tuning for $\overline{\text{IOB}}$ is time varying and depends on the subject's current basal profile [18]

$$\overline{\text{IOB}}(t) = K_{\text{IOB}}(t)\frac{2u_{\text{basal}}(t)}{60K_{\text{DIA}}} \tag{21}$$

where $K_{\text{IOB}}(t)$ is a gain designed to cope with day/night variability and is defined as

$$K_{\text{IOB}}(t) = \begin{cases} 1.3 & \text{if } 07{:}00 < t \leq 23{:}00 \\ 1.1 & \text{otherwise.} \end{cases} \tag{22}$$

Table I shows the parameters value of the insulin and CHO controllers. The parameters for the IFB model of (10) were taken from [20]. The inhibition gains (ν, β, and κ) were manually and individually tuned using a 3-day scenario without exercise. Specifically, we used the percentage time in range 70–180 mg/dl as the objective to be maximized.

The following weights were applied to the CHO control actions:

$$\Gamma_i = [0.025\ 0.025\ 0.025\ 0.1\ 0.4\ 0.2\ 0.125\ 0.1]. \tag{23}$$

The original insulin-only AP system used the same insulin parameters from Table I. In addition, the system considered standard of care rescue CHO to treat hypoglycemia

$$\text{CHO} = \begin{cases} 15 \text{ gr}, & \text{if CGM} < 70 \text{ mg/dl} \\ 0, & \text{otherwise.} \end{cases} \tag{24}$$

Rescue CHO is suggested again if after 15 min CGM has not recovered above 70 mg/dl.

V. Scenario

A challenging scenario with combined meals and unannounced exercise has been used to benchmark the controllers. The duration of the scenario is 15 days, and we use an adult cohort of 10 subjects from the meal simulation model [13]. Meals of 30, 60, and 50 g are scheduled at 8:30, 13:00, and 19:00, respectively. The controller is challenged by continuous aerobic exercise sessions for 50 min at 60% VO2max for the scenario with exercise. Each subject performed a total of eight exercise sessions on alternating days (starting on Day 1). The first four exercise sessions were randomly scheduled at different times (7:00, 10:00, 15:00, or 21:00), and the last four sessions repeated the same time schedule.

TABLE I
Tuning Parameters for the Insulin-Only and CHO Controllers

Parameter	Insulin-only controller	CHO controller
τ_d (min)	90	–
τ	10	–
K_{DIA} (min^{-1})	0.013	–
ω^+ (mg/dl)	350	–
λ	0.1	–
γ	25.2	–
V_I (L)	0.12BW	–
k_e	0.138	–
α	–	4
τ_{CHO} (min)	–	50
ν	–	0
β	–	0.1
κ	50	–
T_{CHO} (gr)	–	7.5
K	–	27

BW corresponds to the subject's body weight in kilograms.

VI. Results

In this section, we compare the original insulin-only AP system that conforms to the PD + SAFE + IFB with the new AP system with CHO recommendations.

Table II show that both controllers have performed well during the night when no disturbances affect the system. The low time in hypoglycemia range during the night is caused by late exercise sessions that affect the beginning of the night period. Nevertheless, the new system has mitigated the hypoglycemia occurrence during the night and significantly increased the minimum measured CGM. During the day, the performance of both systems is reduced by the combined effects of meals and physical activity, e.g., see Fig. 2. However, the new AP system is able to mitigate most hypoglycemias (0.9 versus 0.1, $p < 0.01$). At the same time, the system was able to mitigate hypoglycemia episodes even with less rescue CHO (26.5 gr/day versus 15.5 gr/day). Hypoglycemia mitigation is also shown by the minimum CGM reached during day (42.8 mg/dl versus 59.2 mg/dl, $p < 0.01$) and by the time spent below 70 mg/dl (2.2% versus 0.9%, $p < 0.01$).

The inhibition signals play an important role in stabilizing BG. Fig. 2 reflects the effects of the inhibition at the end of the figure. On that day, patients engaged exercise at 21:00 and CHO were delivered by both controllers. The inhibition signals are able to mitigate the oscillatory behavior that BG presents after delivering rescue CHO, reducing the insulin over-actuation and the consumption of the subsequent rescue CHO. Fig. 3 shows when the new AP system suggests CHO based on the CGM and CGM trend. The distributed points show a negative trend for higher values. The new system

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TABLE II
GLYCEMIC AND TECHNICAL PERFORMANCE WHEN SUBJECTS HAVE MIXED MEALS AND UNANNOUNCED PHYSICAL ACTIVITY

Performance indicator	PD+SAFE+IFB	PD+SAFE+IFB with CHO
Night-time (24:00-06:00 hours)		
Mean CGM (mg/dl)	111.7 (110.0 – 116.5)	112.5 (109.9 – 116.0)
Median CGM (mg/dl)	113.0 (110.7 – 114.7)	112.7 (110.8 – 114.7)
Maximum CGM (mg/dl)	215.3 (207.1 – 236.1)	215.6 (207.1 – 235.5)
Minimum CGM (mg/dl)	42.8 (38.9 – 50.9)	59.2 (47.2 – 64.7)*
% of time CGM		
70-140 mg/dl	95.0 (91.7 – 97.3)	94.6 (90.2 – 97.8)
70-180 mg/dl	98.5 (98.2 – 99.5)	98.9 (98.1 – 99.2)
$>$ 250 mg/dl	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)
$>$ 180 mg/dl	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.4)
$<$ 70 mg/dl	1.5 (0.5 – 1.8)	0.9 (0.3 – 1.2)
$<$ 60 mg/dl	0.2 (0.0 – 0.3)	0.0 (0.0 – 0.0)
$<$ 50 mg/dl	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)
Glycemic variability (IQR) (mg/dl)	15.9 (14.5 – 17.7)	16.9 (13.7 – 21.9)
Daytime (06:00-24:00 hours)		
Mean CGM (mg/dl)	129.7 (122.1 – 135.5)	130.6 (122.2 – 133.4)
Median CGM (mg/dl)	125.2 (120.1 – 130.2)	124.7 (120.2 – 128.8)
Maximum CGM (mg/dl)	215.3 (207.1 – 236.1)	215.6 (207.1 – 235.5)
Minimum CGM (mg/dl)	42.8 (38.9 – 50.9)	59.2 (47.2 – 64.7)*
% of time CGM		
70-140 mg/dl	62.0 (56.5 – 74.6)	62.9 (55.3 – 74.2)
70-180 mg/dl	91.5 (88.8 – 96.9)	92.4 (90.1 – 97.0)*
$>$ 250 mg/dl	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)
$>$ 180 mg/dl	6.3 (1.1 – 9.4)	6.4 (1.1 – 9.8)
$<$ 70 mg/dl	2.2 (1.8 – 3.0)	0.9 (0.2 – 2.2)*
$<$ 60 mg/dl	0.7 (0.4 – 1.1)	0.1 (0.0 – 1.1)
$<$ 50 mg/dl	0.2 (0.0 – 0.3)	0.0 (0.0 – 0.1)
Glycemic variability (IQR) (mg/dl)	44.4 (34.4 – 47.8)	42.5 (34.8 – 49.5)
Postprandial$^+$ indicators		
Excursion (mg/dl)	46.0 (42.0 – 54.0)	45.0 (40.0 – 53.9)*
CGM time in hyperlgycemia $>$ 180 mg/dl (%)	8.8 (2.1 – 13.8)	8.9 (1.9 – 13.8)
CGM time in hypoglycemia $<$ 70 mg/dl (%)	0.7 (0.5 – 1.2)	0.1 (0.0 – 1.0)
Technical performance metrics		
Total daily insulin (IU)	36.5 (31.5 – 40.9)	36.0 (31.1 – 41.7)
Total daily carbohydrates (gr)	26.5 (21.0 – 36.0)	15.5 (12.0 – 20.0)
Total daily hypoglycemia events	0.9 (0.8 – 1.2)	0.2 (0.1 – 0.6)*

The results are median (interquartile range). $^+$ Postprandial = 2 hours following the meal. * P value $<$ 0.05 (Wilcoxon signed rank test).
A hypoglycemia event is defined as blood glucose below 70 mg/dl at least 15 minutes and to consider a new event blood glucose has to return above 70 mg/dl for at least 15 minutes.

was not able to mitigate two severe hypoglycemias for the whole cohort as shown by the two points in the red zone.

VII. DISCUSSION

In this paper, we propose a closed-loop algorithm to prevent hypoglycemia by issuing alarms to encourage patients to consume CHO. The presented control strategy has been designed to avoid exercise-induced hypoglycemia, but it inherently mitigates any disturbance that lowers BG levels and poses a threat of hypoglycemia.

We have already tested the insulin-only portion of the algorithm in clinical trials [12]. The system is being complemented by a feed-forward controller to mitigate announced exercise [18] and a meal detection system [25]. The goal is to add features to the AP to provide as much automatism as possible while ensuring safety.

Our results have shown that BG levels can be predicted, and most hypoglycemia events induced by external disturbances can be avoided. Hypoglycemia is avoided by consuming extra fast-acting CHO. However, under closed-loop operation, the CHO action alone is not enough. The system must be informed of the ingested CHO, otherwise, the insulin controller will react to any BG rise, over-actuating and possibly inducing again hypoglycemia. Coordination mechanisms

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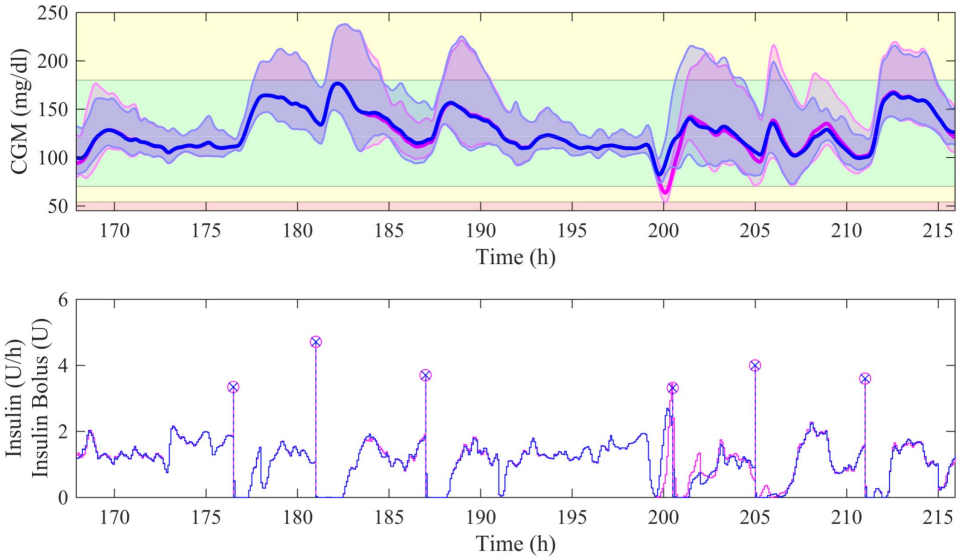

Fig. 2. Representative CGM trajectory (MEAN $\pm$ STD), insulin and bolus decisions for days 7 and 8 of the scenario. The blue curve corresponds to the full algorithm and the magenta curve to the insulin-only controller aided with CHO. Exercise started 07:00 (199 hour) of day 8 and lasted for 50 min.

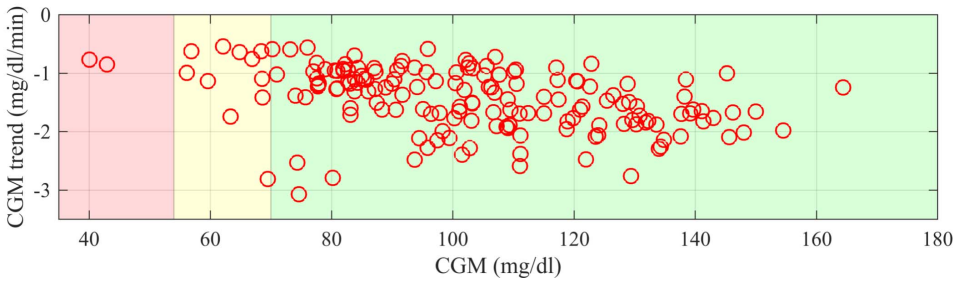

Fig. 3. Phase plane of CGM(k) versus $\dot{\text{CGM}}(k)$ at time instant where CHO is suggested by the algorithm.

between different control actions should be a must have for any multivariable AP system.

A similar strategy in the sense of issuing alarms to encourage patients to consume CHO can be found in [10]. This paper included physical activity two times per day during a period of 3 days. Hypoglycemia was successfully predicted in most cases allowing the system to suggest the appropriate amount of CHO to rise back BG levels. The BG levels at hypoglycemia alarm are higher in average in their approach compared to the proposed algorithm (122 mg/dl versus 102 mg/dl), the average consumption of CHO per alarm was also lower (12.8 gr versus 15 gr). However, the lower consumption of CHO per alarm and the earlier alarm triggering may require the patient to be more dependent on the system. No coordination mechanism with their closed-loop algorithm is used.

Although the proposed closed-loop CHO control strategy is able to prevent most of BG decreases, it suffers from some limitations. Since the patient is in the loop, the CHO control action must be applied by them. Patient behavior not following the recommendations may affect closed-loop performance in terms of hypoglycemia avoidance.

VIII. Conclusion

The proposed insulin-only and CHO recommendation system is able to minimize the risk of hypoglycemia in front of mixed meals and unannounced aerobic exercise sessions. Different internal coordination signals are used by the system to avoid oscillatory behaviors after the consumption of rescue CHO. The performance of the system is evaluated in-silico, and the results reveal that by suggesting CHO in a timely manner most hypoglycemias are avoidable.

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2.3 A hybrid automata approach for monitoring the patient in the loop in artificial pancreas systems

In this publication, we propose a FD methodology to monitor the operation of AP systems under the patient-in-the-loop effect. The algorithm is able to detect patient operation modes and potential faults that can be related to the patient. The candidate's contribution for this publication consisted in the design, development, implementation and testing of a fault detection mechanism for AP systems, contributing to discussion, writing the manuscript and editing the manuscript throughout the review rounds. The candidate was supervised by Dr. Josep Vehí, Dr. B. Wayne Bequette and Dr. Vicenç Puig who contributed to the discussion and reviewed the manuscript.

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CHAPTER 3

DISCUSSION

In this thesis an AP system has been developed and tested in a clinical trial. The main goal has been to develop robust strategies for controlling the BG against big external disturbances, such as meals or exercise. To do so, the previously developed AP system (León-Vargas et al., 2013) has been transformed into a multivariable controller that uses insulin and suggests CHO to avoid hypoglycemia. The second goal was to take into account patient-in-the-loop effects on the overall performance and safety of the AP system. In that line, several methodologies to enhance the robustness of AP systems have been proposed. Firstly, a fuzzy system was designed to keep an AP system tuned during PP. Secondly, a FD system was developed to detect patient modes and potential behavioral faults. The following sections of this chapter summarize the completed work and discuss the benefits and potential limiting factors of the proposed approaches.

3.1 Artificial Pancreas Systems for Controlling Meals and Exercise

In (Beneyto and Vehi, 2017; Beneyto et al., 2018) we proposed a new multivariable AP system that uses insulin infusion and CHO. The system was upgraded with a feed-forward exercise controller (Bertachi, Beneyto, Ramkissoon and Vehi, 2018) and with an adaptive constraint system for the IOB (Bertachi et al., 2020). The whole system has been implemented in the Java Artificial Pancreas (jAP) platform and tested in an inpatient clinical trial.

The motivation behind the development of this AP was to provide the system with the necessary tools to be efficient, safe and robust against meals and exercise. Previous observations of BG control when people with diabetes engage aerobic exercise (Quirós et al., 2018) suggest that insulin only AP systems offer limited protection against exercise induced hypoglycemia. This is caused by the fact that this type of exercise rapidly and significantly lowers BG concentrations (Riddell et al., 2017). The only counteractive action by insulin-only controllers is to cease insulin infusion, and even in that situation patients are at high risk of hypoglycemia. Therefore, additional counteractive control actions that prevent exercise hypoglycemia by offering a way to raise BG levels had to be explored. The immediate option was to follow the bi-hormonal AP approach, where insulin and glucagon are used. Bi-hormonal controllers have been also tested in clinical trials and showed potential to become a reality (El-Khatib et al., 2009; Taleb et al., 2016; Jacobs et al., 2016). However, bi-hormonal systems suffer from several major limitations. Firstly, no stable glucagon formulation was available for daily use (Pohl et al., 2014) until recently when in 2019 the FDA approved the first glucagon based injection analogue GVOKE (Ranjan et al., 2020). Secondly, a bi-hormonal system increases the complexity of the overall control system (Bally and Thabit, 2018). Even though any additional control action would increase the system complexity, including glucagon would also require additional hardware such as a second pump for glucagon since no dual chamber pumps exists.

All that complexity may lead to a system that burdens the daily life of patients and lead to patient dissatisfaction (Barnard et al., 2015).

In that scenario, our approach was to keep using a hybrid uni-hormonal system. Then, we considered rescue CHO for the prevention and treatment of hypoglycemia. To improve how and when CHO were suggested we decided to develop a specific control strategy instead of using heuristic rules for CHO delivery (Turksoy et al., 2016) or additional modules (Liu et al., 2020). Using a control strategy for CHO allow us to individualize the tuning for each patient. Even with the CHO, we soon realized that proper coordination between insulin infusion and CHO was essential to ensure performance and safety. Therefore, we included the concept of carbohydrates on board (COB) and coupled both feedback loops. This prevented the insulin loop to overreact to glucose increase caused by rescue CHO and helped in smoothing the later glucose stabilization. The main drawback of using rescue CHO to avoid hypoglycemia is that it may lead to hyperglycemia. In our approach, we minimize this possibility by taking into account the past control actions and the current COB estimations.

Including CHO also posed patient uncertainty into the system. Clearly, this control action cannot be performed automatically by means of a physical device. Instead, the patient itself has to follow the controller recommendation and consume them. The performance of CHO dependent systems could clearly be degraded with uncooperative patients. Additionally, CHO based systems have restrictions on the CHO delivery. Carbohydrates cannot be delivered continuously, such as insulin, and a CL system should not suggest different amounts of CHO during operation. To cope with this limitation we developed a quantization strategy that enabled the system to suggest a fixed amount of CHO. We decided to use 15 grams of CHO if rescue CHO where suggested. That amount of CHO was selected based on common available products on the market to treat hypoglycemia, such as glucose gels or tablets.

Finally, the whole system was stressed in-silico and validated in an inpatient clinical study conducted at the Hospital Clínic de Barcelona. Results showed the potential benefits of the

system and outperformed the OL therapy. However, further experimentation is still required to assess the performance, robustness and reliability of the system in free living conditions. This study also allowed our consortium to validate for the first time our smartphone based AP platform, the jAP system. The jAP joins as one of the few academic platforms for AP prototyping in the world (Choi et al., 2018; Deshpande et al., 2019; Herrero et al., 2019).

3.2 The Tuning of Artificial Pancreas Systems

Each person with T1D is unique and can exhibit highly different dynamics. Indeed, people with diabetes may have significantly different BG dynamics based on age, sex, weight and other physiological parameters or lifestyles (Miller et al., 2015). Furthermore, patients also show great day to day variability. All these effects combined originate a necessity to develop methodologies to tune and keep AP systems tuned.

During the ClosedLoop4Meals project we detected that the insulin on board (IOB) limit was a fundamental control parameter in our AP approach. Conservative IOB limits would lead to higher median BG levels, but in return, the system would become extremely robust against hypoglycemia occurrence. Contrarily, higher and more aggressive IOB limits would lower BG levels at the cost of having a higher hypoglycemia risk. These findings were specifically crucial during the PP of the conducted clinical trial. In these periods there is a trade off between PP peak and late PP hypoglycemia.

We started in-silico experiments with an adult cohort of 10 patients. The insulin controller was carefully tuned by trial and error for each of the patients under challenging scenarios to achieve satisfactory results. Afterwards we included variations on the IOB limits, with the goal to mimic a misadjusted controller. The results confirmed that the performance decreased significantly, and that a proper method for tuning the controller was needed.

To improve the tuning of the controller we decided to use an adaptive system based on fuzzy logic. Fuzzy systems allowed us to include general concepts provided by expert endocrinologists

into the system. After running the system in-silico we observed how the misadjusted IOB limits converged to the tuned ones and improved the performance results. Because of that, we also included the proportional controller gain into the adaptation strategy. These experiments confirmed that our AP system tuning was key for its success.

Even though the system was only tested in-silico with a small cohort, it showed that proper methodologies for tuning AP systems are needed. However, it should be noted that the scenarios were specifically designed with the ClosedLoop4Meals clinical protocol. As an inpatient clinical trial in a well controlled environment, the scenarios may not fully capture free living conditions. Because of that, there is a possibility that the adaptation strategy will need to be upgraded with newer rules and fuzzy sets.

Other adaptive strategies have been proposed in the literature to tune parts of AP systems. The most widely used is the so-called run-to-run approach (Magni et al., 2009; Toffanin et al., 2017), while others use more traditional adaptive control strategies (Turksoy et al., 2013). However, the uncertainty of how current AP systems are tuned and are kept tuned is still present in the literature. More data will become available as more systems enter the market. Then, data driven approaches may be the way towards proper initialization, tuning and monitoring of these systems (Kushner et al., 2018).

3.3 The Fault Detection and Patient Modes Classification

The performance and safety of AP systems are closely related. For many years, the research community invested resources in developing complex control algorithms without paying much attention on reliability and robustness of such systems. Given the fact that AP systems are being designed for humans, safety should be at the most important level of priority. However, the concepts of fault tolerant control or FD began to appear in the literature only around ten years ago.

The firsts works in FD were essentially oriented and designed for CGM devices. The CGM

technology allowed the development of AP systems in the first place. Therefore, efforts were made to ensure the development of CGM technology. The first FD and calibration algorithms started to be developed during the early 2000's (Lodwig and Heinemann, 2003; Facchinetti et al., 2007; Bequette, 2010), and after each new generation of CGM's new algorithms appeared (Andelin et al., 2016; Biagi et al., 2017; Vettoretti et al., 2019). In the same line, insulin pump faults such as pump obturations, reservoir leakages or overdosing issues were addressed (Herrero et al., 2012; Bequette, 2014).

None of the early works of this decade addressed the issue of having an automatic control system centered on people. We wanted to revisit the concept of having a person in the control loop, which in the case of diabetes resulted in the term patient-in-the-loop. In this line, the role of patients could be classified into two categories based on the implications on the system: situations in which the patient decisions have an impact on the system while it keeps running and situations in which the system must be interrupted. Some issues that may raise from the first category are related to meal or exercise announcements, carbohydrate misestimations or CGM calibrations. All of these actions can be done during CL operation and could compromise the system performance. In this thesis, we address some of these issues by providing a way to detect patient modes. The second category includes actions that may require an interruption of CL operation such as a battery replacement. Clearly, patients will have to wear and use these systems in their day to day life and maintenance of the system will be carried out by them. Therefore, not only the patients are the plant to control, but they also take the role of the operator of the control system. Safety strategies when the system is interrupted must be developed further for a fully fault safe AP.

The works described in (Beneyto et al., 2018; Bertachi, Beneyto, Ramkissoon and Vehi, 2018; Viñals et al., 2020) use a hybrid AP system in which the patient plays fundamental roles. On one hand, the patient is the plant to control. On the other hand, the patient is required to perform actions such as announce meals or exercise or consume rescue CHO. Because of

that, we proposed a FD of patient modes that could be used to monitor the patient state, i.e. monitoring the plant, and that allows the detection of potential actuator faults, i.e. faults related to patient actions such as meal misestimations.

During the research stay at the Rensselaer Polytechnic Institute, we started to investigate the use of multiple models in the context of state observers. Most of the available models in the literature are compartmental and described by a set of nonlinear differential equations. We decided to investigate the use of the Hovorka model, an intermediate complexity model with nine states. The model was able to capture many of the nonlinear behavior of T1D patients, without incorporating excessive complexity in its differential equations.

The detection of patient modes and patient-in-the-loop faults was done by generating residuals and analyzing their consistency at every sampling time. To achieve that, we started investigating observer structures for the Hovorka model. The firstly explored observers where based on the traditional Kalman filter. Particularly, we investigated the performance of the extended and unscented Kalman filters. However, we soon realized that the Hovorka model had observability issues. The observer design step considered a single measurable signal, the BG levels, and a single input signal, the insulin infusion. This resulted in observer designs with extraordinary small gains, making the observer system work as a pure simulator. The model presented several differential equations that were increasing the system complexity and that could be easily removed without losing much of the essential dynamics of the glucose subsystem compartments. Because of that, we reduced the Hovorka model and decided to use the LPV paradigm to allow us the implementation of traditional linear control theory.

The foundation of the LPV Hovorka model was the bounding box approach. This allowed the use of a finite set of models defined at the vertices of a designed polytope. The observability issues were removed by checking and ensuring that the rank of the observability matrix of those systems was of full rank. The traditional linear Kalman filter was then used for state estimation. To do so, we used linear matrix inequalities to design the different observer gains for the vertex

systems in a way that ensured all the interior points of the polytope were included.

For patient-in-the-loop FD we needed to have residuals that were discriminant. The residuals were generated by transforming the observers into interval observers by considering the propagation of uncertainty. Then, the consistency of the generated interval observers was checked at every sampling time. If an interval residual did not include zero within its upper and lower boundaries a binary signal was triggered. With this approach, we could tell in a robust way that the model used for each of the particular observers was not valid anymore.

The bank of observers alone was not able to characterize patient-in-the-loop faults. To do so, we designed a hybrid automaton that tries to mimic a real patient. The automaton included several normal and faulty operational modes. Each of the modes was basically detected by checking on the validity of each of the residuals. Transitions between different modes were triggered by analyzing the residuals and patient inputs. Then, transition events meant a change of patient operational mode and/or patient-in-the-loop faults. After experimenting with the system we obtained reliable transitions between modes. The results are, as far as the authors are concerned, one of the first systems designed specifically to address the patient-in-the-loop problem.

The developed system can easily be upgraded and was designed to be expandable. Additional patient-in-the-loop modes and faults can be considered by adding appropriate modes and transitions into the automaton. Also, the bank of observers can be expanded and the use of additional models can be considered. In theory, any method that generates a set of robust residual signals could be used as a complement for the bank of observers.

Finally, the system has been designed to work with AP systems. However, it can be used in any OL treatment as well. There are many future possibilities for this system, including its testing with traditional MDI therapy.

CHAPTER 4

CONCLUSIONS

This thesis has contributed in developing tools required for the next generation of AP systems. A new approach to control T1D, which include insulin and CHO as control actions, has been proposed and validated in a clinical trial. Furthermore, an algorithm for online tuning of an AP has been proposed. This thesis has also contributed in advancing the state of the art in the patient-in-the-loop paradigm by providing a novel patient mode detection.

4.1 Contributions

The mentioned contributions can be detailed further into more particular ones that have been achieved during the development of the thesis:

- **Controller tuning methodology.** We have proposed a fuzzy strategy to tune and keep an AP system tuned during PP periods. The system uses available metric information collected online for assessing the performance of the control system, and retuning is performed depending on a set of rules developed by engineers and clinicians. It

is an expandable approach that can be used with other AP systems and that directly incorporates the expertise of physicians into the tuning of a controller.

- **New control action.** This work has also introduced a new controller action to the AP systems. CHO were previously used to treat hypoglycemia as a last resource, but never as an active asset. We proposed to incorporate rescue CHO as a secondary control action inside a multivariable controller that also uses insulin.

- **Carbohydrates On Board.** The concept of COB has been used in this work as a key component when using CHO as a control action.

- **Robustness against meals and exercise.** The developed tools were designed to be robust and safe during PP periods and during and after aerobic exercise sessions. By using the proposed approaches the time in hyperglycemia and hypoglycemia levels is decreased when compared to standard up to date treatments.

- **Patient-in-the-loop.** The thesis has contributed in emphasizing the patient-in-the-loop paradigm within AP systems. The concept of patient modes is introduced and a system to detect mode changes is developed and tested. Having a patient monitoring system is an advantage for AP systems. Not only hybrid AP systems can benefit from this, but also fully CL systems could use it to increase performance and safety.

- **Multiple models approach.** The proposed methodology for patient-in-the-loop FD is deeply rooted on using multiple models. Each of the models is used for the detection of specific operational modes. By using multiple models we can characterize the complex dynamics of a T1D patient in a simpler yet robust way.

- **Observer based fault detection.** In this work we have used a bank of interval Kalman observers. The generated residuals showed that they can be used to detect patient modes and faults. However, because of the limitations of AP systems, observer based systems may have issues when trying to perform a full state estimation.

- **Adaptability and expandability.** The design of the tools and algorithms have been done with the goal of usability in mind. All of the systems are easily expandable to include new tools. Also, all of them can be easily adapted to work with other AP systems.

- **Java Artificial Pancreas.** The jAP system has been developed by our consortium by members of the MEDERI laboratory. The controller presented in this work has been implemented in Java and is the first to be used with such platform. To our knowledge, the jAP system is one of the few academic systems in the world and the clinical trial showed its future potential.

- **Extensive validation.** The proposed tools and algorithms have been extensively validated. In-silico simulations using the FDA approved simulator with challenging scenarios were done. Furthermore, a complete clinical trial was also performed with a cohort of 10 adults with T1D.

- Additional contributions of this thesis by working together with other people from MICELAB also include a feed-forward controller for exercise, an adaptation algorithm for IOB constraints and a system for the detection of unannounced aerobic exercise.

4.2 Future Work

The results presented in this thesis are promising and provide hope for T1D patients. Tools to help improve their day to day quality of life were developed and designed for the future AP. However, additional research is needed to further improve the control and patient monitoring, specially in free living conditions. This section discusses potential future pathways that can be developed from the bases of this work.

The fuzzy tuning controller algorithm during PP periods has been shown to be effective. However, the system had several limitations that should be solved in future steps. The first limitation was originated by the scenarios used. We implemented the same scenarios that were

used to validate the controller during the ClosedLoop4Meals project. Therefore, the generated scenarios included only single meals per day. This allowed for better characterization of PP periods without mixed effects from previous meals. The second limitation lies on the fuzzy system. The developed system was a proof of concept strategy that included only triangular or trapezoidal membership functions with a relatively small set of rules. It is expected that the use of more challenging scenarios will also require more complex membership functions and a bigger rule database.

The multivariable controller was developed on top of a previous validated insulin controller. Although it has been designed to work with our insulin controller, the system can also be used by any other single-hormone algorithm. It would be interesting to test other insulin control strategies with the proposed CHO controller with the COB concept at its core.

The conducted clinical trial was promising and suggests that aerobic exercise can be done by patients with T1D if they follow the controller's recommendations. However, the study had some limitations. The biggest limitation was that the experiment was performed in the clinic in a highly controlled environment. This might have minimized patient-in-the-loop behaviors and reduced interactions between the patient and the system. The next step is to conduct a clinical trial in free living conditions using the jAP system.

The patient mode FD system is a first step to automatically monitor the patient. Although it has been used in the context of AP systems, the system can also be used for OL approaches such as MDI. The system can be easily upgraded by adding more observers into the bank, which can use any of the available models in the literature. The hybrid automaton can also be personalized and new operational modes can be added depending on the patient lifestyle. The biggest limitation of the approach is that it was only validated in-silico where patient-in-the-loop behaviors might not match completely real life behaviors. Therefore, a next step would be to implement the system inside the jAP and conduct a clinical trial under free living conditions with both OL and CL approaches.

APPENDIX A

RESULTS OF THE MSAFE-AP CLINICAL TRIAL

In this publication, we present the clinical results obtained in our inpatient study. The control algorithm used for this study is an improved version of the original multivariable controller. The controller is implemented in Java and embedded in a mobile platform for Android, the jAP system. Appendix B includes additional controller documentation. The candidate's contribution for this publication consisted in the conception, design, implementation, testing and validation of all control strategies, performed the statistical analysis, analyzed and interpreted the data, contributing to discussion and writing and editing the manuscript throughout the review rounds. During the development of the work, the candidate worked with Clara Viñals, Arthur Bertachi, Juan-Fernando Martín-SanJosé and Clara Furió-Novejarque. They were assisted by Dr. Marga Giménez, Dr. Ignacio Conget, Dr. Jorge Bondia and Dr. Josep Vehí who conceived and designed the experiments, contributed to discussion and reviewed the manuscript.

Title: Artificial pancreas with carbohydrate suggestion performance for unannounced and announced exercise in type 1 diabetes

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Artificial pancreas with carbohydrate suggestion performance for unannounced and announced exercise in Type 1 Diabetes

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OBJECTIVE—To evaluate the safety and performance of a new multivariable closed-loop glucose controller with automatic carbohydrate suggestion (MCL) during and after unannounced and announced exercise in adults with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS—A randomized, three-arm, crossover clinical trial was conducted. Participants completed a heavy aerobic exercise session including three 15-min sets on a cycle-ergometer with 5 minutes rest in-between. In a randomly determined order, we compared MCL control with unannounced (CLNA) and announced (CLA) exercise to open-loop therapy (OL). Adults with T1D, insulin pump users and HbA_{1c} between 6.0-8.5% were eligible. We investigated glucose control during and 3 hours after exercise.

RESULTS—Ten subjects (40.8±7.0 years-old; an HbA_{1c} of 7.3±0.8%) participated. The use of the MCL in both closed-loop arms decreased the time <70 mg/dl of sensor glucose (0.0%,[0.0-16.8] and 0.0%,[0.0-19.2] vs. 16.2%,[0.0-26.0], (%,[Percentile 10-90]) CLNA, CLA and OL respectively, p=0.047, p=0.063) and the number of hypoglycemic events when compared to OL (CLNA 4 and CLA 3 vs. OL 8; p=0.218, p=0.250). The use of MCL system increased the proportion of time within 70-180 mg/dl (87.8%,[51.1-100] and 91.9%,[58.7-100] vs. 81.1%,[65.4-87.0], (%,[Percentile 10-90]) CLNA, CLA and OL respectively, p=0.227, p=0.039). This was achieved with the administration of similar doses of insulin and less amount of carbohydrates.

CONCLUSIONS—MCL with automatic carbohydrate suggestion performed well and was safe during and after both unannounced and announced exercise maintaining glucose mostly within the target range and reducing the risk of hypoglycemia despite of less amount of carbohydrate intake.

INTRODUCTION

Physical exercise has been shown to improve glycemic control and general wellbeing for people with type 1 diabetes. However, despite growing evidence about the health benefits of regular exercise in diabetes, exercise-associated glycemic imbalance remains a challenge in subjects with type 1 diabetes (1–4). Guidelines for exercise management exist for type 1 diabetes (T1D) subjects, which commonly include recommendations for carbohydrate consumption and basal insulin adjustment (1). Nonetheless, the current exercise strategies remain a burden for most patients in daily life conditions and require high engagement and further individualization (5).

Closed-loop (CL) or artificial pancreas (AP) systems with automatic insulin infusion in response to a continuous glucose monitor (CGM) signal are safe and efficient in free-living conditions (6–8). However, physical exercise is one of the main disturbances that challenge these devices due to rapid changes in insulin sensitivity, limitations in the subcutaneous route, and the lag time and accuracy of glucose sensing in the subcutaneous space (9,10).

Recently, Tagougui et al. (11) reviewed the studies that have examined the performance of AP systems in response to exercise. Several approaches have been used to maintain optimal glycemic control during exercise, such as the use of glucagon, heart rate to automate exercise detection, additional variables to improve glucose predictions, pre-exercise snacks, and a combination of these strategies. Overall, these studies have demonstrated that AP systems are able to maintain glycemic control while reducing the occurrence of hypoglycemia. However, supplemental carbohydrates (CHO) consumption is still required before, during, and/or after exercise to reduce the occurrence of hypoglycemia. Despite the use of different strategies,

there is no clear consensus as to which has the most effective effects on glucose control as results are difficult to compare due to the variations in AP systems, duration of use, exercise protocol, carbohydrate quantities, and outcomes reported.

The SAFE-AP system is a single-hormone hybrid closed-loop (HCL) controller that includes carbohydrates recommendations as an additional control input. It is based on a proportional-derivative (PD) with insulin feedback (IFB) controller that integrates a safety layer with insulin-on-board (IOB) constraints and sliding mode reference conditioning (SMRC) (12–15). The HCL system includes a second feedback loop with a controller that triggers carbohydrates suggestions to the patient (16). Both control loops are coordinated to ensure that the counter-regulatory effect of rescue carbohydrates is not counteracted with insulin. Additionally, if physical activity is announced, the system can also take feed-forward actions to further prevent hypoglycemia (17,18). Mitigation modules to improve safety and performance of the overall system were also used (17,19).

The objective of this study was to evaluate the safety and performance of this new multivariable single-hormone HCL control system with carbohydrate suggestion (MCL) under challenging unannounced and announced exercise in patients with T1D.

RESEARCH DESIGN AND METHODS

Study design and participants

This open-label, randomized, three-arm, crossover, in-hospital clinical trial was conducted at the Hospital Clínic de Barcelona, Spain. The study was performed in compliance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The study was approved by the local Ethics Committee and all subjects gave informed consent. The study is listed on clinicaltrials.gov under the registration number NCT03577158.

The inclusion criteria were: age 18 – 65 years (inclusive), clinical diagnosis of T1D for at least 1 year, HbA_{1c} between 6.0% and 8.5%, on continuous subcutaneous insulin infusion (CSII) for at least 6 months, BMI within 18-30 kg/m^2, and without advanced chronic micro- and macrovascular complications. Subjects with prior history in the last 6 months of at least one episode of severe hypoglycemia, diabetes ketoacidosis requiring hospitalization with hypoglycemia unawareness assessed using a validated questionnaire (20), or who were pregnant or breastfeeding were excluded.

Patients were instructed to wear a CGM device during a 6-day period before the first exercise test. Data from CGM was used to optimize the following parameters: insulin to carbohydrates ratio, sensitivity factor, basal insulin needs. These parameters were used to optimize the overall home blood glucose control (21,22), after which the controller was tuned. Initial IOB during each trial was also estimated from CGM data for the controller initialization.

Randomization and masking

Participants were randomly assigned (1:1:1) to perform physical exercise on three different sequences: MCL with unannounced exercise (CLNA), MCL with announced exercise (CLA), and open-loop (OL) with announced exercise, (sensor augmented pump therapy). There was a

wash-out period of at least 1 week between studies. Each subject underwent an in-hospital standardized physical exercise protocol on three occasions. Participants and investigators analyzing this study data were not masked to treatment.

Procedures

The screening visit included informed consent acquisition, a detailed physical examination, confirmation of the inclusion/exclusion criteria, an EKG, a safety clinical laboratory analysis, and an HbA_{1c} measurement. In women of childbearing age, a urine test for pregnancy was also performed. Participants also answered the short version of the International Physical Activity Questionnaire (23). Participants were randomized into the three sequences and CGM training was given. During three separate in-hospital visits, participants arrived at the investigational clinical site at 8:00h in the morning after having a standardized breakfast of 50g of carbohydrates at home. Although patients received instructions on breakfast protocol, compliance was not checked. At 8:30h the MCL controller was initialized in the closed-loop sequences. The exercise protocol started at 12:00h (t = 0) and consisted of three 15-minute sets on a cycle ergometer (Wattbike Pro, Wattbike Ltd., UK) at 70% of maximum heart rate with 5 minutes of rest between sets. Participants were in MCL or OL until 15:00h (t = 180 minutes). Patients wore a heart rate monitor (Polar RCX3®, Kempele, Findland) to ensure the desired exercise intensity, calculated as:

$$HR_{exercise} = HR_{rest} + \frac{70(HR_{max} - HR_{rest})}{100}$$

where $HR_{exercise}$ is the heart rate (bpm) during the physical activity period, HR_{max} is the maximum heart rate (bpm), and HR_{rest} is the rest heart rate (bpm).

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Exercise announcement (11:40h) was confirmed 20 minutes prior to the start of the activity (12:00h) in both the OL and CLA studies. The OL study used a temporal basal rate of 0% until the completion of the exercise protocol and followed recommended glucose management strategies considering blood glucose concentration before exercise commencement (1). The CLA system initiated the exercise mode (17) upon confirmation of exercise by the user.

Devices and assays

The MCL system was based on a glucose controller (12,15–17,19) built in an Android platform designed for investigational purposes (jAP). The jAP is a configurable and scalable platform in which different AP architectures can be used (unihormonal/bihormonal, with or without additional sensors, selection of different types of controllers). The platform also includes all necessary tools for the correct monitoring and visualization of the user's data, as well as different permission levels for the adjustment of the therapy.

The system was installed in a Samsung S7 (4 GB RAM, 32GB memory) smartphone with Android® 7.0 (kernel 3.18.14-12365438) including only the preinstalled and jAP applications. The smartphone was wirelessly connected to both the insulin pump and CGM using Bluetooth technology. The jAP platform retrieved glucose/insulin data from both the insulin pump and CGM and set insulin treatment according to the selected therapy of either OL or MCL. A backup Asus ZenBook (i7-7500U @ 2.70GHz, 16 GB RAM, Windows 10 Home v18362.418) laptop was prepared for troubleshooting issues and connection errors.

All participants used the same CSII set (Dana Diabecare R, Sooil, Seoul, Korea), CGM (Dexcom G5, Dexcom, San Diego, CA, United States), and glucose meter (Contour Link Meter 2.4, Ascensia Health Care, Basel, Switzerland).

The MCL, which received glucose measurements from one CGM device every 5 minutes, calculated two control actions: insulin delivery and a fast-acting carbohydrate intake suggestion. Calculated insulin was delivered automatically by changing the basal rate of the insulin pump during the next time interval. The control software had two main elements: (1) a multivariable closed-loop control algorithm based on the CGM measurement that computes the insulin infusion and a suggestion of carbohydrate intake (if necessary) every 5 minutes and (2) an exercise mitigation module that triggers feed-forward actions for better glycemic control when exercise is announced. When necessary, suggestions of carbohydrate intake by the controller are given as a predefined amount of fast-acting carbohydrates (15 g). When exercise is announced, the controller may suggest additional pre-exercise carbohydrates that were quantized in multiples of 5 g. This was a manual action performed by the patient.

The MCL system was designed, tuned, and validated using Matlab (R2017a, MathWorks, Natick, MA, USA) (12,15–17,19). The CLNA and CLA version of the controller were implemented in Java 1.8 for their integration within the jAP platform. The MCL system requires insulin, meals, and glucose data from the previous 5 hours to correctly initialize its integrated components.

The time window from the computation of the current control action to the next available measurement was used, among other things, to upload data to a server used as a remote monitoring tool. A web application allowed the authorized users to remotely monitor the status

of the patient in each trial. Data like CGM, infused insulin, IOB and other useful controller parameters were presented in timed graphics in order to follow the whole trial in real time.

Safety monitoring

Arterialized reference blood glucose samples (Yellow Spring Instruments (YSI); YSI 2300 STAT Plus, YSI Inc. Life Sciences, Yellow Springs, OH) were collected every 15 minutes before exercise and during recovery and every 10 minutes during exercise. If any glucose value reading was below 70 mg/dl and the patient showed symptoms of hypoglycemia, 15 g of glucose were provided (Diabalance® gel).

Endpoints

Primary endpoints were the percentage of time < 70 mg/dl of sensor glucose, as well as, the number of hypoglycemic events (plasma glucose < 70 mg/dl) during exercise and recovery (180 minutes). Hypoglycemic events were classified as L1 events if plasma glucose was <70 mg/dl for at least 15 minutes and L2 if it was <54 mg/dl for at least 15 minutes (24).

The secondary outcomes were the following: (1) percentage of time spent in 70-180 mg/dl and >180 mg/dl during exercise and recovery; (2) coefficient of variation (CV) of CGM values during and after exercise (3) total insulin and carbohydrates during, after exercise and on the exercise announcement event.

All study endpoints used are in line with the up to date recommended outcome measures (24,25). CGM sensor values and control action variables analysis during the exercise and recovery periods were also recorded.

Statistical analysis

Due to the exploratory nature of this study, sample size calculations were not formally performed. Comparisons between all three arms (CLNA vs CLA, CLNA vs OL, and CLA vs OL) were performed using the paired nonparametric Wilcoxon signed rank test (MATLAB R2019a, MathWorks, Natick, MA, USA). Descriptive statistics, including the mean, standard deviation (SD), median, 10 - 90 percentile range, coefficient of variation (CV), and interquartile range (IQR) were also computed to describe the sample characteristics. Missing values from the original CGM signal were linearly interpolated for the computation of secondary outcomes.

RESULTS

The baseline characteristics of the cohort are reported in Table 1. All 10 patients completed the study. During the exercise protocol, CGM data were available 93.33% of the time. One patient had an available CGM time below 60% during the OL trial due to constant disconnection of the CGM sensor and therefore, the patient was excluded from the CGM outcomes and from the CLNA vs OL and CLA vs OL comparisons.

The glycemic outcomes were calculated using the glucose readings from the YSI and CGM during the exercise and recovery periods, which resulted in a total of 180 minutes of data for each trial (Tables 2 and 3). The heavy aerobic physical activity generally provoked large and rapid glucose drops as shown in Figure 1.

During this study, a total of 15 hypoglycemic events were recorded by the YSI (4 for the CLNA arm, 3 for the CLA arm and 8 for the OL arm) as reported in Table 2. Participants received supplemental carbohydrates, either as a feed-forward action or as suggestion by the controller on the CLNA/CLA arms and also, following recommended glucose management strategies in the OL arm (1). The CLNA and CLA systems decreased the proportion of time spent in the hypoglycemic ranges (< 70 mg/dl) with values of 0.0% (0.0% – 16.8%) and 0.0% (0.0% - 19.2%) compared to 16.2% (0.0% - 26.0%) for the OL system (Table 2).

The median (10 - 90 percentile ranges) proportion of time spent in range (70-180 mg/dl) for the exercise and recovery period based on CGM sensor was 87.8% (51.1% – 100%) for CLNA, 91.9% (58.7% – 100%) for CLA, and 81.1% (65.4% – 87.0%) for OL. The overall descriptive statistics were more favorable for the CLNA and CLA arms compared to OL, mainly the system achieved tighter control in terms of glucose variability during and after exercise (CV 26.4 mg/dl (22.1 – 46.9), 21.5 mg/dl (13.1 – 55.8), and 49.1 (16.4 – 79.4) for CLNA, CLA, and OL, respectively). CGM values and estimated IOB at the beginning of the physical activity were comparable in all three arms (Table 3).

The improvement of the overall glucose during both CL arms was achieved with a trend to lower amount of carbohydrates when compared to OL, 15.0 g (0.0 – 31.5) for CLNA, 22.5 g (15.0 – 40.5) for CLA, and 32.5 g (0.0 – 40.0) for OL, while infusing similar amounts of insulin in all three arms, see Table 3.

There were no serious adverse events, the full CL period was completed for all subjects, and in no instances was the stopping criteria met. For the entire study period, there were 0

hyperglycemic events involving PG >250 mg/dl. Due to signs and symptoms of hypoglycemia there were two instances that for medical criteria the investigational team gave carbohydrate rescues to the participants before the carbohydrate were suggested by the controller.

DISCUSSION

The results of this study show that the use of the new multivariable single-hormone HCL control system with carbohydrate suggestion is effective and safe in maintaining blood glucose within target values during and after unannounced and announced heavy physical activity. To our knowledge, this is one of the few randomized controlled trials that has compared the performance of a CL controller for unannounced and announced exercise and sensor augmented pump therapy.

Other studies have incorporated bi-hormonal control strategies with glucagon to cope with exercise (26–29). In our case, the glucagon counter-regulatory action is substituted by the suggestion of carbohydrate consumption given by the controller. There are other approaches using an AP system and carbohydrates to compensate the exercise effect (30,31). These strategies mostly consist on ad-hoc modules that encourage the patient to eat rescue carbohydrates in case a hypoglycemic event is predicted. Most common strategies in AP clinical trials involving exercise only use rescue carbohydrates as a reactive action when glucose is below a given threshold for safety, e.g. <70 mg/dl, such as (29,32). A key difference from other AP systems is that the investigated algorithm, MCL, incorporates a specific CL control strategy not only for insulin delivery, but also for suggesting carbohydrates as an additional control

action. By incorporating the carbohydrates as a new control action, this multivariable algorithm intends to optimize the carbohydrate intake required to improve performance and guaranteeing safety. It is a fully multivariable controller with coordination between insulin and carbohydrate intake suggestion. Moreover, the CL controller used a static glucose set-point of 100 mg/dl to assess the ability of the controller to maintain tight glucose control during and after heavy aerobic exercise.

The number of hypoglycemic events in the MCL studies (4 in CLNA, 3 in CLA) is about half that of the OL studies (8 instances). The small sample size of this exploratory study and meticulous adherence to the in-hospital procedures for preventing hypoglycemia implemented by trained investigators prevented the demonstration of statistical significance. Additionally, the trial revealed that the CL strategies decreased the proportion of time spent in the hypoglycemic range (< 70 mg/dl), especially in the CLNA arm. The use MCL system maintained or increased the proportion of time spent within target glucose range with a significant improvement in glucose variability in both, CLNA and CLA arms. The improvement in glucose variability is far from negligible because it is associated to a higher risk of hypoglycemia in the upcoming hours (33).

At the same time, the controllers have reduced the control action efforts in terms of carbohydrate suggestions when compared to standard exercise recommendations in open loop (1). Particularly, the OL arm required twice the carbohydrates as the CLNA. In addition, the CL system was safe with a fixed set-point of 100 mg/dl, while other similar studies used increased set-points during exercise (24,34). Our results are in line with the study performed by Patel et al. (35), that showed in a CL study that using a snacking strategy could help decreasing the

exercise-induced hypoglycemia. Additionally, our approach required a lower quantity of CHO to reduce hypoglycemia.

In this study, 15 and 5-gram glucose gels were used, which were the only source of rescue carbohydrates provided to the subjects. One limitation of this study is that the carbohydrates taken as feed-forward actions 20 minutes before exercise may not have had a full impact on the exercise period due to the high glycemic index and rapid rate of absorption of the gels used. Additional research is required to study the impact of different carbohydrate sources as counteractive measures to physical activity in CL strategies.

Physical exercise has a profound impact on blood glucose control. Depending on the type and duration of the activity as well as the patient's state, blood glucose levels may be difficult to maintain within the target range (1). Numerous factors can alter the performance of HCL controllers, such as over-bolusing of previous meals, which is an event that can lead to high IOB levels at the beginning of physical exercise. We observed a steady decline in blood glucose and a comparable amount of active IOB across all arms during exercise periods. CLNA had a steeper decrease in blood glucose during exercise when compared to CLA and OL. The patient's IOB was postprandial (following the morning breakfast) and glucose was largely in the target range at the start of exercise, regardless of the treatment arm.

CL control could benefit from additional sources of information (e.g., heart rate or energy expenditure) and/or additional control actions such as the use of glucagon. Studies have shown that the use of glucagon may mitigate the risk of hypoglycemia (26–30,32,36). Regardless of the controller used, we observed that proper coordination with the different available control

actions is mandatory. The controller must be aware of control actions performed by the patient, i.e., the act of eating rescue carbohydrates should not be counteracted by the insulin control.

Our study has limitations. It was conducted in a well-controlled in-hospital environment. Free-living studies including more types and durations of physical activities are required in order to fully assess the performance and safety of the CL systems tested. The majority of the controller parameters were kept the same across all patients to generalize the tuning and make it as simple as possible. In free-living conditions, the control parameters should be further individualized to each specific subject and adapted to optimize performance and enhance safety. Due to the small duration and the exploratory nature of this study, it was not possible to address this issue. Since this study protocol ended at 15:00h, the study did not include the assessment of blood glucose levels during the night following exercise. Further investigation is needed to assess the ability of the CL therapy to deal with common exercise complications like overnight hyperglycemia rebound (37–39) or hypoglycemia due to increased insulin sensitivity in a longer post-exercise periods.

In conclusion, the present study demonstrated that both CLA and CLNA control systems performed well and were safe during and after exercise in adults with T1D performing heavy aerobic exercise compared to OL insulin delivery. The system was able to maintain tight glucose control reducing the risk of hypoglycemia despite of less amount of carbohydrate intake.

Finally, longer term outpatient studies are still required to further assess the safety and performance of the SAFE-AP system in free-living conditions.

AUTHOR CONTRIBUTIONS

C. V. performed and supervised all the experimental studies, analyzed and interpreted data and wrote the manuscript.

A. Beneyto conceived, designed, implemented, tested and validated all control strategies, performed the statistical analysis, analyzed and interpreted the data, and wrote the manuscript.

J.F. M. developed and validated the jAP platform, the remote monitoring site, the communication between devices. and revised the manuscript.

C. F. collaborated with the development of the CGM communication and graphical user interface, implemented a hardware-in-the-loop validation system and revised the manuscript.

A. Bertachi contributed to the development of the announced control strategy and revised the manuscript.

J. B. conceived and designed the study, designed and supervised implementation of the jAP system, contributed to the development of control strategies, interpreted data, obtained funding and critically revised the manuscript.

J. V. conceived and designed the control strategies, conceived and designed the study, interpreted data, obtained funding and critically revised the manuscript.

I. G. conceived and designed the study, supervised clinical studies, interpreted data, obtained funding and critically revised the manuscript.

M. G. conceived and designed the study, supervised clinical studies, interpreted data, obtained funding and critically revised the manuscript.

All authors contributed to the review of the report and approved the final version for submission. I.C and M.G are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline characteristics of the cohort. Data presented as Mean ± STD

Characteristic	All (n = 10)	Male (n = 7)	Female (n = 3)
Age (years)	40.8 ± 7.0	41.7 ± 6.9	38.7 ± 8.4
Diabetes onset (years)	24.9 ± 11.6	27.0 ± 10.7	20.0 ± 14.5
Duration using pump (years)	8.1 ± 4.1	7.6 ± 2.4	9.3 ± 7.4
HbA_{1c} (%)	7.3 ± 0.8	7.2 ± 0.9	7.4 ± 0.4
Weight (kg)	76.5 ± 10.7	80.6 ± 9.7	67.0 ± 6.3
Height (cm)	172.9 ± 7.7	176.0 ± 5.9	165.7 ± 6.8
Total Daily Infusion (U)	37.5 ± 5.9	39.1 ± 5.8	33.6 ± 4.7

Table 2. Primary endpoints of the study. Number of hypoglycemic events and the percentage of time < 70 mg/dl of sensor glucose

		CLNA	CLA	OL	p*	p†	p‡
Plasma Glucose (mg/dl)	54 - 70	2	2	4	1.000	0.500	0.688
	<54	2	1	4	1.000	0.625	0.250
	< 70	4	3	8	1.000	0.218	0.250
CGM Glucose (mg/dl)	% <70	0.0† (0.0–16.8)	0.0 (0.0–19.2)	16.2 (0.0–26.0)	1.000	0.047	0.063
	% <54	0.0 (0.0–0.0)	0.0 (0.0–8.4)	0.0 (0.0–6.0)	0.500	0.500	1.000

*P-value between CLNA-CLA. †P-value between CLNA-OL. ‡P-value between CLA-OL.

Data expressed as number or median (10^{th} - 90^{th} percentile ranges).

CGM: continuous glucose monitor.

Table 3. Secondary outcome measures, CGM values and control action variables during the exercise and recovery periods.

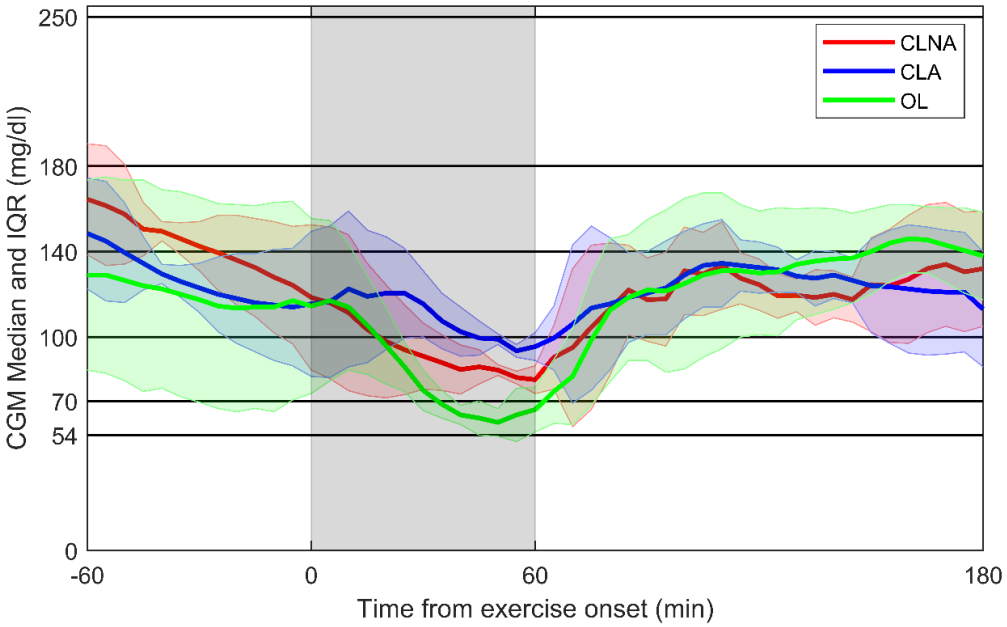
Variable	CLNA	CLA	OL	p*	p†	p‡
Mean Glucose (mg/dl)	120.5 (92.7 – 181.6)	127.1 (84.7 – 189.4)	119.6 (91.9 – 168.5)	0.922	1.000	0.910
Median Glucose (mg/dl)	106.5 (92.5 – 180.5)	119.0 (86.5 – 194.0)	130.0 (85.6 –170.4)	0.826	0.733	0.441
IQR, Glucose (mg/dl)	26.4 (22.1 – 46.9)	21.5‡ (13.1 – 55.8)	49.1 (16.4 – 79.4)	0.625	0.055	0.020
CV (%)	17.8† (9.4 – 31.2)	17.3‡ (10.7 – 25.3)	30.8 (8.5 – 37.4)	0.846	0.027	0.020
% of time						
>250 mg/dl	0.0 (0.0 – 0.74)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	1.000	1.000	1.000
>180 mg/dl	0.0 (0.0 – 48.9)	0.0 (0.0 – 41.4)	0.0 (0.0 – 15.1)	0.813	0.625	0.375
70-180 mg/dl	87.8 (51.1 – 100.0)	91.9‡ (58.7 – 100.0)	81.1 (65.4 – 87.0)	0.688	0.227	0.039
Glucose (mg/dl) at						
Exercise announcement	136.0 (115.8–200.5)	118.0 (98.4–146.4)	118.0 (67.4–209.4)	0.250	0.426	1.000
Exercise start	121.0 (98.4 – 190.4)	114.0 (95.5–141.0)	116.0 (71.0–169.8)	0.359	0.734	0.910
Estimated IOB (U) at						
Exercise announcement	2.9 (2.0 – 4.7)	2.6 (1.8 – 4.2)	2.6 (1.9 – 4.2)	0.846	0.922	0.770
Exercise start	2.4 (1.8 – 4.2)	2.2 (1.5 – 3.6)	2.3 (1.6 – 3.6)	0.695	0.922	0.557
Insulin (U) during						
Exercise	0.0 (0.0 – 0.2)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.1)	1.000	1.000	0.813
Recovery	1.9*, † (0.8 – 2.7)	1.3 (0.3 – 2.5)	1.2 (0.5 – 2.3)	0.020	0.020	0.625
Exercise + Recovery	2.0† (0.8 – 2.7)	1.3 (0.3 – 3.1)	1.3 (0.6 – 2.3)	0.492	0.049	0.695
Carbohydrates (g) during Exercise and recovery	15.0 (0.0 – 31.5)	22.5 (15.0 – 40.5)	32.5 (0.0 – 40.0)	0.148	0.219	0.880

*P-value between CLNA-CLA. †P-value between CLNA-OL. ‡P-value between CLA-OL.

Values expressed as Median (10^{th} - 90^{th} percentile ranges).

IQR, interquartile range; CV coefficient of variation; IOB: insulin on board.

Figure 1. CGM sensor values in Median (IQR) during closed-loop arms (blue, red) and open-loop (green). Exercise started at 12:00h (t = 0 on the x-axis) and finished 60 minutes later.



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APPENDIX B

ADDITIONAL MODULES FOR THE MULTIVARIABLE AP

This appendix presents two modules that were included within the AP system used for the mSAFE-AP clinical trial, which results are included in Appendix A of this thesis. These two modules are included in two publications were contributions from this thesis were used. The first module corresponds to a feed-forward controller to cope with exercise (Bertachi, Beneyto, Ramkissoon and Vehi, 2018). The second module includes an adaptive system for PP periods (Bertachi et al., 2020). Figure B.1 depicts the complete block diagram of the strategy, and outlines the additional included blocks. Red color distinguishes the exercise feed-forward controller blocks, and teal color the PP adaptive system.

B.1 Feed-forward Exercise Controller

The feed-forward exercise actions complement the control algorithm and provide extra safety for the patient when performing aerobic exercise at moderate to high intensity (Bertachi, Beneyto, Ramkissoon and Vehi, 2018). For these actions to take place, the patient must inform to the system that he or she is going to exercise. The patient will have to inform the starting

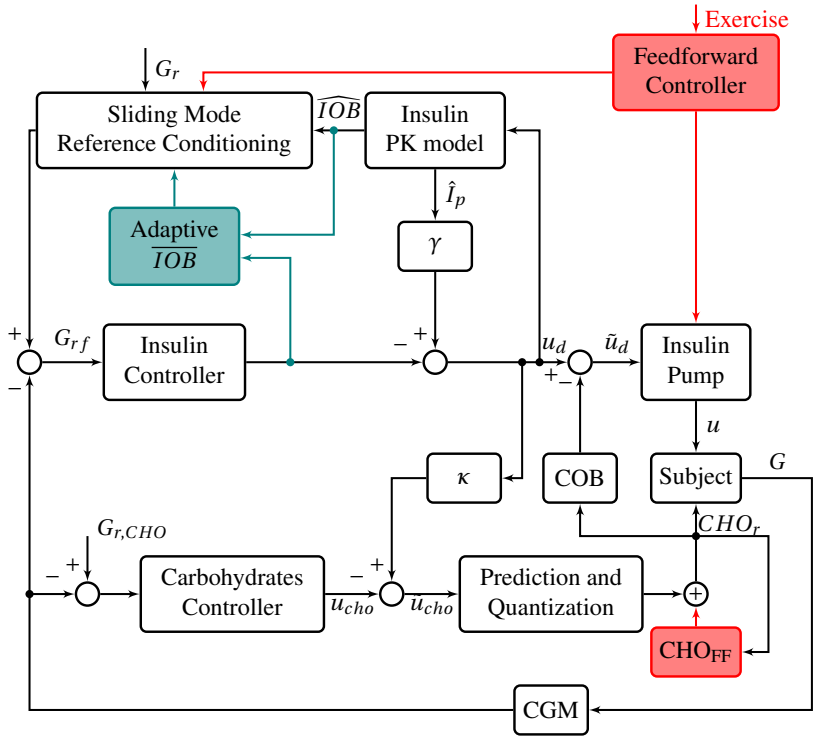

Figure B.1: Multivariable Hybrid Artificial Pancreas used in mSAFE-AP clinical trial.

time and duration of the exercise session. With the provided information, the feed-forward controller will actuate on top of the feedback insulin controller to decrease its aggressiveness during and after the exercise session. Particularly, two sets of actions are performed:

- Suggestion of CHO (CHO_{FF}) depending on the glycemic state and the estimated IOB at the start of the exercise session. At the beginning of the announced exercise session, the feed-forward controller may suggest fast acting CHO according to

$$CHO_{CGM} = \begin{cases} 20, & \text{if } CGM(t) \leq 90 \\ 10, & \text{if } 90 < CGM(t) \leq 124 \\ 0, & \text{otherwise} \end{cases}$$

$$CHO_{IOB} = \left(\widehat{IOB}(t) - \beta_{IOB} IOB_b(t)\right) CR$$

$$CHO_{FF} = 5\lfloor CHO_{CGM} + CHO_{IOB} - COB_2(t) \rceil, \text{ s.t. } CHO_{FF} \leq \frac{\max\left(0,\ \overline{CGM} - CGM(t)\right)}{K_{CHO}}$$

where CHO_{FF} are the final suggested CHO in grams, CHO_{CGM} are the CHO due to the glycemic level of the patient at the start of the exercise session in grams, CHO_{IOB} are the CHO due to the amount of IOB at the start of the exercise session in grams, COB_2 is the COB estimation due to previously given CHO by the feedback controller and may inhibit feed-forward CHO, CR is an individualized insulin-to-CHO ratio, $\overline{CGM}$ is the maximum allowed increase of BG due to CHO_{FF} consumption and is set to 250 mg/dl, β_{IOB} is a tuning gain set to 0.7 and the notation $5\lfloor\rceil$ indicates that CHO are rounded to the nearest 5 grams.

- Gain reduction of the insulin feedback controller to minimize the hypoglycemia risk during and after the exercise session due to an insulin sensitivity increase, see figure B.2.

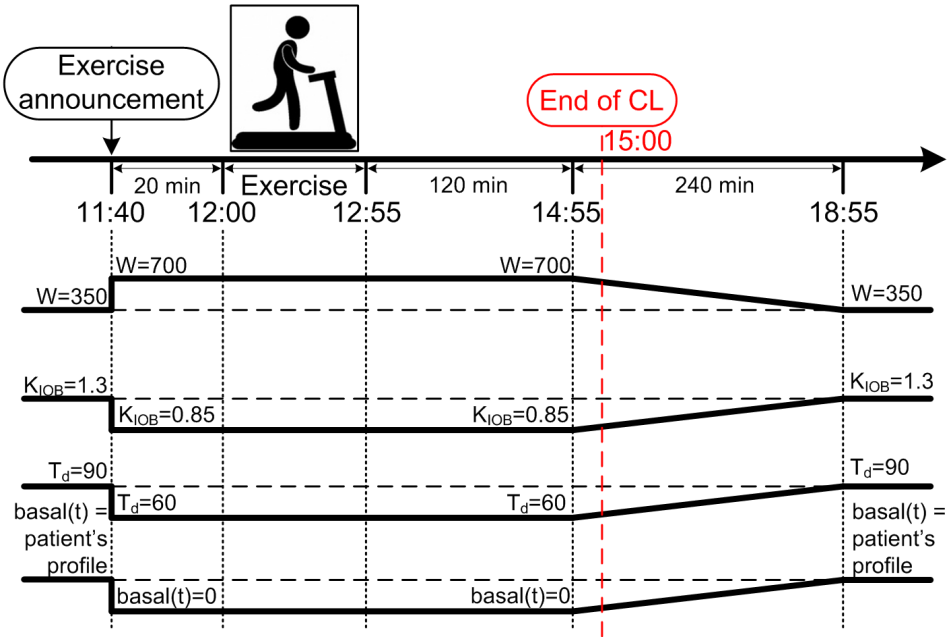

Figure B.2: Insulin controller modified parameters by the feed-forward exercise controller during the mSAFE-AP clinical trial.

The feed-forward adaptation is composed of three different stages. The first one includes a period of 20 minutes and the whole exercise period, the second one ($\Delta_1 = 120$ minutes) follows the ending of the exercise session, and the last stage ($\Delta_2 = 240$ minutes) follows Δ_1.

All the variables are modified using a step following the exercise announcement and are maintained until the end of the Δ_1 period. After that period, the variables are linearly returned to their original values during Δ_2. The adaptation objective is to minimize the risk of hypoglycemia, and thus reduce insulin infusion during exercise, without excessively compromising the system performance (Bertachi, Beneyto, Ramkissoon and Vehi, 2018; Bertachi et al., 2019).

One of the problems of using feed-forward control is that it relies on how accurately is known the effect of a given disturbance on the system, i.e., how accurately you know the disturbance model. Therefore, we included several escape conditions that allow the controller to return earlier to its original tuning. The following rules were used:

1. $CGM(k) > 140 \wedge C\dot{G}M(k) > 0,\ \forall k \in (k-2, \ldots, k)$
2. $C\dot{G}M(k) > 1 \wedge \tilde{u}_d(k) = 0,\ \forall k \in (k-2, \ldots, k)$
3. $C\dot{G}M(k) > 1.5 \wedge \tilde{u}_d(k) = 0,\ \forall k \in (k-1, \ldots, k)$

where $C\dot{G}M$ is the derivative of the CGM signal in mg/dl/min, $\tilde{u}_d$ is the insulin delivered in units/hour and k refers to the current sampling period. If any of the previously mentioned conditions is fulfilled during the Δ_1 period, then the system directly switches to Δ_2.

B.2 Postprandial IOB adaptation

The PP IOB adaptation (Bertachi et al., 2020) is activated after giving an insulin bolus due to a meal announcement. The natural trend of BG after a meal is to rise, and that rise is what we refer as a PP excursion. In the proposed PP strategy we use and augmented bolus, called super-bolus, with the SMRC module that minimizes the risk of PP hypoglycemia. This results

in a singular effect of ceasing, almost instantly, the insulin infusion after the super-bolus. What happens is that the super-bolus, which is given almost as an impulse input, makes the estimated $IOB(t) > \overline{IOB}(t)$ almost instantly. That is the reason why the insulin controller usually suppresses the insulin infusion after a bolus, even if the BG trend is positive. An example of this behavior can be seen in figure B.3.

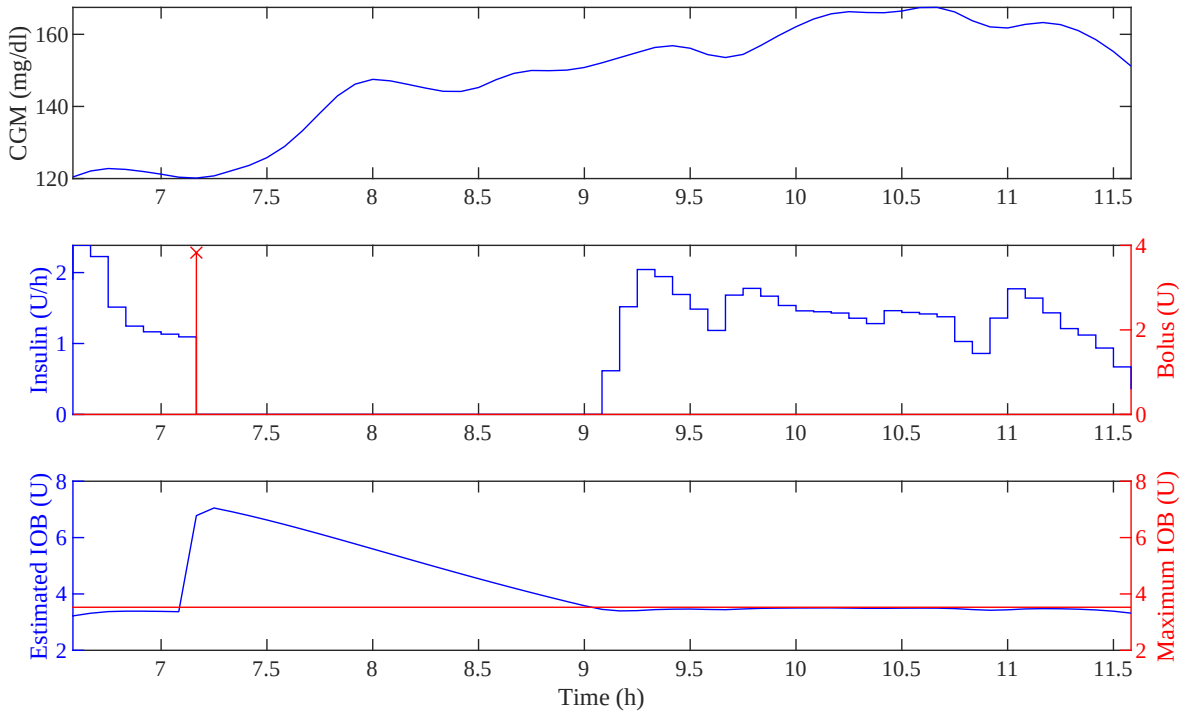

Figure B.3: Representative controller behavior during PP periods without adaptation. Following the super-bolus, the $\widehat{IOB}(t) > \overline{IOB}$. Thus, insulin infusion is zero for almost two hours until $\widehat{IOB}(t) < \overline{IOB}$. After resuming insulin infusion at around 9:00, the SMRC module still supresses insulin infusion due to how close $\widehat{IOB}(t)$ is to $\overline{IOB}$.

It is noticeable in figure B.3 that $\overline{IOB}(t)$ determines when the system can resume insulin infusion during PP periods. A conservative tuning of the SMRC module with a small $\overline{IOB}(t)$ would result in a slow, but safe, BG return to normoglycemia. On the other side, a more aggressive SMRC tuning would result in higher performance, but also a higher risk of hypoglycemia.

The PP IOB adaptation module is designed to adapt the $\overline{IOB}(t)$ during PP periods to allow

insulin infusion even after a super-bolus is given. This allows the system to give insulin even if $\widehat{IOB}(t) > \widehat{IOB}$, and thus improves the performance while maintaining robustness and safety. This module only uses CGM measurements and meal information (time and amount of grams of the meal). The strategy is executed as follows

1. When a meal is announced, compute the following time

$$T_{IOB} = 1.5 M_{CHO}$$

   where T_{IOB} is a time interval in minutes and M_{CHO} is the meal amount in grams.

2. After T_{IOB} minutes, iteratively do

   a) If $CGM(t) > \overline{CGM}$, update $\overline{IOB}(t) := \overline{IOB}_{PP}$ as follows

$$\overline{IOB}_{PP} = \max\left(\widehat{IOB}(k-1), \overline{IOB}_{bl}\right)$$

      where $\overline{IOB}_{PP}$ is the adapted maximum IOB in the PP period, $\overline{CGM}$ is the upper CGM threshold of 150 mg/dl, $\widehat{IOB}(k-1)$ is the estimated IOB in the previous sampling time and IOB_{bl} is the usual $\widehat{IOB}$. This ensures $\widehat{IOB} < \overline{IOB}_{PP}$ in the next time instants, thus allowing insulin infusion again.

   b) The $\overline{IOB}$ is kept at $\overline{IOB}_{PP}$ until $CGM < \underline{CGM}$, with $\underline{CGM} = 140$ mg/dl.

   c) Once $\overline{IOB}$ has returned to IOB_{bl}, the PP adaptation is deactivated.

3. There is no adaptation if $CGM < \underline{CGM}$ after T_{IOB}. However, the system keeps track if $CGM > \underline{CGM}$ so that the adaptation can be applied.

Figure B.4 shows the flowchart of the adaptation system. The variables *PP_state* and *flag_PP* refer to specific boolean variables from the code implementation. On the system initialization both variables are false. One one hand, *PP_state* keeps track if a meal has been consumed and that $\overline{IOB}$ can be adapted. On the other hand, *flag_PP* guarantees that the system only calculates one value for $\overline{IOB}_{PP}$. Figure B.5 shows an operation example with the adaptive PP system on.

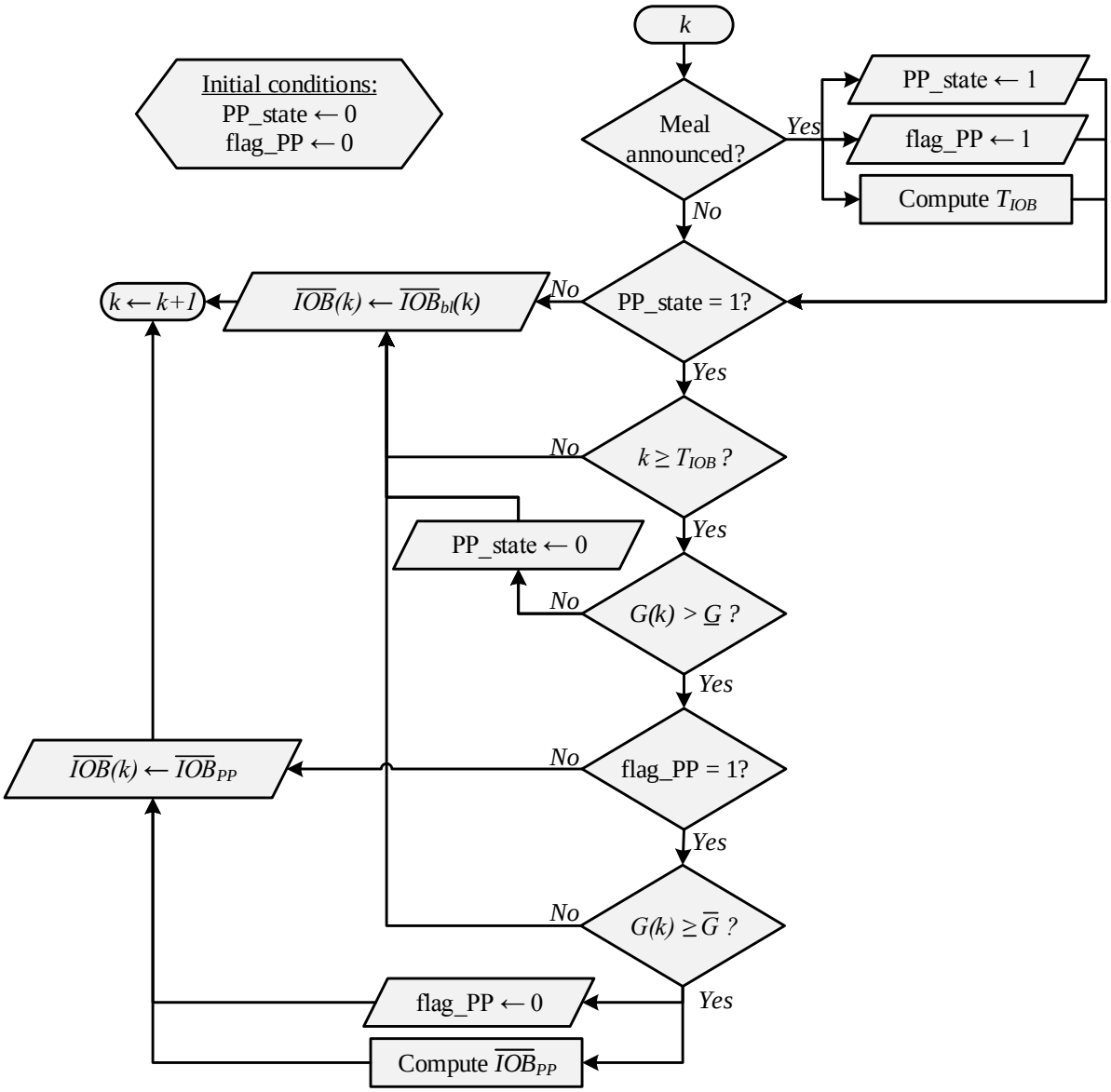

Figure B.4: Flowchart of the PP adaptive system for the $\overline{IOB}$

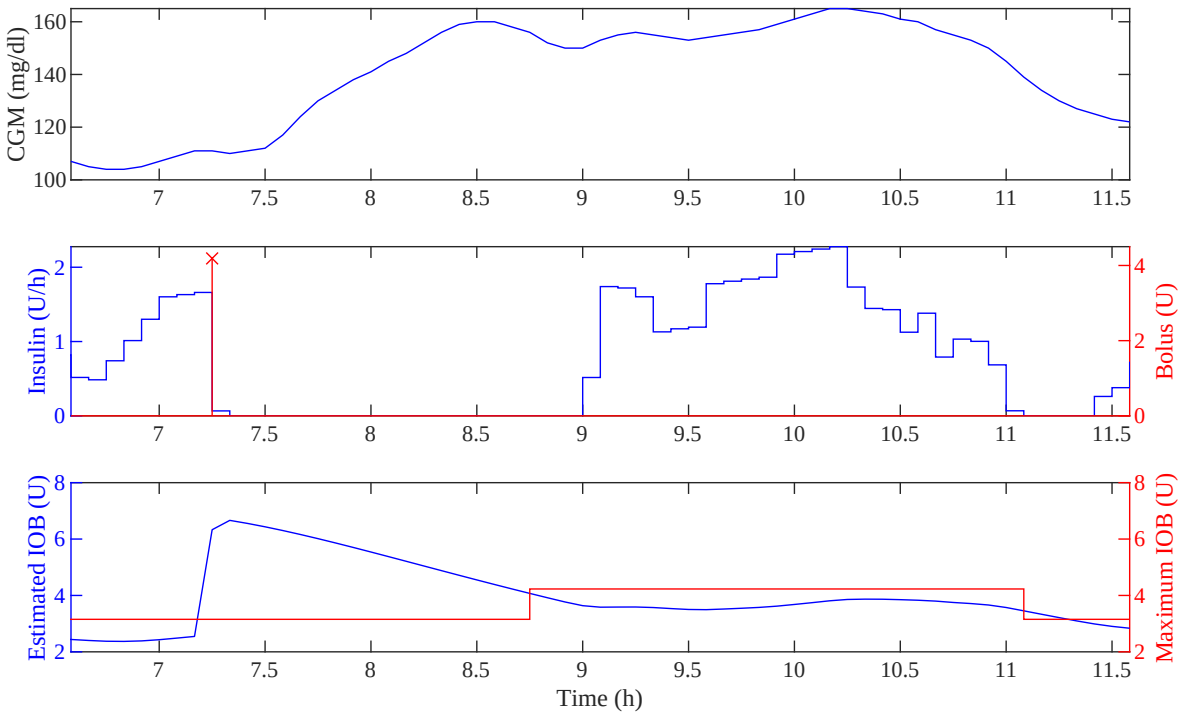

Figure B.5: Representative controller behavior during PP periods with adaptation. The $\overline{IOB}$ is adapted to a new $\overline{IOB}_{PP}$ between 8:45 and 11:05 approximately. This allows the controller to resume insulin infusion, and thus allowing all the infused insulin during 9:00 and 11:05.

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