

UNIVERSITY OF PADOVA

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DEPARTMENT OF INFORMATION ENGINEERING

Ph.D. Course on Information Engineering

Curriculum: Bioengineering

Series: XXIX

# Type 1 diabetes patient decision-making modeling for the in silico assessment of insulin treatment scenarios

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January 31, 2017



# Abstract

In type 1 diabetes (T1D) exogenous insulin is administered to compensate for the absence of endogenous insulin production by pancreas beta-cells. T1D subjects must finely tune insulin doses to maintain blood glucose (BG) concentration within the normal range (70-180 mg/dl). For such a purpose, every day, T1D subjects need to frequently monitor their BG concentration and make several treatment decisions, e.g. the calculation of insulin and carbohydrate (CHO) doses to counterbalance, respectively, high and low BG values. The safety and effectiveness of T1D insulin therapies are normally assessed by clinical trials, which unfortunately are usually time-demanding, expensive and often present constraints of low numerosity and short duration, with consequently low probability of observing rare but risky situations, like severe hypoglycemia. These limitations can be overcome by the use of *in silico* clinical trials, based on computer simulations, that allow to test medical device-based treatments in a large number of subjects, over a long period, under reproducible conditions, at limited costs, and without implicating any risk for real subjects. A popular powerful tool to perform *in silico* clinical trials in T1D is the UVA/Padova T1D simulator, i.e. a model of glucose, insulin and glucagon dynamics in T1D subjects. However, to test insulin therapies in a real-life scenario, the UVA/Padova T1D simulator alone is not sufficient because a mathematical description of other fundamental components, like the device used for glucose monitoring and the patient's behavior in making treatment decisions, is required.

The aim of this thesis is to design a mathematical model of T1D patients making treatment decisions fully usable for the comprehensive *in silico* assessment of insulin treatment scenarios. In particular, in the first part of the thesis we develop three submodels that the UVA/Padova T1D simulator requires (as complement) to pursue this scope. Specifically, we design a model of self-monitoring of blood glucose (SMBG) device, a model of minimally-invasive sensor for continuous glucose monitoring (CGM), and a model of the patient's

behavior in tuning CHO intakes and insulin doses according to SMBG and/or CGM measurements. The parameters of these models are either fitted on real data or derived from literature studies. The overall model, in the following called T1D decision-making (T1D-DM) model, can be used for several *in silico* experiments. To demonstrate its usefulness, in the second part of this thesis we apply the T1D-DM model to assess safety and effectiveness of nonadjunctive CGM use, i.e. the use of CGM measurements to make treatment decisions without requiring confirmatory SMBG measurements collected by fingerstick. This specific application is currently of great scientific and industrial interest for the diabetes technology research community because, until clinical evidence of its safety is provided, nonadjunctive CGM use cannot be approved by U.S. regulatory agencies, like the Food and Drug Administration.

The thesis is organized in six chapters. In Chapter 1, after introducing T1D therapy, the importance of *in silico* clinical trials is discussed, both in general and specifically for the assessment of nonadjunctive CGM use. Then, some state-of-art simulation techniques are briefly introduced discussing their open problems. The aim of the thesis is illustrated at the end of the chapter.

In Chapter 2, we analyse more in depth the limitations of the approaches currently available in the literature for the assessment of insulin treatments. In particular, we demonstrate that a recently proposed simulation method to "replay" *in silico* real-life treatment scenarios has domain of validity limited to small adjustments of basal insulin, calling for the development of more sophisticated techniques like that proposed in this thesis.

In Chapter 3, our simulation method based on the T1D-DM model is presented. This model allows to simulate, in a real-life scenario, the glucose profiles of T1D subjects using SMBG and/or CGM to make treatment decisions. The T1D-DM model is composed of four components: A) the UVA/Padova T1D simulator, B) a model of glucose monitoring devices, C) a model of patient's behavior and treatment decisions and D) a model of the insulin pump. In particular, as far as B) is concerned, two different SMBG error models are derived by data collected with two popular SMBG devices (One Touch Ultra 2 and Bayer Contour Next USB). Using a recently published methodology which takes into account the main sensor error components, a CGM model is derived from data collected by a state-of-art CGM sensor (Dexcom G5 Mobile). Regarding C), a model of the patient's behavior in making treatment decisions based on SMBG and/or CGM, such as administration of insulin boluses and hypotreatments, is designed to simulate treatments based on i)

SMBG, ii) adjunctive CGM, or iii) nonadjunctive CGM. In order to reproduce a real-life scenario, the model includes components describing the mistakes real subjects commonly make, such as miscalculation of meal CHO content and early/delayed insulin administrations.

In Chapter 4 and Chapter 5, two *in silico* trials based on the T1D-DM model are designed to assess nonadjunctive CGM use. In the first trial, nonadjunctive CGM is compared to SMBG and adjunctive CGM over a two-week period in 100 virtual subjects. Results show that the use of CGM (both adjunctive and nonadjunctive) significantly improves glycemic control compared to SMBG, while no significant change is observed between adjunctive CGM and nonadjunctive CGM. This suggests that CGM is ready to substitute SMBG for T1D treatment. In the second trial, the impact of thresholds used for CGM hypo/hyperglycemic alerts on the performance of nonadjunctive CGM use is assessed. Results show that time in hypoglycemia is reduced by nonadjunctive CGM use with any alert setting, while time in hyperglycemia is significantly worsened by nonadjunctive CGM use, compared to SMBG, when the high alert threshold is set to 350 mg/dl or higher.

Finally, the major findings of the work carried out in this thesis, its possible applications and margin of improvements are summarized in Chapter 6.



# Sommario

Nella terapia del diabete di tipo 1 viene somministrata insulina esogena per compensare l'assenza di secrezione di insulina da parte della beta cellule del pancreas. Per mantenere la glicemia ad un livello normale (70-180 mg/dl), i soggetti diabetici di tipo 1 devono accuratamente regolare le proprie dosi di insulina. A questo scopo, essi necessitano ogni giorno di misurare frequentemente la loro glicemia e prendere numerose decisioni terapeutiche, per esempio per calcolare le dosi di insulina e carboidrati necessarie a controbilanciare livelli glicemici rispettivamente elevati e bassi. La sicurezza e l'efficacia di terapie insuliniche per il diabete di tipo 1 sono comunemente valutate in trial clinici, i quali solitamente necessitano di tempi e costi elevati e presentano limiti di bassa numerosità e breve durata, con conseguente ridotta probabilità di osservare situazioni rare seppur rischiose, come ad esempio l'ipoglicemia severa. Queste limitazioni possono essere superate mediante trial clinici simulati, cioè basati su simulazioni al computer, che permettono di testare terapie basate su dispositivi medici in un vasto numero di soggetti, per un lungo periodo, in condizioni riproducibili, a costi limitati e senza comportare alcun rischio per i pazienti reali.

Un popolare strumento per svolgere trial clinici simulati nell'ambito del diabete di tipo 1 è il simulatore UVA/Padova-T1D, un modello che descrive le dinamiche di glucosio, insulina e glucagone nei soggetti diabetici di tipo 1. Tuttavia, al fine di testare terapie insuliniche in uno scenario realistico, il simulatore UVA/Padova-T1D non è da solo sufficiente in quanto necessaria la descrizione matematica di altre componenti fondamentali, come il dispositivo utilizzato per il monitoraggio del glucosio e il comportamento del paziente nel prendere le decisioni terapeutiche.

Lo scopo di questa tesi è la progettazione di un modello matematico del paziente diabetico di tipo 1 e delle decisioni terapeutiche che esso prende, utilizzabile per una completa valutazione in simulazione di terapie insuliniche. In particolare, nella prima parte della tesi vengono sviluppati i tre sottomod-

elli che il simulatore UVA/Padova-T1D necessita (come complemento) per raggiungere tale scopo. Nello specifico, vengono sviluppati un modello del dispositivo pungidito per il monitoraggio della glicemia (SMBG), un modello del sensore minimamente invasivo per il monitoraggio a tempo continuo della glicemia (CGM) e un modello del comportamento del paziente nel regolare le somministrazioni di carboidrati e insulina a seconda delle misure SMBG e/o CGM. I parametri di questi modelli sono fittati su dati reali o derivati da studi di letteratura. Il modello complessivo, chiamato in seguito modello decisionale del diabete di tipo 1 (T1D-DM), può essere impiegato per molti esperimenti simulati. Per dimostrare la sua utilità, nella seconda parte della tesi il modello T1D-DM viene impiegato per valutare la sicurezza e l'efficacia dell'uso "nonadjunctive" del sensore CGM, cioè l'uso delle misure CGM per prendere decisioni terapeutiche senza la necessità di confermarne le letture mediante misure SMBG raccolte con dispositivi pungidito. Questa specifica applicazione è attualmente di grande interesse scientifico e industriale nella comunità della ricerca sulle tecnologie per il diabete poiché, finché non ne viene dimostrata la sicurezza, l'uso "nonadjunctive" del CGM non può essere approvato dalle agenzie regolatorie statunitensi, come la Food and Drug Administration.

La tesi è organizzata in sei capitoli. Nel capitolo 1, dopo aver introdotto la terapia del diabete di tipo 1, viene discussa l'importanza dei trial clinici simulati, sia in generale sia in maniera specifica per la valutazione dell'uso "nonadjunctive" del sensore CGM. In seguito, vengono brevemente introdotte alcune tecniche di simulazione allo stato dell'arte discutendone i problemi aperti. Lo scopo della tesi è illustrato alla fine del capitolo.

Nel capitolo 2 vengono analizzate nel dettaglio le limitazioni degli approcci allo stato dell'arte per la valutazione di terapie insuliniche. In particolare, viene dimostrato che un metodo di simulazione recentemente proposto per riprodurre in simulazione scenari terapeutici della vita reale presenta un dominio di validità limitato a piccole variazioni della dose basale di insulina, suggerendo la necessità di sviluppare tecniche più sofisticate come quella proposta in questa tesi.

Nel capitolo 3 viene presentato il nostro metodo di simulazione basato sul modello T1D-DM. Questo modello consente di simulare, in uno scenario che riproduce la vita reale, i profili glicemici di soggetti diabetici di tipo 1 che utilizzano dispositivi SMBG e/o CGM a supporto delle decisioni terapeutiche. Il modello T1D-DM è composto da quattro componenti: A) il simula-



tore UVA/Padova-T1D, B) un modello dei dispositivi per il monitoraggio del glucosio, C) un modello del comportamento del paziente nel prendere le decisioni terapeutiche e D) un modello della pompa per l'infusione di insulina. Per quanto riguarda B), due modelli dell'errore delle misure SMBG sono derivati utilizzando misure raccolte con due popolari dispositivi SMBG (lo One Touch Ultra 2 e il Bayer Contour Next). Utilizzando un metodo recentemente pubblicato che prende in considerazione le componenti principali dell'errore del sensore, viene derivato un modello delle misure CGM sulla base di dati raccolti con un sensore CGM allo stato dell'arte (Dexcom G5 Mobile). Per quanto concerne C), viene progettato un modello del comportamento del paziente nel prendere le decisioni terapeutiche sulla base di misure SMBG e/o CGM, come la somministrazione di boli di insulina e trattamenti per l'ipoglicemia, al fine di simulare terapie basate su i) SMBG, ii) uso del CGM a supporto dell'SMBG (uso "adjunctive") o iii) uso "nonadjunctive" del CGM. Per riprodurre uno scenario realistico, il modello include componenti che descrivono gli errori comunemente commessi dai pazienti reali, come per esempio gli errori nella stima della quantità di carboidrati contenuti nel pasto e ritardi/anticipi nella somministrazione delle dosi di insulina.

Nei capitoli 4 e 5 vengono progettati due trial clinici simulati basati sul modello T1D-DM per valutare l'uso "nonadjunctive" del sensore CGM. Nel primo trial, l'uso "nonadjunctive" del sensore CGM è confrontato con l'uso dell'SMBG e l'uso "adjunctive" del CGM in 100 soggetti virtuali per un periodo di due settimane. I risultati dimostrano che l'uso del CGM (sia "adjunctive", sia "nonadjunctive") migliora significativamente il controllo glicemico rispetto all'uso dell'SMBG, mentre non si osservano differenze significative tra l'uso "adjunctive" e "nonadjunctive" del sensore CGM. Questo risultato suggerisce che il CGM è pronto per sostituire l'SMBG nel trattamento del diabete di tipo 1. Nel secondo trial, viene valutato come le soglie impostabili per le allerte ipo/iperglicemiche del sensore CGM influenzano le performance dell'uso "nonadjunctive" del CGM. I risultati dimostrano che l'uso "nonadjunctive" del sensore CGM consente di ridurre il tempo in ipoglicemia per qualsiasi impostazione delle allerte, mentre il tempo in iperglicemia viene significativamente peggiorato dall'uso "nonadjunctive" del sensore CGM, rispetto all'SMBG, quando la soglia dell'allerta di iperglicemia è impostata ad un valore maggiore o uguale a 350 mg/dl.

Infine i risultati principali del lavoro svolto in questa tesi, nonché le possibili applicazioni e i margini di miglioramento sono riassunti nel capitolo 6.



# Acknowledgements

Firstly, I would like to thank my advisor, Prof. Giovanni Sparacino, for the continuous support to my Ph.D. study and related research and his patient guidance.

Besides my advisor, I would like to express my sincere gratitude to my co-advisor, Andrea Facchinetti, who helped me a lot during the Ph.D. course, and especially in the work presented in this thesis, giving me precious suggestions and encouragements.

I am also very grateful to Prof. Claudio Cobelli for his invaluable teachings, his constructive critiques and the support of my research activity.

My sincere thanks also goes to Dexcom Inc. that provided me most of the data used in this thesis, and above all, trusted in my work and gave me the privilege to contribute to its dialog with FDA to achieve the approval of Dexcom G5 Mobile nonadjunctive use.

In addition, I would like to thank the reviewers of this thesis, Prof. Andrea Caumo and Ahmad Haidar, for their precious suggestions. I especially thank Ahmad Haidar who also provided part of the data used in this thesis.

I extend my thanks to all my colleagues who shared with me this incredible experience for the stimulating discussions and all the fun we had in the last three years.

Finally, a very special thanks goes to my family and my boyfriend Andrea who supported me with love all the time.



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# Abbreviations

**AR** Autoregressive

**BCN** Bayer Contour Next USB

**BDI** Basal daily insulin

**BG** Blood glucose

**BIC** Bayesian information criterion

**CF** Correction factor

**CGM** Continuous glucose monitoring

**CHO** Carbohydrates

**CR** Carbohydrate-to-insulin ratio

**CvM** Cramér-von-Mises

**FDA** Food and Drug Administration

**HA** High glucose alert

**IG** Interstitial glucose

**ISCT** In silico clinical trial

**KS** Kolmogorov-Smirnov

**LA** Low glucose alert

**MARD** Mean absolute relative difference

**ML** Maximum-likelihood

**OTU2** One Touch Ultra 2

**PDF** Probability density function

**PMC** Number of post-meal checks per day

**SD** Standard deviation

**SMBG** Self-monitoring of blood glucose

**SOGMM** Subcutaneous oral glucose minimal model

**T1D** Type 1 diabetes

**T1D-DM** Type 1 diabetes decision-making

**TDI** Total daily insulin

**YSI** Yellow Springs Instrument

# Chapter 1

## In silico assessment of insulin treatment scenarios in type 1 diabetes: opportunities, methods and open challenges

### 1.1 Type 1 diabetes (T1D) insulin therapy

Type 1 diabetes (T1D) is an autoimmune disease of metabolism in which pancreas beta cells, responsible for the endogenous production of insulin, are destroyed by the body's own immune system [1] [2]. In healthy subjects, insulin promotes the movement of glucose from the blood to cells of body's tissues where it is metabolized for energy production. Patients with T1D, if not properly treated, present persistently high blood glucose (BG) concentration. The standard therapy for the treatment of T1D consists in diet, physical exercise and exogenous insulin administrations that allow to lower the increase in BG concentration produced by food ingestion. Insulin doses can be delivered by multiple daily injections (Figure 1.1, panel A) or insulin pump, which allows the continuous-time injection of insulin in the subcutaneous tissue (Figure 1.1, panel B).

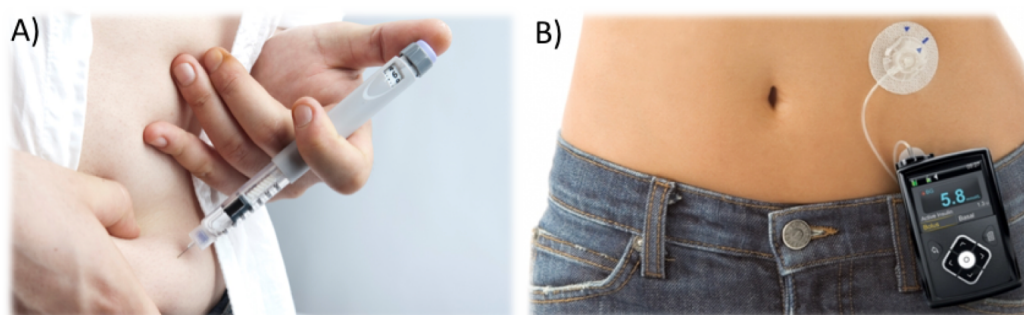
An accurate dosing of insulin is important to maintain BG concentration within the normal range, i.e. 70-180 mg/dl, called also euglycemia. An underestimation of insulin doses may drive to hyperglycemia, i.e. BG concentration greater than 180 mg/dl, which is cause of long-term complications like cardiovascular diseases, retinopathy and kidneys diseases. Conversely, when insulin

## *1 In silico assessment of insulin treatment scenarios in type 1 diabetes: opportunities, methods and open challenges*

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doses are overestimated, BG concentration may fall below 70 mg/dl, in the range of hypoglycemia. Hypoglycemia, if not rapidly detected and mitigated by hypotreatment, e.g. the intake of 15-20 grams of CHO, can dangerously affect the patient's health in the short-term, causing seizure, coma or even death.

In the standard T1D insulin therapy, a basal dose is administered to maintain the BG concentration in euglycemia during the night and during the day if a meal is skipped. In addition, bolus doses are administered at meal times to counterbalance the rise in BG produced by food intake, in this case the dose is called meal bolus, or after meals to treat high BG levels, in this case the dose is called correction bolus [3]. The dose of insulin boluses is calculated by patients themselves according to simple equations based on an estimate of the meal carbohydrate (CHO) content (for meal boluses only), the BG concentration measured at bolus time, insulin on board i.e. the insulin amount of previously injected boluses that is still acting in the body, and two therapy parameters called carbohydrate-to-insulin ratio and correction factor. In particular, the carbohydrate-to-insulin ratio (CR) represents how many grams of CHO are covered by each unit of insulin [4]. The correction factor (CF) represents how much BG is lowered by each unit of insulin [5]. These parameters, as well as the basal insulin dose, are set by the physician according to empirical rules based on patient's parameters like age and body weight [6] [7] [8] and then tuned based on retrospective analysis of BG measurements.



**Figure 1.1:** Insulin delivery via multiple daily injections (A) or via insulin pump (B). (Source: <http://nursingcrib.com/nursing-notes-reviewer/fundamentals-of-nursing/12-tips-for-injecting-insulin/>, <https://www.medtronic-diabetes.ie/what-insulin-pump-therapy>)

## 1.2 Glucose monitoring

### 1.2.1 Self-monitoring of blood glucose (SMBG)

Typically, BG concentration is measured by self-monitoring of blood glucose (SMBG) devices that, as shown in Figure 1.2, allow to measure glucose concentration in a small drop of capillary blood collected by fingerprick [9]. The American Diabetes Association suggests that T1D patients monitor BG by SMBG before meals and snacks, occasionally after meals, at bedtime, when they suspect to have low BG, after treating hypoglycemia until they are back in euglycemia, prior to exercise and critical tasks like driving [10]. The adherence to these recommendations supposes the collection of 7-9 SMBG measurements per day or more. However, several studies demonstrated that T1D subjects test their BG concentration less frequently than recommended, on average 4-5 times per day [11] [12]. The poor adherence to the recommended SMBG testing frequency is caused by the discomfort, and often by the embarrassment, that the patients feel when collecting SMBG measurements, which require the prick of a finger by a lancet device. Of course, a low frequency of SMBG testing significantly deteriorates the quality of glycemic control [12] [13], being more difficult for the patient to detect hyperglycemia and hypoglycemia.



**Figure 1.2:** Measuring BG by a SMBG device. (Source: <http://www.farmaquick.it/blog/salute/come-usare-il-glucometro-per-misurare-la-glicemia/>)

Even when performed frequently, SMBG can still fail to detect risky hypo/hyperglycemic events, because of the sparseness of SMBG measurements. This can be particularly dangerous for patients with impaired awareness of hypoglycemia, in whom the ability to perceive the onset of hypoglycemia is reduced or even absent [14]. In these patients the incidence of severe low glucose episodes that requires external assistance for recovery is up to six fold higher than in subjects with normal awareness of hypoglycemia [15]. The problem of the sparseness of SMBG measurements was overcome by the introduction

of minimally invasive sensors for continuous glucose monitoring (CGM) that will be presented in the next subsection.

## **1.2.2 Continuous glucose monitoring (CGM)**

In the last decade, the monitoring of glucose in T1D has been revolutionized by the introduction of CGM sensors, i.e. minimally-invasive sensors that measure almost continuously glucose concentration in the interstitial fluid of subcutis [16]. A CGM device includes three main components. The first component is a needle electrode (A in Figure 1.3) which is implanted in the subcutaneous tissue of the abdomen or the arm and measures a current signal generated by the glucose oxidation process. The second component is a transmitter (B in Figure 1.3) that converts the current signal in a glucose concentration profile by a calibration process that exploits few SMBG measurements per day. The transmitter also transfers the calibrated glucose concentration profile to the third component, i.e. a receiver (C in Figure 1.3) which displays in real-time glucose concentration measurements and an arrow (evidenced by the red circle in Figure 1.3) indicating glucose rate of change. The receiver also produces auditory alerts in correspondence of hypoglycemic and hyperglycemic events. In last generation CGM systems, the receiver may be either a display device supplied by the manufacturer with the sensor and the transmitter or a smart device, like a mobile phone, equipped with a mobile app for CGM.

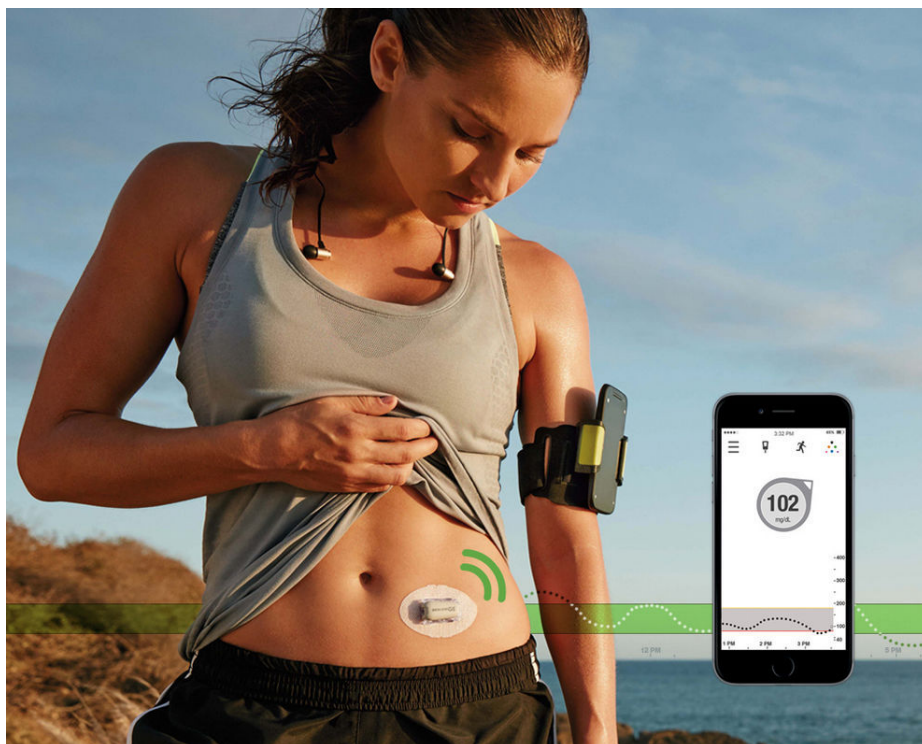
### **An example: the Dexcom G5 Mobile**

One of the most popular last generation CGM devices is the Dexcom G5 Mobile (Dexcom Inc., San Diego, CA) shown in Figure 1.3 and Figure 1.4. The Dexcom G5 Mobile, launched in September 2015, provides a glucose measurement every 5 min for up to 7 days, after which the sensor needle need to be substituted [17]. In addition to glucose readings, the receiver displays a flat arrow when glucose rate of change is between -1 and 1 mg/dl/min, one 45° up/down arrow when glucose is rising/decreasing between 1 and 2 mg/dl/min, one 90° up/down arrow when glucose is rising/decreasing between 2 and 3 mg/dl/min and two 90° up/down arrows when glucose is rising/decreasing more than 3 mg/dl/min.

The Dexcom G5 Mobile generates a low glucose alarm when glucose concentration falls below 55 mg/dl. The alarm is repeated every 30 min until the CGM reading returns above 55 mg/dl. The low glucose alarm cannot be cus-



**Figure 1.3:** Dexcom G5 Mobile system. The system includes a needle sensor (A), a transmitter (B) and a receiver (C), which may be either the Dexcom display device or a mobile phone equipped with the Dexcom G5 Mobile app. (Source: <https://www.dexcom.com/g5-mobile-cgm>)



**Figure 1.4:** Dexcom G5 Mobile system. (Source: <https://www.medicaexpo.com>)

tomized or turned off by the user. The system also provides alerts when CGM glucose reading goes below a low glucose alert threshold and above a high glucose alert threshold. The alert thresholds are set to the default values of 80 mg/dl and 200 mg/dl. However, the user is allowed to customize the alert thresholds or even shut down the use of alerts. The Dexcom G5 Mobile sensor requires a SMBG measurement every 12 hours for the calibration process.

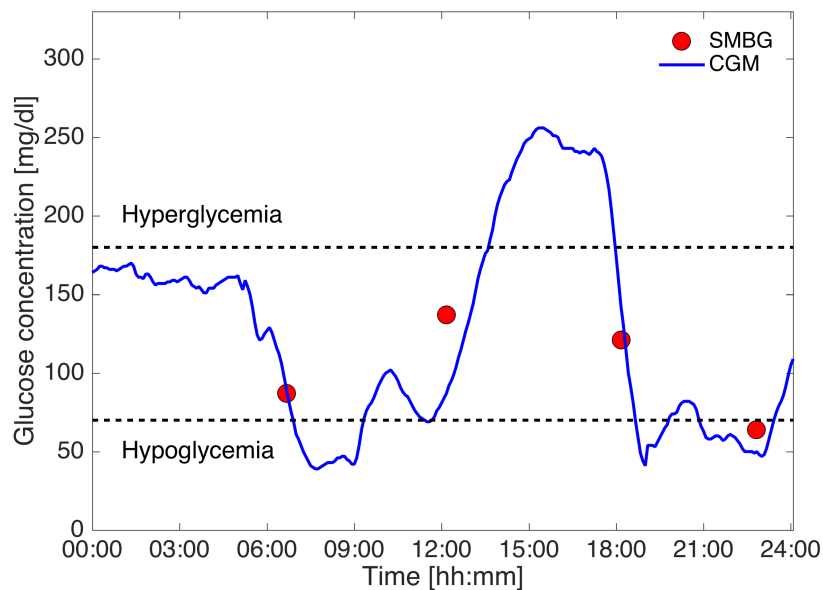
### **Current use of CGM**

Currently, the use of CGM sensors is approved by the U.S. Food and Drug Administration (FDA) for adjunctive use, i.e. to complement, not to substitute, SMBG measurements, which are the only one approved to make treatment decisions, such as calculation of insulin doses. As a consequence, patients in the United States that wear a CGM sensor are supposed to use CGM information just to trigger SMBG checks, and make all the treatment decisions based on SMBG measurements.

Several studies demonstrated that the adjunctive use of CGM can be very beneficial for glycemic control [18] [19] [20] [21] [22] [23]. Indeed, the continuous-time nature of CGM allows to detect dangerous hypo/hyperglycemic events that sparse SMBG measurements may not detect. This is visible in Figure 1.5 where SMBG (red dots) and CGM (blue line) are compared in a representative subject over a day of monitoring. In this example, CGM is able to track one hypoglycemic event and one hyperglycemic event not detected by standard SMBG measurements. Benefits of CGM are even larger thanks to the availability of alerts that promptly advise the patient of hypo/hyperglycemia, even when the patient is not caring about his/her glycemia, e.g. during work or sleep. In particular, low glucose alerts can be life-saving for people with impaired awareness of hypoglycemia, in whom symptoms of hypoglycemia are reduced or even absent.

As far as the use of CGM trend arrows is concerned, there are no officially approved guidelines because CGM trend cannot be confirmed by SMBG and nonadjunctive CGM use, i.e. the use of CGM to make treatment decisions without confirmatory SMBG measurements, has not been approved yet. However, some non-officially approved guidelines to correct insulin doses according to CGM trend arrows are available in the literature. For example, the Diabetes Research in Children Network study group and the Juvenile Diabetes Research Foundation suggest increasing/decreasing the insulin dose of 10%





**Figure 1.5:** CGM trace (blue line) and SMBG measurements (red dots) in a representative subject over a day of monitoring.

or 20% if glucose is rising/decreasing of between 1 and 2 mg/dl/min or more than 2 mg/dl/min, respectively [24] [25]. Another approach is proposed by Scheiner [26], who suggests performing the calculation of insulin doses according to the standard rules, but using in the formulas a glucose value obtained from the CGM measurement by applying a correction for the glucose trend. Specifically, Scheiner suggests increasing/decreasing the CGM reading by 25 mg/dl when glucose is rising/decreasing of between 1 and 2 mg/dl/min, by 50 mg/dl when glucose is rising/decreasing more than 2 mg/dl/min. However, a recent survey demonstrated that several patients actually use CGM trend information to make much larger corrections to insulin dose compared to what recommended [27] [28]. According to this, Pettus et al. recently proposed an approach similar to that of Scheiner, but with more aggressive corrections for glucose trend ( $\pm 50$  mg/dl and  $\pm 100$  mg/dl) [29].

### 1.3 Assessment of insulin treatment scenarios and in silico clinical trails (ISCTs)

The safety and effectiveness of treatments based on drugs and medical devices, e.g. T1D insulin therapies, are normally assessed in clinical trials performed on human subjects, that often incredibly slow down the process of development

and regulatory evaluation of these products because too time-demanding and expensive. As reported in a 2014 briefing of the Tufts Center for the Study of Drug Development, the cost to bring to the market a new pharmaceutical product has been increasing exponentially in the last decades and about the 60% of this cost is due to the clinical assessment [30]. To reduce the burden of time and costs, clinical trials often present a low numerosity and short study duration, with consequently low probability of observing rare but risky situations, e.g. severe hypoglycemia in the case of T1D. These limitations of clinical trials may be overcome by the use of computer simulations in the so-called in silico clinical trials.

An in silico clinical trial (ISCT) is defined as “The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention” [31] [32]. The idea is to recreate the concept of in vivo clinical trial (i.e. trial performed on real patients) in a simulation environment, where virtual subjects are modeled by initializing a disease/intervention model with quantitative information either measured on an individual (subject-specific model), or inferred from population distributions of those values (population-specific model).

The strength of ISCTs is that they can overcome some limitations of clinical trials, such as long duration, elevated costs and, as a consequence, low numerosity. Indeed, given the low cost and time required to run computer simulations, ISCTs can be performed in an incredibly large number of subjects, that would be impossible to enroll in an in vivo clinical trial, because too expensive and time-demanding. The ability of simulating a large number of subjects allows ISCTs to test also high risk situations related to the occurrence of rare events, not observable in in vivo clinical trials because of their limited size and duration. ISCTs are thus unique procedures to test the safety of treatments based on drugs and medical devices under extreme conditions, without exposing human patients to any risk.

In addition, ISCTs allow to run multiple tests on the same virtual subject and thus answer to “what if” questions such as: what if subject A uses a treatment based on drug/device C instead of drug/device B when the same surrounding conditions are maintained? What if subject A uses a treatment based on device C with settings D instead of settings E when the same surrounding conditions are maintained? What if subject A uses a treatment based on device C with performance F instead of performance G when the same surrounding conditions are maintained? Clearly, these kind of questions cannot

be answered by in vivo clinical trials since the same surrounding conditions, including patient's physiology and behaviors, cannot be exactly repeated in real life.

In conclusion, ISCTs are powerful investigation instruments that can be used to reduce, refine or even replace in vivo clinical trials. Of course, an essential requirement to perform large scale ISCTs is the availability of an individualized model of patient's physiological response to the drug- or medical device-based treatment under test that accounts for the inter-individual variability and it is able to describe a large number of individual virtual subjects.

## **1.4 Assessment of nonadjunctive use of CGM via ISCT**

### **1.4.1 Open questions on nonadjunctive CGM use**

So far, CGM sensors have not been approved by U.S. regulatory agencies such as FDA for nonadjunctive use, i.e. to make treatment decisions directly based on CGM information without requiring confirmatory SMBG, mostly because still considered not as accurate as SMBG devices [33]. Several factors were found to affect the accuracy of CGM sensors, such as imperfect calibration, compression of the sensor site, which causes artificially low sensor readings [34], and interfering substances like acetaminophen, which artificially increases the sensor readings [35]. Moreover, the accuracy of CGM sensors in the first day of monitoring may be lower than in the other days, because the foreign body response unleashed by sensor insertion causes a temporary reduction of the sensor sensitivity [36]. Another issue concerns the site of measurement of CGM sensors, i.e. the interstitial fluid. Indeed, as is known, plasma-interstitium kinetics give rise to a physiological delay of interstitial glucose (IG) measurements, e.g. CGM, compared to BG measurements, e.g. SMBG [37].

However, the impact of these factors on sensor accuracy have been mitigated over the years thanks to the progress of CGM technology. For example, the sensor needle was made smaller, thus reducing the foreign body response at its insertion, the sensor membrane was improved to reduce the effect of interfering substances and progress in the signal processing allowed to diminish the effect of artifacts, delay and noise. One of the metrics commonly used

to assess the accuracy of CGM sensors is the mean absolute relative difference (MARD) between CGM readings and BG references. As an example, the MARD of Dexcom CGM sensors was reduced from 26% of the Dexcom STS 3-days [38], released in 2006, to 9% of the Dexcom G5 Mobile [39], released in 2015. Importantly, the accuracy of CGM sensors, and in particular that of the Dexcom G5 Mobile, is reaching that of SMBG devices, which currently ranges between 3% and 15% MARD [40] [41] [42] [43].

Thanks to the progress made in CGM sensors' accuracy, the patients' confidence in CGM sensors has increased. Data collected in the T1D Exchange [44] revealed that about 50% of CGM users reduced the frequency of SMBG tests after starting CGM [45]. This suggests that many people already use CGM to make some treatment decisions without confirmatory SMBG. Signals that the situation is changing come also from Europe, where the Abbott Navigator II (Abbott Diabetes Care, Alameda, CA) has been approved for insulin dose calculation on condition that glucose is not changing rapidly, and the Dexcom G5 Mobile received the CE mark to be used nonadjunctively, unless the symptoms and expectations of the patient does not match CGM readings [46].

Despite these encouraging indications, safety and effectiveness of nonadjunctive CGM use has not been tested in a clinical trial yet. The main reason is that a clinical study that would generate statistically-meaningful clinical data to support the approval of nonadjunctive CGM use may not be feasible to conduct [47]. Indeed, situations that may present risks for the patients, such as severe hypoglycemia, are so varied and rare that they could not be captured in a short clinical trial with a small population enrolled.

#### **1.4.2 Possible solution: ISCT**

As already mentioned, the limitations of in vivo clinical trials can be overcome by the use of ISCTs, which can be particularly appropriate for assessing the safety and effectiveness of nonadjunctive CGM use compared to CGM adjunctive use and SMBG use. Indeed, an ISCT would allow to test T1D treatments in a large number of subjects not only in the average low risk situation, but also in a number of rare, but not-so-rare, high risk situations (e.g. insulin dosing in presence of poor sensor accuracy or large error in CHO counting) which are difficult to observe in small-size in vivo clinical trials because of their low probability of occurrence.

Moreover, an ISCT would permit to compare e.g. CGM use vs SMBG use in

the same virtual subjects, i.e. subjects presenting exactly the same physiological characteristics and the same meal behavior (e.g. time and amount of meals and errors in the estimation of meal CHO content). This would ensure that the differences observed in clinical outcomes of SMBG and CGM treatments are related exclusively to the use of the specific glucose monitoring device and not to other factors, like changes in patient physiology (e.g. due to stress or illness) or eating habits.

Of course, as discussed above, an essential requirement to perform large scale ISCTs is the availability of an individualized model of the patient's physiological response to the treatments under test that accounts for the inter-individual variability and it is able to describe a large number of individual virtual subjects.

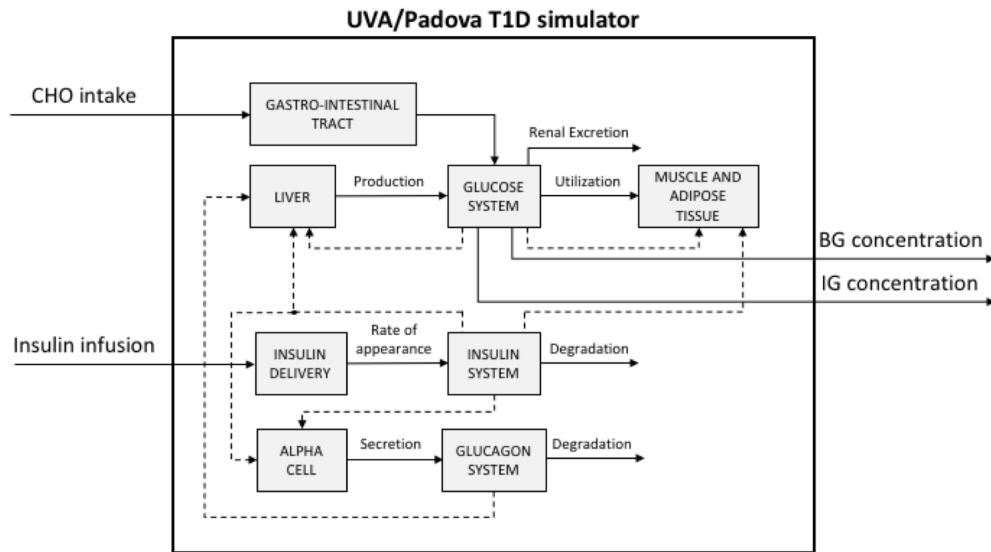
## 1.5 ISCTs in T1D: state of art

Diabetes has been an area of intense modeling development in these last 20 years [48] [49]. Several models of T1D physiology were proposed for the in silico assessment of closed-loop control algorithm, including those of Hovorka et al. [50], Wilinska et al. [51], Kanderian et al. [52] and Haidar et al. [53]. One of the most popular models of T1D patient's physiology is the UVA/Padova T1D simulator, jointly developed by University of Padova and University of Virginia, that will be described in Subsection 1.5.1.

### 1.5.1 The UVA/Padova T1D simulator

The UVA/Padova T1D simulator is a large-scale maximal computer model of glucose, insulin and glucagon dynamics in patients with T1D including 13 differential equations and 36 subject-specific parameters. At difference of previous average models that were able to describe only the characteristics of an "average subject" representative of the entire population, the UVA/Padova T1D simulator is equipped with a cohort of 100 adult, 100 pediatric and 100 adolescent virtual subjects that well span the observed inter-individual variability of key metabolic parameters in the general population of T1D people. The structure of the UVA/Padova T1D simulator is schematized in Figure 1.6. In particular, inputs of the model are CHO intake and insulin infusion, while BG and IG concentration are returned in output.

The history of the UVA/Padova T1D simulator begins in 2006 when 204



**Figure 1.6:** Schematic representation of the UVA/Padova T1D simulator. Note: exogenous glucagon delivery is not shown in the scheme because not used in this thesis.

healthy subjects were studied with the triple-tracer method that allowed to measure not only plasma glucose and insulin, but also crucial fluxes of the glucose-insulin system i.e. plasma rate of appearance of ingested CHO, endogenous glucose production, glucose utilization and insulin secretion [54]. From this unique data set, a large scale maximal mathematical model of glucose-insulin dynamics generated by meals in healthy subjects was developed [55], whose core component was the two-compartment glucose minimal model [56]. This model was then adapted to describe T1D subjects originating the UVA/Padova T1D simulator which in January 2008 was approved by the FDA as a substitute to animal trials for the preclinical testing of certain insulin treatments, including those based on artificial pancreas [57]. In 2013 an updated version of the UVA/Padova T1D simulator was released, and approved by FDA, including an improved model of hypoglycemia and a new model of glucagon dynamic [58]. The 2013 release of the simulator was then validated on 96 post-meal glucose traces recorded in 24 T1D subjects [59]. Finally, the use of the UVA/Padova T1D simulator was extended from a single meal to multiple days by incorporation of a model of intra- and inter-day variability of insulin sensitivity [60] derived from data collected in 20 T1D subjects studied with the triple-tracer method [61]. The 2013 release of the UVA/Padova T1D simulator with incorporation of the time-variability of insulin sensitivity was recently validated on 141 glucose traces collected in 47 T1D subjects [62] and

will be submitted to FDA for approval in the next months.

From its first release, the UVA/Padova T1D simulator has been used by 32 research groups in academia and 5 companies and has led to 1030 publications in peer reviewed journals. In particular, the simulator has been widely adopted by the Juvenile Diabetes Research Foundation Artificial Pancreas Consortium to test closed-loop control algorithms, thus accelerating artificial pancreas studies with a number of regulatory approvals achieved based on simulation only, and considerable savings in money and time.

For all its characteristics, the UVA/Padova T1D simulator looks like a suitable tool to perform ISCTs to assess safety and effectiveness of insulin treatments for the manual control of BG in T1D, i.e. treatments in which the patients themselves manage their diabetes and make treatment decisions (e.g. insulin dosing) based on glucose measurements. However, the UVA/Padova T1D simulator alone is not sufficient to realize such ISCTs, because, besides the physiological response of T1D subjects to CHO intakes and insulin doses, other fundamental components like the glucose measurements collected by SMBG and CGM devices, and the patient's behavior in tuning insulin and CHO doses according to SMBG and/or CGM measurements need to be mathematically described. A recent attempt to circumvent these needs is described in the following subsection.

### 1.5.2 The net effect method

In 2016, a novel simulation approach was developed by Patek et al. to "replay" insulin treatment scenarios [63]. This approach is based on the use of a simplified model of patient's physiology, which is time-invariant, linearized and with most of model parameters fixed to population values, to estimate from CGM and insulin delivery data simultaneously recorded in T1D subjects a signal called (oral glucose) net effect. The net effect is supposed to reflect meals and other sources of BG variability like exercise and time-variability of insulin sensitivity not described by the model. This signal is then used as input of the patient's model to simulate the effect on IG concentration of modified insulin treatments.

The expected advantage of the net effect method is that it allows to circumvent the necessity of mathematically describing sources of glucose variability, like exercise, which are currently not incorporated in the most popular T1D simulators, including the UVA/Padova T1D simulator. However, how

the many assumptions and simplifications on which the method is based influence the method's performance is not clear. Indeed, while the net effect method was only validated by Patek et al. for basal insulin adjustments [63], the reliability of the method to test other therapy modifications, such as modification/addition of insulin boluses and hypotreatments that are required to simulate treatments based on nonadjunctive CGM use, as done by Kovatchev et al. in [64], was never assessed. Therefore a useful step in developing ISCT tools for assessing T1D therapies is to precisely define the domain of validity of the net effect method.

## **1.6 Aim of the thesis and outline**

The primary goal of this thesis is to develop a simulation model of T1D patients making therapeutic decisions based on SMBG and/or CGM measurements usable to test in ISCTs T1D insulin treatments. The secondary goal is to use such a model to assess the safety and effectiveness of nonadjunctive CGM use, in order to provide regulatory agencies, such as FDA, with data for the evaluation of a possible change of CGM sensor's labeling.

To achieve these objectives, in Chapter 2 we first review the net effect method and perform an in silico experiment to assess its validity to test insulin treatment scenarios. Then, in Chapter 3 a new model of T1D patients decision-making is developed for the in silico assessment of insulin treatment scenarios. The model, in the following called T1D decision-making (T1D-DM) model, is constructed by connecting in a common simulation framework the UVA/Padova T1D simulator with new models of SMBG and CGM measurements and the patient's behavior in making treatment decisions based on these glucose measurements. In Chapter 4 the usefulness of the T1D-DM model is shown by the design of an ISCT to assess the safety and effectiveness of nonadjunctive CGM use compared to SMBG use and CGM adjunctive use. In Chapter 5 a second ISCT is designed to assess the influence of alert settings on nonadjunctive CGM use performance. To conclude, final considerations on the work carried out in this thesis as well as its future developments are discussed in Chapter 6.



## Chapter 2

# Modeling approaches for in silico assessment of insulin treatments: critical review of the net effect method

In this chapter, we first review the net effect method (Section 2.1), describe its applications in the literature (Section 2.2) and evidence its critical assumptions (Section 2.3). Then, by using the UVA/Padova T1D simulator we assess the validity of the net effect method in four case studies (Section 2.4 and Section 2.5). Our final considerations are reported at the end of the chapter (Section 2.6).<sup>1</sup>

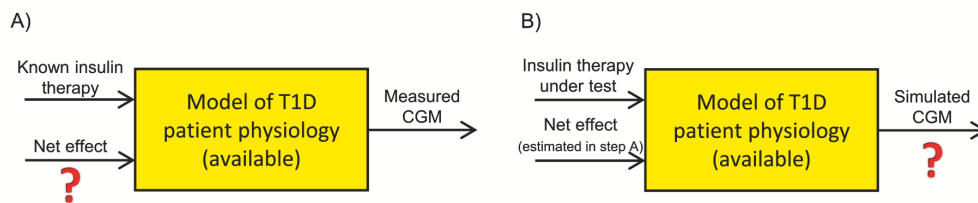
### 2.1 The net effect method

The net effect method is a model-based simulation method proposed by Patek et al. [63] to test in silico insulin treatment scenarios. The method is schematized in Figure 2.1. Given a model of T1D patient physiology, CGM and insulin pump data simultaneously recorded in a T1D patient in a certain time window are used to retrospectively estimate a signature of BG variability, called net effect (Figure 2.1, panel A). This net effect signal is assumed to reflect a combination of components contributing to the patient's glucose variability in the specific time window studied, including meals, variation in insulin sensitivity and exercise. The net effect signal estimated from the patient's data

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<sup>1</sup>The present chapter is part of the journal paper [65].

is then used as a forcing input to the patient model (Figure 2.1, panel B) to predict the effect of a modified insulin therapy on the patient's glucose concentration in the same time window where data for the net effect estimation were collected. As already anticipated, the net effect method circumvents the necessity of mathematically describing sources of glucose variability, like exercise, which are currently not incorporated in the most popular T1D simulators, including the UVA/Padova T1D simulator. Below the main features and assumptions of the net effect method are summarized.



**Figure 2.1:** The steps of the net effect method. Step A (retrospective): the net effect signal is estimated from measured CGM data, insulin therapy and a model of T1D patient physiology with known parameters. Step B (prospective): The net effect signal, estimated in step A, is used as forcing input of the T1D patient physiology model to predict glucose concentration in consequence of a given insulin therapy.

### 2.1.1 Pre-processing

CGM recordings are divided in multiple segments that include a time frame of interest, e.g. an entire day. In order to mitigate measurement error affecting CGM data, a retrofitting procedure is applied in which CGM time series are first interpolated via cubic spline and, then properly scaled and shifted to force the resulting signal to pass through the available SMBG samples. The operation is done by considering a portion of data before the beginning and after the end of the time frame of interest to ensure that the net effect estimation in the time frame of interest is free of edge effects.

### 2.1.2 Patient model

#### Continuous-time model

The model used to describe T1D patient physiology in the net effect methodology is the subcutaneous oral glucose minimal model (SOGMM). In particular,

plasma glucose and insulin dynamics are described by the nonlinear glucose minimal model [66]:

$$\dot{G}(t) = -(S_g + X(t)) \cdot G(t) + S_g + R_a(t)/V_g \quad (2.1)$$

$$\dot{X}(t) = -p_2 \cdot X(t) + p_2 \cdot S_I \cdot (I(t) - I_b) \quad (2.2)$$

where  $G(t)$  [mg/dl] is BG concentration (with basal value  $G_b$  [mg/dl]),  $R_a(t)$  [mg/min/kg] is the glucose rate of appearance,  $I(t)$  [mU/L] is plasma insulin concentration (with basal value  $I_b$  [mU/L]) and  $X(t)$  [1/min] is the deviation from basal of remote insulin (with basal value  $X(0) = 0$ ). Model parameters are fractional glucose effectiveness  $S_g$  [1/min], the distribution volume of glucose  $V_g$  [kg/dl], the rate constant of the remote insulin compartment  $p_2$  [1/min] and insulin sensitivity  $S_I$  [1/min/mU/L].

The relationship between BG concentration,  $G(t)$ , and IG concentration,  $G_{sc}(t)$ , (sc for subcutaneous) is described by the following differential equation:

$$\dot{G}_{sc}(t) = -k_{sc} \cdot (G_{sc}(t) - G(t)) \quad (2.3)$$

where  $k_{sc}$  [1/min] is the rate constant of plasma-interstitium exchange.

A two-compartment linear model is used to describe the glucose gastrointestinal tract:

$$\dot{Q}_1(t) = -k_\tau \cdot Q_1(t) + \omega(t) \quad (2.4)$$

$$\dot{Q}_2(t) = -k_{abs} \cdot Q_2(t) + k_\tau \cdot Q_1(t) \quad (2.5)$$

where  $Q_1(t)$  [mg] and  $Q_2(t)$  [mg] are the amount of glucose in the two compartments,  $\omega(t)$  [mg/min] is the rate of ingested glucose and  $k_\tau$  [1/min] and  $k_{abs}$  are rate constants associated with oral glucose absorption. The mass of the second compartment of the gastrointestinal submodel  $Q_2(t)$  is related to glucose rate of appearance  $R_a(t)$  of eq. 2.1 as follows:

$$R_a(t) = \frac{Q_2(t) \cdot k_{abs} \cdot f}{BW} \quad (2.6)$$

where  $f$  [dimensionless] is the fraction of intestinal absorption which actually appears in plasma and  $BW$  [kg] is the subject's body weight.

The transport of insulin from the pump to plasma is described by the following three-compartment linear model:

$$\dot{I}_{sc1}(t) = -k_d \cdot I_{sc1}(t) + J_{ctrl}(t) \quad (2.7)$$

$$\dot{I}_{sc2}(t) = -k_d \cdot I_{sc2}(t) + k_d \cdot I_{sc1}(t) \quad (2.8)$$

$$\dot{I}_p(t) = -k_{cl} \cdot I_p(t) + k_d \cdot I_{sc2}(t) \quad (2.9)$$

where  $I_{sc1}(t)$  [mU] and  $I_{sc2}(t)$  [mU] are insulin mass in two subcutaneous compartments,  $I_p(t)$  [mU] plasma insulin,  $J_{ctrl}(t)$  [mU/min] the pump insulin infusion rate and  $k_d$  [1/min] and  $k_{cl}$  [1/min] are rate constants of subcutaneous insulin transport. Plasma insulin concentration  $I(t)$  of eq. 2.2 is related to plasma insulin  $I_p(t)$  as follows:

$$I(t) = \frac{I_p(t)}{V_I \cdot BW} \quad (2.10)$$

where  $V_I$  [L/kg] is the distribution volume of insulin.

### Model linearization and discretization

In order to define and compute the net effect, eq. 2.1 of SOGMM is first linearized about the steady state corresponding to basal glucose concentration  $G_b$  and basal plasma insulin  $I_b$ :

$$\dot{G}(t) = -S_g \cdot G(t) - G_b \cdot X(t) + S_g \cdot G_b + \frac{R_a(t)}{V_g} \quad (2.11)$$

From the linearized continuous-time model described by eqs. 2.11 and 2.2-2.10, the following state-space continuous-time representation is derived:

$$\dot{\mathbf{x}}_c(t) = \mathbf{A}_c \cdot \mathbf{x}_c(t) + \mathbf{B}_c \cdot u_c(t) + \mathbf{G}_c \cdot \omega(t) \quad (2.12)$$

$$y_c(t) = \mathbf{C}_c \cdot \mathbf{x}_c(t) \quad (2.13)$$

where  $\mathbf{x}_c(t)$  is the 8x1 vector containing the difference between the variables of the model at time  $t$ , i.e.  $G(t)$ ,  $X(t)$ ,  $I_{sc1}(t)$ ,  $I_{sc2}(t)$ ,  $I_p(t)$ ,  $G_{sc}(t)$ ,  $Q_1(t)$ ,  $Q_2(t)$ , and their steady state values;  $u_c(t)$  [mU/min] is the difference between the insulin delivery rate at time  $t$ ,  $J_{ctrl}(t)$ , and the basal insulin delivery rate,  $J_{basal}(t)$ ;  $\omega(t)$  is the rate of ingested glucose (as in eq. 2.4);  $y_c(t)$  is the difference between subcutaneous glucose concentration at time  $t$ ,  $G_{sc}(t)$ , and  $G_b$ ;  $\mathbf{A}_c$ ,  $\mathbf{B}_c$ ,  $\mathbf{G}_c$ , and  $\mathbf{C}_c$  are matrices defined as follows:

$$A_c = \begin{bmatrix} -S_g & -G_b & 0 & 0 & 0 & 0 & 0 & \frac{k_{abs} \cdot f}{BW \cdot V_g} \\ 0 & -p_2 & 0 & 0 & \frac{p_2 \cdot S_I}{V_I \cdot BW} & 0 & 0 & 0 \\ 0 & 0 & -k_d & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & k_d & -k_d & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_d & -k_{cl} & 0 & 0 & 0 \\ k_{sc} & 0 & 0 & 0 & 0 & -k_{sc} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -k_\tau & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & k_\tau & -k_{abs} \end{bmatrix} \quad (2.14)$$

$$B_c = [00100000]^T, \quad G_c = [000000010]^T, \quad C_c = [000000100]^T \quad (2.15)$$

The continuous-time state-space model of eqs. 2.12-2.13 is discretized using a first-order approximation with step  $h=5$  min, leading to:

$$x(k+1) = A \cdot x(k) + B \cdot u(k) + G \cdot \omega(k) \quad (2.16)$$

$$y(k) = C \cdot x(k) \quad (2.17)$$

where  $x(k)$ ,  $u(k)$ ,  $\omega(k)$ ,  $y(k)$  with  $k=1, \dots, T$  are the samples of  $x_c(t)$ ,  $u_c(t)$ ,  $\omega_c(t)$ ,  $y_c(t)$ , respectively, and matrices  $A$ ,  $B$ ,  $G$  and  $C$  are:

$$A = h \cdot A_c + I_8, \quad B = h \cdot B_c, \quad G = h \cdot G_c, \quad C = C_c \quad (2.18)$$

with  $I_8$  representing the 8x8 identity matrix.

Finally, having defined vectors  $\tilde{y} = [y(0) y(1) \dots y(T)]^T$ ,  $\tilde{u} = [u(0) u(1) \dots u(T-1)]^T$  and  $\tilde{\omega} = [\omega(0) \omega(1) \dots \omega(T-1)]^T$ , assuming that the initial state vector  $x(0)$  is zero (for this reason an appropriate burn-in period is considered to avoid occurrence of edge effects in the timeframe of interest), eqs. 2.16-2.17 can be rewritten in compact form as:

$$\tilde{y} = \Theta \cdot \tilde{u} + \Omega \cdot \tilde{\omega} \quad (2.19)$$

where matrices  $\Theta$  and  $\Omega$  are:

$$\Theta = \begin{bmatrix} C \cdot B & 0 & \dots & 0 \\ C \cdot A \cdot B & C \cdot B & \ddots & \vdots \\ \vdots & \vdots & \ddots & 0 \\ C \cdot A^{T-1} \cdot B & C \cdot A^{T-2} \cdot B & \dots & C \cdot B \end{bmatrix} \quad (2.20)$$

$$\mathbf{\Omega} = \begin{bmatrix} \mathbf{C} \cdot \mathbf{G} & 0 & \dots & 0 \\ \mathbf{C} \cdot \mathbf{A} \cdot \mathbf{G} & \mathbf{C} \cdot \mathbf{G} & \ddots & \vdots \\ \vdots & \vdots & \ddots & 0 \\ \mathbf{C} \cdot \mathbf{A}^{T-1} \cdot \mathbf{G} & \mathbf{C} \cdot \mathbf{A}^{T-2} \cdot \mathbf{G} & \dots & \mathbf{C} \cdot \mathbf{G} \end{bmatrix} \quad (2.21)$$

### Model parameters

Ten out of thirteen parameters required to define matrix  $\mathbf{A}_c$ , and thus  $\mathbf{\Theta}$  and  $\mathbf{\Omega}$ , are fixed to population values, i.e.  $S_g=0.01000$  [1/min],  $V_g=1.60000$  [kg/dl],  $p_2=0.02000$  [1/min],  $k_{abs}=0.01193$  [1/min],  $f=0.90000$  [dimensionless],  $V_I=0.06005$  [L/kg],  $k_{sc}=0.09088$  [1/min],  $k_{\tau}=0.08930$  [1/min],  $k_d=0.02000$ , and  $k_{cl}=0.16000$  [1/min]. The model only includes three patient-specific parameters i.e.  $BW$  (easily measured),  $G_b$  and  $S_I$  that, according to Patek et al. [63], can be approximated by the following empirical relationships:

$$G_b = HbA1c \cdot 28.7 - 46.7 \quad (2.22)$$

$$S_I = e^{-6.4417 - 0.063546 \cdot TDI_{whole} + 0.057944 \cdot TDI_{basal}} \quad (2.23)$$

where  $HbA1c$  is the patient glycated haemoglobin,  $TDI_{whole}$  is the patient total daily insulin whose basal fraction is  $TDI_{basal}$ .

### 2.1.3 Net effect estimation and simulation

The core idea of the net effect method consists in solving the inverse problem associated with eq. 2.19 to estimate  $\tilde{\omega}$  from  $\tilde{\mathbf{y}}$  and  $\tilde{\mathbf{u}}$  assuming that  $\mathbf{\Theta}$  and  $\mathbf{\Omega}$  are available. In practice, given a segment of data obtained as in Section 2.1.1, the vector  $\tilde{\mathbf{y}}$  is computed as the difference between CGM pre-processed data and  $G_b$ . Similarly, given a parallel segment of insulin pump data, the vector  $\tilde{\mathbf{u}}$  is obtained as the difference between pump data and basal insulin delivery rate,  $J_{basal}$ . This retrospective procedure corresponds to panel A in Figure 2.1. The resulting estimate of the input  $\tilde{\omega}$ , in the following denoted by  $\hat{\omega}$ , ideally should represent the rate of ingested glucose, but in practice it is a signal that comprises not only meals but also other components that contribute to BG variability and are not taken into account by the patient model, e.g. circadian insulin sensitivity, physical exercise and discrepancies due to model linearization and use of population values for model parameters. For this reason, in Patek et al. [63] the estimate  $\hat{\omega}$  is called (oral glucose) net effect. Details on its computation are reported in Patek et al. [63].

Once the net effect has been estimated, it can be used in a prospective way (Figure 2.1, panel B) to predict *in silico* the effect on IG concentration of using a modified insulin therapy,  $J_{ctrl}^{mod}(t)$ , instead of the original one,  $J_{ctrl}(t)$ . In particular, a new vector  $\tilde{\mathbf{u}}^{mod} = [u^{mod}(0) u^{mod}(1) \dots u^{mod}(T-1)]^T$  is defined, whose elements are obtained as the difference between samples of the modified insulin therapy and the original basal insulin ( $u^{mod}(k) = J_{ctrl}^{mod}(k) - J_{basal}(k)$ ). Then, the net effect,  $\hat{\omega}$ , and the modified insulin vector,  $\tilde{\mathbf{u}}^{mod}$ , are used as new inputs in the model of eq. 2.19 to simulate a new glucose profile,  $\tilde{\mathbf{y}}^{mod}$ :

$$\tilde{\mathbf{y}}^{mod} = \Theta \cdot \tilde{\mathbf{u}}^{mod} + \Omega \cdot \hat{\omega} \quad (2.24)$$

Since every time a modified insulin therapy is tested the net effect  $\hat{\omega}$  is not changed, i.e. it is the same estimated from the original insulin vector  $\tilde{\mathbf{u}}$ , the net effect simulation method is based on the assumption that the net effect is independent from insulin.

## 2.2 Use of the net effect in the literature

In Patek et al. [63], the net effect method was applied to data simulated by the UVA/Padova T1D simulator in order to validate its ability to predict the effect of changes in basal insulin on mean glucose concentration. In particular, for each virtual subject the basal insulin adjustment required to produce a variation of  $\pm 10\%$  and  $\pm 20\%$  of average BG concentration was determined by the net effect method. Then, Patek et al. verified that when the same basal insulin adjustments are applied to the UVA/Padova T1D simulator, the obtained BG profiles present a MARD of about 5% and 8% compared to the glucose profiles predicted by the net effect method.

In another work, the method was applied to a real data set, collected in 56 T1D subjects, to compare insulin therapies calculated directly from CGM data, i.e. simulating a nonadjunctive use of CGM [64]. In particular, after estimating the net effect signal for each pair of CGM and insulin segments in each individual of the data set, the following modifications were produced in patients' therapies according to CGM: a) modification of pre-existing boluses that were recalculated by using CGM measurements and then adjusted to account for CGM trend; b) addition of post-meal correction boluses whenever the CGM profile (or its 30 min ahead prediction) went over 180 mg/dl and thus an high glucose alert would have been generated; and c) addition of 15-g hypotreat-

ments whenever the CGM profile (or its 20 min ahead prediction) went under 70 mg/dl and thus a low glucose alert would have been generated. The authors evaluated the glycemic control achieved by nonadjunctive use of CGM for different values of sensor accuracy and found that decreasing the sensor MARD below 10% does not significantly improve glycemic outcomes. This result was used in work by Kovatachev et al. [67] and Castle et al. [33] to comment the improved accuracy of the Dexcom G5 Mobile sensor.

## **2.3 Critical assumptions**

The net effect method is based on several assumptions and simplifications. First of all, the model used to describe the T1D patient glucose-insulin physiology is linearized about the steady state corresponding to basal glucose and insulin concentration. Consequently, the model cannot properly describe the patient glucose-insulin dynamics when its states significantly move from basal, e.g. during meals. In addition, the net effect model does not properly consider either the inter-subject variability, since ten out of thirteen of the model parameters are fixed to population values, or the intra-subject variability, because all model parameters are constant over time. Another critical assumption is the independence of the net effect signal from the insulin therapy: according to this assumption, in the net effect method new IG traces are simulated by varying the insulin therapy while keeping the net effect signal fixed; this is not correct since the net effect signal is estimated from both CGM and insulin pump data and, thus, it depends on the insulin therapy.

How these assumptions and simplifications can affect the results obtained by the net effect method is not clear. Indeed, the use of the net effect method was validated only to design basal insulin adjustments [63], but not for the more complex therapy modifications a), b) and c) described in Section 2.2.

## **2.4 Assessment of the net effect method's domain of validity by the UVA/Padova T1D simulator**

Since the net effect signal cannot be used to predict the effect of therapy modifications outside the time window where data for its estimation were collected, in order to assess the domain of validity of the net effect method it would be necessary to have CGM data collected in the same patient, in the same time



window, but with different insulin therapies, which is clearly impossible in real life. For this reason, the domain of validity of the net effect method can only be assessed in simulation, where the same time window, with identical patient's physiological characteristics and behavior, can be reproduced.

Here, the net effect method is tested on glucose and insulin data of virtual subjects simulated by the updated version of the UVA/Padova T1D simulator obtained by incorporating the model of intra- and inter-day variability of insulin sensitivity [60] in the last FDA-accepted version of the simulator [58]. For each subject, the test is performed in six steps:

1. IG and insulin profiles are simulated over 2 days with the UVA/Padova T1D simulator. Meal times are set to 07:00, 13:00, and 19:00. The CHO content of breakfast, lunch and dinner is sampled from Gaussian distributions with mean equal to 40 g, 80 g and 70 g, respectively, and standard deviation equal to 20%. Patients are treated by the optimal basal insulin infusion rate provided by the simulator and meal insulin boluses, which are calculated using CR and CF parameters of the simulator and SMBG measurements simulated by the two-zone skew-normal probability density function model derived from a data set collected by the One Touch Ultra 2 (LifeScan Inc., Milpitas, CA) device [68], as later described in this thesis in Section 3.2.
2. As in Patek et al. [63], a 24-h time frame of interest is selected, and IG, and insulin data simulated between 8 h before the beginning and 4 h after the ending of the time frame of interest are extracted from the whole simulated profiles. Then, the net effect profile  $\hat{\omega}$  is estimated from the selected IG data,  $\tilde{y}$ , and insulin data,  $\tilde{u}$ , considering the first 8 h and the last 4 h as burn-in and burn-out periods. Here, the net effect is estimated from the true IG profile instead of the retrofitted CGM profile, i.e. the assumption of no errors in the retrofitting process is made.
3. A modified insulin profile,  $\tilde{u}^{mod}$ , and/or a modified net effect profile,  $\hat{\omega}^{mod}$ , are defined in order to simulate changes in the patient therapy, like changes in basal/bolus insulin or addition of hypotreatments.
4. A modified IG profile,  $\tilde{y}_{n.e.}^{mod}$ , is calculated by using the model of eq. 2.19 with inputs  $\hat{\omega}^{mod}$  and  $\tilde{u}^{mod}$ .
5. The same modifications of the therapy performed in step 3 are made on the insulin therapy and CHO intake in the UVA/Padova T1D simulator

and a new IG profile is obtained,  $\tilde{y}_{sim}^{mod}$ . Then,  $\tilde{y}_{n.e.}^{mod}$ , which represents the effect of therapy modifications made in step 3 predicted by the net effect method, is compared to  $\tilde{y}_{sim}^{mod}$ , which represents the true effect of the same therapy modifications. If the net effect method works correctly,  $\tilde{y}_{n.e.}^{mod}$  should replicate  $\tilde{y}_{sim}^{mod}$ .

6. Finally, the new IG profile,  $\tilde{y}_{sim}^{mod}$ , and the modified insulin profile,  $\tilde{u}^{mod}$ , are used to estimate a new net effect signal,  $\hat{\omega}_{sim}^{mod}$ , i.e. the signature of BG variability that best explains the relationship between  $\tilde{u}^{mod}$  and  $\tilde{y}_{sim}^{mod}$  according to the model of eq. 2.19. Ideally, if the assumption of independence between net effect and insulin therapy is correct,  $\hat{\omega}_{sim}^{mod}$  should be equal to the net effect estimated from original data,  $\hat{\omega}$  (or  $\hat{\omega}^{mod}$  if it has been modified in step 3).

The six-step method described above is used to test the net effect method in four case studies, in which four therapy modifications are simulated: modification of basal insulin, modification of pre-existing boluses, addition of new boluses, addition of new hypotreatments. These four therapy modifications reflect those applied in the literature applications of the net effect method [63], [64]. In each case study, IG and insulin data of a representative virtual subject are used. In particular, a time frame of IG and insulin data suitable for its application is selected from a larger database in order to test each therapy modification in a realistic scenario (e.g. to test the addition of new boluses and hypotreatments, a virtual subject who presents an hyperglycemic and hypoglycemic event, respectively, is selected). Note that the representative subjects, and the associated time frames of data, are not extreme cases since they are selected before applying the net effect method and, thus, without knowing the performance of the net effect method on these data. The four case studies and the related results are presented in the following section.

## 2.5 Results

### 2.5.1 Case study 1: modification of basal insulin

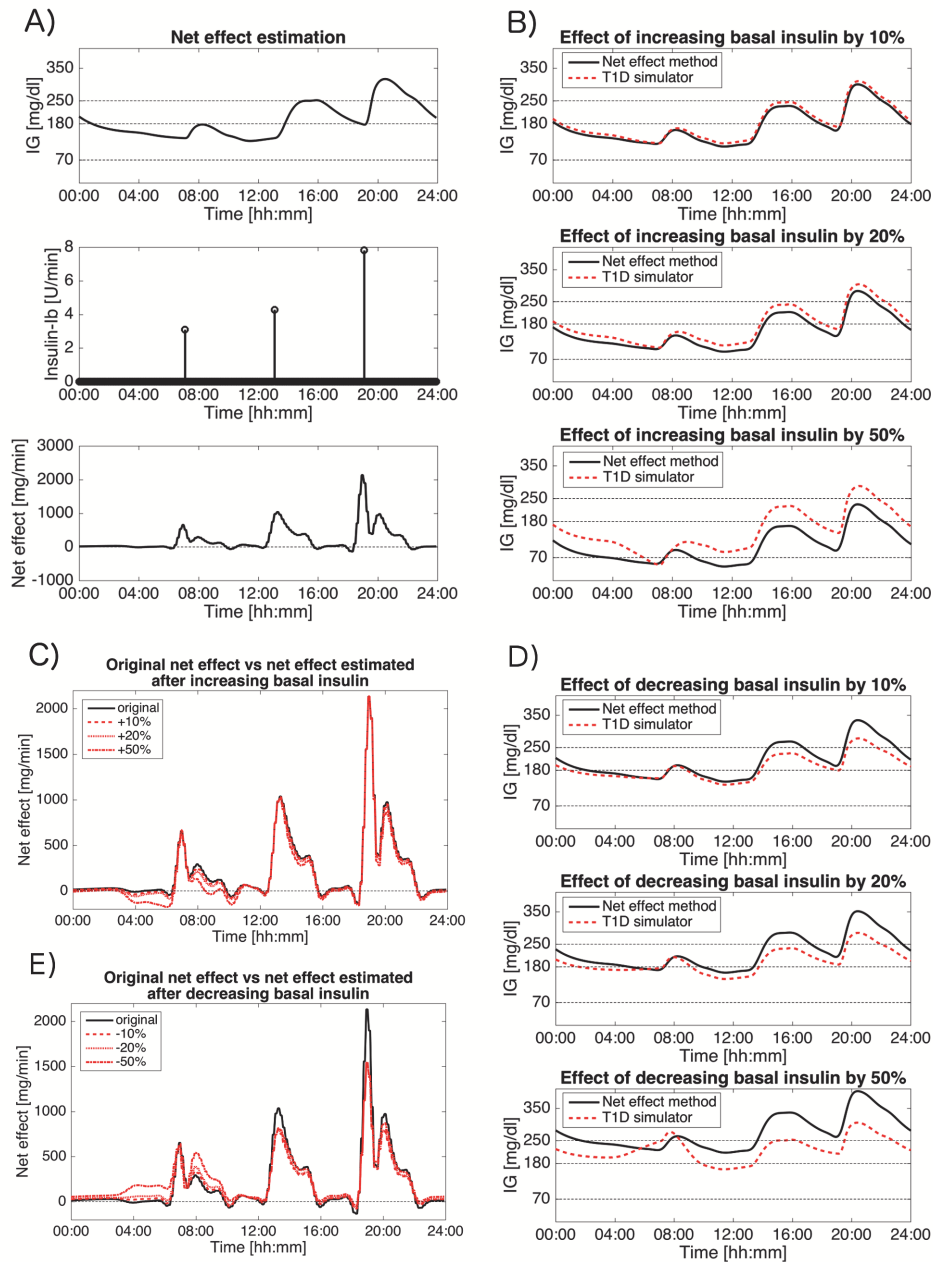
The use of the net effect method to predict the effect of modifying basal insulin delivery is tested on the representative virtual subject #1. In the bottom panel of Figure 2.2A we report the net effect profile that is estimated from the IG profile (top panel) and the insulin boluses (middle panel) in a 24-h time

frame of interest. The estimated net effect, which ideally should be the rate of CHO intake in mg/min, is actually a more complex signal which includes both oscillations related to meals and other oscillations that result from other components that contribute to BG variability and are not considered by the simplified glucose-insulin model used in the net effect method, such as the inter-subject variability of model parameters, the nonlinearity of the patient model and the time-variability of insulin sensitivity. For this reason, the net effect signal presents even negative values (e.g. between time 18:00 and 19:00) and, thus, it becomes difficult to interpret from a physiological point of view.

The original insulin therapy in the middle panel of Figure 2.2A is then modified in order to simulate an increase of basal insulin of 10%, 20% and 50%. In Figure 2.2B, the IG profiles resulting from a basal insulin increase of 10% (top), 20% (middle) and 50% (bottom) according to the net effect method (black solid line) are compared to those obtained when the same basal insulin modifications are performed in the UVA/Padova T1D simulator (red dashed line). From this comparison, we can observe that, for modest changes of basal insulin, like +10% or +20%, the net effect method is able to reproduce quite faithfully the IG curves generated by the UVA/Padova T1D simulator (the net effect method underestimates time above 180 mg/dl of 1h for basal insulin increase of 10%, of 1.9 h for basal insulin increase of 20%). However, for larger modifications of basal insulin, like +50%, the net effect method does not accurately reproduce the effect on IG obtained by the UVA/Padova T1D simulator and drives to an overestimation of 6.4 h of the time in hypoglycemia (BG<70 mg/dl) and an underestimation of 5.1 h of time in hyperglycemia (BG>180 mg/dl).

This is visible also in Figure 2.2C, where the original net effect (black solid line) is compared to the net effect profiles estimated after basal insulin is modified in the UVA/Padova T1D simulator by +10% (red dashed line), +20% (red dotted line) and +50% (red dash-dot line). A possible reason of the observed discrepancies is that, while in the UVA/Padova T1D simulator, after a change of basal insulin, insulin boluses have been recalculated since the glucose concentration at the time of the calculation of the bolus has changed, in the net effect approach insulin boluses remain the same provided in the original insulin therapy. Indeed, since the net effect method operates retrospectively, it does not allow to introduce additional modifications of the therapy as a consequence of the new glucose profile. For example, in the representative subject of Figure 2.2, when basal insulin is increased of 50%, in the UVA/Padova T1D

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**Figure 2.2:** Case study 1 (modification of basal insulin), virtual subject #1. A) IG data (top), insulin data (middle) and estimated net effect (bottom) in a time frame of interest. B) IG profile predicted by the net effect method (black solid line) and IG profile obtained by the UVA/Padova T1D simulator (red dashed line) when basal insulin is increased by 10% (top), 20% (middle) and 50% (bottom). C) Original net effect (black solid line) and net effect re-estimated after basal insulin is increased in the UVA/Padova T1D simulator by 10% (red dashed line), 20% (red dotted line) and 50% (red dash-dot line). D) IG profile predicted by the net effect method (black solid line) and IG profile obtained by the UVA/Padova T1D simulator (red dashed line) when basal insulin is decreased by 10% (top), 20% (middle) and 50% (bottom). E) Original net effect (black solid line) and net effect re-estimated after basal insulin is decreased in the UVA/Padova T1D simulator by 10% (red dashed line), 20% (red dotted line) and 50% (red dash-dot line).

simulator the meal boluses become 1.2 U, 3.4 U and 7.0 U respectively, i.e. lower than the original boluses whose values were 3.1 U, 4.3 U and 7.8 U.

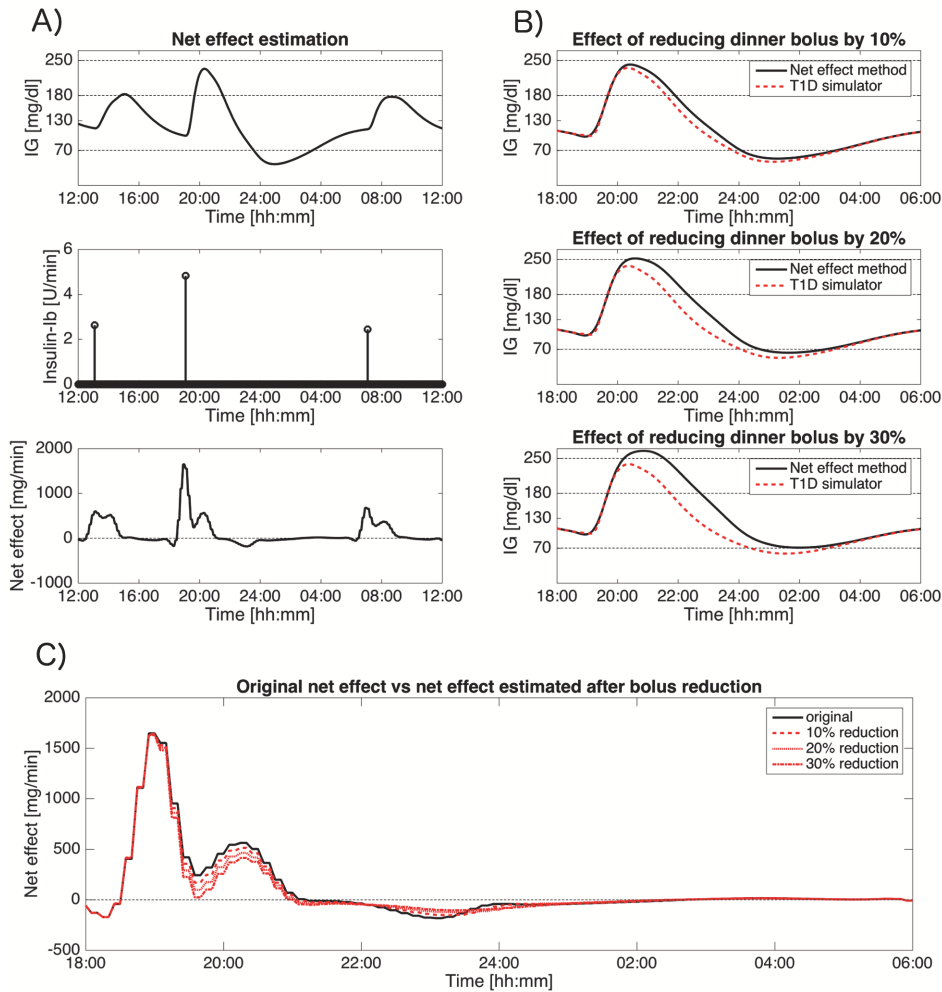
In Figure 2.2D, the effect of decreasing basal insulin by 10%, 20% and 50% is shown in the same virtual subject using the net effect method (black solid line) and the UVA/Padova T1D simulator (red dashed line). While for a 10% decrease of basal insulin the clinical outcomes predicted by the net effect method are similar to those obtained by the UVA/Padova T1D simulator (the net effect overestimates time in hyperglycemia by 1.7 h), for basal insulin adjustment of -20% and -50% the net effect method significantly overestimates time in hyperglycemia by 4.3 h and 3.6 h, respectively and time in severe hyperglycemia (BG>250 mg/dl) by 4.7 h and 7.5 h, respectively. In Figure 2.2E discrepancies can be observed between the net effect estimated from original data (black solid line) and the net effect estimated after basal insulin is decreased by 10% (red dashed line), 20% (red dotted line) and 50% (red dash-dot line).

## 2.5.2 Case study 2: modification of pre-existing boluses

Virtual subject #2 presents a nocturnal hypoglycemia, probably because of an elevated dose of insulin at dinner time (Figure 2.3A, top panel). The aim here is to investigate how much the dinner insulin bolus should be reduced in order to avoid the nocturnal hypoglycemia. For this purpose first, the net effect profile is estimated from IG and insulin profiles (Figure 2.3A, bottom panel). Then, the effect of reducing the dinner bolus by 10%, 20% and 30% is tested using the net effect model.

In Figure 2.3B, the IG profile obtained by the net effect method (black solid line) for a 10% (top), 20% (middle) and 30% (bottom) reduction of the dinner bolus can be compared to the IG profile obtained by the UVA/Padova T1D simulator (red dashed line) when the same bolus reductions are applied. When the dinner bolus is reduced by 10% and 20%, the net effect method underestimates time in hypoglycemia of 0.5 h and 0.9 h, respectively. When a 30% reduction is applied to the dinner bolus, while the net effect method predicts that such a reduction is sufficient to prevent the nocturnal hypoglycemia, in the UVA/Padova T1D simulator a hypoglycemic event of duration 2.6 h is still present. The hypoglycemic event is prevented in the UVA/Padova T1D simulator only when the dinner bolus is reduced by at least 50% (results not shown). This means that the net effect method is significantly underestimating the reduction of the insulin bolus required to avoid the nocturnal hypoglycemia.

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**Figure 2.3:** Case study 2 (modification of pre-existing boluses), virtual subject #2. A) IG data (top), insulin data (middle) and estimated net effect (bottom) in a time frame of interest. B) IG profile predicted by the net effect method (black solid line) and IG profile obtained by the UVA/Padova T1D simulator (red dashed line) when dinner bolus is decreased by 10% (top), 20% (middle) and 30% (bottom). C) Original net effect (black solid line) and net effect re-estimated after dinner bolus is decreased in the UVA/Padova T1D simulator by 10% (red dashed line), 20% (red dotted line) and 30% (red dash-dot line).

This case study confirms the criticality of one of the net effect method assumptions: the independence between the net effect and the insulin therapy. If this assumption were true, the net effect estimated from the original IG and insulin profile (Figure 2.3C, black solid line) and the three net effects obtained after modifying the dinner bolus by -10%, -20% and -30% in the UVA/Padova T1D simulator (Figure 2.3C, dashed, dotted and dash-dot line, respectively) would be identical. However, as shown in Figure 2.3C, the assumption of independence between net effect and insulin therapy is not valid since the four

net effect profiles are very different from each other.

### 2.5.3 Case study 3: addition of new boluses

Virtual subject #3 presents hyperglycemia after breakfast (Figure 2.4A, top panel). Let us use the net effect method to see the effect of adding a correction bolus, e.g. of 2 U 2 h after breakfast (i.e. at 09:00) in response to a high glucose alert of the CGM sensor. After estimating the net effect trace (Figure 2.4A, bottom panel) and adding the correction bolus to the original insulin therapy, the net effect method produces the IG profile reported by black solid line in Figure 2.4B. When the same correction bolus is added to the insulin therapy used to generate the subject with the UVA/Padova T1D simulator, the resulting IG profile is the one represented by red dashed line in Figure 2.4B.

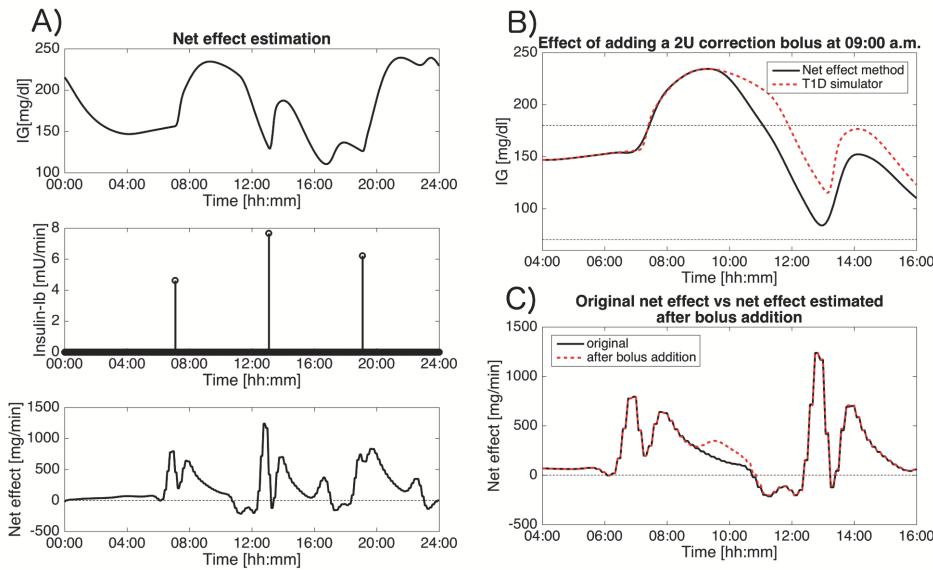
Here the net effect method underestimates time in hyperglycemia of 1 h, since the correction bolus has a greater impact according to the net effect method than that it actually has in the UVA/Padova T1D simulator. This discrepancy is likely due to an overestimation of the patient's insulin sensitivity in that particular period of the day and to the limitations of net effect model that is linearized about the basal state and does not properly take into account the inter- and intra-subject variability of physiology.

Again, if we compare the net effect profile estimated from original data (Figure 2.4C, black solid line) and the one estimated from the IG profile obtained in the UVA/Padova T1D simulator after adding the correction bolus (Figure 2.4C, red dashed line), a significant difference between the two profiles can be noted between 09:00 and 11:00, which violates the assumption of independence between net effect and insulin therapy.

### 2.5.4 Case study 4: Addition of hypotreatments

Here we test the effect of adding a hypotreatment in response to a low glucose alert of the CGM sensor. Virtual subject #4 is a good candidate for such a purpose, since presenting a hypoglycemia around midnight (Figure 2.5A, top panel). The net effect profile estimated from IG and insulin data is reported in Figure 2.5A, bottom panel. Since no information on how to add hypotreatments to the net effect is provided in Patek et al. [63], we decided to add an impulse to the net effect signal at the time in which IG crosses the hypoglycemic threshold (70 mg/dl) in order to simulate the intake of 15 g of CHO

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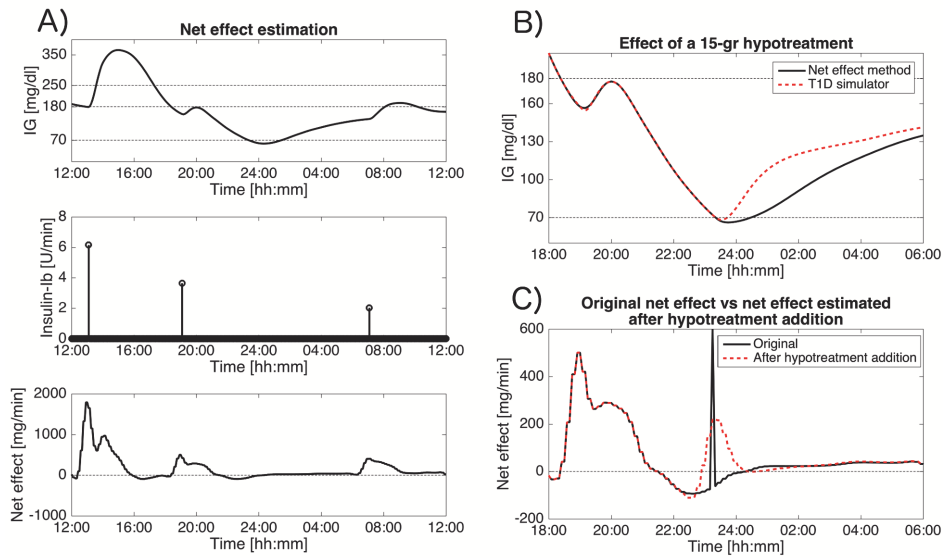
**Figure 2.4:** Case study 3 (addition of new boluses), virtual subject #3. A) IG data (top), insulin data (middle) and estimated net effect (bottom) in a time frame of interest. B) IG profile predicted by the net effect method when a 2 U correction bolus is added at 09:00 (black solid line) and IG profile obtained when the same bolus is added in the UVA/Padova T1D simulator (red dashed line). C) Original net effect (black solid line) and net effect re-estimated after a 2-U correction bolus is added at 09:00 in the UVA/Padova T1D simulator (red dashed line).

(Figure 2.5C, black solid line). The IG profile obtained by the modified net effect is reported in Figure 2.5B (black solid line), together with the IG profile simulated adding the 15-g hypotreatment in the UVA/Padova T1D simulator (red dashed line).

The net effect method performs suboptimally also in this case by overestimating the time in hypoglycemia: when the hypotreatment is introduced in the UVA/Padova T1D simulator the duration of the hypoglycemic event is 21 min, while the time spent in hypoglycemia predicted by the net effect method is 67 min. This means, for instance, that the hypotreatment seems to be effective to limit the time spent in hypoglycemia by the patient, while the indication given by the net effect is the opposite.

In line with the other three case studies, also here the net effect signal estimated from the IG profile obtained by the UVA/Padova T1D simulator after the addition of the hypotreatment (Figure 2.5C, red dashed line) presents significant differences compared to the original net effect (black solid line) both before and after the time of the hypotreatment.





**Figure 2.5:** Case study 4 (addition of hypotreatments), virtual subject #4. A) IG data (top), insulin data (middle) and estimated net effect (bottom) in a time frame of interest. B) IG profile predicted by the net effect method when a 15-g hypotreatment is added after IG crosses the hypoglycemic threshold (black solid line) and IG profile obtained in the UVA/Padova simulator when the same hypotreatment is introduced (red dashed line). C) Original net effect with addition of a 15-g hypotreatment at 09:00 (black solid line) and net effect re-estimated after the same hypotreatment is added in the UVA/Padova simulator (red dashed line).

## 2.6 Discussion, open problems and possible solutions

The net effect method was applied to data simulated using the UVA/Padova T1D simulator to test its ability to correctly predict the IG concentration that would result from real-life therapy modifications and, hence, determine the domain of validity of the method. Specifically, four case studies were investigated: basal insulin modifications, changes of pre-existing boluses, addition of new boluses and addition of new hypotreatments.

First, we noticed that the net effect signals (Figures 2.2A, 2.3A, 2.4A and 2.4A, bottom panels) are difficult to interpret, e.g. they can take even negative values. Indeed, the net effect signal reflects physiological perturbations related to meals and other oscillations deriving from components of glucose variability not considered in the core linearized and discretized time-invariant model employed. The comparison with the reference provided by the UVA/Padova T1D simulator showed that the net effect method is able to reproduce quite ac-

curately only the effect on IG concentration due to small adjustments of basal insulin (e.g. +10%, +20% or -10%). However, when larger adjustments of basal insulin are performed (e.g. +50% or -20% and -50%) or boluses and hypotreatments are changed, the estimation of the IG profile by the net effect method is significantly different from that obtained by the UVA/Padova T1D simulator. The discrepancies between the two IG profiles can be so important that inaccurate inferences on the modified insulin therapies may occur.

The suboptimal behavior of the net effect method is caused by the many simplifications introduced in the patient model, such as the model linearization and absence of inter- and intra-subject variability of physiological parameters, and by the unrealistic assumption of independence between net effect and insulin therapy (see discrepancies observed in Figures 2.2C, Fig. 2.2E, Fig. 2.3C, Fig. 2.4C and Fig. 2.5C between the original net effect and the one re-estimated after introducing the therapy modifications in the UVA/Padova T1D simulator).

Another limiting aspect of the net effect method is the fact that it works retrospectively on real data. Therefore, when testing the effect of a certain therapy modification, the net effect method does not allow to modify the subsequent treatment decisions according to the new predicted IG profile, as a real subject would do in reality.

In conclusion, the domain of validity of the net effect method seems to be limited to small variations of basal insulin, while in all the other scenarios, i.e. larger adjustments of basal insulin (e.g. +50% and -50%) or changes of pre-existing boluses, addition of new boluses and addition of new hypotreatments, the net effect is providing inaccurate results. As a consequence, the net effect method is not appropriate to test insulin treatment scenarios for the manual control of glycemia, e.g. the nonadjunctive use of CGM sensors, but more sophisticated simulation techniques need to be developed.

In particular, we believe an appropriate model for the in silico testing of insulin treatments should: i) include a non-linearized model of glucose-insulin dynamics accounting for the inter-individual variability, by patient-specific parameters, and the intra-individual variability of insulin sensitivity, ii) reliably describe the variability of the measurement error of glucose monitoring devices, iii) allow a real-time update of patient's therapeutic decisions during the assessment according to well defined behavioral rules. These three important requirements will be considered by our novel simulation approach based on the T1D decision-making model, which is presented in the next chapter.

# Chapter 3

## Development of a T1D patient decision-making model

### 3.1 Overview of model development

The T1D decision-making (T1D-DM) model is a mathematical model of T1D patients making treatment decisions, like insulin dosing or CHO intake, based on SMBG and/or CGM measurements. The model receives in input the pattern of meals in the specific scenario the user need to simulate and patient-specific parameters describing patient's physiology and behavior when dealing with glucose monitoring and making treatment decisions. The model output is the patient's BG concentration that is simulated every minute, thus resulting in a quasi-continuous-time profile.

The T1D-DM model has been constructed by interconnecting four main components in the feedback scheme of Figure 3.1. The first component (block A in Figure 3.1) is the UVA/Padova T1D simulator, which receives in input the CHO intake and subcutaneous infusion of insulin and generates in output the BG and IG concentration profiles of a virtual subject defined by a specific set of physiological parameters. The second component (block B in Figure 3.1) is a model of the device used for glucose monitoring that, starting from the BG and the IG concentration profiles generated by the UVA/Padova T1D simulator, simulates SMBG and CGM measurements by using models of the SMBG and CGM measurement error. The third component (block C in Figure 3.1) mathematically describes the patient's behavior in making treatment decisions based on glucose monitoring by implementing the decision rules normally used by T1D patients for the calculation of insulin boluses and tuning of CHO intake.

Finally, the last component (block D in Figure 3.1) is a model of the infusion of insulin via insulin pump which adds to the insulin boluses returned by the patient's behavior model the basal insulin dose, delivered at constant infusion rate.

While the UVA/Padova T1D simulator and the insulin pump model were previously developed by University of Padova in collaboration with University of Virginia, the models of device for glucose monitoring and patient's behavior and treatment decisions are developed in this thesis as described in the following sections of this chapter. In particular, the model of SMBG and CGM measurements implemented in the device for glucose monitoring model are described in Section 3.2 and Section 3.3, respectively. The model of the patient's behavior and treatment decisions is illustrated in Section 3.4.

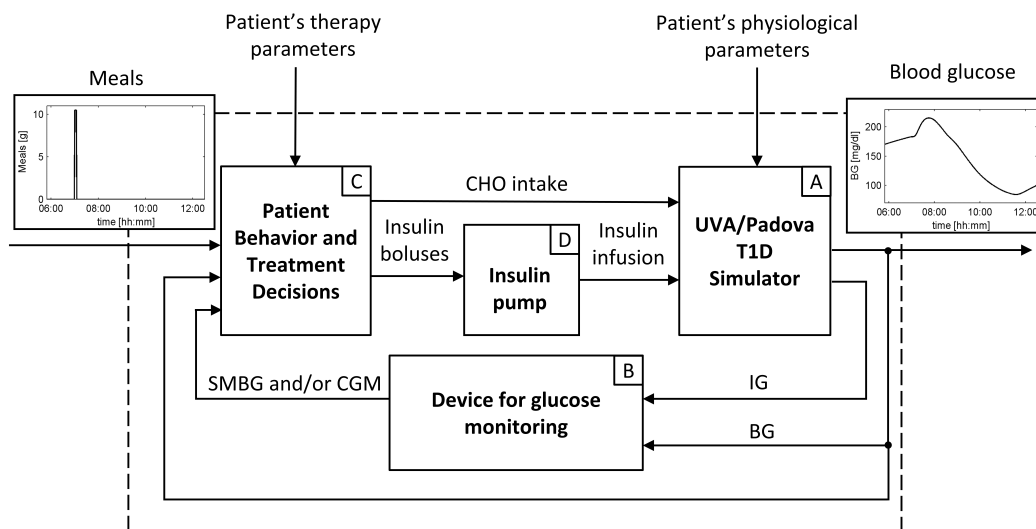


Figure 3.1: Schematic representation of the T1D-DM model

## 3.2 Development of the SMBG error model

In order to simulate SMBG measurements, a mathematical model of the SMBG measurement error is required. Some examples of models of the statistical distribution of the SMBG measurement error can be found in the literature. These models normally assume i) uncorrelation between consecutive SMBG (at variance with CGM, whose quasi-continuous nature allowed descriptions of the measurement error autocorrelation by using 1<sup>st</sup> or 2<sup>nd</sup> order autoregressive models [69] [70] [71] [72]) and ii) the error to be proportional to the glucose

concentration (i.e. relative) all over the entire glucose range and described by a Gaussian function [73] [74] [75]. However, to the best of our knowledge, this simple model has never been validated and several evidences in the literature suggest that this particular model is suboptimal.

While the assumption of uncorrelation between samples is reasonable because of the sparseness of SMBG measurements (usually collected 4-5 times per day), the main critical point concerns the use of a single canonical probability density function (PDF) valid over the entire BG range. As a matter of fact, the scatter plots reported in [76] [77] [78] show that neither absolute nor relative error of SMBG data presents constant mean and standard deviation (SD) over the entire BG range, suggesting that a multi-zone model, i.e. a function with different parameters in different BG ranges, is properly needed to describe SMBG error distribution.

Attempts to deal with this issue include the work by Breton and Kovatchev [79], where a Gaussian model with zero mean and SD dependent on the BG value was adopted, and that by Karon et al. [80], where SMBG measurements were simulated by two different strategies (the first exploiting the Gaussian distribution model with different values of mean and SD, the second based on a Gaussian distribution model whose mean is sampled from a pool of high-accuracy reference measurements) which were subsequently empirically validated [81]. In [82] a bivariate kernel density model of SMBG measurements given reference values was derived for the Abbott Optium Xceed (Abbott Diabetes Care, Alameda, CA) device.

Another critical point concerns the symmetry assumption of SMBG measurement error distribution made with the Gaussian model. The histograms reported in [83] show that some SMBG devices present an asymmetric error distribution, calling for the use of models of the PDF allowing for non-zero skewness.

Here, a new methodology, described in detail in Subsection 3.2.3, is proposed to derive a model of the PDF of SMBG measurement error, in which the variability of SMBG error characteristics with BG is dealt with by the use of multiple PDF models in different zones of the glucose range. Moreover, the asymmetry of SMBG error data distribution is taken into account by the use of PDF models allowing for non-zero skewness. The method is tested on two databases, presented in Subsection 3.2.1, that comprise One Touch Ultra 2 (OTU2; Lifescan Inc., Milpitas, CA) and Bayer Contour Next USB (BCN; Bayer HealthCare LLC, Diabetes Care, Whippany, NJ) data and reference BG sam-

ples measured by a gold standard laboratory instrument. Results of the new methodology are reported in Subsection 3.2.4 and compared to the use of literature models. Finally, in Subsection 3.2.5 we illustrate how the models derived by this methodology can be used in the T1D-DM model to simulate SMBG measurements<sup>1</sup>.

#### **3.2.1 Databases**

##### **OTU2 database**

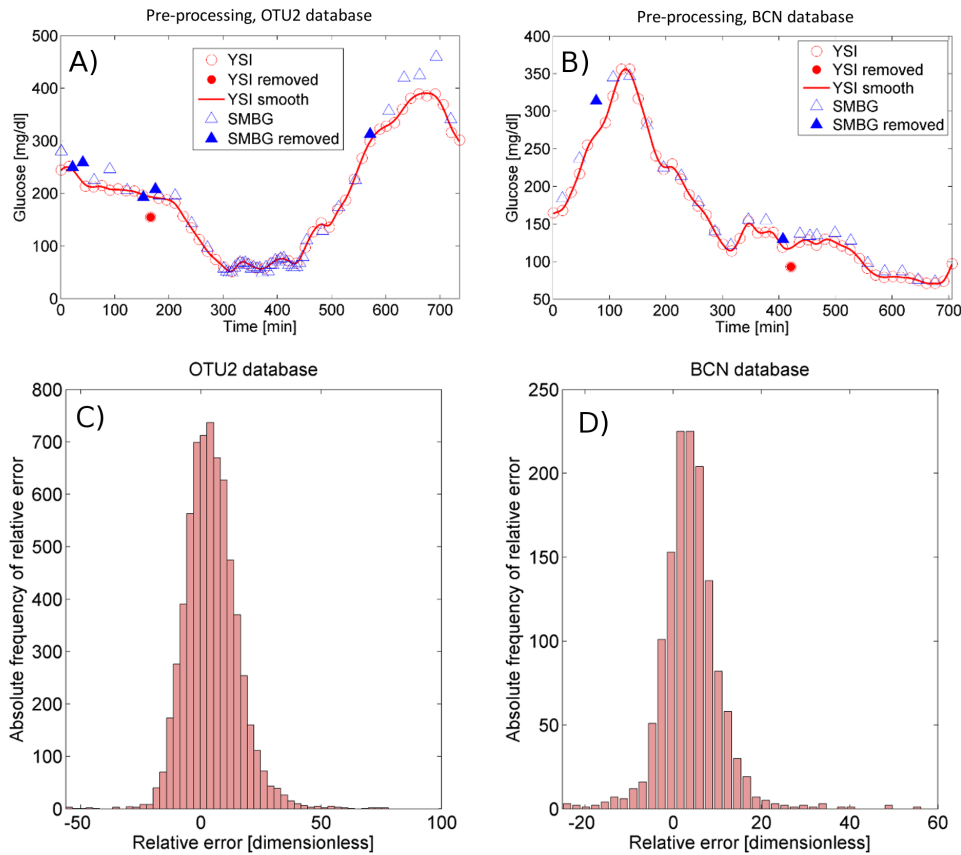
The OTU2 database was obtained from a larger database collected in a multicenter study conducted in 2011 (the original specific aim was to assess the accuracy of a CGM sensor) [85]. For our purpose it is relevant to report, in particular, that 72 subjects (60 with T1D, 12 with T2D) participated in three clinical sessions in which SMBG measurements were collected twice per hour for a 12-hour period by the OTU2. A total of 6906 SMBG samples were collected (on average 95 samples per subject). In parallel to SMBG, highly accurate reference BG measurements were obtained every 15 minutes by using a high accuracy and precision laboratory equipment, the Yellow Springs Instrument (YSI; YSI Inc., Yellow Springs, OH). During the clinical sessions, CHO and insulin administrations were manipulated in order to make patients' BG concentration vary in a wide range, as visible in Figure 3.2, panel A where the SMBG and the YSI samples collected in a representative subject are represented by blue triangles and red circles, respectively.

##### **BCN database**

The BCN database was extracted from a larger database collected in a multicenter study conducted in 2014 (the original specific aim was to assess the accuracy of a CGM sensor) [39]. For our purpose, the study involved 51 subjects (44 with T1D, 7 with T2D) who participated in a 12-hour clinical session in which BG concentration was monitored every 30 minutes by an SMBG device, the BCN, and every 15 minutes by YSI. A total of 1410 SMBG measurements were collected (on average 27 per subject). Similarly, to the OTU2 database, diet and insulin therapy were manipulated in order to make BG vary in a wide range. Figure 3.2, panel B shows a representative dataset.

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<sup>1</sup>This section is part of the papers [68] and [84].



**Figure 3.2:** Panels A and B illustrate the pre-processing performed on a 12-hour YSI sequence of OTU2 and BCN database, respectively. The continuous line represents the quasi continuous-time smoothed profile obtained from YSI measurements (empty circles) after removing inaccurate samples (full circles). Triangles represent all available SMBG measurements. SMBG samples within YSI gaps are removed from the analysis (full triangles). Histograms (absolute frequencies) of the SMBG relative error in OTU2 and BCN database are reported in panels C and D, respectively.

### 3.2.2 Data pre-processing

To correctly evaluate realizations of SMBG measurement error, each SMBG sample need to be matched to a corresponding gold standard measurement, i.e. ideally a YSI value collected at the same time. Unfortunately, since both the OTU2 and BCN database were originally collected to assess CGM sensors, thus with a scope different from the present work, here SMBG and YSI measurements are not necessarily temporally aligned. Consequently, the two measurements cannot be directly compared. To circumvent this problem, data are pre-processed as follows.

First, YSI measurements considered not compatible with the BG pattern are removed from the analysis (see e.g. the full red circle in Figure 3.2, panels A

and B). In particular, we adopt an empirical rule according to which the  $j^{\text{th}}$  YSI sample (empty red circles in Figure 3.2, panels A and B),  $YSI_j$  is removed if  $YSI_j < YSI_{j-1} - \Delta_1$ ,  $YSI_j < YSI_{j+1} - \Delta_2$  and  $YSI_{j+1} > YSI_{j-1} - \Delta_3$ , or  $YSI_j > YSI_{j-1} + \Delta_1$ ,  $YSI_j > YSI_{j+1} + \Delta_2$  and  $YSI_{j+1} < YSI_{j-1} + \Delta_3$ . Different values for  $\Delta_1$ ,  $\Delta_2$  and  $\Delta_3$  are used in different parts of the BG range: when  $YSI_j \leq 100$  mg/dl,  $\Delta_1 = \Delta_2 = 15$  mg/dl and  $\Delta_3 = 5$  mg/dl; when  $YSI_j > 100$  mg/dl,  $\Delta_1 = 15\% \cdot YSI_{j-1}$ ,  $\Delta_2 = 15\% \cdot YSI_{j+1}$  and  $\Delta_3 = 5$  mg/dl.

Then, from each 12-hour YSI sequence, a YSI smoothed profile (red line in Figure 3.2, panels A and B) is reconstructed on a temporal grid with 1-min step by the nonparametric approach described in De Nicolao et al. [86], assuming measurement error to be uncorrelated, with zero-mean and with constant coefficient of variation equal to 2%, according to specifications of the YSI glucose analyzer [87]. Notably, the use of a maximum-likelihood (ML) smoothing criterion in this method limits the risk of introducing distortion/bias in the profile reconstructed from the YSI samples (as witnessed by the representative examples of Figure 3.2, panels A and B).

Each SMBG sample (empty blue triangles in Figure 3.2, panels A and B) is then matched to the nearest (in time) sample of the YSI smoothed profile. In this way, the matching error, i.e. the temporal distance between the SMBG sample and the reference sample, is no greater than 30 sec. Note that when one or more YSI samples are missing, and thus two consecutive YSI measurements are 30 min or more far from each other, the reconstruction of the YSI smoothed profile over the gaps is considered not reliable and SMBG measurements falling inside these gaps are excluded from the analysis (full blue triangles in Figure 3.2, panels A and B). As a result, 4.37% and 3.05% of available SMBG measurements are excluded from the analysis, respectively for OTU2 and BCN database. Specifically, for OTU2 and BCN respectively, 20 and 4 SMBG samples are excluded in severe hypoglycemia ( $BG \leq 50$  mg/dl), 13 and 4 in mid hypoglycemia ( $50 < BG \leq 70$  mg/dl), 144 and 19 in euglycemia ( $70$  mg/dl  $< BG < 180$  mg/dl), 66 and 8 in mid hyperglycemia ( $180$  mg/dl  $\leq BG < 250$  mg/dl) and 59 and 8 in severe hyperglycemia ( $BG \geq 250$  mg/dl).

At the end of the pre-processing step, the SMBG samples selected for the analysis result well distributed in the glyceic range, with a number of samples in hypoglycemia and hyperglycemia sufficiently high to allow an accurate description of SMBG measurement error also in these extreme conditions. In particular, the SMBG samples selected for the analysis are distributed in the glyceic range as follows: 356 (OTU2) and 123 (BCN) samples are in se-



vere hypoglycemia, 930 (OTU2) and 159 (BCN) in mid hypoglycemia, 2958 (OTU2) and 463 (BCN) in euglycemia, 1479 (OTU2) and 399 (BCN) in mid hyperglycemia, 881 (OTU2) and 222 (BCN) in severe hyperglycemia.

The obtained SMBG-YSI matched pairs are used to calculate SMBG absolute and relative errors. In the bottom panels of Figure 3.2, the histogram of SMBG relative error is reported for OTU2 (panel C) and BCN (panel D) databases. Both meters present a unimodal, positively biased and skewed distribution. The BCN shows a significantly lower error variability than the OTU2. Note that the histogram of BCN error presents some outliers, i.e. high values in the tails (e.g. values lower than -10 and greater than 30 with significantly greater than zero absolute frequency), which suggests that an efficient way to describe the PDF of the error in this database should be modeling non-outlier central part of the distribution separately.

### 3.2.3 Method for modeling the SMBG error PDF

#### Absolute and relative error computation

For each SMBG sample  $x_i$ ,  $i = 1, \dots, n_{tot}$  ( $n_{tot}$  indicating the total number of SMBG measurements selected for the analysis in the pre-processing step) both absolute and relative (in percentage) errors are computed using the reference values  $r_i$ ,  $i = 1, \dots, n_{tot}$ :

$$e_i^{abs} = x_i - r_i, e_i^{rel} = \frac{x_i - r_i}{r_i} \cdot 100 \quad (3.1)$$

Then, error data are divided into two parts. The first part, with cardinality  $n_{training}$ , is used as training set to derive the model of SMBG error PDF. The second part of the database, with cardinality  $n_{test}$ , is used as test set to validate the model.

#### SMBG model derivation (training set)

Absolute and relative errors of training set can be displayed in a scatter plot vs reference glucose in order to visually assess if the characteristics of error distribution (e.g. mean and dispersion) significantly vary within the reference glucose range. Changes in the dispersion of absolute and relative errors with reference glucose are quantified by analyzing the sample SD. In particular, first a uniform grid  $g_i$   $i = 1, \dots, n_g$ , where  $n_g$  is the number of points in the grid, is defined in the glucose range with step  $S$  (e.g.  $S=5$  mg/dl). Then, intervals

centered at points  $g_i$   $i = 1, \dots, n_g$  with half-width  $L$  (e.g.  $L=15$  mg/dl) are defined. Finally, the sample SD of absolute and relative error samples in each interval  $g_i \pm L$  is calculated, which approximates the SD of error (absolute or relative) at the glucose point  $g_i$ . The plot of sample SD values versus glucose points  $g_i$   $i = 1, \dots, n_g$  allows to analyze how the SD of error (absolute or relative) varies in the glucose range and identify zones of the glucose range in which either absolute or relative error presents approximately a constant SD distribution.

In each constant-SD zone, the distribution of the error (absolute or relative) in the training set, here represented by the continuous random variable  $Y$ , is fitted by ML using a certain PDF model. In particular, first, a Lilliefors test of normality is applied to error (absolute or relative) with significance level  $\rho$ . Then, if the Lilliefors test cannot reject the normality hypothesis, the Gaussian PDF model is used. Conversely, if the Lilliefors test rejects the normality hypothesis, the skew-normal PDF model is employed. The skew-normal PDF [88] is described by the following equation:

$$f_Y(y) = \frac{2}{\omega} \cdot \phi\left(\frac{y - \xi}{\omega}\right) \cdot \Phi\left(\alpha \cdot \frac{y - \xi}{\omega}\right) \quad (3.2)$$

where  $\phi(\cdot)$  and  $\Phi(\cdot)$  are, respectively, the PDF and the cumulative distribution function of the standard Gaussian random variable, while the scalars  $\xi$ ,  $\omega$  and  $\alpha$  are, respectively, the location, scale and skewness parameters of the skew-normal PDF. The skew-normal PDF model allows to describe both positively ( $\alpha > 0$ ) or negatively ( $\alpha < 0$ ) skewed PDF. When  $\alpha$  is equal to zero, the skew-normal PDF becomes the Gaussian PDF.

Let us define  $\mathbf{y} = [y_1, \dots, y_n]^T$  as the vector of  $n$  samples of the error (absolute or relative), i.e.  $n$  realizations of  $Y$ , falling within one of the identified constant-SD glucose zones. Then, the parameters of the skew-normal PDF that best reproduces the distribution of data in  $\mathbf{y}$  are estimated by maximizing the log-likelihood function:

$$l(\xi, \omega, \alpha) = -n \cdot \log(\omega) - \frac{1}{2} \mathbf{z}^T \mathbf{z} - \sum_{i=1}^n \log(2\Phi(\alpha z_i)) \quad (3.3)$$

where  $z_i$ ,  $i = 1, \dots, n$  are the  $n$  components of  $\mathbf{z} = (\mathbf{y} - \xi \cdot \mathbf{1}_n) / \omega$ , with  $\mathbf{1}_n$  representing the  $n \times 1$  unitary vector.

If the error (absolute or relative) distribution does not present a significant number of left or right outliers, i.e. values in the left or right tails of the error

histogram with significantly greater than zero frequency, the model of eq. 3.2 should be sufficiently accurate to describe the error PDF. On the contrary, if the SMBG error presents non-negligible left or right outliers, it is more convenient to use a composite model in which the distributions of outliers and non-outliers are described by different PDF models. Here, we propose a model obtained combining the skew-normal PDF and the exponential PDF. To derive such a model, two thresholds must be identified,  $T_1$  and  $T_2$ , in order to separate the non-outlier region,  $T_1 \leq y \leq T_2$ , from the left outlier region,  $y < T_1$ , and the right outlier region,  $y > T_2$ . Let us define a discrete random variable  $V$  that can assume three values: 0, with probability  $p_V(0)$ , when the SMBG error  $y$  is not an outlier; 1, with probability  $p_V(1)$ , when  $y$  is a left outlier; 2, with probability  $p_V(2)$ , when  $y$  is a right outlier. Then, the model defined for the PDF of  $Y$ ,  $f_Y(y)$ , is conditioned by the value of  $V$ . In particular, when  $V = 0$  the conditional PDF of  $Y$  given  $V$ ,  $f_{Y|V}(y|0)$ , is the skew-normal PDF model of eq. 3.2, whose parameters are identified by ML as described above. When  $V = 1$ ,  $f_{Y|V}(y|1)$  is described by an exponential PDF model reversed with respect to the ordinate axis and shifted left of  $T_1$ :

$$f_{Y|V}(y|1) = \begin{cases} \lambda_1 \cdot e^{\lambda_1(y+T_1)} & y \leq T_1 \\ 0 & y > T_1 \end{cases} \quad (3.4)$$

When  $V = 2$ ,  $f_{Y|V}(y|2)$  is described by an exponential PDF model shifted right of  $T_2$ :

$$f_{Y|V} = \begin{cases} \lambda_2 \cdot e^{-\lambda_2(y-T_2)} & y \geq T_2 \\ 0 & y < T_2 \end{cases} \quad (3.5)$$

Parameters  $\lambda_1$  and  $\lambda_2$  are estimated by ML by inverting the sample mean of left or right outliers properly shifted and reversed. Finally, the PDF of  $Y$  is obtained as:

$$f_Y(y) = f_{Y|V}(y|0) \cdot p_V(0) + f_{Y|V}(y|1) \cdot p_V(1) + f_{Y|V}(y|2) \cdot p_V(2) \quad (3.6)$$

where the values  $p_V(1)$  and  $p_V(2)$  are estimated by dividing the number of observed left or right outliers for the total number of observed error values in the specific constant-SD zone, while  $p_V(0)$  is found as:

$$p_V(0) = 1 - p_V(1) - p_V(2) \quad (3.7)$$

**Model validation (test set)**

The model identified in each constant-SD zone for absolute or relative error is validated by two-sample Kolmogorov-Smirnov (KS) and Cramér-von Mises (CvM) goodness-of-fit tests. For such a purpose, M random samples are simulated by drawing  $n_{test}$  values from the model identified in each zone, being  $n_{test}$  the cardinality of the test set. In particular, SMBG error values are drawn from the exponential PDF of left outliers with probability  $p_V(1)$ , from the exponential PDF of right outliers with probability  $p_V(2)$  and from the skew-normal PDF of non-outliers with probability  $p_V(0)$ . If the model does not include outliers' description, then  $p_V(1)=p_V(2)=0$  and all the  $n_{test}$  SMBG error values are drawn from the skew-normal PDF.

In order to sample a random number  $y$  from a skew-normal PDF, with generic parameters  $\xi$ ,  $\omega$  and  $\alpha$ , a three step method is provided by Azzalini [88]. First, two values  $u_0$  and  $u_1$  having marginal PDF  $N(0, 1)$  and correlation  $\delta = \alpha / \sqrt{1 + \alpha^2}$  are generated by sampling  $u_0$  and  $r$  from independent  $N(0, 1)$  random variables and defining  $u_1 = \delta \cdot u_0 + \sqrt{1 - \delta^2} \cdot r$ . Then, in the second step, a random number  $z$  sampled from a skew-normal PDF with parameters  $\xi=0$ ,  $\omega=1$  and  $\alpha \neq 0$  is obtained as:

$$z = \begin{cases} u_1 & \text{if } u_0 \geq 0 \\ -u_1 & \text{otherwise} \end{cases} \quad (3.8)$$

As third step, the realization sampled from the skew-normal PDF with parameters  $\xi$ ,  $\omega$  and  $\alpha$  is finally obtained setting  $y = \xi + \omega \cdot z$ .

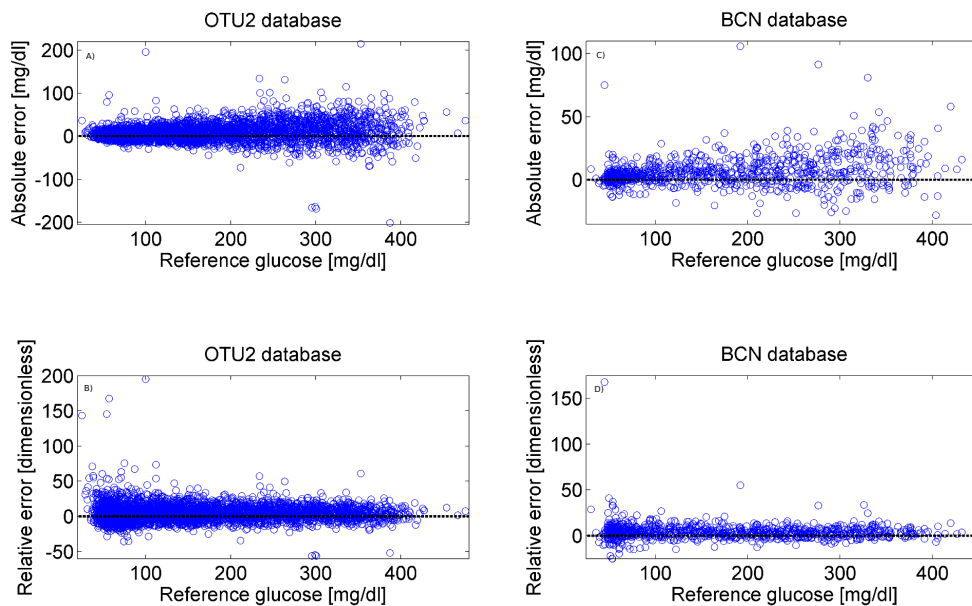
Each of the M simulated samples is compared to the test set by performing, with significance level  $\beta$ , the two-sample KS and CvM tests, i.e. nonparametric tests for the null hypothesis  $H_0$ ="the two samples are drawn from the same distribution" based on a measure of distance between the empirical distribution functions of the two samples. The empirical distribution function,  $\hat{F}$ , of a generic random sample,  $Y_j$   $j = 1, \dots, n$ , is defined as  $\hat{F}(y) = \frac{1}{n} \cdot \sum_{j=1}^n I_{[-\infty, y]}(Y_j)$ , where  $I_{[-\infty, y]}$  is 1 if  $Y_j \leq y$  and 0 otherwise, and represents an estimate of the cumulative distribution function. The percentage of simulated samples for which KS and CvM tests reject  $H_0$  is calculated, that is expected to be small if the identified model of SMBG error PDF performs well.

This validation is performed N times (e.g. N=100), to avoid that the results of the validation can be dependent on the particular realization of random samples. Therefore, KS and CvM tests are performed on N groups of

M random samples and the average, minimum and maximum values of the percentage of samples for which  $H_0$  is rejected are calculated.

### 3.2.4 Results

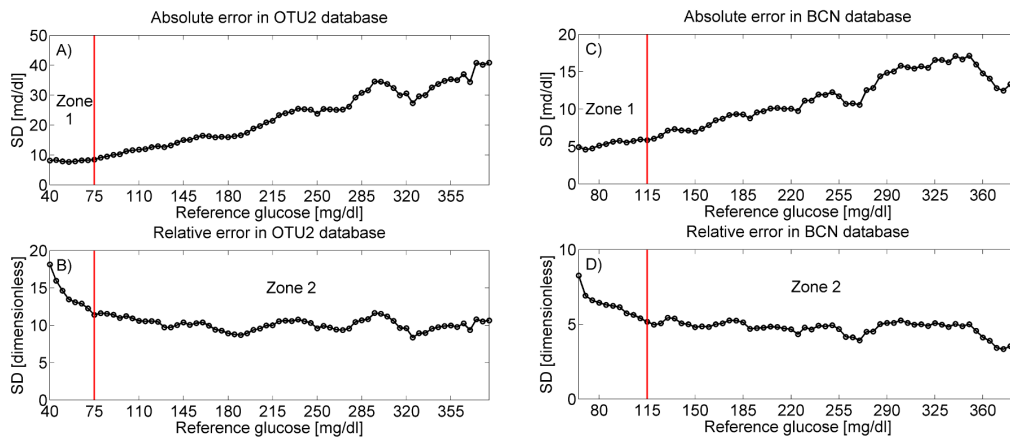
For each SMBG sample, absolute and relative errors have been computed as described by eq. 3.1. Then, the whole set of SMBG error data, with cardinality  $n_{tot}$ , was divided into a training set with cardinality  $n_{training}=2/3 \cdot n_{tot}$  and a test set with cardinality  $n_{test}=1/3 \cdot n_{tot}$ . The scatter plots of Figure 3.3 report, vs reference glucose values, absolute and relative errors in the training set, which result positively biased and with non-uniform dispersion over the entire reference glucose range for both OTU2 (panels A and B respectively) and BCN (panels C and D respectively).



**Figure 3.3:** Scatter plots of absolute and relative error vs reference glucose for the training set of OTU2 (panels A and B respectively) and BCN (panels C and D respectively) database.

In Figure 3.4 the SD of absolute (top panels) and relative (bottom panels) error in the training set is displayed for increasing glucose values. In particular, the sample SD of absolute and relative error in the training set was computed on glucose intervals of half-width  $L=15$  mg/dl centered at the points of a glucose grid with uniform step  $S=5$  mg/dl. This representation allows to analyze how the SD of absolute and relative error varies in the glucose range. For the OTU2, the SD of absolute error (panel A) is approximately constant for glucose

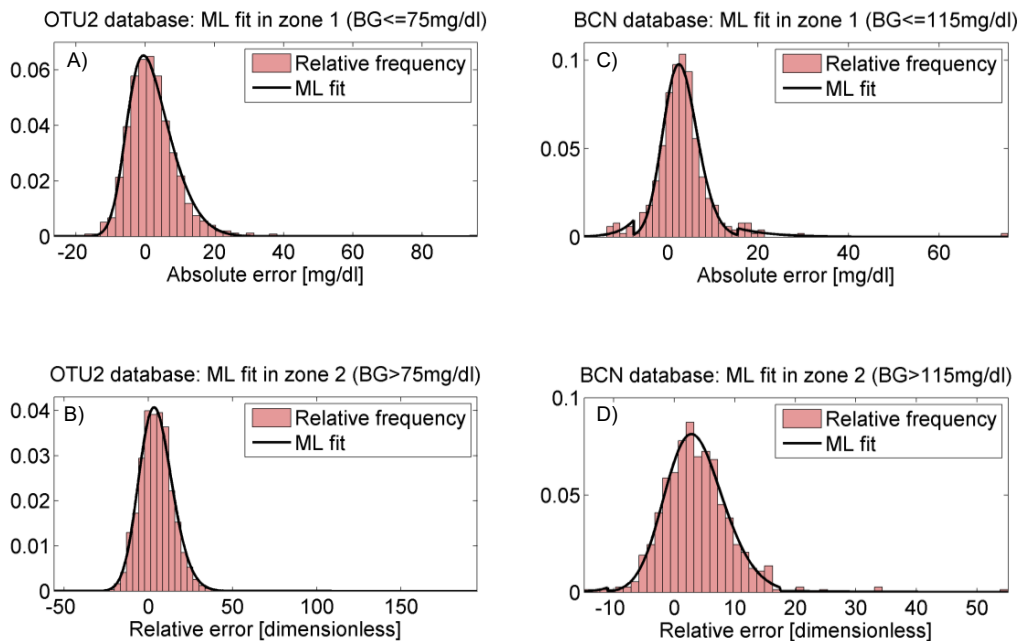
values lower than 75 mg/dl, while an increasing trend is observed for glucose values greater than 75 mg/dl; conversely, the SD of relative error (panel B) presents a decreasing trend for glucose values lower than 75 mg/dl, while appearing approximately constant for glucose values greater than 75 mg/dl. Therefore, two constant-SD zones were identified: zone 1, i.e.  $BG \leq 75$  mg/dl, with constant-SD absolute error; zone 2, i.e.  $BG > 75$  mg/dl, with constant-SD relative error. For BCN, the SD of absolute and relative error in the training set is reported respectively in panel C and D. Again, two zones are identified: zone 1, i.e.  $BG \leq 115$  mg/dl, with constant-SD absolute error; zone 2, i.e.  $BG > 115$  mg/dl, with constant-SD relative error. Note that, for both the OTU2 and the BCN database, the absolute or relative error in zone 1 and 2 is not correlated with the reference BG, as visible in the scatter plots of Figure 3.3.



**Figure 3.4:** Absolute and relative error SD vs reference glucose for the training set of OTU2 (panels A and B respectively) and BCN (panels C and D respectively) database. The thresholds to separate zone 1 from zone 2 (75 mg/dl in OTU2 database, 115 mg/dl in BCN) are evidenced by vertical red lines.

The histograms of Figure 3.5 represent the relative frequency of absolute error in zone 1 (top panels) and relative error in zone 2 (bottom panels), calculated in the training set of OTU2 (left panels) and BCN (right panels) database. For both databases, the Lilliefors test rejected the normality hypothesis for the absolute error in zone 1 and the relative error in zone 2, using as significance level  $\rho=5\%$  ( $p$ -value=0.001). This result suggests that the Gaussian PDF is not a proper model to accurately describe the observed SMBG error distribution. For OTU2, since the error distributions in zone 1 and 2 do not show significant outliers, a simple skew-normal PDF model (black line) was fitted by ML both in zone 1 (panel A) and 2 (panel B). The values of location, scale and skewness parameters identified in zone 1 and 2 are reported in Table 3.1, while mean

and SD are reported in Table 3.2. In particular, both error models present a significant positive mean (2.01 mg/dl in zone 1, 4.73% in zone 2) and positive skewness ( $\alpha=2.72$  in zone 1 and  $\alpha=1.41$  in zone 2). For BCN, some outliers are visible in the error distribution of training set data both in zone 1 (panel C) and 2 (panel D). In particular, in zone 1 values lower than -7.5 mg/dl were considered left outliers and values greater than 15.5 mg/dl were considered right outliers, while in zone 2 we considered left outliers values under -11%, right outliers values over 17.5%. Left and right outliers' distributions were fitted by the exponential PDF models of eqs. 3.4 and 3.5, while non-outliers' distribution was fitted by the skew-normal PDF of eq. 3.2. The parameters of the identified models are reported in Table 3.1 (last two rows), while mean and SD of the models are reported in Table 3.2 (last two rows). Panels C and D of Figure 3.5 show how the composite PDF obtained by eq. 3.6 (black line) well approximates the error distribution of training set data respectively in zone 1 and 2.



**Figure 3.5:** Panels A and B report the ML fit of the skew-normal PDF (black line) against histograms of, respectively, absolute and relative error (red bars) in zone 1 and 2 of the training set of OTU2 database. Panel C and D report the ML fit of the PDF model obtained as combination of the skew-normal and the exponential PDF (black line) against histograms of, respectively, absolute and relative error (red bars) in zone 1 and 2 of the training set of BCN database.

For validation purposes, the identified PDF model was used to generate,

### 3 Development of a T1D patient decision-making model

**Table 3.1:** Model parameters identified in zone 1 and 2 of OTU2 and BCN training set data.

Database	Zone	Non-outliers			Left outliers			Right outliers		
		$\xi$	$\omega$	$\alpha$	$\lambda_1$	$T_1$	$P_V(1)$	$\lambda_2$	$T_2$	$P_V(2)$
OTU2	1	-5.37	9.86	2.72	-	-	-	-	-	-
	2	-3.83	13.17	1.41	-	-	-	-	-	-
BCN	1	-0.23	5.05	1.36	0.30	-7.5	0.032	0.13	15.5	0.038
	2	-0.71	6.54	1.46	0.46	-11.0	0.005	0.06	17.5	0.011

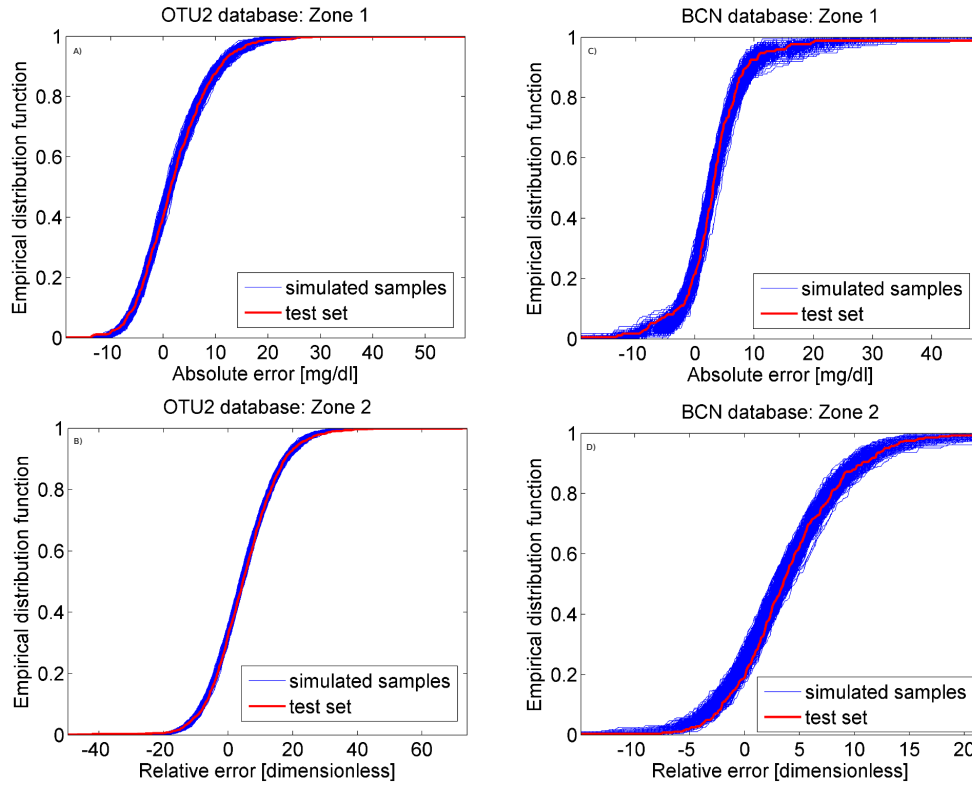
**Table 3.2:** Mean and SD of identified models in zone 1 and 2 of OTU2 and BCN training set data.

Database	Zone	Mean	SD
OTU2	1	2.01	6.54
	2	4.73%	10.00%
BCN	1	3.33	4.03
	2	3.82%	5.26%

for each zone,  $M=500$  random samples having cardinality equal to the number of error data available in the test set for the same glucose zone. As visible in Figure 3.6, the empirical distribution functions of random samples simulated by the identified PDF model (blue solid lines) are very similar to the empirical distribution function calculated for test set data (red solid line) both in zone 1 and 2 of OTU2 (panels A and B, respectively) and BCN database (panels C and D, respectively). Two-sample KS and CvM tests are performed with significance level  $\beta=5\%$  on  $N=100$  groups each containing  $M=500$  simulated random samples. In OTU2 database, on average, the KS test rejects  $H_0$  for the 0.53% (0.00%-1.40%) of zone 1 simulated samples and the 1.94% (0.40%-4.6%) of zone 2 simulated samples, while the CvM test rejects  $H_0$  for the 0.94% (0.00%-2.20%) of zone 1 simulated samples and the 4.15% (1.40%-6.60%) of zone 2 simulated samples. In BCN database, on average, the KS test rejects  $H_0$  for the 0.75% (0.00%-1.80%) and 1.43% (0.40%-2.60%) of zone 1 and 2 simulated samples, respectively, while the CvM test rejects  $H_0$  for the 0.95% (0.20%-2.20%) and 2.56% (1.40%-4.00%) of zone 1 and 2 simulated samples, respectively. Since, for almost all the simulated random samples,  $H_0$  cannot be rejected, we can conclude that the two-zone skew-normal models derived for OTU2 and BCN accurately reproduce the SMBG error distribution observed in the test set.

Two-sample KS and CvM tests also demonstrate that the identified two-zone skew-normal models outperform simpler Gaussian models like the single-





**Figure 3.6:** The empirical distribution function of simulated random samples (blue line) and test set data (red line) is reported for zone 1 and 2 of OTU2 database (panels A and B respectively) and BCN database (panels C and D respectively).

zone Gaussian model, previously used in the literature to describe SMBG relative error distribution, and the two-zone Gaussian model in which a Gaussian (instead of skew-normal and exponential) PDF is used to describe absolute error in zone 1 and relative error in zone 2. Indeed, when the single-zone Gaussian model is used, the two tests reject  $H_0$  for almost the 100% of simulated samples (on average, the KS test rejects  $H_0$  for the 99.44% of OTU2 simulated samples and 100.00% of BCN simulated samples, while the CvM test rejects  $H_0$  for the 99.85% of OTU2 simulated samples and 100.00% of BCN simulated samples). When the two-zone Gaussian model is used,  $H_0$  is rejected for more than 50% of zone 1 simulated samples (on average: 49.80%, for KS, and 70.00%, for CvM, in OTU2 database; 59.21%, for KS, and 81.63%, for CvM, in BCN database) and more than 10% of zone 2 simulated samples (on average: 27.06%, for KS, and 24.03%, for CvM, in OTU2 database; 14.20%, for KS, and 20.67%, for CvM, in BCN database).

Remark 1. The sparseness of SMBG data (4-5 samples per day) suggests assuming that measurement errors can be considered uncorrelated. To sup-

port reliability of this hypothesis, we evaluated, a posteriori, the autocorrelation function for each SMBG error sequence (both absolute and relative) corresponding to a specific subject. Results show that, for both absolute and relative error, in both OTU2 and BCN databases, the coefficients of the mean normalized autocorrelation function never overtake 0.5, confirming that uncorrelation of errors seems a reasonable assumption. Of course, a more detailed and precise assessment of the autocorrelation of the SMBG measurement error would require a separate study, with scope different from that of the present work and, remarkably, ad hoc data sets consisting of SMBG measurements frequently collected in parallel to high accuracy BG reference samples.

Remark 2. The threshold dividing the two constant-SD zones is 75 mg/dl for OTU2 and 115 mg/dl for BCN. These results are, not surprisingly, coherent with the requirements (in terms of accuracy) imposed to SMBG devices by the standard ISO 15197. Indeed, the 2003 standard [89] requires that 95% of the SMBG values should have an absolute error lower than 15 mg/dl for glucose concentration lower than 75 mg/dl and a relative error lower than 20% in the rest of the range, while the 2013 standard [90] requires that 95% of the SMBG values should have an absolute error lower than 15 mg/dl for glucose concentration lower than 100 mg/dl and a relative error lower than 15% in the rest of the range. In particular, the 75 mg/dl threshold we found for OTU2, which was approved by FDA in 2006, reflects the same partition defined by standard ISO 15197:2003, while the 115 mg/dl threshold we found for BCN, which was approved by FDA in 2012, is similar to the one defined by the standard ISO 15197:2013.

#### 3.2.5 Simulation of SMBG measurements in the T1D-DM model

Models of the PDF of SMBG measurement error developed by the new methodology are of straightforward application in several in silico studies of clinical interest, including the simulation of SMBG measurements in the T1D-DM model presented in this thesis. In particular, the model of either the OTU2 or the BCN measurement error PDF can be used in the device for glucose monitoring model to simulate SMBG measurements starting from the BG value returned by the UVA/Padova T1D simulator, whenever the patient's behavior and treatment decisions model requests a BG check by SMBG. Specifically, if the simulated BG value,  $BG^{sim}$ , is in the zone 1 of the SMBG error PDF model,

the SMBG absolute error,  $err^{abs}$ , is sampled from the PDF model identified in zone 1. Then, the simulated SMBG measurements,  $SMBG^{sim}$ , is obtained as follows:

$$SMBG^{sim} = err^{abs} + BG^{sim} \quad (3.9)$$

Conversely, if  $BG^{sim}$  is in zone 2, the SMBG relative error,  $err^{rel}$ , is sampled from the PDF model identified in zone 2. Then,  $SMBG^{sim}$  is obtained as follows:

$$SMBG^{sim} = err^{rel} \cdot BG^{sim} / 100 + BG^{sim} \quad (3.10)$$

### 3.3 Development of the CGM error model

In order to simulate CGM quasi continuous-time traces a model of the CGM sensor error is required. Some approaches to model the CGM sensor error were proposed in the literature. Breton and Kovatchev [69], for instance, proposed a model in which errors due to BG-to-IG kinetics are described by a first-order linear time-invariant dynamic model with fixed time-constant, calibration error by a linear first-order time-invariant function, and sensor noise by a first order autoregressive (AR) model. A second model was proposed by Lunn et al. [70] in which, at difference of model by Breton and Kovatchev, the time-constant of the model describing BG-to-IG kinetics is individualized. Another approach was developed by Facchinetti et al. [71] in which, at difference of previous methods, the time variability of sensor calibration error is coped with by the use of a linear function with time-variant parameters. This method was first designed using data collected by Dexcom 7 Plus sensor [71], and then applied to a second data set collected by Dexcom G4 PLATINUM system [72]. However, a model for the generation of CGM sensors presently on the market, e.g. the Dexcom G5 Mobile, is currently not available in the literature.

Here, the method by Facchinetti et al. is applied to data collected by the Dexcom G5 Mobile system in order to derive a model of this last generation CGM sensor, representing the state-of-art in CGM technology. In particular, data used for model identification are described in Subsection 3.3.1, details on the modeling method by Facchinetti et al. are given in Subsection 3.3.2, while results of model identification are presented in Subsection 3.3.3. Eventually, in Subsection 3.3.4 we describe how the derived CGM error model is used in the T1D-DM model for CGM traces simulation.

### 3.3.1 Database

Data were provided by Dexcom, Inc. and includes the 51 recordings of the study published by Bailey et al. [39] and additional 25 monitorings acquired in a pre-pivotal study performed with the same protocol (unpublished). In particular, data were collected in 76 adults, each monitored for 7 days by the Dexcom G5 Mobile CGM device calibrated every 12 hours by the BCN SMBG device. In addition, each subject underwent a 12-h clinical session in which BG concentration was monitored by high accuracy and precision YSI every 15 min. Clinical sessions were scheduled either on day 1 (23 subjects), day 4 (28 subjects) or day 7 (25 subjects) of CGM monitoring.

### 3.3.2 Modeling method

A method to model the CGM sensor error was recently developed by Facchinetti et al. [72], which takes into account the three main sources of CGM sensor error: the distortion introduced by BG-to-IG kinetics, the calibration error and the sensor noise. In particular, the CGM trace between two consecutive calibrations,  $y_{CGM}$ , is described by the following equation:

$$y_{CGM}(kT) = a(kT) \cdot x_{IG}(kT) + b(kT) + r(kT) \quad k = 1, \dots, N \quad (3.11)$$

where  $T$  is the sensor sampling period,  $x_{IG}(kT)$  is the IG value at time  $kT$  and  $a(kT)$  and  $b(kT)$  are linear polynomials in time of order  $m$  and  $l$  describing the sensor calibration error:

$$a(kT) = \sum_{i=1}^m a_i \cdot (kT)^i, \quad b(kT) = \sum_{j=1}^l b_j \cdot (kT)^j \quad (3.12)$$

The IG profile,  $x_{IG}(kT)$ , is described by the convolution of the BG profile,  $x_{BG}(kT)$ , and the impulse response of the BG-to-IG kinetics system that is described by a first-order dynamic system with unitary gain and time constant  $\tau$  [1/min]:

$$x_{IG}(kT) = x_{BG} \otimes \frac{1}{\tau} \cdot e^{-\frac{kT}{\tau}} \quad (3.13)$$

Finally,  $r(kT)$  is the residual trace representing the additive measurement noise in [mg/dl].

In work published by Facchinetti et al. in 2014 [71] and 2015 [72], the model of eqs. 3.11-3.13 was identified on databases in which glucose was monitored

simultaneously by multiple CGM sensors per subject and YSI during 12-h clinical sessions. Polynomials' parameters,  $a_i$ ,  $i = 1, \dots, m$  and  $b_j$ ,  $j = 1, \dots, l$ , and plasma-interstitium time constant,  $\tau$ , were estimated by non-linear least squares, while optimal values for the polynomials' orders,  $m$  and  $l$ , were selected according to the Bayesian information criterion (BIC), an index that is much lower much better the goodness of fit and lower the number of model parameters to identify are. On Dexcom 7 Plus data, the optimal orders selected by Facchinetti et al. were  $m = l = 1$  regardless of the day of CGM monitoring [71]. On Dexcom G4 PLATINUM data, where clinical sessions were performed in day 1, 4 and 7 of CGM monitoring, in day 1 selected optimal orders were  $m = l = 1$ , while in day 4 and 7 selected optimal orders were  $m = l = 0$  [72].

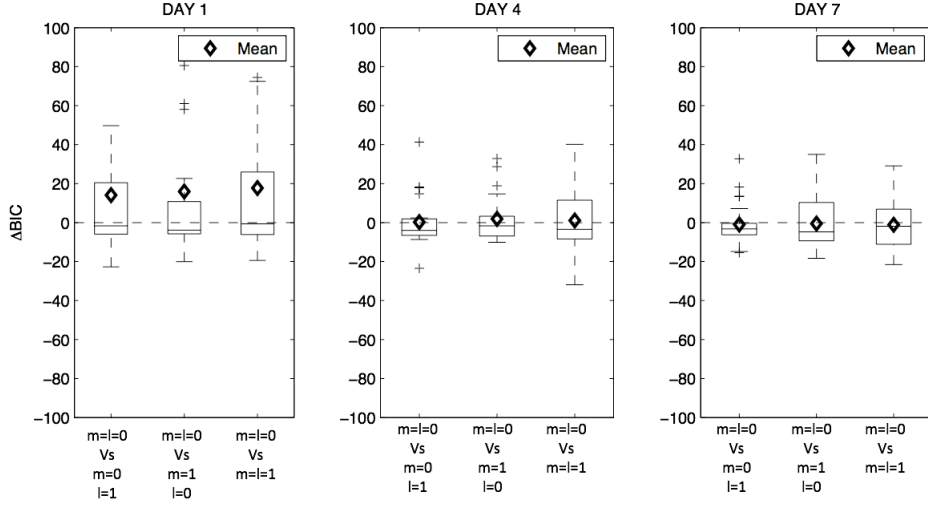
The availability of multiple sensor traces collected in parallel in the same subject allowed Facchinetti et al. to dissect the additive measurement noise of each sensor into two components: one common to all the sensors worn by the same subject and one specific of each sensor. Each of these components was modeled by an AR model whose order was selected again resorting to BIC.

Here, the method by Facchinetti et al. is applied to data described in Sub-section 3.3.1 to derive a model the Dexcom G5 Mobile system. Results are presented in the following section.

### 3.3.3 Results for Dexcom G5 data

Optimal values for polynomials' orders are selected according to BIC. Four candidate combinations of orders are considered i.e.  $m = l = 0$ ,  $m = 1$   $l = 0$ ,  $m = 0$   $l = 1$  and  $m = l = 1$ . Higher order values are not considered because previous experiments [71] [72] showed that the use of the quadratic or cubic terms is superfluous to describe Dexcom CGM sensors' error.

In Figure 3.7, the difference in BIC values of  $m = l = 0$  vs other orders' combinations ( $\Delta BIC$ ) is displayed via boxplot representation for day 1 (left panel), 4 (middle panel) and 7 (right panel). Mean of  $\Delta BIC$  is represented by black diamond. Looking at  $\Delta BIC$  in day 1, we can observe that the use of a linear term in the offset ( $m = 0$ ,  $l = 1$ ), in the gain ( $m = 1$ ,  $l = 0$ ), or both ( $m = 1$ ,  $l = 1$ ) of eq. 3.11 drives to better performance than using constant gain and offset ( $m = l = 0$ ), being  $\Delta BIC$  in this day on average significantly positive. Conversely in days 4 and 7, the simpler model with  $m = l = 0$  presents similar performance to the other models, since  $\Delta BIC$  is on average close to zero.



**Figure 3.7:** Boxplot representation of  $\Delta BIC$  between model with orders  $m = l = 0$  vs models with orders  $m = 0, l = 1$ ,  $m = 1, l = 0$  and  $m = l = 1$  in day 1 (left panel) 4 (middle panel) and 7 (right panel).

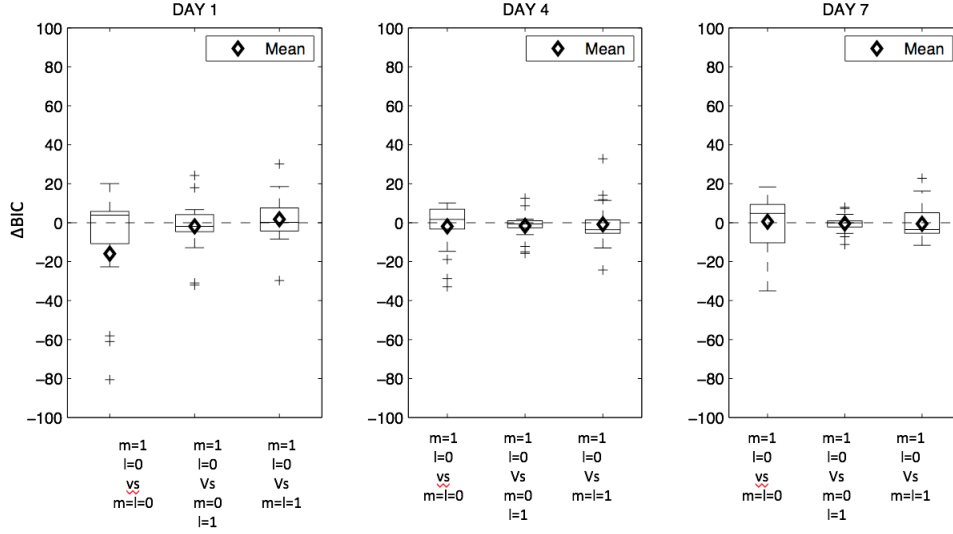
In Figure 3.8, the  $\Delta BIC$  values of  $m = 1, l = 0$  vs other orders' combinations is displayed via boxplot representation. Looking at day 1 (left panel of Figure 3.8), the model with orders  $m = 1, l = 0$  performs significantly better than the model with  $m = l = 0$ , slightly better than the model with  $m = 0, l = 1$  and equivalently to the model with  $m = l = 1$ . In day 4 (middle panel of Figure 3.8) and 7 (right panel of Figure 3.8), the compared models present similar performance.

In conclusion, the model we select is the model with a linear term in the gain ( $m = 1$ ) and constant offset ( $l = 0$ ) described by the following equation:

$$y_{CGM}(kT) = (a_0 + a_1 \cdot kT) \cdot x_{IG}(kT) + b_0 + r(kT) \quad k = 1, \dots, N \quad (3.14)$$

being this the best model to describe CGM data in day 1 according to BIC, and presenting equivalent performance to the other models tested in day 4 and 7. Parameters  $a_0, a_1, b_0$  and  $\tau$  are estimated by non-linear least squares by fitting the model of eq. 3.14 using CGM data as samples of  $y_{CGM}$  and YSI data as samples of  $x_{BG}$ . Mean and SD of estimated parameters are reported in Table 3.3 separately for day 1, 4 and 7.

Residual traces,  $r(kT)$ , are then fitted to a model of the sensor noise. Since in this database each subject wore one sensor only, it is not possible to distinguish the sensor-specific component from the common component. Therefore, each residual trace is treated as a single sensor-specific component and modeled by



**Figure 3.8:** Boxplot representation of  $\Delta BIC$  between model with orders  $m = 1$   $l = 0$  vs models with orders  $m = 0$   $l = 0$ ,  $m = 0$   $l = 1$  and  $m = l = 1$  in day 1 (left panel) 4 (middle panel) and 7 (right panel).

**Table 3.3:** CGM error model parameters identified on Dexcom G5 Mobile data in day 1, 4 and 7. For sensor-specific parameters ( $a_0$ ,  $a_1$ ,  $b_0$ ,  $\tau$  and  $\sigma^2$ ) median and interquartile range (in brackets) of values estimated for all sensors are reported.

Parameter	Day 1	Day 4	Day 7
$a_0$	1.04	1.04	1.02
[dimensionless]	(1.00 - 1.10)	(0.96 - 1.10)	(0.95 - 1.09)
$a_1$	0.02	-0.02	0.06
[1/days]	(-0.26 - 0.24)	(-0.13 - 0.12)	(-0.04 - 0.18)
$b_0$	-8.75	-1.42	0.10
[mg/dl]	(-15.80 - 2.20)	(-9.50 - 6.20)	(-6.18 - 7.07)
$\tau$	7.37	6.76	6.53
[min]	(5.63 - 11.67)	(5.00 - 9.02)	(6.04 - 10.83)
$\sigma^2$	7.64	6.51	6.33
[mg <sup>2</sup> /dl <sup>2</sup> ]	(3.75 - 15.86)	(3.98 - 9.04)	(4.46 - 11.18)
$c_1$	1.27	1.17	1.10
[dimensionless]			
$c_2$	-0.42	-0.36	-0.26
[dimensionless]			

AR model of order  $q$ . In line with previous studies, the optimal order of the AR model according to BIC results 2. Residual traces are then fitted with the AR model of order 2 described by the following equation:

$$r(kT) = c_1 \cdot r((k-1)T) + c_2 \cdot r((k-2)T) + \epsilon(kT) \quad (3.15)$$

where  $\epsilon(kT)$  is the input white noise with mean equal to 0 and variance,  $\sigma^2$ . In particular, we assume that model coefficients,  $c_1$  and  $c_2$  are constant across sensors, when the same day of monitoring is considered, i.e. all the sensors present, in the same day, the same degree of autocorrelation of the measurement noise, while  $\sigma^2$ , i.e. the magnitude of the input white noise, was allowed to vary from day to day and from sensor to sensor. Median and interquartile range of estimates of  $\sigma^2$ , as well as the values identified for  $c_1$  and  $c_2$ , are reported in Table 3.3 (last 3 rows).

#### 3.3.4 Simulation of CGM measurements in the T1D-DM model

The model of CGM sensor error derived on Dexcom G5 Mobile data, as illustrated in Section 3.3.3, can be employed to simulate CGM traces. Here, in particular, the model of eq. 3.14 is implemented in the device for glucose monitoring model of the T1D-DM model to simulate CGM traces starting from the IG profile returned by the UVA/Padova T1D simulator, as described below.

The insertion of a new sensor is simulated every 7 days. For each sensor, model parameters  $a_0$ ,  $a_1$ ,  $b_0$  and  $\sigma^2$  are updated at sensor calibration times, scheduled every 12 hours (at 6:00 am and 6:00 pm of each day), as recommended for the Dexcom G5 Mobile sensor. At each calibration time, parameters  $a_0$ ,  $a_1$ ,  $b_0$  and  $\sigma^2$  are sampled from a day-specific joint statistical distribution derived from parameters' values identified on clinical data. In particular, a specific joint statistical distribution is derived for days 1, 4 and 7 using the parameters estimated in these days, as in Subsection 3.3.3, and assuming that  $a_0$ ,  $a_1$ ,  $b_0$  are normally distributed, while  $\sigma^2$  follows a log-normal distribution. This assumption is supported by the Lilliefors test for normality that, when applied, with 5% significance level, to samples of  $a_0$ ,  $a_1$ ,  $b_0$  and  $\log(\sigma^2)$  estimated from data, cannot reject the null hypothesis that data comes from a normally distributed population.

Since in the clinical data used for CGM model identification the YSI references were collected only in day 1, 4 or 7, it is not possible to derive a joint statistical distribution of model parameters specific for days 2, 3, 5 and 6. However, it is reasonable to assume that CGM performance in days 2-3 are similar to CGM performance in day 4 as well as CGM performance in days 5-6 are similar to those in day 7. Indeed, at the start of CGM monitoring, sensor performance are affected by the foreign body immune response to the sensor needle insertion. This phenomenon induces a time-variability of sensor sensitivity



### 3.4 Development of the model of patient's behavior and treatment decisions

that in general is more pronounced in the first day of monitoring and then gradually decreases till extinguishing in the last days of monitoring. Therefore,  $a_0$ ,  $a_1$ ,  $b_0$  and  $\sigma^2$  in days 2-3 are simulated by sampling random values from the model parameters' distribution derived from day 4 data, while the same parameters in days 5-6 are simulated by the distribution derived from day 7 data.

Analogously, coefficients of the AR model  $c_1$  and  $c_2$  are fixed to day-specific values using day 1 estimates in day 1, day 4 estimates in days 2-4 and day 7 estimates in days 5-7.

Once the CGM glucose profile has been generated, trend arrows are calculated applying the same algorithm implemented in the Dexcom G5 Mobile system (proprietary code provided by Dexcom, Inc.). High and low glucose alerts are also generated whenever the simulated CGM glucose profile crosses the patient's high and low glucose alert thresholds, which are set to customizable values. Finally, low glucose alarms are generated whenever the simulated CGM glucose profile goes below 55 mg/dl and are repeated if CGM glucose readings persist below 55 mg/dl for 30 min after the preceding low glucose alarm.

## **3.4 Development of the model of patient's behavior and treatment decisions**

In this section the patient's behavior and treatment decisions model is described, which simulates the patient's behavior in using SMBG and/or CGM information to make treatment decisions like tuning meal insulin doses and triggering correction boluses and intake of rescue CHO to treat hyperglycemia and hypoglycemia, respectively <sup>2</sup>. In particular, the model inputs are meals, the BG values returned by the UVA/Padova T1D simulator, and SMBG measurements and CGM output (including glucose readings, trend arrows, alerts and alarms) which are simulated by the device for glucose monitoring model. The model outputs are insulin boluses, obtained as the sum of meal boluses and correction boluses, and CHO intake, obtained as the sum of meals' CHO and hypotreatments.

The patient's behavior and treatment decisions model can have different configurations depending on the type of glucose monitoring device used for

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<sup>2</sup>This section is part of the works [91] [92].

T1D therapy. In the following subsections we will describe three configurations of the T1D patient's behavior and treatment decisions model that reproduce the standard treatment based on SMBG, the adjunctive use of CGM sensor and the nonadjunctive use of CGM sensor. It is important to note that to allow the simulation of a realistic scenario, the patient's behavior and treatment decision model includes also components describing the mistakes commonly made by patients in the management of their diabetes, e.g. errors in CHO counting and early/delayed meal insulin bolus administrations.

### 3.4.1 SMBG treatment

When a SMBG-based treatment is simulated the structure of the patient's behavior and treatment decisions model is the one reported in Figure 3.9. In particular, meals boluses,  $MB_{SMBG}$  [U], are calculated based on the patient's estimate of meal's CHO content,  $C\hat{H}O$  [g], and the SMBG measurement simulated at the time of the meal bolus,  $G_{SMBG}$  [mg/dl], according to the standard formula:

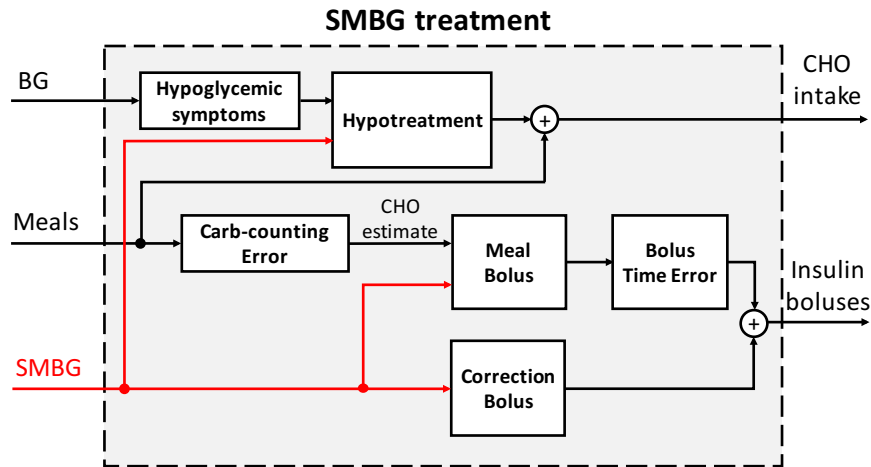
$$MB_{SMBG} = \frac{C\hat{H}O}{CR} + \frac{G_{SMBG} - G_{target}}{CF} \quad (3.16)$$

where CR [g/U] and CF [mg/dl/U] and  $G_{target}$  [mg/dl] are patient-specific parameters of the insulin therapy. In particular, CR is the CHO-to-insulin ratio and represents how many grams of CHO each unit of insulin covers, CF is the correction factor and represents the change in BG produced by each unit of insulin, and  $G_{target}$  is the post-meal BG target.

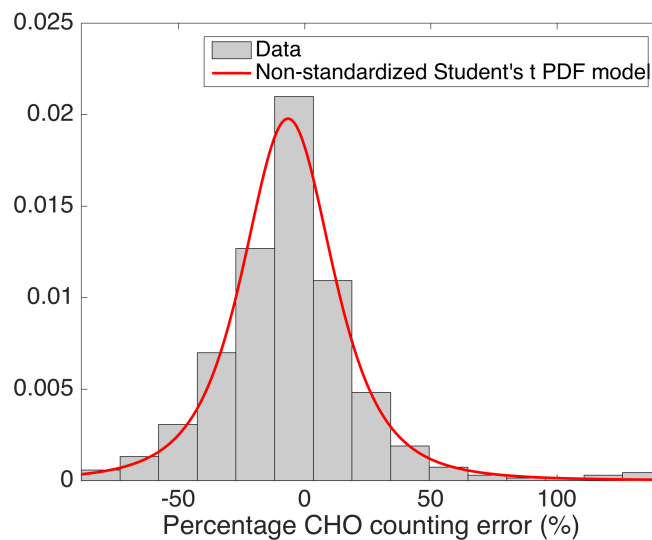
The estimate of meal's CHO content is simulated by using a model of the CHO counting error. This model was derived from data published by Brazeau et al. [93] in which the CHO content of 448 meals was estimated by T1D patients and in parallel assessed by a dietitian using a computerized analysis program. In particular, first the percentage error of CHO counting was calculated for each meal using dietitian assessment as reference. Then, a non-standardized Student's t PDF was fitted by ML to percentage error data. The resulting non-standardized Student's t PDF model presents 3 degrees of freedom and location and scale parameters equal to -6.6 and 18.78 respectively. Such PDF model is reported in Figure 3.10 by red line together with the histogram of percentage CHO counting error data. In the T1D-DM model, the percentage error in CHO counting is generated by drawing random samples from the identified non-standardized Student's t model.

Each meal bolus is administered at a time randomly selected with uniform

### 3.4 Development of the model of patient's behavior and treatment decisions



**Figure 3.9:** Schematic representation of the T1D patient's behavior and treatment decisions model for standard treatment based on SMBG.



**Figure 3.10:** Non-standardized Student's t PDF model (red line) fitted on percentage CHO counting error extracted from data of Brazeau et al. [93] (grey histogram).

probability between 10 min before and 10 min after the starting of the meal, in order to simulate early/delayed insulin administrations that commonly occur in real life.

Correction boluses are simulated whenever a routine SMBG check reveals hyperglycemia, i.e. the SMBG measurement is greater or equal than 180 mg/dl, and at least 2 hours passed since the last insulin bolus. This second condition is necessary to avoid the risk of insulin stacking, i.e. the patient having too much insulin still acting in the body. Routine SMBG checks include pre-sleep

SMBG checks, simulated at 10:00 pm, and post-meal SMBG checks simulated 2 h after the meal, whose frequency can be suitably set according to the kind of population the user is interested in testing. The calculation of correction boluses,  $CB_{SMBG}$  [U], is given by the following equation:

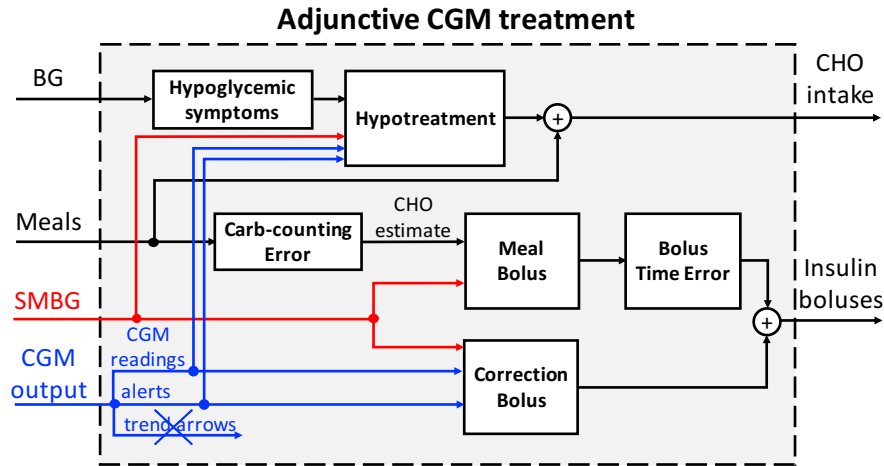
$$CB_{SMBG} = \frac{G_{SMBG} - G_{target}}{CF} \cdot C_{IOB} \quad (3.17)$$

where  $C_{IOB}$  [dimensionless] is a factor that corrects the bolus dose to account for insulin on board, i.e. the fraction of previously administered boluses still acting in the body. The value of  $C_{IOB}$  is established for each correction bolus by an empirical rule commonly adopted by the patients: when less than 4 h passed since last insulin bolus  $C_{IOB}$  is set to 0.5, otherwise  $C_{IOB}$  is set to 1, i.e. the entire correction dose is administered.

Hypotreatments are generated in response to the occurrence of hypoglycemic symptoms. In particular, each virtual subject is associated to a hypoawareness threshold, i.e. the glucose level at which the patient starts feeling hypoglycemic symptoms. Whenever the BG concentration simulated by the UVA/Padova T1D simulator falls below this level, hypoglycemic symptoms are generated and a SMBG check for hypoglycemia is triggered. If the SMBG measurement is lower or equal than 70 mg/dl and at least 15 min passed since last CHO intake, a hypotreatment is given. During waking hours (06:00 am – 10:00 pm), the amount of the hypotreatment is set to 15 g if  $SMBG > 55$  mg/dl or 20 g if  $SMBG \leq 55$  mg/dl, and a re-check for hypoglycemia is simulated 15 min after the first hypotreatment with probability 10%. If at the re-check the SMBG measurement is lower or equal than 70 mg/dl, another hypotreatment is given. During sleeping hours (10:01 pm – 05:59 am), the amount of the hypotreatment is set to 25 g whatever the SMBG measurement is and no re-checks for hypoglycemia are simulated. Hypotreatments are also generated, with the same rules, if a SMBG routine check (post-meal or pre-sleep) reveals hypoglycemia ( $SMBG \leq 70$  mg/dl).

#### 3.4.2 Adjunctive CGM treatment

When treatment based on adjunctive CGM is simulated, both SMBG measurements and CGM output are given in input to the patient's behavior and treatment decisions model, as shown in the scheme of Figure 3.11. In particular, all treatment decisions are made by using SMBG measurements, while CGM



**Figure 3.11:** Schematic representation of the T1D patient's behavior and treatment decisions model for treatment based on adjunctive use of CGM.

information is only used to trigger SMBG checks. More precisely, whenever CGM readings, alerts and alarms detect hypo/hyperglycemic events, the patient checks his/her BG concentration by SMBG and finally makes the treatment decision based on the SMBG measurement. CGM trend arrows are not used in the adjunctive CGM treatment, because their value cannot be confirmed using SMBG.

In the adjunctive CGM treatment scenario, meal boluses are generated as for the SMBG treatment, according to eq. 3.16.

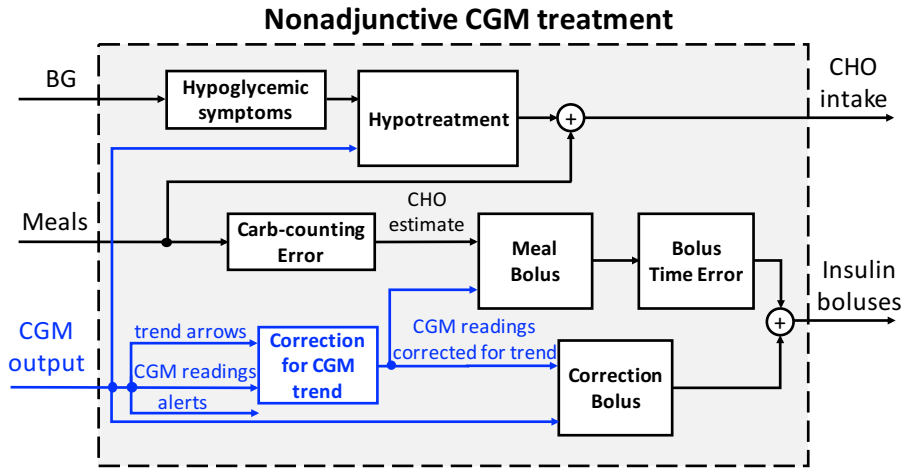
Correction boluses are given after a pre-sleep check (at 10:00 pm) or after a SMBG check for hyperglycemia, if the SMBG measurement is greater or equal than 180 mg/dl. SMBG checks for hyperglycemia are generated 2 h after the meal if CGM is greater than the high alert threshold and whenever a CGM high alert goes off and at least 2 h passed since last insulin bolus. The dose of correction boluses is calculated as in the SMBG treatment by eq. 3.17.

SMBG checks for hypoglycemia are triggered in response to hypoglycemic symptoms, i.e. when BG goes below the threshold of hypoglycemia awareness, and in response to CGM low glucose alerts and alarms. Then, hypotreatments are generated if measured SMBG is lower or equal than 70 mg/dl and at least 15 min passed since last CHO intake. During waking hours (06:00 am – 10:00 pm), the amount of the hypotreatment is set to 15 g if  $SMBG > 55$  mg/dl, 20 g if  $SMBG \leq 55$  mg/dl, and a re-treatment is provided if at 30 min after the previous hypotreatment CGM is displaying a glucose value below 70 mg/dl and a confirmatory SMBG check confirms that BG is lower than 70 mg/dl. During

sleeping hours (10:01 pm – 05:59 am), the amount of the hypotreatment is set to 25 g whatever the SMBG measurement is and no re-checks for hypoglycemia are simulated after the first hypotreatment. Hypotreatments are also generated independently of symptoms and CGM alerts and alarms if a pre-sleep or post-meal SMBG measurement reveals hypoglycemia.

### 3.4.3 Nonadjunctive CGM treatment

In the nonadjunctive use of CGM, patients make all the treatment decisions based on CGM output, including CGM readings, alerts and trend arrow, without using confirmatory SMBG measurements. The structure of the patient's behavior and treatment decisions model with nonadjunctive CGM use is shown in Figure 3.12.



**Figure 3.12:** Schematic representation of the T1D patient's behavior and treatment decisions model for treatment based on nonadjunctive use of CGM.

Meal boluses,  $MB_{nonadj}$  [U], are calculated by the following equation:

$$MB_{nonadj} = \frac{CHO}{CR} + \frac{\tilde{G}_{CGM} - G_{target}}{CF} \quad (3.18)$$

where  $\tilde{G}_{CGM}$  [mg/dl] is the CGM glucose reading at the time of the bolus corrected according to the CGM trend arrow to account for the glucose rate of change. This correction is performed according to the guideline proposed by

Scheiner [26]:

$$\tilde{G}_{CGM} = \begin{cases} G_{CGM} & \text{if } |A_{CGM}| < 1 \\ G_{CGM} + 25 \text{ mg/dl} & \text{if } A_{CGM} = 1 \\ G_{CGM} - 25 \text{ mg/dl} & \text{if } A_{CGM} = -1 \\ G_{CGM} + 50 \text{ mg/dl} & \text{if } A_{CGM} \geq 2 \\ G_{CGM} - 50 \text{ mg/dl} & \text{if } A_{CGM} \leq -2 \end{cases} \quad (3.19)$$

where  $G_{CGM}$  [mg/dl] and  $A_{CGM}$  [mg/dl/min] represent the glucose reading and the trend arrow, respectively, displayed by CGM at the time of bolus calculation. In particular,  $A_{CGM}$  is equal to 0 when the trend arrow is flat,  $\pm 1$ ,  $\pm 2$  and  $\pm 3$  when CGM displays a  $45^\circ$  up/down arrow, a  $90^\circ$  up/down arrow and two  $90^\circ$  up/down arrows, respectively. Time variability of meal boluses administration is simulated as for SMBG and adjunctive CGM treatments.

Correction boluses may be triggered in response to CGM high alerts or CGM routine checks, which the patient is supposed to perform 2 h after each meal and before sleeping (at 10:00 pm), according to CGM reading and trend arrow. More precisely, correction boluses are generated if a CGM high alert goes off, at post-meal checks if CGM reading is above the high alert threshold or at pre-sleep checks, if one of the following two conditions is verified: i) CGM reading is between 180 mg/dl and 249 mg/dl with flat or rising trend arrow, ii) CGM reading is greater or equal than 250 mg/dl regardless of the trend arrow. All correction boluses are given if at least 2 h passed since last insulin bolus. The calculation of correction bolus dose,  $CB_{nonadj}$  [U], is performed by the following formula:

$$CB_{nonadj} = \frac{\tilde{G}_{CGM} - G_{target}}{CF} \cdot C_{IOB} \quad (3.20)$$

where  $\tilde{G}_{CGM}$  is the CGM glucose reading at the time of the bolus corrected according to the CGM trend arrow as in eq. 3.19.

Hypotreatments are generated in response to CGM low alerts and alarms or hypoglycemic symptoms. More precisely, a hypotreatment is triggered if at least 20 min passed since last CHO intake and a CGM alarm goes off, or a CGM alert goes off and the CGM reading is lower than 70 mg/dl or between 70 mg/dl and 80 mg/dl with decreasing trend arrow. Hypotreatments are also generated at CGM routine checks (at 10:00 pm and 2 h after meals) if the

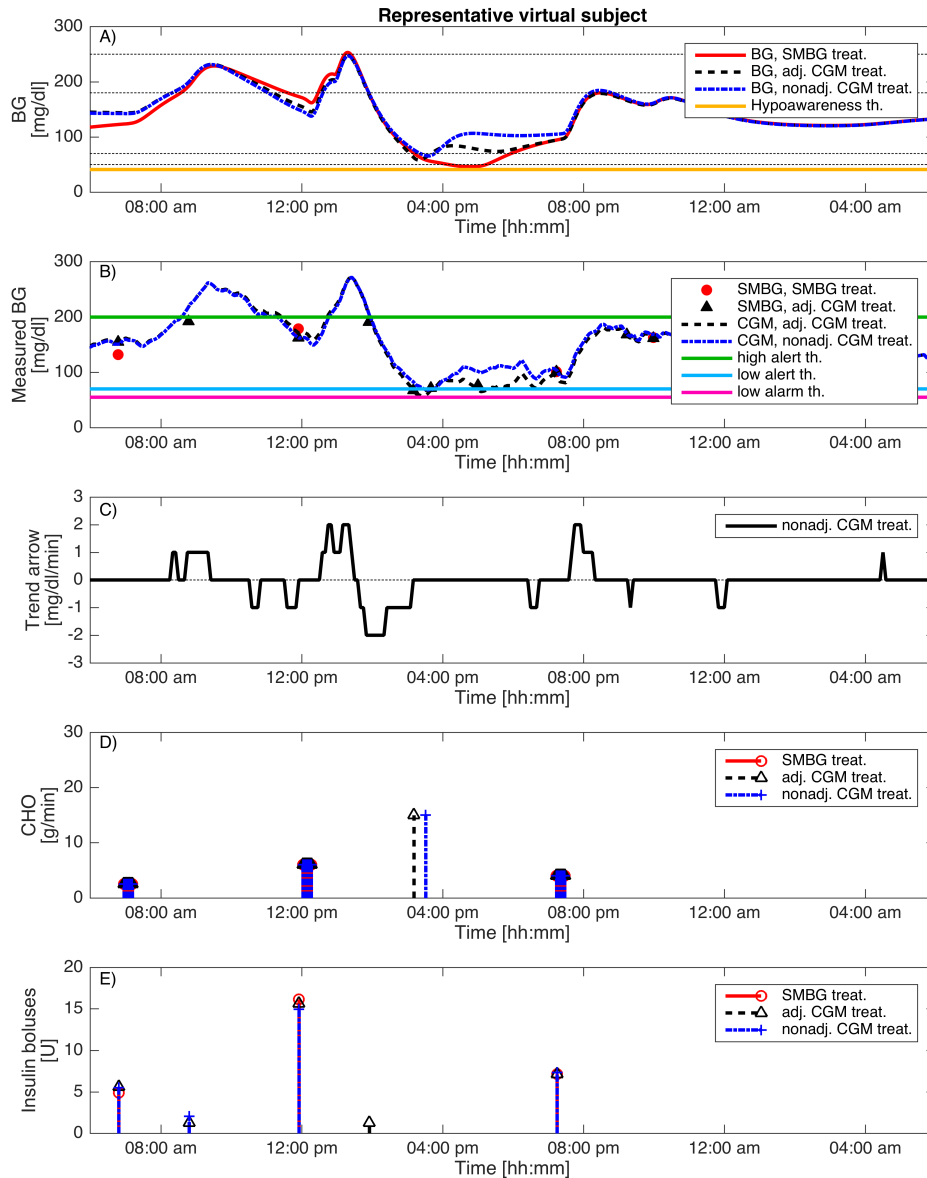
CGM reading is lower than 70 mg/dl or between 70 mg/dl and 80 mg/dl with decreasing trend arrow. When symptoms of hypoglycemia are present (i.e. BG is lower or equal than the hypoawareness threshold), if CGM is consistent with symptoms, i.e. the CGM reading is lower than 70 mg/dl or between 70 mg/dl and 80 mg/dl with decreasing trend arrow, then a hypotreatment is given, if at least 15 min passed since last CHO intake. Otherwise, if CGM is not consistent with symptoms, then a SMBG check is simulated and the treatment decision is made according to the rules of the SMBG-based treatment. In addition, we assume that during waking hours (6:00 am – 10:00 pm) the patients with CGM low alert set at a glucose values greater than 70 mg/dl keep checking their CGM after the low alert goes off and, when the CGM reading goes below 70 mg/dl, take a hypotreatment if at least 20 min passed since last CHO intake. During waking hours, after the first hypotreatment, a re-treatment is given after 20 min if the CGM reading is below 70 mg/dl and current CGM reading is lower or equal than the previous reading, after 30 min if the CGM reading is below 70 mg/dl regardless of the glucose rate of change. The amount of the hypotreatment is set according to the most recent CGM reading and the time of the day. During waking hours, the hypotreatment amount is set to 15 g if the CGM reading is greater than 55 mg/dl, 20 g if the CGM reading is lower or equal than 55 mg/dl. During night, the hypotreatment amount is set to 25 g regardless of the CGM reading and no re-treatment is simulated.

### **3.5 Use of the comprehensive T1D-DM model: Simulation of a representative virtual subject's day**

To show its usefulness here we illustrate how the T1D-DM model can deal with different treatment scenarios in a representative virtual subject. In particular, Figure 3.13 displays one day with SMBG treatment, adjunctive use of CGM and nonadjunctive use of CGM. The considered virtual subject, especially, has impaired awareness of hypoglycemia, with hypoawareness threshold equal to 41 mg/dl (orange horizontal line in Figure 3.13, panel A), does not test post-meal glucose in the SMBG treatment after any meal, and uses both high and low glucose alerts in the adjunctive and nonadjunctive CGM treatment scenarios, with high alert threshold equal to 200 mg/dl (green horizontal line in Figure 3.13, panel B) and low alert threshold equal to 80 mg/dl (light blue horizontal line in Figure 3.13, panel B).



### 3.5 Use of the comprehensive T1D-DM model: Simulation of a representative virtual subject's day



**Figure 3.13:** One-day simulation with the T1D-DM model in a representative virtual subject. Panel A: Simulated BG [mg/dl] for treatments based on SMBG (red solid line), adjunctive CGM (black dashed line) and nonadjunctive CGM (blue dash-dot line). The orange horizontal line represents hypoawareness threshold. Panel B: SMBG measurements [mg/dl] used in the SMBG treatment are reported by red circles. SMBG and CGM measurements [mg/dl] used in the adjunctive CGM treatment are represented by black triangles and black dashed line, respectively. The CGM trace [mg/dl] used in the nonadjunctive CGM treatment is the blue dash-dot line. Thresholds of high and low glucose alert and low glucose alarm are reported by green, light blue and magenta horizontal lines, respectively. Panel C: CGM trend arrow [mg/dl/min] used in the nonadjunctive CGM treatment scenario. Panel D: Rate of ingested CHO [g/min] in the SMBG (red solid line), adjunctive CGM (black dashed line) and nonadjunctive CGM (blue dash-dot line) treatments. Panel E: Insulin boluses [U] in the SMBG (red solid line), adjunctive CGM (black dashed line) and nonadjunctive CGM (blue dash-dot line) treatments.

### *3 Development of a T1D patient decision-making model*

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Panel A reports the subject's BG concentration [mg/dl] for treatment based on SMBG (red solid line), adjunctive CGM (black dashed line) and nonadjunctive CGM (blue dash-dot line). The glucose measurements used in each treatment are represented in Figure 3.13, panel B: red circles are the SMBG measurements used in the SMBG treatment, black triangles and black dashed line are, respectively, the SMBG and CGM measurements used in adjunctive CGM treatment, while blue dash-dot line is the CGM trace used in the nonadjunctive CGM treatment. The black line in Figure 3.13, panel C represents the trend arrows used in the nonadjunctive CGM treatment. Insulin boluses [U] and CHO intake [g/min] returned in output by the patient's behavior and treatment decisions model are reported in Figure 3.13, panel D and panel E respectively, for SMBG treatment (red solid line with circles as markers), adjunctive CGM treatment (black dashed line with triangles as markers) and nonadjunctive CGM treatment (blue dash-dot line with crosses as markers).

In this example, the subject takes 38 g of CHO for breakfast at 06:57 am and takes an insulin bolus of about 5 U, 9 min before the start of breakfast, based on a CHO count of 34 g. In the adjunctive CGM treatment, 2 h after breakfast CGM displays a glucose value of 215 mg/dl that is greater than the high glucose alert threshold. Therefore, the subject tests his BG by SMBG and takes a correction bolus since the SMBG measurement is 192 mg/dl, thus greater than 180 mg/dl. A correction bolus is taken at the same time also in the nonadjunctive CGM scenario, because 2 h after breakfast CGM displays a glucose reading of 215 mg/dl, i.e. above the high alert threshold, and a 45° up trend arrow. In particular, in the nonadjunctive CGM scenario, the calculation of the correction bolus is performed using the CGM reading increased by 25 mg/dl to account for the increasing trend arrow. Thanks to the correction bolus, the subject spends more time in the euglycemic range (70-180 mg/dl) during late morning in the scenarios using CGM compared to that using SMBG only.

At 12:02 am the subject takes 90 g of CHO for lunch, estimates that the lunch contains 112 g of CHO and based on this estimate takes a lunch bolus of about 15 U, 7 min before the start of lunch. In the adjunctive CGM scenario, the subject checks his BG by SMBG 2 h after lunch, since CGM is displaying a glucose value greater than the high alert threshold. Based on that, the subject takes a correction bolus because the SMBG measurement is equal to 191 mg/dl and, thus, greater than 180 mg/dl. Conversely, in the nonadjunctive CGM scenario the subject does not take any post-lunch correction bolus, since 2 h after lunch CGM displays a glucose reading of 220 mg/dl, i.e. above the high

alert threshold, but with one 90° down trend arrow.

In the SMBG scenario, between 03:12 pm and 05:56 pm the subject experiences a long hypoglycemic event, probably because of the overestimation of lunch CHO content. Nevertheless, the subject does not take any hypotreatment since he/she is not aware of the hypoglycemia being BG above his/her hypoawareness threshold (the minimum BG level is 46.11 mg/dl).

In the adjunctive CGM scenario, CGM provides a low glucose alert at 03:05 pm, therefore the subject, even if not experiencing hypoglycemic symptoms, tests BG by SMBG. Since measured SMBG is equal to 67.41 mg/dl, the subject takes 15 g of CHO to treat the hypoglycemia. After 30 min, the subject sees that the CGM reading is still below 70 mg/dl and thus re-check his BG by SMBG. This time SMBG is above 70 mg/dl and the subject does not take any additional treatment. The total duration of the hypoglycemic event in this treatment scenario is 37 min.

In the nonadjunctive CGM treatment, CGM provides a low glucose alert at 03:15 pm, but since CGM is displaying a glucose value of 77 mg/dl with flat trend arrow the subject does not take any hypotreatment and checks his/her CGM in the next minutes. After 15 min, the CGM reading becomes 69 mg/dl, thus the subject decides to take a 15-g hypotreatment. Twenty min after the hypotreatment, the CGM reading is equal to 73 mg/dl, thus above 70 mg/dl, and the subject does not take any additional treatment. The total duration of the hypoglycemic event in this scenario is reduced to 25 min.

In the adjunctive CGM scenario, another low glucose alert goes off at 04:50 pm, but the subject after measuring a BG value of 71.35 mg/dl by SMBG decides not to take any hypotreatment. At 07:14 pm the subject takes 60 g of CHO for dinner and takes an insulin bolus of about 7 U, 1 min after the start of dinner, without making errors in CHO counting. A pre-sleep check is performed at 10:00 pm by SMBG in the SMBG and adjunctive CGM scenarios, by CGM in the nonadjunctive CGM scenario. In all the scenarios, measured BG is in the euglycemic range thus no correction bolus/hypotreatment is taken. The subject spends the rest of the night in the euglycemic range in all the treatment scenarios.

## 3.6 Discussion

In this chapter, a T1D-DM model has been developed, which describes the T1D patient making treatment decisions based on glucose monitoring data.

Such a model includes a reliable and validated T1D physiological model, i.e. the UVA/Padova T1D simulator, which importantly describes the inter-subject variability of physiology and the intra-subject time-variability of insulin sensitivity. Starting from the glucose concentration profile generated by the physiological model, the T1D-DM model simulates both SMBG and CGM measurements according to SMBG and CGM error models.

A new methodology to derive a model of the PDF of the SMBG measurement error has been proposed, whose main novelties are the multi-zone approach, which consists in dividing the glucose range into zones with constant-SD absolute or relative error, and the use of the skew-normal PDF model, fitted in each identified zone, which allows to describe both symmetric and asymmetric PDFs. The distribution of outliers, possibly present in the data, is described by a separately identified exponential PDF. This methodology was applied to two databases allowing to derive two-zone PDF models of OTU2 and BCN measurement error, which showed significantly better performance than simpler Gaussian models used in the literature according to goodness-of-fit tests.

In order to simulate CGM measurements, a model of the CGM sensor error has been derived for the Dexcom G5 Mobile device by using a recently proposed methodology which takes into account the principal sensor error components. This allowed us to derive a mathematical description of one of the last generation CGM sensors, previously not available in the literature.

Finally, a model of the patient's behavior in making treatment decisions, like insulin dosing and treatment of hypoglycemia, has been built. Thanks to the incorporation of components describing common mistakes made by the patients in T1D treatment, like errors in CHO counting and meal bolus administration time, the model allows to reproduce a realistic treatment scenario. Specifically, three configurations have been designed for the model, which represent the patient's behavior with treatment based on SMBG use, adjunctive CGM use and nonadjunctive CGM use.

The potential utility of the T1D-DM model has been shown in the example of Section 3.5, where we illustrated a day of treatment with SMBG, adjunctive CGM and nonadjunctive CGM use simulated by the T1D-DM model in a representative virtual subject. In particular, the example demonstrated that the T1D-DM model is suitable to perform ISCTs assessing the efficacy of insulin treatments. Indeed, the model allows to simulate realistic treatment scenarios, in which both inaccuracy of glucose monitoring devices and patient's behav-

ior in making treatment decisions (including mistakes commonly made by patients in real-life) are properly considered. Importantly, the T1D-DM model allows to compare different insulin treatments in the same virtual subjects on the same meal scenario, which would not be possible in real-life trials, thus eliminating the influence of possible confounding factors on the effectiveness of the assessed insulin treatments. The T1D-DM model also overcomes some limitations of the net effect method, like the linearity and the lack of inter- and intra-subject variability in the model used to describe patient's physiology, and the issues deriving from working retrospectively on real data, e.g. impossibility of updating the patient's decisions in real-time after a therapy modification and impossibility of modifying the meal scenario.

Eventually, we would like to remark that T1D-DM model can be used for several *in silico* applications. A straightforward application of the T1D-DM model is the *in silico* assessment of safety and effectiveness of nonadjunctive CGM use compared to SMBG and adjunctive CGM use, which is the object of Chapter 4.



## Chapter 4

# Use of T1D-DM model in an ISCT to assess safety and efficacy of nonadjunctive CGM use vs SMBG and adjunctive CGM use

The T1D-DM model presented in the previous chapter is a suitable tool to develop ISCTs to assess insulin treatments. The model in particular allows to simulate realistic scenarios by reproducing the behavior of real subjects in making treatment decisions, including possible mistakes in the therapy such as miscalculation of meal CHO content. A direct application of the T1D-DM model is its use to design ISCTs to assess the safety and effectiveness of nonadjunctive CGM use. In this chapter, a first ISCT based on the T1D-DM model is designed for comparing nonadjunctive use of CGM vs adjunctive use of CGM and standard SMBG treatment in a population of virtual subjects reflecting the characteristics of a general population of T1D subjects <sup>1</sup>.

### 4.1 Design of the ISCT

A two-week simulation is performed in the population of 100 T1D adult virtual subjects of the UVA/Padova T1D simulator with three treatment scenarios: standard treatment based on SMBG, adjunctive use of CGM and nonadjunctive use of CGM. In particular, SMBG and CGM measurements are simulated using the model of measurement error derived for the BCN and the

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<sup>1</sup>This chapter is part of the work [92].

Dexcom G5 Mobile, respectively, as described in the previous chapter. The parameters characterizing the virtual subjects' behavior concerning meals, use of SMBG/CGM and insulin therapy are set in order to reflect the behavior of a general population of T1D subjects, as described in Subsection 4.1.1.

### **4.1.1 Setting of simulation parameters**

Three meals per day are randomly generated for each subject assuming meal time uniformly distributed in the interval 06:30 am – 08:00 am for breakfast, 11:30 am – 01:00 pm for lunch, 06:30 pm – 08:00 pm for dinner. Meal amount is randomly sampled from a uniform distribution with mean and SD derived from data published by Brazeau et al. [93]. In particular, mean $\pm$ SD of the distribution of meal amount is 58.2 $\pm$ 22.5 for breakfast, 77.7 $\pm$ 27.0 for lunch, 83.9 $\pm$ 32.3 for dinner.

According to evidences reported by Geddes et al. [94], we assume that the 25% of virtual subjects has impaired awareness of hypoglycemia, i.e. they start feeling the symptoms of hypoglycemia at a glucose level lower than normal, while the remaining 75% presents normal awareness of hypoglycemia. The hypoawareness threshold is randomly selected in the range 40-50 mg/dl for patients with impaired awareness of hypoglycemia, 50-60 mg/dl for patients with normal awareness of hypoglycemia according to Fanelli et al. [95], where the hypoawareness threshold was assessed by stepped hypoglycemia clamp in normal subjects and subjects with impaired awareness of hypoglycemia.

When the SMBG-based treatment is simulated, in all subjects SMBG measurements are generated at the beginning of each meal for the calculation of meal boluses and at 10:00 pm for pre-sleep checks. In addition, post-meal SMBG checks are simulated 2 h after meals in a fraction of subjects, according to data about frequency of SMBG testing reported in the literature. In particular, according to Cariou et al. [96], the 33% of subjects tests more than 5 times per day, while in the T1D Exchange [97], 7% of the subjects reports having tested more than 9 times per day before starting using CGM. Considering that the first 5 tests per day are likely related to pre-meal boluses, pre-sleep check, exercise and hypoglycemia treatments, we assume that post-meal tests are performed in 33% of the subjects, and in particular, 7% of the subjects tests after 3 meals per day, 13% after 2 meals per day (randomly chosen) and 13% after 1 meal per day (randomly chosen).

Concerning CGM high and low alert thresholds, the Dexcom G5 Mobile



system has default alert settings at 200 mg/dl (high alert) and 80 mg/dl (low alert) [17]. However, users often customize alert settings based on their needs. The distribution of alert settings in our virtual subject population was simulated by exploiting data (gathered by Dexcom, Inc.) about alert thresholds used by actual Dexcom G5 Mobile users (technical support repository data between August 2014 and May 2015). Based on these data, the low alert threshold is set to 70 mg/dl and 80 mg/dl for 26% and 60% of virtual subjects respectively, while the remaining 14% of the virtual subjects does not use the low alert but only uses the 55 mg/dl alarm. The high alert threshold is set to 180, 200, 250, 300, 350 and 400 mg/dl for 21%, 27%, 24%, 14%, 3% and 1% of the subjects respectively, while the remaining 10% of the subjects does not use the high alert.

Therapy parameters  $CR$ ,  $CF$  and basal daily insulin ( $BDI$ ) have been calculated for each subject by using the guidelines by Davidson et al. [6] based on patient body weight ( $BW$ ) [lb] and total daily insulin ( $TDI$ ) [U]:

$$CR = 2.8 \cdot \frac{BW}{TDI} \quad (4.1)$$

$$CF = \frac{1700}{TDI} \quad (4.2)$$

$$BDI = 0.47 \cdot TDI \quad (4.3)$$

The TDI of each subject is calculated using the optimal values of  $CR$  and  $BDI$  provided by the UVA/Padova T1D simulator for each subject,  $CR_{opt}$  [g/U] and  $BDI_{opt}$  [U], assuming an average daily carb dose of 220 g:

$$TDI = \frac{220g}{CR_{opt} + BDI_{opt}} \quad (4.4)$$

Target BG,  $G_{target}$  in eq. 3.16, 3.17, 3.18 and 3.20, is set to the basal glucose level provided by the UVA/Padova T1D simulator for each subject.

Eventually, it is important to note that for each subject SMBG use, adjunctive CGM use and nonadjunctive CGM use are compared over the same meal scenario, i.e. the same realization of meals' amount, time, CHO counting error and bolus time error is simulated for the three treatments. Also the hypoaawareness threshold and the other therapy parameters are the same in the three treatments when the same subject is considered. Moreover, for each subject realizations of CGM sensor error are the same in treatments based on adjunctive CGM and nonadjunctive CGM. In this way, we ensure that when comparing

the three treatments, differences in the glycemic outcomes are only generated by the different treatments tested and are not influenced by other confounding factors.

## **4.2 Metrics**

The nonadjunctive use of CGM for T1D treatment is compared to use of SMBG only, and adjunctive CGM based on glycemic outcomes commonly used to assess glycemic control in T1D. In particular, per each subject five time-related outcomes are assessed, i.e. time spent between 70 mg/dl and 180 mg/dl ( $T_{70-180}$ ) [h/day], below 70 mg/dl ( $T_{<70}$ ) [min/day], below 50 mg/dl ( $T_{<50}$ ) [min/day], above 180 mg/dl ( $T_{>180}$ ) [h/day] and above 250 mg/dl ( $T_{>250}$ ) [h/day]. The use of these outcomes was recently recommended by the Juvenile Diabetes Research Foundation for the assessment of glycemic control in artificial pancreas studies [98]. A paired two-tailed sign test is then performed to determine if statistically significant differences are present between median outcomes of nonadjunctive CGM treatment vs SMBG and nonadjunctive vs adjunctive CGM treatment. In addition, the year rate of events below 70 mg/dl and 50 mg/dl, defined as the total number of events below 70 mg/dl and 50 mg/dl normalized per subject per year, is also assessed and compared between treatments, as well as the duration [min] of events below 70 mg/dl and 50 mg/dl.

All the metrics are first assessed in the entire monitoring period and then separately on day 1 of CGM monitoring (i.e. on first and eighth day of our 14-day simulation), being the first 12-24 hours after sensor insertion the most critical for CGM sensor accuracy due to the foreign body response [36].

## **4.3 Results**

Results of the ISCT are shown in this section. First, in Subsection 4.3.1 the clinical outcomes obtained with treatment based on adjunctive CGM use are compared to outcomes of a real database in order to understand if the T1D-DM model is able to well reproduce the glycemic variability observed on real data. Then, in Subsection 4.3.2 clinical outcomes achieved by nonadjunctive use of CGM are compared to those achieved by SMBG use and adjunctive use of CGM to determine if CGM can safely substitute SMBG in T1D treatment.

### 4.3.1 Adjunctive CGM: comparison with real data

To determine if the T1D-DM model is able to well reproduce the real-life behavior of a general T1D population, glycemic outcomes obtained in the scenario with adjunctive CGM use are compared to those calculated in a database (courtesy of Dexcom, Inc.) collected in 51 subjects using CGM in adjunct to SMBG [39]. In this database, which was also used for SMBG and CGM model derivation (see Section 3.2.1 and Section 3.3.1), the 51 participants wore the Dexcom G5 Mobile system for 7 days and used the BCN SMBG device to collect confirmatory fingersticks and calibrate the CGM sensor (twice a day). Since the original purpose of this study was to evaluate the accuracy of the Dexcom G5 Mobile, the data set also includes high-accuracy and precision YSI measurements that were recorded in 12-hour clinical sessions, during which insulin doses and CHO intake were manipulated in order to have CGM measurements in a wide range of BG concentration, including severe hyper/hypoglycemia.

The glycemic outcomes described in Section 4.2 are assessed on the 51 CGM traces collected in this database, removing from the analysis the portion of data recorded during YSI clinical sessions, since the manipulations performed in clinic, which include induced hypo/hyperglycemia, would affect glycemic outcomes. In addition, day 1 of monitoring is also removed from the assessment because notably CGM is less accurate in day 1 than in the rest of the sensor life, thus significantly high/low CGM values in day 1 may be the result of bias in the sensor measurements rather than actual high/low BG values.

Median and interquartile range of  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  are reported in Table 4.1 for the BG profiles obtained by the T1D-DM model with adjunctive CGM use (second column) and the CGM traces of the real database (third column). A good agreement between simulation and data is achieved for all the metrics, except  $T_{<70}$  which is significantly lower in simulated BG profiles. A two-tailed Wilcoxon test is applied to determine if medians of time-related clinical outcomes obtained from our simulations with treatment based on adjunctive use of CGM are statistically significantly different from those obtained from data. P-values are reported in the fourth column of Table 4.1. The only statistical significant difference is found for  $T_{<70}$  (p-value=0.0066), while no statistically significant difference is found for the other outcomes (p-value>0.05).

Rate and duration of events below 70 mg/dl and below 50 mg/dl are also

#### 4 Use of T1D-DM model in an ISCT to assess safety and efficacy of nonadjunctive CGM use vs SMBG and adjunctive CGM use

**Table 4.1:** Median (interquartile range) of metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated from the BG profiles simulated by the T1D-DM model with adjunctive CGM use (second column) and from the CGM traces of a real database (third column). P-values resulting from the two-tailed Wilcoxon test are reported in the fourth column.

<b>Metric</b>	<b>T1D-DM model</b>	<b>Real data</b>	<b>P-value</b>
$T_{70-180}$ [h/day]	15.82 (13.69 - 18.10)	15.82 (12.55 - 17.63)	0.5800
$T_{<70}$ [min/day]	24.36 (10.82 - 50.10)	44.90 (15.66 - 85.12)	0.0066
$T_{<50}$ [min/day]	1.97 (0.00 - 7.93)	2.97 (0.00 - 10.58)	0.6620
$T_{>180}$ [h/day]	7.47 (5.38 - 9.93)	7.28 (4.16 - 10.27)	0.5853
$T_{>250}$ [h/day]	1.75 (0.93 - 2.65)	1.67 (0.59 - 4.25)	0.9783

compared between simulation and data. As reported in Table 4.2, 518 events below 70 mg/dl per year with 30-min median duration and 112 events below 50 mg/dl per year with 25-min median duration are observed in CGM data. On simulated data, 229 events below 70 mg/dl per year with median duration of 51 min are identified and 99 events below 50 mg/dl with median duration of 23 min. While a good agreement is achieved for rate and duration of events below 50 mg/dl, events below 70 mg/dl are more frequent on data but with shorter duration.

In conclusion, glycemic outcomes related to euglycemia, hyperglycemia, severe hyperglycemia and severe hypoglycemia of BG profiles obtained by the T1D-DM model well match the outcomes calculated on CGM traces in the database we analyzed. The only difference is found in metrics related to hypoglycemia ( $T_{<70}$ , rate and duration of events below 70 mg/dl). A possible reason for this discrepancy could be that, despite including many sources of errors in the T1D treatment like miscalculation of meal CHO content and errors in meal bolus time and therapy parameters (CR, CF and BDI), the T1D-DM model, and in particular the UVA/Padova T1D simulator, still does not include some contributors of real-life glycemic variability, like physical exercise, which are known to increase the risk of hypoglycemia. However, the discrepancy on these metrics is not critical for drawing solid conclusions from the simulation scenarios we designed. In fact, the lower rate of both time below 70 mg/dl and rate of events below 70 mg/dl influences both SMBG-based and CGM-based

**Table 4.2:** Rate [events/year] and median (interquartile range) of duration [min] of events below 70 mg/dl and 50 mg/dl in BG profiles simulated by the T1D-DM model with adjunctive CGM use (third column) and in CGM traces of a real database (fourth column).

Metric		T1D-DM model	Real data
Events below 70 mg/dl	Rate [events/year]	229	518
	Duration [min]	51 (40.25 - 63)	30 (10 - 55)
Events below 50 mg/dl	Rate [events/year]	99	112
	Duration [min]	23 (16 - 33)	25 (10 - 40)

treatments in the same way, and thus does not affect our results on the comparison of SMBG-based and CGM-based treatments simulated by the T1D-DM model.

### 4.3.2 Nonadjunctive CGM use vs SMBG use and adjunctive CGM use

In this subsection the glycemic outcomes resulting from treatments based on SMBG use, adjunctive CGM use and nonadjunctive CGM use are compared. The aim is to understand if nonadjunctive CGM use is as safe as SMBG use and adjunctive CGM use. Results are analyzed first considering the entire period of CGM monitoring, and then focusing on day 1 of CGM monitoring, which represents the worst case for CGM accuracy.

#### Entire CGM monitoring period

The distribution of time-related glycemic outcomes calculated over the entire CGM monitoring period (days 1-14 of simulation), using the 100 virtual subjects' BG profiles, is shown in Figure 4.1 via a boxplot representation in which the horizontal red line represents the median, the blue box the interquartile range, black dashed lines the whiskers and red crosses the outliers. In particular, the distribution of  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  is reported in panel A, B, C, D and E, respectively, for SMBG use (left), adjunctive CGM use (middle) and nonadjunctive CGM use (right). This representation shows that the

#### 4 Use of T1D-DM model in an ISCT to assess safety and efficacy of nonadjunctive CGM use vs SMBG and adjunctive CGM use

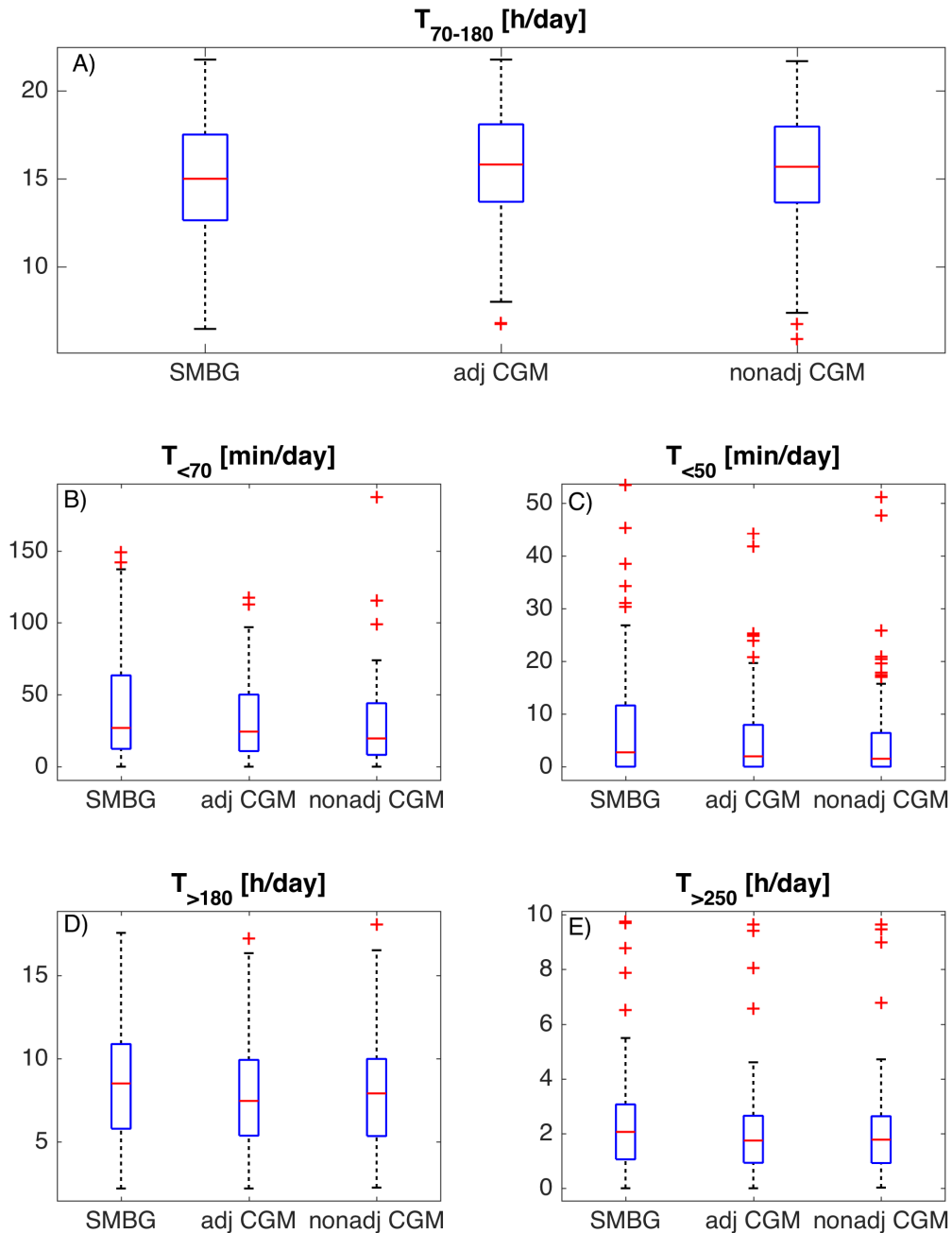
**Table 4.3:** Metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated for treatments based on SMBG, adjunctive CGM use and nonadjunctive CGM use simulated for two-weeks in 100 adult virtual subjects by the T1D-DM model. Median (interquartile range) of the outcomes is reported in columns 2-4. P-values of the paired two-tailed sign test comparing nonadjunctive CGM use vs SMBG use and nonadjunctive CGM use vs adjunctive CGM use are reported in columns 5-6.

<b>Metric</b>	<b>SMBG (A)</b>	<b>adj CGM (B)</b>	<b>nonadj CGM (C)</b>	<b>P-value C vs A</b>	<b>P-value C vs B</b>
$T_{70-180}$ [h/day]	15.00 (12.64-17.52)	15.82 (13.69-18.10)	15.69 (13.65-17.98)	<0.00001	0.76418
$T_{<70}$ [min/day]	26.93 (12.39-63.43)	24.36 (10.82-50.10)	19.64 (8.21-44.11)	<0.00001	<0.00001
$T_{<50}$ [min/day]	2.72 (0.00-11.61)	1.97 (0.00-7.93)	1.50 (0.00-6.39)	0.00002	0.01866
$T_{>180}$ [h/day]	8.51 (5.80-10.87)	7.47 (5.38-9.93)	7.92 (5.35-9.98)	0.00004	0.01241
$T_{>250}$ [h/day]	2.06 (1.06-3.06)	1.75 (0.93-2.65)	1.78 (0.92-2.63)	<0.00001	0.01543

use of CGM (both adjunctive and nonadjunctive) drives to a reduction of the time spent below 70 mg/dl, below 50 mg/dl, above 180 mg/dl and above 250 mg/dl and an increase of time spent in the euglycemic range (70-180 mg/dl), compared to the use of SMBG. If we compare adjunctive CGM use to nonadjunctive CGM use, no difference is visible in the distribution of  $T_{70-180}$ ,  $T_{>180}$  and  $T_{>250}$ , while  $T_{<70}$  and  $T_{<50}$  are concentrated to smaller values with nonadjunctive CGM use.

Median and interquartile range (in brackets) of time-related outcomes are reported in Table 4.3 for the three treatment scenarios. In particular, the nonadjunctive use of CGM (fourth column of Table 4.3), compared to SMBG (second column of Table 4.3), increases median  $T_{70-180}$  from 15.00 h/day to 15.69 h/day, reduces median  $T_{<70}$  from 26.93 min/day to 19.64 min/day, almost halves median  $T_{<50}$  reducing it from 2.72 min/day to 1.5 min/day, decreases median  $T_{>180}$  from 8.51 h/day to 7.92 h/day and  $T_{>250}$  from 2.06 h/day to 1.78 h/day. The paired two-tailed sign test, with 5% significance level, detects statistically significant differences between nonadjunctive CGM use and SMBG use for all the outcomes considered (p-values reported in the fifth column of Table 4.3).

Compared to adjunctive CGM use, nonadjunctive use of CGM drives to



**Figure 4.1:** Boxplot of  $T_{70-180}$  (panel A),  $T_{<70}$  (panel B),  $T_{<50}$  (panel C),  $T_{>180}$  (panel D) and  $T_{>250}$  (panel E) for treatments based on SMBG (left), adjunctive CGM use (middle) and nonadjunctive CGM use (right) simulated for two weeks in 100 adult virtual subjects by the T1D-DM model.

#### 4 Use of T1D-DM model in an ISCT to assess safety and efficacy of nonadjunctive CGM use vs SMBG and adjunctive CGM use

**Table 4.4:** Rate [events/year] and median (interquartile range) of the duration [min] of events below 70 mg/dl and below 50 mg/dl obtained in 100 virtual subjects simulated for two weeks with treatment based on SMBG, CGM adjunctive use and CGM nonadjunctive use.

Metric		SMBG	adj CGM	nonadj CGM
Events below 70 mg/dl	Rate [events/year]	225	229	206
	Duration [min]	56 (45 - 73)	51 (40.25 - 63)	50 (36 - 62)
Events below 50 mg/dl	Rate [events/year]	128	99	84
	Duration [min]	26.5 (19 - 35)	23 (16 - 33)	22 (14 - 32)

equivalent median time  $T_{70-180}$  and median  $T_{>250}$ , slightly higher median  $T_{>180}$  (7.47 h/day with adjunctive use, 7.92 h/day with nonadjunctive use), but lower median  $T_{<70}$  (24.36 min/day with adjunctive use, 19.64 min/day with nonadjunctive use) and  $T_{<50}$  (1.97 min/day with adjunctive use, 1.5 min/day with nonadjunctive use). Such differences are because in the treatment based on nonadjunctive use of CGM, which includes the use of trend arrows, the treatment of hyperglycemia is less aggressive and the treatment of hypoglycemia is more preventing. Indeed, in this treatment, when the CGM reading is between 180 mg/dl and 250 mg/dl correction boluses are given only if the trend arrow is flat or upward, and when CGM reading is between 80 mg/dl and 70 mg/dl hypotreatments are given if the trend arrow is downward. Conversely, in the treatment based on adjunctive CGM use, correction boluses and hypotreatments are given when SMBG measurements are above 180 mg/dl and below 70 mg/dl, respectively, regardless of the trend arrow. P-values obtained by the paired two-tailed sign test between median outcomes with adjunctive CGM use and nonadjunctive CGM use are reported in the sixth column of Table 4.3. No statistically significant difference is found in median  $T_{70-180}$  (p-value>0.05), but statistically significant differences in  $T_{<50}$ ,  $T_{<70}$ ,  $T_{>180}$  and  $T_{>250}$  are found (p-value<0.05).

Finally, in Table 4.4 we report the rate [events/year] of events below 70 mg/dl and events below 50 mg/dl and the median and the interquartile range (in brackets) of their duration [min], for the three treatment scenarios considered. Compared to SMBG, nonadjunctive use of CGM reduces both the rate and the median duration of events below 70 mg/dl and events below 50



mg/dl, with best results achieved for events below 50 mg/dl, whose rate and median duration are reduced of about 34% and 17%, respectively. Compared to adjunctive CGM use, the nonadjunctive use of CGM drives to equivalent duration but significantly lower rate of both events below 70 mg/dl (event rate reduced from 229 events/year to 206 events/year) and events below 50 mg/dl (event rate reduced from 99 events/year to 84 events/year).

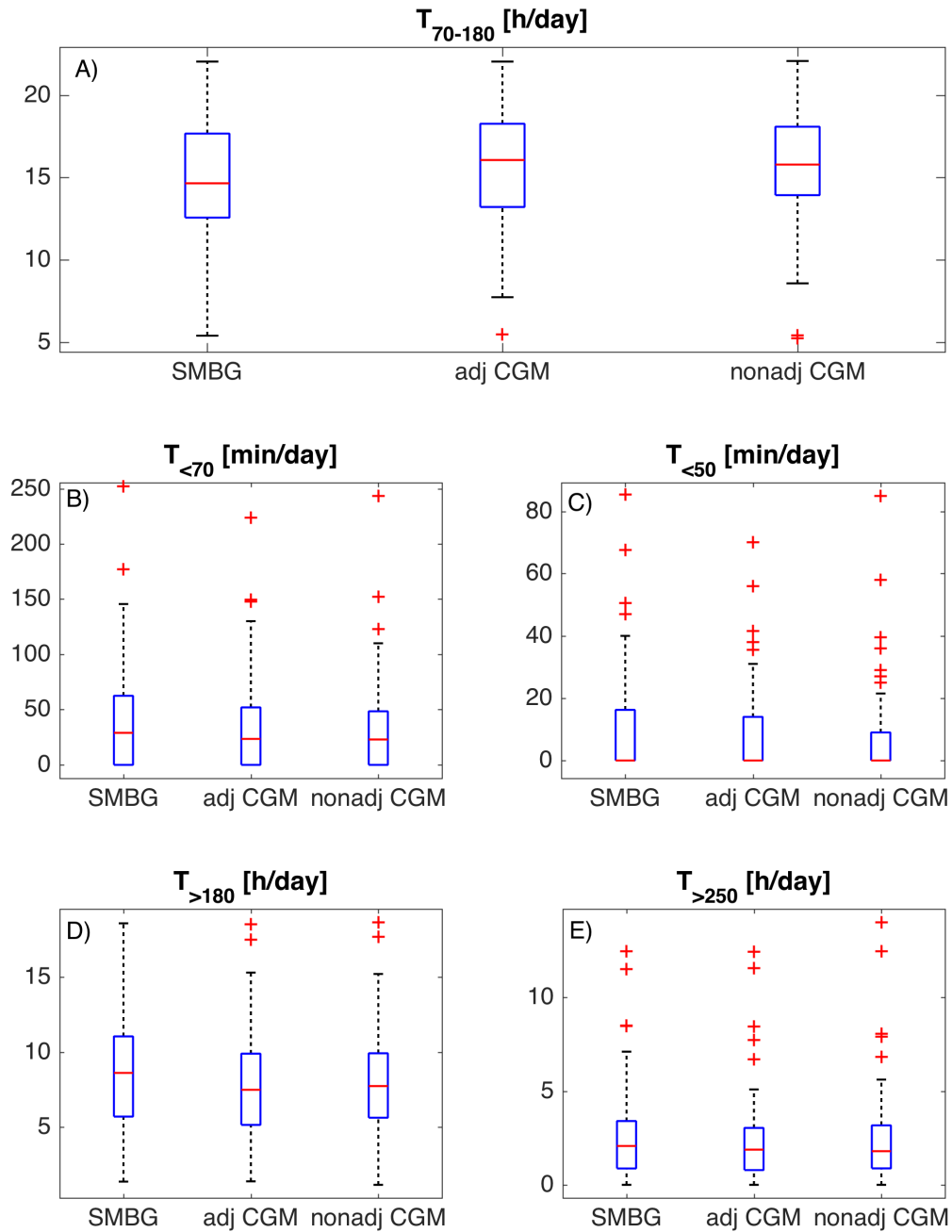
### Day 1 of CGM monitoring

Since CGM sensors generally present the worst performance in the first day of monitoring, because of the immune response to the sensor insertion and difficulty in sensor calibration, here the metrics obtained with the three treatments under test are separately assessed on day 1 of CGM monitoring (days 1 and 8 of the entire simulation period). In Figure 4.2 the boxplot of  $T_{70-180}$  (panel A),  $T_{<70}$  (panel B),  $T_{<50}$  (panel C),  $T_{>180}$  (panel D) and  $T_{>250}$  (panel E), evaluated on day 1 of CGM monitoring, are reported for treatment based on SMBG use (left), adjunctive CGM use (middle) and nonadjunctive CGM use (right). From this representation we can observe that nonadjunctive use of CGM drives to an improvement of the time spent in euglycemia ( $T_{70-180}$ ) and severe hypoglycemia ( $T_{<50}$ ) compared to both SMBG use and adjunctive use of CGM. Compared to SMBG, the use of CGM allows to improve time in hypoglycemia ( $T_{<70}$ ) with similar performance for adjunctive and nonadjunctive use. Finally, metrics related to hyperglycemia ( $T_{>180}$  and  $T_{>250}$ ) with nonadjunctive use of CGM are slightly worsen in comparison to adjunctive CGM use, but anyway improved compared to SMBG use.

In Table 4.5 the median and the interquartile range (in brackets) of time-related glycemetic outcomes, calculated on day 1 of CGM monitoring, are reported for SMBG use (second column), adjunctive CGM use (third column) and nonadjunctive CGM use (fourth column). In particular, both median and interquartile range of metrics with nonadjunctive use of CGM are improved compared to SMBG treatment. The improvement is found statistically significant ( $p$ -value $<0.05$ ), according to paired two-tailed sign test, for all the outcomes except for  $T_{>180}$  for which no statistically significant difference is found between nonadjunctive CGM use and SMBG use (see  $p$ -values reported in the fifth column of Table 4.5). Compared to adjunctive use of CGM, nonadjunctive CGM use drives to similar median and interquartile range of metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{>180}$ ,  $T_{>250}$  and equal median but significantly reduced interquartile

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**Figure 4.2:** Boxplot of  $T_{70-180}$  (panel A),  $T_{<70}$  (panel B),  $T_{<50}$  (panel C),  $T_{>180}$  (panel D) and  $T_{>250}$  (panel E) calculated on day 1 of CGM monitoring for treatments based on SMBG (left), adjunctive CGM use (middle) and nonadjunctive CGM use (right) simulated for two weeks in 100 adult virtual subjects by the T1D-DM model.

**Table 4.5:** Metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated on day 1 of CGM monitoring for treatments based on SMBG, adjunctive CGM use and nonadjunctive CGM use, simulated for two-weeks in 100 adult virtual subjects by the T1D-DM model. Median (interquartile range) of the outcomes is reported in columns 2-4. P-values of the paired two-tailed sign test comparing nonadjunctive CGM use vs SMBG use and nonadjunctive CGM use vs adjunctive CGM use are reported in columns 5-6.

<b>Metric</b>	<b>SMBG (A)</b>	<b>adj CGM (B)</b>	<b>nonadj CGM (C)</b>	<b>P-value C vs A</b>	<b>P-value C vs B</b>
$T_{70-180}$ [h/day]	14.66 (12.57-17.67)	16.07 (13.22-18.27)	15.79 (13.93-18.09)	0.00194	0.19360
$T_{<70}$ [min/day]	29 (0.00-62.50)	23.50 (0.00-52.00)	23.00 (0.00-48.50)	0.00954	0.34247
$T_{<50}$ [min/day]	0.00 (0.00-16.25)	0.00 (0.00-14.00)	0.00 (0.00-9.00)	0.00126	0.87463
$T_{>180}$ [h/day]	8.61 (5.70-11.05)	7.49 (5.15-9.90)	7.74 (5.63-9.92)	0.05743	0.08913
$T_{>250}$ [h/day]	2.08 (0.88-3.40)	1.88 (0.79-3.04)	1.80 (0.88-3.18)	0.01240	0.04701

**Table 4.6:** Rate [events/year] and median (interquartile range) of the duration [min] of events below 70 mg/dl and below 50 mg/dl obtained in day 1 of CGM monitoring in 100 virtual subjects simulated for two weeks with treatment based on SMBG, adjunctive CGM use and nonadjunctive CGM use.

<b>Metric</b>		<b>SMBG</b>	<b>adj CGM</b>	<b>nonadj CGM</b>
Events below 70 mg/dl	Rate [events/year]	254	248	232
	Duration [min]	56 (44 - 68.75)	50 (41 - 62)	50 (37.25 - 60)
Events below 50 mg/dl	Rate [events/year]	135	106	102
	Duration [min]	29.5 (20 - 37)	26.5 (18 - 33)	23 (16 - 30)

range of  $T_{<50}$ . The only statistically significant difference on median outcomes is detected for  $T_{>250}$  (see p-values reported in the sixth column of Table 4.5).

Eventually, in Table 4.6 the year rate and the median and the interquartile range of duration [min] of events below 70 mg/dl and events below 50 mg/dl are reported for the three treatments tested. Concerning events below 70 mg/dl, nonadjunctive CGM use allows to reduce the number of events per

year compared to both SMBG and adjunctive CGM use, while the median duration of events is equal between adjunctive and nonadjunctive use of CGM and reduced compared to standard treatment based on SMBG. With regard to events below 50 mg/dl, nonadjunctive CGM use drives to reduced year rate and event duration compared to SMBG treatment and treatment with adjunctive use of CGM.

#### **4.4 Summary outcome of the ISCT**

To summarize, this ISCT demonstrated that, in a population of 100 adult virtual subjects which reflects the characteristics of a general population of T1D adults, nonadjunctive CGM use is safe and effective in improving glycemic control compared to standard SMBG treatment, driving to an increase of the time spent in euglycemia, and a reduction of the time spent in hypoglycemia and hyperglycemia. Of note, both the year rate and the duration of events below 50 mg/dl and 70 mg/dl are reduced compared to SMBG use.

The trial also demonstrated that nonadjunctive CGM use drives to equivalent time in euglycemia, slightly increased time in hyperglycemia but reduced time in hypoglycemia compared to adjunctive use of CGM, suggesting that nonadjunctive CGM use is as safe as adjunctive CGM use and thus CGM can safely replace SMBG for making T1D treatment decisions.

These considerations still hold when glycemic control is separately assessed in day 1 of CGM monitoring, thus suggesting that CGM can be safely used nonadjunctively also in the first day after sensor insertion.

# Chapter 5

## Use of T1D-DM model in ISCT to assess the influence of alert settings on nonadjunctive CGM use

In this chapter, the T1D-DM model is used to design a second ISCT whose aim is to assess how the setting of customized high and low glucose alert influences the glycemic control achieved by nonadjunctive CGM use compared to standard treatment based on SMBG.

### 5.1 Design of the ISCT

Simulations are performed on the 100 adult virtual subjects of the UVA/Padova T1D simulator over a two-week period. Two treatments are compared: standard treatment based on SMBG with 4 different frequencies of post-meal checks vs nonadjunctive use of CGM with 21 different alert settings. The final aim is to identify if for certain combinations of high and low glucose alert threshold nonadjunctive use of CGM introduces additional risks compared to standard SMBG treatment. As in the ISCT of Chapter 4, SMBG and CGM measurements are simulated using the error models of BCN and the Dexcom G5 Mobile, respectively, derived in Chapter 3.

#### 5.1.1 Setting of simulation parameters

Three meals per day are simulated sampling meals' amount and time as in the previous ISCT. As already mentioned, the SMBG treatment is repeated for all the subjects with 4 different number of post-meal checks per day (PMC),

i.e. 0, 1, 2 or 3. In case of PMC lower than 3, meals with post-meal checks are randomly selected. As in the previous ISCT, pre-sleep SMBG checks are also simulated every day at 10:00 pm. Note that the 4 repetitions of SMBG treatment differs for the frequency of post-meal checks only. The realizations of SMBG error, meals' amount, time, CHO counting error and bolus time error as well as all the other simulation parameters remain the same when the same subject is considered. This allows us to isolate the effect of post-meal check frequency on SMBG treatment performance.

The nonadjunctive CGM use is repeated for 21 representative alert settings derived by combining 3 values for the low alert (LA) threshold, i.e. 80 mg/dl, 70 mg/dl, and 55 mg/dl, and 7 values for the high alert (HA) threshold, i.e. 180 mg/dl, 200 mg/dl, 250 mg/dl, 300 mg/dl, 350 mg/dl, 400 mg/dl or not used. It is useful to remark that we do not investigate the use of LA thresholds lower than 55 mg/dl, because in the Dexcom G5 Mobile system, even when the LA is not used, the low glucose alarm set at 55 mg/dl is still active. Therefore, the case with LA set to 55 mg/dl actually includes all the cases in which the LA is set to values lower than 55 mg/dl or not used. Note that at each repetition we only change the value of alert thresholds, while the other simulation parameters and realizations of CGM sensor error, meals' amount, time, CHO counting errors and bolus time errors remain exactly the same, letting us isolate the effect of alert settings on nonadjunctive CGM performance.

Therapy parameters are set as in the previous ISCT, thus  $CR$ ,  $CF$ ,  $BDI$  are calculated according to guidelines by Davidson et al. [6] and  $G_{target}$  is set to the basal BG value specific of each virtual subjects.

Finally, all the simulations are repeated twice, first assuming that subjects present a normal awareness of hypoglycemia, then assuming subjects suffer from impaired awareness of hypoglycemia. In the first case, the threshold of hypoglycemia awareness is uniformly sampled in the interval 50-60 mg/dl, while in the second case in the interval 40-50 mg/dl. This allows us to analyze nonadjunctive CGM use performance also in the population of subject with impaired awareness of hypoglycemia which present the highest risk of severe hypoglycemia.

Overall, 50 simulations [(4 repetitions of SMBG treatment + 21 repetitions of CGM treatment)  $\times$  2 hypoawareness states] are performed per subjects, for a total of 5.000 two-week simulations. Note that the meal scenario, including meals' time, amount, CHO counting errors and meal bolus time error, is fixed for each subjects. In this way, for each subject, SMBG and nonadjunctive CGM

use are compared over the same meal scenario, ensuring that differences in glycemic outcomes are only caused by the different treatment used and not by other confounding factors.

## 5.2 Metrics

The glycemic control achieved in each virtual subject by the treatments under test is assessed by evaluation of  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$ . In addition for each subject we also calculate  $\Delta T_{70-180}$  [h/day],  $\Delta T_{<70}$  [min/day],  $\Delta T_{<50}$  [min/day],  $\Delta T_{>180}$  [h/day] and  $\Delta T_{>250}$  [h/day], i.e. the difference between  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  with treatment based on nonadjunctive CGM use and the same metrics with worst-case SMBG treatment. More precisely, for each metric related to the time spent in a certain zone of the glycemic range we identify among the four post-meal check frequencies tested with SMBG treatment the one that represents the worst case for SMBG treatment. Our expectation is that PMC equal to 0 represents the worst case for  $T_{>180}$ ,  $T_{>250}$  and  $T_{70-180}$ , while PMC equal to 3 represents the worst case for  $T_{<70}$  and  $T_{<50}$ . Then, for each alert setting tested, the difference between the metric with nonadjunctive CGM use and the worst-case SMBG treatment is calculated. A paired sign test on the median is also applied to determine if differences observed between the metrics are statistically significant. Finally, the alert settings that drives to statistically significant deterioration of metrics with nonadjunctive CGM use compared to worst-case SMBG treatment are identified.

The analysis is performed separately in the population with normal and impaired awareness of hypoglycemia. First the assessment is performed in the entire CGM monitoring period, then separately on day 1 of CGM monitoring, being this day the most critical for CGM accuracy.

## 5.3 Results

Results of the ISCT designed for assessing the influence of alert settings on safety and effectiveness of nonadjunctive CGM use are presented in this section, first for the entire CGM monitoring period, then separately for day 1 of CGM monitoring (i.e. days 1 and 8 of simulation).

### 5.3.1 Entire CGM monitoring period

In Figure 5.1, panels from top to bottom report the median values of metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated in 100 adult virtual subjects with normal (left) and impaired (right) awareness of hypoglycemia simulated over a two-week period. In particular, in each panel of Figure 5.1, the red horizontal lines represent metric's median value for the SMBG treatment with PMC equal to 0 (solid line), 1 (dashed line), 2 (dash-dot line) and 3 (dotted line), while the blue curves represent the metric's median value obtained using CGM nonadjunctively with LA threshold equal to 80 mg/dl (dashed line with squared markers), 70 mg/dl (solid line with circular markers) and 55 mg/dl (dotted line with triangular markers), on varying HA threshold (values on the x-axis). Median values of metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  obtained for SMBG treatment with different PMC are also reported in Table 5.1 and Table 5.2, together with the interquartile range (in brackets), for subjects with normal and impaired awareness of hypoglycemia, respectively. In Table 5.3 and Table 5.4 median and interquartile range (in brackets) of outcomes obtained for nonadjunctive CGM use with different settings of LA and HA is tabulated for subjects with normal and impaired awareness of hypoglycemia, respectively.

From the representation of Figure 5.1 it is immediate to note that, when CGM is used nonadjunctively, the HA threshold mainly influences metrics  $T_{70-180}$ ,  $T_{>180}$  and  $T_{>250}$ , while not affecting metrics  $T_{<70}$  and  $T_{<50}$ , whose curves on varying HA threshold appear flat. A complementary behavior is obtained for the LA threshold, which mainly influences metrics  $T_{<70}$  and  $T_{<50}$ , without showing any impact on metrics  $T_{70-180}$ ,  $T_{>180}$  and  $T_{>250}$ , as demonstrated by the overlapping of these metrics' curves with different values of LA threshold.

Looking at Figure 5.1, we can also observe that, both in the SMBG treatment and in the treatment based on nonadjunctive CGM use, the level of hypoglycemia awareness only affects metrics  $T_{<70}$  and  $T_{<50}$ , while  $T_{70-180}$ ,  $T_{>180}$  and  $T_{>250}$  present a similar pattern in the populations with normal and impaired awareness of hypoglycemia.

If we compare nonadjunctive CGM use to SMBG use, we can make the following observations. First of all, median  $T_{70-180}$  is improved compared to best case with SMBG, i.e. SMBG with PMC=3, only when HA threshold is 180 mg/dl or 200 mg/dl. By increasing HA threshold,  $T_{70-180}$  progressively

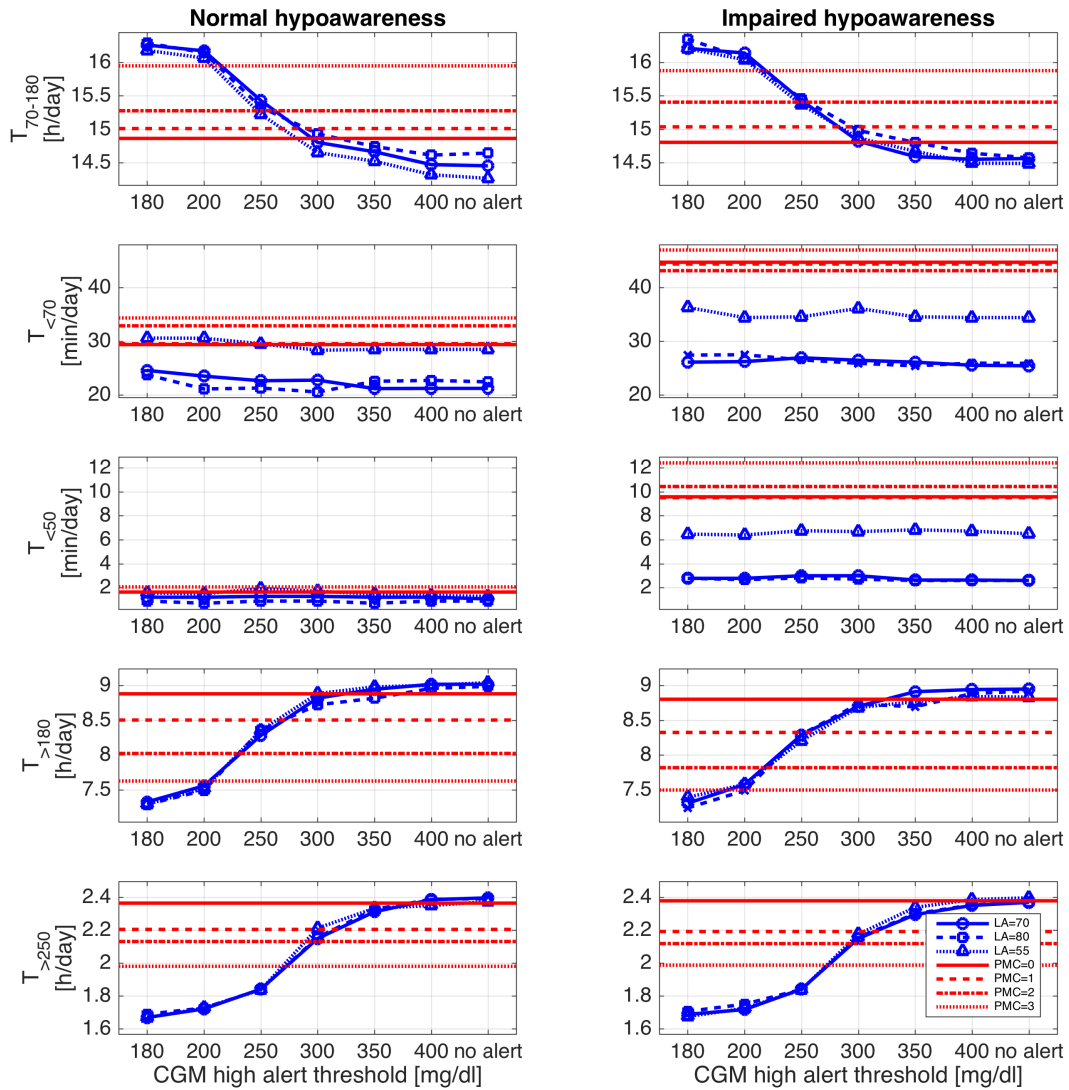


decreases till becoming lower than that obtained with worst-case SMBG treatment, i.e. SMBG treatment with  $PMC=0$ , when HA is greater or equal than 350 mg/dl. Similar observations can be made for metrics  $T_{>180}$  and  $T_{>250}$ . In particular, for low values of HA threshold, like 180 mg/dl and 200 mg/dl,  $T_{>180}$  with nonadjunctive CGM use is lower than best case with SMBG, i.e. SMBG with  $PMC=3$ , and then progressively increases with HA threshold, till becoming equivalent to or slightly higher than worst-case with SMBG when HA threshold is greater than 350 mg/dl. The behavior of  $T_{>250}$  is very similar with the only difference that  $T_{>250}$  with nonadjunctive CGM use becomes greater than best case with SMBG, i.e. SMBG with  $PMC=3$ , only for HA greater than 250 mg/dl.

Concerning metrics related to hypoglycemia, in the population with normal awareness of hypoglycemia,  $T_{<70}$  with nonadjunctive CGM use and LA threshold equal to 55 mg/dl results equivalent to best case with SMBG treatment, i.e. SMBG with  $PMC=0$ . When LA is equal to 70 mg/dl or 80 mg/dl,  $T_{<70}$  with nonadjunctive CGM use is significantly lower than  $T_{<70}$  in the best-case SMBG scenario, with small differences between LA equal to 70 mg/dl and 80 mg/dl. In the population with normal awareness of hypoglycemia, median  $T_{<50}$  is very close to 0 both in SMBG and CGM treatment (slightly smaller values are obtained with CGM treatment and LA threshold equal to 80 mg/dl and 70 mg/dl), since in this population symptoms of hypoglycemia appears at glucose levels greater than 50 mg/dl, thus allowing the patient to act to prevent severe hypoglycemia even in the SMBG treatment where LA is not available.

In the population with impaired awareness of hypoglycemia, median values of both  $T_{<70}$  and  $T_{<50}$  are significantly reduced with nonadjunctive CGM use compared to best case with SMBG for all the values of LA threshold. Indeed, in this population symptoms of hypoglycemia appears at glucose levels lower than 50 mg/dl, thus the use of LA, even when set to 55 mg/dl, allows to reduce the incidence of severe hypoglycemia compared to the SMBG treatment. Also in this population not significant differences are visible in median  $T_{<70}$  and  $T_{<50}$  with LA threshold equal to 70 mg/dl and 80 mg/dl. The reason is that according to the behavioral rules of nonadjunctive CGM use adopted for hypoglycemia treatment (see Section 3.4.3), when LA is set to 80 mg/dl, the patient takes a hypotreatment after a LA goes off only if CGM is displaying a downward trend arrow, otherwise the patient waits till CGM reads a glucose values lower than 70 mg/dl before treating.

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**Figure 5.1:** Panels from top to bottom show the median of metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated in 100 adult virtual subjects with normal (left) and impaired (right) awareness of hypoglycemia. In each panel, red horizontal lines represent the metric's median value when SMBG treatment is used with PMC equal to 0 (solid line), 1 (dashed line), 2 (dash-dot line) and 3 (dotted line). Blue curves represent metric's median value obtained for nonadjunctive CGM use on varying HA threshold with LA threshold equal to 80 mg/dl (dashed line with squared markers), 70 mg/dl (solid line with circular markers) and 55 mg/dl (dotted line with triangular markers).

**Table 5.1:** Median (interquartile range) of metrics  $T_{70-180}$  (second column),  $T_{<70}$  (third column),  $T_{<50}$  (fourth column),  $T_{>180}$  (fifth column),  $T_{>250}$  (sixth column) obtained in 100 adult virtual subjects with normal awareness of hypoglycemia simulated for two weeks with treatment based on SMBG and different number of post-meal checks per day (first column).

PMC	$T_{70-180}$ [h/day]	$T_{<70}$ [min/day]	$T_{<50}$ [min/day]	$T_{>180}$ [h/day]	$T_{>250}$ [h/day]
3	15.95 (13.50-17.83)	34.32 (14.18-57.60)	2.07 (0.00-9.21)	7.63 (5.47-10.19)	1.98 (0.88-2.75)
2	15.28 (13.12-17.62)	32.85 (14.28-58.46)	1.64 (0.00-8.68)	8.02 (5.52-10.41)	2.13 (0.92-2.89)
1	15.01 (12.78-17.62)	29.50 (12.57-54.42)	1.64 (0.00-7.86)	8.50 (5.79-11.10)	2.20 (1.00-3.13)
0	14.86 (12.15-17.30)	29.35 (10.18-53.07)	1.64 (0.00-7.96)	8.88 (6.12-11.42)	2.36 (1.04-3.41)

**Table 5.2:** Median (interquartile range) of metrics  $T_{70-180}$  (second column),  $T_{<70}$  (third column),  $T_{<50}$  (fourth column),  $T_{>180}$  (fifth column),  $T_{>250}$  (sixth column) obtained in 100 adult virtual subjects with impaired awareness of hypoglycemia simulated for two weeks with treatment based on SMBG and different number of post-meal checks per day (first column).

PMC	$T_{70-180}$ [h/day]	$T_{<70}$ [min/day]	$T_{<50}$ [min/day]	$T_{>180}$ [h/day]	$T_{>250}$ [h/day]
3	15.88 (13.50-17.66)	47.00 (18.18-79.88)	12.43 (3.64-24.75)	7.50 (5.50-9.69)	1.99 (0.87-2.70)
2	15.41 (13.01-17.48)	43.14 (17.00-74.74)	10.43 (3.50-24.46)	7.82 (5.64-10.33)	2.12 (0.89-2.87)
1	15.04 (12.77-17.50)	44.09 (17.21-71.89)	9.50 (2.96-23.93)	8.32 (5.73-10.75)	2.19 (0.95-3.13)
0	14.80 (12.27-17.22)	44.71 (14.03-71.10)	9.57 (3.43-22.75)	8.80 (5.86-11.26)	2.38 (1.02-3.34)

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**Table 5.3:** Median (interquartile range) of metrics  $T_{70-180}$  (third column),  $T_{<70}$  (fourth column),  $T_{<50}$  (fifth column),  $T_{>180}$  (sixth column),  $T_{>250}$  (seventh column) obtained in 100 adult virtual subjects with normal awareness of hypoglycemia simulated for two weeks with treatment based on nonadjunctive use of CGM and 21 different combinations of LA (first column) and HA (second column).

LA [mg/dl]	HA [mg/dl]	$T_{70-180}$ [h/day]	$T_{<70}$ [min/day]	$T_{<50}$ [min/day]	$T_{>180}$ [h/day]	$T_{>250}$ [h/day]
80	180	16.29 (14.01-18.68)	23.71 (6.82-38.96)	0.89 (0.00-4.00)	7.29 (5.04-9.44)	1.69 (0.76-2.64)
80	200	16.15 (13.89-18.08)	21.07 (7.46-38.03)	0.71 (0.00-4.18)	7.49 (5.41-9.80)	1.73 (0.77-2.65)
80	250	15.33 (13.10-17.47)	21.25 (7.39-37.89)	0.89 (0.00-4.29)	8.36 (6.02-10.44)	1.84 (0.89-2.73)
80	300	14.93 (12.54-17.32)	20.50 (7.39-38.71)	0.89 (0.00-3.82)	8.72 (6.25-11.02)	2.16 (1.02-2.96)
80	350	14.74 (12.30-17.30)	22.50 (7.21-38.78)	0.71 (0.00-3.68)	8.82 (6.36-11.33)	2.33 (1.03-3.17)
80	400	14.61 (12.25-17.37)	22.68 (7.21-38.46)	0.89 (0.00-3.54)	8.96 (6.30-11.40)	2.39 (1.03-3.29)
80	not used	14.64 (12.17-17.22)	22.39 (7.14-37.78)	0.89 (0.00-3.43)	8.99 (6.40-11.42)	2.39 (1.07-3.37)
70	180	16.26 (13.94-18.47)	24.53 (8.78-42.07)	1.21 (0.00-5.57)	7.33 (5.16-9.47)	1.67 (0.76-2.62)
70	200	16.17 (13.92-18.06)	23.46 (8.50-42.17)	1.21 (0.00-5.79)	7.56 (5.36-9.76)	1.72 (0.78-2.62)
70	250	15.43 (13.03-17.48)	22.60 (8.00-39.25)	1.29 (0.00-6.04)	8.28 (6.06-10.49)	1.84 (0.91-2.75)
70	300	14.80 (12.50-17.37)	22.71 (7.96-40.10)	1.29 (0.00-5.43)	8.82 (6.19-11.08)	2.15 (1.02-2.97)
70	350	14.66 (12.32-17.35)	21.14 (7.68-39.03)	1.21 (0.00-5.57)	8.94 (6.31-11.34)	2.31 (1.04-3.18)
70	400	14.47 (12.19-17.34)	21.18 (7.68-39.21)	1.21 (0.00-5.32)	9.02 (6.32-11.49)	2.39 (1.04-3.28)
70	not used	14.45 (12.23-17.25)	21.18 (6.89-37.89)	1.07 (0.00-5.11)	9.02 (6.35-11.49)	2.40 (1.09-3.37)
55	180	16.18 (13.77-18.25)	30.57 (11.50-51.46)	1.57 (0.00-7.04)	7.30 (5.18-9.62)	1.67 (0.76-2.59)
55	200	16.06 (13.70-17.98)	30.53 (14.14-50.10)	1.50 (0.00-7.00)	7.52 (5.33-9.76)	1.73 (0.77-2.62)
55	250	15.22 (12.90-17.33)	29.50 (10.36-50.10)	1.93 (0.00-7.28)	8.35 (6.00-10.46)	1.84 (0.91-2.74)
55	300	14.65 (12.26-17.16)	28.28 (10.71-48.07)	1.71 (0.00-7.32)	8.88 (6.24-11.14)	2.21 (1.03-3.00)
55	350	14.52 (11.98-16.99)	28.46 (10.18-49.53)	1.46 (0.00-7.18)	8.98 (6.34-11.41)	2.33 (1.03-3.29)
55	400	14.32 (11.94-17.00)	28.46 (10.18-47.96)	1.36 (0.00-6.86)	9.00 (6.34-11.49)	2.35 (1.04-3.34)
55	not used	14.26 (11.85-16.98)	28.46 (8.57-46.92)	1.29 (0.00-6.61)	9.04 (6.41-11.53)	2.37 (1.05-3.44)

**Table 5.4:** Median (interquartile range) of metrics  $T_{70-180}$  (third column),  $T_{<70}$  (fourth column),  $T_{<50}$  (fifth column),  $T_{>180}$  (sixth column),  $T_{>250}$  (seventh column) obtained in 100 adult virtual subjects with impaired awareness of hypoglycemia simulated for two weeks with treatment based on nonadjunctive use of CGM and 21 different combinations of LA (first column) and HA (second column).

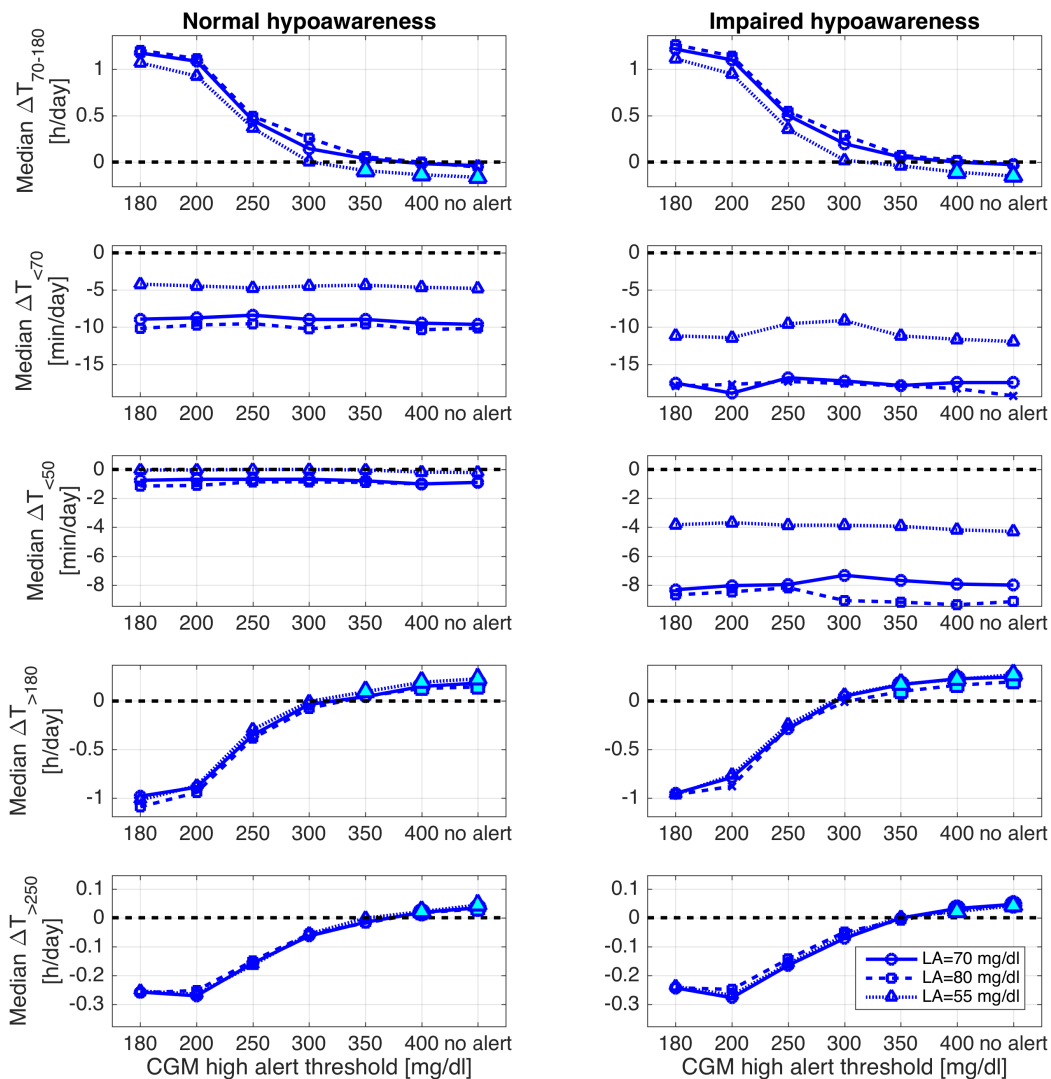
LA [mg/dl]	HA [mg/dl]	$T_{70-180}$ [h/day]	$T_{<70}$ [min/day]	$T_{<50}$ [min/day]	$T_{>180}$ [h/day]	$T_{>250}$ [h/day]
80	180	16.35 (14.02-18.76)	27.39 (7.46-46.25)	2.79 (0.00-7.53)	7.24 (5.07-9.37)	1.71 (0.76-2.66)
80	200	16.06 (13.79-18.13)	27.46 (7.71-46.50)	2.68 (0.00-8.00)	7.49 (5.25-9.68)	1.75 (0.76-2.66)
80	250	15.46 (13.08-17.60)	26.50 (7.89-44.00)	2.82 (0.00-7.57)	8.29 (5.78-10.32)	1.84 (0.91-2.74)
80	300	14.98 (12.60-17.32)	25.85 (7.86-45.21)	2.71 (0.00-7.78)	8.73 (6.24-10.89)	2.16 (1.02-2.99)
80	350	14.80 (12.30-17.30)	25.39 (8.82-41.53)	2.61 (0.00-8.07)	8.69 (6.37-11.21)	2.30 (1.03-3.20)
80	400	14.64 (12.25-17.36)	25.89 (8.82-41.64)	2.61 (0.00-7.71)	8.88 (6.31-11.28)	2.35 (1.03-3.30)
80	not used	14.57 (12.25-17.22)	25.85 (7.64-41.07)	2.61 (0.00-7.32)	8.92 (6.41-11.41)	2.37 (1.08-3.39)
70	180	16.21 (13.96-18.55)	26.07 (9.61-45.89)	2.79 (0.00-9.00)	7.31 (5.14-9.40)	1.69 (0.76-2.62)
70	200	16.14 (13.82-17.98)	26.18 (9.71-44.96)	2.79 (0.00-9.86)	7.58 (5.25-9.78)	1.72 (0.76-2.62)
70	250	15.43 (13.03-17.58)	26.89 (8.89-44.53)	3.00 (0.00-9.53)	8.29 (6.01-10.42)	1.84 (0.92-2.71)
70	300	14.82 (12.49-17.42)	26.43 (9.14-43.85)	3.00 (0.00-9.75)	8.70 (6.19-10.96)	2.15 (1.01-2.96)
70	350	14.59 (12.23-17.43)	26.07 (9.21-42.46)	2.64 (0.00-9.86)	8.91 (6.31-11.16)	2.29 (1.03-3.18)
70	400	14.55 (12.19-17.43)	25.50 (9.46-43.03)	2.64 (0.00-8.82)	8.94 (6.31-11.22)	2.35 (1.03-3.30)
70	not used	14.56 (12.18-17.34)	25.39 (8.82-42.71)	2.61 (0.00-8.82)	8.95 (6.35-11.41)	2.37 (1.07-3.40)
55	180	16.20 (13.74-18.17)	36.28 (14.18-59.35)	6.46 (1.61-15.21)	7.39 (4.98-9.38)	1.67 (0.77-2.61)
55	200	16.04 (13.52-17.87)	34.39 (15.64-59.92)	6.39 (1.61-15.21)	7.58 (5.39-9.80)	1.72 (0.79-2.62)
55	250	15.37 (12.88-17.29)	34.53 (12.03-55.10)	6.75 (1.93-14.78)	8.20 (5.95-10.41)	1.84 (0.92-2.75)
55	300	14.87 (12.30-17.05)	36.10 (12.43-55.49)	6.68 (1.71-15.46)	8.68 (6.20-11.09)	2.18 (1.01-2.97)
55	350	14.67 (12.07-16.89)	34.53 (11.89-54.85)	6.82 (1.82-14.96)	8.77 (6.24-11.23)	2.34 (1.03-3.16)
55	400	14.49 (11.93-16.90)	34.39 (11.89-54.49)	6.71 (1.68-15.07)	8.84 (6.26-11.29)	2.39 (1.05-3.30)
55	not used	14.49 (11.86-16.89)	34.39 (11.32-54.10)	6.50 (1.68-14.75)	8.83 (6.31-11.45)	2.40 (1.05-3.37)

To determine when nonadjunctive CGM use introduces additional risks compared to standard SMBG treatment, the difference between glycemic outcomes with nonadjunctive CGM use and worst-case SMBG treatment, i.e.  $\Delta T_{70-180}$ ,  $\Delta T_{<70}$ ,  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$ , is computed. According to the median outcomes showed in Figure 5.1, SMBG treatment with PMC=0 is considered the worst case for  $T_{70-180}$ ,  $T_{>180}$  and  $T_{>250}$ , while SMBG treatment with PMC=3 is considered the worst case for  $T_{<70}$  and  $T_{<50}$ . The median values of  $\Delta T_{70-180}$ ,  $\Delta T_{<70}$ ,  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  are reported from top to bottom in Figure 5.2 for patients with normal (left) and impaired (right) awareness of hypoglycemia. In particular, in each panel of Figure 5.2, the three blue curves represent the difference between the metric with nonadjunctive CGM use and worst-case SMBG use on varying HA threshold for LA equal to 80 mg/dl (dashed line with squared markers), 70 mg/dl (solid line with circular markers) and 55 mg/dl (dotted line with triangular markers). The paired one-tailed sign test with 5% significance level is applied to determine if the median difference of outcomes indicates a statistically significant deterioration of the outcome with nonadjunctive CGM use compared to worst-case SMBG treatment. In Figure 5.2, we evidence by light blue markers the combinations of LA and HA thresholds for which the median value of  $\Delta T_{70-180}$  is statistically significantly lower than 0 and the median values of  $\Delta T_{<70}$ ,  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  are statistically significantly greater than 0.

In the population with normal awareness of hypoglycemia,  $\Delta T_{70-180}$  is statistically significantly lower than zero, which means a statistically significant deterioration of  $T_{70-180}$  is achieved by nonadjunctive CGM use compared to worst case with SMBG (i.e. SMBG with PMC=0 in this case), only when LA threshold is set to 55 mg/dl and HA threshold is greater or equal than 350 mg/dl. In the population with impaired awareness of hypoglycemia, a statistically significant deterioration of  $T_{70-180}$  is detected again when LA is set to 55 mg/dl and HA threshold is greater or equal than 400 mg/dl.

Concerning  $T_{>180}$ , the sign test reveals a statistically significant deterioration, i.e. a value of  $\Delta T_{>180}$  significantly positive, when the HA threshold is greater or equal than 350 mg/dl, regardless of the LA setting, both in the normal and impaired hypoawareness population. Similarly,  $\Delta T_{>250}$  is found statistically significantly greater than 0 and, thus a statistically significant deterioration of  $T_{>250}$  is present, when HA is set to 400 mg/dl or higher, regardless of the LA threshold, both in the normal and impaired hypoawareness population.

Finally, both in the normal and impaired hypoawareness population,  $\Delta T_{<70}$  and  $\Delta T_{<50}$  are never statistically significantly greater than 0, which means for none alert settings, nonadjunctive CGM use deteriorates  $T_{<70}$  and  $T_{<50}$  compared to worst-case SMBG treatment (i.e. SMBG with PMC=3 in this case).



**Figure 5.2:** Panels from top to bottom show the median of  $\Delta T_{70-180}$ ,  $\Delta T_{<70}$ ,  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  calculated in 100 adult virtual subjects with normal (left) and impaired (right) awareness of hypoglycemia. In particular, in each panel, blue curves represent the metric's median value on varying HA threshold with LA threshold equal to 80 mg/dl (dashed line with squared markers), 70 mg/dl (solid line with circular markers) and 55 mg/dl (dotted line with triangular markers). Filled markers indicate the alert settings for which median  $\Delta T_{70-180}$  is statistically significantly lower than 0, and median  $\Delta T_{<70}$  and  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  are statistically significantly greater than 0, according to the paired one-tailed sign test with 5% significance level.

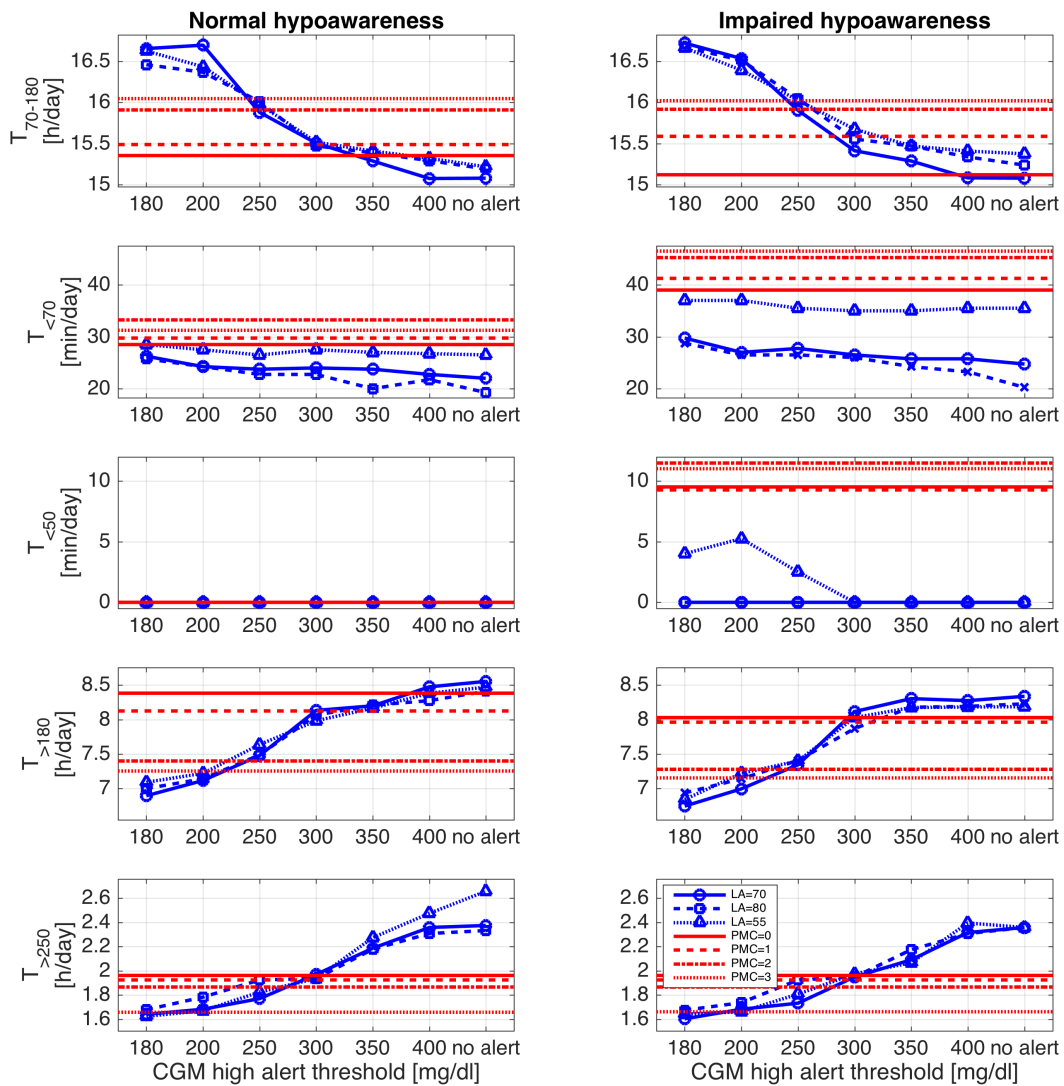
### 5.3.2 Day 1 of CGM monitoring

Glycemic outcomes are also assessed separately on day 1 of CGM monitoring, being this day the most critical for CGM accuracy. Median values of metrics  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated on day 1 of CGM monitoring for SMBG treatment and nonadjunctive CGM use are reported in Figure 5.3 for different values of PMC with SMBG and LA and HA thresholds with CGM. From this representation we can observe that in day 1 of CGM monitoring, glycemic outcomes present a similar pattern to that obtained in the entire CGM monitoring period and already commented above. The only difference is visible for  $T_{>250}$ , since nonadjunctive CGM use seems to be less effective in reducing time spent above 250 mg/dl in day 1 of CGM monitoring compared to the entire monitoring period. Indeed, even when the HA is set to 180 mg/dl, median  $T_{>250}$  in the CGM scenario results similar, and not significantly inferior as when assessed in the entire monitoring period, to that achieved with best-case SMBG scenario, i.e. SMBG use with PMC=3. In Figure 5.4, the median difference between outcomes with nonadjunctive CGM use and worst-case SMBG use is displayed. Also in this case, the worst-case SMBG scenario is the one with PMC=0 for  $T_{70-180}$ ,  $T_{>180}$  and  $T_{>250}$ , the one with PMC=3 for  $T_{<70}$  and  $T_{<50}$ . The alert settings for which a statistically significant deterioration of metrics with nonadjunctive CGM use compared to worst-case SMBG (i.e. median  $\Delta T_{70-180}$  is significantly lower than 0 and median  $\Delta T_{<70}$ ,  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  are significantly greater than 0) is obtained according to the paired one-tailed sign test with 5% significance level are evidenced by light blue markers.

From this representation we can observe that the only case in which  $\Delta T_{70-180}$  results statistically significantly lower than 0, and thus nonadjunctive CGM use drives to a statistically significant deterioration of  $T_{70-180}$ , is when LA is set to 55 mg/dl and HA is not used in the population with normal awareness of hypoglycemia. Regarding metrics related to hyperglycemia, a statistically significant deterioration of  $T_{>180}$  (i.e. significantly positive value of  $\Delta T_{>180}$ ), is obtained when setting LA to 55 mg/dl without using HA in the normal hypoawareness population, and when setting LA to 55 mg/dl and using a HA threshold greater or equal than 350 mg/dl or when not using the HA, regardless of the LA threshold, in the impaired hypoawareness population. Considering  $T_{>250}$ , the only case in which a statistically significant deterioration is obtained with nonadjunctive CGM compared to worst-case SMBG is when

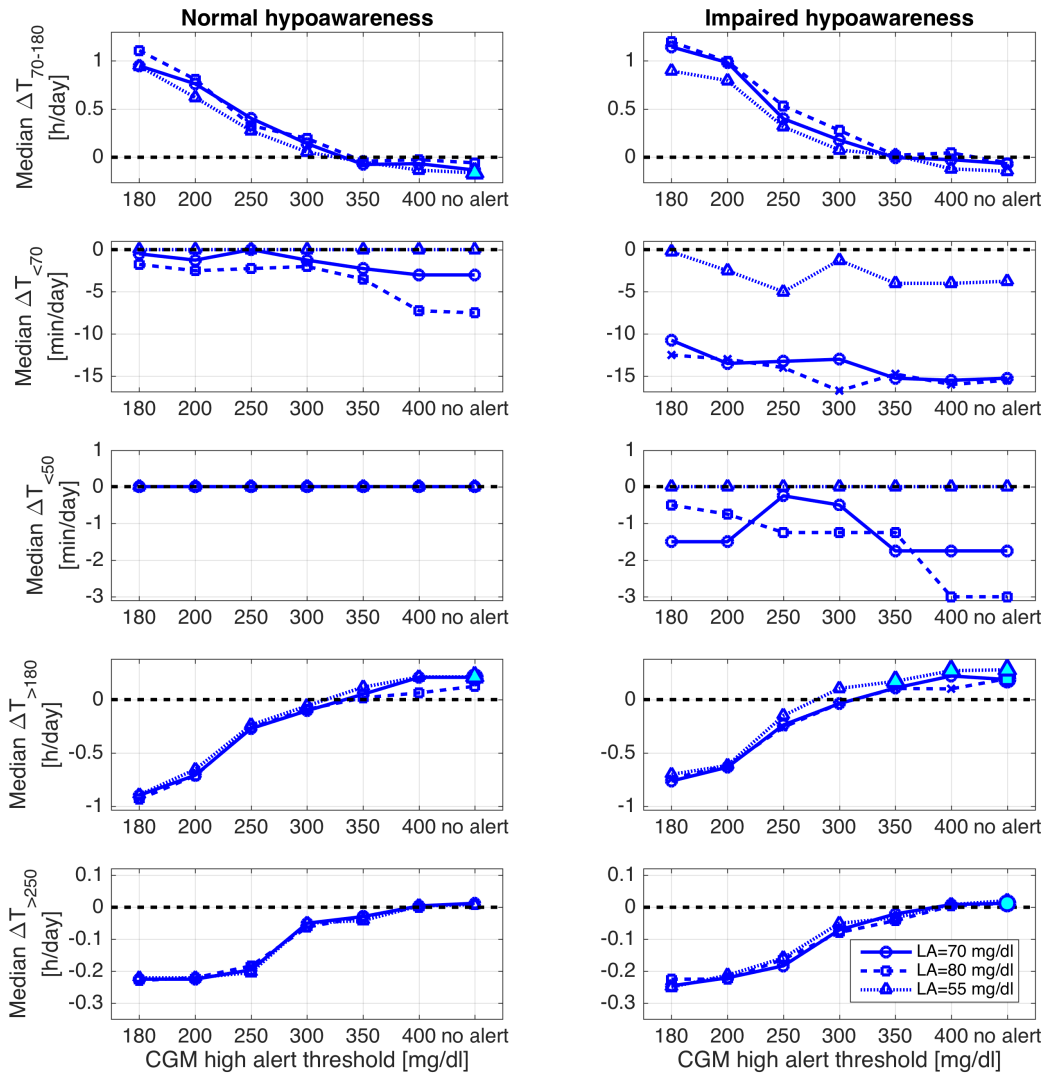


LA is set to 70 mg/dl and HA is not used in subjects with impaired awareness of hypoglycemia. Finally, as already noted in the entire CGM monitoring period, for none of the alert settings  $\Delta T_{<70}$  and  $\Delta T_{<50}$  are statistically significantly greater than 0. This means that, for any alert setting, even in the first day of monitoring, nonadjunctive CGM use does not increase the risk of hypoglycemia and severe hypoglycemia compared to worst-case SMBG treatment.



**Figure 5.3:** Panels from top to bottom show the median of  $T_{70-180}$ ,  $T_{<70}$ ,  $T_{<50}$ ,  $T_{>180}$  and  $T_{>250}$  calculated on day 1 of monitoring in 100 adult virtual subjects with normal (left) and impaired (right) awareness of hypoglycemia. In each panel, red horizontal lines represent the metric's median value when SMBG treatment is used with PMC equal to 0 (solid line), 1 (dashed line), 2 (dash-dot line) and 3 (dotted line). Blue curves represent metric's median value obtained for nonadjunctive CGM use on varying HA threshold with LA threshold equal to 80 mg/dl (dashed line with squared markers), 70 mg/dl (solid line with circular markers) and 55 mg/dl (dotted line with triangular markers).

## 5 Use of T1D-DM model in ISCT to assess the influence of alert settings on nonadjunctive CGM use



**Figure 5.4:** Panels from top to bottom show the median of  $\Delta T_{70-180}$ ,  $\Delta T_{<70}$ ,  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  calculated on day 1 of CGM monitoring in 100 adult virtual subjects with normal (left) and impaired (right) awareness of hypoglycemia. In particular, in each panel, blue curves represent the metric's median on varying HA threshold with LA threshold equal to 80 mg/dl (dashed line with squared markers), 70 mg/dl (solid line with circular markers) and 55 mg/dl (dotted line with triangular markers). Filled markers indicate the alert settings for which median  $\Delta T_{70-180}$  is statistically significantly lower than 0, and median  $\Delta T_{<70}$  and  $\Delta T_{<50}$ ,  $\Delta T_{>180}$  and  $\Delta T_{>250}$  are statistically significantly greater than 0, according to the paired one-tailed signed test with 5% significance level.

### 5.4 Summary outcome of the ISCT

To sum up, this ISCT demonstrated that nonadjunctive CGM use is effective in increasing time in euglycemia ( $T_{70-180}$ ) and reducing time in hyperglycemia

( $T_{>180}$ ) and severe hyperglycemia ( $T_{>250}$ ), compared to SMBG treatment, when the HA is used and set to a value close to the hyperglycemia threshold, e.g. 180 mg/dl or 200 mg/dl. Conversely, when HA is not used or set to a high level, e.g. 400 mg/dl, nonadjunctive CGM use drives to an increase of time in hyperglycemia and severe hyperglycemia, and thus a decrease of time in euglycemia, compared to the standard SMBG treatment.

The trial also evidenced that nonadjunctive CGM use does not introduce additional risk of hypoglycemia or severe hypoglycemia compared to SMBG use, for any alert setting. Indeed, even when the LA is not used, the presence of the low glucose alarm at 55 mg/dl, which cannot be disabled, and thus it is equivalent to use a LA set at 55 mg/dl, protects the patient from too low BG levels and, especially in subjects with impaired awareness of hypoglycemia, allows to reduce the time spent in hypoglycemia ( $T_{<70}$ ) and severe hypoglycemia ( $T_{<50}$ ). Of course, the effectiveness of nonadjunctive CGM use in reducing the time spent in hypoglycemia and severe hypoglycemia is greater when LA is set to a higher value, e.g. 70 mg/dl or 80 mg/dl.

Overall, nonadjunctive CGM use shows the best performance in terms of glycemetic control when LA is set to 80 mg/dl and HA is set to 180 mg/dl. These considerations apply when the assessment is performed both in the entire CGM monitoring period and separately in day 1 of CGM monitoring. This means that the use of CGM to make treatment decisions in the first day after sensor insertion does not introduce additional risks compared to its use in the other days of CGM monitoring.



# Chapter 6

## Conclusions and future developments

### 6.1 Summary of the main findings

ISCTs are used more and more by both industries and regulatory agencies to support or even substitute in vivo clinical trials, since they allow to overcome some limitations of in vivo clinical trials such as elevated time and costs, low numerosity and impossibility to test high-risk situations. The primary aim of this thesis was to develop a simulation model of T1D patients decision-making, usable to perform ISCTs to assess T1D insulin treatment scenarios.

For such a purpose, we first reviewed the net effect method, a simulation approach recently proposed by Patek et al. [63] for the in silico assessment of insulin treatment scenarios (Chapter 2). In particular, by an in silico experiment based on the UVA/Padova T1D simulator, we demonstrated that, despite some interesting ideas, the net effect method is based on several assumptions (e.g. independence between insulin therapy and net effect) and simplifications (e.g. model linearization about basal state and use of population parameters) that limit its domain of validity to small adjustments of basal insulin, while more sophisticated techniques need to be developed for assessing other treatment scenarios.

A different simulation approach was proposed in Chapter 3 based on the T1D-DM model, i.e. a model of T1D patients making treatment decisions according to glucose monitoring (SMBG and/or CGM). The model was constructed by interconnecting the UVA/Padova T1D simulator and an insulin pump model, which had been previously developed by University of Padova

in collaboration with University of Virginia, with models of the device used for glucose monitoring and the patient's behavior in making treatment decisions, which were developed in this thesis.

Given the simplicity of SMBG error's literature models, which do not accurately describe the variability observed on SMBG error data, in this thesis we proposed a new methodology to model the PDF of SMBG error (Subsection 3.2.3), which deals with the variability of error dispersion in the glucose range by dividing the glucose range in zones with constant-SD absolute/relative error, and the asymmetric nature of SMBG error distribution by fitting in each zone the skew-normal PDF model. The method was applied to derive models of OTU2 and BCN devices, which outperformed the simpler models used so far in the literature according to goodness-of-fit tests. Regarding the model of CGM error, the accuracy of Dexcom G5 Mobile system was characterized (Section 3.3) by applying the method recently proposed by Facchinetti et al. [72], which takes into account the main sources of sensor error, i.e. BG-to-IG kinetics distortions, calibration error and measurement noise.

In Section 3.4, a model describing the patient's behavior in making treatment decisions, like meal insulin dose calculation and treatment of hyperglycemia and hypoglycemia, was developed. In particular, three configurations were designed representing treatments based on SMBG, adjunctive CGM use and nonadjunctive CGM use. Remarkably, components describing the common mistakes patients are used to doing in the manual control of glycemia, like errors in CHO counting and early/delayed meal bolus administrations, are included in the model to allow the simulation of a real-life treatment scenario.

The developed T1D-DM model is a suitable tool to perform ISCTs assessing insulin treatment scenarios, since it properly takes into account the inter- and intra-subject variability of physiology and it simulates patients' decisions according to glucose measurements real-time generated by the model. In Chapter 4, the T1D-DM model was used to design an ISCT comparing nonadjunctive CGM use to standard SMBG use and adjunctive CGM use in 100 virtual subjects reflecting the characteristics of a general T1D population. Glycemic outcomes obtained with adjunctive CGM use were in good agreement with those of a clinical data set, thus confirming the reliability of scenarios generated by the T1D-DM model. The only discrepancy was observed for time and rate of hypoglycemia (higher in real data than simulation), probably because of the current lack of a model of exercise in the UVA/Padova T1D simula-

tor. However, this equivalently influences SMBG- and CGM-based treatments and, thus, does not alter the ISCT outcome. The trial, in particular, demonstrated that nonadjunctive CGM use is effective in reducing time spent in hypo/hyperglycemia as well as the year rate and duration of hypoglycemic events compared to SMBG, while presenting equivalent performance to adjunctive CGM use. This suggests that CGM can be safely used to make treatment decisions without the necessity of confirming its readings by SMBG, thus making T1D management easier and less uncomfortable for the patients.

A second ISCT was performed in Chapter 5 to assess the influence of alert settings on nonadjunctive CGM use. The trial demonstrated that for all the considered alert settings nonadjunctive CGM use drives to equivalent or reduced time in hypoglycemia compared to SMBG, with major benefits for patients with impaired awareness of hypoglycemia. Conversely, time in hyperglycemia is reduced by nonadjunctive CGM use only when HA is set closely to 180 mg/dl and significantly increased when HA is not used or set to a very high value (e.g. 400 mg/dl). Overall, best glycemetic control was achieved with LA and HA set to 80 mg/dl and 180 mg/dl, respectively.

Note that in both the ISCTs, SMBG and CGM measurements were simulated using models of BCN and Dexcom G5 Mobile devices. As a consequence, the outcome of the ISCTs is valid for these specific monitoring devices and cannot be generalized to all the SMBG/CGM devices. Of course, as soon as suitable data are available, it will be interesting to perform the same ISCTs with models of different SMBG/CGM devices.

## 6.2 Possible applications of the T1D-DM model

In this thesis the T1D-DM model has been used to design two ISCTs to assess nonadjunctive CGM use. Recently, we used the T1D-DM model to perform an ISCT, similar to the first presented in this thesis, to assess the safety and effectiveness of Dexcom G5 Mobile nonadjunctive use, whose results were presented at the FDA Clinical Chemistry and Clinical Toxicology Devices Advisory Panel of July 21<sup>st</sup>, 2016 to support the regulatory approval of the Dexcom G5 Mobile for nonadjunctive use. A positive feedback came from the panel that voted 8/10 in favor of the approval of Dexcom G5 Mobile for nonadjunctive use [99] [100]. The outcome of the panel, in particular, evidenced that both industries and regulatory agencies are relying more and more on ISCTs based on simulation models, like the T1D-DM model developed in this thesis,

to support or even substitute the clinical assessment of medical device-based treatments.

Another straightforward application of the T1D-DM model is its use for the *in silico* comparison of literature guidelines for using CGM trend information to make treatment decisions, e.g. those proposed by Scheiner [26], which were implemented in this thesis, Pettus et al. [29], the Diabetes Research in Children Network [24] and the Juvenile Diabetes Research Foundation [25]. The T1D-DM model can also be a helpful tool to design and optimize new guidelines for calculating insulin doses based on CGM information, including CGM trend.

Thanks to its versatility, the T1D-DM model can be used to assess in realistic multiple-day scenarios several other CGM-based algorithms, e.g. algorithms for decision-support systems. For instance, we are currently using the T1D-DM model for investigating the efficacy of algorithms for CGM-based real-time automatic optimization of CR, e.g. those proposed by Herrero et al. [101] [102], and CGM-based basal insulin attenuation, e.g. those proposed by Hughes et al. [103] and Patek et al. [104].

### 6.3 Margins for further development of the T1D-DM model

Despite the T1D-DM model in its current shape is able to reproduce realistic treatment scenarios, as confirmed by the comparison of simulated data with real data performed in Subsection 4.3.1, there are still some parts of the model that can be further improved, provided that suitable data becomes available. The UVA/Padova T1D simulator, for example, could be enhanced by incorporating models of physical exercise and stress, which contributes to glycemic variability in real life and are currently not included in the model.

Regarding the modeling of SMBG measurement error, in Section 3.2 of this thesis we proposed a new methodology according to which the variability of SMBG error dispersion over the glucose range is handled by identifying glucose zones in which SMBG absolute/relative error presents constant SD. An alternate strategy, which would be interesting to investigate, is the description of either absolute or relative error of SMBG by a PDF model with parameters varying with BG concentration. However, such a strategy requires a denser database of SMBG measurements than those employed in this thesis, to ensure that the chosen PDF model accurately describes SMBG error at a local level



(i.e. when BG is fixed, and thus the PDF model's parameters are constant).

As far as the model of CGM error is concerned, in Section 3.3 of this thesis a model of the Dexcom G5 Mobile is derived by the methodology of Facchinetti et al. [72], which takes into account the main components of CGM sensor error. However, this methodology does not include any explicit description of sensor's artifacts. To reproduce the sensor's behavior more realistically, a model of CGM artifacts, e.g. that recently proposed by Facchinetti et al. [105] or Emami et al. [106], should be incorporated in the T1D-DM model.

One of the most important features of the T1D-DM model is that it includes a realistic model of patient's behavior in making treatment decisions, including components describing the common mistakes made by patients in real life. In particular, in Section 3.4 of this thesis, the errors in CHO counting are simulated by a single non-standardized Student's t PDF model fitted on real data collected for different types of meals (breakfast, lunch and dinner). The modeling of CHO counting could be further improved by identifying a specific model of CHO counting error for each meal of the day (e.g. patients could be more accurate in CHO counting at breakfast, which presents a less variable CHO content), and by considering a possible correlation between CHO counting error and meal's CHO content (e.g. patients may tend to overestimate small meals and underestimate bigger meals). Another aspect of patient's behavior that could be further investigated is the responsiveness to hypoglycemic symptoms and CGM glucose alerts. Indeed, the behavioral model presently in the T1D-DM model assumes the patient immediately responds to both the appearance of hypoglycemic symptoms and CGM high/low glucose alerts. At difference, in real life, patients may react to symptoms or alerts with a certain delay, e.g. depending on the activity they are involved in. The current lack of a model of patient's responsiveness to hypoglycemic symptoms and CGM alerts may be one of the causes for which the time spent in hypoglycemia in our simulations resulted shorter than that reported in the clinical trial we used for comparison. However, unfortunately, no data are currently available to us to derive such a model.

Finally, the T1D-DM model currently simulates insulin delivery via insulin pump. However, the applicability of the model could be further extended by incorporating a model of insulin administration via multiple daily injections.



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