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CONDITION ASSESSMENT OF PATIENTS WITH TYPE 1 DIABETES USING COMPOSITIONAL DATA ANALYSIS

Lyvia Biagi

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LYVIA REGINA BIAGI SILVA BERTACHI

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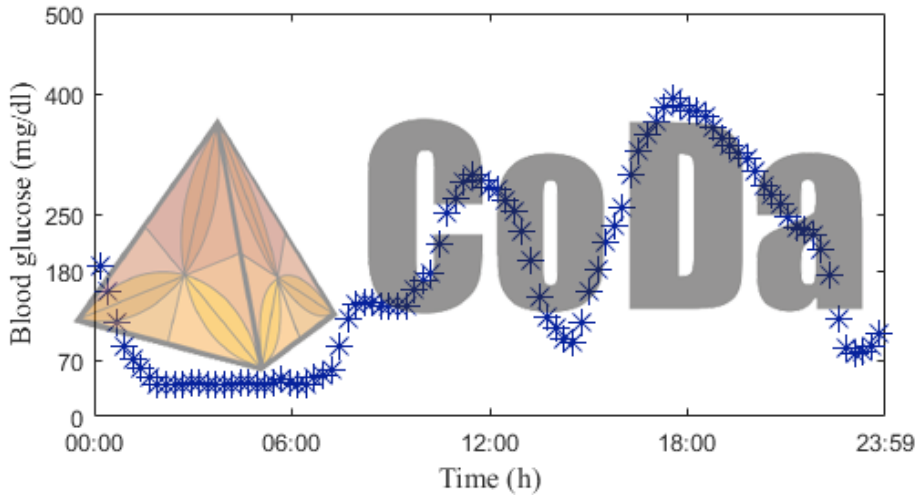

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2019

DOCTORAL PROGRAMME IN TECHNOLOGY

Supervised by: Josep Vehí Casellas and Josep Antoni Martín-Fernández

Presented in partial fulfillment of the requirements for a doctoral degree from the University of Girona

DOCTORAL THESIS

CONDITION ASSESSMENT OF PATIENTS WITH TYPE 1 DIABETES USING COMPOSITIONAL DATA ANALYSIS

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

By:

Lyvia Regina Biagi Silva Bertachi

Supervisors:

Josep Vehí

Josep Antoni Martín-Fernández

Dedicated to my beloved parents, Regina and Aylton,
my loving husband, Arthur, and
my lovely baby girl, Vivian.

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Lyvia Regina Biagi Silva Bertachi
Girona, Spain
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List of Publications

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

1. **Lyvia Biagi**, Charrise M. Ramkissoon, Andrea Facchinetti, Yenny Leal and Josep Vehí. Modeling the Error of the Medtronic Paradigm Veo Enlite Glucose Sensor, *Sensors*, 17(6): 1361, **2017** (Biagi et al., 2017c).

2. **Lyvia Biagi**, Arthur H. Bertachi, Ignacio Conget, Carmen Quirós, Marga Giménez, Javier F. Ampudia-Blasco, Paolo Rossetti, Jorge Bondia, and Josep Vehí. Extensive Assessment of Blood Glucose Monitoring During Postprandial Period and Its Impact on Closed-Loop Performance, *Journal of Diabetes Science and Technology*, 11(6):1089-1095, **2017** (Biagi et al., 2017b).

3. **Lyvia Biagi**, Arthur Bertachi, Carmen Quirós, Marga Giménez, Ignacio Conget, Jorge Bondia, and Josep Vehí. Accuracy of Continuous Glucose Monitoring before, during, and after Aerobic and Anaerobic Exercise in Patients with Type 1 Diabetes Mellitus, *Biosensors*, 8(1):22, **2018** (Biagi et al., 2018d).

4. **Lyvia Biagi**, Arthur Bertachi, Marga Giménez, Ignacio Conget, Jorge Bondia, Josep A. Martín-Fernández, and Josep Vehí. Individual Categorisation of Glucose Profiles Using Compositional Data Analysis, *Statistical Methods in Medical Research*, **2019** (Published on 2018 online ahead of print) (Biagi et al., 2018a).

5. **Lyvia Biagi**, Arthur Bertachi, Marga Giménez, Ignacio Conget, Jorge Bondia, Josep A. Martín-Fernández, and Josep Vehí. Probabilistic Model of Transition Between Categories of Glucose Profiles in Patients with Type 1 Diabetes Using a Compositional Data Analysis Approach, *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

6. Carmen Quirós, Arthur Bertachi, Marga Giménez, **Lyvia Biagi**, Judith Viaplana, Clara Viñals, Josep Vehí, Ignacio Conget, and Jorge Bondia. Control de la glucemia durante el ejercicio físico aeróbico y anaeróbico mediante un nuevo sistema de páncreas artificial, *Endocrinología, Diabetes y Nutrición*, 65(6):342-347, **2018** (Quirós et al., 2018).

7. Josep Vehí, Ivan Contreras, Silvia Oviedo, **Lyvia Biagi**, and Arthur Bertachi. Prediction and Prevention of Hypoglycaemic Events in Type-1 Diabetic Patients using Machine Learning, *Health Informatics Journal*. Accepted.

8. 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*. Accepted.

Conferences

1. **Lyvia Biagi**, Arthur H. Bertachi, Ignacio Conget, Carmen Quirós, Marga Giménez, Francisco J. Ampudia-Blasco, Paolo Rossetti, Jorge Bondia, and Josep Vehí. Accuracy of Continuous Glucose Monitoring During Postprandial Period and Its Influence on Closed-Loop Performance, In *10th International Conference on Advanced Technologies & Treatments for Diabetes*, *Paris - France*, page A39, **2017** (*abstract*) (Biagi et al., 2017a).

2. **Lyvia Biagi**, Arthur Bertachi, Carmen Quirós, Marga Giménez, Ignacio Conget, Jorge Bondia, and Josep Vehí. Accuracy and Precision of Continuous Glucose Monitoring before, during and after Aerobic and Resistance Exercise in Subjects with Type 1 Diabetes, In *11th International Conference on Advanced Technologies & Treatments for Diabetes*, *Vienna - Austria*, pages A92-A93, **2018** (*abstract*) (Biagi et al., 2018e).

3. **Lyvia Biagi**, Arthur Bertachi, Josep Antoni Martín-Fernández, and Josep Vehí. Compositional Data Analysis of Type 1 Diabetes Data, In *3rd International Workshop on Knowledge Discovery in Healthcare Data, Stockholm - Sweden*, pages 8-12, **2018** (*full-paper*) (Biagi et al., 2018b).

4. Arthur Bertachi, **Lyvia Biagi**, Ivan Contreras, Ningsu Luo, and Josep Vehí. Prediction of Blood Glucose Levels And Nocturnal Hypoglycemia Using Physiological Models and Artificial Neural Networks, In *3rd International Workshop on Knowledge Discovery in Healthcare Data, Stockholm - Sweden*, pages 85-90, **2018** (*full-paper*) (Bertachi et al., 2018).

5. Ivan Contreras, Arthur Bertachi, **Lyvia Biagi**, Josep Vehí, and Silvia Oviedo. Using Grammatical Evolution to Generate Short-term Blood Glucose Prediction Models, In *3rd International Workshop on Knowledge Discovery in Healthcare Data, Stockholm - Sweden*, pages 91-96, **2018** (*full-paper*) (Contreras et al., 2018).

6. **Lyvia Biagi**, Arthur Bertachi, Josep Antoni Martín-Fernández, and Josep Vehí. Categorization and Prediction of Glucose Profiles of Type 1 Diabetes Patients Based on a Compositional Data Analysis Approach, In *12th International Conference on Advanced Technologies* & *Treatments for Diabetes, Berlin - Germany*, page A-70, **2019** (*abstract*) (Biagi et al., 2019b).

7. Arthur Bertachi, **Lyvia Biagi**, Ivan Contreras, and Josep Vehí. Prediction of nocturnal hypoglycemic events in adults with type 1 diabetes, In *12th International Conference on Advanced Technologies* & *Treatments for Diabetes, Berlin - Germany*, page A-71, **2019** (*abstract*) (Bertachi et al., 2019).

8. **Lyvia Biagi**, Arthur Bertachi, Josep Antoni Martín-Fernández, and Josep Vehí. Compositional Data Analysis of Glucose Profiles of Type 1 Diabetes Patients, In *12th IFAC Symposium on Dynamics and Control of Process Systems, including Biosystems (DYCOPS 2019), Florianópolis - Brazil*, pages 1006-1011, **2019** (*full-paper*) (Biagi et al., 2019a).

9. Arthur Bertachi, Clara Viñals, **Lyvia Biagi**, Ivan Contreras, Marga Giménez, Ignacio Conget, and Josep Vehí. Machine learning forecasting nocturnal hypoglycemia in type 1 diabetes under multiple daily injections using continuous glucose monitoring and physical activity monitor, In *55th European Association for the Study of Diabetes Annual Meeting, Barcelona - Spain*, **2019**. Submitted (*abstract*).

Book chapters

1. **Lyvia Biagi**, Arthur Bertachi, Josep Antoni Martín-Fernández, and Josep Vehí. Compositional Data Analysis of Daily Glucose Profiles of Type 1 Diabetes Patients, In *II Conference of Pre-doctoral Researchers Abstract Book* edited by Miquel Solà, pages 115-116, **2018** (Biagi et al., 2018c).

2. Ivan Contreras, Arthur Bertachi, **Lyvia Biagi**, Silvia Oviedo, Charrise Ramkissoon and Josep Vehí. Artificial Intelligence for Decision Support Systems in Diabetes, In *Artificial Intelligence in Precision Health: From concept to applications* edited by Debmalya Barh. Submitted.

LIST OF FIGURES

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Acronyms and Abbreviations

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

Acronyms and abbreviations

AP	Artificial Pancreas
BG	Blood Glucose
BG-IG	Blood to Interstitium Glucose
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CoDa	Compositional Data
CL	Closed-Loop
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DM	Diabetes Mellitus
DSS	Decision Support System
FDA	Food and Drug Administration
HbA_{1c}	Glycated Hemoglobin
LD	Linear Discriminant
LOOCV	Leave-One-Out Cross-Validation
MARD	Mean Absolute Relative Difference
MDI	Multiple Daily Injections
OL	Open-Loop
PA	Physical Activity
PARD	Precision Absolute Relative Difference
PP	Postprandial Period
SAP	Sensor-Augmented Pump
SMBG	Self-Monitoring of Blood Glucose
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TIR	Time in Range
UdG	University of Girona - *Universitat de Girona*
UPV	Polytechnic University of Valencia - *Universitat Politècnica de València*

TABLE OF CONTENTS

Abstract

Type 1 Diabetes Mellitus (T1DM) is a disease related to the autoimmune process of pancreatic β-cell destruction that leads to absolute insulin deficiency. Although T1DM occurs most frequently in children and adolescents, it can develop at any age. People with T1DM need exogenous insulin to maintain glucose at proper levels and avoid hyperglycemia. However, if insulin is over delivered, it may cause hypoglycemic events. If not properly treated T1DM may lead to several complications over time, including blindness, kidney failure, cardiovascular complications, and even death.

Insulin infusion in T1DM patients can be performed with multiple daily injections (MDI); however, treatment with continuous subcutaneous insulin infusion (CSII) therapy provides improvements in glycemic control. Current T1DM management technology allows the integration of continuous glucose monitoring (CGM) and CSII. One example of such technology is the artificial pancreas (AP), which is a closed-loop (CL) system for the automatic control of glucose. The AP integrates a CGM device, an insulin pump and a control algorithm.

However, even with the advances in diabetes technology, achieving optimal glycemic control is still a major hurdle due to the large intra-patient variability, and CGM plays an essential role for individuals with T1DM, allowing them to follow blood glucose levels in real time. These devices are recognized for improvements in glucose control and for providing relevant information not only regarding patient's glucose profile but also lifestyle. Moreover, CGM technology has been changing how glycemic control is assessed, and there is an open discussion on considering the values obtained by CGM into different ranges of glucose instead of considering only the glycated hemoglobin test.

This thesis is devoted to describe the condition assessment of patients with T1DM through the analysis of glucose data obtained from CGM. Firstly, this work focuses on understanding and dissecting the measures obtained from CGM sensors. For that, a model of the error of a CGM sensor has been obtained and the accuracy of the CGM has been assessed during challenging conditions. Secondly, a novel approach for the categorization of daily glucose profiles based on the analysis of compositional data (CoDa) is proposed. This methodology considers the analysis of time spent in different glucose ranges by individuals with T1DM. CoDa analysis is related to the analysis of vectors of positive components that describe the contribution of parts to some whole. Last, a probabilistic model of transition between different categories of periods of glucose data obtained with CoDa analysis is presented.

The aforementioned approaches were evaluated considering T1DM data sets obtained from real patients using CGM devices. The obtained results are promising and could contribute to

the advances in the development of technologies and also to assist both physicians and T1DM patients in the management of T1DM.

RESUMEN

La diabetes Mellitus tipo 1 (T1DM) es una enfermedad relacionada con el proceso autoinmune de destrucción de las células beta pancreáticas que puede implicar una deficiencia absoluta de insulina. Aunque la T1DM ocurre más frecuentemente en niños y adolescentes, puede desarrollarse a cualquier edad. Las personas con T1DM requieren insulina exógena para mantener los niveles de glucosa apropiados y evitar eventos de hiperglicemia. Sin embargo, si la insulina se entrega en exceso, puede causar eventos de hipoglicemia. Si no se trata adecuadamente, la T1DM conlleva muchas afectaciones con el paso del tiempo, incluyendo ceguera, falla renal, complicaciones cardiovasculares, e incluso la muerte.

La infusión de insulina en pacientes con T1DM puede realizarse con múltiples inyecciones diarias (MDI); sin embargo, el tratamiento con la terapia continua de infusión subcutánea de insulina (CSII) provee mejoras en el control glicémico. Las tecnologías actuales para la gestión de la T1DM permiten la integración del monitoreo continuo de glucosa (CGM) y la terapia CSII. Un ejemplo de esta tecnología es el páncreas artificial (AP), que es un sistema de lazo cerrado (CL) para el control automático de la glucosa. El AP integra un dispositivo CGM, una bomba de insulina y un algoritmo de control.

Sin embargo, incluso con los avances en tecnologías para la diabetes, alcanzar un control glicémico óptimo tiene una gran dificultad debido a la variabilidad intrapaciente, y el CGM juega un rol esencial para los individuos con T1DM, permitiéndoles seguir sus niveles de glucosa en sangre en tiempo real. Estos dispositivos son reconocidos por mejorar el control de glucosa y por proveer información relevante no solo respecto al perfil de glucosa del paciente, sino también de su estilo de vida. Además, la tecnología CGM ha venido cambiando la forma en la que se evalúa el control glicémico, y hay una discusión abierta sobre considerar los valores obtenidos por CGM en diferentes rangos de glucosa en lugar de considerar solo la prueba de hemoglobina glucosilada.

Esta tesis está dedicada a describir la evaluación de la condición de los pacientes con T1DM a través del análisis de datos de glucosa obtenidos de CGM. En primer lugar, este trabajo se enfoca en entender y diseccionar las medidas obtenidas usando sensores CGM. Para ello, se ha obtenido un modelo de error de un sensor CGM y se ha evaluado la precisión del CGM en condiciones difíciles. En segundo lugar, se presenta un nuevo enfoque para la caracterización de perfiles de glucosa diarios con base en el análisis de datos composicionales (CoDa). Esta metodología considera el análisis del tiempo en diferentes rangos de glucosa de individuos con T1DM. El análisis CoDa está relacionado con el análisis de vectores de componentes positivas que describen la contribución de las partes a un todo. Finalmente, se presenta un modelo de

transición probabilístico entre diferentes categorías de periodos de datos de glucosa que fue obtenido usando técnicas CoDa.

Los enfoques mencionados fueron evaluados usando sets de datos de pacientes reales con T1DM que utilizan dispositivos CGM. Los resultados obtenidos son prometedores y podrían contribuir a los avances en el desarrollo de tecnologías y también para ayudar tanto a los médicos como a los pacientes en la gestión de la T1DM.

RESUM

La diabetis mellitus de tipus 1 (T1DM) és una malaltia relacionada amb el procés autoimmune de destrucció de cèl·lules β pancreàtiques que condueix a una deficiència absoluta d'insulina. Tot i que la T1DM es produeix amb major freqüència en nens i adolescents, pot desenvolupar-se a qualsevol edat. Les persones amb T1DM requereixen d'insulina exògena per a mantenir la glucosa en els nivells adequats i evitar la hiperglicèmia. No obstant, si l'insulina s'ha lliurat en excés, pot causar esdeveniments hipoglucèmics. Si no es tracta correctament, la T1DM pot provocar diverses afeccions amb el pas del temps, incloent ceguesa, insuficiència renal, complicacions cardiovasculars i, fins i tot, la mort.

La infusió d'insulina en pacients amb T1DM es pot realitzar amb múltiples injeccions diàries (MDI); tanmateix, el tractament amb la teràpia contínua d'infusió subcutània d'insulina (CSII) proporciona millores en el control glucèmic. La tecnologia actual de gestió de la T1DM permet la integració de la monitorització contínua de glucosa (CGM) i la teràpia CSII. Un exemple d'aquesta tecnologia és el pàncrees artificial (AP), que és un sistema en llaç tancat (CL) per al control automàtic de la glucosa. L'AP integra un dispositiu CGM, una bomba d'insulina i un algoritme de control.

No obstant, fins i tot amb els avenços en tecnologies per a la diabetis, assolir un control glucèmic òptim segueix tenint una dificultat important a causa de la gran variabilitat intrapacient, i la CGM té un rol essencial per als individus amb T1DM, permetent-los seguir els nivells de glucosa en sang en temps real. Aquests dispositius són reconeguts per millorar el control de la glucosa i per proporcionar informació rellevant, no només del perfil de glucosa del pacient, sinó també del seu estil de vida. A més, la tecnologia CGM ha anat canviant la manera en què es valora el control glucèmic, i hi ha una discussió oberta sobre considerar els valors obtinguts per CGM en diferents rangs de glucosa en lloc de considerar només la prova d'hemoglobina glucosilada.

Aquesta tesi està dedicada a descriure l'avaluació de la condició dels pacients amb T1DM mitjançant l'anàlisi de dades de glucosa obtingudes de CGM. En primer lloc, aquest treball es centra a comprendre i separar les mesures obtingudes utilitzant sensors CGM. Per aquesta raó, s'ha obtingut un model de l'error d'un sensor CGM i s'ha avaluat la precisió de la CGM en condicions difícils. En segon lloc, es proposa un nou enfocament per a la categorització de perfils de glucosa diaris basats en l'anàlisi de dades composicionals (CoDa). Aquesta metodologia considera l'anàlisi del temps en els diferents rangs de glucosa per part d'individus amb T1DM. L'anàlisi CoDa està relacionat amb l'anàlisi de vectors de components positives que descriuen la contribució de les parts a un tot. Finalment, es presenta un model de transició probabilístic

entre diferents categories de períodes de dades de glucosa obtingudes amb tècniques CoDa.

Els enfocaments esmentats es van avaluar utilitzant conjunts de dades de pacients reals amb T1DM que utilitzen dispositius CGM. Els resultats obtinguts són prometedors i podrien contribuir als avenços en el desenvolupament de tecnologies i també per ajudar tant als metges com als pacients en la gestió de la T1DM.

CHAPTER 1

INTRODUCTION

Diabetes Mellitus (DM) is a collection of disorders characterized by high levels of blood glucose (BG) and glucose intolerance due to either ineffectiveness of insulin's action or insulin deficiency, or a combination of them. Type 1 Diabetes Mellitus (T1DM) is related to the autoimmune process of pancreatic β-cell destruction that leads to absolute insulin deficiency. T1DM occurs most frequently in children and adolescents, although it can be developed at any age. Type 2 Diabetes Mellitus (T2DM) is the most common form of the disease, accounting for around 90% of the cases, and is characterized by disorders of insulin resistance and insulin secretion (DeFronzo et al., 2015). T2DM is more commonly presented in older adults, but due to the rising levels of physical inactivity, obesity and poor diet, it is becoming more frequent in younger adults.

Figure 1.1 shows the BG regulatory system for healthy individuals. When BG levels are high, pancreatic β-cells promote insulin release, which stimulates the formation of glycogen and its storage in the liver. Also, it stimulates the glucose uptake by muscle and fat cells, which lowers BG levels. When BG levels are low, pancreatic α-cells promote glucagon release, which stimulates the breakdown of glycogen, raising BG levels.

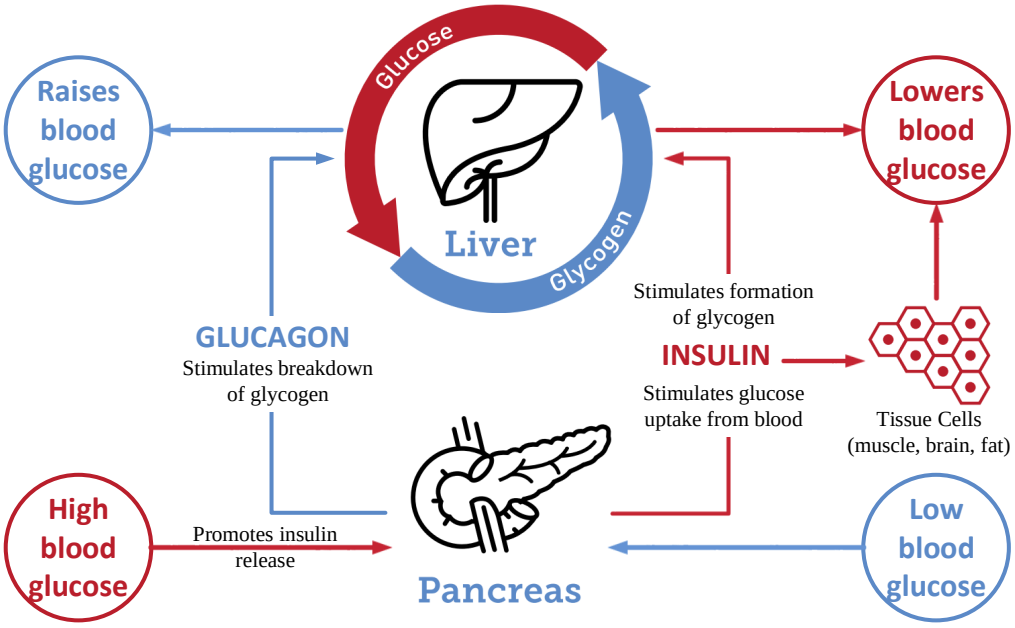

Figure 1.1: Blood glucose regulatory system for healthy individuals (International Diabetes Federation, 2017).

According to the International Diabetes Federation (2017), diabetes is one of the largest global health emergencies of the 21st century. The disease affects more than 425 million people world-wide, and this number may increase in 48% by 2045. Figure 1.2 shows the total number of adults between 20 and 79 years with diabetes in the last years and the projection for 2045.

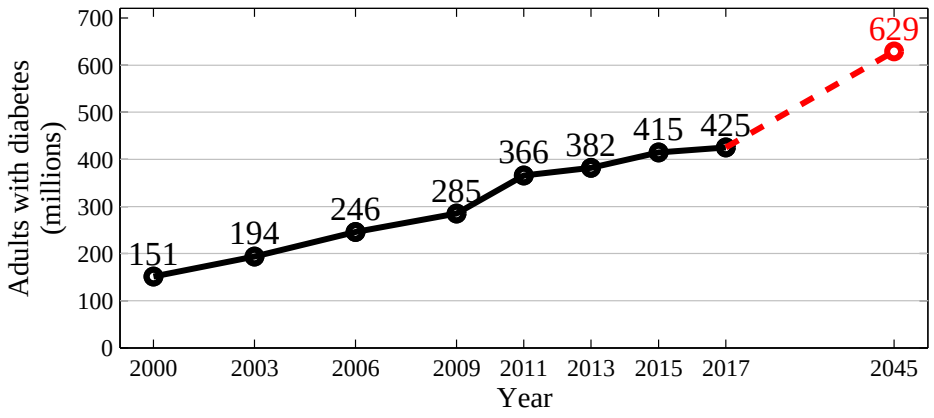

Figure 1.2: Total number of adults with diabetes (20-79 years). Adapted from the International Diabetes Federation (2017).

The absence of insulin or insulin resistance in subjects with DM leads to hyperglycemia, which can cause damage to several body organs and lead to complications such as cardiovascular disease, neuropathy, nephropathy and eye disease, leading to retinopathy and blindness (International Diabetes Federation, 2017). People with T1DM need exogenous insulin to maintain glucose at proper levels. Insulin can be administered through conventional or intensive insulin therapy. Conventional insulin therapy consists in one or two daily insulin injections, while intensive insulin therapy consists in the administration of either three or more daily insulin injections or with insulin pump. A study involving more than 1440 T1DM individuals and comparing intensive and conventional insulin therapy was performed by the Diabetes Control and Complications Trial (DCCT) Research Group (DCCT, 1993). The study showed that intensive insulin therapy can prevent or delay the aforementioned diabetes complications. However, the incidence of hypoglycemic episodes was also higher when the intensive therapy was considered. Hypoglycemia is also a complication of diabetes that can lead to seizures, loss of consciousness, coma, and even death.

Subjects with diabetes must monitor their BG levels regularly. A marker for the glycemic control in T1DM or T2DM patients is the glycated hemoglobin (HbA_{1c}). This measure is an indicator of the degree of glycemic control and reflects the average BG levels over approximately three months (Kovatchev et al., 2002; American Diabetes Association, 2018a). Patients with diabetes should perform this test routinely, as a part of continuing care.

Self-monitoring of blood glucose (SMBG) is desirable for all patients with diabetes to achieve glucose control and prevent hypoglycemia (Benjamin, 2002). The test is performed with a glucometer, a portable device for glucose monitoring, and a small sample of blood, usually extracted from a fingertip. Patients are encouraged to have at least four SMBG tests each day (DeFronzo et al., 2015), because there is an association with increased frequency of SMBG and lower HbA_{1c} (Miller et al., 2013). Continuous glucose monitoring (CGM), on the other hand, provides information in a frequency (1-5 minutes samples) that would be

impracticable with intermittent capillary BG and can display instantaneous real-time BG levels (Rodbard, 2016).

CGM consists of a subcutaneous sensor that estimates BG from measurements of interstitial glucose and was initially used as a method for retrospective review of glucose profiles in those with T1DM. The first generations of CGMs approved by the Food and Drug Administration (FDA) beginning in 1999 were able to provide significant clinical benefits as an adjunct to standard SMBG (Bode, 2000; Mastrototaro, 2000; Cobelli et al., 2011; Peyser et al., 2014). It was only in the end of 2016 that FDA approved the non-adjunctive use of CGM for diabetes treatment decisions (Shapiro, 2017), meaning that patients could rely on CGM readings for insulin dosing without the need of SMBG or laboratory testing.

The most common method for intensive treatment of T1DM is multiple daily injections (MDI) (McGill and Ahmann, 2017); however, treatment with continuous subcutaneous insulin infusion (CSII) therapy provides improvements in glycemic control (Beck et al., 2017b). Current T1D management technology allows the integration of CGM and CSII, such as the the sensor-augmented pump (SAP) therapy, which can limit the duration and severity of hypoglycemic events. Basal insulin delivery can be automatically suspended in response to a detected or even predicted low glucose level. Comparing to the usage of CSII without CGM, there is evidence that the frequency of severe hypoglycemic events is reduced when SAPs are considered, either with or without the automatic suspension of basal insulin (Teich et al., 2019). These technologies are thought to be the beginning of home-use automated devices for T1DM.

The artificial pancreas (AP) is a closed-loop (CL) system for the automatic control of glucose. The AP integrates a CGM device, an insulin pump and a control algorithm. The development of the AP dates from the 1960's, when it was established the possibility of external BG regulation through intravenous glucose measurement and insulin and glucose infusion (Cobelli et al., 2011). Even though the intravenous route of glucose measurements and insulin infusion is only suitable for inpatient use, it inspired the development of new

technologies. Figure 1.3 shows a diagram of the AP system and its main components. CGM system is responsible for measuring glucose values, and a controller algorithm determines the amount of insulin that the insulin pump should deliver to the patient.

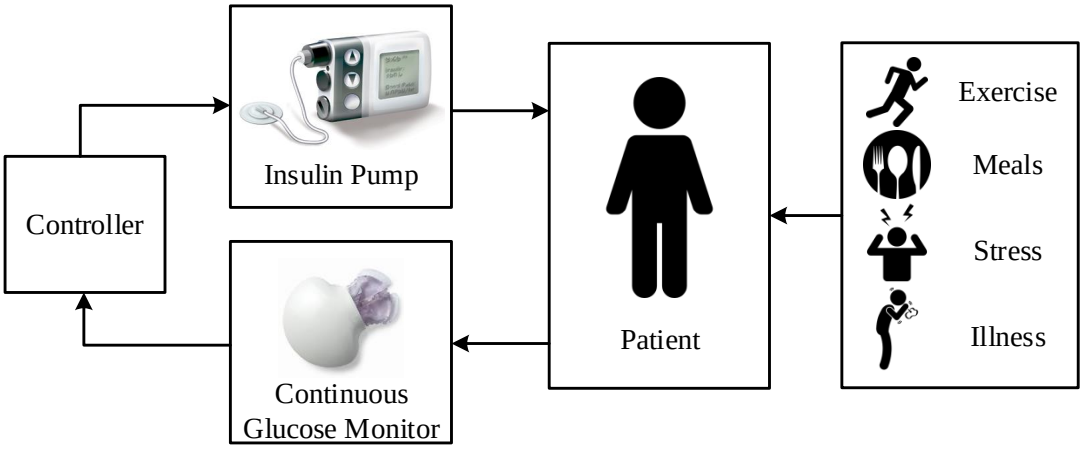

Figure 1.3: Diagram of the artificial pancreas system.

The challenges for the development of AP are multiple: the accuracy of CGMs should be improved; there are great physiological delays because of the subcutaneous insulin infusion compared to pancreatic secretion; the patient has great physiological variability; and there are major disturbances such as food intake, exercise, illness and stress.

The AP development is increasing consistently over the past decade. Bertachi et al. (2018) presented an extensive review of clinical trials involving CL systems, in which the authors reported that clinical trials assessing AP performance are moving from very controlled inpatient settings to outpatient settings with patients under free-living conditions. The first commercial CL system was first approved by the FDA in 2017. The Medtronic MiniMed 670G (Medtronic, Northridge, CA, USA) is a hybrid CL system, i.e., although the system is able to automatically increase, decrease and suspend insulin delivery according to the CGM data, previous to the initiation of bolus insulin delivery, patient must inform the system the amount of meal carbohydrate (CHO) and confirm bolus insulin designated by the system. Results of a multicenter pivotal trial reported by Garg et al. (2017) showed that the system increased time in target,

reduced HbA_{1c} and hypo- and hyperglycemia in both adults and adolescents. However, this hybrid CL system presents with non-modifiable BG targets of 120 and 150 mg/dL, which may not be suitable for those patients who find the BG target of 120 mg/dL too high, or during exercise, when 150 mg/dL has been shown to be too low (Weaver and Hirsch, 2018). It is fundamental that both clinicians and patients understand the benefits and limitations of the CL systems. As new diabetes technologies come to market, more effective strategies for optimizing their usage are required, ensuring that research finding may be indeed translated to clinical practice (Berget et al., 2019; Messer, 2019).

Even though HbA_{1c} has been considered the gold standard for assessing glycemic management in T1DM patients, the measure does not provide indication of hypoglycemia, glycemic variability or daily patterns of glycemia. There is a wide range of mean glucose concentrations and glucose profiles that can be associated with a given HbA_{1c}. This can be observed in Figure 1 from Kovatchev et al. (2002) and Suh and Kim (2015), which both show that individuals with the same HbA_{1c} may present different incidence of adverse events and patterns of glucose variability. Beck et al. (2017a) also reported that HbA_{1c} may not be a good indicator of an individual's glycemic control. Also, according to Beck (2019), HbA_{1c} may not be a feasible outcome to clinical trials due short duration of studies or crossover trials.

Beck et al. (2019) assessed the association between time in range (TIR), i.e. BG between 70 mg/dL and 180 mg/dL with the development or progression of diabetes complications, considering the DCCT dataset. The authors concluded that TIR, especially when measured with CGM could have advantages as outcome metrics in clinical trials. Lu et al. (2018) analyzed retrospective CGM data on individuals with T2DM and also reported that TIR was associated with diabetes retinopathy, i.e. those patients with vision-threatening retinopathy presented with the lowest TIR. According to Hirsch et al. (2019), those evidence supports that TIR should be accepted as outcome for clinical trials along with HbA_{1c}, however the transition to the usage of TIR may not be as easy for providers and payers (Hirsch, 2019).

Additionally to the definition of TIR, in order to standardize clinical practice recommendations, different levels of hypo- and hyperglycemia according to glucose thresholds have been defined by The American Diabetes Association (2018b), which had already been presented earlier by Agiostratidou et al. (2017):

- Hyperglycemia
  - Level 1 (elevated glucose):
    $180 \text{ mg/dL} < BG \leq 250 \text{ mg/dL}$
  - Level 2 (very elevated glucose):
    $BG > 250 \text{ mg/dL}$
- Hypoglycemia
  - Level 1 (measurable glucose concentration that can alert a person to take action):
    $54 \text{ mg/dL} \leq BG < 70 \text{ mg/dL}$
  - Level 2 (measurable glucose concentration that needs immediate action):
    $BG < 54 \text{ mg/dL}$

It is clear that CGM plays a critical role in the most recent technologies for managing the glucose levels in individuals with T1DM. These devices provide relevant information not only regarding patient's glucose profile but also lifestyle. CGM allows monitoring the occurrence of adverse events, playing an important role in assessing the effectiveness and safety of treatment in diabetes. The use of data obtained from sensor-based systems as well as electronic health records, in combination with methods for data analysis facilitates the implementation of preventive, predictive, personalized and participatory diabetes care (Zarkogianni et al., 2015).

Even though the use of CGM improves glycemic control and its efficacy in diabetes management is recognized, the devices are still afflicted with errors related to accuracy, drift, time lags, calibration and noise, which affect the precision and accuracy of BG results (Facchinetti et al.,

2014, 2015). Additionally, the analysis of glucose data obtained from CGM allows the creation of tools for evaluation of similar glucose profiles according to glycemic control. Contreras et al. (2016) presented a hierarchical clustering methodology based on normalised compression distance to identify multiple profiles for both simulated and real T1DM data using a symbolic representation of the time series discretized into different glucose ranges. The authors observed that their methodology was able to categorize days according to different insulin requirements. The information obtained by procedures like that could be incorporated in a decision support system (DSS) to enhance existing analysis platforms. A clinical DSS is supposed to effectively integrate relevant clinical data and generate patient-specific reports, providing recommendation and reminders in order to relieve the burden that affects physicians in taking clinical decisions during consultations (Sim et al., 2017).

In the described context, there are great research opportunities associated with the analysis of CGM data obtained from real T1DM patients that will allow the creation of decision support tools to assist patients and physicians to improve patients' glycemic control.

1.1 Objectives

The research work presented in this thesis is devoted to describe the condition assessment of patients with data obtained exclusively from CGM. Firstly, the work consists in the analysis of CGM measures in different situations. Then, the work is dedicated to the analysis of glucose profiles, following a new approach, that considers the amounts of time spent in different glucose ranges during a limited duration of time as compositional data (CoDa). According to Aitchison (1986), the relevant information of a composition is contained in the ratios between its components. And since standard multivariate analysis is designed for unconstrained multivariate data, they are not valid for CoDa. However, traditional statistical methods can be applied after CoDa has been transferred to the real space, through the expression in logratio coordinates. Therefore, the objectives of this study are:

- To understand and dissect the measures obtained from CGM sensors used by T1DM patients.

  To accomplish that objective, a model of the error of a CGM sensor is presented, allowing the analysis and comparison of several components of the CGM error between different brands and models of glucose sensors.

- To analyse CGM data from T1DM patients during challenging situations, such as meals and physical activity (PA).

  The accuracy of CGM sensor is analyzed considering data obtained in two previous clinical studies, one during postprandial period (PP) and the other, during aerobic and anaerobic PA. The accuracy is assessed considering the mean absolute relative difference (MARD). Results are compared with previous works.

- To categorize daily glucose profiles of T1DM patients obtained from CGM sensors using a novel approach based on CoDa analysis of time spent in different glucose ranges.

  The categorization of glucose profiles is performed considered data of T1DM patients in free-living conditions. Complete daily glucose profiles are categorized according to an approach that considers the relation between the amounts of time spent in different glucose ranges.

- To obtain a probabilistic model of transition between different categories of periods of glucose data that could assist both physicians and T1DM patients in managing the condition.

  A similar approach for the categorization of glucose profiles is now applied to periods of 24-h and 6-h of duration, at different times of the day. Retrospectively, a probabilistic model of transition between categories of periods is proposed.

1.2 Research Context and Data Sets

The Spanish Consortium on Artificial Pancreas and Diabetes Technology joined in 2018 the Spanish excellence diabetes research center *Centro de Investigación Biomédica en Red en Diabetes y Enfermedades Metabólicas Asociadas* (CIBERDEM). This Consortium comprises several engineering and clinical groups in Spain, such as:

- MiceLab

  The MiceLab group is an interdisciplinary research group of the Institute of Informatics and Applications (IIIA) of the University of Girona (*Universitat de Girona* - UdG). The group is one of the leading groups in Europe with more than 14 years researching AP development. Experienced researchers from the control engineering field with expertise in systems and control theory, modelling and control of biomedical systems, uncertain dynamical systems, robust and predictive control and DSS (MiceLab).

- MEDERI Living Lab and Tecnodiabetes

  The MEDERI Living Lab (Medical Devices Research & innovation Living Lab) is a multidisciplinary research group committed with innovation in the field of health technology, which was created in 2014 by the *Instituto Universitario de Automática e Informática Industrial* (Institute ai2) of the Politechnic University of Valencia (*Universitat Politècnica de València* - UPV) (MEDERI). The Tecnodiabetes consists of a MEDERI Living Lab initiative to bring research and innovation in diabetes to people living with the disease (Tecnodiabetes).

- IDIBAPS

  The IDIPAPS (*Institut d'Investigacions Biomèdiques August Pi i Sunyer*) was founded in 1996, as a public consortium whose members are the Catalan Government, the Hospital Clínic of Barcelona (CLÍNIC), the University of Barcelona's School of Medicine and

the CSIC Biomedical Research Institute in Barcelona. IDIBAPS is a centre for research of excellence that tackles high-prevalence, high-morbidity and high-mortality diseases (IDIBAPS).

In addition to the aforementioned research groups, clinic researchers from the *Hospital Clínico de Valencia* and *Hospital Francesc de Borja de Gandia* are also members of the CIBERDEM. The main research objective of the group consists on the development and validation of new AP systems to improve the efficiency and safety of food intake and exercise. Ongoing projects and concluded projects that are related do the development of this doctoral thesis are listed below:

- CIBERDEM (2018-current)

  Incorporation of new groups to the CIBER consortium.

- mSAFE-AP (2016-current)

  Solutions for the improvement of efficiency and safety of the AP by fault-tolerant multivariable control architectures.

- SAFE-AP (2014-2016)

  New methods for the efficiency and safety of home AP.

- CLOSEDLOOP4MEAL (2011-2014)

  New strategies for postprandial glycemic control using insulin pump therapy in T1DM.

Further details about the projects listed above, as well as their related clinical studies are described on the webpages of MiceLab and Tecnodiabetes. Additionally, information about projects concluded previously can be found.

Data obtained from two clinical studies related to the projects CLOSEDLOOP4MEAL and SAFE-AP, both designed by the Spanish Consortium on Artificial Pancreas and Diabetes Technology, were object of the studies from which this thesis was derived. The following

sections will briefly describe the clinical trials and relevant work developed with each data set that are related with the development of this thesis.

1.2.1 Closed-Loop 4 Meals - CL4M

It was a coordinated project performed between UdG and UPV, financed by the Ministry of Science and Innovation (*Ministerio de Ciencia e Innovación* DPI2010-20764-C02-01) from 2011 to 2014. The main objective was to develop new strategies for the PP glycemic control in patients with T1DM, aiming to avoid complications related to hypoglycemia.

In a clinical study, twenty subjects with T1DM underwent an 8-hour standardized mixed meal test (60 g of CHO) on 4 occasions. On 2 occasions (open-loop (OL)), conventional CSII was used and boluses were based on the individual insulin-to-carbohydrates ratios. On the other two occasions, after a meal-announcement, an augmented bolus was given, followed by manual adjustments of the basal rate every 15 minutes according to a CL controller recommendation (ClinicalTrials.gov, 2015).

CSII was carried out with the Medtronic Paradigm Veo insulin pump (Northridge, CA, USA) and CGM using the second generation Medtronic Paradigm Veo Enlite sensors (Northridge, CA, USA). Two CGMs were inserted on either side of the umbilicus 24–48 h before the meal tests. In all subjects, calibration of CGM was performed according to the manufacturer's instructions using the Contour Next Link (Ascensia Diabetes Care Holdings AG, Basel, Switzerland, Formerly Bayer). BG concentrations were measured every 15 min with a YSI 2300 Stat Plus Glucose Analyzer (YSI 2300, YSI Incorporated Life Sciences, Yellow Springs, OH, USA).

The study was designed to analyze and compare the efficacy and safety of CL algorithm implementing sliding mode reference conditioning, adapted from a previous study (Revert et al., 2013), to current OL therapy during the PP. Results of this clinical trial were presented by Rossetti et al. (2017). Not only the CL sessions presented better plasma glucose control than the OL sessions, but also the TIR was higher when the CL controller was used.

A work related to the operation of CGMs of the CL4M clinical trial was presented by Biagi et al. (2017b). Their work assesses the accuracy of the CGMs during PP. Results showed that sensors presented lower accuracy in the ranges related to hypoglycemia and sensors with better accuracy in the CL sessions presented less time spent in hypoglycemia, indicating that the performance of CL algorithm to control PP was related to sensor accuracy.

Another paper that considered the CL4M data set presented a model of the error of the CGM used in the clinical trial (Biagi et al., 2017c). The method is an enhanced version of a methodology previously presented by Facchinetti et al. (2014, 2015) and allowed the dissection of the the sensor error into its main key components, i.e., the delay due to the plasma-to-interstitium kinetics by assuming a physiological model of blood-to-interstitium kinetics, the calibration error that includes a model sensor sensitivity drift in time, and the measurement noise. A model of the sensor error allows the simulation of reliable CGM traces, which can permit testing CGM-based applications employing this specific model of CGM.

1.2.2 SAFEAP Project

It was also a coordinated project performed between UdG and UPV, financed by the Ministry of Economy and Competitiveness (*Ministerio de Economía y Competitividad* DPI2013-46982-C2-1-R) from 2014 to 2018. The main objective was to study the impact of aerobic and resistance exercise in glucose control.

In a clinical study, six patients with T1D were enrolled at the Clinic University Hospital of Barcelona. The study was a longitudinal, prospective, interventional study with a primary objective of the analysis of the limits of performance of a CL controller when challenged by PA and, as a secondary objective, the analysis of the impact of exercise in CGM accuracy. Each subject underwent three aerobic and three anaerobic exercise tests, completing six experiments in about nine weeks. CSII was carried out with the Paradigm Veo insulin pump and the day before the test, the patient inserted two second generation of Enlite glucose sensors, both by

Medtronic Minimed (Northridge, CA, USA), subcutaneously at home. Sensors were inserted in the abdomen. During the whole duration of the experiment, patients also used a Fitbit Charge HR activity tracker (Fitbit Inc., San Francisco, CA, USA). BG samples were measured every 15 min using a YSI 2300 Stat Plus Glucose Analyzer (YSI 2300, YSI Incorporated Life Sciences, Yellow Springs, OH, USA).

Results of the exercise sessions presented by Quirós et al. (2018) showed that the mean glucose level in aerobic sessions were lower than in the anaerobic sessions. Also, the TIR for the aerobic sessions was higher for the aerobic sessions, showing that the BG response to aerobic and anaerobic exercise is different. The work presented by Biagi et al. (2018d) assesses the accuracy of the sensors used during aerobic and anaerobic sessions of exercise. Their results indicate that the accuracy of CGM sensors might be more affected by aerobic exercise, however, sensors return to regular operation few hours after the end of exercise sessions.

The work presented by Biagi et al. (2018a) also considered the SAFEAP data set. The authors presented an approach for the individual categorization of glucose profiles based on a CoDa analysis. CoDa involves vectors of positive components that describe the contributions of parts to some whole (Aitchison, 1986). In the approach presented by Biagi et al. (2018a), the authors considered the relative contributions of time spent in different glucose ranges during a day as CoDa. This approach had been previously presented by several different studies. In time use analysis, basic methods for the comparison of groups of CoDa were presented by Martín-Fernández et al. (2015). Approaches to assess time spent in sleep, sedentary behavior and different intensities of PA and their effects on health markers were presented by Dumuid et al. (2017a); Chastin et al. (2015); Pedišić et al. (2017); Dumuid et al. (2017b). Mert et al. (2016) also used CoDa analysis in healthcare, through the analysis of epidemiologic information.

Another paper that also considered the SAFEAP data set has been recently submitted for publication (article presented in Section 2.5 of this compendium). The work continues with the CoDa-approach of glucose profiles and the aim is to move towards a decision support tool

based on the probabilistic model of analysis of transitions of consecutive periods. After the categorization of 24-h and 6-h periods, a retrospective analysis of the data is performed and a probabilistic model of transition between category of previous 24-h period to a subsequent 6-h period is obtained. The work presented by Biagi et al. (2018a) introduced the analysis of daily glucose profiles from 00:00 to 24:00, this new approach presents the analysis of glucose periods of different lengths at distinct times of the day: at 00:00, 06:00, 12:00 and 18:00.

1.3 Thesis Structure

This thesis is organized as follow: 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.

CHAPTER 2

CONDITION ASSESSMENT OF PATIENTS WITH TYPE 1 DIABETES USING COMPOSITIONAL DATA ANALYSIS

This Chapter consists of five sections. Section 2.1 presents a paper which consists of the modeling of the error of a glucose sensor. Section 2.2 consists of a paper in which the analysis of BG monitoring during PP and its impact on CL performance is presented. Section 2.3 presents a paper in which the accuracy of CGM before, during and after aerobic and anaerobic PA in patients with T1DM is analyzed. Section 2.4 presents a paper with the categorization of glucose profiles using CoDa analysis. Section 2.5 corresponds to the paper in which the probabilistic model of transition between categories obtained with CoDa analysis is presented:

- **2.1 Modeling the Error of the Medtronic Paradigm Veo Enlite Glucose Sensor**
- **2.2 Extensive Assessment of Blood Glucose Monitoring During Postprandial Period and Its Impact on Closed-Loop Performance**
- **2.3 Accuracy of Continuous Glucose Monitoring before, during, and after Aerobic and Anaerobic Exercise in Patients with Type 1 Diabetes Mellitus**

- **2.4 Individual Categorization of Glucose Profiles Using Compositional Data Analysis**

- **2.5 Probabilistic Model of Transition Between Categories of Glucose Profiles in Patients with Type 1 Diabetes Using a Compositional Data Analysis Approach**

2.1 Modeling the Error of the Medtronic Paradigm Veo Enlite Glucose Sensor

The candidate's contribution for this publication consisted in pre-processing the data obtained in the clinical trial, researching data, modeling the sensor error, writing the manuscript, contributing to discussion, and editing the manuscript throughout the review rounds. During the development of the work, the candidate worked with her colleague Dr. Charrise Ramkissoon, and they were assisted by Dr. Andrea Facchinetti, Dr. Yenny Leal and Dr. Josep Vehí.

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Article

Modeling the Error of the Medtronic Paradigm Veo Enlite Glucose Sensor

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Abstract: Continuous glucose monitors (CGMs) are prone to inaccuracy due to time lags, sensor drift, calibration errors, and measurement noise. The aim of this study is to derive the model of the error of the second generation Medtronic Paradigm Veo Enlite (ENL) sensor and compare it with the Dexcom SEVEN PLUS (7P), G4 PLATINUM (G4P), and advanced G4 for Artificial Pancreas studies (G4AP) systems. An enhanced methodology to a previously employed technique was utilized to dissect the sensor error into several components. The dataset used included 37 inpatient sessions in 10 subjects with type 1 diabetes (T1D), in which CGMs were worn in parallel and blood glucose (BG) samples were analyzed every 15 $\pm$ 5 min Calibration error and sensor drift of the ENL sensor was best described by a linear relationship related to the gain and offset. The mean time lag estimated by the model is 9.4 $\pm$ 6.5 min. The overall average mean absolute relative difference (MARD) of the ENL sensor was 11.68 $\pm$ 5.07% Calibration error had the highest contribution to total error in the ENL sensor. This was also reported in the 7P, G4P, and G4AP. The model of the ENL sensor error will be useful to test the in silico performance of CGM-based applications, i.e., the artificial pancreas, employing this kind of sensor.

Keywords: continuous glucose monitor; artificial pancreas; type 1 diabetes; sensor error; measurement noise; calibration error; enlite sensor

1. Introduction

The continuous glucose monitor (CGM) was initially used as a method for retrospective review of glucose profiles in those with type 1 diabetes (T1D). The first generations of CGMs approved by the Food and Drug Administration (FDA) beginning in 1999 were able to provide significant clinical benefits as an adjunct to standard self-monitoring of blood glucose (SMBG) [1–4]. Shortly after, real-time devices came about providing online glucose readings, but were widely acknowledged to have insufficient accuracy and reliability [5]. Nowadays, subsequent sensor generations are able to collect continuous (1–5 min sampling period) data for 7–14 days and can be used to determine glucose fluctuations. These new CGMs are recognized to be useful in the management of diabetes and can be used to improve glycemic control [6]. Despite these advantages, CGMs are still afflicted with errors related to accuracy, drift, time lags, calibration and noise, which affect the precision and

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accuracy of the blood glucose (BG) results [7–9]. Some of these errors are depicted in Figure 1, which shows a representation of the dataset used in this study. BG references were frequently collected every 15 ± 5 min for 8 h (linearly interpolated by a straight line), and CGM time series (other lines) are measured simultaneously using 2 second generation Medtronic Paradigm Veo Enlite (ENL) sensors (Northridge, CA, USA) in a T1D patient during a meal test. The top plot shows an example of an open-loop (OL) meal test with CGM (sensor 1) showing a slight continuous overestimation and CGM (sensor 2) showing a significant underestimation until time 210 min, likely due to a drift-in-time of sensor sensitivity. The bottom plot shows an example of a closed-loop (CL) meal test with CGM (sensor 2) displaying a time-lag at approximately time 43 min for about 1 h. All CGM time series exhibit random zero-mean measurement noise.

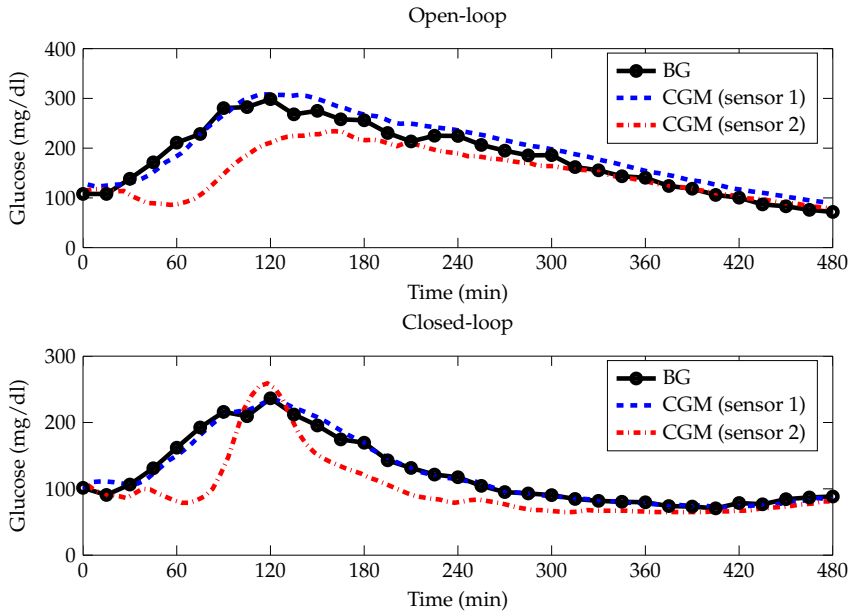

Figure 1. Representative example of the dataset employed in this paper. BG references frequently collected every 15 ± 5 min for 8 h (linearly interpolated by a straight line), and CGM time series (other lines) are measured simultaneously using $n = 2$ second generation Medtronic Paradigm Veo Enlite sensors (Northridge, CA, USA) in a type 1 diabetic patient during an open loop (top) and closed loop (bottom) meal test. BG, blood glucose; CGM, continuous glucose monitor.

It is important to emphasize that most CGMs estimate BG from measurements of interstitial glucose (IG) [10]. The effects of calibration and blood-to-interstitium glucose (BG-IG) dynamics as potential confounders of the accuracy of CGMs are reported by [10,11]. As a result of recalibration and modeling of the IG dynamics, the authors found that the sensor accuracy is heavily dependent on the calibration procedures.

The availability of models of CGM sensor error is important for several CGM-based applications. First, the knowledge on the statistical nature of the error can be incorporated into CGM data signal processing algorithms to optimize their performance, e.g., to improve digital filters for denoising and calibration algorithms to reduce sensor inaccuracy. Second, a dissection of the error into its main components can give insight into which sources of error are prevalent in a specific sensor. Thirdly, it can be used to enhance the reliability of simulated CGM traces generated via e.g., the University of Virgina (UVA)/Padova T1D simulator [12]. Additionally, models of CGM sensor error can be used to improve the safety of an artificial pancreas (AP) system by allowing a controller to make more informed

decisions based on known sensor error. As the efficacy of AP systems increase, more attention must be given to the overall safety of the system, with CGM error being a major contributor to the conservative approach to control in the AP. As knowledge of CGM errors grow, the ability to create and test more robust controllers increases. Finally, as recently seen with the Dexcom G5 Mobile sensor (San Diego, CA, USA), the availability of a detailed model of CGM sensor error allows specific sensors to be tested in silico [13] to determine if they can be safe and effective for non-adjunctive therapeutics decisions, i.e., insulin dosing [14,15].

In the past, several strategies to derive CGM sensor error characteristics have been proposed. Breton et al. [16] described sensor error using a first-order diffusion model and an autoregressive moving average (ARMA) model was considered to model the time dependency of consecutive errors. The authors analyzed two different datasets of the Abbott FreeStyle Navigator sensor (Chicago, IL, USA). A posteriori calibration was used to minimize the glucose discrepancy between sensor and reference. The authors noticed that the errors tend to be positive when the BG rate of change is negative and negative when the BG rate of change is positive, and that consecutive sensor errors are highly interdependent. Those procedures allowed the design of a simulator of sensor errors, but the model cannot describe errors due to calibration and sensor drift nor deal with interindividual variability of the BG-IG kinetics, although random fluctuations on CGM data were described in [17]. Laguna and colleagues [18] analyzed and modeled the error of the Dexcom SEVEN PLUS (7P; San Diego, CA, USA) and the first generation Medtronic Paradigm Veo Enlite sensors (Northridge, CA, USA) using a dataset of 12 subjects that wore the two sensors simultaneously. The sensor error was separated into lag time, the error stationarity, the error probability distribution, and the time correlation.

Recently, a technique to model the CGM sensor error from multiple simultaneous CGM traces has been developed by Facchinetti and colleagues [7,8] and it has been validated on CGM sensors of different generations produced by Dexcom Inc. (San Diego, CA, USA). In contrast to previous CGM error models, which cannot describe errors due to calibration and sensor drift nor deal with interindividual variability of the BG-IG kinetics. This method is innovative because it allows the sensor error to be dissected into its main key components, i.e., the delay due to the plasma-to-interstitium kinetics by assuming a physiological model of BG-IG kinetics, the calibration error that includes a model sensor sensitivity drift in time, and the measurement noise. In this paper, we apply a refined and enhanced version of the technique by Facchinetti and colleagues [7,8] to derive the sensor error model of the ENL sensor and we compare the results with those of the Dexcom 7P, the G4 PLATINUM (G4P)(San Diego, CA, USA), and the advanced G4 for artificial pancreas studies (G4AP) by Facchinetti and colleagues [7,8].

As discussed previously, the availability of the model of the ENL sensor error, which has not yet been derived, will be important to (i) simulate reliable CGM traces using T1D simulators, which will allow the pre-clinical in silico testing of CGM-based applications employing the ENL sensor, and (ii) test in silico if the ENL sensor is safe and effective for non-adjunctive use. Finally, this work will prove the reproducibility of the methodology proposed by Facchinetti and colleagues [7,8] to any sensor provided that suitable data is available.

2. Research Design and Methods

2.1. Study Population

Twenty patients with T1D were enrolled, ten at the Clinic University Hospital of Barcelona, Barcelona, Spain and ten at the Clinic University Hospital of Valencia, Valencia, Spain. The protocol was approved by the Ethics Committees of both hospitals (clinical settings). The selection criteria included the following: age between 18 and 60 years, duration of at least six months of continuous subcutaneous insulin infusion (CSII) therapy, body mass index (BMI) between 18 and 30 kg/m^2, and HbA1c level between 6.0% and 8.5%. Patients on any experimental drug or use of an experimental device during the past 30 days were excluded. Patients with hypoglycemia unawareness, progressive

fatal diseases, impaired hepatic or renal function, noncompliance, and/or, pregnant women were also excluded. See Table 1 for the demographic characteristics of the subject population.

Table 1. Demographic characteristics for the dataset used.

Number of T1D Patients	**10**
Sex	2 m, 8 f
Age (years)	44.5 ± 10.7
HbA1c (%)	7.9 ± 0.5
Body Mass Index (kg/m^2)	27.6 ± 2.5
Time with T1D (years)	23.1 ± 9.7
Time with pump (years)	8.5 ± 4.4

Abbreviation: T1D, type 1 diabetes.

2.2. Study Procedures

This was a randomized, prospective, one-way, repeated measures (four periods, two sequences) crossover study in subjects with T1D under continuous subcutaneous insulin infusion (CSII) [19,20]. Subjects underwent an 8-hour standardized mixed meal test (60 g carbohydrate, CH) on 4 occasions; on 2 occasions (CL1 and CL2), after a meal-announcement an augmented bolus was given, followed by manual adjustments of the basal rate every 15 min obtained via a CL controller; and on the other two occasions (OL1 and OL2), conventional CSII was used and boluses were based on the individual insulin-to-carbohydrate (I:CH) ratios. All subjects were randomly assigned to either sequence 1 (OL1-CL1-OL2-CL2) or 2 (CL1-OL1-CL2-OL2) with a wash-out period of at least 1 week between studies.

CSII was carried out with the Medtronic Paradigm Veo insulin pump (Northridge, CA, USA) and CGM using the second generation Medtronic Paradigm Veo Enlite sensors (Northridge, CA, USA). Two CGMs were inserted on either side of the umbilicus 24–48 h before the meal tests. In all subjects, calibration of CGM was performed according to the manufacturer's instructions using the Contour Next Link (Ascensia Diabetes Care Holdings AG, Basel, Switzerland, Formerly Bayer). BG concentrations were measured every 15 ± 5 min with a YSI 2300 Stat Plus Glucose Analyzer (YSI 2300, YSI Incorporated Life Sciences, Yellow Springs, OH, USA).

2.3. Dataset

It is important to note that the trial was not designed to derive the error of the ENL sensor; the dataset was acquired for other purposes. The study was designed to analyze and compare the efficacy and safety of a newly developed CL algorithm implementing sliding mode reference conditioning (SMRC), adapted from a previous study [21], to current OL therapy during the postprandial period. It was only upon retrospective analysis that it was discovered that the data could be used to model the sensor error.

In total, 80 sessions were obtained; however, to be suitable for modeling, sensors must be inserted on the same day and only data in 10 patients fit this criteria. Therefore, 40 sessions were appropriate for the modeling approach used. From these 40 sessions, an additional three sessions were removed due to sensor malfunctions (i.e., signal loss). YSI data was interpolated via Bayesian smoothing [22] to one reading per minute and then aligned to CGM data to obtain a smooth BG profile.

2.4. CGM Error Model

The strategy employed to identify and model the sensor error is described in [7,8]. This approach was first used in [7] to model the 7P sensor error using 4 sensors in parallel ($n = 4$). The authors then followed the same methodology in [8] to model the 7P, G4P, and G4AP sensors using 2 sensors in parallel ($n = 2$). For completeness, all equations have been provided in this section. Figure 2 shows a

schematic representation of CGM data streams ($i = 1, \ldots, n$) and the attribution of sensor error to the CGM output. The blocks represent the three components of the error: BG-IG kinetics, calibration error, and random measurement noise.

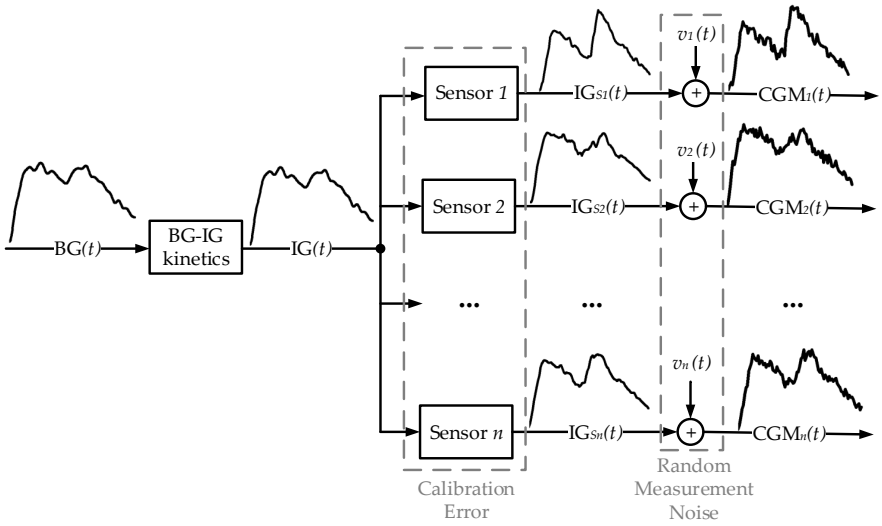

Figure 2. Description of how n parallel CGM signals are modeled. From left to right: transformation of the blood glucose (BG) signal into the interstitium glucose (IG) signal (BG-IG kinetics). Then, each of the n CGM sensors measures the IG signal, generating the IG_{Si} profile, which is susceptible to calibration error. Finally, the measured CGM_i is subject to random measurement noise, v_i.

The IG concentration is converted into a BG concentration signal through BG-IG kinetics. The IG signal does not account for physiological variability due to perturbative influences such as physical activity and is therefore, assumed to be equivalent for all CGM channels in each subject. Each of the i-th sensors ($i, \ldots, n$) measures the IG signal and generates the IG_{Si} profile.

Finally, the resultant BG output from each CGM sensor is affected by measurement noise $v_i(t)$:

$$\mathrm{CGM}_i(t) = \mathrm{IG}_{Si}(t) + v_i(t). \tag{1}$$

2.4.1. BG-IG Kinetics

The transformation of the BG signal to IG signal is modeled using the linear time-invariant two-compartment model, described in [23]. BG and IG concentrations are related by a convolution equation

$$\mathrm{IG}(t) = h(t) * \mathrm{BG}(t), \tag{2}$$

where

$$h(t) = \frac{1}{\tau} e^{-t/\tau}. \tag{3}$$

$h(t)$ is the impulse response of the BG-IG system and τ is its respective time constant.

2.4.2. Calibration Error

The relationship between IG and IG_{Si} is described as:

$$\mathrm{IG}_{Si}(t) = a_i(t)\mathrm{IG}(t) + b_i(t), \tag{4}$$

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where $a_i(t)$ is time-varying gain and $b_i(t)$ is the offset, both specific to the i-th sensor.

Polynomial models are used to obtain a flexible description for gain ($a_{ik}, k = 0, \ldots, m$) and offset ($b_{ik}, k = 0, \ldots, l$) both specific to the i-th sensor, described as:

$$a_i(t) = \sum_{k=0}^{m} a_{ik} t^k, \tag{5}$$

$$b_i(t) = \sum_{k=0}^{l} b_{ik} t^k, \tag{6}$$

where m and l are the degrees of the polynomials and will be determined from the dataset.

2.4.3. Measurement Noise

The zero-mean random measurement noise $v_i(t)$ that affects CGM_i signal is assumed to be composed by two signals: a common component $\text{cc}(t)$ and a sensor specific component $\text{ssc}_i(t)$:

$$v_i(t) = \text{cc}(t) + \text{ssc}_i(t), \tag{7}$$

where $\text{cc}(t)$ is common for all n residual profiles and $\text{ssc}_i(t)$ is specific to the i-th sensor and uncorrelated with the other sensors. Both $\text{cc}(t)$ and $\text{ssc}_i(t)$ are modeled as autoregressive (AR) processes:

$$\text{cc}(t) = \sum_{k=1}^{r} \beta_k \text{cc}(t-k) + w_{cc}(t), \tag{8}$$

$$\text{ssc}_i(t) = \sum_{k=1}^{q} \alpha_{ik} \text{ssc}_i(t-k) + w_i(t), \tag{9}$$

where r and q are the orders of the AR processes, $\{\beta_k, k = 0 \ldots r\}$ and $\{\alpha_{ik}, k = 0 \ldots q\}$ are the model parameters, and $w_{cc}(t)$ and $w_i(t)$ are zero-mean white noise processes.

2.5. Identification of the Unknown Parameters

First, the identification of the parameters of the submodels described in Equations (2), (5), and (6) was performed for all polynomial degrees of m ($m = 0, \cdots, 3$) and l ($l = 0, \cdots, 3$) in all combinations via nonlinear least squares. All estimations were done using MATLAB (Mathworks, Inc., Natwick, MA, USA). The use of nonlinear least squares simultaneously estimates all parameters at once to obtain a high goodness of fit; however, this approach may inherently produce undesirable parameters. To determine the precision of estimation, the coefficient of variation (CV) was calculated for each of the estimated parameters, and then the number of parameters that were estimated with elevated precision ((CV) < 20%) were counted.

Following the parameters estimation, the residual profile $\text{res}_i(t)$ was then computed:

$$\text{res}_i(t) = \text{CGM}_i(t) - \left(\sum_{k=0}^{m} \hat{a}_{ik} t^k \left(\frac{1}{\hat{\tau}} e^{-t/\hat{\tau}} * \text{BG}(t) \right) + \sum_{k=0}^{l} \hat{b}_{ik} t^k \right), \tag{10}$$

where $\hat{\tau}, \hat{a}_{i1}, \ldots, \hat{a}_{im}$, and $\hat{b}_{i1}, \ldots, \hat{b}_{il}$ are the outputs obtained for each combination of m and l. Except for $\hat{\tau}$, which is obtained for each individual, the other parameters represent a set of numerical values for each sensor and for each individual.

Next, the optimal order of the model was chosen by minimizing the Bayesian Information Criterion (BIC):

$$\text{BIC}_i = d \ln(\text{RSS}_i) + p \ln(d), \tag{11}$$

where d is the total number of CGM data available in each sensor and each patient, $p = (m + l + 3)$ is the number of parameters, and RSS_i is the residual sum of squares as follows:

$$\text{RSS}_i = \frac{1}{d_i} \sum_{j=1}^{d_i} \eta_j^2, \tag{12}$$

where d_i is the number of CGM samples of the i-th sensor and η is the uncorrelated version of measurement noise v_i. The BIC is a criterion for model selection among a set of models. The BIC index takes into account the statistical goodness of fit (first half of Equation (11)) and the number of parameters estimated (second half of Equation (11)), by imposing a penalty for increasing the number of parameters.

Next, to determine the optimal orders of m and l, ΔBIC was calculated as:

$$\Delta\text{BIC} = \text{BIC}_{\text{LO}} - \text{BIC}_{\text{EHO}}, \tag{13}$$

where BIC_{LO} is the lower order BIC and BIC_{EHO} is the equal or higher order BIC, determined by p. The advantages in the use of ΔBIC are: (i) it is more compact, requiring less boxplots to be plotted with no need to look at the absolute values of BIC and (ii) it is easier to read, where the distribution to the zero line is used to determine whether a more complex model should be used or not. In addition, comparing BIC values is equal to looking at the differences between the BIC for two selected models, i.e., the ΔBIC. The following steps were used to improve the choice of the orders m and l with respect to [7,8], where the orders were selected only by visual inspection of the ΔBIC boxplots. First, a t-test was performed on all combinations of BIC_{LO} and BIC_{EHO}. For normally distributed data, p-values were calculated using the *ttest*, a parametric contrast technique; all other data were analyzed using the Wilcoxon Ranksum test, a nonparametric contrast technique (α = 0.05 was considered to be the threshold of significance). The pairs of BIC_{LO} and BIC_{EHO} that obtained a statistically significant result were then ranked. The percentage of positive values and the mean of ΔBIC were used as determinants of model performance. The highest product between percentage of positive values and the mean of ΔBIC indicated the model with the highest performance.

After the optimal orders of m and l were determined, the realizations of common component, $\text{cc}(t)$, and sensor specific component, $\text{ssc}(t)$, were obtained. The availability of multiple sensors enables the decomposition of measurement noise into these two components described as follows:

$$\widehat{\text{cc}}(t) = \frac{1}{n} \sum_{i=1}^{n} \text{res}_i(t), \tag{14}$$

$$\widehat{\text{ssc}_i}(t) = \text{res}_i(t) - \widehat{\text{cc}}(t). \tag{15}$$

$\widehat{\text{cc}}(t)$ and $\widehat{\text{ssc}_i}(t)$ were then modeled as AR processes of orders r and q (Equations (8) and (9)), which were determined by minimizing the calculated BIC_{AR}:

$$\text{BIC}_{\text{AR}} = n \ln(\text{lss}) + k \ln(n), \tag{16}$$

where n is the length of the data ($\text{cc}(t)$ or $\text{ssc}_i(t)$), k is the order of the AR process, and lss is the loss function output of the MATLAB function *ar*. For each time series of $\text{cc}(t)$ or $\text{ssc}_i(t)$, BIC_{AR} was calculated for all values of k, ranging from 1 to 15. The value of k that resulted in the lowest BIC_{AR} was saved in a vector. The mode of these vectors, i.e., the orders that resulted in the minimum BIC_{AR} most often, determined the optimal orders of the AR processes of both $\text{cc}(t)$ or $\text{ssc}_i(t)$. The goodness of the AR model of optimal order (AR(optimal order)) was tested using the Anderson–Darling test. These time series objects were then merged and the population AR processes for both common component and sensor specific component were identified using their previously determined optimal orders.

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3. Results

The investigation of all combinations of m and l ranging from 0 to 3 produced intriguing hybrid results. Figure 3a depicts the boxplots of the ΔBIC between the non-hybrid models: constant versus linear ($p = 0.0004$), linear versus quadratic ($p = 0.877$) and quadratic versus cubic ($p = 0.298$). Ultimately, there were two models that we found to have the highest performances: the linear ($m = l = 1$) and the linear-quadratic ($m = 1$, $l = 2$). A summary of the results can be found in Figure 3b, where boxplots of the differences in BIC values between constant versus linear (left), constant versus linear-quadratic (middle) and linear versus linear-quadratic (right) are depicted.

The introduction of the linear term to the constant model as seen in the left boxplot has an average of 14.05 and is positive in about 62% of the cases ($p = 0.0004$), while the introduction of the linear term for m and quadratic term for l compared to the constant model is positive in 65% of the cases with an average of 16.14 ($p = 0.0002$). The right boxplot directly compares the linear model with the linear-quadratic model, which do not have a difference that is statistically significant ($p = 0.317$). The average of the right boxplot is 2.1 and is positive in about 46% of the cases.

Upon close inspection of the positivity, the mean, and the parameters estimated (see Table 2), it was found that the linear-quadratic model exhibited a performance that was only marginally higher than that of the linear model ($p = 0.0002$ vs. $p = 0.0004$) and the use of a more complex model could not be justified. Therefore, we chose to model the sensor error using the linear model because of its low complexity and high performance.

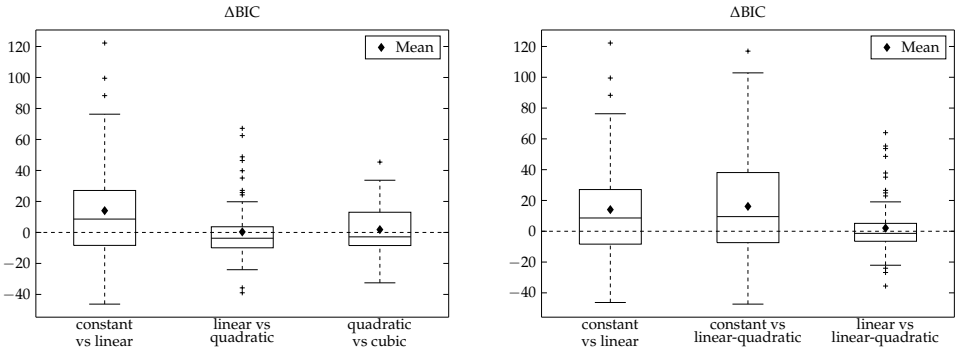

Figure 3. Boxplots of ΔBIC. (**a**) comparison between the non-hybrid models. (**b**) determination of the orders m and l of the polynomials $a_i(t)$ and $b_i(t)$. BIC, Bayesian information criterion.

3.1. Parameters Estimated

To further compare the linear and linear-quadratic models, their parameters seen in Table 2 were analyzed. Table 2 reports the mean, standard deviation (SD), and percentage of values estimated with a CV < 20%. The use of CV allows us to ensure that all parameters were estimated with reasonable precision.

A t-test was performed between the common estimated parameters (τ, a_0, a_1, b_0, and b_1) of both models and no statistically significant difference was found ($p = 0.052$, $p = 0.927$, $p = 0.882$, $p = 0.777$, and $p = 0.946$, respectively). Looking at both the SD and the number of estimated parameters with a CV < 20%, it can be seen that the SD for the parameters estimated by the linear-quadratic model are larger, which infers a higher variability with no considerable increase in precision, reflected in the CV < 20%. These comparisons further indicate that the linear model is the model of choice. Figure 4 shows the distributions of τ, a_0, a_1, b_0, and b_1 obtained applying a kernel density estimation procedure for the optimal orders $m = l = 1$.

Table 2. Mean, standard deviation, 50th, 5th, and 95th percentile values for parameters generated considering models of order $m = l = 1$ and $m = 1$, $l = 2$ and percentage of values estimated with a coefficient of variation lower than 10%, 20% and 30% for the second generation Medtronic Paradigm Veo Enlite (ENL) sensor.

Model	Parameter	Mean	SD	Percentile			% of Values Estimate with		
				50th	5th	95th	CV < 10%	CV < 20%	CV < 30%
ENL	τ	9.4	6.5	8.4	0.3	23.4	92	95	95
$m = 1$	a_0	1.1	0.4	1.1	0.7	1.8	100	100	100
$l = 1$	a_1	−0.0009	0.0016	−0.0005	−0.0044	0.0009	74	85	91
$p = 5$	b_0	−11.2	38.8	−0.5	−90.7	36.1	80	88	92
day 2	b_1	0.09	0.19	0.05	−0.13	0.52	70	81	86
	τ	10.1	7.0	9.3	1.5	24.3	97	97	97
ENL	a_0	1.1	0.4	1.1	0.6	1.8	100	100	100
$m = 1$	a_1	−0.0010	0.0018	−0.0010	−0.0041	0.0030	77	89	91
$l = 2$	b_0	−10.5	44.7	−9.0	−73.7	48.5	76	89	95
$p = 6$	b_1	0.09	0.47	0.03	−0.31	0.78	72	84	92
day 2	b_2	0.0000	0.0008	0.0001	−0.0012	0.0008	72	82	89

Abbreviations: SD, standard deviation; CV, coefficient of variation.

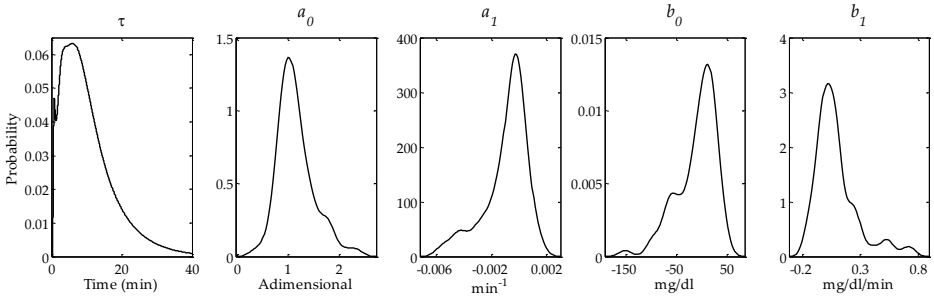

Figure 4. Probability density functions of parameters τ, a_0, a_1, b_0, and b_1 obtained applying a kernel density estimation procedure.

The mean and median of the estimated parameter of τ were 9.4 ± 6.5 min and 8.4 (5th = 0.3, 95th = 23.4) min, respectively. The gain parameters, a_0 and a_1, of the calibration error were estimated as 1.1 ± 0.4 min (median = 1.1 (5th = 0.7, 95th = 1.8)) and −0.0009 ± 0.0016 min (median = −0.0005 (5th = −0.0044, 95th = 0.0009), respectively. The offset parameters, b_0 and b_1, of the calibration error were estimated as −11.2 ± 38.8 mg/dL (median = −0.5 (5th = −90.7, 95th = 36.1)) and 0.09 ± 0.19 mg/dL/min (median = 0.05 (5th = −0.13, 95th = 0.52)), respectively.

3.2. Measurement Noise Level

Both $\mathrm{cc}(t)$ and $\mathrm{ssc}_i(t)$ have been modeled as realizations of AR processes. These signals can be optimally described by AR models of order 3, for $\mathrm{cc}(t)$ and order 2, for $\mathrm{ssc}_i(t)$. Table 3 reports the median variance of $\mathrm{cc}(t)$ and $\mathrm{ssc}_i(t)$ for the ENL (day 2), 7P (day 2) [7], G4P, and G4AP (day 4) [8] sensors. Regarding the variance of the processes, the variance of $\mathrm{cc}(t)$ is significantly greater than the variance of the $\mathrm{ssc}_i(t)$ (median values are 27.4 and 8.7 $\mathrm{mg}^2/\mathrm{dL}^2$, respectively, $p < 0.0001$ Wilcoxon Ranksum test).

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Table 3. Median variance of $\mathrm{cc}(t)$ and $\mathrm{ssc}(t)$ for the second generation Medtronic Paradigm Veo Enlite (ENL) sensor and the Dexcom SEVEN PLUS (7P), G4 PLATINUM (G4P), and advanced G4 for artificial pancreas studies (G4AP) sensors.

	Day of Analysis	Median Variance	
		$\mathrm{cc}(t)$	$\mathrm{ssc}(t)$
ENL	2	27.4	8.7
7P [A]	2	57.6	31.5
G4P [B]	4	36.3	11.7
G4AP [B]	4	31.0	8.9

[A] Values reported in [7]; [B] Values reported in [8].

The goodness of the identified AR model was validated by applying the Anderson–Darling test to the prediction-error times series $e(t)$ (further information can be found in Facchinetti et al. [7]). It was found that 86.5% of the $\mathrm{cc}(t)$ time series and 67.6% of the $\mathrm{ssc}_i(t)$ time series passed the Anderson–Darling test, signifying that these processes through AR processes of order 3 and 2, respectively, are appropriate. The population AR processes for both $\mathrm{cc}(t)$ and $\mathrm{ssc}(t)$ are described as:

$$\mathrm{cc}(t) = 1.584\,\mathrm{cc}(t-1) - 0.8842\,\mathrm{cc}(t-2) + 0.1798cc(t-3) + w_{cc}(t), \tag{17}$$

where $w_{cc}(t) = N(0, 3.98\ \mathrm{mg}^2/\mathrm{dL}^2)$ and

$$\mathrm{ssc}(t) = 1.367\,\mathrm{ssc}(t-1) - 0.4816\,\mathrm{ssc}(t-2) + w(t), \tag{18}$$

where $w(t) = N(0, 2.54\ \mathrm{mg}^2/\mathrm{dL}^2)$.

3.3. Sensor Error Dissection

We used the mean absolute relative difference (MARD) to quantify the error components and overall error. The three key components of sensor error are the BG-IG diffusion process, calibration error (calibration), and measurement noise (noise). Figure 5 shows the CGM error of the ENL sensor obtained in this study. It should be noted that the sum of the components is greater than the global MARD because the global MARD does not take into account that the two signals are measured in two different compartments. Therefore, a bias exists allowing the error of one CGM to be canceled out by the accuracy of the other and vice versa. Table 4 includes our obtained values along with the values presented by Facchinetti and colleagues [7,8]. The global mean MARD was 11.7%, the MARD related to the BG-IG was 3.6%, the MARD related to calibration was 11.3%, and the MARD related to noise was 4.2%.

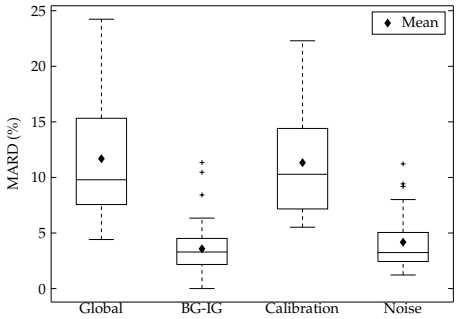

Figure 5. Boxplots of the mean absolute relative difference (MARD).

Table 4. Mean absolute relative difference (mean and median) values of the second generation Medtronic Paradigm Veo Enlite (ENL) sensor and the Dexcom SEVEN PLUS (7P), G4 PLATINUM (G4P), and advanced G4 for artificial pancreas studies (G4AP) sensors.

Sensor	Day of Analysis	MARD %				
			Global	BG-IG	Calibration	Noise
ENL	2	Mean	11.7	3.6	11.3	4.2
		Median	9.8	3.3	10.3	3.2
7P [A]	2	Mean	14.2	3.5	12.8	5.6
7P [B]	1	Median	14.1	6.8	14.1	5.4
G4P [B]	1, 4, 7	Median	11.2	4.4	9.4	3.7
G4AP [B]	1, 4, 7	Median	10.0	3.4	9.4	3.7

[A] Values reported in [7]; [B] Values reported in [8]. Abbreviations: MARD, mean absolute relative difference; BG-IG, blood glucose to interstitium glucose.

4. Discussion

This paper presents a sensor error model to represent the ENL sensor. This methodology dissects the sensor error into the delay due to the BG-IG kinetics, the calibration error, and the measurement noise. This is the first time that this methodology has been applied to the ENL sensor. The results are then compared to previously existing models of the 7P, G4P, and G4AP sensors, derived using the same methodology.

In Facchinetti et al. [7,8], $m = l = 0$ (constant), $m = l = 1$ (linear), $m = l = 2$ (quadratic), and $m = l = 3$ (cubic) were discussed in detail with a remark in Facchinetti et al. [7] stating that cases with $m \neq l$ were investigated but did not produce interesting results for their specific dataset. In contrast, when all combinations of m and l ranging from 0 to 3 were investigated in our dataset, we obtained intriguing non-hybrid and hybrid results. The boxplots of ΔBIC of the non-hybrid models exhibits more complex behavior, where the cubic model outperforms the quadratic model (Figure 3a), which was not seen in Facchinetti and colleagues [7,8]. As a result, the same methodology used by Facchinetti and colleagues [7,8], which relies on a visual inspection of the boxplots of the ΔBIC to choose model orders could not be implemented. Instead, an improved method that uses a statistical analysis of ΔBIC to determine the suitable model to represent the CGM error in the ENL sensor was employed. In the end, the linear model was chosen to model the ENL sensor.

The 7P sensor in Facchinetti et al. [7] was analyzed on day 2 after insertion and also obtained the optimal orders of $m = l = 1$, whereas, in Facchinetti et al. [8], the G4P and G4AP sensors were analyzed on days 1, 4 and 7 after insertion. Day 1 for both sensors obtained an optimal order of $m = l = 1$; however, on days 4 and 7, for both the G4P and G4AP, an optimal order of $m = l = 0$ was found. According to Facchinetti et al. [8], this lower order model found for days 4 and 7 is indicative that the time-variance of the calibration parameters of the G4P and G4AP sensors [24,25] tends to decrease during monitoring. The parameter values for the ENL sensor, the 7P sensor, and the G4P and G4AP sensors can be found in Tables 2, 5, and 6, respectively.

Table 5. The 50th, 5th, and 95th percentile values for the parameters of the Dexcom SEVEN PLUS (7P) sensor and percentage of values estimated with a coefficient of variation lower than 10% and 30%.

Model	Parameter	Percentile			% of Values Estimate with	
		50th	5th	95th	CV < 10%	CV < 30%
	τ	6.7	2.2	12.5	97	97
7P	a_0	1.1	0.5	2.4	100	100
$m = l =$ **1**	a_1	0.0002	−0.0044	0.0012	79	94
day 2	b_0	−14.8	−225.9	63.4	83	95
	b_1	0.04	−0.14	0.70	77	94

Values reported in [7]. Abbreviation: CV, coefficient of variation.

Table 6. Mean and standard deviation values for parameters and percentage of values estimated with a coefficient of variation lower than 20% for the Dexcom G4 PLATINUM (G4P) and advanced G4 for artificial pancreas studies (G4AP) sensors.

Model	Parameter	Mean	SD	% of Values Estimate with
				CV < 20%
	τ	9.7	3.6	–
G4P	a_0	1.16	0.31	100
$m = l =$ **1**	a_1	−0.000116	0.000791	97
day 1	b_0	−9.4	55.6	97
	b_1	0.0027	0.1289	91
G4P	τ	9.7	3.6	–
$m = l =$ **0**	a_0	1.04	0.16	100
day 4	b_0	2.8	15.8	100
G4P	τ	9.7	3.6	–
$m = l =$ **0**	a_0	1.05	0.18	100
day 7	b_0	1.9	25.6	100
	τ	7.7	3.0	–
G4AP	a_0	1.09	0.26	100
$m = l =$ **1**	a_1	−0.000060	0.000615	94
day 1	b_0	−6.4	50.1	94
	b_1	0.0133	0.1090	90
G4AP	τ	7.7	3.0	–
$m = l =$ **0**	a_0	1.05	0.15	100
day 4	b_0	−2.6	14.9	100
G4AP	τ	7.7	3.0	–
$m = l =$ **0**	a_0	1.07	0.13	100
day 7	b_0	−0.9	16.2	100

Values reported in [8]. Abbreviations: SD, standard deviation; CV, coefficient of variation.

The median value of τ reported in Facchinetti et al. [7] for the 7P sensor was 6.7 (5th = 2.2, 95th = 12.5) min. The mean values of τ reported in Facchinetti et al. [8] for the G4P and G4AP sensors were 9.7 $\pm$ 3.6 min and 7.7 $\pm$ 3 min, respectively. The τ of the ENL sensor has a similar average to that of the G4P but a higher amount of variability. The differences of τ seen between sensors can be attributed to greater delay variability, with respect to physiological variability and metabolic conditions [18], as well as varying sensor conditions, i.e., a larger range of CGM values in Christiansen et al. [24] and Garcia et al. [25]. Furthermore, the estimated τ for the G4P sensor is higher (Table 6) than that reported in Keenan et al. (7.94 $\pm$ 6.48 min) [26], where the same sensor was

analyzed. The variability observed in the time lag is well explained by the complexity of the plasma to interstitial glucose relationship [27].

The gain (a_0 and a_1) and the offset (b_0 and b_1) of the calibration error revealed that the G4P and G4AP sensors outperformed both the 7P and ENL sensors, while the a_0 parameter was estimated similarly for all sensors. The a_1, b_0, and b_1 parameters all had a higher mean and variation in the ENL sensor when compared to the G4P and G4AP sensors on day 1. The ENL and 7P sensors had similar median estimations for all parameters except b_0, where the 7P sensor exhibited a greater amount of error , possibly attributed to sensor drift and the accuracy of the estimated background current.

It has been observed that the CV found for the 7P, G4P and G4AP sensors are higher for the estimated parameters of a_1, b_0, and b_1. It is possible that the equation used to describe calibration error does not capture the behavior of the ENL sensor entirely and higher order models may be required as found by Laguna et al. [18] to explain the filtering and calibration algorithms used in this particular sensor.

In Facchinetti et al. [8], the authors report the median variance of $\mathrm{cc}(t)$ and $\mathrm{ssc}_i(t)$ for days 1, 4, and 7 of the G4P and the G4AP (Table 3). Day 1 infers that the sensor has been very recently inserted, while day 7 is near the end of the life of the sensor. Therefore, day 4 (standard working modality), which is not affected by the Foreign Body Response (FBR) or sensor hydration in the early stages of insertion [28,29] nor biofouling in the later stages of the sensor life [30], is the most appropriate day to compare to the ENL sensor on day 2. These values of variance are lower than those of the 7P, G4P, and G4AP sensors.

As reported in [7,8] we found that calibration error had the highest contribution to the global error observed. However, there was also a large number of outliers, showing that there may be higher variability in the error experienced by the ENL sensor than that of the 7P, G4P, and G4AP sensors. The BG-IG compares BG and IG time series, calibration compares IG with IG_{Si} and noise compares IG_{Si} and CGM_i. Table 4 includes our obtained values along with the values presented in [7,8].

In [7], the mean MARD values for the 7P on day 2 are presented, while, in [8], the median MARD values of the 7P on day 1, and the G4P and G4AP on days 1, 4 and 7 are shown (Table 4). The comparison of the mean values between the ENL and 7P sensors [7] revealed a MARD reduction in not only the global analysis, but also in two of the three error components. The global mean MARD, the mean MARD related to calibration, and the mean MARD related to the noise of the ENL sensor all showed reductions when compared to the 7P, G4P, and G4AP sensors. The only error component that showed a higher value on the mean MARD was the BG-IG. The IG profile was obtained using the parameter τ and, as affirmed in [7], the estimation of τ is much more robust when multiple CGM sensors are present. Four CGM sensors in parallel ($n = 4$) were used in [7], while, in our study and in [8], two sensors in parallel ($n = 2$) were used.

The comparison of the median values between the ENL and the 7P, G4P, and G4AP sensors [8] showed a MARD reduction in the global analysis and in two of the three error components (Table 4). The global median MARD, the median MARD related to the noise, and the median MARD of the BG-IG of the ENL sensor all showed reductions when compared to the 7P, G4P, and G4AP. The median MARD related to calibration showed a reduction when compared to the 7P, but increased when compared to the G4P and G4AP. On average, all of the components showed a reduction of the median MARD of approximately 39% (7P), 9% (G4P) and 2% (G4AP). The global median MARD was reduced more than 30% (7P), 12% (G4P), and 2% (G4AP). In [8], only the day 1 MARD values were reported for the 7P, while the MARD data for days 1, 4 and 7 were aggregated for the G4P and G4AP. This aggregation of data amplifies the CGM error experienced, by combining the day of insertion (day 1) in which the signal is often unstable and more likely to be inaccurate [29] with the error near the end of the sensor life (day 7) [30].

A further comparison of the study protocol must be done to explain differences in the results we obtained compared to those of [7,8]. The protocol for Facchinetti et al. [7] can be found in Castle et al. [31], and, for Facchinetti et al. [8], the protocol can be found in Bailey et al. [32] (7P),

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Christiansen et al. [24] (G4P), and Garcia et al. [25] (G4AP). Table 7 presents the amount of subjects, inpatient sessions, duration of sessions, and the day at which the sensor was analyzed for all the studies compared in this paper. In this study and Castle el al. [31], the trials were done in a relatively controlled environment. In our CGM dataset, a rate of change between −1 and 1 mg/dL/min for 77.34% of the time was observed (Figure 6) and 97.76% of the values were in the euglycemic and hyperglycemic range (Table 8). While, in Bailey et al. [32], Christiansen et al. [24], and Garcia et al. [25], the meals, insulin doses, and meal timing were manipulated to obtain a full range of glucose values (from <60 mg/dL up to 400 mg/dL) during the in-clinic sessions.

Table 7. The total amount of subjects, in-clinic sessions, duration of each session, and number of days after sensor insertion for the datasets compared of the second generation Medtronic Paradigm Veo Enlite (ENL) sensor and the Dexcom SEVEN PLUS (7P), G4 PLATINUM (G4P), and advanced G4 for artificial pancreas studies (G4AP) sensors.

Sensor/Trial	Subjects	Sessions	Duration (h)	Sensor Day
ENL	10	37	8	2
7P [31]	19	36	9	2
7P [32]	53	53 *	8	1, 4, 7
G4P [24] G4AP [25]	36	108 *	12	1, 4, 7

* Not explicitly stated; calculated from known information.

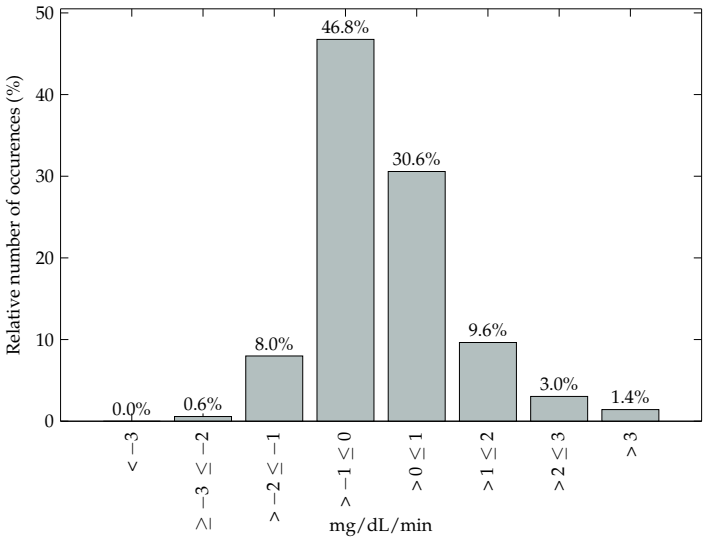

Figure 6. Glucose rate of change during trials.

Table 8. Samples separated per glycemic range. Time (%) and mean absolute relative difference (mean and standard deviation).

Glycemic Range (mg/dL)	*n*	Time	MARD	
		%	Mean	SD
<70	160	2.25	16.59	13.60
70–180	4584	64.45	12.60	10.84
>180	2369	33.31	9.57	9.08
Overall	7113	100	11.68	10.48

Abbreviations: MARD, mean absolute relative difference; SD, standard deviation.

This explains the higher MARDs presented in Facchinetti et al. [8], where it has been shown that, during rapidly changing conditions such as during a large meal or a hypoglycemic episode, CGM performance is poor [23,33–36]. It has been reported that, when compared, the G4P and ENL sensors exhibit a lower performance, especially in the hypoglycemic range [37]. To improve the comparison between the ENL, 7P, G4P, and G4AP sensors, datasets of the ENL and 7P sensors with similar conditions should be observed modeled. However, acquiring such a dataset is not easy and very expensive, since it requires an ad hoc trial and hospitalization for several hours in order to acquire frequent BG measurements in parallel to CGM data along with further safety measures for obtaining a full range of glucose values. At this point in time, this is the dataset available for the modeling of the error of the ENL sensor. With the availability of a dataset that observes a full range of glucose values as seen in [24,32], the ENL sensor error model and the comparison between sensors can be further improved.

Additionally, as seen in Table 7, 10 subjects were used in this study. In order to derive a solid model CGM sensor error, the dataset should be sufficiently large and represent the T1D population and its variability well. However, as stated above, acquiring such a dataset is difficult and very expensive. As previously mentioned and pointed out by Rossetti et al. [20], the dataset used in this paper was not acquired to derive CGM error model, but to compare CL and OL treatment during postprandial period. However, the dataset was suitable (even if not optimal) for the derivation of ENL sensor error into its different components and for comparing the resultant model with the previously decomposed error of other CGM sensors described in [7,8]. The ENL sensor error model could be refined with the availability of a larger dataset.

5. Conclusions

Not all CGMs are equal, and modeling and dissecting the error of various sensors allows us to understand the different errors that can be specific to a brand or model. In the present paper, we have modeled the ENL sensor, which is manufactured by Medtronic. The purpose of this paper was to apply an improved version of a previously presented CGM error modeling procedure [7,8], highlight any errors or sensor behavior that may be unique to the ENL sensor, and to compare sensor error in the ENL sensor to the error found in several sensors manufactured by Dexcom: the 7P, G4P, and G4AP.

The dissection of the sensor error into different components provided evidence that a large portion of CGM accuracy is related to the calibration, which was also reported by Facchinetti and colleagues [7,8]. The values of the mean and median MARD of the different components of the error showed a reduction in the majority of cases when compared to the values in Facchinetti and colleagues [7,8]. However, we must highlight that not only were the sensors that were analyzed different, there was also a large variation with regard to the day of sensor insertion and the protocol of the clinical trials conducted. The ENL sensor should be modeled using the same protocol found in Facchinetti et al. [8]. This will allow a more direct comparison of the ENL sensor to the 7P, G4P, and G4AP sensors Facchinetti et al. [8].

The models produced in this paper and by Facchinetti and colleagues [7,8] are intended to be used to create a sensor model bank that can be employed in a simulator to create more realistic simulations

of real-life conditions and be used to enhance the performance of an AP system. Future works will compare the error created by the implementation of these models versus those of current simulators, which use white noise to create CGM error. Furthermore, additional models for each day of sensor life will be helpful in understanding the performance of the ENL sensor.

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Author Contributions: L.B. and C.R. modeled the sensor error, researched data, wrote the manuscript, contributed to discussion, and reviewed/edited the manuscript. A.F., Y.L., and J.V. provided guidance in modeling, contributed to discussion, and reviewed/edited the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

7P: SEVEN PLUS Sensor
AP: Artificial Pancreas
AR: Autoregressive
ARMA: Autoregressive Moving Average
BG: Blood Glucose
BG-IG: Blood-to-Interstitium Glucose Kinetics
BIC: Bayesian Information Criterion
BMI: Body Mass Index
CGM: Continuous Glucose Monitor
CH: Carbohydrate
CL: Closed-Loop
CSII: Continuous Subcutaneous Insulin Infusion
CV: Coefficient of Variation
ENL: Second Generation Medtronic Paradigm Veo Enlite Sensor
FDA: Food and Drug Administration
FBR: Foreign Body Response
G4AP: Advanced G4 Sensor for Artificial Pancreas Studies
G4P: G4 PLATINUM Sensor
IG: Interstitial Glucose
MARD: Mean Absolute Relative Difference
OL: Open-Loop
SD: Standard Deviation
SMBG: Self Monitoring Blood Glucose
SMRC: Sliding Mode Reference Conditioning
T1D: Type 1 Diabetes

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2.2 Extensive Assessment of Blood Glucose Monitoring During Postprandial Period and Its Impact on Closed-Loop Performance

The candidate's contribution for this publication consisted in pre-processing the data obtained in the clinical trial, researching data, analyzing CGM accuracy and precision during PP, writing the manuscript, contributing to discussion, and editing the manuscript throughout the review rounds. During the development of the work, the candidate worked with her colleague Arthur Bertachi. They were assisted by Dr. Ignacio Conget, Dr. Carmen Quirós, Dr. Marga Giménez, Dr. F. Javier Ampudia-Blasco, Dr. Paolo Rossetti, Dr. Jorge Bondia and Dr. Josep Vehí, who provided guidance to the analysis of accuracy, contributed to discussion, reviewed the manuscript and designed the clinical study from which the data was derived.

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Extensive Assessment of Blood Glucose Monitoring During Postprandial Period and Its Impact on Closed-Loop Performance

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Abstract

Background: Closed-loop (CL) systems aims to outperform usual treatments in blood glucose control and continuous glucose monitors (CGM) are a key component in such systems. Meals represents one of the main disturbances in blood glucose control, and postprandial period (PP) is a challenging situation for both CL system and CGM accuracy.

Methods: We performed an extensive analysis of sensor's performance by numerical accuracy and precision during PP, as well as its influence in blood glucose control under CL therapy.

Results: During PP the mean absolute relative difference (MARD) for both sensors presented lower accuracy in the hypoglycemic range (19.4 ± 12.8%) than in other ranges (12.2 ± 8.6% in euglycemic range and 9.3 ± 9.3% in hyperglycemic range). The overall MARD was 12.1 ± 8.2%. We have also observed lower MARD for rates of change between 0 and 2 mg/dl. In CL therapy, the 10 trials with the best sensor spent less time in hypoglycemia (PG < 70 mg/dl) than the 10 trials with the worst sensors (2 ± 7 minutes vs 32 ± 38 minutes, respectively).

Conclusions: In terms of accuracy, our results resemble to previously reported. Furthermore, our results showed that sensors with the lowest MARD spent less time in hypoglycemic range, indicating that the performance of CL algorithm to control PP was related to sensor accuracy.

Keywords

accuracy, closed-loop control, continuous glucose monitoring, postprandial period, type 1 diabetes

Achieving recommended glycemic targets is difficult for patients with type 1 diabetes (T1D), despite high motivation and substantial time spent for controlling in everyday life. Currently, despite increasingly effective treatments and glucose monitoring systems, the majority of individuals with T1D still cannot achieve recommended glycemic goals. In this context, there is an increasing awareness that maybe the best solution for T1D patients could be a closed-loop system that can independently restore insulin needs and provide good glycemic balance. This system can deliver insulin automatically, by continuous subcutaneous insulin infusion (CSII). In addition, a designed glycemic control algorithm calculates de amount of insulin to be delivered based on continuous glucose measurements obtained by means of a subcutaneous glucose sensor connected wireless to a glucose monitor, that is, continuous glucose monitoring (CGM).[1]

Accuracy of CGMs' measurements has been improved over the years, and the FDA has recently approved the commercialization of a closed-loop (CL) device that relies on

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Table 1. Demographic Characteristics of the Data Set Used.

Characteristic	Overall
Number of T1D patients (n)	20
Gender (M/F) (n)	7/13
Age (years)	40.7 ± 10.4
HbA1c (%)	7.8 ± 0.7
BMI (kg/m^2)	25.7 ± 3.0
Diabetes duration (years)	22.2 ± 9.9
Time with CSII (years)	7.2 ± 4.4

Values are mean ± SD unless otherwise noted.

CGM measures to automatically delivery insulin to T1D patients. As CGM measures the glucose in the interstitial fluid, there is a physiological delay due to the fact that glucose must be transported from blood to interstitium. Besides that, inherent sensor properties and the dynamic profile of PG excursions affect sensors' accuracy.[2-4] Therefore, a mismatch in relation to the blood glucose measurements is still present. Consequently, these differences diminish controller's performance and glycemic management, but it is not an impediment for the usage in CL systems.[5] In a previous study,[6] the consequences of CGM limitations were analyzed in-silico in CL performance, by incorporating real CGM device characteristics into the UVa/Padova simulator. This study showed that poorly CGM performance might have a relevant impact on closed-loop outcomes. In addition, in another study, lack of CGM accuracy resulted in poor post-breakfast control and patients with most hypoglycemic alarms were also those with the highest CGM's errors.[7]

In this study, an evaluation of numerical and clinical accuracy of Paradigm Veo® system with the Enlite-2 sensors® (ENL; Medtronic MiniMed, Northridge, CA) was performed during postprandial period (PP), using data obtained from a previous closed-loop clinical trial.[8] In addition to this, the individual performance closed-loop trials across the study was also assessed according to the accuracy of the sensors in each trial.

Methods

Study Procedure, Devices and Population

Twenty T1D subjects underwent an 8-hour standardized mixed meal test (60 g carbohydrate, CHO) on 4 occasions. On 2 occasions (open loop [OL]), conventional CSII was used and boluses were based on the individual insulin-to-carbohydrates ratios. On the other two occasions, after a meal-announcement, an augmented bolus was given, followed by manual adjustments of the basal rate every 15 minutes according to a CL controller recommendation.

CSII was carried out with the Paradigm Veo insulin pump and CGM using ENL. Two CGM were inserted at least 24 hours before the meals tests and were calibrated using the Contour® Next Link (Ascensia Diabetes Care Holdings AG, Basel, Switzerland; formerly Bayer) 30 minutes before a lunch meal. Although two sensors were used during the study for safety and regulatory reasons, only one was used to feed the CL algorithm. The second sensor was used just in case of failure or malfunction of the first sensor. Definition of the primary CGM (hereafter Main CGM) was performed automatically by the system, based on an accuracy analysis prior to the start of the CL operation. Malfunction has been defined as absolute relative difference (ARD) greater than 30% between CGM and plasma glucose (PG) reference at two consecutives samples or greater than 40% at one-time point.

Two venous lines were prepared, one for arterialized venous blood sampling and the other for insulin/glucose infusion, if required. PG samples were measured every 15 minutes using YSI 2300 Stat Plus Glucose Analyzer (YSI Inc, Yellow Springs, OH, USA). To ensure comparable metabolic conditions between studies, subjects received intravenous infusion of regular human insulin or glucose to maintain PG at 90-100 mg/dl, until the beginning of studies at 12:00. During an 8-h period, postprandial glucose was monitored and OL or CL insulin therapies were applied. Following insulin administration, if PG fell below 70 mg/dl during two consecutive readings, a fixed amount of 15 g of oral glucose was administered to prevent hypoglycemia. Table 1 summarizes the main demographics characteristics of the patients included in this study. Figure 1 shows the protocol details during the sessions. More information about the trial can be found elsewhere.[8]

Data Analysis

CGM data were registered every 5 minutes and PG data were recorded every 15 minutes. To align CGM and PG data, CGM data were linearly interpolated and rounded to 1 sample per minute. Missing data were not interpolated.

In this work, the accuracy and precision of the CGM sensors were evaluated by the mean absolute relative difference (MARD) and precision absolute relative difference (PARD).[9-13] Due to the specific conditions and duration of the trial, we perform the analysis of the short-term MARD (during 8-h) in this work, however, the term MARD is used in the text. The performance of the CL trials was assessed according to the 10 best and worst accurate sensors, sorted by the MARD. Clinical accuracy was analyzed with the Clarke's error grid analysis (EGA),[14] International Organization for Standardization (ISO) criteria (ISO 15197:2013),[15] and Bland-Altman analysis.[16]

Overall average and aggregated MARD and PARD were calculated for all sessions and categorized into glucose ranges <70, 70-180, and >180 mg/dl, as it was performed in other studies.[10,11] The average MARD and PARD results were evaluated as averages across all the sessions. MARD and error (error = PG – CGM) were also analyzed according to the PG rate of change.

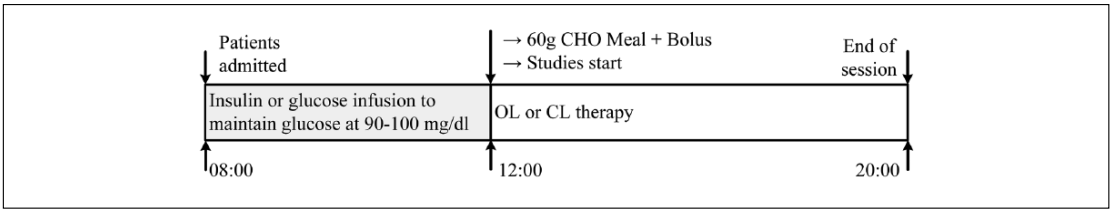

Figure 1. Protocol design of the OL and CL sessions.

Table 2. MARD for the 10 Best and 10 Worst Main Sensors of the CL Trials.

	Main CGM	
	Average MARD (%)	Aggregated MARD (%)
10 best sensors	4.5 ± 0.9	4.5 ± 4.7
n	10	327
10 worst sensors	19.8 ± 7.5	19.8 ± 13.0
n	10	335

Relative differences were evaluated as averages across all the sessions (n = 74 and n = 148, for PARD and MARD, respectively). The aggregated MARD and PARD were calculated as the aggregated mean of overall data. The average MARD and PARD in the glucose ranges considered only the sessions that presented hypoglycemic or hyperglycemic events. Aggregated MARD and PARD in the glucose ranges considered all MARD and PARD data categorized in each glucose range. For the CL sessions, the average and aggregated MARD results of the Main CGM were compared with the results of both CGMs (ie, if only 6 of all the sessions presented hypoglycemic events, the MARD results on the hypoglycemic range will count with n = 12 when both CGMs are considered or n = 6, if only the Main CGM is considered).

Different values of average and aggregated MARD and PARD are expected due to the number of individual paired data points is not exactly the same from subject to subject as well as the amount of time spent in each glucose concentration.

The MARD of the main sensor of CL trials was sorted ascendingly. The 10 most accurate sensors were chosen as the 10 best CL sensors. The 10 least accurate sensors were chosen as the 10 worst CL sensors. This allowed the evaluation of the effects of the accuracy of the sensors in the CL trials.

Times in each glycemic range were calculated for PG and CGM measurements for the sessions with 10 best and 10 worst CL sensors. Results were analyzed through mean ± standard deviation (SD) and median (interquartile range [IQR]). The Anderson-Darling normality test was used to determine the normality of the data. For data that does not follow a normal distribution, the sign test was used. A significance level of .05 was considered.

Results

The impact of accuracy of CGM was observed during 8-hour PP. During the CL sessions, a meal bolus was combined with the controller's insulin infusion, as a feedforward action, to reduce the prandial peak. It is well known that meals are the major disturbance that causes large glycemic excursions. In our study, even with a meal contending 60 grams of CHO, the majority (77.1%) of the rates of change of glycemia were between –1 and 1 mg/dl/min.

Effects of the CGM Accuracy in Closed-Loop Performance

Table 2 presents the MARDs of the 10 best and 10 worst main sensors of the CL trials. Both average and aggregated MARDs of the 10 best are about 15.3% lower than average and aggregated MARD of the 10 worst sensors.

Table 3 presents the time (in minutes) spent in, above, and below the range for 10 best CL sensors and 10 worst CL sensors, calculated either with PG or CGM measurements. Table 4 shows the glucose rescues during the CL therapy. In only one of the 10 trials that considered the best sensors occurred hypoglycemia and administration of oral glucose (rescue) one time. When the 10 trials with the worst sensors were considered, in five trials there was administration of oral glucose, with a total of 13 rescues. Figure 2 shows the mean values of CGM and PG readings for the 10 CL trials with worst MARD. Figure 2a represents the 5 trials in which no glucose rescues were required, and Figure 2b shows the 5 trials in which glucose rescues were necessary.

MARD and PARD

Table 5 shows the average and aggregated MARD and PARD for all sessions. The overall average and aggregated MARD were equal to 12.0 ± 7.5% (n = 148, 74 sessions, 2 sensors per session) and 12.0 ± 11.2% (n = 4851), respectively.

Average and aggregated MARD in the euglycemic range were equal to 12.5 ± 8.2 (n = 148) and 12.3 ± 11.5 (n = 3216), respectively. These values were higher than the values obtained in the hyperglycemic range, where better accuracy was achieved.

Table 3. Time Spent In, Above, and Below the Range in Each 10 Best CL Sensors and 10 Worst CL Sensors, Calculated Either With PG or CGM Measurements.

		Time in, above, and below range (min)					
		70-180		>180		<70	
	Study	Mean	Median (IQ range)	Mean	Median (IQ range)	Mean	Median (IQ range)
PG	10 best sensors	403 ± 94	443 (375-481)	76 ± 96	39 (0-106)	2 ± 7	0 (0-0)
	10 worst sensors	396 ± 94	420 (375-477)	53 ± 95	2 (0-95)	32 ± 38	19 (0-65)
P			.5078		.7266		.0313
CGM	10 best sensors	408 ± 94	454 (364-480)	67 ± 98	0 (0-117)	4 ± 11	0 (0-0)
	10 worst sensors	360 ± 102	328 (302-472)	54 ± 66	32 (0-97)	65 ± 61	71 (0-126)
P			.7539		1		.0313

Results are shown in minutes.

Table 4. Glucose Rescues During CL Therapy.

	Trials with glucose rescue	Total of rescues
10 best sensors	1	1
10 worst sensors	5	13

Figure 3 shows an illustration of the CGMs readings considering the best and the worst average PARD values between all sessions. PG reference is also shown. Figure 3a shows that the readings of CGM1 and CGM2 almost overlap each other, which indicates a good precision. Figure 3b shows the worst average PARD value obtained between all sensors. This graph illustrates a lack of precision between this pair of CGMs. Considering Figure 3b, at the beginning of the session, both CGMs present small variations in relation to the PG reference. After approximately one hour of the beginning of the session, both sensors diverge from the PG reference: CGM1 is higher than PG reference and CGM2 is lower than PG reference. CGM1 is overestimating PG, it could lead to excessive insulin delivery and development of hypoglycemia. Analogously, CGM2 is underestimating PG, which could lead to hyperglycemia due to the lack of insulin. However further conclusions regarding the error must take into account the control algorithm embedded in each CL system.

MARD—Main CGM

Table 6 compares the value of the MARD for the CL trials using both CGM sensors and using the Main CGM. It is clear that the overall average and aggregated MARD values for the Main CGM are lower than when both CGMs are considered. This happens due to the procedure of switching between the two CGMs to use the best one as the input of the control algorithm.

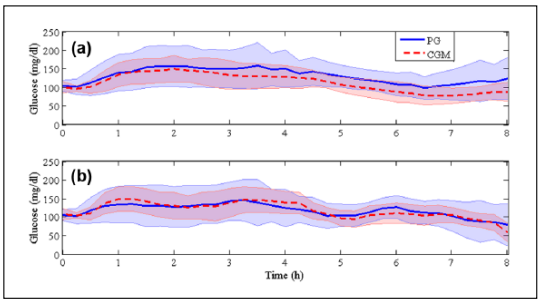

Figure 2. Mean ± SD of PG and CGM readings for the CL trials with 10 worst MARD. (a) Sessions in which glucose rescues were not required. (b) Sessions in which glucose rescues were necessary due to PG readings below 70 mg/dl.

Accuracy According to PG Rate of Change

Table 7 shows the MARD, median ARD and the mean error related to the PG rate of change. We observed an increase in MARDs as absolute value of rate of change increases, especially for negative values of changes. In accordance with other publication,[17] sensor errors tend to be positive (CGM readings lower than PG) when the PG rate of change is positive and negative (CGM readings higher than PG) when the PG rate of change is negative.

Table 5. Average and Aggregated MARD and PARD for All Sessions.

	Average	Aggregated	Average	Aggregated
	MARD, %	MARD, %	PARD, %	PARD, %
Overall	12.0 ± 7.5	12.0 ± 11.2	13.4 ± 12w.9	13.4 ± 15.8
n	148	4851	74	35196
<70 mg/dl	18.9 ± 11.9	18.8 ± 14.0	25.4 ± 18.9	29.7 ± 20.8
n	42	182	24	1248
70-180 mg/dl	12.5 ± 8.2	12.3 ± 11.5	13.5 ± 13.1	13.7 ± 16.5
n	148	3216	74	23922
>180 mg/dl	10.3 ± 8.7	10.4 ± 9.6	11.3 ± 12.0	10.7 ± 11.3
n	112	1453	57	10026

Data are expressed as Mean ± SD. MARD is categorized by PG reference and PARD is categorized by average of sensors readings.

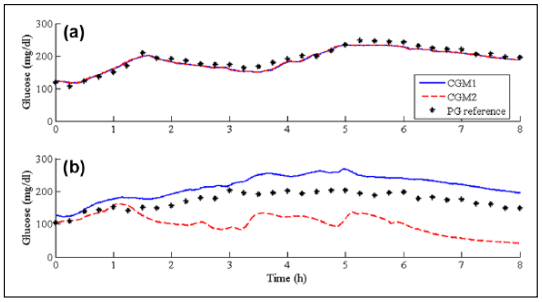

Figure 3. Illustration of CGMs readings considering (a) the best average PARD values between all sessions and (b) the worst average PARD values between all sessions.

Analysis of Clinical Accuracy

The analysis of clinical accuracy has been performed using Clarke EGA, ISO Criteria and Bland-Altman Analysis. Considering both CGM sensors and all sessions (n = 2630), the EGA yielded 83.45%, 15.32%, 0.02%, 1.22%, and 0.00% of paired measurement results in zones A, B, C, D, and E, respectively. According to the ISO Criteria, 82.05% of the data pairs were considered correct and 17.95%, incorrect. Considering the Bland-Altman analysis, the mean of the differences between PG and CGM readings is equal to 2.44 ± 23.73 mg/dl, with agreement limits of +48.96 mg/dl and –44.07 mg/dl. Numerically, 94.9% of the data lied between the agreement limits.

Discussion

In our study, ENL showed in the PP numerical accuracy closed to that previously reported in different glucose ranges in other time periods of the day and tends to be lower with higher rates of change in glucose. More importantly, our results indicate that the accuracy of the sensor could be strongly related to the controller's performance in CL trials.

We evaluated the consequences of the CGM accuracy in the performance of our CL studies using data from the best and worst accurate sensors according to MARD. The performance of these trials was assessed by the time spent in each predefined glycemic range and also by the quantity of glucose rescues for hypoglycemia that were administered during the sessions. Considering PG readings, the median time spent in euglycemic range was comparable for the trials with both 10 best and 10 worst sensors (443 vs 420 minutes). The analysis of the same metric using CGM readings showed greater difference (454 vs 328 minutes). However, no statistical difference has been observed in the results.

There was a significant reduction in the time spent in the hypoglycemic range, when 10 best and worst sensors were compared, for both PG and CGM measures. For both PG and CGM readings, the median time spent in hypoglycemic range for the 10 best sensors was 0 minutes. Whereas the median time spent in the hypoglycemic range during the trials with the 10 worst sensors was 19 and 71 minutes, for PG and CGM readings, respectively. Moreover, regarding to the number of rescues in case of hypoglycemia (PG < 70 mg/dl), there was only one case of administration of oral glucose when the best sensors were considered, while there were five trials that required administration of oral glucose when the worst sensors were used.

To analyze the type of error that induces hypoglycemic events, the 10 worst CL sessions according to MARD were divided in two groups: sessions with and without glucose rescues. Each one of these groups contains five sessions. According to Figure 2a, the mean values of CGM readings are consistently below the mean values of PG readings for the trials that did not require glucose rescues. However, in Figure 2b the mean values of CGM and PG readings the same behavior is not noticed. During different times of the sessions the mean CGM readings are higher than the mean PG readings, which led to excessive insulin delivery for the five sessions that required glucose rescues.

So far, to the authors knowledge, no other publications reported PARD results for ENL, impeding a direct comparison

Table 6. MARD of CL Sessions: MARD of Both CGM Sensors Compared With Main CGM.

	Both CGMs		Main CGM	
	Average MARD, %	Aggregated MARD, %	Average MARD, %	Aggregated MARD, %
Overall	12.1 ± 8.2	12.1 ± 11.7	10.7 ± 7.1	10.8 ± 10.3
n	74	2439	37	1220
<70 mg/dl	19.4 ± 12.8	19.4 ± 14.2	17.6 ± 10.3	17.8 ± 12.4
n	28	110	14	56
70-180 mg/dl	12.2 ± 8.6	11.9 ± 11.4	11.0 ± 8.1	10.7 ± 10.2
n	74	1924	37	962
>180 mg/dl	9.3 ± 9.3	11.4 ± 12.2	7.8 ± 6.6	9.2 ± 9.5
n	46	405	23	202

Data are expressed as Mean ± SD.

Table 7. Mean and Median ARD Related to the PG Rate of Change.

Rate of change, mg/dl/min	MARD, %	Median ARD (IQ range), %	Mean error, mg/dl
< –3 (n = 14)	16.95 ± 11.08	14.12 (8.04-29.04)	–4.86 ± 20.17
≥ –3 ≤ –2 (n = 28)	22.81 ± 17.02	17.48 (12.45-29.99)	–11.63 ± 26.25
> –2 ≤ –1 (n = 382)	16.63 ± 13.86	13.62 (5.77-22.57)	–6.37 ± 20.62
> –1 ≤ 0 (s 2195)	11.85 ± 10.85	8.93 (3.86-16.38)	–0.39 ± 16.06
> 0 ≤ 1 (n = 1429)	11.06 ± 10.21	7.97 (4.11-14.64)	1.5 ± 14.98
> 1 ≤ 2 (n = 489)	11.00 ± 11.50	7.13 (3.20-14.49)	5.94 ± 14.77
> 2 ≤ 3 (n = 132)	11.61 ± 11.71	8.77 (3.63-14.48)	9.38 ± 13.57
> 3 (n = 36)	17.7 ± 13.85	15.69 (6.42-26.11)	16.98 ± 14.75

and evaluation of our results. Pleus and his colleagues[11] presented an evaluation of average and aggregated PARD of Dexcom G4® stand-alone CGM system (Dexcom, San Diego, CA) for 7 days, including periods of induced glucose excursions. Overall average and aggregated PARD presented by them was considerably lower than the values our study. In their study, overall PARD equals to 7.3 ± 1.9 (n = 10), and 7.3 ± 8.1 (n = 96 430), average and aggregated, respectively. Our values are about 80% higher than the values obtained by Pleus et al.[11]

We observed different values of average and aggregated PARD for different glucose ranges. Sensor precision is poor in the hypoglycemic range, according to our results. Pleus and his colleagues[11] showed that the G4 sensor is less precise during the hypoglycemic range. For both sensors, the best PARD results were obtained in the hyperglycemic range.

The average and aggregated MARD obtained in our study are lower than the values obtained by Kropff and his colleagues,[18] but they used a previous version of the sensor than the one we used in our project. In both studies the worst performance was obtained in the hypoglycemic range. In another study,[19] two Enlite sensors were inserted in the abdomen and evaluated for 24 hours in adults in a clinical research center. Similarly to our trial, sensors were calibrated at the beginning of each visit but with the possibility of being recalibrated posteriorly. Overall median ARD was 12.6% when CGM measures were compared with venous blood samples, a value almost identical to the MARD obtained by us.

The effects of rate of change in MARD has also been investigated by Pleus and colleagues.[20] Their results indicates that faster glucose concentration changes result in a more pronounced apparent decrease in accuracy. However, in our results, the MARD for glucose values rising between 2 and 3 mg/dl/min was smaller than the MARD for glucose values falling between –2 and –1 mg/dl/min (11.61 vs 16.63%).

Finally, the comparison of the accuracy between the Main sensor and both sensors showed, as expected, that the values presented for the Main CGM were lower than the values for both CGM. It should be pointed out that this comparison is far from a realistic situation because in real-life use of CGM (including CL systems) only one CGM device will be used.

In addition to the previously mentioned novelties, our study has also some limitations. Our study was designed and performed in a controlled clinical research in-patient environment and during the PP using a single meal with a specific composition. This limits extrapolation of results to daily life conditions usage of CGM.

Conclusions

In this work we analyzed the short-term accuracy of the ENL sensor during PP considering operation in OL and CL. In summary, the ENL showed in the postprandial period accuracy closed to that previously reported in previous studies.

We also noticed that lower errors are related to lower rates of change of glucose.

Considering the sensors used during CL operation, we noticed the trials with the 10 best sensors spent less time in the hypoglycemic range than the trials with the 10 worst sensors and required less glucose rescues. For the trials with worst sensors that did not require glucose rescues, the mean value of PG was consistently higher than the mean value of CGM.

Abbreviations

ARD, absolute relative difference; CGM, continuous glucose monitor; CHO, carbohydrate; CL, closed loop; CSII, continuous subcutaneous insulin infusion; EGA, error grid analysis; ENL, Paradigm Veo system with the Enlite-2 sensors; IQR, interquartile range; ISO, International Organization for Standardization; MARD, mean absolute relative difference; OL, open loop; PARD, precision absolute relative difference; PG, plasma glucose; PP, postprandial period; SD, standard deviation; T1D, type 1 diabetes;

Authors' Note

An abstract containing partial results from this study was presented in a poster presentation at the Advanced Technology and Therapeutics in Diabetes (ATTD) Conference in Paris, February 15-18, 2017.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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2.3 Accuracy of CGM before, during, and after Aerobic and Anaerobic Exercise in Patients with Type 1 Diabetes Mellitus

The candidate's contribution for this publication consisted in pre-processing the data obtained in the clinical trial, researching data, analyzing CGM accuracy during aerobic and anaerobic exercise sessions, writing the manuscript, contributing to discussion, and editing the manuscript throughout the review rounds. During the development of the work, the candidate worked with her colleague Arthur Bertachi. They were assisted by Dr. Carmen Quirós, Dr. Marga Giménez, Dr. Ignacio Conget, Dr. Jorge Bondia and Dr. Josep Vehí, who provided guidance to the analysis of accuracy, contributed to discussion, reviewed the manuscript, conceived and designed the experiments from which the data was derived.

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Article

Accuracy of Continuous Glucose Monitoring before, during, and after Aerobic and Anaerobic Exercise in Patients with Type 1 Diabetes Mellitus

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Abstract: Continuous glucose monitoring (CGM) plays an important role in treatment decisions for patients with type 1 diabetes under conventional or closed-loop therapy. Physical activity represents a great challenge for diabetes management as well as for CGM systems. In this work, the accuracy of CGM in the context of exercise is addressed. Six adults performed aerobic and anaerobic exercise sessions and used two Medtronic Paradigm Enlite-2 sensors under closed-loop therapy. CGM readings were compared with plasma glucose during different periods: one hour before exercise, during exercise, and four hours after the end of exercise. In aerobic sessions, the median absolute relative difference (MARD) increased from 9.5% before the beginning of exercise to 16.5% during exercise ($p < 0.001$), and then decreased to 9.3% in the first hour after the end of exercise ($p < 0.001$). For the anaerobic sessions, the MARD before exercise was 15.5% and increased without statistical significance to 16.8% during exercise realisation ($p = 0.993$), and then decreased to 12.7% in the first hour after the cessation of anaerobic activities ($p = 0.095$). Results indicate that CGM might present lower accuracy during aerobic exercise, but return to regular operation a few hours after exercise cessation. No significant impact for anaerobic exercise was found.

Keywords: continuous glucose monitoring; accuracy; exercise; physical activity; type 1 diabetes

1. Introduction

Continuous glucose monitoring (CGM) is associated with improvement in glycaemic control in patients with type 1 diabetes (T1D), reducing glycated haemoglobin (HBA_{1C}) percentage without increasing the occurrence of hypoglycaemic episodes [1–3]. Using a minimally invasive sensor inserted in the subcutaneous tissue, patients can follow their readings in real-time, allowing them to make changes in their therapy to improve glycaemic variability and metabolic control safely. Additionally, CGM data allows physicians to visualise individualised glycaemic traces along consecutive days, and then improve patients' insulin treatment.

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Although regular physical activity (PA) is recommended for patients with T1D to improve overall health conditions [4], diabetes management in front of exercise is not a trivial task and monitoring glucose levels before, during, and after physical activity is fundamental to maintaining plasma glucose (PG) levels in euglycaemic ranges during and after exercise [5]. Artificial pancreas systems (also referred to as closed-loop systems) rely on CGM readings to automatically calculate at every sampling time the necessary insulin dose to keep patients' PG levels in safe ranges [6]. In 2017, the first artificial pancreas system hit the market in United States, although still requiring patient intervention at mealtimes [7].

PA has been identified as one of the major challenges facing artificial pancreas systems [8]. PA is also a hurdle for CGM accuracy, due to changes in subcutaneous tissue circulation, variations in oxygen concentration of blood, increase in body temperature, mechanical forces where the sensor is placed, and rapid glucose changes in glucose concentrations caused by exercise [9]. Nevertheless, if CGM accuracy is poor, the closed-loop performance may be deteriorated [10] and thus increase the intrinsic risk of hypo- and hyperglycaemia caused by PA. Several studies have reported the impact of PA in the accuracy of current-generation CGM systems [9,11–13]. To the best of our knowledge, no study has yet investigated the "dynamic" behaviour of the accuracy of CGM devices in face of exercise, as measured at time intervals before, during, and after exercise sessions. Thus, the aim of this study is to evaluate the accuracy of CGM before, during, and after aerobic and anaerobic exercise sessions performed by patients with T1D. In addition, the post-exercise period was split into four consecutive 1-h periods, allowing visualisation of the accuracy of CGM devices along the recovery period.

2. Materials and Methods

2.1. Study Population

Six patients with T1D were enrolled at the Clinic University Hospital of Barcelona. The protocol was approved by the Ethics Committee of the hospital. Subjects were eligible to participate if they were between 18 and 60 years old, with a body mass index (BMI) between 18 and 30 kg/m^2, HbA_{1C} between 6.0% and 8.5%, and were on continuous subcutaneous insulin infusion (CSII) for at least six months. Patients using any experimental drug or device in the past 30 days were excluded. Patients with progressive fatal diseases, hypoglycaemia unawareness, a history of drug or alcohol abuse, impaired hepatic, neurological, endocrine, or other systematic diseases apart from T1D, and/or pregnant women were also excluded. Table 1 shows the demographic characteristics of the study population.

Table 1. Characteristics of the patients.

Number of Patients (Females)	6 (1)
Age (years) *	36.7 ± 8.9
HbA_{1C} (%) *	7.9 ± 0.5
Body mass index (kg/m^2) *	24.6 ± 1.0
Time with T1D (years) *	25.2 ± 12.7
Time with pump (years) *	4.8 ± 1.7

* Data expressed as mean ± standard deviation. T1D, type 1 diabetes.

2.2. Study Procedures

The study was a longitudinal, prospective, interventional study with a primary objective of the analysis of the limits of performance of a closed-loop controller when challenged by PA and, as a secondary objective, the analysis of the impact of exercise in continuous glucose monitoring accuracy. Each subject underwent three aerobic and three anaerobic exercise tests, completing six experiments in about nine weeks. CSII was carried out with the Paradigm Veo® insulin pump and the day before the test, the patient inserted two Enlite-2 sensors®, both by Medtronic Minimed (Northridge,

CA, USA), subcutaneously at home. Sensors were inserted in the abdomen. Patients arrived at the research unit at 8:00, after a standardised breakfast at home. PG samples were measured every 15 min using a YSI 2300 Stat Plus Glucose Analyser (YSI Inc., Yellow Springs, OH, USA). In cases where PG readings were below 80 mg/dL, measurements were performed every five minutes. To ensure comparable metabolic conditions between studies, subjects received intravenous infusion of regular human insulin to maintain plasma glucose at 150 mg/dL until the beginning of studies at 11:00, according to a feedback insulin infusion method. Just before 11:00 patients ingested 23 grams of carbohydrates (15 g as gel—*Diabalance gel de glucosa acción rápida* (Esteve, Barcelona, Spain) and 8 g as an isotonic drink—100 mL of Aquarius (The CocaCola Company, Atlanta, GA, USA)). At 10:45, the closed loop system started and at 11:00 the exercise protocol started. Two exercise protocols were considered: aerobic and anaerobic. The trials with aerobic exercises consisted of three series of 15 min of cycle-ergometer at 60% of the individual maximal O_2 consumption (VO_2max), with 5 min of rest between sets. In the trials with anaerobic exercises, the patient performed five sets of eight repetitions of four different exercises at 70% of the maximum capacity with 90 s of rest between sets of weightlifting.

2.3. Data and Statistical Analysis

Median absolute relative difference (MARD) was analysed in six different periods (P0 to P5, all lasting one hour). P0 is the one-hour period before the exercise session, P1 is during the exercise, and P2 to P5 are the periods after the exercise session (comprising 4 h post-exercise). In total, 36 exercise sessions were performed, in which two sensors were used per patient. From these 36 sessions, seven complete sessions and two sensors were discarded due to a malfunction of YSI or CGM unit. The total number of sensors analysed for the aerobic and anaerobic sessions was 31 and 25, respectively.

CGM data were recorded every five minutes. In order to align CGM and PG data, CGM data were linearly interpolated and rounded to one sample per minute. Missing data were not interpolated. MARD was computed per sensor, considering all periods (P0 to P5), in order to check for outliers. After that, the detected outlier sensors were also discarded, giving rise to a final number of sensors analysed for the aerobic and anaerobic sessions of 28 and 22, respectively.

Sensor accuracy is presented for each period and compared between them. In addition, the mean PG of each period is also presented, considering that accuracy may be deteriorated in the hypoglycaemic range [10,14]. Descriptive statistics of the MARD results are given as medians (interquartile range (IQR)). A comparison of medians from MARDs in different periods was performed with the two-sided Wilcoxon rank sum test, considering a significance level of 0.05. Paired PG reference and CGM readings for both aerobic and anaerobic exercises are given using the Clarke error grid analysis [15].

3. Results

3.1. Aerobic Exercise

Figure 1 illustrates CGM and PG measurements during the entire period of accuracy analysis. During this period, the mean CGM was 142.53 $\pm$ 14.64 mg/dL and the mean PG was 130.53 $\pm$ 14.98 mg/dL. Table 2 presents the values of median PG and accuracy for all the periods P0–P5 and the amount "*n*" of paired CGM and PG samples in each period for MARD computation. Table 3 depicts the *p*-value between each period.

The results showed a degradation of accuracy caused by the onset of aerobic exercise. Additionally, the MARD obtained during P1 was significantly different when compared with the remaining periods, evidencing the effects caused by aerobic exercise on CGM accuracy. The Clarke error grid analysis showed that 99.7% of the points during all the periods were in Zones A and B, considered clinically acceptable. During the exercise period (P1), the red points illustrated in Figure 2 were distributed as follows: Zone A: 63.9%, Zone B: 35.2%, Zone C: 0.0%, Zone D: 0.9%, and Zone E: 0.0%.

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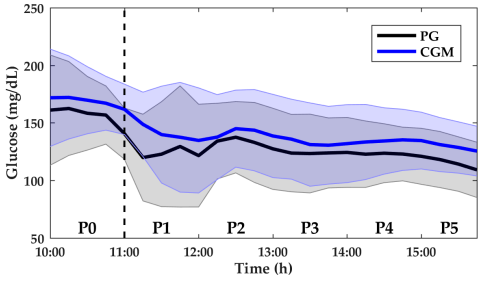

Figure 1. Plasma glucose (PG) and continuous glucose monitoring (CGM) measurements from P0 to P5 for aerobic sessions. Data shown are mean ± standard deviation (SD). PG is denoted by the black solid line and black-shaded area. CGM is denoted by the blue solid line and blue-shaded area. The vertical dashed line indicates the start of aerobic exercise sessions.

Table 2. Values of PG and accuracy of CGM for aerobic exercise sessions.

	P0	P1	P2	P3	P4	P5
PG (mg/dL)	155.0 (135.3–174.5)	120.5 (99.5–149.9)	124.0 (106.8–155.8)	114.5 (101.3–146.3)	118.3 (104.5–143.8)	111.5 (101.0–129.8)
MARD (%)	9.5 (4.7–13.9)	16.5 (7.6–23.5)	9.3 (5.4–16.3)	11.6 (6.5–17.5)	11.3 (6.2–16.0)	12.9 (4.7–18.8)
n	112	108	108	108	108	108

Data are expressed as the median (interquartile range). PG, plasma glucose; CGM, continuous glucose monitor; MARD, median absolute relative difference.

Table 3. *p*-Value between each period analysed for aerobic exercise.

	P0	P1	P2	P3	P4	P5
P0	–	<0.001	0.986	0.177	0.281	0.060
P1	<0.001	–	<0.001	<0.01	<0.001	<0.05
P2	0.986	<0.001	–	0.189	0.346	0.075
P3	0.177	<0.01	0.189	–	0.683	0.452
P4	0.281	<0.001	0.346	0.683	–	0.241
P5	0.060	<0.05	0.075	0.452	0.241	–

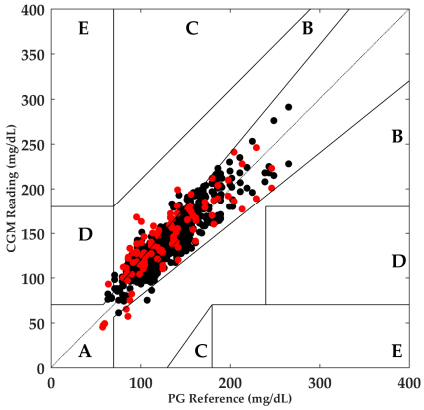

Figure 2. Clarke error grid analysis of CGM and PG values for aerobic exercise. Zone A: 81.6%, Zone B: 18.1%, Zone C: 0.0%, Zone D: 0.3%, Zone E: 0.0%. Red points illustrate the readings during P1. CGM, continuous glucose monitor; PG, plasma glucose.

3.2. Anaerobic Exercise

In the anaerobic exercise sessions, the mean CGM was 147.82 ± 16.29 mg/dL and the mean PG was 139.75 ± 16.58 mg/dL. Figure 3 shows CGM and PG over the whole period. Table 4 presents the MARD for each period as well as the median PG values. Table 5 depicts the *p*-value between each period.

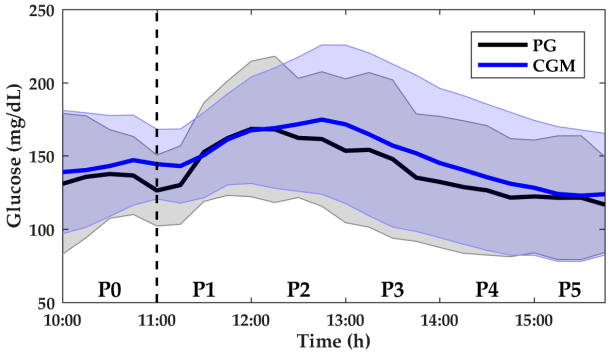

Figure 3. PG and CGM measurements from P0 to P5 for anaerobic sessions. Data shown are mean ± SD. PG is denoted by the black solid line and black-shaded area. CGM is denoted by the blue solid line and blue-shaded area. The vertical dashed line indicates the start of the anaerobic exercise sessions. PG, plasma glucose; CGM, continuous glucose monitor; SD, standard deviation.

Table 4. Values of PG and accuracy of CGM for anaerobic exercise sessions.

	P0	P1	P2	P3	P4	P5
PG (mg/dL)	124.5 (110.8–155.8)	138.0 (118.3–160.0)	157.5 (139.5–195.0)	149.3 (108.5–179.8)	138.5 (84.5–159.0)	129.8 (88.3–150.8)
MARD (%)	15.5 (6.5–26.4)	16.8 (7.9–24.5)	12.7 (4.9–20.3)	14.3 (4.8–26.5)	14.3 (7.9–19.7)	12.3 (5.7–18.8)
n	*n* = 76	*n* = 86	*n* = 88	*n* = 88	*n* = 89	*n* = 88

Data are expressed as median (interquartile range). PG, plasma glucose; CGM, continuous glucose monitor; MARD, median absolute relative difference.

Table 5. *p*-Value between each period analysed for anaerobic exercise.

	P0	P1	P2	P3	P4	P5
P0	–	0.993	0.095	0.709	0.287	<0.05
P1	0.993	–	0.063	0.798	0.171	<0.05
P2	0.095	0.063	–	0.188	0.444	0.691
P3	0.709	0.798	0.188	–	0.458	0.076
P4	0.287	0.171	0.444	0.458	–	0.223
P5	<0.05	<0.05	0.691	0.076	0.223	–

Different from what was observed in the aerobic results, the onset of anaerobic exercise did not have an influence on MARD. Despite the fact that the MARD slightly increased during P1 compared with P0 (16.8% vs. 15.5%), this increase was not statistically significant. In the following period, a greater drop in MARD was observed; however, no statistical significance was observed. Considering the entire period, 99.4% of the paired points were distributed in Zones A and B in the Clarke error grid. In the exercise period (P1), the red points illustrated in Figure 4 were distributed as follow: 61.6% were in Zone A and the remaining 38.4% were in Zone B.

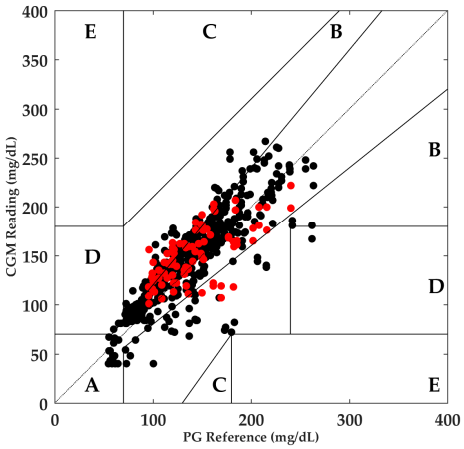

Figure 4. Clarke error grid analysis of CGM and PG values for anaerobic exercise. Zone A: 70.5%, Zone B: 28.9%, Zone C: 0.0%, Zone D: 0.6%, and Zone E: 0.0%. Red points illustrate the readings during P1. CGM, continuous glucose monitor; PG, plasma glucose.

4. Discussion and Conclusions

An unexpected MARD difference in the period of P0 between aerobic and anaerobic exercise was found (MARD = 9.5% vs. 15.5%, $p < 0.01$), probably due to random factors. However, this fact did not affect the purpose of the analysis, which was the characterisation of the MARD degradation, if any, in both types of exercise. Indeed, such degradation was found in the case of aerobic exercise, with a 73% increment in MARD (from 9.5% to 16.5%, $p < 0.001$) during the time the exercise was performed. This might be due to O_2 changes, microcirculation perturbation, or movement around or within the insertion area and sensor during the cycling exercise. However, after exercise cessation, the MARD value returned to values comparable to the baseline (see Table 3). A non-statistically significant increase was observed in the MARD during the anaerobic sessions (from 15.5% to 16.8%, $p = 0.993$). However, such small differences may have been affected by the elevated MARD during P0 as well as by the small size of the cohort. These facts hinder any definitive conclusion about the behaviour of the MARD during this kind of exercise. The MARD for P5 (the fourth hour after the end of exercise sessions) was similar to that found in Reference [10], which reports an overall mean absolute relative difference for the same sensor during the postprandial period of 12.0%. Additionally, the results for P5 are similar to the MARD presented in Reference [11] (11.95%), which is result of the analysis of the accuracy of the first- and second-generation Enlite sensors during a rest period. These results indicate that the sensors, even if affected by exercise, might be able to return to their regular operation a few hours after exercise cessation.

Additionally, a trend in the overestimation of CGM can be observed during all of the periods analysed for aerobic trials. In the anaerobic trials, no such trend was observed. Although CGM overestimated PG in three different periods (P0, P3, P4), this trend did not occur in the remaining periods.

The impact of physical activity on CGM accuracy was also observed by other studies [9,11–13]. In Reference [9], CGM accuracy was also affected by aerobic exercise in pregnant women with T1D that undertook 55 min of moderate walking on a treadmill. During the exercise period, the MARD was greater than that during sedentary period (18.4% vs. 11.5%, $p < 0.001$). In Reference [11], the authors showed that two different CGM systems, Dexcom G4 Platinum (Dexcom, San Diego, CA, USA) and Medtronic Paradigm Veo Enlite systems, presented lower performance during continuous and interval exercise sessions when compared with a rest period. Furthermore, they observed a trend in the Medtronic Paradigm Veo Enlite system to obtain worse accuracy during continuous exercise than interval exercise. Although in our work patients only used the second-generation Enlite sensors

(in Reference [11] the first-generation sensors were used in 55% of the experiments), continuous aerobic exercise had a more negative impact in CGM accuracy. In Reference [12], no statistically significant difference was observed in CGM accuracy during continuous and high-intensity interval exercise (HIIE) in young adults with T1D, and the MARDs achieved in this study were similar to the MARD obtained in another inpatient study [14] that considered the same sensor, but without exercise. In Reference [13], the authors detected a trend caused by HIIE in the overestimation of CGM for different levels of intensity. However, for continuous exercise, CGM only overestimated the reference levels for low-intensity activity.

An important limitation in our study is the small size of the cohort. Only six patients were enrolled in this study, with a single female. However, three sessions per exercise type were performed by each patient, using two simultaneous sensors in each session. Another limitation was that there were no variations in the level of exercise intensity for any type of exercise. This impeded the assessment of the effects of exercise intensity on CGM performance. The difference observed in the MARD before the onset of exercise (P0) did not allow a direct comparison between each type of exercise.

CGM technology helps patient to improve overall glycaemic control. The focus of the present paper was to analyse CGM accuracy in different exercise conditions. We concluded that the accuracy of the second-generation Medtronic Enlite sensor is affected by aerobic exercise. Further improvement of CGM technology may be needed in order to reassure robustness and safety during PA.

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Author Contributions: L.B. and A.B. performed the analysis of accuracy, researched the data, and wrote the manuscript. C.Q., M.G., I.G., J.B., and J.V. conceived and designed the experiments, provided guidance to the analysis of accuracy, contributed to the discussion, and reviewed the manuscript. C.Q. performed the experiments.

Conflicts of Interest: The authors declare no conflict of interest.

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2.4 Individual Categorization of Glucose Profiles Using Compositional Data Analysis

The candidate's contribution for this publication consisted in pre-processing the data obtained in the clinical trial, researching data, performing the categorization of glucose profiles using CoDa analysis, contributing to discussion, writing the manuscript and editing the manuscript throughout the review rounds. During the development of the work, the candidate worked with her colleague Arthur Bertachi. They were supervised by Dr. Josep Antoni Martín-Fernández and Dr. Josep Vehí. Dr. Marga Giménez, Dr. Ignacio Conget and Dr. Jorge Bondia contributed to the discussion.

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Individual categorisation of glucose profiles using compositional data analysis

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Abstract

The aim of this study was to apply a methodology based on compositional data analysis (CoDA) to categorise glucose profiles obtained from continuous glucose monitoring systems. The methodology proposed considers complete daily glucose profiles obtained from six patients with type 1 diabetes (T1D) who had their glucose monitored for eight weeks. The glucose profiles were distributed into the time spent in six different ranges. The time in one day is finite and limited to 24 h, and the times spent in each of these different ranges are co-dependent and carry only relative information; therefore, CoDA is applied to these profiles. A K-means algorithm was applied to the coordinates obtained from the CoDA to obtain different patterns of days for each patient. Groups of days with relatively high time in the hypo and/or hyperglycaemic ranges and with different glucose variability were observed. Using CoDA of time in different ranges, individual glucose profiles were categorised into groups of days, which can be used by physicians to detect the different conditions of patients and personalise patient's insulin therapy according to each group. This approach can be useful to assist physicians and patients in managing the day-to-day variability that hinders glycaemic control.

Keywords

Continuous glucose monitoring, type 1 diabetes, compositional data analysis, decision support system, diabetes management

1 Introduction

Patients with type 1 diabetes (T1D) need exogenous insulin replacement to regulate blood glucose (BG) levels due to autoimmune destruction of pancreatic beta cells. Insulin must be infused properly to avoid elevated levels of BG (hyperglycaemia). However, if over-delivered, glucose levels may fall to dangerously low levels (hypoglycaemia). Both conditions, hyper- and hypoglycaemia, lead to several complications over time, including blindness, kidney failure, cardiovascular complications and even death.[1] Physicians adjust insulin dosing according to individual requirements, which are normally based on patient characteristics, such as body weight and carbohydrate intake.[2] However, a major hurdle to achieve optimal glycaemic control is the large intra-patient variability that stems from the activity of a complex metabolic system and individual behavioural characteristics.[3] Moreover, it is difficult for physicians to predict patient's day-to-day activities in order to set different profiles of insulin dosing to adjust for patient's behaviour.

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Insulin infusion in T1D patients can be performed with multiple daily injections; however, treatment with continuous subcutaneous insulin infusion (CSII) therapy provides improvements in glycaemic control.[4] Current T1D management technology allows the integration of continuous glucose monitoring (CGM) and CSII. The use of these devices makes it possible to acquire data in real time and apply different methods to extract features to support patients and physicians. For instance, software like Carelink Personal (Medtronic Minimed, Northridge, CA, USA) and Clarity (Dexcom, San Diego, CA, USA) support patients and physicians in diabetes management by providing reports for the review and analysis of overall glucose management. This software allows visualisation of trends in diabetes data, analysis of the average day and the possibility of analysing how much time was spent in the individual's target BG range. Usually, pie charts show the percentage of time spent in, above, and below the individual's target BG range. However, to date, this has been used for simple descriptive purposes and to encourage individuals to increase the time spent in their target ranges, which would improve glycaemic control.

One possibility for the analysis of glucose data is to categorise different groups of glucose profile days according to the patient's glycaemic control. This information would assist physicians in finding different patterns of days for each patient, which would in turn ease the burden caused by the need to provide more accurate therapies to reduce day-to-day glycaemic variability. In the study by Contreras et al.,[5] the authors presented a hierarchical clustering methodology based on normalised compression distance (NCD) to classify days according to daily sets of BG readings, which were expressed using a symbolic representation of the time series discretised into different glucose ranges. The authors observed that their methodology, despite not having any information regarding insulin infusion in advance, was able to categorise days according to different insulin requirements.

Compositional data analysis (CoDA), which refers to the analysis of compositional data (CoDa), involves vectors of positive components that describe the contribution of parts to some whole.[6] For example, the time spent in different activities during a day are relative contributions to the 24-h time budget and are therefore compositional data, as described by previous studies.[7–11] Martín-Fernández et al. presented basic methods for comparing groups of CoDa,[7] while approaches based on CoDA to assess time spent in physical activity, sedentary time and sleep and their effects on health markers have been presented by several studies.[8–11] Other applications of CoDA in healthcare include the analysis of epidemiologic information.[12]

The aim of this paper is to present a novel methodology to categorise BG profiles of T1D patients. Instead of analysing time series, we aim to analyse the distribution of time spent in different glucose ranges during a 24-h period, using a CoDa approach. The levels of BG determine an individual's glucose profile when discretising the time spent in different glucose ranges; therefore, a CoDa approach is appropriate. The main objective is to create a decision support tool to assist patients and physicians to improve patients' glycaemic control based on the categorisation of different groups of days. This will allow the creation of personalised insulin-dosing profiles for different sets of days to reduce the impact of day-to-day variability in glycaemic control. This paper is organised as follows. First, concepts of CoDA, such as the representation in coordinates, the problem of zeros and the compositional biplot are explained. The dataset and the methodology developed for the categorisation of glucose profiles are then illustrated, followed by a discussion of the results. Finally, conclusions are provided.

2 CoDA

A vector $\mathbf{x} = [x_1, x_2, \ldots, x_D]$ with D parts, positive components $x_1, x_2, \ldots, x_D$ and $\sum_{i=1}^{D} x_i = C$, in which C is a non-informative closure constant is a compositional vector. In our case, $\mathbf{x}$ is a per-patient vector of time spent in different BG ranges, and D is the number of glucose ranges. Time spent in each glucose range could be measured as percentages of the day or as minutes or hours, as the data carry only relative information. The set of real positive vectors closed to a constant C is called the simplex ($\mathcal{S}^D$), as first described by John Aitchison.[6]

The misinterpretation of correlations of parts of a composition was recognised over a century ago.[13] Standard multivariate analysis is designed for unconstrained multivariate data; as such, they are not valid for CoDa.[6] The methodology developed by John Aitchison assumes that the relevant information of a composition is contained in the ratios between its components.[6]

2.1 Representation in coordinates

The lack of meaningful definitions of independence for sets of proportions with the absence of satisfactory parametric classes of distributions causes difficulties in handling statistics in the simplex.[6] The statistical analysis in the simplex can be transferred to the real space through the expression of CoDa in logratio

coordinates, on which traditional statistical methods can be applied.[6] One way to obtain these coefficients is the *centred log-ratio* (*clr*) transformation

$$\mathrm{clr}(\mathbf{x}) = \left[\ln\left(\frac{x_1}{g(\mathbf{x})}\right), \ln\left(\frac{x_2}{g(\mathbf{x})}\right), \ldots, \ln\left(\frac{x_D}{g(\mathbf{x})}\right)\right] \tag{1}$$

where $g(\mathbf{x})$ is the geometric mean of $\mathbf{x}$. This transformation projects $\mathcal{S}^D$ to the real space $\mathcal{R}^D$, and thus singularity of the covariance matrix occurs (dimensionality of compositional data is just D–1). The *isometric log-ratio* (*ilr*) transformation provides an expression of $\mathbf{x}$ in terms of its orthonormal logratio coordinates.[14] An *ilr* vector can be viewed as the coordinates of a composition with respect to an orthonormal basis $\mathbf{e}_1, \mathbf{e}_2, \ldots, \mathbf{e}_{D-1}$ on the simplex[15]

$$\mathrm{ilr}(\mathbf{x}) = \mathrm{clr}(\mathbf{x}) \cdot \Phi^t \tag{2}$$

where Φ is the $(D-1) \times D$-matrix whose ith row is the vector $clr(\mathbf{e}_i)$, for $i = 1, \ldots, D-1$.

A particular system of *ilr* coordinates can be obtained through sequential binary partition (SBP), which allows partitioning of compositional vectors into balances between two groups of parts that can be selected by the user in order to improve the interpretability of the results when some kind of affinity between parts is previously established.[16,17]

CoDa statistical analysis is conveniently performed after choosing orthonormal logratio coordinates. One method to do so is to select the orthonormal basis using a principal balances method.[18] This method automatically achieves an SBP using some criterion to maximise the variance explained by the balances. Another possibility is to create the SBP using expert knowledge complemented by the interpretation of basic descriptive statistics.

The matrix Φ can be obtained from the $(D-1) \times D$ sign matrix $\mathbf{S} = [s_{ij}]$ resulting from the SBP.[19] The Φ_{ij} entry of Φ is defined as follows

$$\begin{aligned} \Phi_{ij} &= 0, && \text{if} \quad s_{ij} = 0; \\ \Phi_{ij} &= +\frac{1}{\#_i^+}\sqrt{\frac{\#_i^+ \cdot \#_i^-}{\#_i^+ + \#_i^-}}, && \text{if} \quad s_{ij} > 0; \\ \Phi_{ij} &= -\frac{1}{\#_i^-}\sqrt{\frac{\#_i^+ \cdot \#_i^-}{\#_i^+ + \#_i^-}}, && \text{if} \quad s_{ij} < 0 \end{aligned} \tag{3}$$

where $\#_i^+$ and $\#_i^-$ are the number of parts in the ith row of $\mathbf{S}$ coded by +1 and –1, respectively. The parts that are coded by +1 are designated to be on the numerator of the *ilr* coordinate, whereas the parts coded by –1 are designated to be on the denominator of the *ilr* coordinate.

According to this approach, the distance between compositional vectors, that is, the Aitchison distance, is defined as the Euclidean distance between their *clr* or *ilr* coordinates. This allows for using distance-based clustering techniques in CoDA.[20] Graphical representation of CoDa in the simplex and in the space of coordinates has been presented by Palarea-Albaladejo et al.[20,21]

2.2 Treatment of zeros

CoDA is based on logarithms of ratios. Both operations require non-zero elements in the data matrix; therefore, the logratio methodology must be preceded by proper handling of zero values.[22] Rounded zeros are non-zero data that cannot be observed because their value is below the detection limit (DL). The logratio expectation-maximisation (EM) replacement is a multivariate method for the imputation of rounded zeros from continuous data.[23] This method imputes values that incorporate information about the relative covariance structure.

2.3 Compositional biplot

The biplot represents, by means of a two-rank approximation, the rows and columns of any matrix.[24] The biplot, when adapted for CoDa, is applied to the *clr* coefficients (*clr*-biplot) and was proved to be a useful exploratory tool.[15] The variables in the biplot are depicted by rays emanating from the origin, as can be seen in Figure 1, which is an example *clr*-biplot of a composition with six parts. Observation of instances is not shown. The lengths and directions of these rays are important for the interpretation of variances and covariances, respectively.

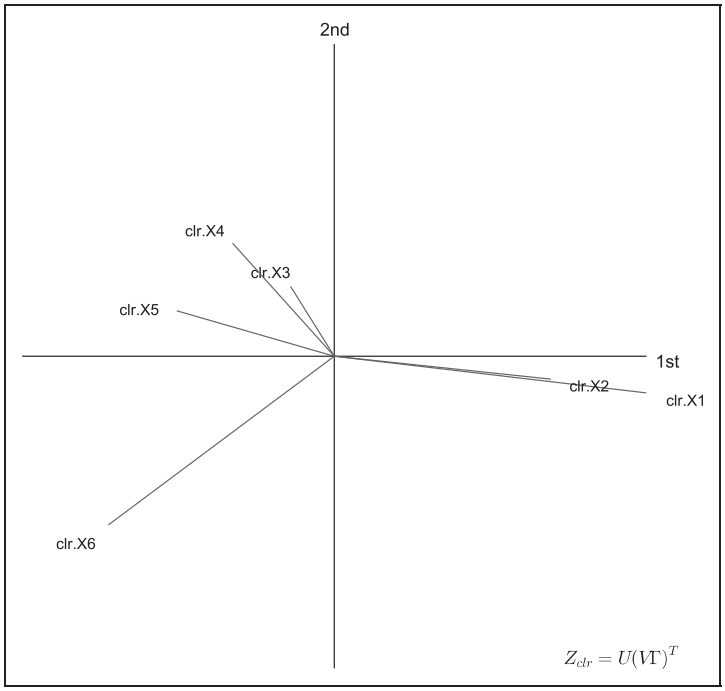

Figure 1. Example of a *clr*-biplot of a composition with six parts. Six vertices, one for each part of the composition, are connected to the origin through six rays. The longer the ray, the higher the variance of the *clr*-coordinate in that part. Observation of instances is not shown.

The origin of the biplot represents the centre of the compositional dataset. Six vertices, one for each part of the composition, are connected to the origin through six rays, which provide information on the relative variability of the compositional dataset. The longer the ray, the higher the variance of the *clr*-coordinate in that part. Links are joins of two vertices, and, similar to the rays, provide information on the relative variability between those two parts. The lengths of links are approximately proportional to variance of simple logratios between single parts. For instance, the link formed by vertices X3 and X4 is much shorter than the link formed by X3 and X6. Therefore, the relative variability between parts X3 and X4 is lower than that between parts X3 and X6. Vertices X1 and X2 are almost coincident. This means that the relative variability between these two parts is approximately zero.

The exploratory analysis of a compositional dataset may be commenced by interpreting the biplot of *clr*-transformed data. The cumulative total variance (not shown) retained by the biplot expresses the quality of the representation of (D–1)-dimensional logratio data into a two-dimensional graph. A high percentage of variance retained by the *clr*-biplot means that it provides a good representation of the data in real space. The *clr*-biplot enables the discovery of statistical relationships between logratios of the parts and potential clusters of similar compositions.[15,20]

3 Materials and methods

3.1 Database

Six patients with T1D receiving CSII used the Paradigm Veo system with the second generation of the Enlite sensor for CGM (Medtronic Minimed, Northridge, CA, USA) and a Fitbit Charge HR activity tracker (Fitbit Inc., San Francisco, CA, USA) for approximately eight weeks. Demographic characteristics are shown in Table 1. Data are expressed as mean ± standard deviation (SD). All patients provided written informed consent for research participation.

Table 1. Demographic characteristics for the dataset used.

Number of T1D patients (females)	6 (1)
Age (years)	36.7 ± 8.9
HbA1c (%)	7.9 ± 0.5
BMI (kg/m^2)	24.6 ± 1.0
Time with T1D (years)	25.2 ± 12.7
Time with pump (years)	4.8 ± 1.7

T1D: type 1 diabetes; BMI: body mass index; HbA1c: haemoglobin A1c.

Table 2. Summary of the data of six patients: number of complete days per patient; number of days with manually reported physical activity; number of days corresponding to weekends; average calories and steps for the complete days analysed; compositional centre (geometric mean of the amounts of time spent in each glucose range); number of hypoglycaemic episodes; average duration of hypoglycaemic episodes and average blood glucose levels.

	#Days	#Reported Exercise	#Weekends	Calories	Steps	<60 (min)	60–70 (min)	70–140 (min)	140–180 (min)	180–250 (min)	>250 (min)	#Hypo events	T Hypo (min)	Avg BG (mg/dL)
P1	18	7	5	2444.3	6464.0	4.0E–02	7.2	416.5	278.1	420.0	16.0	0.72	56.2	168.2
P2	31	7	11	3276.2	15,230.1	0.9	3.2	643.0	325.0	153.2	3.2	1.03	44.8	145.2
P3	40	7	9	2732.6	7821.6	1.3E–02	0.3	465.6	339.4	201.9	1.7	0.43	33.8	156.0
P4	44	8	13	3174.3	10,790.0	1.8	10.8	586.2	286.4	258.6	34.0	1.05	56.7	153.9
P5	29	2	8	1769.8	7276.4	0.9	5.1	343.1	259.0	326.8	98.6	1.03	63.2	179.0
P6	15	2	3	2550.0	10,523.5	9.5E–03	0.1	237.9	283.4	441.9	52.9	0.53	43.8	177.6

The CGM data acquired from the six patients during the eight-week monitoring period were used to validate our proposal. As the CGM system used by patients recorded BG measurements every 5 min, a complete day was supposed to have 288 samples. The number of complete days per patient, starting at 00:00 and ending at 24:00, varies because of CGM or insulin pump malfunction at different periods in the day. The data have been pre-processed to remove days with large periods of missing data.

Patients one to six are, henceforth, referred as P1 to P6. Table 2 reports the number of complete days per patient, the number of days in which each patient manually reported some physical activity, the number of days that correspond to weekends, the average number of calories and steps recorded by the activity tracker in the days analysed (#Days, #Reported Exercise, #Weekends, Calories and Steps, respectively). Additionally, the compositional centre of the dataset is presented (geometric mean of the amounts of time spent in each glucose range), number of hypoglycaemic episodes, average duration of hypoglycaemic episodes and average BG levels (#Hypo events, T Hypo and Avg BG, respectively).

Figure 2 summarises the methodology for the categorisation of glucose profiles. This methodology is applied individually for each patient. Each step is described in detail in the following sections.

3.2 Definition of six glucose ranges

In this paper, we performed an analysis of the glucose time series considering six defined glucose ranges. Glucose categories are defined according to ranges that are related to different clinical diagnoses and safety measures.[25] Basic outcome measures to be reported for artificial pancreas clinical trials are obtained by the analysis of CGM time in different glucose ranges.[26] Considering the recommendations for the analysis of glucose data in the ranges and distribution of the CGM data available in the database, we defined six glucose ranges: <60 mg/dL, 60–70 mg/dL, 70–140 mg/dL, 140–180 mg/dL, 180–250 mg/dL, >250 mg/dL, and formed the composition $\mathbf{x} =$ [X.60, X.60.70, X.70.140, X.140.180, X.180.250, X.250].

The 24-h glucose profile was split into time spent in the six aforementioned glucose ranges. The times spent in different ranges can be considered as relative contributions to the 24-h glucose profile. The amounts of time spent in each of the defined ranges are co-dependent and limited to 24 h; therefore, they should be analysed as CoDa.

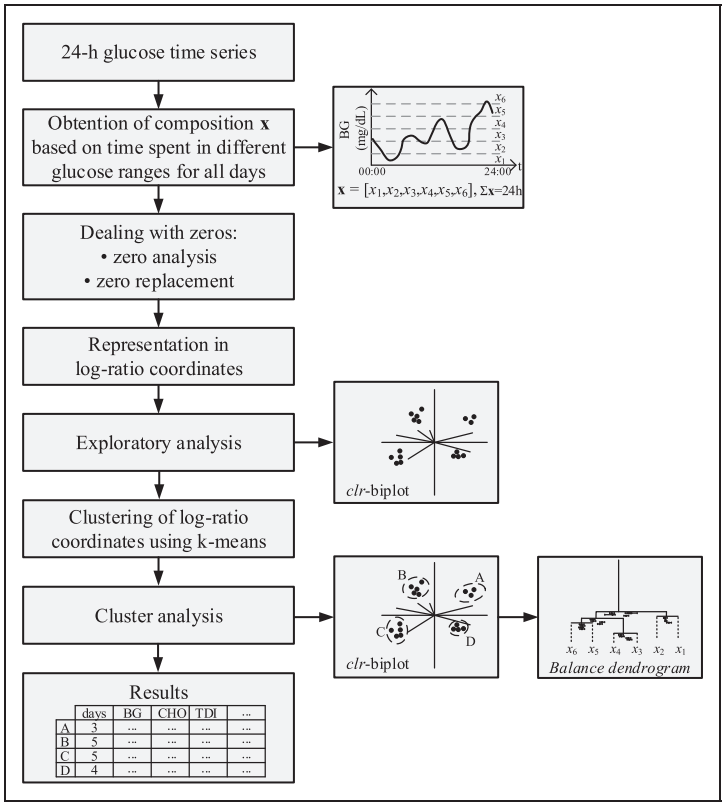

Figure 2. Summary of the methodology for categorisation of glucose profiles.
CHO: carbohydrate intake; TDI: total daily insulin; BG: blood glucose.

3.3 Dealing with zeros

Initially, the zero patterns of the dataset of each patient were analysed with the zPatterns function from the R package zCompositions.[23] During the whole period of analysis, there was no glucose range that was always zero for any patient. Thus, we considered that these zeros were rounded zeros from continuous data and not essential zeros.[22]

The CGM records one sample every 5 min. Therefore, the DL was set to $DL = 5/1440 = 0.0035$ (5 min out of the 1440 min per day in a determined glucose range). The replacement of zeros was performed with the lrEM function from the same R package, considering a matrix of DLs.

We identified three different general patterns of zeros: non-consecutive zeros, two consecutive zeros and three consecutive zeros. The DLs of these three different zero patterns were determined as described in Table 3. Other methodologies to determine the DL of the dataset were tested; however, placing a lower DL on zero parts that are further from the non-zero parts had less effect on the variability.

Table 2 summarises the data of six patients. Variables were calculated per patient/day: the overall compositional mean is presented through the time in minutes of BG values in each of the defined glucose ranges (after the imputation of the zeros), the mean number of hypoglycaemic episodes (#Hypo, where the hypoglycaemic event is defined as BG below 70 mg/dL for at least 15 min[27]), the average duration of the episodes in minutes per event (T Hypo), and the average BG in mg/dL (Avg BG). Because of the difference in patients' profiles regarding the central tendency of the compositions and the number and duration of hypoglycaemic events, an individual methodology to obtain patterns of days is necessary. Hence, we decided to perform an individualised analysis of each patient's days, therefore discarding the influence of inter-patient variability.

Table 3. Detection limits (DL) for different zero patterns in the dataset.

Pattern of zero	DL		
Non-consecutive zero	0.0035		
Two consecutive zeros	Most extreme 0.0012		Closer to the non-zero 0.0023
Three consecutive zeros	Most extreme 0.0004	Intermediate 0.0008	Closer to the non-zero 0.0023

Table 4. Sequential Binary Partition defined for the logratio coordinates.

i	X.60	X.60.70	X.70.140	X.140.180	X.180.250	X.250
1	+1	+1	−1	−1	−1	−1
2	+1	−1	0	0	0	0
3	0	0	−1	−1	+1	+1
4	0	0	0	0	−1	+1
5	0	0	+1	−1	0	0

3.4 The logratio coordinates

After the zero replacement, an SBP was defined for the logratio coordinates of the data according to Table 4. In our case, the SBP was defined according to the clinical interpretation of time spent in different glucose ranges which represent different situations (occurrence of hypo- and hyperglycaemic events) complemented with the analysis of the distribution of the CoDa variables described by the *clr*-biplots. This sign matrix (**S**) serves to build the matrix Φ of the *clr*-transformed vectors of the orthonormal basis $\mathbf{e}_1, \mathbf{e}_2, \ldots, \mathbf{e}_{D-1}$.[19] Both *clr*-biplot and *ilr*-coordinates through the SBP were done with CoDaPack.[28] The balance dendrogram[29] allowed the analysis of the SBP and the variances of each balance.

The first coordinate (ilr_1) can be interpreted as a balance between the logratio of the geometric mean of the times spent in <60 and 60–70 mg/dL (with +1 at the first line in the sign matrix of Table 4) and the geometric mean of all the other times (with −1 in the sign matrix). The expression to calculate this logratio coordinate is

$$ilr_1 = \sqrt{\frac{4}{3}} \ln \frac{(\text{X.60} \cdot \text{X.60.70})^{1/2}}{(\text{X.70.140} \cdot \text{X.140.180} \cdot \text{X.180.250} \cdot \text{X.250})^{1/4}} \tag{4}$$

The ilr_1 can be interpreted as the relationship between the time spent in the hypoglycaemic ranges and the time spent in the normo- and hyperglycaemic ranges. The second coordinate (ilr_2, corresponding to the second row of Table 4) is equal to the logratio of the times spent in <60 and between 60 and 70 mg/dL

$$ilr_2 = \sqrt{\frac{1}{2}} \ln \frac{\text{X.60}}{\text{X.60.70}} \tag{5}$$

The ilr_2 can be interpreted as the balance between the time spent in severe and moderate hypoglycaemia.

The ilr_3 is the balance between the logratio of the geometric mean of the times spent between 180–250 and >250 mg/dL and the geometric mean of the times spent between 70–140 and 140–180 mg/dL, that is, the balance between time spent in the hyperglycaemic and normoglycaemic ranges

$$ilr_3 = \ln \frac{(\text{X.180.250} \cdot \text{X.250})^{1/2}}{(\text{X.70.140} \cdot \text{X.140.180})^{1/2}} \tag{6}$$

Table 5. Cumulative variance retained by the *clr*-biplot for each patient, number of groups obtained per patient and number of days in each group.

	Cumulative Variance retained (%)	#Groups	Type of group (#days per group)
P1	92.33	3	B(7), C(6), D(5)
P2	93.13	4	A(12), B(4), C(10), D(5)
P3	91.79	4	A(13), B(9), C(13), D(5)
P4	87.02	4	A(10), B(13), C(11), D(10)
P5	92.50	3	A(7), C(12), D(10)
P6	93.14	3	A(6), B(5), C(4)

The ilr_4 is equal to the logratio of the times spent in >250 and between 180 and 250 mg/dL. It is the ratio between the time spent in severe and moderate hyperglycaemia

$$ilr_4 = \sqrt{\frac{1}{2}} \ln \frac{\text{X.250}}{\text{X.180.250}} \tag{7}$$

The ilr_5 is equal to the logratio of the time spent in lower (70–140 mg/dL) and upper (140–180 mg/dL) normoglycaemic ranges

$$ilr_5 = \sqrt{\frac{1}{2}} \ln \frac{\text{X.70.140}}{\text{X.140.180}} \tag{8}$$

3.5 Cluster analysis

Once the logratio coordinates were obtained, a k-means algorithm[30] was applied to the coordinates to check for different patterns of days. This clustering algorithm is based on squared Euclidean distance. We considered the function k-means from the R package cluster with 25 random repetitions of the selection of initial centres. The algorithm was tested for several numbers of groups. The choice of k was based on the analysis of the generated groups and its distribution on the *clr*-biplot, considering also the percentage of variance retained. We also observed the interpretability of the clinical outcomes after the obtainment of the groups. Additionally, the clusters of data were also analysed through silhouette validation (see Supplementary file). The groups of days obtained per patient were analysed in terms of minimums and maximums of parts (amount of time in different glucose ranges) and ratios (*ilr*-coordinates,) and through the logratios between the compositional centre of each group with the whole centre.

In addition, the following measurements were obtained for each group: average blood glucose (Avg BG), blood glucose variation (BGV), low blood glucose risk index (LBGI) and high blood glucose risk index (HBGI),[31] #Hypo and T Hypo. The information regarding insulin therapy is also provided: total daily insulin (TDI) expressed in units of insulin (UI), the daily ratio of basal and bolus (basal/bolus), carbohydrate intake (CHO) expressed in exchanges (e.g. 1 exchange is equivalent to 10 g of CHO), and the relationship between bolus insulin and carbohydrates (bolus:CHO). Additionally, we assessed common lifestyle habits, such as days with reported physical activity and weekends, in relation to the final categorisation of the groups.

4 Results

4.1 Categorisation of days

The results of all patients are summarised in Tables 5 to 9 and Figure 3. Results of one representative patient are presented in Figures 4 to 6, and detailed in the Supplementary file. The results must be interpreted in a relative sense, considering the dominance of one or more variables with respect to the others, and not in an absolute way. Given the final categorisation of days of all patients, four types of days were obtained. The days were characterised

Table 6. Comparison between the compositional centre of each group with the whole centre.

	Group	X.60	X.60.70	X.70.140	X.140.180	X.180.250	X.250
P1	B	−3.37	−0.76	0.36	0.17	−0.02	−3.03
	C	−2.30	−0.26	−0.39	−0.07	0.02	2.62
	D	7.47	1.38	−0.04	−0.15	0.00	1.10
P2	A	1.99	2.38	0.26	−0.04	−0.85	−3.26
	B	−3.17	−2.99	−0.53	0.73	0.38	−2.62
	C	−3.18	−3.01	−0.11	−0.13	0.77	3.58
	D	4.11	2.70	0.01	−0.22	0.20	2.76
P3	A	3.51	4.42	0.38	−0.22	−0.44	−3.48
	B	−3.37	−3.65	0.19	0.34	−0.41	−3.21
	C	−2.84	−3.52	−0.49	−0.02	0.42	4.12
	D	4.34	4.21	−0.08	0.02	0.78	4.10
P4	A	1.42	1.36	0.27	0.07	−0.29	−3.11
	B	−2.83	−3.09	−0.07	0.19	0.02	0.18
	C	−0.69	0.93	0.10	−0.05	0.01	1.16
	D	3.02	1.64	−0.29	−0.26	0.25	1.60
P5	A	4.12	2.34	0.37	0.26	−0.38	−1.98
	C	−3.50	−3.03	−0.53	0.02	0.38	0.46
	D	1.31	2.00	0.37	−0.21	−0.19	0.83
P6	A	5.31	5.57	0.63	−0.01	−0.46	0.23
	B	−2.90	−3.15	0.47	0.43	0.03	−1.54
	C	−4.34	−4.42	−1.53	−0.53	0.65	1.59

Note: Values are expressed per part and represent relative proportion to the mean composition.

Table 7. Minimums and maximums of the *ilr*-coordinates for all groups.

		ilr_1		ilr_2		ilr_3		ilr_4		ilr_5	
	Group	min	max	min	max	min	max	min	max	min	max
P1	B	−10.58	−6.37	−6.67	−4.01	−4.01	−2.05	−5.53	−2.60	0.20	0.71
	C	−10.02	−7.22	−7.01	−3.53	−1.76	1.07	−0.93	0.26	−0.85	1.22
	D	−3.18	−0.82	−0.15	1.41	−2.94	0.59	−4.99	0.20	0.04	0.75
P2	A	−3.08	1.37	−2.25	0.59	−7.74	−3.57	−5.19	−2.96	−0.14	1.28
	B	−7.83	−7.47	−1.16	−0.93	−5.96	−3.22	−5.20	−4.38	−0.73	0.06
	C	−10.15	−5.80	−1.17	−0.89	−1.95	0.75	−2.28	−0.11	−0.01	1.06
	D	−3.15	−0.73	−0.65	1.18	−2.56	−0.63	−1.94	0.38	0.05	1.09
P3	A	−4.69	2.21	−4.27	0.29	−7.71	−3.21	−6.11	−3.72	−2.02	2.10
	B	−12.20	−10.02	−2.41	−1.78	−7.75	−3.56	−6.06	−2.86	−0.88	1.29
	C	−13.77	−12.39	−2.03	−1.55	−2.81	2.32	−2.30	0.87	−1.77	1.42
	D	−7.08	−2.10	−3.72	0.20	−1.38	0.43	−1.91	−0.31	−0.19	0.56
P4	A	−4.86	−0.43	−2.70	0.36	−4.22	−1.84	−4.16	−2.68	0.00	1.20
	B	−8.33	−7.14	−1.63	−0.90	−4.15	0.19	−4.26	0.82	−0.47	1.18
	C	−5.91	−3.88	−2.74	−2.04	−1.71	0.27	−1.76	0.47	0.13	1.49
	D	−3.66	0.26	−1.51	1.47	−1.22	0.45	−1.33	0.75	−0.42	1.11
P5	A	−2.84	0.72	−1.76	1.70	−4.13	−0.05	−3.33	−0.59	−0.26	1.61
	C	−10.79	−7.77	−1.76	−1.41	−3.04	2.34	−3.76	0.36	−1.24	0.66
	D	−6.07	−1.04	−3.15	0.00	−1.98	0.66	−1.28	1.15	−0.33	1.98
P6	A	−6.27	−1.60	−3.79	−0.29	−2.12	0.68	−4.33	−0.07	−0.78	1.84
	B	−15.20	−11.23	−2.18	−1.51	−3.30	−0.88	−4.67	−0.61	−0.52	0.29
	C	−15.69	−14.21	−2.03	−1.70	0.61	3.40	−1.20	−0.30	−3.25	0.35

Table 8. Summary of clinically relevant data per group.

	Group	Avg BG (mg/dL)	BGV (mg/dL)	LBGI	HBGI	#Hypo (events/day)	T Hypo (min/event)	bolus:CHO (UI/ex)	basal/ bolus	TDI (UI)	CHO (ex)
P1	B	151.6	44.4	0.6	5.3	0.4	20.0	1.1	1.5	35.5	13.0
	C	191.0	58.5	0.3	12.2	0.3	22.5	1.2	1.3	39.0	14.5
	D	163.9	65.0	2.4	8.7	1.6	78.1	1.2	1.2	37.4	13.9
P2	A	129.1	35.7	1.3	2.5	1.7	39.3	1.0	1.1	41.1	20.8
	B	158.5	31.8	0.2	5.3	0.0	0.0	1.4	1.1	44.6	16.5
	C	163.4	56.1	0.4	7.7	0.0	0.0	1.3	1.0	44.4	18.1
	D	137.0	56.8	2.4	4.7	2.4	54.2	1.1	0.9	44.7	22.3
P3	A	132.6	37.7	1.0	3.2	0.9	32.1	1.4	1.0	40.2	14.5
	B	150.8	32.6	0.2	4.4	0.0	0.0	1.5	1.1	38.9	13.0
	C	178.0	50.1	0.1	9.6	0.0	0.0	1.8	0.8	44.7	13.8
	D	169.4	55.7	0.6	8.2	1.0	38.0	1.9	0.9	41.7	13.0
P4	A	133.2	39.9	1.2	3.2	1.6	42.5	1.1	0.8	47.6	25.6
	B	160.7	49.1	0.3	6.7	0.0	0.0	1.7	0.8	46.6	21.1
	C	156.0	60.7	0.7	6.9	1.0	33.6	1.3	0.8	47.4	21.7
	D	163.5	69.2	2.0	8.9	1.8	83.3	1.3	0.8	47.9	21.4
P5	A	139.8	51.6	2.7	4.8	2.1	84.7	3.1	1.0	46.4	7.9
	C	203.7	59.4	0.1	14.4	0.0	0.0	3.6	0.6	67.6	13.8
	D	176.6	79.6	1.1	11.3	1.5	41.7	2.7	0.7	59.7	14.1
P6	A	161.4	56.6	1.1	7.9	1.3	43.8	1.3	1.2	44.9	16.8
	B	168.7	42.1	0.1	7.3	0.0	0.0	1.4	1.2	45.0	15.8
	C	213.0	43.5	0.0	15.1	0.0	0.0	1.6	1.0	49.0	16.1

CHO: carbohydrate intake; TDI: total daily insulin; BG: blood glucose; BGV: BG variation; LBGI: low BG risk index; HBGI: high BG risk index.

Table 9. Number of days with manually reported physical activity, number of days corresponding to weekends, average calories and average steps for each group of days after categorisation.

Patient	Group	#Reported Exercise	#Weekends	Calories	Steps
P1	B	4	3	2366.4	7742.2
	C	1	2	2589.8	5641.2
	D	2	0	2347.4	6173.2
P2	A	3	2	3433.6	17,301.1
	B	0	3	2924.0	10,045.3
	C	2	3	3143.9	13,607.1
	D	2	3	3440.0	17,541.3
P3	A	2	3	2586.6	6204.7
	B	3	2	2887.2	9454.6
	C	1	3	2787.8	8336.6
	D	1	1	2690.2	7747.2
P4	A	0	1	3004.0	8745.4
	B	4	5	3265.8	11,426.2
	C	3	4	3483.7	13,755.2
	D	1	3	2885.0	8745.8
P5	A	1	3	1925.9	10,244.4
	C	1	1	1722.6	6277.1
	D	0	4	1706.0	6189.4
P6	A	0	0	2551.5	10,382.3
	B	1	2	2735.8	14,072.2
	C	1	1	2315.5	6299.5

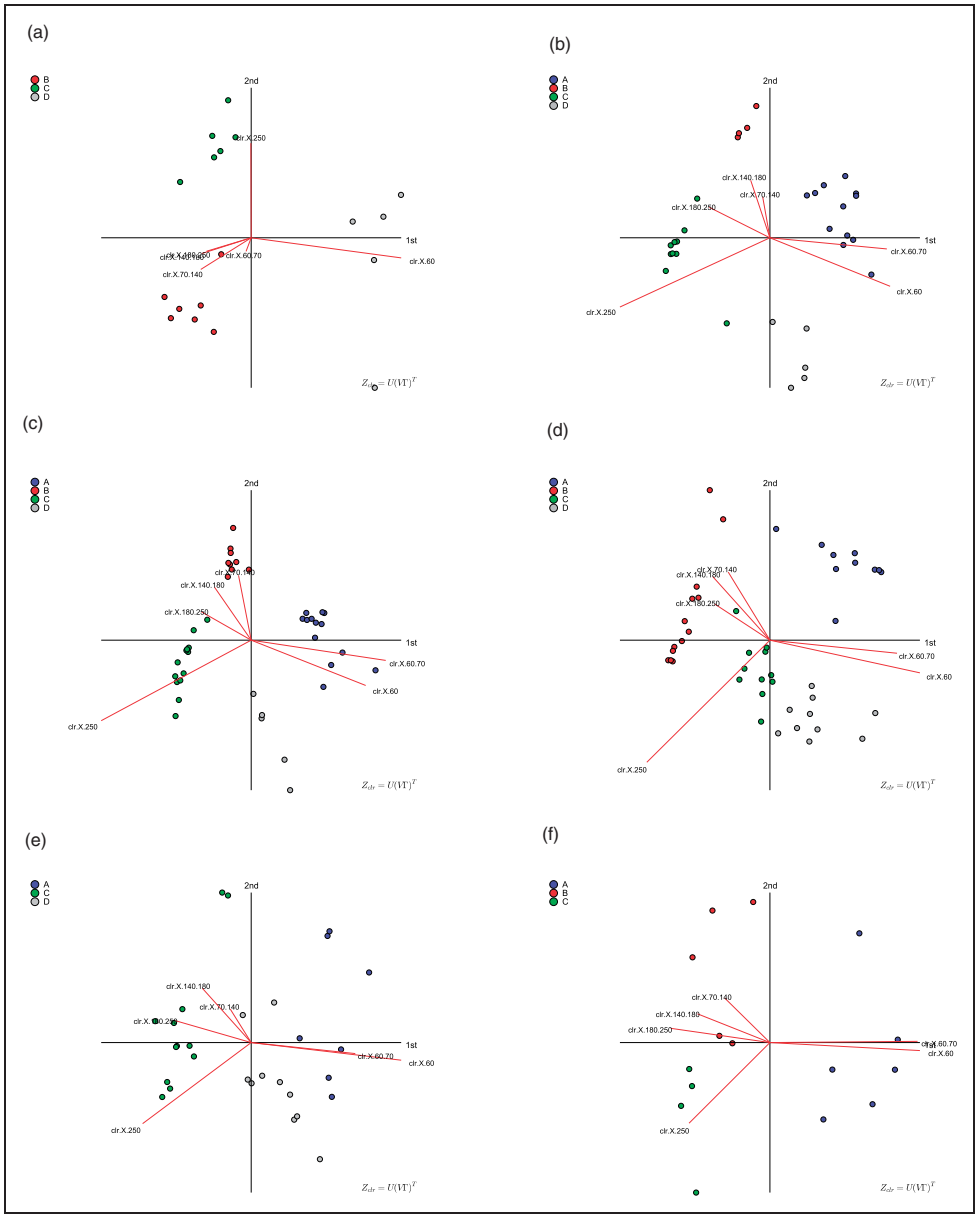

Figure 3. The *clr*-biplots of days of all patients. Each red ray emanating from the origin of the biplots represents the variables of the composition (time in each glucose range). The marks represent the days and are labelled according to the groups obtained after clustering. Days closer to determined rays are characterised by relatively high values in the parts correspondent to those rays. (a) The *clr*-biplot of days of P1 with 92.33% of the cumulative variance retained. (b) The *clr*-biplot of days of P2 with 93.13% of the cumulative variance retained. (c) The *clr*-biplot of days of P3 with 91.79% of the cumulative variance retained. (d) The *clr*-biplot of days of P4 with 87.02% of the cumulative variance retained. (e) The *clr*-biplot of days of P5 with 92.50% of the cumulative variance retained. (f) The *clr*-biplot of days of P6 with 93.14% of the cumulative variance retained.

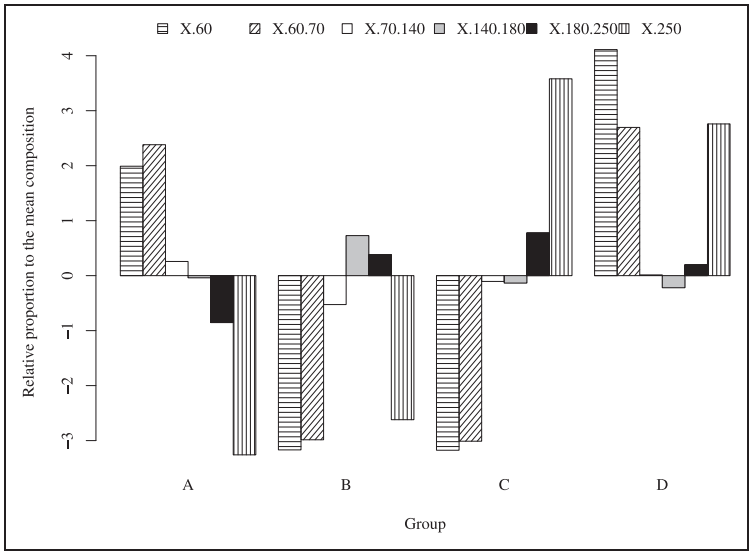

Figure 4. Geometric mean barplot of groups of P2. Comparison of the centre of each group with the whole centre. Positive bars reflect relative mean values of a part above the overall composition. Analogously, negative bars reflect relative mean values of a part below the overall composition.

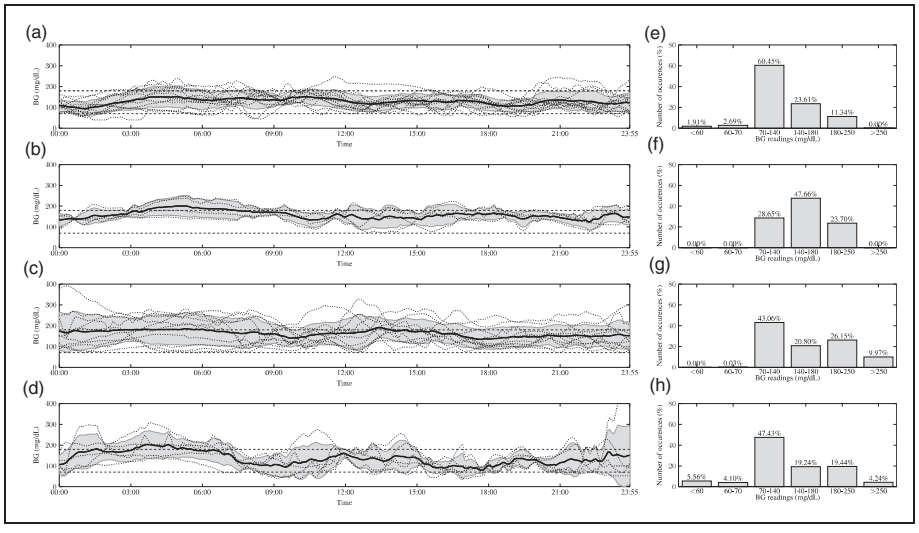

Figure 5. Four groups of days were obtained for patient 2 (P2) after the categorization with CoDA: A, B, C and D. These groups are displayed from top to bottom: (a), (b), (c) and (d) show the glucose profiles for each group. The solid line and shaded area represent mean $\pm$ SD. Dotted lines represent single days of the respective group, and dashed lines at 70 and 180 mg/dL are thresholds to improve visual interpretation. (e), (f), (g) and (h) illustrate the histogram of the data of each group, considering the glucose ranges adopted for the discretization of the continuous signals.

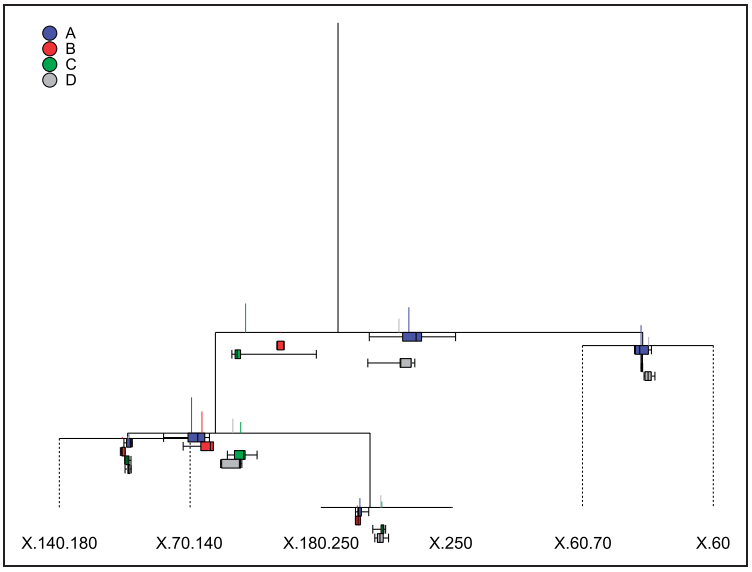

Figure 6. Balance dendrogram for days of P2. Labels A, B, C and D represent the four groups of days obtained after clustering. Each horizontal bar represents an *ilr*-coordinate. Black vertical lines represent the variance of each coordinate. Coloured vertical lines represent the variance of each group in that coordinate. Coloured box-plots summarise the statistics for each balance and each group. Boxplots closer to one side of the tree indicate that the geometric mean of a group of parts on this side, on average, dominate on parts of the other side.

in terms of relative time spent by the individuals in determined glucose ranges during a day according to the logratio approach. Groups of days were generically described as A, B, C and D:

- A – days with relatively high amounts of time in the hypoglycaemic ranges
- B – days with relatively low amounts of time in the ranges related to hypo- and hyperglycaemia
- C – days with relatively high amounts of time in the hyperglycaemic ranges
- D – days with relatively high amounts of time in the ranges related to hypo- and hyperglycaemia

Patients P2, P3 and P4 presented with four types of days, while the remaining patients presented with only three types of days. Even though the days of different patients were categorised separately, it was upon retrospective analysis that we noticed that groups from different patients presented similar characteristics regarding the relative interpretation of time spent in different glucose ranges. Still, even though groups of days of different patients may present the same category, it must be highlighted that the results must be interpreted individually per patient. Table 5 shows the cumulative variances retained by the *clr*-biplot for each patient, the number of groups obtained per patient, the types of groups obtained per patient and the number of days in each group. The high percentages of variances expressed for all patients mean that the biplots are good representations of the CoDa in two dimensions.

4.2 The *clr*-biplots of all patients

Figure 3 shows the *clr*-biplots of the days of all patients representing the groups of days obtained after clustering. The markers represent one day. The relative variability between parts X.70.140 and X.180.250 is lower than the relative variability between parts X.70.140 and X.250, because the link formed by the vertices X.70.140 and X.180.250 is much shorter than the link formed by X.70.140 and X.250.

Regardless of the categorisation of days, it can be observed in Figure 3 that, for most patients (except P1 – Figure 6(a)), the variables X.60 and X.60.70 are on the opposite side with respect to the first axis (horizontal axis)

than the rest of the parts. Days close to those variables are related to the fact that the individual experienced hypoglycaemic events during those days. Those facts supported the definition of the SBP, presented in Table 4. Additionally, this definition of SBP assigned largest variability to the first coordinate (ilr_1) for all patients.

4.3 The geometric mean barplot

Figure 4 shows the compositional geometric mean barplot of groups of P2. Positive bars reflect relative mean values of a part above the overall composition. Analogously, negative bars reflect relative mean values of a part below the overall composition. Similarly, Table 6 shows the logratios between the centre of each group and the overall centre for all patients. Positive values reflect the relative mean of a part above the overall composition, and negative values reflect relative mean of a part below the overall composition. For detailed interpretation of the geometric barplot along with the *clr*-biplot of P2, see the Supplementary file.

The general description of the characteristics of groups of days for each patient initially presented in section 4.1 is consistent with the values presented in Table 6. Days of type A presented with positive values in the parts below 60 and between 60–70 mg/dL and negative values in the parts between 180–250 and above 250 mg/dL. Days of type B presented with negative (or very low values) in the parts below 60, between 60–70, 180–250 and above 250 mg/dL. Days of type C mostly presented with negative values in the parts below 60 and between 60–70 mg/dL and positive values in the parts between 180–250 and above 250 mg/dL. Days of type D presented with positive values in the parts below 60, between 60–70, and above 250 mg/dL. Most of the groups presented with values close to the whole centre when parts between 70–140, 140–180 and 180–250 mg/dL were analysed. The values of Table 6 can be interpreted in terms of the original values. For example, the values below 60 mg/dL during the days of group A in patient P2 are approximately 7.32 (exp(1.99)) times the average time in this range considering the mean composition. This value decreases to 4.16% (exp(−3.18)) when data in group C for the same patient are considered.

A similar inference can be made by observing Figure 5, which depicts all days of P2 considering the categorisation obtained. On the left panels, the daily glucose profiles of the groups are shown. The solid line and shaded area represent mean ± SD. Dotted lines represent single days of the respective group and dashed lines at 70 and 180 mg/dL are thresholds to improve visual interpretation. On the right panel, the histogram is presented according to the ranges considered for the CoDA approach. The overall distribution of time in each glucose range is presented for all days in each group. Detailed interpretation of the glucose profiles and histograms of P2, illustrated on Figure 5, are presented in the Supplementary file.

4.4 The balance dendrogram

Figure 6 shows the balance dendrogram representing the SBP defined in Table 4 for P2. The groups are represented by different colours. Each horizontal bar represents an *ilr*-coordinate. Black vertical lines represent the variance of each coordinate. Coloured vertical lines represent the variance of each group in that coordinate. Coloured boxplots summarise the statistics for each balance and each group. Positive values in one coordinate indicate that the geometric mean of the group of parts corresponding to the numerator of the logratio is higher than that corresponding to the denominator of the logratio. Similarly, boxplots closer to one side of the tree indicate that the geometric mean of a group of parts on this side, on average, dominates on the parts of the other side. The balance dendrograms of all patients, considering the SBP defined in Table 4, is presented in the Supplementary file.

As it can be observed in Figure 6 and also in the balance dendrogram of all patients (Supplementary file), the longest vertical bar corresponds to the first coordinate (ilr_1). It means that this logratio has high variability in comparison with the other balances. The shortest vertical bar corresponds to the fifth coordinate (ilr_5). It means that this logratio has the lowest variability in comparison with the other balances.

When comparing the total variance of ilr_1 (largest vertical bar) with the corresponding bars for each group (within group variance), we state that this logratio is very useful to interpret the differences among the groups (between variance). Note that the boxplots of groups B and C are placed entirely on the left half of the first horizontal bar. This indicates that the geometric mean of parts (X.70.140, X.140.180, X.180.250 and X.250) of groups B and C is higher than the geometric mean of parts (X.60 and X.60.70). Table 7 shows the minimums and maximums of each *ilr*-coordinate for all groups. Although the ranges of each coordinate are different between groups and patients, it is possible to note some similarities regarding the separation of groups according to the determined coordinates.

Groups B and C presented with high negative values in the first coordinate (ilr_1) for all patients. This is because these groups are characterised by relatively low amounts of time spent in the hypoglycaemic ranges (the numerator of ilr_1). Additionally, ilr_1 separates groups A and D from groups B and C for all patients, except for P4, in which only group D is separated from groups B and C. One can interpret the values of Table 7 in terms of the original values. For example, if ilr_1 for P2 in group A takes values between -3.08 and 1.37, it means that on average, the time spent below 60 and between 60 and 70 mg/dL is greater than 6.9% $\left(\exp\left(\frac{-3.08}{\sqrt{\frac{4}{3}}}\right)\right)$ the mean time spent in the rest of the glucose ranges; however, it can take a maximum of 3.29 $\left(\exp\left(\frac{1.37}{\sqrt{\frac{4}{3}}}\right)\right)$ times the average of these parts. Instead, because the ilr_1 of P2 in group C has a range from -10.15 to -5.80, in the days of this group, time below 60 and between 60 and 70 mg/dL is between 0.015% $\left(\exp\left(\frac{-10.15}{\sqrt{\frac{4}{3}}}\right)\right)$ and 0.659% $\left(\exp\left(\frac{-5.80}{\sqrt{\frac{4}{3}}}\right)\right)$ of the time in the rest of glucose ranges.

The second coordinate (ilr_2) separates group D from group C for P1, P2 and P4. Groups A and B presented with high negative values in the third coordinate (ilr_3) for all patients; this is because these groups are characterised by relatively low amounts of time spent in the hyperglycaemic ranges (the numerator of ilr_3). Furthermore, the third coordinate (ilr_3) separates group C from group B for P1, P2, P3 and P6. The fourth coordinate (ilr_4) separates groups C and D from group A for P2, P3 and P4, and separates group C from group B for P1, P2 and P3. There is no separation between groups for any of the patients when the fifth coordinate (ilr_5) is analysed. Even though the groups diverge between the logratios of amounts of time spent in other glucose ranges (or groups of ranges), there is no difference between groups considering the ratio between time spent in the lower and upper normoglycaemic ranges for any patient.

4.5 Clinical analysis of groups

Table 8 allows multi-factorial analysis of the clinically relevant data obtained from the groups. The lowest BGV is presented for the days of group B for all patients, except for P4 and P5 (which does not present with days of group B). Analogously, the days classified in group D for all patients presented with the highest BGV.

The days of group C of all patients, except P4, presented with the highest average BG of all groups; however, only for P1, P3, P5 and P6 is the HBGI considered high (HBGI > 9.0). Besides that, the days of group C for all patients, except P1, did not present with hypoglycaemic events. Similarly, the days of group A of all patients presented with the lowest average BG.

Although the average duration of the hypoglycaemic events presented by the days of group D of P1, group D of P4, and group A of P5 is comparably high, only the days of group A of P5 presented with a moderate LBGI (LBGI between 2.5 and 5.0), while the others presented with a low LBGI. Group A of P5 presented with the highest average duration of hypoglycaemic events, even though it presented with the lowest TDI and lowest CHO compared to the other groups of days of the same patient. The average amount of CHO for the days of group A of P5 is approximately half that of the other groups of the same patient. This might indicate the patient's lifestyle alteration during days of this type, for example, a different diet. It is important to mention that the CGM-pump system automatically records readings of glucose and insulin delivery. Data for CHO intake are manually inserted by the user, and although it is susceptible to uncertainties, it also provides information about the patient's behaviour regarding the usage of the device.

Despite the fact that the days of type A of P2 presented with both TDI and a bolus:CHO ratio lower than the other groups of days of this patient, the days of group A presented with an average of 1.7 hypoglycaemic events/day. Similar to the days of group A, the days of group D of P2 are also characterised by hypoglycaemic events; however, not only is the average number of hypoglycaemic events higher in group D than in group A (2.4 vs. 1.7 events/day) but also the duration of the events (54.2 vs. 39.3 min/event). Even though group A of P3 presents with the lowest bolus:CHO ratio and the highest CHO between all other groups of this patient, hypoglycaemic events were also noted in the days of this group.

Table 9 shows the number of days in which each patient manually reported some physical activity, the number of days that correspond to weekends, the average calories and average steps recorded by the activity tracker after the categorisation of groups.

Although it is well known that glycaemic control can be affected by several lifestyle factors, and that the fear of hypoglycaemia and loss of glycaemic control are barriers to exercises in the T1D population,[32] no pattern could be

found regarding the distribution of weekends and exercise sessions between the resultant categories of groups. Weekends and days with reported physical activity were categorised either in groups of days with more susceptibility to hypo- or hyperglycaemic events, good glucose control or high glucose variability.

In relation to the average calories burned and the number of steps for each group of days, different inferences can be made for different patients. For instance, in days of groups A and D of P2, which are, respectively, characterised by the existence of hypoglycaemic events and high glucose variability for this patient, the average number of steps and calories burned was much higher than in the other groups. Alternatively, in days of type B, which are characterised by the lowest glucose variability for patients P1, P3 and P6, these patients presented with the highest average number of steps comparing with other groups of days. The average number of steps of days of group C for patients P1 and P6 is lower than the other groups of days for the same patients. Days of group C of P4 showed the highest average number of steps between other groups for the same patient.

Our analysis indicates that different lifestyles and living habits may have variable effects on glycaemic control and could possibly lead to divergent categories of days for different patients; this shows that deeper analysis on the causes of glycaemic variability should be performed individually because of inter-patient variability. Thus, in order to provide meaningful information for insulin adjustments, it is not enough to have only the information regarding weekends, reported exercise, calories and steps, showing that novel approaches to deal with large intra-patient variability are necessary.

5 Discussion

The logratio analysis must be interpreted in a relative sense. Variables should be interpreted in terms of dominance with respect to other variables. The analysis of glucose data was performed in this paper by considering the time spent by T1D patients in different glucose ranges during a 24-h period. The amounts of time spent in different glucose ranges during a 24-h time period have been compared to the geometric mean of time spent in all glucose ranges and to the geometric means of time spent in other glucose ranges, which allowed to obtain of different groups of days. Groups of days were compared separately with the geometric mean of the whole dataset, which is a measure of the central tendency of the amounts of time spent in each glucose range per day. So far, the analysis has considered only complete days, starting at 00:00 and ending at 24:00, and a reasonable categorisation of days was obtained. This categorisation of profiles can be performed at any time of the day, considering the last 24-h of glucose data. Even though more effort is necessary to allow the analysis in real time, the authors foresee that it is possible to obtain a predictive model based on a CoDa approach, which would allow the adjustment of insulin dosing accordingly.

Currently, the categorisation of groups of days could work as a promising indicator for physicians. It could also work as an additional analysis tool, helping physicians to visualise different patterns of days that require adjustment of the current insulin therapy, and possibly to create different profiles of therapy for each type of day. Nevertheless, further analysis of the current therapy simultaneously with the categorisation of glucose profiles should be performed in order to match the insulin requirements of different categories of days. The ''traditional'' analysis of glucose time series still recognises time-related trends and allows the visualisation of frequencies, intensities and durations of hypo- and hyperglycaemic patterns. The CoDa approach can be applied for the analysis of glucose data considering different periods of time; however, a combination of the information of the category of day obtained with the CoDA of the 24-h glucose profiles with the glucose trends of those days may provide optimal support for physicians to make decisions. Furthermore, following future refinements, the approach will provide additional personalised information that would help to manage glucose variability.

6 Conclusion

In this paper, we presented a novel methodology based on CoDA to classify daily glucose profiles. Considering a limited dataset composed of complete daily glucose profiles collected from six patients, this individualised methodology was shown to be suitable for categorisation of intra-patient variability into different groups.

This methodology could be used as an analysis tool for physicians by helping them to decide the groups of days that require adjustment and to individually tailor a patient's insulin dosing profile according to the final categorisation. Furthermore, the information obtained from this approach could also be used as input to a decision support system, helping the automatic optimisation of a BG control algorithm.

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Supplementary file: Individual Categorisation of Glucose Profiles Using Compositional Data Analysis

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1 The *clr*-biplot

Figure 1 shows the *clr*-biplot of P2. The variables X.60 and X.60.70 are on the opposite side with respect to the first axis (horizontal axis) than the rest of the parts. The days of group A are very close to the rays of variables X.60 and X.60.70, i.e. the days of this group are characterised by relatively high values in the parts correspondent to blood glucose (BG) <60 mg/dL and between 60-70 mg/dL. The barplot of days of this group, as shown in Figure 2, confirms the suggestion of the biplot, which is that the days of this group are characterised by relatively high values in the parts corresponding to BG <60 mg/dL and between 60-70 mg/dL, and relatively low values in the part correspondent to BG >250 mg/dL. In the days of group A, the patient spent relatively more time in the low glucose ranges and less time in the highest glucose range.

The days of group B are close to the rays of variables X.70.140 and X.140.180 (Figure 1). This suggests that the days of group B are characterised by relatively high values in the parts corresponding to BG between 70-140 mg/dL and 140-180 mg/dL. However, the barplot of this group (Figure 2) shows that the days of group B are characterised by relatively low values in the parts correspondent to BG <60 mg/dL, between 60-70 mg/dL, and >250 mg/dL, which means that in the days of this group, the patient spent relatively less amounts of time in the extreme glucose ranges (high and low), and not necessarily more time in the normoglycaemic ranges than the whole composition.

The days of group C are characterised by relatively high values in the parts correspondent to BG between 180-250 mg/dL and >250 mg/dL, as shown in the biplot (Figure 1). The barplot related to this group (Figure 2) shows that the days of this group are also characterised by relatively low values in the parts correspondent to BG <60 mg/dL and between 60-70 mg/dL,; however, unlike the days of groups A and B, the days of group C are characterised by relatively high values in the part correspondent to BG >250 mg/dL. In days of group C, the patient spent relatively more time in the highest glucose range and less time in the low glucose ranges.

The days of group D are in the opposite direction of the rays of variables X.70.140 ans X.140.180; the biplot (Figure 1) suggests that the days of this group are characterised by relatively low values in the parts correspondent to BG between 70-140 mg/dL and 140-180 mg/dL. However, as shown in the barplot of Figure 2, the days of group D are characterised by relatively high values in the parts correspondent to BG <60 mg/dL, between 60-70 mg/dL, and >250 mg/dL, and by the fact that the patient spent relatively more time in the extreme glucose ranges (high and low), and not necessarily less time in the normoglycaemic ranges than the whole composition.

2 Glucose profiles and distribution of time in different ranges

Figure 3 depicts all days of P2 considering the categorisation obtained. On the left panels, the daily glucose profiles of the groups are shown. The solid line and shaded area represent mean ± standard deviation (SD) . Dotted lines represent single days of the respective group and dashed lines at 70 and 180 mg/dL are thresholds to improve visual interpretation. On the right panel, the histogram is presented according to the ranges considered for the Compositional Data Analysis (CoDA) approach.

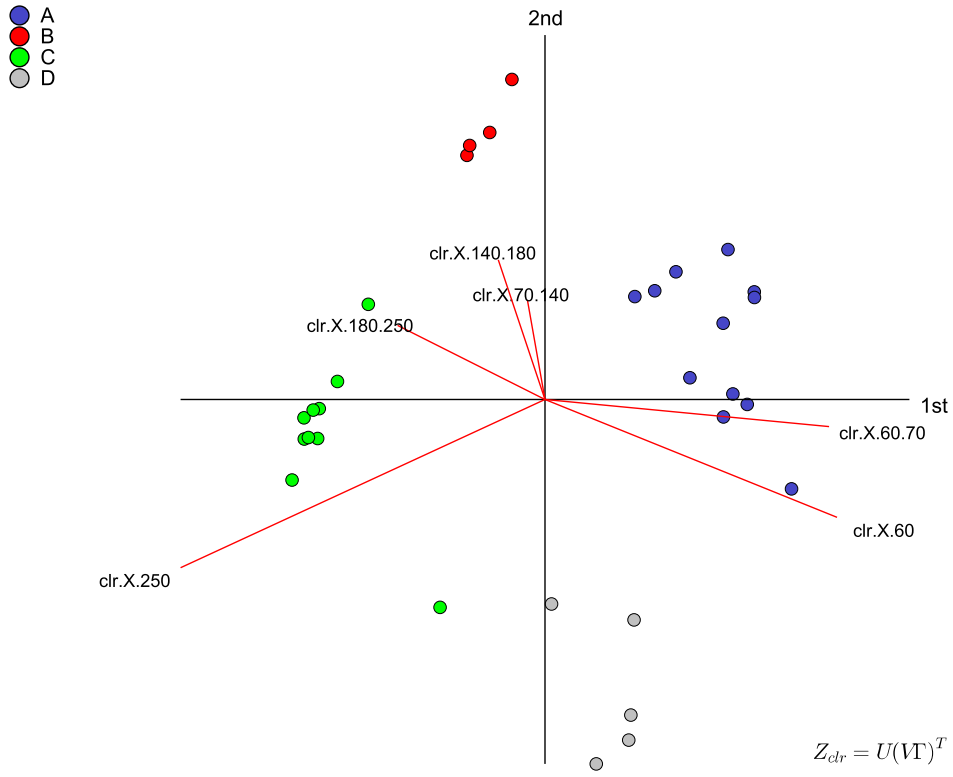


Figure 1: The *clr*-biplot of days of P2. Each red ray emanating from the origin of the biplot represent the variables of the composition (time in each glucose range). The marks represent the days and are labeled according to the groups obtained after clustering. Days closer to determined rays are characterized by relatively high values in the parts correspondent to those rays.

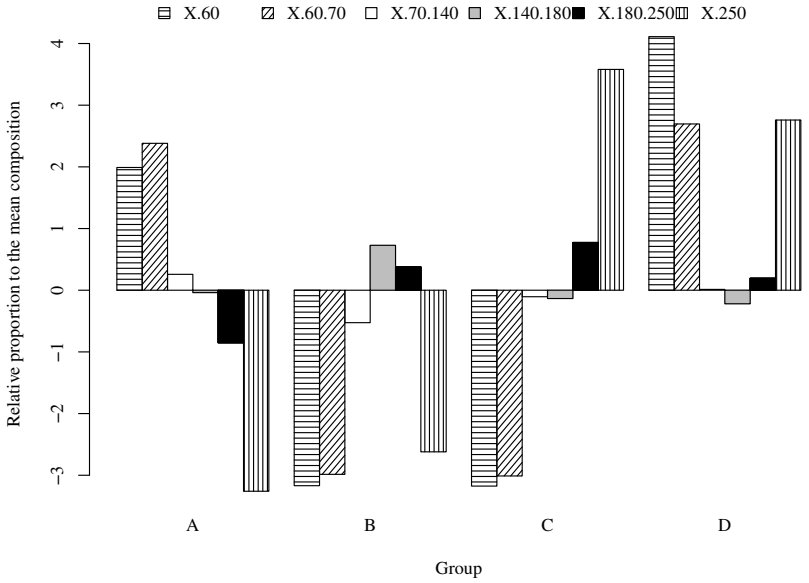


Figure 2: Geometric mean barplot of groups of P2. Comparison of the centre of each group with the whole centre. Positive bars reflect relative mean values of a part above the overall composition. Analogously, negative bars reflect relative mean values of a part below the overall composition.

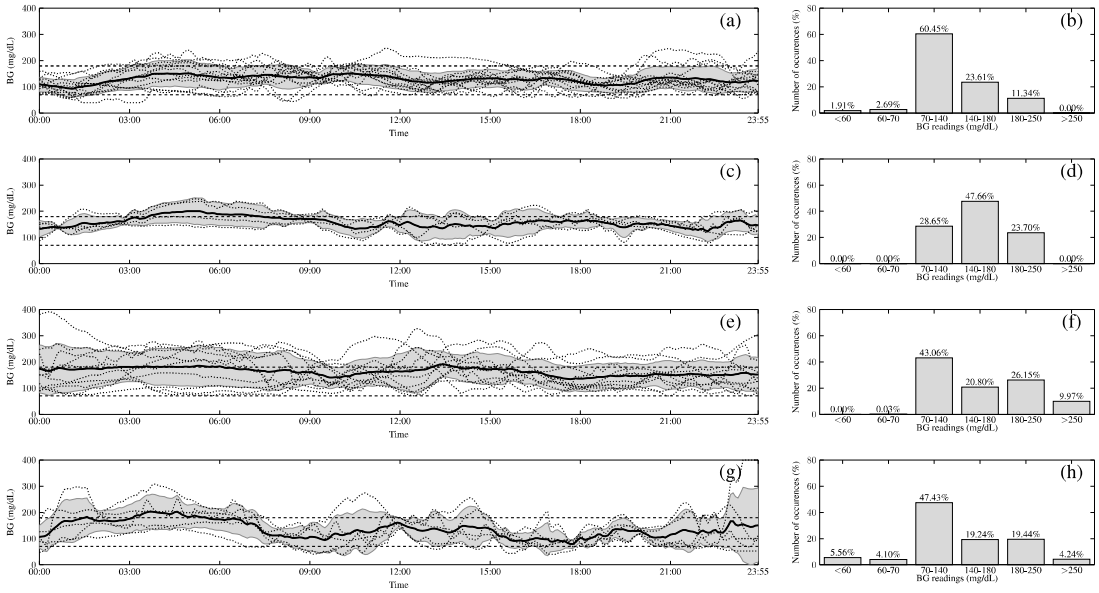


Figure 3: Days of patient 2 (P2) after categorisation with CoDA. From top to bottom: Groups A, B, C, and D. (a), (c), (e), and (g) show the glucose profiles for each group. The solid line and shaded area represent mean ± SD. Dotted lines represent single days of the respective group and dashed lines at 70 and 180 mg/dL are thresholds to improve visual interpretation. (b), (d), (f), and (h) illustrate the histogram of the data of each group, considering the glucose ranges adopted for the discretisation of the continuous signals.

Single days of group A are characterised by the fact that the individual spent time with their glucose level under the threshold of 70 mg/dL or above 180 mg/dL. However, as shown by the daily glucose profiles and in the histogram, during days of this type, the patient has not spent time with glucose above 250 mg/dL.

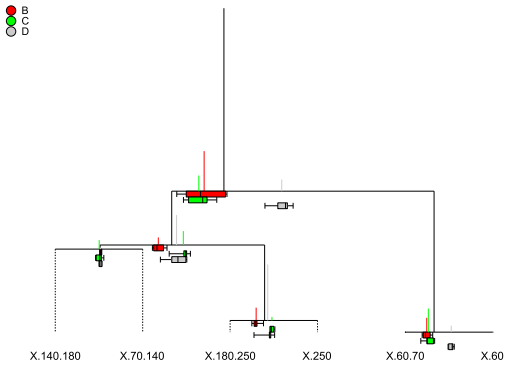
As for days of group A, days of group B also do not present with occurrences of BG readings above 250 mg/dL. However, unlike the days of group A, the days of group B do not present with occurrences of BG readings below 70 mg/dL. This can be observed in both the daily glucose profiles and in the histogram. Comparing the histograms of days of type A and B, one can notice that there is an increase on time spent in the upper normoglycaemic range (140-180 mg/dL) and lower hyperglycaemic range(180-250 mg/dL).

Days of group C present with negligible occurrence of BG readings below 70 mg/dL. In contrast to the days of both groups A and B, the days of group C present with occurrences of BG readings above 250 mg/dL. Comparing the histograms of groups B and C, although there is an increase in time spent in the lower normoglycaemic range (70-140 mg/dL), time in the upper normoglycaemic range (140-180 mg/dL) is decreased. However, time in the hyperglycaemic ranges (between 180-250 and above 250 mg/dL) is higher than those presented by both groups A and B.

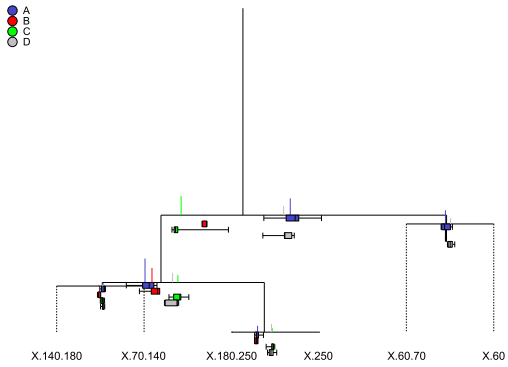
As for the days of group C, the days of group D are also characterised by the fact that the individual spent time with their BG above 250 mg/dL. However, during the days of this group, the individual also spent time with their BG under 70 mg/dL. The characteristic of high glucose variability across days in this group can be verified in the graph of the daily glucose profiles and in the histogram, in which occurrences of BG readings in all glucose ranges are presented.

3 Balance dendrograms

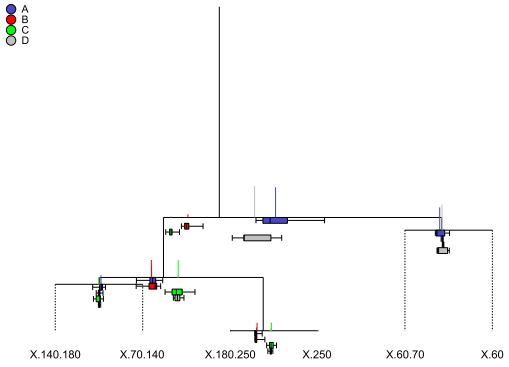
Figure 4 shows the balance dendrogram for all patients. The groups are represented by different colours. Each horizontal bar represents an *ilr*-coordinate. Black vertical lines represent the variance of each coordinate. Coloured vertical lines represent the variance of each group in that coordinate. Coloured box-plots summarise the statistics for each balance and each group. Positive values in one coordinate indicate that the geometric mean of the group of parts corresponding to the numerator of the logratio are higher than that corresponding to the denominator of the logratio. Similarly, boxplots closer to one side of the tree indicate that the geometric mean of a group of parts on this side on average, dominate on parts of the other side.



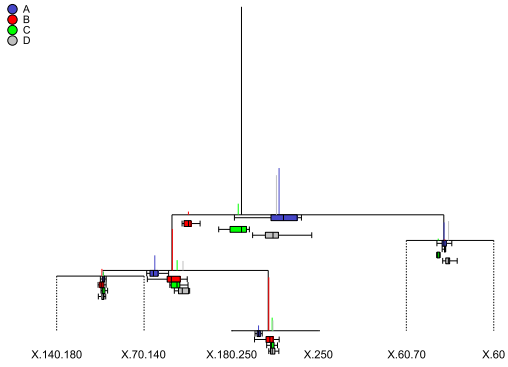
(a) Balance dendrogram of days of P1.



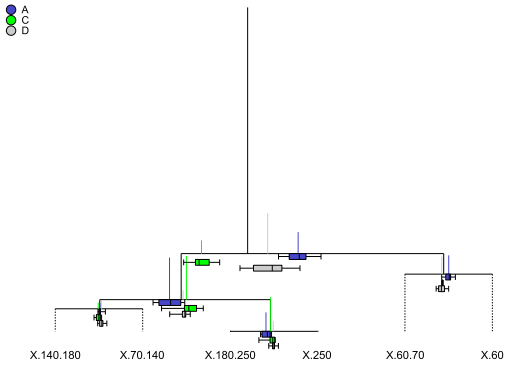
(b) Balance dendrogram of days of P2.



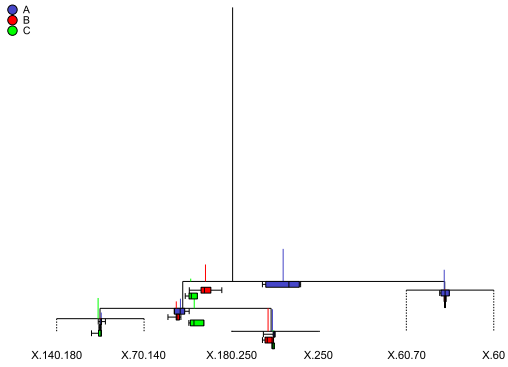
(c) Balance dendrogram of days of P3.



(d) Balance dendrogram of days of P4.



(e) Balance dendrogram of days of P5.



(f) Balance dendrogram of days of P6.

Figure 4: Balance dendrograms for days of all patients. Labels A, B, C, and D represent the groups of days obtained after clustering. Each horizontal bar represents an *ilr*-coordinate. Black vertical lines represent the variance of each coordinate. Coloured vertical lines represent the variance of each group in that coordinate. Coloured box-plots summarise the statistics for each balance and each group. Boxplots closer to one side of the tree indicate that the geometric mean of a group of parts on this side, on average, dominate on parts of the other side.

4 Silhouette Coefficient

The silhouette coefficient was used to validate the clustering method. The silhouette index has a range of -1 to +1. Values close to 0 indicate that the sample is between neighbouring clusters, positive values indicate good classification, and negative values indicate that the sample has been assigned to the wrong cluster. The silhouette indexes per sample were all positive, indicating that there was no misclassification between groups. The averages of the silhouette coefficients of the groups obtained for each patient are shown in Figure 5; the values range from 0.44 to 0.90, showing that the CoDa based approach performs satisfactorily for the classification of daily glucose profiles.

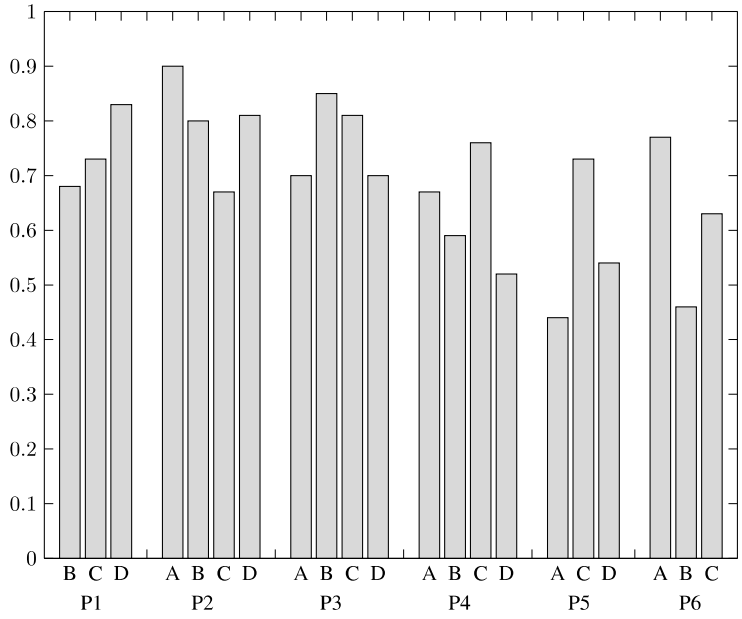


Figure 5: Silhouette coefficients of all groups and patients.

5 Script

5.1 Obtainment of the compositional vector

The matlab file `Data_glucose.mat` contains daily glucose profiles available for each patient. Each glucose profile corresponds to 1440 minutes (or 24-h), sampled every 5 minutes, hence, each glucose profile contains 288 samples. The compositional vector is obtained by the computation of the amounts of time spent in the glucose ranges defined according to Equation 5.1. Values are presented in mg/dL.

$$\begin{cases} \text{Glucose} < 60 \\ 60 \leq \text{ Glucose } < 70 \\ 70 \leq \text{ Glucose } \leq 140 \\ 140 < \text{ Glucose } \leq 180 \\ 180 < \text{ Glucose } \leq 250 \\ \text{Glucose} > 250 \end{cases} \tag{1}$$

5.2 Zero analysis and replacement

The patterns of the zeros of the dataset were analysed with the `zPatterns` function from the R package `zCompositions`.

```
install.packages("zCompositions")
library(zCompositions)
zPatterns(dataset,label=0, cell.labels=c("Zero","Non-zero"),bar.labels=TRUE)
```

After that, the matrix of detection limits (DL) was generated according to described in Table 3 of the Main Manuscript. The matrix of DL was used as input to the zero replacement process, which was performed with the `lrEM` from the same R package.

```
dataset_zero_replaced <- lrEM(dataset, label = 0, dl = DL_matrix, ini.cov = "multRepl")
```

Data can be exported to a `.csv` file:

```
write.table(dataset_zero_replaced, file="Data_Patient_X.csv", sep=';')
```

5.3 The logratio coordinates

Logratio coordinates were analysed through CoDaPack:

```
File > Import > Import CSV/Text Data...
Import .csv file from containing folder
```

In CoDaPack, the user can analyse the *clr*-biplot of the dataset.

```
Graphs > CLR biplot
Select variables from the Available data
Accept
```

The user can obtain the coordinates according to the SBP presented in Table 4 of the Main Manuscript:

```
Data > Transformations > ILR
Select variables from the Available data
Define base: Paste the SBP in the field defined base or
Manually define the base through the menu "Define Mannually"
Accept
```

The balance dendrogram can also be obtained in CoDaPack:

```
Graphs > Balance dendrogram
Select variables from the Available data
Define base: Paste the SBP in the field defined base or
Manually define the base through the menu "Define Mannually"
Accept
```

The generated coordinates can be exported to a RData file:

```
File > Export > Export Data to RData...
Select variables from the Available data
Define Dataframe names
Accept
```

5.4 Cluster analysis

The cluster analysis was performed in RStudio with the *ilr*-coordinates obtained from the SBP using CoDaPack. It is important to highlight that the coordinates could have been obtained directly in R, using the functions provided by the package `Compositions` or in other softwares as well, following the equations 1 to 8 described in the Main Manuscript. For the cluster analysis in R, package `Cluster` is required:

```
library(cluster)
```

The k-means algorithm is applied to the coordinates. The three arguments provided are the dataset (the coordinates), the number of groups (k) and the number of repetitions of selection of initial centres (nstart).

```
cl <- kmeans(coordinates, k, nstart = 25)
```

After the obtainment of groups, the user can export the dataset from R to a `.csv` file and return to CoDaPack to perform the analysis of groups.

2.5 Probabilistic Model of Transition Between Categories of Glucose Profiles in Patients with Type 1 Diabetes Using a CoDa Approach

The candidate's contribution for this publication consisted in pre-processing the data obtained in the clinical trial, researching data, performing the categorization of glucose profiles using CoDa analysis, obtaining the probabilistic model of transition between categories of glucose profiles, contributing to discussion, and writing the manuscript. During the development of the work, the candidate worked with her colleague Arthur Bertachi. They were supervised by Dr. Josep Antoni Martín-Fernández and Dr. Josep Vehí. Dr. Marga Giménez, Dr. Ignacio Conget and Dr. Jorge Bondia contributed to the discussion.

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Probabilistic Model of Transition Between Categories of Glucose Profiles in Patients with Type 1 Diabetes Using a Compositional Data Analysis Approach

Lyvia Biagi, Arthur Bertachi, Marga Giménez, Ignacio Conget, Jorge Bondia, Josep Antoni Martín-Fernández, Josep Vehí*

***Abstract*—The occurrence of adverse events and the quality of glucose control in type 1 diabetes (T1D) are usually measured through the time spent in different glucose ranges. As the time in one day is finite and limited to 24h, the times spent in different glucose ranges during one day are codependent and carry only relative information, Compositional Data (CoDa) analysis is appropriate to deal with this type of data. This work proposes a CoDa approach applied to glucose profiles obtained from six T1D patients using continuous glucose monitor (CGM). Glucose profiles of 24-h and 6-h duration were categorized according to the relative interpretation of time spent in different glucose ranges at different times of day, with the objective of presenting a probabilistic model of prediction of category of the next 6-h period based on the category of the previous 24-h period. A discriminant model for determining the category of the 24-h periods was obtained and leave-one-out cross-validation was performed, achieving an average above 94% of correct classification. A probabilistic model of transition between the category of the past 24-h of glucose to the category of the future 6-h period was obtained. Results show that the approach based on CoDa is suitable for the categorization of glucose profiles giving rise to a new analysis tool. Additionally, it can be used as a complementary tool for the prediction of different categories of glucose control, which could be very helpful for patients, to anticipate the occurrence of potential adverse events or undesirable variability and for physicians to assess patients' outcomes and then tailor their therapies.**

***Index Terms*—Type 1 Diabetes, Compositional Data Analysis, Decision Support System, Diabetes Management, Probabilistic Model of Transition.**

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I. Introduction

TYPE 1 diabetes (T1D) is an autoimmune disease characterized by destruction of pancreatic beta cells. Individuals with T1D rely on external insulin to regulate blood glucose (BG) levels. Insulin infusion can be performed either with multiple daily injections (MDI) or with continuous subcutaneous insulin infusion (CSII). In order to avoid both high and low levels of BG (hyper- and hypoglycemia, respectively), insulin must be properly infused. Both hyper- and hypoglycemia lead to several complications over time: blindness, kidney failure, cardiovascular complications, and even death [1].

Insulin dosing is usually adjusted by physicians according to patient's characteristics, such as carbohydrate intake and body weight [2]. Even though current T1D technology allows the combination of continuous glucose monitoring (CGM) and CSII, achieving optimal glycemic control is very complicated due to large intra-patient variability [3]. Changes in glycemia are consequences of the circadian rhythm of hormones responsible for the glucose metabolism and carbohydrate intake, and glycemic variability is increased in people with diabetes [4]. Dealing with the complex behavioural characteristics of patients with T1D makes it difficult for physicians to adjust proper insulin dosing profiles to handle patient's activities. The effective integration of relevant clinical data in a decision support system would be able to relieve the burden that affects physicians in taking clinical decisions during consultations of patients with T1D and would help optimize insulin delivery therapy [5].

The time spent in, above and below the target glucose range are commonly presented for descriptive purposes and to encourage patients with T1D to increase the time spent in their target ranges, which would improve the quality of glucose control. The time spent in different glucose ranges indicate the occurrence of different levels of hypo- and hyperglycemic events, and these times, during a day, are relative contributions to the 24-h time budget. Several works presented approaches for different activities performed during a 24-h period using Compositional Data (CoDa) analysis [6]–[12]. Since times spent in different glucose ranges are co-dependent and carry

CHAPTER 3

DISCUSSION

The results presented in this thesis considered the analysis of CGM data from two data sets obtained in two clinical studies designed by the Spanish Consortium on Artificial Pancreas and Diabetes Technology. The works compiled in the previous chapter presented an analysis of accuracy of CGM during PP and during PA. Also, a model of the CGM error was derived. A tool for categorization of glucose profiles based on CoDa analysis and a probabilistic model of transition between categories of glucose profiles were also obtained. The following sections of this chapter depict a brief discussion on the analysis of accuracy of the CGM sensors as well as the model of the CGM sensor. Also, the works in which CoDa analysis of glucose data obtained from CGM is done are discussed.

3.1 Analysis of the CGM accuracy and modeling of the CGM error

CGM accuracy is affected by several factors: a physiological delay related to the glucose transport from blood to interstitium, where glucose is measured by CGM devices, inherent

sensor properties and the dynamic profile of BG excursions (Cengiz and Tamborlane, 2009; Cobelli et al., 2016; Castle and Ward, 2010).

The accuracy of the the second generation of the Medtronic Enlite sensor has been evaluated in two scenarios in this work: during PP period and during PA. Glucose fluctuations during PP are one of the main contributors to hyperglycemia and glucose variability. PA is also a hurdle for CGM accuracy due several reasons: changes in subcutaneous tissue circulation, variations in oxygen concentration of blood, increase in body temperature, mechanical forces where the sensor is placed, and rapid glucose changes in glucose concentrations caused by exercise (Kumareswaran et al., 2013). Both PP and PA are challenging situations for CL systems.

In Biagi et al. (2017b), the authors evaluated numerical and clinical accuracy of the second generation of the Medtronic Enlite sensor during PP. The authors also analyzed the impact of CGM accuracy on CL performance. MARD and the precision absolute relative difference (PARD) were considered for the calculation of accuracy and precision of CGM sensors during PP. Both MARD and PARD presented higher values when the analysis was performed in the hypoglycemic range, showing that both accuracy and precision are degraded with low values of glucose (see Table 5 of Section 2.2).

The effects of sensor accuracy in the CL sessions was computed considering the 10 most and 10 least accurate sensors for the CL sessions. During the sessions that considered the 10 least accurate sensors, the patients spent more time in the hypoglycemic range, requiring a higher amount of glucose rescues (see Tables 3 and 4 of Section 2.2). These facts indicate that the performance of the CL algorithm during PP was related to sensor accuracy.

In Biagi et al. (2018d), the authors presented an evaluation of the dynamic behaviour of the accuracy of the second generation of the Medtronic Enlite sensor before, during and after aerobic and anaerobic exercises sessions. The MARD was computed at different periods: one hour before exercise, during exercise, and four hours after the end of exercise. MARD increased during exercise realization when compared with the MARD before exercise initialization,

for both aerobic and anaerobic sessions. After exercise, MARD decreased, for both aerobic and anerobic sessions (see Tables 2 and 4 of Section 2.3). However, this variation, was only significant for the aerobic sessions, showing that CGM might present lower accuracy during this type of exercise, but it is able to return to regular operation after exercise cessation. No significant impact was found for anaerobic exercise.

The works described by Biagi et al. (2017b, 2018d) evaluated the accuracy of the second generation of the Medtronic Enlite sensor during PP and PA. The work presented by Biagi et al. (2017c) presented a sensor error model to represent the same glucose sensor. This methodology allowed the dissection of the sensor error into the delay due to the blood-to-interstitium glucose (BG-IG) kinetics, the calibration error, and the measurement noise. It was the first time that this methodology has been applied to the Enlite sensor. The results were compared to previously existing models of CGMs sensors from other manufacturers, derived using the same methodology, with results presented in Facchinetti et al. (2014, 2015).

The MARD was used to quantify the error components and overall error. The three key components of sensor error are the BG-IG diffusion process, calibration error, and measurement noise. The results presented by Biagi et al. (2017c) showed that calibration error had the highest contribution to the global error observed, which had already been shown by Facchinetti et al. (2014, 2015) (see Table 4 of Section 2.1). However, the authors noticed that there may be higher variability in the error experienced by the Enlite sensor than that reported by Facchinetti et al. (2014, 2015) for other sensors.

The mean MARD of the Enlite sensor presented by Biagi et al. (2017c) was lower than the values presented by Facchinetti et al. (2014) in the global, calibration and noise analysis. The mean MARD related to BG-IG was higher, however, this component is related to the time lag, and the estimation of this parameter is more robust when multiple sensors are considered. The median MARD presented for the Enlite sensor was also lower than the values presented by Facchinetti et al. (2015) in the global, noise and BG-IG analysis. The median MARD related to

the calibration was lower than the values presented for one of the sensor models, and higher than the presented by the other two sensor models (see Table 4 of Section 2.1).

Besides the difference in the day of sensor insertion between the works presented by Biagi et al. (2017c) and the works presented by Facchinetti et al. (2014, 2015) (see Table 3 of Section 2.1), a further comparison of the study protocol must be done to explain differences in the results presented by the aforementioned works. It is well known that CGM sensors present lower performance in the hypoglycemic range and during rapidly changing conditions such as during a large meal or a hypoglycemic episode (Kropff et al., 2014; Rebrin et al., 1999; Rebrin and Steil, 2000; Steil et al., 2005; Wilson et al., 2007; Schmidt et al., 2012). Most of the CGM values presented by Biagi et al. (2017c) were in the euglycemic and hyperglycemic range (97.76% of the values) (see Table 8 of Section 2.1), and during 77.34% of the time, a rate of change between -1 and 1 mg/dL/min was observed (see Figure 6 of Section 2.1). Those values explain the lower MARDs presented by Biagi et al. (2017c).

Even though the data set used was not acquired to derive the Enlite sensor error model and only 10 subjects were used, the derivation of the CGM error into its different components was possible (even if not optimal) and the resultant model was compared with the models of other CGM sensors previously presented (Facchinetti et al., 2014, 2015), as summarized in the previous paragraphs and detailed in Tables 3, 4, 6 and 7 of the Section 2.1.

3.2 Compositional Data Analysis Applied to Glucose Profiles Obtained from CGM

Although CGM are still afflicted with errors and lack of accuracy, the devices play an essential role for individuals with T1DM, allowing them to follow BG levels in real time. However, the accuracy and reliability of CGM has been improved over the last years. Recently, some models have been labeled as factory-calibrated and also approved as a non-adjunctive device

for diabetes management. Thus, new generations of CGM devices tends to eliminate SMBG tests, increasing its acceptability and usage. Additionally, the possibility of acquiring data and applying methods for extracting features can support patients and physicians in the arduous work of coping with glucose variability and achieving glycemic control.

The work presented by Biagi et al. (2018a) presents an approach based on CoDa analysis for the categorization of glucose profiles obtained from CGM. It was the first application of CoDa analysis to daily glucose profiles obtained from patients with T1DM. Instead of the analysis of glucose time series, the work performs the analysis of the relative interpretation of time spent in different glucose ranges during a 24-h period.

The results presented in the aforementioned work were interpreted in a relative sense, considering the relative information of one or more variables with respect to the others, and not in an absolute way. After the categorization of days, performed per patient, the days were characterized in terms of relative time spent by the individuals in determined glucose ranges during a day according to the log-ratio approach. The days of different patients were categorized separately, but the authors noticed that groups from different patients presented similar characteristics regarding the relative interpretation of time spent in different glucose ranges. The results, though, were interpreted individually per patient. Clusters of groups of days were generically described according to the relative amounts of time spent in the hypo- and hyperglycemic ranges (see Tables 6 and 7, and Figure 4 of Section 2.4).

To improve the interpretation of the groups of days considering the analysis of the log-ratio coordinates, the compositional biplot (Pawlowsky-Glahn et al., 2015) and the balance dendrogram (Thió-Henestrosa et al., 2008) were considered (see Figures 3 and 6 of Section 2.4). Also, the authors performed a multi-factorial analysis of the clinically relevant data obtained from the groups (see Table 8 of Section 2.4). After the creation of clusters of days, the number of days in which each patient manually reported some PA, the number of days corresponding to weekends, the average calories and average steps recorded by the activity tracker were also

reported (see Table 9 of Section 2.4). Although it is well known that glycemic control can be affected by several lifestyle factors, and that the fear of hypoglycemia and loss of glycemic control are barriers to exercise in the T1D population Riddell et al. (2017), no pattern was found regarding the distribution of weekends and exercise sessions between the resultant categories of groups. Weekends and days with reported PA were categorized either in groups of days with more susceptibility to hypo- or hyperglycemic events, good glucose control, or high glucose variability. Even though the results presented in Biagi et al. (2018d) have shown that during PA, CGM might present lower accuracy, this analysis was performed only during the exercise sessions and in its following hours, in clinical settings. In the work presented by Biagi et al. (2018a), in which the categorization of glucose profiles has been introduced, complete days in free-living conditions were analyzed. Furthermore, the occurrence of PA in a determined day was self-reported by the patients, and the work did not consider the nature of the PA indicated.

The authors concluded that divergent categories of days may be resultant of the variable effects on glycemic control caused by different lifestyles and living habits of the patients. That reinforces the need of individual and deeper analysis of glycemic variability due to inter-patient variability. Thus, novel approaches to deal with large intra-patient variability are necessary, it is not enough to have only the information regarding weekends, reported exercise, calories and steps in order to provide meaningful information for insulin adjustments.

The categorization of profiles performed by Biagi et al. (2018a) considered only the analysis of complete days, starting at 00:00 and ending at 24:00, and a reasonable clustering of days was obtained. This categorization of profiles can be performed at any time of the day, considering the last 24-h of glucose data. The authors foresee that it is possible to obtain a predictive model based on a CoDa approach, which would allow the adjustment of insulin dosing of patients with T1DM accordingly. In the form in which is was presented, the categorization of groups of days could work as a promising indicator for physicians. It could also work as an additional analysis tool, helping physicians to visualize different patterns of days that require adjustment

of the current insulin therapy, and possibly to create different profiles of therapy for each type of day.

In the work presented in Section 2.5, a probabilistic model of transition between the category of the previous 24-h period to the next 6-h period is present. The categorization of periods was performed following the CoDa approach presented by Biagi et al. (2018a,b). Figure 3.1 summarizes the methodology for the categorization of glucose profiles considered in the works presented in Sections 2.4 and 2.5. Dashed portion of the figure are common steps considered for both Sections 2.4 and 2.5. The remaining steps are exclusive of the work presented in Section 2.5. In the works presented by Biagi et al. (2018a,b), only daily glucose profiles from 00:00 to 24:00 were considered. In this new approach, the analysis is performed considering both 24-h and 6-h periods at different times of the day: 00:00, 06:00, 12:00 and 18:00. Also, the glucose ranges considered in this work followed the definitions of hyper- and hypoglycemia described in Agiostratidou et al. (2017) and by the American Diabetes Association (2018b).

Periods of different duration were categorized separately. Similarly to Biagi et al. (2018a), periods of different duration were described according to the relative amounts of time spent in different levels of hypo- and hyperglycemia (see Tables V and VI of Section 2.5). After the categorization of the 24-h periods, a discriminant analysis method was applied to each patient's 24-h periods from 00:00 to 24:00 to find a discrimination rule that would be used to assign any individual 24-h composition at different times (00:00, 06:00, 12:00 and 18:00) to a group. A linear discriminant (LD) model was considered, and the discriminant rule was based on functions on the composition of time spent in different glucose ranges. The discrimination functions used to classify the data were calculated considering the information included in the composition and its accuracy was evaluated using leave-one-out cross-validation (LOOCV). The average classification accuracy obtained for all the patients was 94.92% (see Table VII of Section 2.5), showing that the LD models were suitable for the categorization of glucose profiles.

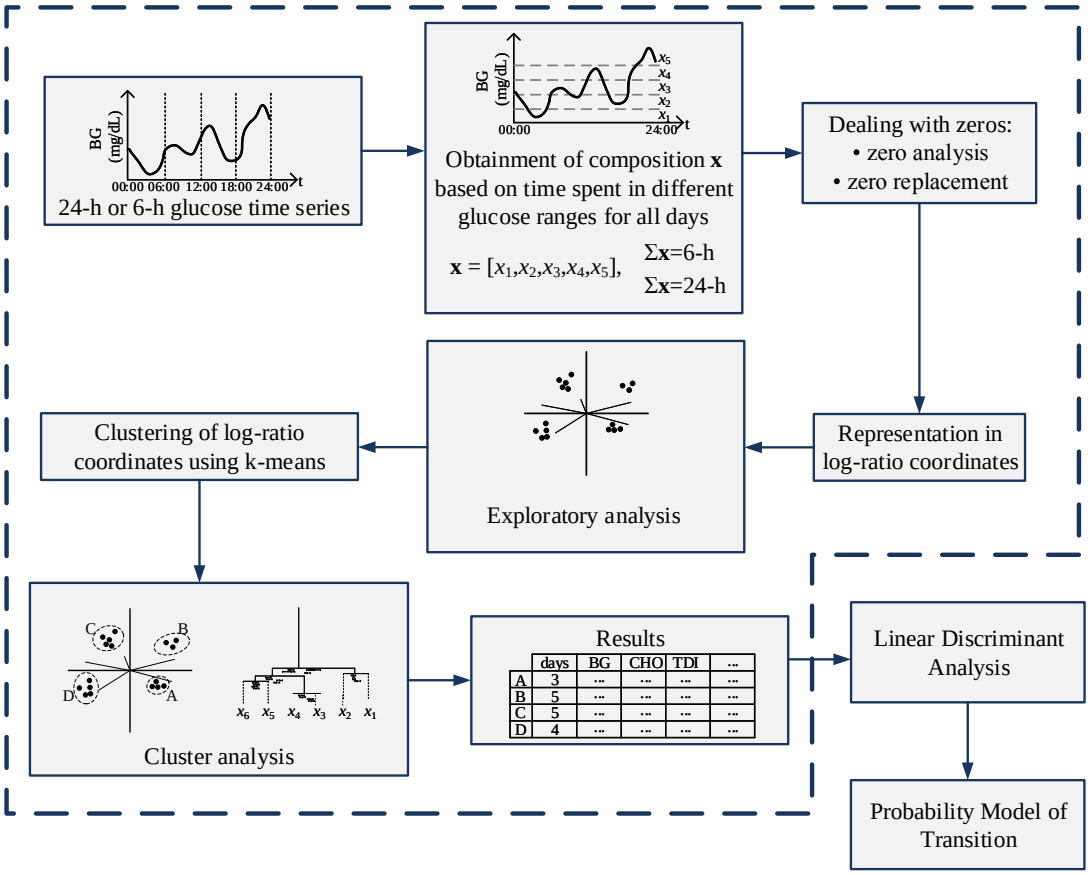

Figure 3.1: Summarized methodology for the categorization of glucose profiles using CoDa analysis considered in the works presented in Sections 2.4 and 2.5. Dashed portion of the figure are common steps considered for both Sections 2.4 and 2.5. The remaining steps are exclusive of the work presented in Section 2.5.

A retrospective analysis of the data after the proper categorization of the periods was performed which allowed to obtain the probability model of transition between category of previous 24-h period to a subsequent 6-h period. This analysis was performed at different times of the day: at 00:00, 06:00, 12:00 and 18:00. We count the number of times a patient moved from determined category of 24-h period to a category of 6-h period. These values were expressed it in terms of probabilities of transition at different times of the day (see Table VIII of Section 2.5). The probabilities of transition would allow that patients take corrective actions, such as adjust basal insulin, take some CHO, or correction bolus, in order to avoid undesirable events that have been predicted.

The work presented a first approach based on CoDa analysis creating a probabilistic model of transition between categories at different times of the day. The analysis was performed considering a data set composed with 24-h and 6-h periods of glucose data, at different times of the day. These times, however, were chosen globally for all patients to comprise approximations of day-times where relevant events occur: such as sleep time, waking up and breakfast, lunch and dinner. It is expected that in the future the models can be adjusted, considering flexible periods according to patients' routine.

Even though the analysis was performed considering a limited data set, the results presented are promising. The linear model presented showed to be adequate for the discrimination of previous glucose profiles. The probabilistic model of transition, regardless of being obtained retrospectively, enables the patient to identify evidence-based actions that would be of benefit and to anticipate the occurrence of adverse events. Nevertheless, a more representative model of transitions between periods would be required, including additional analysis of the insulin therapy of each patient and a more extensive data set. The usage of these information could also support physicians to assess patients' outcomes and tailor their insulin dosing profile.

CHAPTER 4

CONCLUSIONS

This thesis described the condition assessment of patients with T1DM using CoDa analysis. Data obtained from two clinical trials designed by Spanish Consortium on Artificial Pancreas and Diabetes Technology were object of the studies of the works that formed the compendium of publications presented in this thesis.

All of the papers presented the analysis of data obtained from CGM. These devices, even though are recognized for improvements in glucose control and for providing detailed and reliable glucose information, have their performances still affected with errors.

An analysis of accuracy of CGM sensors has been performed during PP and PA in this work. Also, a model of sensor error has been presented. The model and dissection of the sensor error allows the understanding of different components of the error, however, this analysis must take into account the conditions related to data acquisition, such as protocol of the clinical trial and day in which the sensor was inserted.

Not only the sensor performance is related to different ranges of glucose, but also the quality of glucose control is usually measured by the times spent by individuals in different glucose ranges that determine the occurrence of adverse events. A first approach applying the log-ratio

transformation to the amounts of time spent in different glucose ranges during a 24-h time period allowed the obtainment of different categories of days. This categorization of groups of days could work as a promising indicator for physicians, and work as a complement to the "traditional" analysis of glucose time series. It could also work as an additional analysis tool, helping physicians to visualize different patterns of days that require adjustment of the current insulin therapy, and possibly to create different profiles of therapy for each type of day.

Also following the CoDa approach, another work presented the categorization of both 24-h and 6-h periods of glucose profiles. However, while the previously described work have presented only the analysis of glucose profiles from 00:00 to 24:00, a novel approach considered a LD model for the categorization of daily glucose data at different times of day. Additionally, a probabilistic model of transition between the category of the previous 24-h to the next 6-h period has been proposed.

4.1 Contributions

The following contributions resulted from the work developed in this thesis:

- Analysis of accuracy of the second generation of the Medtronic Enlite CGM sensor operating during challenging situations, such as PP and aerobic and anaerobic PA. Those analysis showed that the performance of CL control during PP was related to sensor accuracy and that CGM might present lower accuracy during aerobic PA.
- Model of the error of the second generation of the Medtronic Enlite sensor among with its dissection into several components. The modeling and dissection of the sensor error could be applied to different brands and models of CGM sensors.
- Novel approach for the categorization of daily glucose profiles based on CoDa analysis. This method when combined with the conventional analysis of glucose trends may provide optimal support for physicians to make decisions. Also, following future refinements,

the approach will provide additional personalized information that would help to manage glucose variability.

- Probabilistic model of transition between categories of glucose profiles based on a CoDa analysis approach. This method works as a complimentary tool for the prediction of different categories of glucose control, which could assist patients to take correction measures ahead of adverse situations. The usage of these information could assist patients to identify evidence-based actions that would be of benefit and to anticipate the occurrence of adverse events.

4.2 Future Work

Even though the results presented in this thesis are promising and provide an additional analysis tool for physicians, further analysis of the current insulin therapy simultaneously with the categorization of glucose profiles should be performed in order to match the insulin requirements of different categories of days.

The analysis of insulin therapy could also be performed considering a CoDa approach similar to that presented for glucose profiles. Insulin data can be obtained both from CSII and MDI and a physiological model of insulin absorption (Wilinska et al., 2005) can be used. Personalized ranges of insulin, according to patients' individualized insulin requirements can be obtained. It is expected that the analysis of both basal and bolus insulin absorption profiles could also indicate lifestyle alterations in individuals with T1DM.

The probabilistic model of transition between categories of glucose profiles was obtained considering a limited data set. When additional data are available, it would be possible to update the probabilistic models of transition during the visits to the physicians. Likewise, the availability of new data could also support the creation of models with a fixed quantity of periods in analysis, where the incorporation of more recent data would imply in the disposal of

the earliest data.

Considering similar technique of the categorization of glucose profiles, using the log-ratio approach for the analysis of time spent in different glucose ranges, it is possible to obtain linear models where CoDa are involved (Tolosana-Delgado and van den Boogaart, 2011; Dumuid et al., 2017a). That is, instead of using the categories of past data to predict the categories of future data, linear regression models could be applied to the log-ratio coordinates of past data in order to obtain a model able to predict the composition of the future data. This linear model can also be applied after the categorization of data.

All the analysis performed in this work were performed in a retrospective way and more effort is necessary to allow the analysis in real time. However, a development of a system that allows the analysis and application of the aforementioned methodologies in real time is expected. This system will support the clinical application of the methods, which will be of benefit of both physicians and patients.

Following future refinements, information obtained from the condition assessment approaches presented in this work could be used as input to a DSS, or even be incorporated in an AP system, allowing personalized detection and identification for different patient conditions. Providing additional personalized information would help to cope with the glucose variability and help the automatic optimization of a BG control algorithm.

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