Enabling Physical Activity for Type 1 Diabetes Mellitus by Real Time Risk Assessment and Treatment Advice

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A Dissertation

Presented to

the faculty of the School of Engineering and Applied Science

University of Virginia

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in partial fulfillment

of the requirements for the degree

Doctor of Philosophy

by

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May

2015

APPROVAL SHEET

The dissertation

is submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

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2015

Abstract

Type1 diabetes (T1D) is an immune disease characterized by the destruction of the beta cells of the pancreas responsible for the production of insulin, a hormone that plays a primary role in blood glucose regulation. People with T1D are faced with daily challenges of optimization since they require multiple daily infusions of optimal insulin doses. One of the major disturbances of glycemic control is physical activity. Despite its benefits, exercise is usually associated with higher risks of low glucose levels. The fear of hypoglycemia results in either avoidance of engaging in a physical activity or over-compensatory treatment behaviors that lead to a worse metabolic control.

This dissertation project focuses on enabling physical activity for T1DM patients by generating real time feedback of the current risks associated with exercise and advising on insulin dose adjustments and carbohydrate intakes.

Using linear statistics techniques, we identified the major factors predictive of the post exercise glycemic response in a relatively large dataset of T1D patients. Based on this analysis, we developed a classification method able to warn T1D patients in advance of a high risk for hypoglycemia associated with physical activity, potentially allowing patients to delay exercise or take preventive actions.

The linear statistical models were the foundation in the design and implementation of a decision support system (DSS) for people with T1D to safely engage in a physical

activity. The DSS has built-in optimized strategies to mitigate the risk of exercise-induced low glucose levels. The system has been validated in the University of Virginia/University of Padova FDA approved T1D simulator and will be deployed in clinical trials in the near future.

Dedication

TO MY FATHER. MAY HE REST IN PEACE.

Acknowledgements

I would like to acknowledge the Jayne Koskinas Ted Giovanis Foundation for Health and Policy for providing the funding for this work.

I would like to thank the Center for Diabetes Technology, at its head the director Boris Kovatchev.

I would like to express my deepest gratitude to Marc Breton, my advisor, for his constant high quality guidance and encouragement, Boris Kovatchev, my mentor, who helped me better understand and define my research, Eric Renard, my advisor and medical mentor, for his continued support and Steve Patek, my co-advisor, for giving me the opportunity to start this process and encouraging me to continue to its completion.

I also want to extend my gratitude to my medical mentor Daniel Chernavvsky and my colleague Edward Ortiz for their help and insightful comments.

An overwhelming gratitude is in order for my Mom, whose support for my achievements, constant sacrifices and unconditional love has provided an overwhelming source of encouragement. Thanks to my brother Anis for his wise advice and insights.

Finally, I owe my utmost gratitude to my wife, Asma, who has been on my side all along and made this process an enjoyable one in large part thanks to her unwavering support, patience and love.

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List of Abbreviations

ADA	American Diabetes Association
AIC	Akaike Information Criterion
AP	Artificial Pancreas
BG	Blood Glucose
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BPM	Beat Per Minute
(C) DSS	(Clinical) Decision Support System
CEU	Contrast-Enhanced Ultrasound
CGM(S)	Continuous Glucose Monitoring (System)
CHO	Carbohydrate
CR	Carb ratio
CSII	Continuous Subcutaneous Insulin Infusion
CTR	Control to Range
DiAs	Diabetes Assistant
DirectNet	Diabetes Research in Children Network

EGP	Endogenous Glucose Production
FDA	Food and Drug Administration
FL	Fuzzy Logic
FPE	Final Prediction Error
GCRC	General Clinical Research Center
HbA1c	Glycated Hemoglobn
HR	Heart Rate
ID	Intradermal
IE	Insulin Effectiveness
II	Inhaled Insulin
IQR	Interquartile Range
IV	Intravenous
LBGI	Low Blood Glucose Index
LGS	Low Glucose Suspend
MA	Mean Activity
MDI	Multiple Daily Injections
MDL	Minimum Description Length
mHealth	mobile Health
MPC	Model Predictive Control
MSE	Mean Squared Errors
PID	Proportional-Integral-Derivative
ROC	Receiver Operating Characterisitc
SC	Subcutaneous
SD	Standard Deviation
SI	Insulin Sensitivity

SMBG	Self Monitoring Blood Glucose
SRM	Structural Risk Minimization
TDI	Total Daily Insulin
TID(M)	Type 1 Diabetes (Mellitus)
T2D(M)	Type 2 Diabetes (Mellitus)
UVA	University of Virginia
USAID	United States Agency for International Development
VCU	Virginia Commonwealth University
WHO	World Health Organization

Chapter 1

Introduction

In this chapter, we provide an introduction to the research presented in this dissertation. We first present the thesis statement, then an overview of the research framework, the problem we are solving, the system engineering approach, and finally the main contributions of this work.

1.1. Thesis statement

We believe that diabetes management around exercise can be less cumbersome, more effective and efficient for people with type 1 diabetes (T1D). Our ultimate goal is to design a diabetes decision support system to improve blood glucose control during and immediately after engaging in a physical activity.

1.2. Overview

Diabetes is of relevance because of the social, economic and health burden it places on countries, and on individuals and their families. Costs of diabetes are manifested in both direct and indirect costs that put pressure on individuals, societies and governments. In 2013, the American Diabetes Association released new research showing that the total costs of diagnosed diabetes in the U.S. have risen to $245 billion in 2012 from $174

billion in 2007, a 41 percent increase over five years. These and many other factors make diabetes one of the most economically-relevant global health issues.

Diabetes is one of the most common disorders of the endocrine system. It is either caused by the body's inability to produce insulin or to respond to the action of insulin or both. The treatment goal of diabetes is the active maintenance of blood sugar levels within a near-normal target range. Thus, diabetes is a prime example of an enormous health care problem for which solutions include preventative measures, innovative drug delivery and integration of advanced technologies aiming personalized treatment, behavioral modification, and synergistic drug-device integration.

In this dissertation, we are particularly interested in T1D which is an autoimmune disease where the pancreas stops producing insulin due to the specific destruction of the beta cells of the pancreatic islets. Hence, glucose regulation in T1D can only be achieved by exogenous insulin delivery, either through multiple daily injections or continuous subcutaneous infusion form a wearable pump. Patients with T1D constantly have to optimize their insulin doses which is a challenge especially in case of disturbances of the metabolic system such as meals, exercise, stress… Physical activity in T1D are our main focus in this work.

Exercise and physical activity are known to be both tools for and barriers to an effective glucose control due to their destabilizing effect on glucose homeostasis. Despite its well-established short and long term benefits on health, exercise can also cause high and low blood glucose levels in patients with diabetes. This is caused by a multitude of factors among which the nature of exercise, the circulating "on board" insulin, the timing and type of food consumption and even the possible stress of competition. Therefore, clinical guidelines have been created to assist patients managing their diabetes during and after

engaging in a physical activity: they include taking “exercise carbs”, modifying insulin delivery rates or a combination of both depending on the type, intensity and duration of the activity.

In an effort to benefit glycemic control during exercise in T1D, we adopted a holistic system engineering approach where we used both medical and engineering knowledge and expertise. The problem was then decomposed into three main sub-problems: understand the exercise and quantify its effect on glucose fluxes, develop a mathematical model to predict the glycemic state and complete the implementation of a prototype of a decision support system DSS).

We started by understanding the problem and identifying the main factors explaining changes in glucose dynamics during and immediately after exercise. Those parameters had to be clinically relevant and conform to clinical guidelines.

We used the identified parameters and built a mathematical and engineering relevant “exercise model” related to the effect of physical activity on the glycemic state of the patients. The exercise model has been trained and tested using already available data collected during different clinical studies. The validation was then conducted on a more recently collected data set. The model enables the prediction of the glycemic state of the patient with the presence of physical activity using very accessible parameters such as blood glucose measures and insulin injection history.

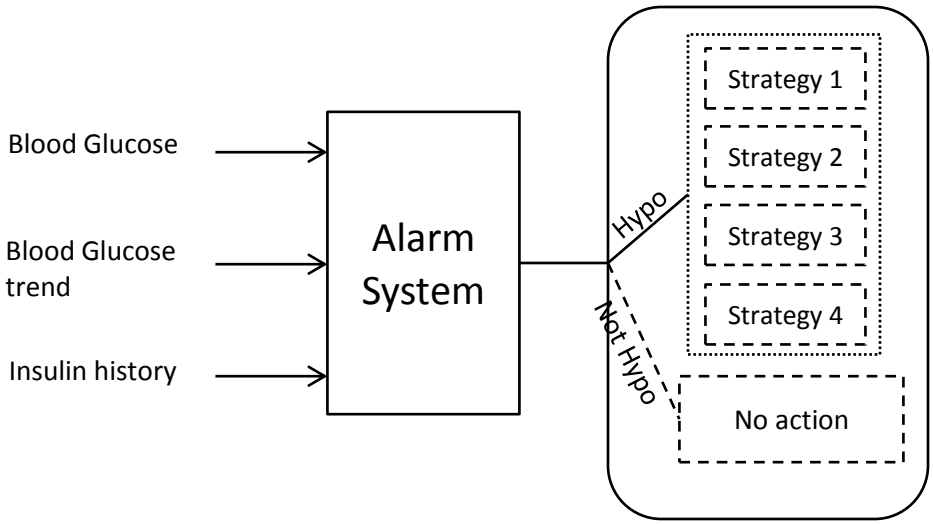

Figure 1. 1: Decision Support System

After obtaining the necessary mathematical model, we had the foundation for an alarm system that can warn patients of potential exercise-induced low glucose levels. In order to complete the development of the DSS, we defined different sets of strategies that are compliant with the clinical guidelines and we tested their efficacy in tandem with the alarm system (Figure 1.1). To further elaborate a fully closed-loop system, we developed an exercise detection algorithm based on heart rate and accelerometer signals. With this algorithm, patients will not be required to indicate that they start exercising: the DSS will be able to start the prevention process based on low glucose exercise prediction.

The main contribution of this work is the development of a prototype for a decision support system that mitigates the risk for hypoglycemia by detecting exercise, predicting low glucose events and taking the appropriate preventative actions. This system will be implemented with the intention to be deployed in clinical trials.

Chapter 2

Background

In this chapter, we present general concepts related to type 1 diabetes, the major disturbances (i.e. meals, physical activity, stress and others), the diabetes technologies (i.e. glucose meters, glucose monitors, insulin pumps, insulin pens, artificial pancreas), and concepts of modeling, which provide a framework for the work that follows.

2.1. Type 1 diabetes mellitus

Diabetes is a common metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The exposure to hyperglycemia leads to long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels [1]. Diabetes is broadly classified into three categories: type 1 diabetes, type 2 diabetes and gestational diabetes. All are caused by genetic and environmental factors.

Type 1 Diabetes Mellitus (T1DM) is the result of immune mediated destruction of the beta-cells, the cells responsible for insulin secretion. Individuals affected by T1DM require insulin therapy to control hyperglycemia. Living with T1DM is a constant problem of optimization of insulin doses: an over-dose leads to hypoglycemia (low blood glucose) and a mealtime or basal suboptimal dosage might lead to hyperglycemia which determines long-term complications.

In contrast, Type 2 diabetes is caused by an inadequate insulin secretion that cannot overcome the prevailing defects in insulin action, which leads to hyperglycemia. People with type 2 diabetes are exposed to associated adverse cardiovascular risk factor such as dyslipidemia and hypertension. Gestational diabetes is very similar to Type 2 but develops only during pregnancy and generally ends with it; though women who had gestational diabetes have been shown more prone to develop Type 2 diabetes later in life.

Over time, diabetes leads to complications such as: diabetic retinopathy, which leads to blindness; diabetic neuropathy, which leads to high risk of foot ulceration, limb loss and kidney failure. The World Health Organization (WHO) estimates that 180 million people worldwide have diabetes. Diabetes is ranked fifth cause of death in cause-specific mortality. Previously considered diseases for the rich and elderly, diabetes has now taken hold in development countries (3 out of 4 people now live in developing countries). Diabetes impacts negatively on many aspects of global development, including economic and human development. The WHO projects that China and India will lose 558 and 237 billion USD respectively in foregone national income as a result of largely preventable deaths from diabetes, heart disease and stroke [2].

In this work, we focus on type 1 diabetes mellitus. Due to insufficient supply of insulin, patients with T1DM require exogenous insulin to maintain normal glucose levels, defined as BG levels between 70 and 130 mg/dl before a meal and lower than 180 mg/dl after a meal according to the American Diabetes Association. This insulin therapy implies having multiple daily injections of short and long acting insulin, and frequently (several times a day) checking blood glucose levels using the proper instruments.

Intensive insulin therapy has been shown to reduce chronic complications [3][4][5], but may increase the risk for severe hypoglycemia. Therefore, hypoglycemia has been

identified as one of the major barriers to intensive diabetes management [6][7]. People with T1DM are dealing daily with an optimization problem: the right type and amount of insulin has to be injected at the right time in order to avoid severe hypoglycemia or prolonged hyperglycemia.

2.2. Diabetes 101: major disturbances from daily life on glycemic control

Maintaining normal blood glucose levels in T1DM is a constant challenge for patients and their surroundings. The human body is subject to disturbances that affects the glucose dynamics such as meals, exercise and stress factors.

2.2.1.Meals

Meals are one of the most challenging disturbances in glucose control. Patients need to calculate the adequate insulin needed to maintain a safe blood sugar. This process is prone to mistakes due to different factors: under or over-estimation of the amount of carbohydrate intake, insulin dose or both. For example, in functional insulin therapy [8], the calculations are based on an estimation of the meal size and an insulin-to-carb ratio (CR). In real life, meal size calculations are far from being perfect which often leads to under/over-dosing of insulin. In addition, the glycemic index of the meals has a direct effect on the postprandial glucose excursion: a low glucose index diet has been proven to reduce glucose excursions and improve glycemic control [9],[10]. On the one hand, overestimating the insulin doses around meals can lead to life-threatening hypoglycemic events. On the other hand, underestimating the insulin doses might lead to high postprandial BG values which lead to greater glycemic variability in comparison with people with lower BG values after meals [11].

2.2.2. Physical activity

Exercise is recommended and even prescribed to patients with diabetes [96]. However, especially in T1DM, the fear from exercise-induced hypoglycemia results in bad metabolic control due to over-compensatory treatment behaviors [12], [84]. Furthermore, it has been shown that exercise masks symptoms of hypoglycemia which leads to unrecognized hypoglycemia events [130]. This can lead to unconsciousness, brain damage and even death [136],[137]. The metabolic effect of physical activity on glucose uptake is very complex and variable from patient to patient, and within the same patient. Diverse factors such as fitness level, type of exercise, duration, and intensity play a large role in affecting post exercise glycemia.

2.2.3. Stress and other factor

When the patient is stressed, the blood glucose sugar levels can rise [13] as stress hormones like epinephrine and cortisol kick in raising blood sugar to help boost energy when it's needed most (fight-or-flight response). Both physical and emotional stress can prompt an increase in these hormones, resulting in an increase in blood glucose levels. In addition, hormonal fluctuations (menstrual cycle, circadian clocks, digestive hormones) can have profound effects on glucose metabolism [13], [99], [104], [142].

2.3. Patient Oriented Diabetes Technology

Research efforts in diabetes have led to the development and commercialization of different diabetes technology tools to empower patients and enables them to better control their disease. These technologies are a set of different devices that can be categorized in three main areas: blood glucose sensing, insulin administration and closed/open loop diabetes management.

2.3.1 Glucose sensing

Optimal diabetes management relies on the frequency and accuracy of blood glucose measurements. Research and development efforts have been improving the tradeoff frequency, accuracy and ease of use. The glucose sensing devices fall in two main categories: Self-Monitoring Blood Glucose (SMBG) meters and Continuous Glucose Monitors (CGM).

a. Self-Monitoring Blood Glucose (SMBG)

SMBG is the most traditional mode of blood glucose sensing: it involves a finger prick to obtain a sample of the capillary blood ranging from 0.3-1.5 microliters [14]. The sample is then analyzed on a strip, a concentration of capillary glucose is provided to the user almost instantaneously. Despite the difference in accuracy between the SMBG meters in the market, all of the currently FDA approved meters are within 10-15% of laboratory plasma glucose values. The accuracy is dependent on the meter and user technique.

Guidelines for SMBG in type 1 diabetes recommend a 3 to 4 time daily measurements: one from each pre-prandial and postprandial [15]. Collecting data in these important times provide more information to the patients and clinicians to build a daily profile of blood glucose and to tune/adjust the insulin dosing. The major limitation of the SMBG sensing is the difficulties to capture the trend of the BG values in real time throughout the day.

Using an SMBG meter can help people with diabetes have a better management of their disease [16]:

- It facilitates the development of a personalized blood glucose profile which will help healthcare providers make a better decision for a treatment plan.

- It helps patients make better day-to-day decisions in the insulin doses or even better choces with the type of diet or physical activity they should be doing.
- It improves the detection of severe and dangerous hypoglycemia or hyperglycemia.
- It plays a big role in diabetes education and empowers the patient with more information about the effect of their lifestyle and interventions on their glycemic control.

b. Continuous Glucose Monitors (CGM)

Continuous glucose monitoring is a real time glucose sensing technique based on interstitial glucose concentration. CGM devices have three parts: a small filament that gets inserted subcutaneously, a transmitter that sits on the sensor and sends the measurements wirelessly, and a handheld device that receives the BG values and display them to the user.

One of the advantages of using CGM is the frequency and availability of the measurement which gives the patients the option to react to BG trends. In addition, real time glucose monitoring is clinically important in identifying postprandial hyperglycemia, overnight hypoglycemia, masked hypoglycemia and daily glucose trends. Studies have shown that T1DM patients who are using CGM at least 60 % of the time have significant improvement in glycemic control [17]. Real time CGM has also been proven to reduce HbA1C in adults with T1DM [18] and glucose variability [19].

Nevertheless, a difficulty has been noticed in incentivizing patients to regularly use CGM devices over an extended period of time, especially in children and adolescents. In addition to users who found CGM too annoying and not user friendly, others have stopped using it because of insurance adoption and inaccuracy [27][28]. Furthermore,

insulin therapy is intended to be based on BG in the plasma, but CGM sensors reside in the subcutaneous tissue. This introduces a lag between the sensor measurement and the BG in plasma. Sensor lag and inaccuracy led to CGM devices being only intended for use in conjunction with SMBG.

2.3.2 Insulin administration

Although most T1DM patients are using subcutaneous insulin injections, other modes of insulin administration exist and some are under investigation.

- **Subcutaneous insulin**

Subcutaneous insulin is the most common mode of insulin administration. It can be either performed using simple syringes with needles, insulin pens or insulin pumps.

Insulin pens are disposable and reusable pen devices that are designed to provide options for multiple daily injections (MDI), delivering rapid and long-acting insulin and insulin premixes [29]. Several studies have shown the advantages of using insulin pens over simple syringes such as better accuracy and more convenience for patients[30].

Insulin pump technology also provides another alternative to MDI therapy. The most current pumps are small devices with an insulin reservoir, a battery and a computerized control mechanism. A cannula placed subcutaneously delivers a continuous infusion of insulin. This therapy is called continuous subcutaneous insulin injections (CSII). Two types of deliveries are available through a pump: basal injections in the form of small quantities of insulin continuously infused throughout the day, and bolus injections for meals or high blood glucose corrections. When used properly, continuous subcutaneous injections have been shown to improve glycemic control and therefore lower long term complications related to Diabetes [31].

- **Inhaled insulin (II)**

Inhaled insulin is a type of short-acting insulin. It was approved by FDA in 2006 but has had limited adoption. Inhaled insulin is recommended around meals because of its earlier peak of action. Basal insulin meals should still be covered using long-acting insulin. It has been demonstrated that inhaled insulin improves glycated hemoglobin levels (HbA1c) and prevents the occurrence of severe hypoglycemia without having secondary effects on pulmonary functions [32].

- **Transdermal insulin**

Transdermal insulin is a type of insulin that is absorbed through the skin using patches. The insulin patch uses the propagation of a unique and special ultrasound transmission that first dilates the pores and then pushes insulin into the dermis region of the skin. While still in clinical trials, insulin patches can work with both rapid and long-acting insulin [33].

- **Smart insulin**

Smart insulin is a type of insulin that has been chemically modified to react to glucose in bloodstream. It is automatically activated when glucose levels are too high. A recent study shows the effectiveness of smart insulin in mice [34]. With one single daily injection of the modified hormone, the glucose control around a simulated meal was found to be better than long-acting insulin [34].

2.3.3 The role of modern computation tools: the rise of Artificial Pancreas platforms

In the last decade, the combined availability of commercial devices allowing to frequently measure glucose (glucose sensor) and adjust insulin doses (insulin pump) led

to the research development of an insulin dosing system consisting of a glucose sensor, an insulin pump and a control algorithm: the Artificial Pancreas (AP) [35] also known as closed loop control of blood glucose in diabetes.

The development of an AP system can be traced back 50 years ago. In fact, the feasibility of an external blood glucose regulation was established by Kadish [36] in 1964. The system -clinically validated and later on commercialized as the "biostator"- uses intravenous glucose measurements and intravenous infusion of glucose and insulin to maintain normal BG.

The most recent versions of AP platforms are based on off the shelf commercially available continuous glucose monitors and insulin pumps. Academic and industrials focused their efforts on the development of minimally invasive subcutaneous systems. The loop is closed using a control algorithm that takes as input the BG measurements and computes the right amount of insulin to be injected (See Figure 2.1).

Two major approaches exist to achieve glucose regulation in the artificial pancreas: the unihormonal approach using only an insulin pump to lower BG and the biohormonal approach using both insulin to lower BG and glucagon to increase BG. The unihormonal AP has been shown to be feasible using PID control algorithm [37][38], MPC control algorithm [39], modular control to range approach [40], and FL control algorithm [41]. The bihormonal approach to closed loop control has also been tested in clinical trials mainly by two groups in Boston and Oregon [42][44].

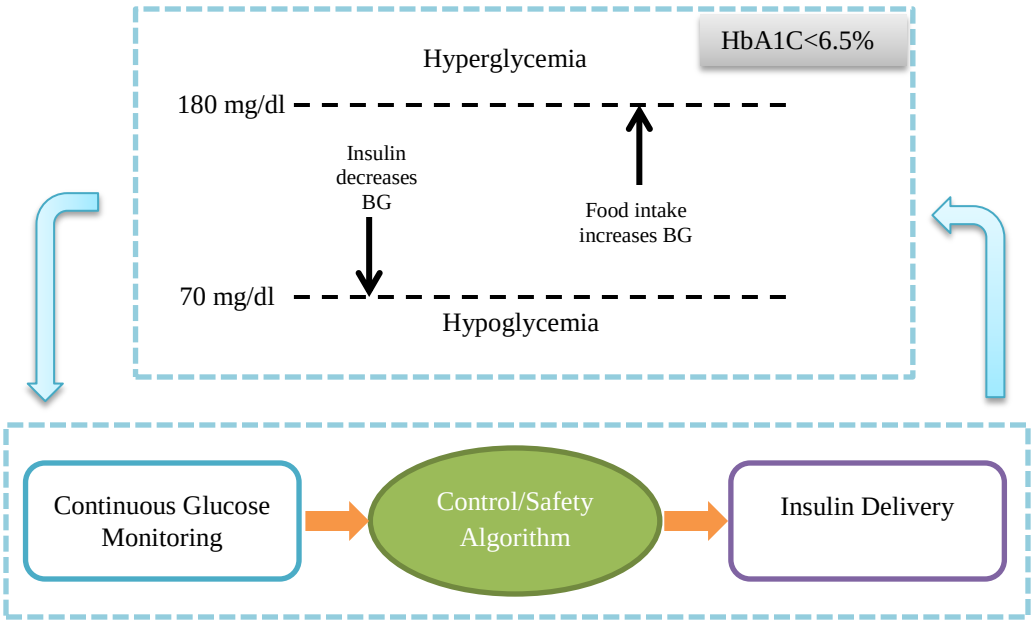

Figure 2. 1: Closed loop control

In this work, we used the University of Virginia "DiAs" artificial pancreas platform [46]. DiAs is based on a smartphone communicate wirelessly to a continuous glucose sensor (Dexcom) and an insulin pump (Tandem, Medtronic, Insulet Omnipod). DiAs has two modes of operations:

- Open loop mode in which the pump is controlled using the patient's bsal pattern and bolus delivery parameters (carb-ratio and correction factor). The blood glucose values received from the CGM are displayed on the main interface.
- Closed loop mode in which the smartphone is running a closed loop control algorithms responsible for the appropriate insulin injections to keep the patients glucose values in the safe range of 70 to 180 mg/dl. Patients are still required but only during meal time.

2.3.4 T1DM simulator

One of the notable achievements in the design of a closed loop glucose control system is the Food and Drug Administration approval of the University of Virginia-University of Padova T1DM Simulator as a substitute to animal trials in the preclinical testing of closed loop control algorithms [48]. The simulator is used to check the safety, stability, assess limitations and eliminate ineffective control algorithms. Avoiding the expensive and time consuming animal trials gives an edge and further the development of AP systems. The T1DM simulator is based on a metabolic model developed by the University of Virginia group in conjunction with the University of Padova group.

The simulation model describes the physiological events that occur after a meal. 204 healthy individuals underwent a triple tracer meal protocol to provide model independent estimates of major glucose and insulin fluxes such as rate of appearance in plasma of ingested glucose, glucose production and glucose utilization [49]. The model has 13 differential equations and 35 parameters, 26 of which are free and 9 derived from steady state constraints (Table 2.1).

The sample mean and covariance matrix of the log-transformed parameter vector, together with the assumption of a multivariate log-transform distribution uniquely identified the parameter distributions. The model was extended for T1DM patients by assuming the same inter-subject variability but adjusting the population averages, and replacing the insulin secretion by exogenous insulin (injection through insulin pump and transport to the blood) [50].

$\dot{G_p} = -k_2 \cdot G_p + k_1 \cdot G_t - U_{ii} - E_t + k_{p1} - k_{p2} \cdot G_p - k_{p3} \cdot I_d + \frac{f \cdot k_{abs} \cdot Q_{gut}}{BW}$
$\dot{G_t} = -k_1 \cdot G_t + k_2 . G_p - \frac{(V_{m0} + V_{mx} \cdot X) G_t}{K_{m0} + G_t}$
$\dot{G_{sc}} = -k_{sc}(G_{sc} - \frac{G_p}{V_g})$
$\dot{I_p} = -(m_2 + m_4) \cdot I_p + m_1 \cdot I_l + k_{a1} \cdot I_{sc1} + k_{a2} \cdot I_{sc2}$
$\dot{I_l} = -(m_1 + m_3) \cdot I_l + m_2 \cdot I_p$
$\dot{I_1} = -k_i(I_1 - \frac{I_p}{V_i})$
$\dot{I_d} = -k_i(I_d - I_1)$
$\dot{X} = -p_{2h}(X - (\frac{I_p}{V_i} - I_b))$
$\dot{I_{sc1}} = -k_d \cdot I_{sc1} - k_{a1} \cdot I_{sc1} + \frac{J(t)}{BW}$
$\dot{I_{sc2}} = k_d \cdot I_{sc1} - k_{a2} \cdot I_{sc2}$
$\dot{Q_{sto1}} = -k_{gri} \cdot Q_{sto1} + M(t)$
$\dot{Q_{sto2}} = -k_{empt} \cdot Q_{sto2} + k_{gri} \cdot Q_{sto1}$
$\dot{Q_{gut}} = k_{abs} \cdot Q_{gut} + k_{empt} \cdot Q_{sto2}$

Table 2. 1: In-silico subject described by 13 differential equations

Where G_p = glucose in plasma (mg/kg)

Gt = glucose in tissues (mg/kg)

Ra = glucose rate of appearance in plasma (mg/kg/min),

E = renal excretion (mg/kg/min)

VG = distribution volume of glucose (dl/kg)

Ip = mass of insulin in plasma (pmol/kg)

IL = mass of insulin in liver (pmol/kg)

I = plasma insulin concentration (pmol/kg)

VI = distribution volume of insulin (l/kg)

m1, m2 = rate parameters between liver and plasma (min-1)

Id = delayed insulin signal

I1 = insulin signal realized in the chain of two compartments

ki = rate parameter accounting for the delay between insulin signal and insulin action

Ib = basal insulin

X = insulin in the interstitial of fluid

I = insulin concentration in plasma

p2h = rate constant of insulin action on glucose utilization

Qsto = amount of glucose in stomach (mg)

Qsto1 = amount of glucose in solid phase (mg)

Qsto2 = amount of glucose in liquid phase (mg)

Qgut = mass of glucose in the intestine (mg)

kgri = rate of grinding (min-1)

kempt = rate constant of gastric emptying (min-1)

kabs = rate constant of intestinal absorption (min-1)

BW = body weight (kg)

Isc1 = amount of nonmonomeric insulin in subcutaneous space

Isc2 = amount of monomeric insulin in subcutaneous space

kd = rate constant of insulin dissociation

ka1 = rate constant of nonmonomeric insulin absorption

ka2 = rate constant of monomeric insulin absorption

As shown in Figure 2.2, the simulator has four main components: in silico T1DM patient population, in silico blood glucose sensor to mimic the continuous glucose monitor behavior, an in silico pump to mimic the subcutaneous insulin kinetics and finally a controller to be able to place control algorithms for in silico testing.

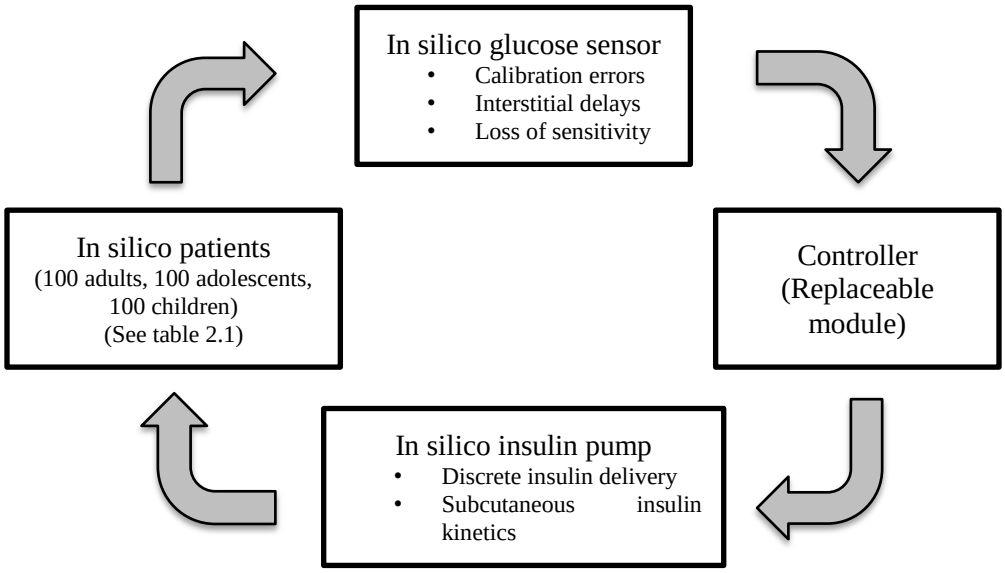

Figure 2. 2: Principal components of T1DM simulator

Three hundred in silico subjects (100 adults, 100 adolescents, and 100 children) were generated by randomly sampling from the population distribution. The parameters of the inslico population cover key parameter distributions observed in the in vivo such as liver glucose effectiveness, liver insulin sensitivity, rate constant of liver insulin action, peripheral glucose effectiveness, peripheral insulin sensitivity and rate constant of peripheral insulin action.

In silico Glucose sensors had to be developed by integrating sensor specific errors capable of reproducing the interstitial time lag, calibration bias and random noise of subcutaneous CGM devices. Based on the analysis of sensor errors, random calibrations errors had been generated. The component of sensor errors was the result of combining blood-to-interstitium glucose transport and a nonwhite noise [45].

An in silico pump was developed to approximate subcutaneous insulin kinetics taking into account both the time/dynamics of insulin transport from subcutaneous tissue to blood and the discrete insulin infusion based a stepwise basal pump rate and insulin boluses. The two compartment model is detailed by Dalla Man et Al [47].

The simulator was validated through several experiments in T1DM and shown to represent adequate glucose fluctuations in T1DM during meals. The validity of computer simulations to test new closed-loop control algorithms adapted for CGM and insulin pump delivery was demonstrated by the approval from the FDA for a clinical trial, entirely based on in silico tests [48].

2.4. Modeling

In many ways, all physiological systems are known by their complexity. The human body and more specifically the glucose and insulin kinetics are not an exception. In this section we present a few concepts in relation to the modeling work, the types of models and the model selection process.

2.4.1. General concepts

The human physiology is complex and the availability of measurements to understand the dynamics of this complexity is very limited. Modeling enables the extension of the measurements which might increase the understanding of physiological complexity.

Systems can be represented by various types of models: mathematical, conceptual, graphical… The main goal includes describing, interpreting, explaining, predicting, testing hypothesis, testing control algorithms, designing experiment, inferring measurements and assessing organ functions [51]. In this work, we are interested in mathematical modeling of glucose dynamic during exercise in T1DM.

2.4.2. Modeling approaches

There are two fundamentally distinct approaches we could adopt:

- Black box modeling approach: this is a data-driven method. Based on experimental data collected about the system, input/output descriptions should be derived in order to find the quantitative descriptions of the physiology. This type of model is particularly useful when there is not enough understanding of the dynamics of the system.
- Explicitly represent the underlying physiology: this type of modeling requires greater understanding of the dynamics of the system. This approach provides a way to express the different features directly as parameters and variables in the model. However, any model is by definition an approximation of reality.

Regardless of the type of the model, there is a trade-off between accuracy and bias. The complexity of the model is usually offset by its increased bias. Bossel et al. [52] define the best model as "the simplest one that fulfills its specific purpose". They also characterize a too complex model as one that could harm and prevent from seeing the real problem.

2.4.3. Model selection

Model selection is estimating the performance of different models to choose the best one. If enough data is available, the best approach is to randomly divide it into a training set (two thirds) and a validation set (one third). Another testing set/subset of data is very important to test the final chosen model.

In general, model selection methods are either analytical (AIC, BIC, MDL, SRM) or by efficient sample re-use (bootsrap and cross-validation). In our work, we mainly used Akaike's information criterion (AIC) and cross-validation.

a. Akaike's information criterion (AIC)

AIC accounts for the prediction error but also includes a penalty proportional to the complexity of the model measured by the number of parameters to be estimated in the model (parsimony principle) [157]. The general definition of AIC is as follows:

$$AIC = 2k - 2\ln(L)$$

Where k is the number of parameters and L is the likelihood function of the estimated model.

When the errors are independent and normally distributed:

$$AIC = 2k + n(\ln\left(2\,\pi\,\frac{RSS}{n}\right) + 1)$$

Where RSS represents the sum of the squared errors and n is the number of observations.

The terms that are model independent are then dropped:

$$AIC = 2k + n(\ln\left(2\,\pi\,\frac{RSS}{n}\right))$$

The model with minimum AIC is the better model.

b. K-fold Cross-validation

Cross-validation is one of the simplest and most widely used method for estimating prediction error. K-fold cross validation consists of splitting the data into K equal-sized subsets. Figure 2.3 illustrates the scenario of K=7.

1	2	3	4	5	6	7
Train	Train	Train	Train	Test	Train	Train

Figure 2. 3: Splitting data into K =7 for K-fold cross validation

For the Test set (K^{th} part), we fit the model to the other K-1 subsets of the data and calculate the prediction error of the fitted model when predicting the K^{th} subset of the data. We repeat the procedure for k=1,…,K and combine the K estimates of prediction error.

2.5. Exercise and type 1 diabetes

One of the main objectives of this work is to understand the glucose dynamics during and immediately after mild to moderate exercise in T1DM patients. In this section, we give a brief literature review on the effect of exercise in general on the glucose metabolism and we focus on its specific effect on the management of type 1 diabetes.

2.5.1. Health benefits of regular physical activity

There are numerous benefits of regular exercise. It has been shown that physical activity improves insulin action, lowers blood glucose levels, improve body mass index (BMI), and reduces multiple risk factors for cardiovascular disease [53][54][55][58]. These

important metabolic changes explain the significant role of exercise in prevention of type 2 diabetes. Even though blood glucose management can be more challenging in presence of exercise for type 1 diabetes, most of the same metabolic benefits and other health benefits are the same.

2.5.2. Exercise physiology

Physical activity and exercise are common stressors that cause disturbance on glucose homeostasis and energy needs. Exercise can be classified into two main categories: aerobic and anaerobic, depending on the speed and force of the muscle contraction and the energy expenditure [61]. These two types have different effects on glucose levels in people living with diabetes [62].

At the onset of moderate intensity exercise, the glucose disposal into peripheral muscles increases. Unless there is an increase in the endogenous glucose production by the liver, blood glucose levels would drop. In the case of an intense exercise (typically lasts a few seconds), the hepatic glucose productions increases and exceeds the muscular glucose disposal [65]. In diabetic people, this would result in hyperglycemia since there is no endogenous insulin production.

With the presence of physical activity, a hormonal network is activated to ensure the control of glucose homeostasis. In people without diabetes, endogenous insulin secretion normally decreases during exercise which is an essential step to allow the increase in hepatic glucose production to maintain normal blood glucose [56][57]. Depending on the intensity, exercise causes the release of glucose-raising hormones such as epinephrine and norepinephrine. Other hormones like glucagon, cortisol and growth hormone have a great impact on the primary fuel substrates (i.e. carbohydrates, protein and fat use to produce energy [59]. In individuals dependent on exogenous insulin, these

counterregulatory hormones can be altered. As an example, in type 1 diabetes, current evidence show that growth hormone secretion during exercise is normal as long as normal blood glucose levels are maintained but suppressed during hyperglycemia [60].

In patients with T1DM, the glucose control during exercise is very challenging. In fact, insulin levels cannot change fast enough in response to exercise especially with other suboptimal or over-abundant hormonal responses [62]. Hence, the risk for hyper and hypoglycemia events induced by exercise in T1DM.

2.5.3. Exercise-induced Hypoglycemia and hyperglycemia

As shown in Figure 2.4, during aerobic exercise in type 1 diabetes, insulin levels do not decrease (due to exogenous injections). The high insulin concentration not only limits the glucose production by the liver but also facilitates glucose disposal through skeletal muscles. As a consequence of the impaired glucose production and utilization, severe hypoglycemia is more likely to occur.

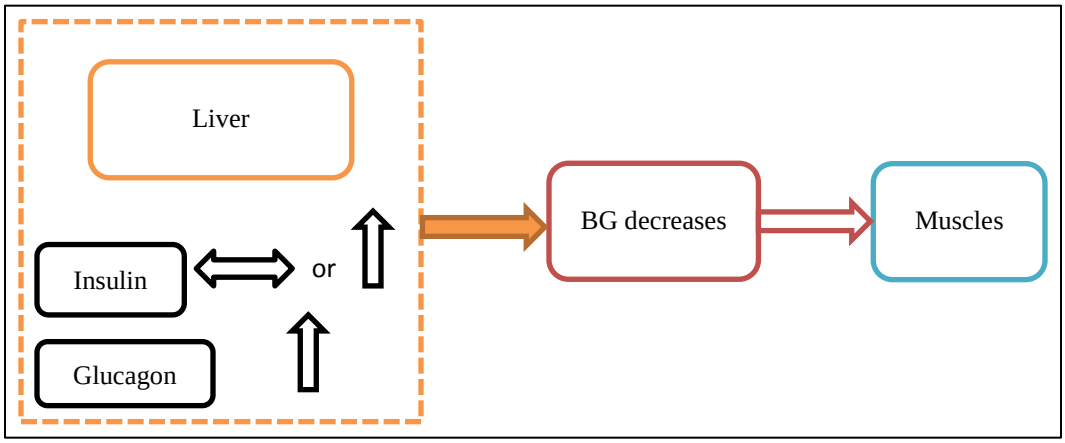

Figure 2. 4: Aerobic exercise physiology in T1DM

In contrast, during anaerobic exercise, due to the rise in counter-regulatory hormones (catecholamine) and insufficient insulin in the body, the glucose production by the liver increases and limits the glucose disposal into skeletal muscle (Figure 2.5). In this case, the impaired glucose production and utilization causes BG to increase and hyperglycemia might occur.

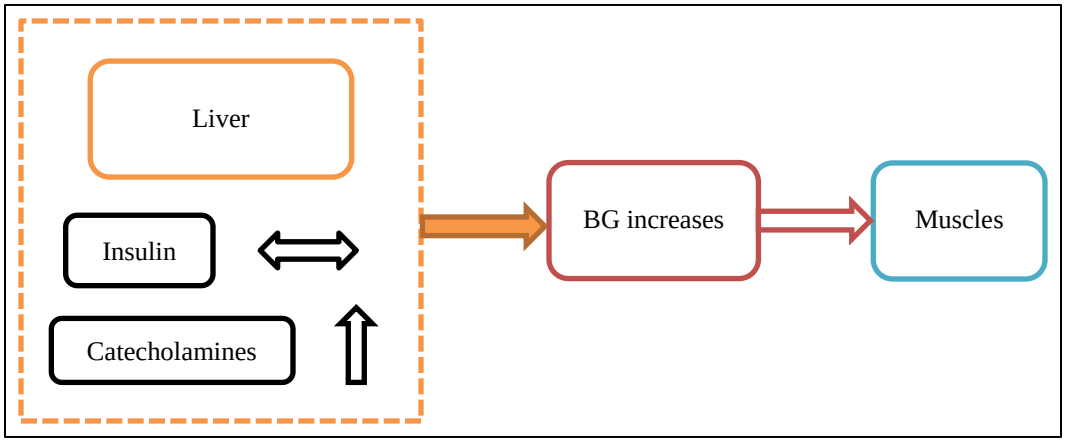

Figure 2. 5: Anaerobic exercise physiology in T1DM

In addition to internal patients' metabolism and hormonal responses, the effect of exercise on the glucose dynamics in T1DM is influenced by the type, intensity and duration. In this work, we focus on a mild to moderate aerobic exercise for a period of 30 to 45 minutes.

Table 2.2 presents a summary of the factors that cause hypoglycemia and hyperglycemia. Details are presented in the next teo sections.

Hypoglycemia	Hyperglycemia
• Hyperinsulinemia (no reduction of insulin injections during exercise) • Prolonged aerobic mild to moderate activity • Impaired glucose counterregulatory response	• Hypoinsulinemia (i.e. pump disconnection/malfunction) • Very high intensity exercise • Intermittent high intensity exercise • High consumption of carbohydrates • Imbalance between glucose production and glucose disposal.

Table 2. 2: Main causes for exercise-induced hypoglycemia and hyperglycemia

2.5.4. Causes for exercise-induced hypoglycemia

Many factors contribute to exercise-induced low glucose values. Causes include defective counterregulatory mechanisms, acutely increased insulin mobilization and sensitivity, increased glucose utilization, and replenishment of glycogen stores. With or without symptoms, hypoglycemia can result from one or a combination of more than one of those factors.

- **Impaired counterregulatory responses**

In nondiabetic people, there are mechanisms to prevent hypoglycemia such as the activation of neuroendocrine, autonomic nervous system and metabolic glucose counterregulatory mechanisms. In type 1 diabetes, these mechanisms' efficiency can be reduced due to sequences of stress or severe multiple hypoglycemia events caused by intensive insulin treatment [63]. This is also impacted by the duration of T1DM.

- **Acute and delayed effects of hypoglycemia**

In type 2 diabetes, the glucose regulation can generally be managed through lifestyle management alone. In this case, the risk for developing a hypoglycemia during exercise is minimal and no extreme measures are needed to maintain normal glucose levels [64].

In insulin dependent individuals, adding physical activity to their daily life represents a challenge in their diabetes management. They are exposed to more risks during and after exercise [66],[67] Even though different types and intensities have different effects on acute glucose levels, any form of physical activity can be accompanied by a life threatening risk for hypoglycemia during and even after up to 31 hours in the recovery period [68]. High intensity intermittent exercise increases significantly the depletion of muscle glycogen and insulin sensitivity which might lead to a late onset of hypoglycemia. The restoration of muscle glycogen by an accelerated blood glucose uptake might also increase the risk for delayed hypoglycemia [69].

- **Nocturnal hypoglycemia following physical activity**

Jones et al. [70] have demonstrated that sleeping reults in impaired counterregulatory hormones responses to hypoglycemia with or without diabetes which makes the detection of overnight exercise-induced hypoglycemia very difficult. Multiple studies have shown the effect of exercise on nocturnal hypoglycemia:

    - MacDonald et al. [71] have shown that 16% of people with T1DM have symptoms of hypoglycemia during sleep, 6 to 16 hours after a high intensity exercise.
    - The DirectNet study [72] (Diabetes Research in Children Network) showed that in children with T1DM, 28% have experienced severe

hypoglycemia (less than 60 mg/dl) and the frequency of nocturnal hypoglycemia doubled following a moderate exercise in the afternoon.

- McMahon et al [88]. have demonstrated that the glucose uptake increased during and immediately after exercise in youth with T1DM. A biphasic response in glucose requirements has been noticed in the 7 to 11 hour window following an afternoon exercise.

- **Hypoglycemia unawareness**

Hypoglycemia unawareness is known to be the result of reduced sympathetic neural response to decreasing blood glucose levels. The risk of hypoglycemia unawareness is related to the impaired counterregulatory hormone response (i.e. low levels of epinephrine and norepinephrine) [73],[74],[75].

The most common reason of developing hidden synptoms of hypoglycemia is the frequency of low blood glucose levels but it can be reversed by avoiding severe hypoglycemia events for a period of 2 to 3 weeks [76].

- **Effects of prior exercise and hypoglycemia**

In people with T1DM, antecendent hypoglycemia causes acute counterregulatory failure during a subsequent mild to moderate exercise which results in an impaired neuroendocrine and autonomic nervous system response [77]. Antecedent events of increase in cortisol levels might also lead to an exercise related counterregulatory response failure [79].

Not only the frequency of hypoglycemia even effects the counterregulatory response but also the severity. Galassetti et al. showed that acute counterregulatory failure during

prolonged mild to moderate exercise may be induced in a dose-dependent fashion by differing depths of antecedent hypoglycemia starting at 70 mg/dl in adullts with T1DM [78].

2.5.5. Causes for exercise-induced hyperglycemia

Aerobic exercise is typically associated with increased risk for hypoglycemia. However, certain types of exercise may lead to hyperglycemia. More specifically, above a certain level of lactate threshold, exercise tends to increase blood glucose levels. Patients with diabetes. This is mainly due to the fact that there is no internal compensation to increase insulin levels in the bloodstream.

Hight intensity short intermittent exercise is well known to increase hepatic glucose production through the increase in catecholamines [65]. In nondiabetic people, the high catecholamine presence is compensated by an increase in insulin secretion by the end of the activity. In diabetic people, insulin needs might double after stopping the physical activity. If the insulin needs are not met, the state of hyperglycemia might last for several hours [80], [81].

In a recent study by Yardley et al. [82],for people with T1DM performing moderate to heavy intensity exercise, the use of insulin pumps helped limit postexercise hyperglycemia without causing more risk of late onset hypoglycemia. But, careful attention is needed to achieve such results. In fact, insulin infusion profiles need to be changes at the right time and with the right set of parameters.

Hyperglycemia and ketoacidosis during exercise may cause hydration and have negative effect on performance and may even lead to severe illness. Rapid ketone production can cause abdominal pain and vomiting.

Chapter 3

Identification of main factors explaining glucose dynamics during and immediately after moderate exercise in patients with type 1 diabetes

3.1. Introduction

Physical activity is recommended by the American Diabetes Association for all people with Diabetes, including those with type 1 diabetes (T1D), because of its various beneficial effects[83],[84]. Exercise has been proven to ameliorate the quality of life, body composition, blood pressure and possibly decreases the risk of diabetes-related complications and mortality [83].

However, in terms of benefits associated with exercise, a paradox exists for T1D patients. Indeed, there is no clear evidence about its benefits on glucose control [85]. On the contrary, severe hypoglycemia may occur during, immediately after or several hours after physical activity [83],[88].

Exercise-induced hypoglycemia leads to impaired glucose control and requires patients to adopt strategies and actions to prevent these potentially severe events. In this regard,

clinical guidelines recognize that patients with T1D using short acting insulin therapy have to regularly check their blood glucose levels and modify their insulin therapy while taking into account their carbohydrate intake [89]. This might be a difficult task since prevention of hypoglycemia must be compatible with the leading objective of tight glycemic control to prevent long-term complications [90].

In recent years, researchers have made significant advances in the development of an artificial pancreas (AP) [35]. Based on subcutaneous glucose measurements from a continuous glucose monitoring device, the control algorithm of an artificial pancreas calculates and orders the appropriate amount of insulin through an insulin infusion pump [91]. These smart insulin delivery systems have been proven to prevent hypoglycemia for T1DM patients [92],[93],[94],[95],[96],[97]. Other investigators have also suggested that the use of dual hormone delivery (insulin and glucagon) is more effective in order to prevent hypoglycemia [100],[102],[103],[42],[104],[105],[106]. While such systems have been proven successful in steady states, their success has been limited with the presence of disturbances such as meals and physical activity.

Thanks to the availability of specific body sensors (i.e. heart rate, galvanic skin temperature, accelerometers) and multisensory devices (i.e. Zephyr Bioharness^{TM}, Bodymedia armband^{TM}), some closed loop control algorithms including their inputs have reduced the occurrence of immediate or late onset exercise-induced hypoglycemia [107],[108],[109] . However, due to the complexity of the effect of exercise on the glucose dynamics, artificial pancreas models still show limited progress in preventing hypoglycemia during and immediately after engaging in a physical activity.

Most information that is commonly delivered to T1D patients by healthcare professionals regarding exercise management is not evidence based [97] .In this work, we try to reduce

this gap. We conducted a meta-analysis on data collected during clinical trials with T1D patients. We applied multiple linear regression techniques to identify the main parameters impacting the glucose dynamics during and immediately after mild to moderate exercise. We then used the multiple linear regression model to predict the glycemic drop induced by exercise and ultimately better inform a closed loop artificial pancreas algorithm.

3. 1. Clinical guidelines for exercise and diabetes

Given its several benefits, exercise has been considered a cornerstone in diabetes management. Healthcare providers are encouraged to prescribe physical activity and exercise to patients with diabetes. In T1D, glycemic control is highly affected by the timing, the type, the intensity and the duration of the physical activities. In this section, we provide a summary of the current clinical guidelines on how to prevent hypoglycemia and hyperglycemia for T1D patients participating in a physical activity.

3.1.1. Clinical guidelines for prevention of hyperglycemia

The American Diabetes Association released a set of recommendations to prevent worsening the metabolic control with physical activity:

- "Avoid physical activity if blood glucose is higher than 250 mg/dl and ketosis is present"
- "Use caution if blood glucose is higher than 300 mg.dl and no ketosis is present"

Exercise should be avoided when hyperglycemia is accompanied by a relative deficiency in insulin because the combination creates an exaggerated counterregulatory hormonal response resulting in high blood glucose levels and a rise in ketosis [98]. Another less cautious strategy in avoiding hyperglycemia is the correction by an insulin bolus injection of 0.5 to 2.5 units when BG is higher than 300 mg/dl without significant ketones [99].

This action should be taken with extreme caution since the glucose uptake can rapidly result in hypoglycemia.

According to these guidelines, patients with T1D have to use blood glucose meters to check their glucose levels before engaging in any physical activity.

3.1.2. Clinical guidelines for prevention of hypoglycemia.

De fao et al. [86] summarized the list of preventative action to be taken by insulin dependent diabetic patients. These actions can be categorized in four main sets and only applicable for the prevention of hypoglycemia during and immediately after exercise and do not apply for the late onset of hypoglycemia:

Self-monitoring of blood glucose and establishment of blood glucose goals

- Before starting the exercise session, check blood glucose
- Before starting, delay the exercise session if blood glucose is less than 80 mg/dl
- Before starting, delay the exercise session if blood glucose is greater than 250 mg/dl; you can exercise only if blood ketones are negative
- During prolonged exercise check blood glucose every 30 min of exercise

Carbohydrate (food) intake

- Before starting, ingest 20–60 g of simple carbohydrates if blood glucose is less than 120 mg/dl
- During prolonged exercise supplement with 20–60 g of simple carbohydrates, every 30 min (preferably, make a decision on the basis of blood glucose trend)

Insulin dosage adjustment

- Inject regular insulin or fast-acting insulin analogues into abdominal subcutaneous region
- Cut the dosage of short-acting insulin analogue by 10–40% before the exercise, dependent on duration, intensity of the session and previous experience
- Cut the dosage of basal insulin analogue by 30–50% before the exercise, dependent on duration, intensity of the session and previous experience
- After exercise, cut the usual short-acting insulin dosage by 10–30%

In this chapter, we apply statistical modeling techniques to identify the main parameters that explain the glucose dynamics during and immediately after exercise. The main goal is to define clinically relevant parameters and quantify their effects.

3.2. Materials and Methods:

3.2.1. Participants:

Fifty nine patients with T1D were enrolled in four different randomized cross-over clinical studies (NCT01418703, NCT01390259, NCT01582139, 2009-A00421-56, 2010-A00538-31) at the University of Virginia Clinical Research Unit (Charlottesville Virginia) and Montpellier University Hospital Clinical Investigation Center (Montpellier, France); Demographics are presented in Table 1.

	Adults	Adolescents
Number	47	12
Age (years)	42±10	14±1.4
Gender (M/F)	29 / 18	8 / 4
Body Wight (kg)	71.4±10. 6	60.7±12.6

Table 3. 1: Demographics of the participants of the clinical trials used for the meta-analysis of glucose evolution at exercise in patients with type 1 diabetes.

In all four studies, the participants exercised on a bike at 50 % of VO_{2max}. All exercise sessions were between 3 pm and 5 pm.

$VO2_{max}$ is the maximal oxygen consumption of the body during an incremental exercise (in this case on an ergometer) which reflects the aerobic physical fitness of an individual [110].

For further test and validation, we used an independent data set from an ongoing clinical trial at the Virginia Commonwealth University clinical research services unit and the University of Virginia clinical research unit. The trial's participants are 14 adolescents with an age of 14.9 ±1.1 years. They were admitted twice for a 24 hours period, had regular meals and an aerobic exercise on a bike at 50% VO_{2max} for 45 minutes.

3.2.2. Protocols:

Study 1: This study was designed to establish the feasibility of a control-to-range (CTR) closed loop system informed by heart rate (HR) and assess the effect of the HR information on the risk for hypoglycemia during and after exercise. Subjects were randomized to determine the order of each admission (control: CTR, experimental:

CTR+HR). Each subject was admitted twice. Each admission lasted for 26 hours (24hours in closed loop) with 30 minutes of mild exercise on a cycle ergometer at a rate of perceived exertion of 9-10 on the Borg scale [100] between 3 pm and 5 pm. Three meals were given identically in each admission: a light breakfast at 8 a.m., an early lunch at 11 a.m. and dinner at 7 p.m.

Study 2: This study was designed to compare the glycemic control by two different closed loop control algorithms to the glycemic control in open loop mode in patients with T1D. Each patient was admitted three times. The admissions were randomized and each one lasted for 24 hours (23 hours of closed-loop if it was a closed-loop admission) with 30 minutes of exercise on a cycle ergometer at 50 % level of VO_{2max} between 3 pm and 4 pm.. Three meals were identically given to the patient in each admission: a breakfast at 8 am, lunch at noon and dinner at 7 pm.

Study 3: This study was designed to evaluate an automated glycemic control by an algorithm limiting prolonged hypoglycemia and hyperglycemia episodes by maintaining the blood glucose in a secure interval in patients with T1D. The system to be evaluated used an insulin pump to manage insulin delivery during meals and moderate physical activity in order to demonstrate its capacity to avoid important glycemic excursions. The admissions were randomized. Each participant was admitted twice, each admission lasted for 24 hours (22 hours of closed-loop if it was a closed-loop admission) with 30 minutes of exercise on a cycle ergometer at 50 % of VO_{2max} between 4 pm and 5 pm. Three standard meals were given to the participants: breakfast at 8 am, lunch at noon and dinner at 7 pm.

Study 4 and 5: These two studies were designed to demonstrate the feasibility of a modular control to range systems in T1D. The system was based on continuous glucose monitoring and targeted to avoid hypoglycemia and prolonged hyperglycemia episodes.

Each participant was admitted 6 times (in the MDB003 study) or 5 times (in the MDB005 study), each admission lasted for 24 hours and all admissions were randomized. The management of insulin delivery was challenged by meals (breakfast at 8 am, lunch at 11 am and dinner at 7pm) and exercise on a cycle ergometer for 30 minutes at 50 % Pmax between 4 pm and 5 pm.

3.2.3. Data cleaning:

We eliminated every admissions where the patient has received a hypoglycemia treatment within the 4 hours preceding the beginning of exercise. Those data points were eliminated because we are only interested in the effect of the exercise on the glucose dynamics and in the case of a carbohydrate treatment just before the activity, the main effect would highly depend on the quantity of CHO intake. Hence, 83.2% of the initial data was retained. The total final data set includes 94 admissions, 52% of which were in closed-loop using three different control algorithms.

The data was then separated to two thirds for training and one third for testing.

3.2.4. Methods:

We conducted a multiple linear regression analysis on the clean data set. The list of predictors used in the regression includes:

- BG_{start} : the blood glucose level at the beginning of exercise
- S_0: the slope of blood glucose for one hour before exercise
- IOB: the relative insulin on board as an indicator of the remaining insulin in the bloodstream. IOB is calculated by taking into account the 4 hour insulin bolus history and subtracting the basal infusion

- IOB_{abs}: the absolute insulin on board is calculated by taking into account all insulin bolus history (meal, basal and corrections) for last 4 hours preceding exercise.,
- TDI: the total daily insulin delivery
- the ratio $\frac{\mathrm{IOB}_{abs}}{\mathrm{TDI}}$: as an indicator of body insulin exposure,
- the ratio $\frac{\mathrm{TDI}}{\mathrm{BW}}$ where BW is the body weight
- the age as a categorical variable: 1 for adults and 0 for adolescents
- the body weight BW
- the gender: 1 for male and 0 for female

The response variable used in this meta-analysis is the slope change $\boldsymbol{\delta}$ of the blood glucose levels at the beginning of exercise. The slope change represents the additional glucose utilization due to the presence of the physical activity.

$$\boldsymbol{\delta = S_{ex} - S}$$

$\boldsymbol{S_{ex}}$ is the slope of the blood glucose values for the hour preceding the exercise (red line in Figure 3.1).

$\boldsymbol{S}$ is the slope of blood glucose values during exercise (Blue line in Figure 4.1).

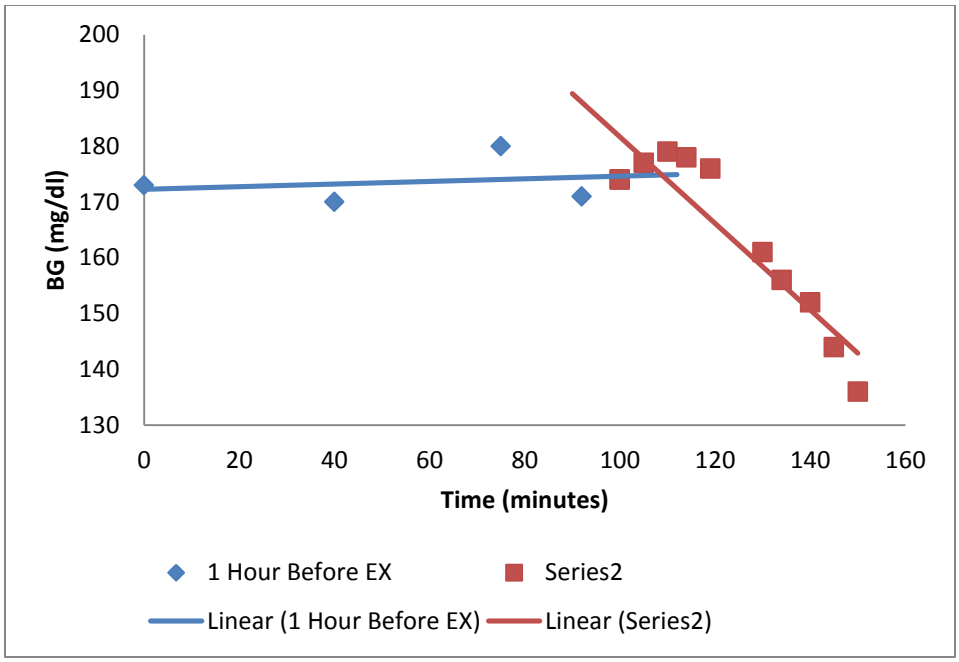

Figure 3. 1. Slope change calculation

To identify the most significant predictors, we used a backward stepwise selection that starts with a full model and sequentially deletes the predictor that has the least impact on the fit [122]. Akaike's Information Criterion [113],[114] (AIC) was used to compare the models. AIC accounts for the prediction error but also includes a penalty that is proportional to the complexity of the model measured by the number of parameters to be estimated in the model.

3.3. Results

The observation of the relationship between the exercise-induced slope change and the blood glucose at the beginning of exercise shows a clear linear relationship with an R-squared of 0.5 and a Pearson correlation factor of 0.73. (Figure 3.2)

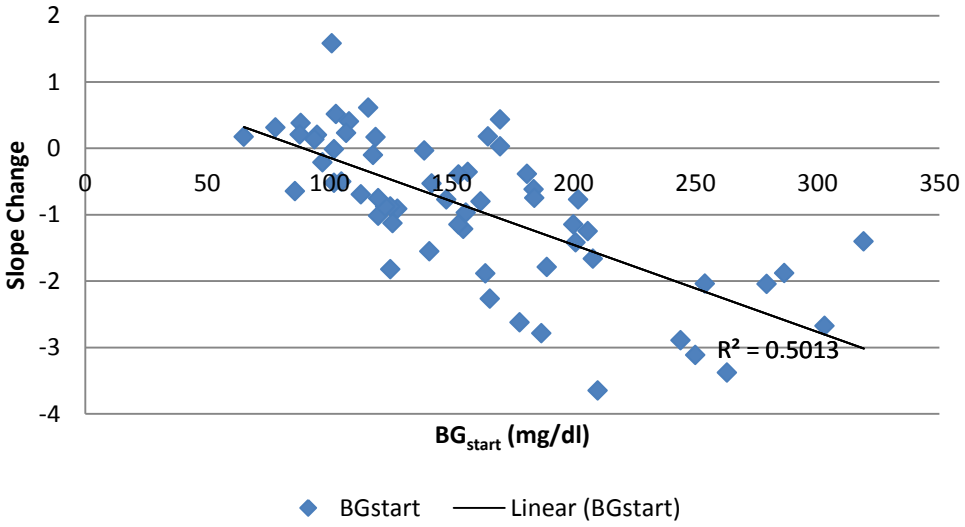

Figure 3. 2. – Correlation between the slope change of blood glucose levels at exercise and the blood glucose levels at the beginning of exercise in patients with type 1 diabetes.

The observation of the relationship between the exercise-induced slope change and the body exposure to insulin also shows a linear relationship with a Pearson correlation factor of 0.55. (Figure 3.3)

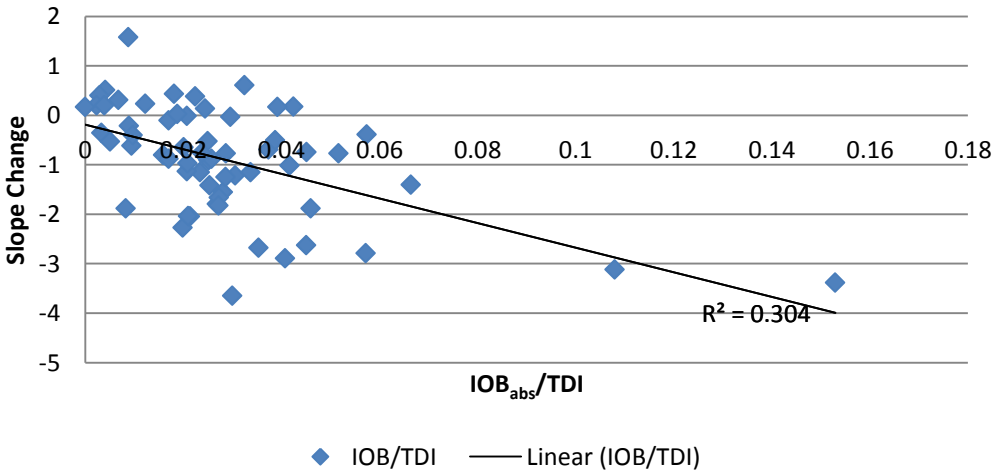

Figure 3. 3. Correlation between the slope change of blood glucose levels at exercise and the body exposure to insulin, expressed as IOB_{abs}/TDI, at the beginning of exercise in patients with type 1 diabetes.

As shown in Table 3.2, the blood glucose at the beginning of exercise (BG_{start}), the body exposure to insulin ($\frac{\mathrm{IOB}_{abs}}{\mathrm{TDI}}$) and the initial slope S_0 were significant at 0.05. The stepwise regression model (equation 1) has an AIC of 124 and R-squared of 0.6.

The multiple linear regression model is represented in Equation . The coefficients $\beta 0, \beta 1, \beta 2$ and $\beta 3$ quantify the effect of each parameter on the exercise-induced additional glucose utilization.

$$SlopeChange = \beta 0 + \beta 1 \,.\, BGstart + \beta 2 \,.\, \frac{IOB_{abs}}{TDI} + \beta 3 \,.\, AGE + \mathcal{E} \quad \text{(Equation 1)}$$

Predictors	Coefficient Estimate	p-value
Intercept	1.729	5.44 e-06
IOB_{abs}/TDI	-10.403	0.0197
BG_{start}	-0.012	8.43 e-08
Age (categorical)	-0.591	0.02

Table 3. 2: Stepwise Regression results for the identification of factors determining slope change of blood glucose levels at exercise in patients with type 1 diabetes.

The residuals of the multiple linear regression model have a normal distribution. Furthermore, the residuals vs fitted plot (Figure 3.4- top right plot) shows a non-significant heteroscedasticity in the data. However, we can see a slight concentration of the data on right of the top right figure 3.4

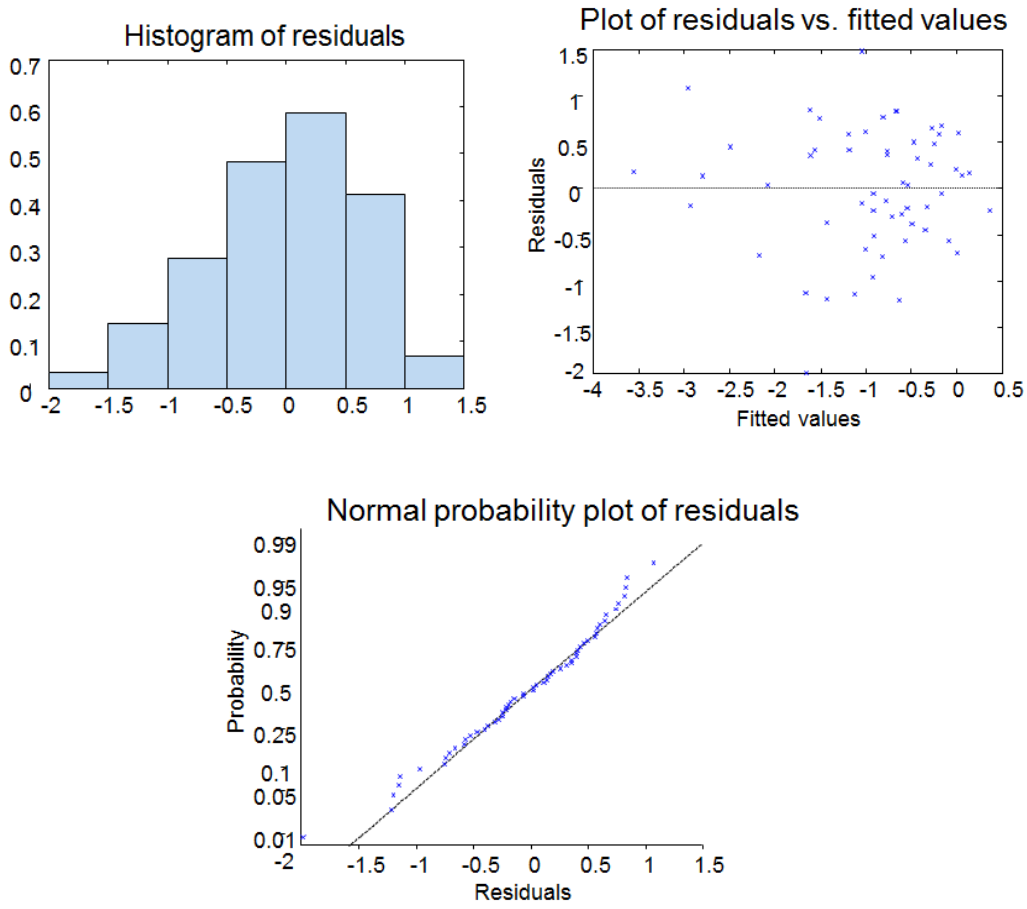

Figure 3. 4. Model residuals

Assuming that the change in glucose is linear in 5 minutes interval, we can use the result $\boldsymbol{\delta_{est}}$ (Slope change estimation) from the model in Equation1 to predict the blood glucose value during 30 minutes of mild exercise.

$$\boldsymbol{BG_{est} = BG_{start} + \delta_{est} \times T}$$

In figure 3.5, we predict blood glucose during exercise. These patients were selected based on their positions in regions on Figure 3.3 (Slope change vs $\frac{IOB}{TDI}$).

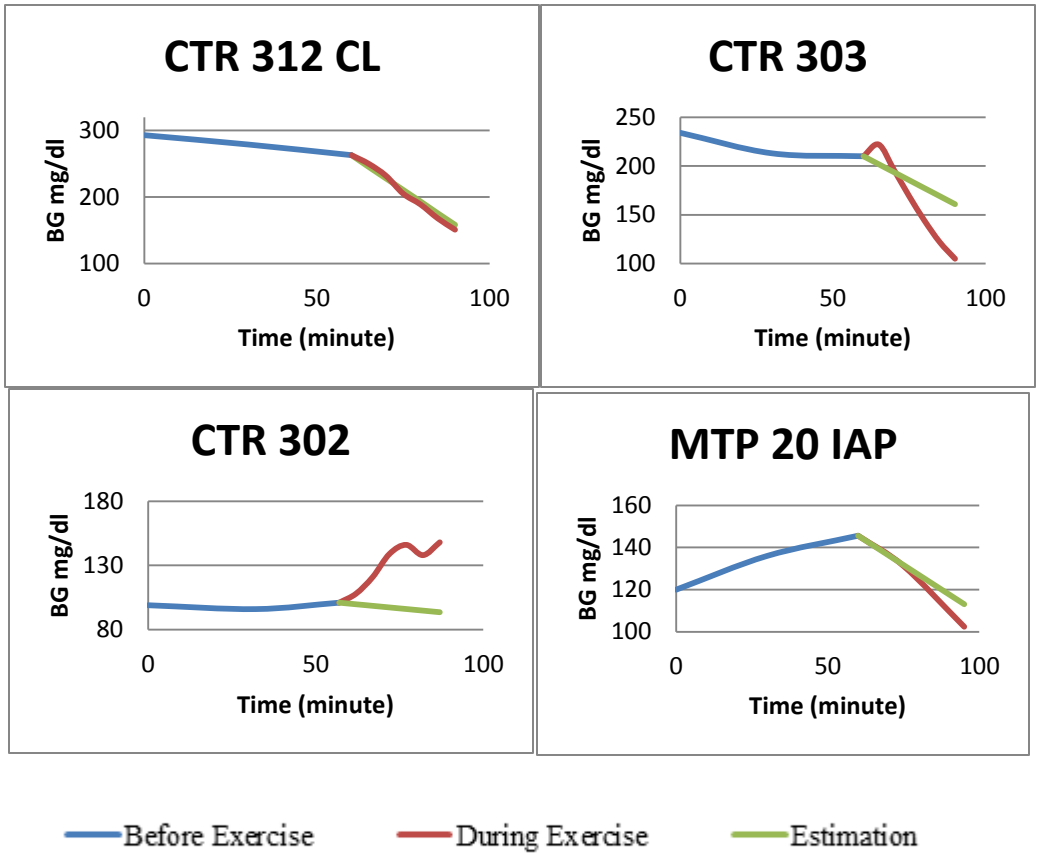

Figure 3. 5. Prediction of blood glucose based on the multiple linear regression model

Based on some patients' data from the testing set (Figure 3.3), the blood glucose prediction is good when the slope change is negative. However, the increase in blood glucose is not detected in patients situated in the top left corner of figure 3.5 (low IOB values). An example is patient CTR 302 (Figure 3.5, bottom left). This might be due to the fact that the increase might not be the effect of the exercise (preceding unregistered CHO intake due to the low initial BG during the clinical trials), or to higher intensity exercise than initially planned.

The validation of the results on the independent data set from the UVA/VCU clinical trial was conducted through the observation of the "new" data points compared to the data

used for training and testing. As shown in Figure 3.6, there is a clear linear relationship between the additional glucose utilization and the body exposure to insulin.

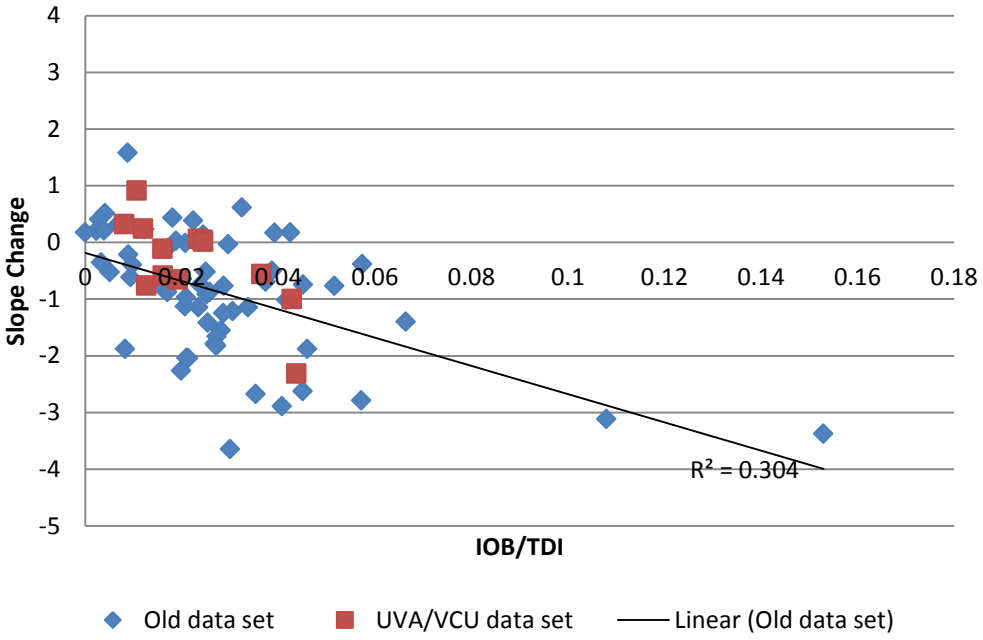

Figure 3. 6. Observation of the UVA/VCU ongoing trial data-Correlation between the slope change and IOB/TDI

The observation of the relationship between the slope change and the initial blood glucose at the beginning exercise shows a clear linear correlation as well (Figure 3.7).

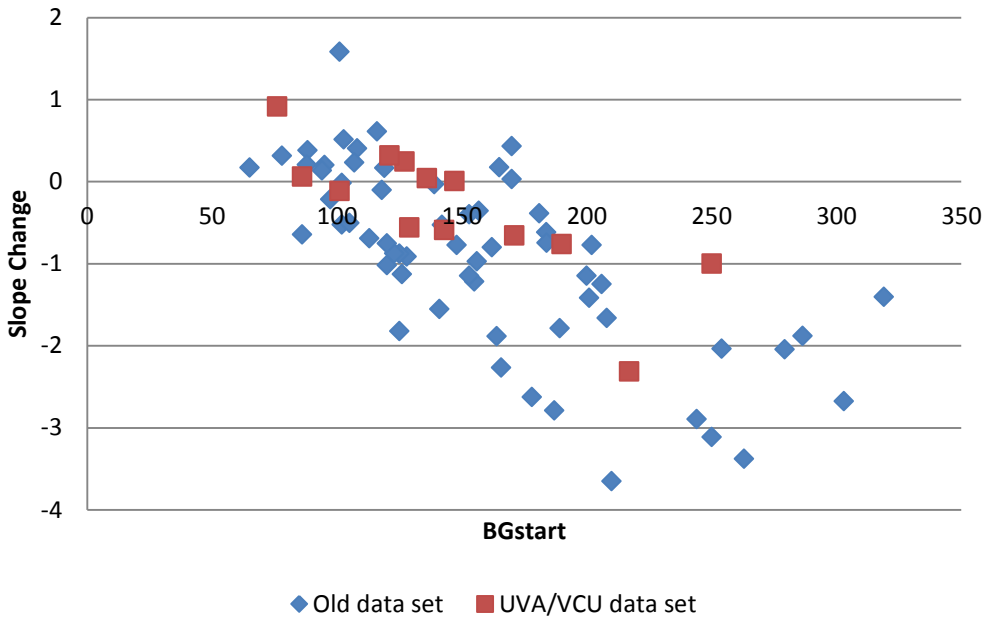

Figure 3. 7. Observation of the UVA/VCU ongoing trial data-Correlation between the slope change and the initial blood glucose

The parameters identified in this regression analysis are related mainly to the levels of blood glucose at the moment of exercise and to the level of circulating insulin in the blood stream. Even though the accuracy of the models in predicting hyperglycemia is not significant, we were able to quantify the effect of those clinically relevant factors and show the association between low blood glucose values and the insulin on board.

3.4. Discussion

We demonstrated the relationships of BG_{start}, $\frac{IOB_{abs}}{TDI}$ and age with the blood glucose drop induced by exercise. As a matter of fact, it appears we were able to provide evidence-based information about the main clinical factors that healthcare providers have been educating patients on.

BG_{start} reflects the metabolic state of the patient right at the beginning of exercise. The ratio $\frac{IOB_{abs}}{TDI}$ quantifies the body exposure to insulin when the exercise starts. Age also was a factor that shows a difference between adults and adolescents in regards to the immediate effect of exercise. This might be explained by the high growth hormone level in adolescents which is known to be an antagonist to the metabolic action of insulin [106], [112]. It might also be related to the fact that adults have a higher muscle mass and lower insulin resistance than adolescents.

We recognize some limitations in this work. In fact, we were not able to identify the impact of the time, duration or type of physical activity on the glucose dynamics. We also assume that the relationships between the parameters are linear, which is not the case due to the complexity of the metabolic changes induced by exercise. However, we were able to identify these main parameters and quantify their effects. Of note, the multiple linear regression was only successful in predicting the glycemic drop induced by exercise but was limited in predicting the rise in blood glucose. For this reason, it will only be applied to closed loop algorithmic control in order to prevent hypoglycemia during and immediately after mild to moderate physical activity.

In the context of artificial pancreas development, researchers have been working on various strategies to design control algorithms and safety supervision modules: Proportional Integral Derivative (PID)[91],[38], Model Predictive Control (MPC)[115],[116],[50] ,[117], Fuzzy Logic (FL)[118],[119] and safety supervision. Most of these approached are based on either predicting the blood glucose or the rate of change of the blood glucose. Whatever the chosen strategy for closed-loop control, the results provided by the multiple linear regression could be used to estimate directly the rate of change at the beginning of exercise. It can also be used to estimate the blood glucose levels during and immediately after exercise. In the safety supervision module introduced

in the UVA system [120],[121], the insulin delivery is in inverse proportion to the predicted risk for hypoglycemia using a T1D physiological model to estimate the patient's metabolic state. In such a system, the use of the blood glucose prediction described in this chapter would result in more conservative insulin infusion rates.

The respective roles of the blood glucose level and the body exposure to insulin at the beginning of exercise will be prospectively assessed in a forthcoming clinical trial in order to validate these factors as the key determinants of glucose drop at exercise in T1D patients.

Chapter 4

Exercise oriented decision support system for patients with T1DM alerting for risk of low glucose

4.1. Introduction

People with type 1 diabetes mellitus (T1DM) are at continual risk for hypoglycemia, which is recognized as one of the principal impediments to optimal glycemic control.[122]-[124]

Physical exercise in T1DM has been associated with many health benefits such as reduced cardiovascular risks, and improved psychological well-being, and possible benefits in bone-health. [125]-[127] However exercise also leads to an imbalance between hepatic glucose production and glucose disposal into muscle [88], increased insulin sensitivity related to glucose transporter type 4 translocation up-regulation,[128],[129] and impaired counter-regulatory hormonal response [128],[130]. In the absence of sufficient insulin reduction and/or carbohydrate supplementation, hypoglycemia often occurs during exercise, as well as during early and late recovery [131]-[133].

Despite growing awareness of exercise benefits, fear of hypoglycemia often results in avoidance of physical activity [134] or in over-compensatory treatment behaviors leading to worsened metabolic control [135], [12].Exercise has also been shown to mask hypoglycemic symptoms, thereby facilitating repeated exposure to unrecognized hypoglycemia and potentially causing hypoglycemia-associated autonomic failure [130] with all of its negative consequences.[136],[137] As a consequence, many people with T1DM engage in less exercise than their non-diabetic counterparts [87]. This finding is partly driven by patients' fear of hypoglycemia and lack of tools and/or knowledge on how to avoid hypoglycemic events [87].

To harness the benefits of exercise, people with T1DM must therefore carefully balance insulin regimen and carbohydrate intake before, during and after exercise bouts. Such a balancing act is further complicated by the multitude of factors that may affect the glycemic response to exercise, such as: (i) the type, intensity, and duration of physical activity, (ii) past insulin doses, and (iii) past food intake. In addition, the characteristics of exercise have been shown to influence the effect of exercise on glycaemia. For example, the type of activity (e.g. aerobic exercise vs. resistance training) can generate very different glycemic signatures [138],[139]. Independently of the type of activity *intense exercise* may also trigger the release of counter-regulatory hormones (glucagon, epinephrine) leading to lasting effects on glycemic balance [140]-[142]; longer exercise has also been shown to be associated with more hypoglycemia during but more significantly after the activity [143],[144]. Past treatments are also a critical factor in the glycemic response to exercise; for example past insulin doses, or more specifically circulating levels of insulin during and after exercise, can significantly increase the drop in glycaemia [82]; and past food intake, as well as compensatory carbohydrate intake

during and after exercise are highly relevant to the resulting glycemic balance [12],[145],[146].

Strategies for adaptation to exercise primarily involve adjustment of insulin regimen and carbohydrates [12],[82]-[154]. Some decision support systems have appeared and have shown promises in avoiding immediate hypoglycemia [12]. Nonetheless, these are still in early development as noted in Robertson et al. [155]: "Currently, no evidence-based guidelines exist on the amount and timing of increased carbohydrate to limit post-exercise hypoglycemia. However, reductions in basal insulin, low glycemic index snacks (with no bolus), or reduced boluses at post-exercise meals will usually reduce the problem." Additionally they remain nonspecific to the patient's physiology and behavior, which can limit their acceptance [156].

In this chapter, we develop a model for prediction of low glucose based on data collected in 4 different clinical studies where patients with T1D had to exercise at a moderate intensity level. The model is then used as the foundation for a predictive classifier of the risk for hypoglycemia.

4.2. Data and Methods:

4.2.1. Participants and Protocols:

We used the same data set described in sections 3.2.1 and 3.2.2

4.2.2. Data cleaning:

We proceeded with the same data cleaning method described in section 3.2.3

4.2.3. Modeling:

We conducted a regression analysis on the cleaned data set. The list of predictors used in the regression includes the blood glucose at the beginning of exercise (BGstart), the slope of blood glucose from one hour before exercise (S_0), the relative insulin on board (IOB) as an indicator of the remaining insulin in the body(calculated by taking into account insulin doses injected within the 4 hours before exercise and subtracting the basal dose), the absolute insulin on board (IOBabs, absolute refers to the fact that insulin injections are not offset by basal), the total daily insulin (TDI), the ratio $\frac{\mathrm{IOB_{abs}}}{\mathrm{TDI}}$ as an indicator of body insulin exposure, the ratio $\frac{\mathrm{TDI}}{\mathrm{BW}}$ (where BW is the body weight) reflecting sensitivity to insulin, the age (as a categorical variable, 1 for adults and 0 for adolescents), the body weight and the gender (1 for male and 0 for female).

The response variable was H, obtained by applying a threshold BGthresh on the actual blood glucose values BGend at the end of exercise.

$$\mathrm{H} = \begin{cases} 1, & \mathrm{BG_{end}} < \mathrm{BG_{thresh}} \\ 0, & \mathrm{BG_{end}} \geq \mathrm{BG_{thresh}} \end{cases} \quad \text{(Equation 1)}$$

The BGthresh was chosen to be 80 mg/dl for the initial model construction.

Since our outcome of interest is a binary variable H, we used a logistic regression model which arises from the desire to model the forthcoming probabilities of H via linear functions of the predictors[122] (BGstart, S0, IOB, IOBabs , TDI, $\frac{\mathrm{IOB_{abs}}}{\mathrm{TDI}}$,$\frac{\mathrm{TDI}}{\mathrm{BW}}$, age, BW, Gender). The model is specified in terms of logit transformation of the probability (definition of logit in page 54) of having a BG level below the defined threshold at the end of exercise (equation 2).

Instead of searching through all possible subsets of the predictors, we used a backward stepwise selection which starts with a full model and sequentially deletes the predictor

that has the least impact on the fit [157] Akaike's Information Criterion [113][114]. (AIC) was used to compare the models. The AIC gives statistical significance for the balance of adaptation and complexity of a model and quantifies the relative goodness of fit for various parameters: in essence, AIC rejects large prediction errors but also includes a penalty that is proportional to the complexity of the model. The preferred model is the one with the lowest.

	Deviance	**AIC**
<none>	33.93	42.93
+Age	33.26	43.26
+Gender	33.42	43.42
$-\frac{\mathbf{IOB}_{abs}}{\mathbf{TDI}}$	39.81	45.81
-S_0	40.416	46.41
-G_{start}	73.895	79.89

Table 4. 1. Stepwise regression results (R statistics software)

As shown in Table 4.2, the stepwise regression model has an AIC of 42.93 and a deviance of 34.93. It includes three main factors: BG_{start}, $\frac{IOB_{abs}}{TDI}$ and the initial slope S_0.

$$Logit(P) = \beta 0 + \beta_1.\ BG_{start} + \beta_2.\ \frac{IOB_{abs}}{TDI} + \beta_3.\ S_0 \text{ (Equation 2)}$$

$$Where \begin{cases} Logit(P) = Log(\frac{P}{1-P}) \\ P = \frac{e^{\beta 0 + \beta_1.\ BG_{start} + \beta_2.\frac{IOB_{abs}}{TDI} + \beta_3.S_0}}{1 + e^{\beta 0 + \beta_1.\ BG_{start} + \beta_2.\frac{IOB_{abs}}{TDI} + \beta_3.S_0}} \end{cases}$$

Logit(P) is the logit transform of the probability of having a BG level below the defined threshold immediately after exercise.

The results of the logistic regression (shown in Table 4.3) suggest that higher $\frac{\text{IOB}_{\text{abs}}}{\text{TDI}}$ levels result in a higher likelihood of exercise induced low glucose. However, higher BG_{start} and initial slope S_0 result in lower likelihood of having low glucose values at the end of exercise. $100 \times (e^{\beta_{i\cdot}} - 1)$ reflects the percentage change in the odds with a unit change of every predictor while holding other predictors The ratio $\frac{\text{IOB}_{\text{abs}}}{\text{TDI}}$ has the most significant effect on the likelihood of exercise induced low glucose levels.

Predictors	**Coefficient Estimate**	**p-value**
Intercept	8.682	0.0003
$\frac{\textbf{IOB}_{\textbf{abs}}}{\textbf{TDI}}$	69.572	0.02
$\textbf{BG}_{\textbf{start}}$	-0.082	0.0004
$\textbf{S}_{\textbf{0}}$	-1.869	0.03

Table 4. 2. Logistic regression model coefficients (R statistics software)

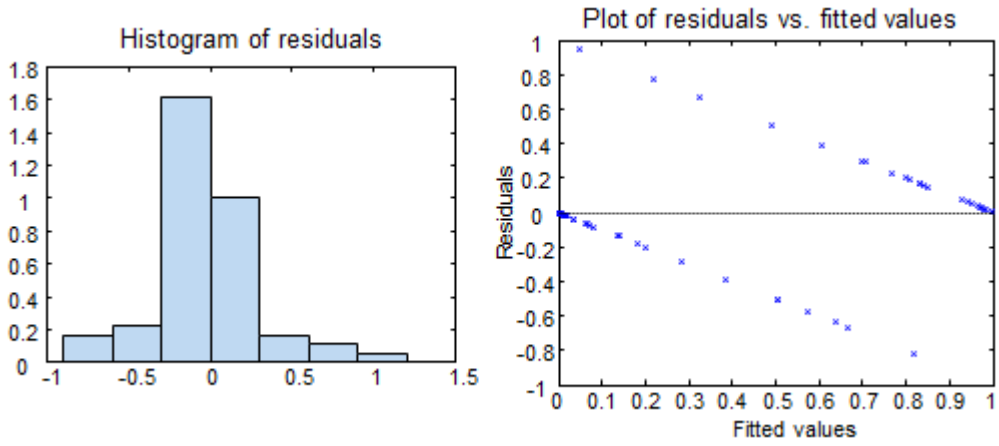

Figure 4. 1: Logistic regression model diagnostic

The logistic regression model (equation 2) was the foundation for the exercise-induced low glucose state classifier. To obtain the classifier, a detection threshold DET_{thresh} is needed to classify the prediction results.

$$\hat{H}_{est} = \begin{cases} 1, & \text{Logit(P)} \geq \text{DET}_{\text{thresh}} \\ 0, & \text{Logit(P)} < \text{DET}_{\text{thresh}} \end{cases}$$

Furthermore, the response variable used in the logistic regression model is constructed using the threshold BG_{thresh} applied to values of blood glucose at the end of exercise (Equation 1). To optimize the classifier, both DET_{thresh} and BG_{thresh} can be tuned.

We varied BG_{thresh} between 80 mg/dl and 120 mg/dl with a step of 10 mg/dl. DET_{thresh} was also varied between 0 and 1 with a step of 0.1.

4.3. Results

Receiver Operating Characteristic (ROC) curves were used to assess the performances of the different classifiers corresponding to each set of (BG_{thresh}, DET_{thresh}). For every value of BG_{thresh} we obtain a curve (colored lines in Figure 1) which is constructed by the variation of DET_{thresh}.

As shown in Figure 4.1, the best glycemic state prediction is for a BG_{thresh} of either 90 mg/dl or 100 mg/dl and a DET_{thresh} of 0.4. Therefore, on the training data, the performance of the classifier is at more than 90 % true positive rate.

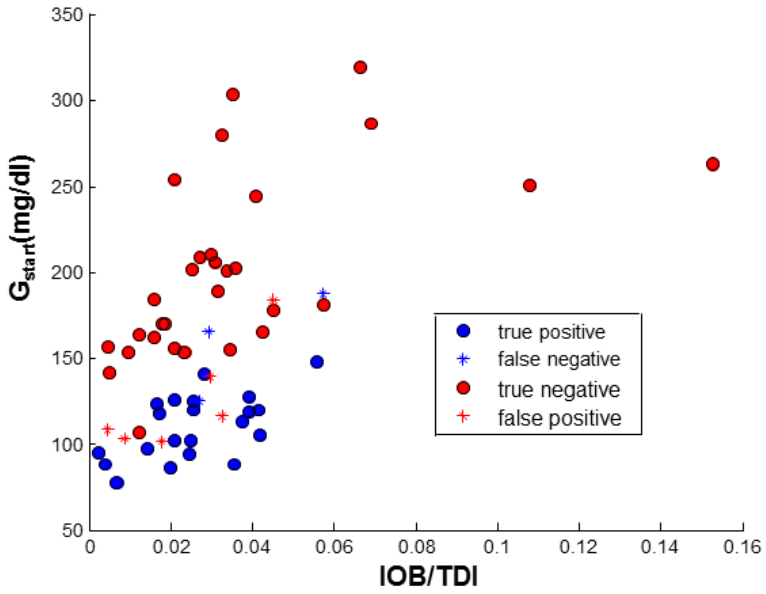

Figure 4. 2: Classification results on training data

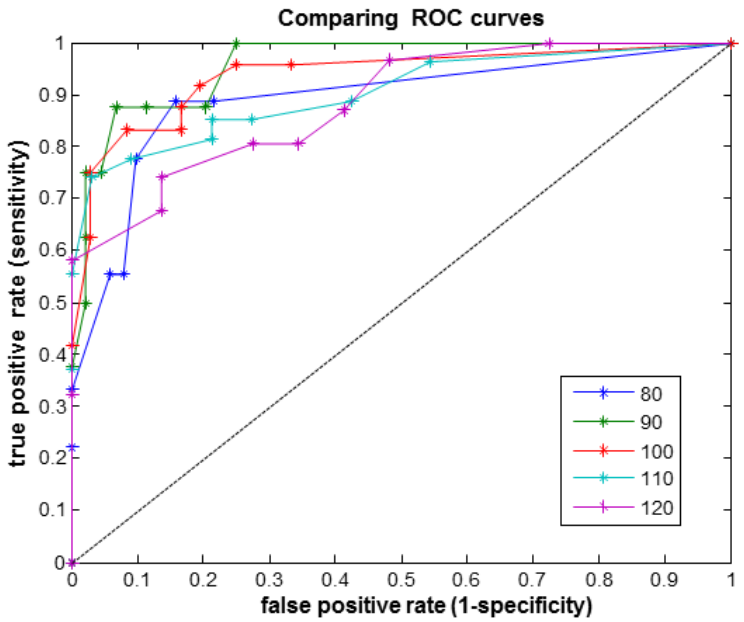

Figure 4. 3: ROC comparison through the variation of DET_{thresh} and BG_{thresh}

The classifier was validated using the testing data set (one third of the initial data set). Only one false positive registered with a true positive rate of 86 %. It is true that the classifier missed a low glucose value but the patient did not actually experience any

exercise induced hypoglycemia event. This is one of the advantages of using a threshold of 100 mg/dl instead of an actual hypoglycemia threshold of 65 mg/dl.

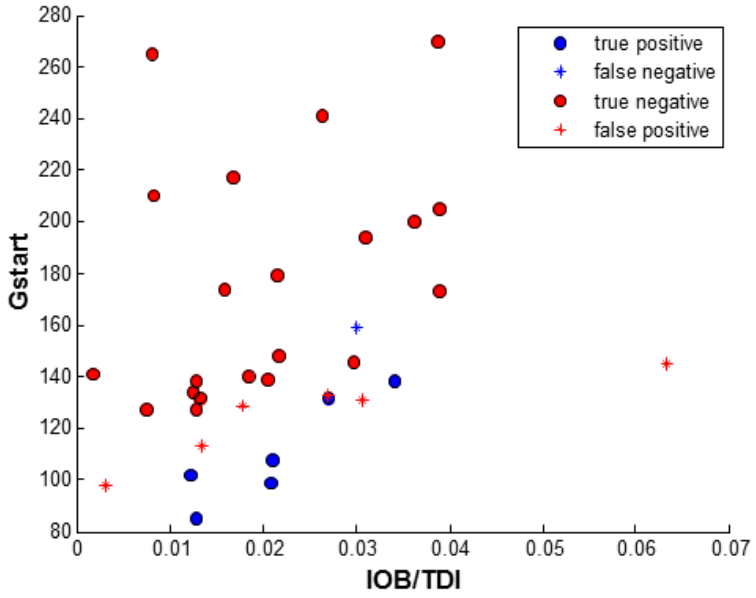

Figure 4. 4: Classification results on testing data set

		Predicted	
		Hypo	Not hypo
Actual	Hypo	6	1
	Not hypo	6	21

Table 4. 3. Classification performance on testing data set

The comparison of the ROC curves in Figure 4.2 does not provide a clear superiority in terms of performance. Furthermore, we need a better understanding of the impact of the variation of the parameters on the sensitivity and specificity. For this purpose, cross validation was applied to the total 94 data points. The same technique was used for tuning DETthresh and BGthresh (variation of DETthresh between 0 and 1 with a step of 0.1 and variation of BGthresh between 80 mg/dl and 120 mg/dl with a step of 10 mg/dl). Two

hundred iterations were repeated to randomly separate the data set to a training set (two thirds of the data) and a testing set (one third of the data). The best performance is captured by the red ROC curve in Figure 4.4 and it corresponds to a BG_{thresh} of 100 mg/dl and a DET_{thresh} of 0.4.

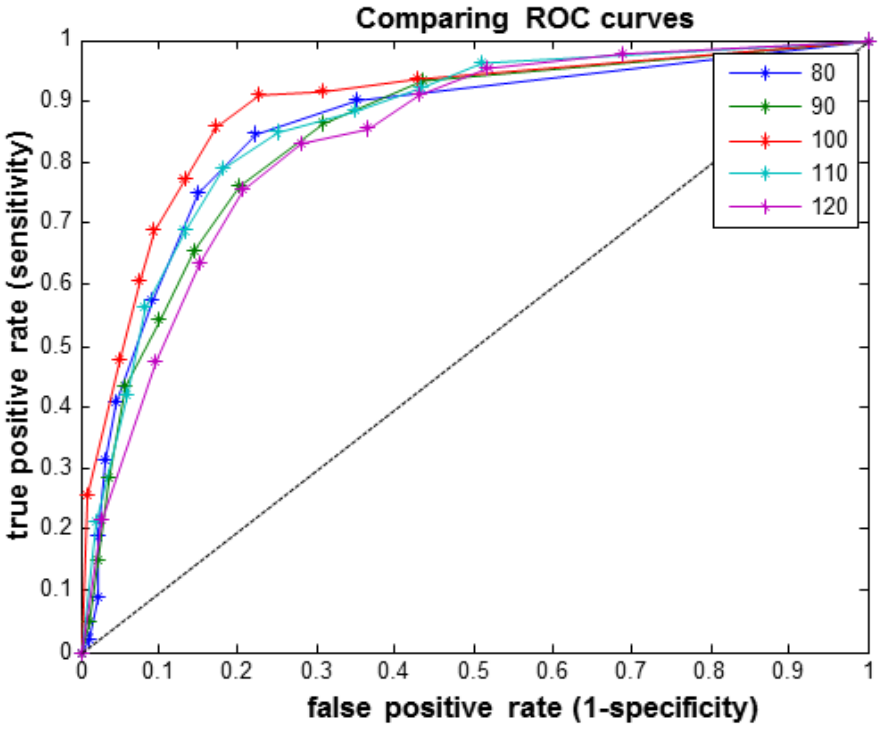

Figure 4. 5: Cross Validation results

4.4. Simulation results

To further validate the results, we used the UVA/PADOVA T1DM metabolic simulator [158], [159], [48] developed by our group in conjunction with the University of Padova, Italy. The Simulator has been accepted by the Food and Drug Administration as a substitute for pre-clinical trials of insulin treatments strategies. It is based on a simulation model that describes the physiological events that occur after a meal [48]. The effect of

physical activity has then been added [158] using the results of a study on healthy subjects.

The parameters BG at the beginning of exercise and body exposure to insulin have been modified in the simulator to match their respective distributions in the data set used for training and testing.

- **In silico scenario description**

We used an in-silico population of 100 adults with T1D. The scenario included a total period of 6 hours of pre-exercise observation with 45 minutes of mild exercise

Exercise starts at the beginning of the simulation (time =0) and continues until minute 45. No meals were given as disturbances.

- **In silico results**

We compared the simulation results with the predictions from the exercise-induced low glucose classifier developed in this work.

As shown in Figure 4.5, only three false negatives were registered. The true positive rate was 85 % with a false positive rate of 15 %. These results are comparable to the results obtained by the analysis of the real data collected in the different clinical trials.

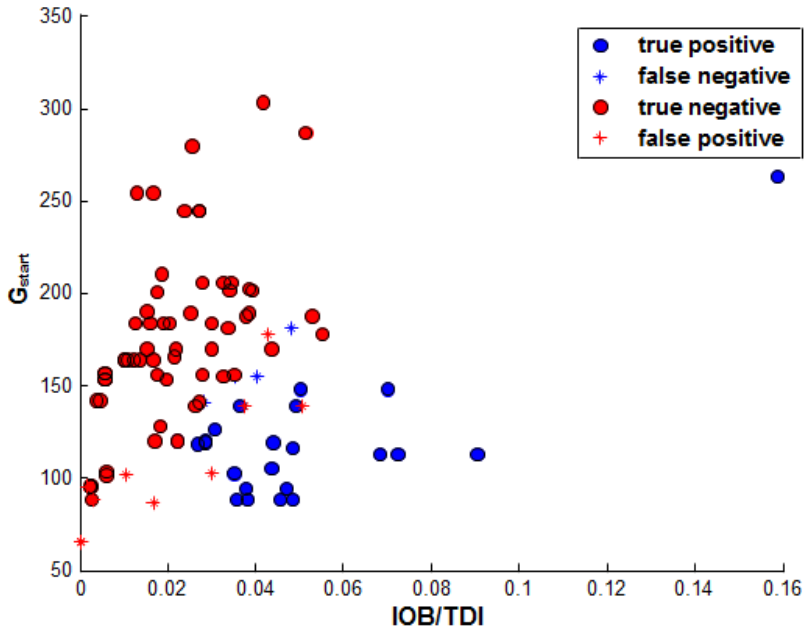

Figure 4. 6: Simulation results

4.5. Independent validation

A new independent data set from the UVA/VCU clinical trial was used to further validate the exercise classifier. As shown in Figure 4.6, the exercise classifier performed at a 100 % true positive rate with 33 % of false positives. These results are comparable to the results obtained through the analysis of original data set, the cross validation and the simulations (see section 4.3 and 4.4).

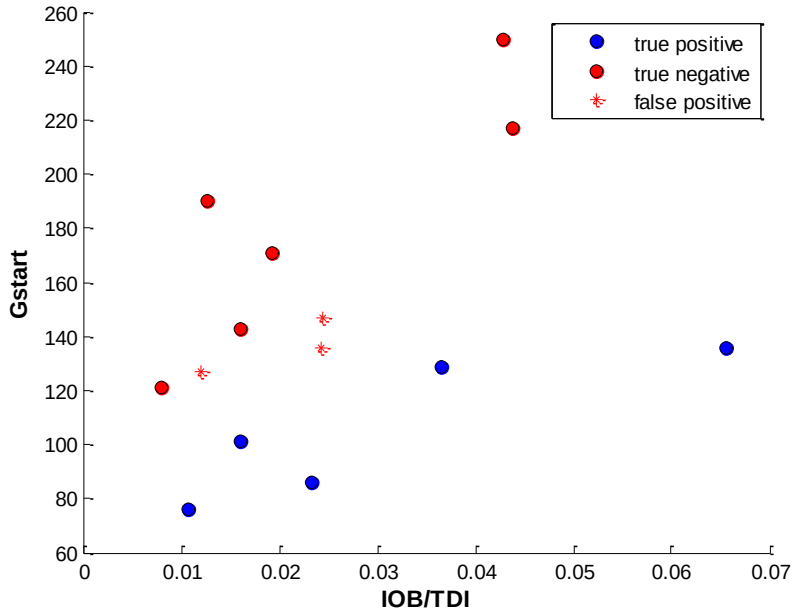

Figure 4. 7: Independent validation results

4.6. Discussion

Our goal was to develop a predictive exercise-induced low glucose classifier by deriving a logistic regression model from data collected in different studies. On one hand, using stepwise logistic regression, we were able to identify the main parameters to predict low glucose immediately after a mild to moderate physical activity in T1DM. BG_{start} reflects the initial metabolic state. $\frac{\mathrm{IOB}_{abs}}{\mathrm{TDI}}$ echos the body insulin exposure. And finally, the initial slope S_0 reflects the inertia of the metabolic state.

On the other hand, we were able to derive a logistic regression model which served as a foundation for the predictive exercise-induced low glucose. The classifier showed promising results using the already collected data, in different trials with different designs, with a true positive rate of 86 % on the testing data. This classifier could be of a great value to inform patients with T1D on the risk of projected hypoglycemia in the presence of a mild to moderate exercise.

The models developed in this work have limitations in the number of predictors. In fact, the logistic regression model does not take into consideration the type, the intensity or the duration of exercise. The classifier based on the model was tuned based on ROC curves comparison and cross validation techniques. The tuned blood glucose threshold based on which we construct the response value is 100 mg/dl. This value is optimal in terms of performance. However, since 80 mg/dl is more relevant as a hypoglycemia threshold, the decrease in performance might be tolerated.

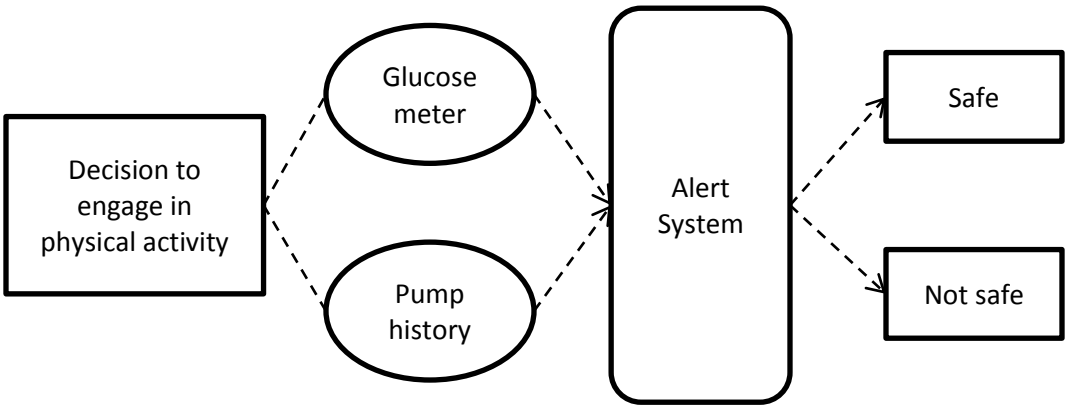

Figure 4. 8: Exercise-induced hypoglycemia alert system for T1DM patients

Based on the results presented in this chapter, a Decision Support System will be designed for T1DM patients. An alert will be triggered to inform the patient on the risk for hypoglycemia. The patient will be advised to wait until the insulin is cleared or eat a snack before/during exercise. Figure 4.7 illustrates a use case of such a system.

The classifier developed in this work will be integrated in a pump companion system with the intention to be deployed in a clinical trial with T1DM patients in order to assess its clinical performances..

Chapter 5

Decision Support System for T1DM patients' safety during and immediately after a mild to moderate physical activity

The development of Decision Support Systems (DSS) can be traced back to more than 50 years ago. DSS emerged from the outgrowth of the management information systems area. Various definitions have been suggested [160],[161],[162],[163] but they all agree that these systems are designed to aid a decision maker in solving unprogrammed, unstructured (or semistructured) problems. The DSS technology and applications have been evolving significantly as a result of the continuing technological and organizational evolutions [164]. Such systems have a wide range of applications. In fact, they are extensively used in:

- Business and management [165]: the charts and graphics help managers make a better allocation of resources. The executive dashboards and performance software enable faster and more efficient decision making.
- Agricultural production [166]: during the 80s, the USAID financed the development of a DSS to enable rapid assessment of agricultural productions

systems which allowed faster decision making and evidence-driven policy making.

- Railroad maintenance [167]: the Canadian National Railway has developed a system to determine which equipment and rail needs maintenance at a specific time. This DSS allows them to make better-informed decisions to avoid hundreds of derailments every year.
- Medical diagnosis/healthcare delivery: Clinical Decision Support Systems [168] have been developed to assist patients and healthcare professionals in making better diagnosis and analysis of patient data.

The list above is not exclusive. Theoretically, DSS can be built in any knowledge area. In this chapter, we focus on a Clinical Decision Support Systems (CDSS). We give a background based on the literature and we present the design of a decision support system for patients with T1DM to safely engage in a physical activity.

5.1. Introduction

Decision Support Systems (DSS) are information technology based solutions that are designed to support complex problem solving and decision making [169]. Such systems are based on the foundation of the theoretical framework from Hertbert Simon's work during the late 1950s. His work focused on studies of organizational decision making. The technical work was carried out at MIT by Gerrity and Ness in the 1960s [170]. The design of DSS is based on three main components: The first is the access to internal and external data, information and knowledge, and the capability to manage the data. The second is the modeling of the data. The third is the delivery of the evidence based decision through a user interface [171].

DSS applications started originally in business and management applications but expanded to different areas where decision support is needed. In the healthcare space, DSS systems are known as Clinical Decision Support Systems (CDSS). CDSS provide a variety of advice and recommendations including diagnostic suggestions and evidence-based treatment recommendations. These systems, when implemented properly, have been proven to reduce medical error [172] and increase health care quality and efficiency [175]. The recent evolution in mobile platforms (i.e. smartphones, tablets) and the availability of affordable physiological sensors have led to the development of the so-called mobile Health (mHealth). The system we are presenting in this work falls in the mHealth category. Such systems empower patients with more personalized care and safety measures to prevent short and long term complications.

There is a wide range of literature on best practices for CDSS design and implementation. Kawamoto, et al [173]. did a review of the research literature and identified design properties that are correlated with successful CDSS. The review showed that:

- Computer-based decision support is more effective than manual processes.
- Automatic decision support that fits into the workflow is more likely to be used.
- Providing actions for the users is more effective than providing simple assessments.
- Providing information at the time of the decision-making is more likely to have impact on the outcome.

Following this set of best practices, we will develop the foundation of a decision support system for type 1 diabetes patients to enable them to have a safe physical activity by preventing hypoglycemia. Patients will be encouraged to use wearable sensors for

automatic detection of exercise. The system will take actions right at the beginning of exercise by either automatic adjustments or prompting advice to the patient.

An estimated 300,000 people are currently using insulin pumps worldwide. 20% of type 1 diabetes patients have access to pump therapy in the United States [174], compared to 1.3% in the United Kingdom. Roughly, 10 % of those pump users have access to continuous glucose monitors. Those numbers limit the target population of the artificial pancreas systems to only 2 % of type 1 diabetes patients. In order to be able to address the safety issues related to hypoglycemia and exercise to the larger T1DM population, we did not limit this work to using the AP platform as the foundation for an exercise-induced hypoglycemia safety system. We designed a more generic DSS that takes very accessible blood glucose and insulin parameters as input and suggests/recommends an action to the patient based on the prediction algorithms.

In this chapter, we focus on developing a decision support system for type 1 diabetes patients who are engaging in a physical activity. We designed and implemented an automatic exercise detection module based on off the shelf commercial devices. This module is then integrated in the artificial pancreas platform and it was used and validated in clinical trials involving patients with T1DM. In the second part, we define and compare different sets of actions and strategies based on the already developed models presented in the previous chapters.

5.2. Exercise detection

In order to be able to react to the effect of exercise on blood glucose dynamics, we need to be able to detect its presence. Nowadays, some available off-the-shelf wearable devices make it easier to capture motion data in real time. Recent research has shown that wearable accelerometers, for example, can be used to reliably detect the presence and

even the type of physical activity [176],[177],[178],[179]. Heart Rate (HR) is also a useful signal to detect exercise and, may be, determine the intensity since it correlates with energy expenditure for aerobic exercise [180],[181]. The relationship between HR and exercise intensity is linear [182] and it can describe the fitness level [183].

Using a Heart Rate signal to inform an artificial pancreas has been shown to be effective in preventing exercise-induced hypoglycemia [107]. As shown in Figure 5.1, during the same feasibility study, the HR increased consistently in 19 out of 20 admissions and bypassed the threshold of 125% of the resting heart rate in an average time of 8:02 minutes. Informing the closed loop control algorithm using HR protected against hypoglycemia by changing the insulin infusion rate to be more conservative. However, HR alone provides little information of the nature of the physical activity, and it is influenced by other factors such as emotional states, fitness levels and ambient temperatures. Furthermore, the increase in HR induced by exercise is highly variable between individuals. For highly trained competitive athletes, a bigger effort is needed to observe a significant change in HR. Moreover, autonomic neuropathy in patients with advanced diabetes history may affect HR variations, including basal accelerated HR at rest and reduced increase at exercise.

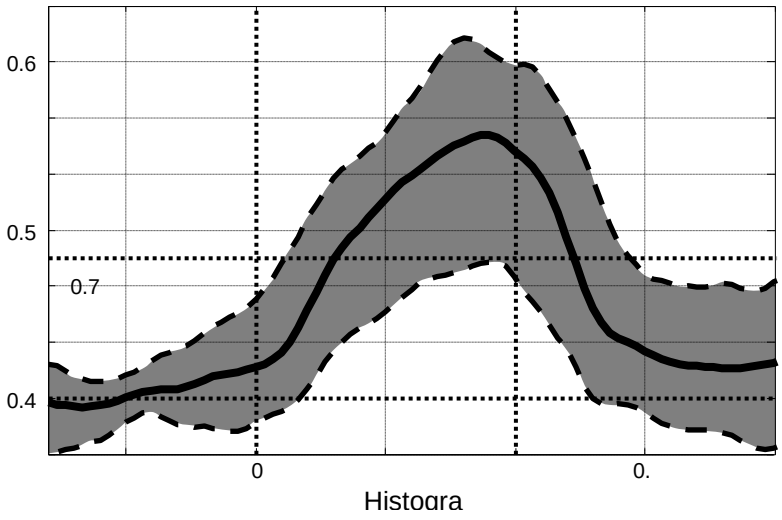

Figure 5. 1: Relative heart rate during exercise [107] (the gray area represents the 90th percentile)

Using accelerometers might be the remedy for the limitations of HR signals. Real-time algorithms have been developed and its effectiveness have been established in the real-time automatic recognition of physical activity [184],[185]. The accuracy of these algorithms reaches more than 90% and it can, in some cases, identify the intensity when coupled with HR [185]. Few studies have used accelerometers to enhance closed loop blood glucose control in T1DM. However, preliminary trials and simulations have shown promising results [109].

5.2.1. Integration of an "Exercise mode" in the DiAs artificial pancreas platform

The Center for Diabetes Technology research team at the University of Virginia has developed a mobile Artificial Pancreas platform: "DiAs"- for Diabetes Assistant -, a system composed of an Android smart phone running the control algorithms and communicating with a Dexcom continuous glucose monitor and an insulin pump. DiAs

has been tested with success in several clinical trials to evaluate the control and safety algorithms efficiency around exercise. It has a modular architecture that allows the step-wise introduction of control algorithms [187].

As shown by Figure 5.2, the different modules of DiAs are all centered on one structured database "Biometrics Content Provider" and supervised by a master threading and checking module "Supervisor". The modules in the bottom are the drivers for the different hardware components including the continuous glucose monitors and the insulin pumps. The green modules are the control modules that could be replaced and/or modified by the research team.

Integration of physical activity in DiAs requires the creation of an Exercise Module (highlighted in Figure 5.2) that has three main roles: communicate with the sensors, write in the database and more importantly detect/classify the exercise.

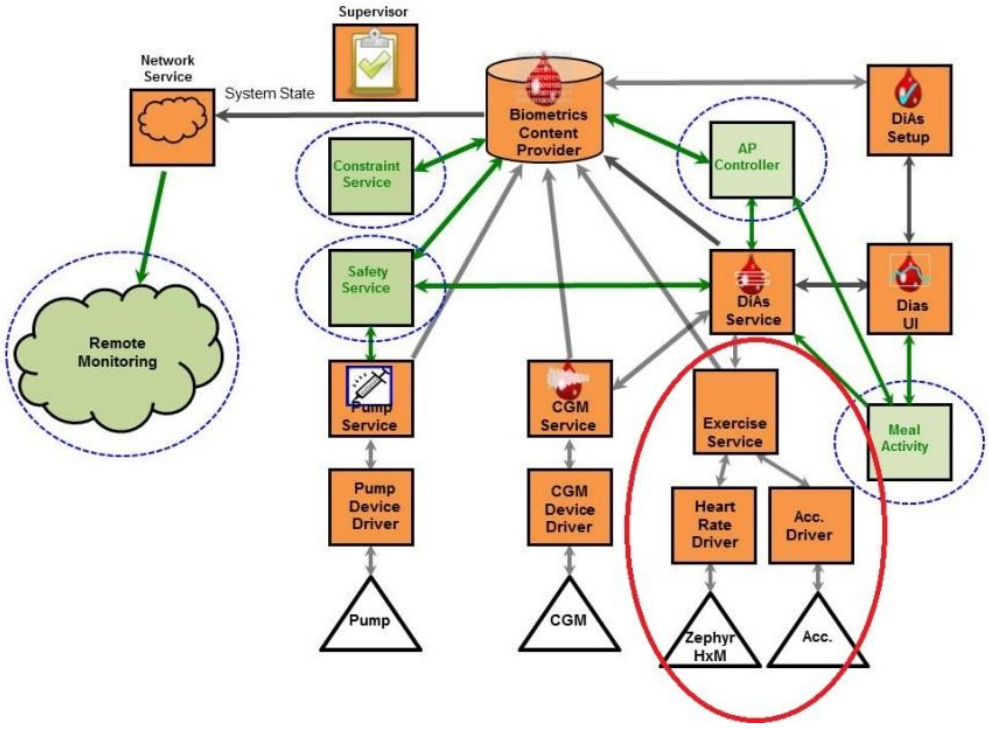

Figure 5. 2: DiAs architecture

5.2.2. Integration of Heart Rate (HR module)

Heart Rate (HR) is the most basic signal used to detect the presence of physical activity. In order to be integrated in DiAs, the HR monitor has to be Bluetooth enabled and has to provide an Android sdk for easy and fast implementation.

Few commercial devices meet the requirements and the Zephyr HxM was selected. It is a Bluetooth Chest Strap that provides the HR/RR intervals, the distance and speed of movement. The HR values range between 50 and 240 BPM. The communication range is 10 m and the battery life is about 26 hours. The advantage of the Zephyr HxM is that it has an Android sdk for fast implementation. However, this device communicates with DiAs every second which shortens the battery life on the system. This issue still has to be addressed.

Based on Heart Rate, the exercise is detected in real time using equation 1 as a function of the resting heart rate $HR_{resting}$ which is determined by the average heart rate over an hour of no physical activity.

$$EX = \begin{cases} 1, \ HR \geq 1.25 \times HR_{resting} \\ 0, \ HR < 1.25 \times HR_{resting} \end{cases} \quad \text{(Equation 1)}$$

This module has been deployed in ongoing clinical trials on patients with T1DM at the University of Virginia Clinical Research Unit and the Virginia Commonwealth University Clinical Research Services Unit.

5.2.3. Integration of Accelerometers (Acc module)

As discussed in the previous section, HR alone is not a reliable signal to automatically detect physical activity. As a remedy, we integrated accelerometers into the DiAs platform. The sensors have to be wireless Bluetooth enabled and portable.

Few commercial devices meet the requirements and the Zephyr Bioharness was selected. It is a Bluetooth enabled chest strap that provides a wide range of signals: HR, RR intervals, breathing rate, posture, activity level, peak acceleration, speed and distance, and GPS.

$$VMU = \sqrt{x^2 + y^2 + z^2} \quad \text{(Equation2)}$$

$$MA = \frac{\sum_{i=1}^{n} VMU_i}{n}$$

Where VMU is the vector magnitude units, x, y and z are the 3 axis of the accelerometer, MA is the mean activity and n is the number of VMU samples.

We used the raw signal of the triaxial accelerometer to extract the mean activity (MA) parameter. The integrated signal for movement over time is represented by vector magnitude units (VMU) [188]. The MA is then obtained by averaging the VMU over one minute of time.

We conducted simple analysis on data collected doing daily activities. Figure 5.3 shows a portion of the data set and using the observation and simple comparison with the annotated times of the activities, we chose a threshold of 0.1 (red line in Figure 5.3).

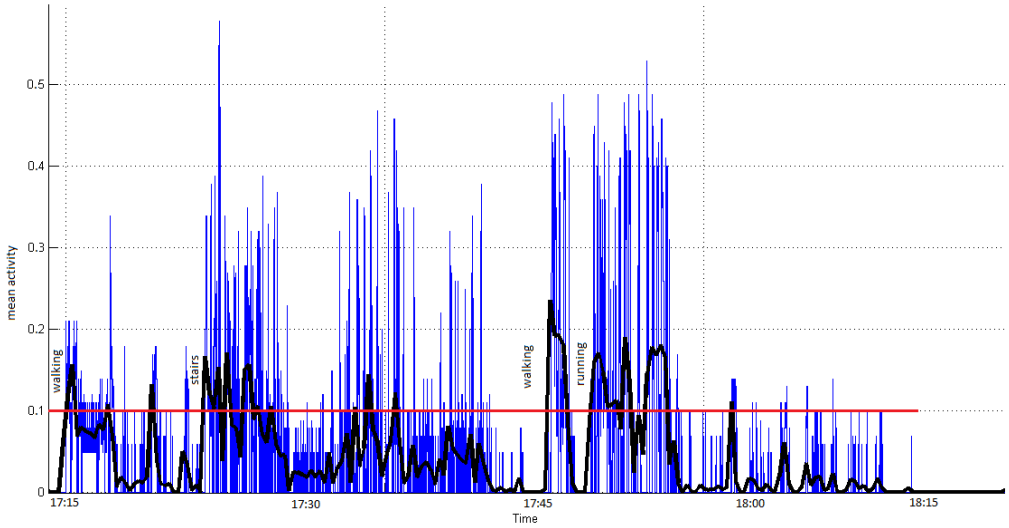

Figure 5. 3: Mean activity over time. (the red line is the detection threshold, the bold dark line is the average)

The detection algorithm runs once every 5 minutes to determine the average of MA based on which we detect exercise by applying a detection threshold of 0.1 as shown in equation 3.

$$EX = \begin{cases} 1, \ avg(MA) \geq 0.1 \\ 0, \ avg(MA) < 0.1 \end{cases} \qquad \text{(Equation 3)}$$

The module was deployed in clinical trials with patients with T1DM in diabetes summer camps both in Virginia and California.

5.3. Actions and advice for T1DM patients to safely engage in a physical activity

5.3.1. State of the art heart rate informed control to range algorithm (HR CTR)

To complement closed loop Control Algorithms, Safety Algorithms are designed to reduce short-term risk for hypoglycemia by discontinuing or reducing basal insulin.

Safety Algorithms strategies range from pump shutoff when hypoglycemia detected [189],[190], Insulin On Board Computations [191], “brakes” approach [192] and “semi-closed-Loop” glucose control[193]. In recent pilot studies, Heart Rate informed Safety Algorithms have shown efficiency in preventing immediate risk for hypoglycemia induced by exercise [107].

The current Safety System (SSM) is based on the Control to Range (CTR) algorithm and exercise detection using the Heart Rate signal. The detection is based on a 125% value of the resting HR threshold. The exercise indicator is set to 1 if the HR value is above the threshold and 0 otherwise.

The SSM reduces the basal rate automatically based on the glycemic risk index introduced by Dr Kovatchev [194]. As shown in Figure 5.4, the glucose target is 110 mg/dl and any deviation from this value increases the risk for hypo/hyperglycemia. The values below 110 mg/dl increase rapidly the risk for hypoglycemia, in contrast with values above 110 mg/dl which increase the hyperglycemia risk slowly.

In response to the exercise indicator, in the HR-Enhanced CTR (HR CTR), the risk function is shifted to redefine the target value at 140 mg/dl. In Figure 5.4, the blue line represents the new risk function: in the presence of exercise, the risk for hypoglycemia increases and the risk for hyperglycemia decreases.

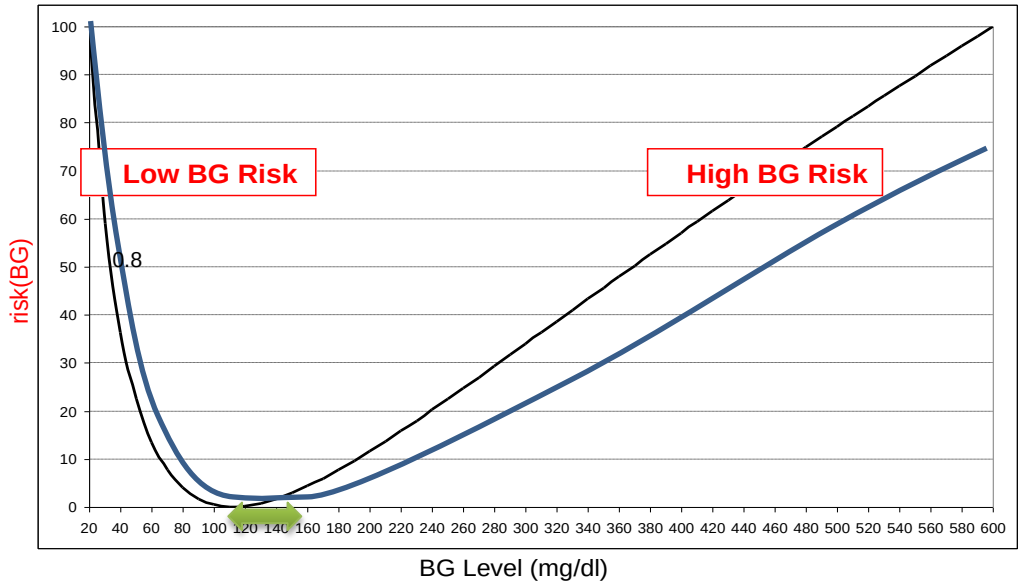

Figure 5. 4: The risk function in the original BG scale: original risk function in black, shifted exercise-induced risk function in blue

The HR-CTR algorithm has been tested in a clinical study [107]. 12 adults with T1DM have been admitted twice (one with CTR and one with HR CTR) for a period of 26 hours with a 30-minute moderate exercise in the afternoon. Around exercise, the number of hypoglycemia events decreased by 3-fold without any induced hyperglycemia as observed in the time spent in range [70-180 mg/dl].

5.3.2. Methods

We used the FDA approved T1DM simulator. We ran simulations on 100 in-silico adults with type 1 diabetes. The exercise was mild with duration of 45 minutes. No meals were given during the total period of the simulation (4 hours). The exercise starts right at the beginning of the simulation.

To match the same set of data we used to develop the exercise classifier presented in chapter 4, we solved the steady state equations for a given initial blood glucose (BG_{init}) and a given level of insulin on board (IOB_{init}). We executed the following steps:

$$\dot{X} = f(X, BG, J)$$

Where X has 13 state equations, BG is the blood glucose level and J is the insulin infusion variable.

Step 1: Fix $BG=BG_{init}$

Step 2: solve the steady state equation

$$\dot{X} = f(X, BG_{init}, J)=0$$

Step 3: introduce a disturbance; then fix the insulin injection vector to match the wanted value of IOB_{init}

$$J = g(IOB) \quad \rightarrow \quad J_{init} = g(IOB_{init})$$

Step 4: solve the steady state equation again for BG_{init} and IOB_{init}

$$\dot{X} = f(X, BG_{init}, J)=0 \quad \rightarrow \quad \begin{Bmatrix} BG_{init} \\ IOB_{init} \\ Slope_{init} \end{Bmatrix}$$

We test 4 different strategies:

- **S0:** "null" strategy, we do not take any action
- **S1:** We use the HR CTR algorithm in closed loop simulations. This algorithm applies more aggressive breaks on insulin injections during exercise.
- **S2-a:** We use the exercise classifier to detect low glucose. We suspend insulin injections for the duration of exercise (45 minutes). This action is only taken when low glucose is predicted.
- **S2-b:** We use the exercise classifier to detect low glucose. The action is to suspend insulin injections for one hour. This action is only taken when low glucose is predicted.

- **S2-c:** We use the exercise classifier to detect low glucose. The action is to suspend insulin injections for two hours. This action is only taken when low glucose is predicted.
- **S2-d:** We use the exercise classifier to detect low glucose. The action is to give 16 grams CHO as a hypoglycemia treatment when hypoglycemia is detected. The treatment is given every 15 minutes during the exercise if the blood glucose levels are lower than 70 mg/dl. This action is only taken when low glucose is predicted.
- **S2-e:** We use the exercise classifier to detect low glucose. The action is to give $\propto$ grams per Kg CHO as a hypoglycemia treatment when hypoglycemia is detected. The treatment is given every 15 minutes during the exercise if the blood glucose levels are lower than 70 mg/dl. This action is only taken when low glucose is predicted.

All the strategies above can be classified in four pools as presented in Figure 5.5. We derive the best of each of the "CHO treatment" strategy and the "pump shutdown" strategy and then we compare them with the "null" strategy and the state of the art closed loop algorithm.

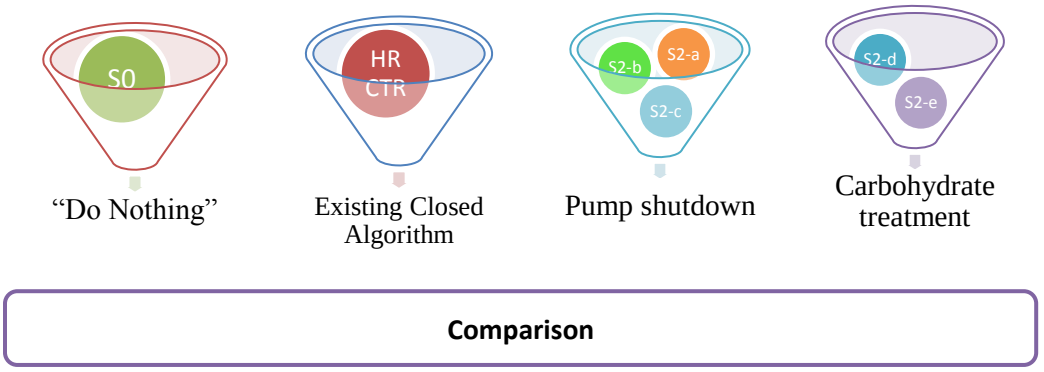

Figure 5. 5: Actions' strategies to prevent exercise-induced hypoglycemia

The comparison will be based on the percentage time in severe hypoglycemia (<50 mg/dl), percentage time below 70 mg/dl and percentage time above 180 mg/dl. We use observations of the traces of blood glucose as well.

5.3.3. Results and analysis

a. Low Glucose Suspend (LGS) strategy

To compare the difference LGS strategies, we use the blood glucose evolution in time for the 100 T1DM adults for the period of 4 hours. We use the mean and the interquartile range (IQR) of the blood glucose values. We use two colors (blue and red) for each strategy, the third color (purple) is the intersection of both IQRs.

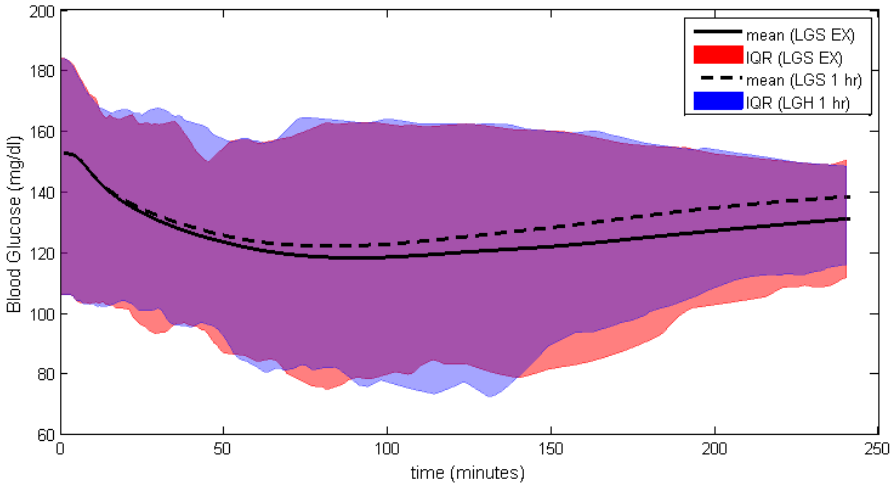

Figure 5. 6: Comparison of S2-a and S2-b

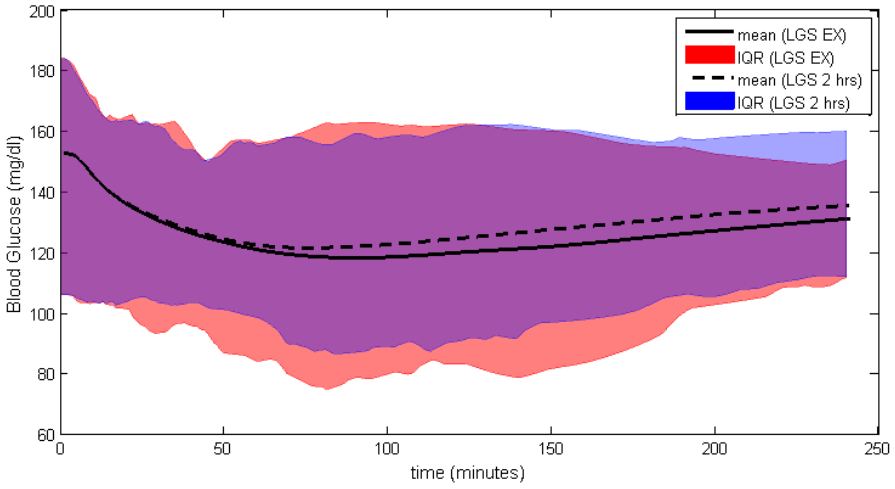

Figure 5. 7: Comparison of S2-a and S2-c

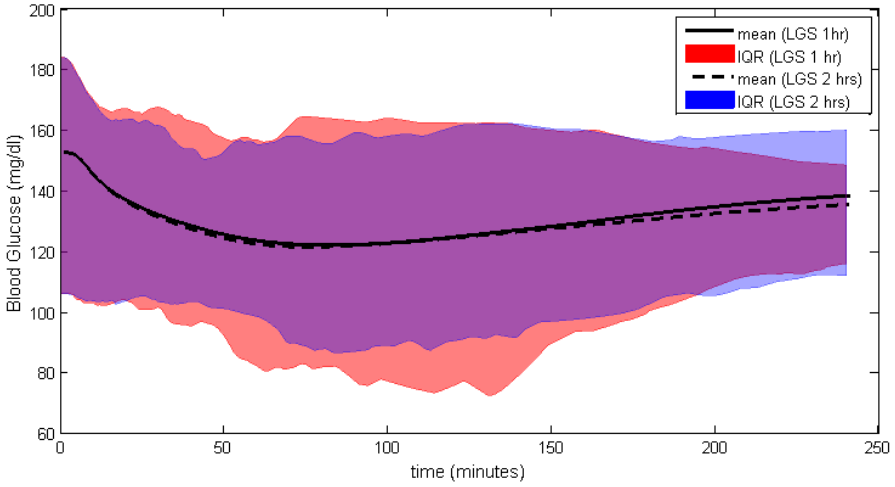

Figure 5. 8: Comparison of S2-b and S2-c

As shown in Figures 5.6, 5.7 and 5.8, the LGS 2 hours shows higher capabilities of keeping the patients in the 70 – 160 mg/dl range. It is the best strategy to prevent hypoglycemia during and immediately after exercise. However, we note that there is a rebound after 90 minutes of post-exercise period. To avoid high glycemic values, we might suggest an option of injecting a small correction bolus: the strategy can require the measurement of blood glucose after 2 to 3 hours to correct the high levels. We might also integrate the treatment advice system in a closed loop artificial pancreas platform.

b. Carbohydrate treatment

One of the strategies to protect against hypoglycemia is to give a hypoglycemia treatment to the patient if we predict exercise-induced hypoglycemia. We have two options to determine the amount of carbohydrates given to the patients:

- *Option 1:* Give 16 grams for all patients
- *Option 2:* Define $\mathbf{CHO} = \propto \times \mathbf{BW}$ where BW is the bodyweight and $\propto$ is a coefficient.

In order to compare the different options, we ran simulation by varying $\propto$ (0.1, 0.3,0.5, 0.7) and including the fixed 16 grams treatment.

As shown in Figues 5.9 and 5.10, giving more carbohydrate per kg (higher $\propto$) does not impact significantly the prevention of hypoglycemia but it increases the rebound after the end of exercise.

For the in silico adult population, the average bodyweight is 69.7±12.4 Kg which means that $\propto$ falls in the range [0.05 – 0.41]. Hence, the low impact on the hypoglycemia prevention and the rebound of blood glucose right after exercise (Figure 5.9 and 5.10).

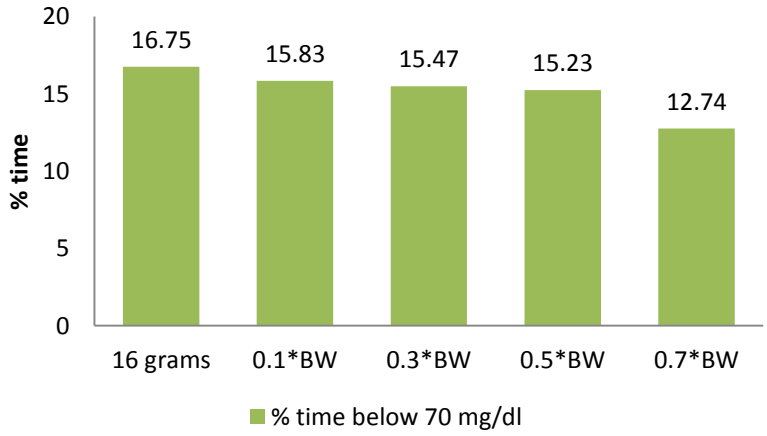

Figure 5. 9: Comparison of the percentage time below 70 mg/dl for different CHO treatment values as a function of the BW and the fixed value of 16 grams

We decided to use $\propto = 0.3$ to continue the comparison. Note that this $\propto$ value has its limitations. This strategy will only be valid for adults. In fact, adolescents have much lower bodyweight which will decrease the amount of carbohydrate treatment obtained by the 0. 3 coefficient. For example, in the in silico adolescent population the bodyweight is 48.8 kg ±8.2 which means the carbohydrate treatments will be in the range of 12.8 to 17.1 grams which is lower than the current clinical guidelines of 15 to 20 grams.

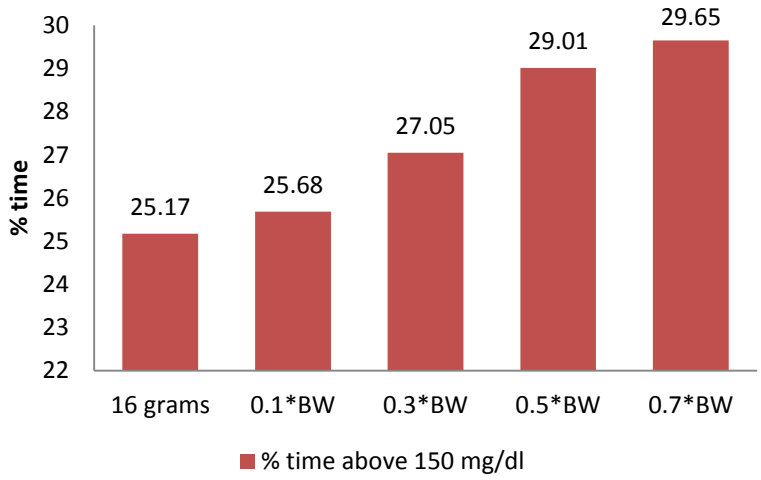

Figure 5. 10: Comparison of the percentage time above 150 mg/dl for different carbohydrate treatment values as a function of the body weight and the fixed value of 16 grams

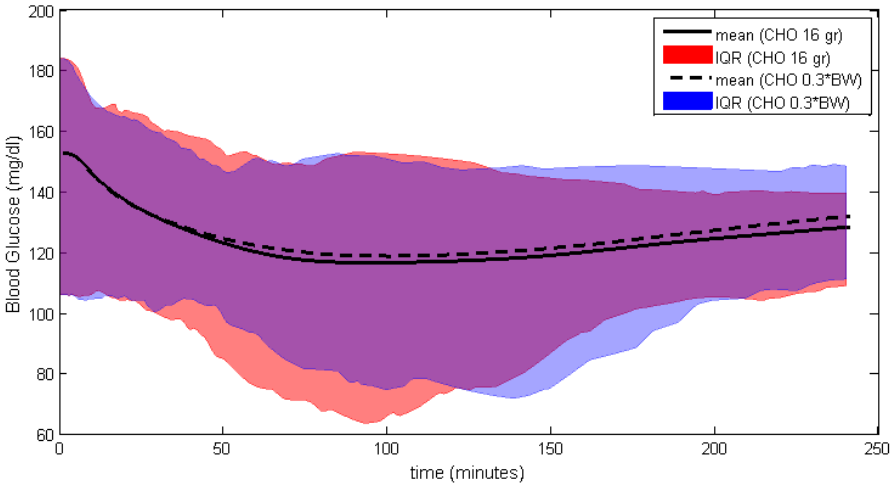

Figure 5. 11: Comparison of S2-d and S2-e

Using the graphics of mean and IQR evolution of blood glucose values, we compared further the fixed 16 grams treatment to the 0.3*BW treatment. The latter shows higher performance in preventing hypoglycemia during and immediately after the physical activity.

We chose the strategy S2-d with $\propto = 0.3$ as the best strategy using carbohydrate treatments to prevent hypoglycemia.

c. Comparison with "Do Nothing"

As shown in Figures 5.11 and 5.12, using the "LGS 2 hours" and the 0.3 * BW carbohydrate treatment improves significantly the glycemic control during and immediately after exercise. Figure 5.16 shows an improvement of more than 50% in the percentage of time spent in severe hypoglycemia.

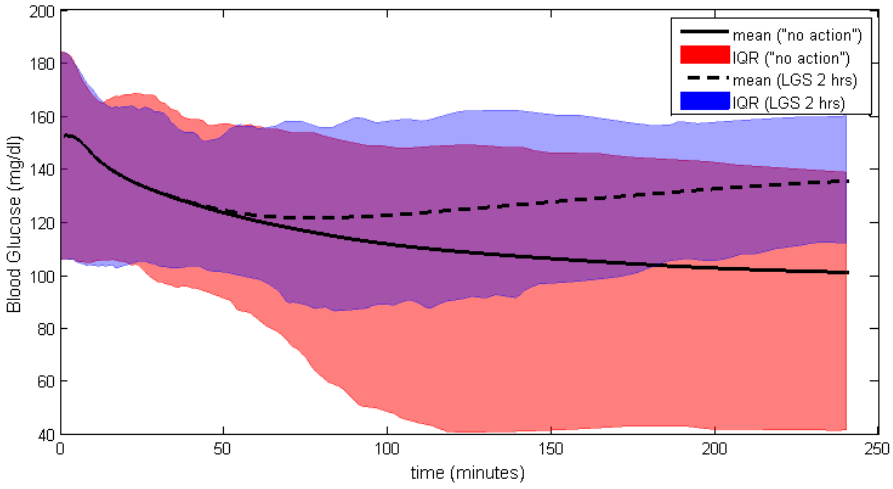

Figure 5. 12: Comparison of S0 and SS2-c

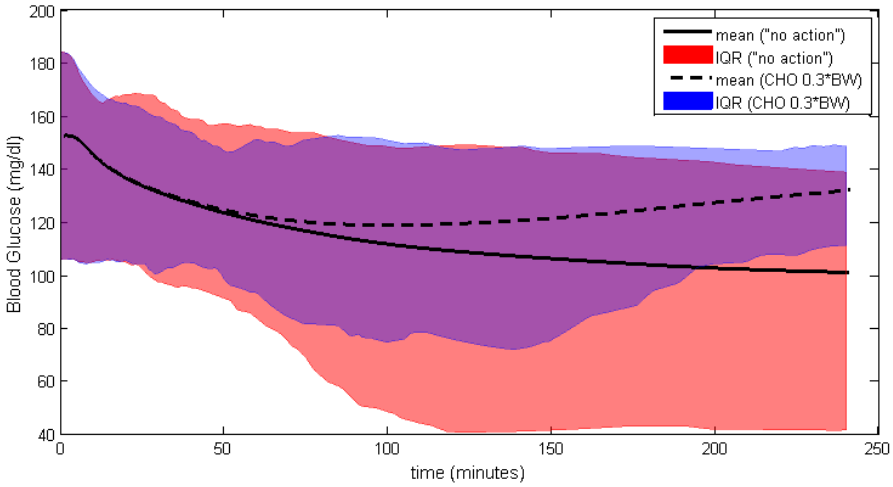

Figure 5. 13: Comparison of S0 and S2-e

Since we have proven the efficacy of both low glucose suspend and carbohydrate treatment strategies, we compared their performances using the same blood glucose trend graphics. Figure 5.14 shows the superiority of “LGS 2 hours” over the “0.3*BW CHO treatment.

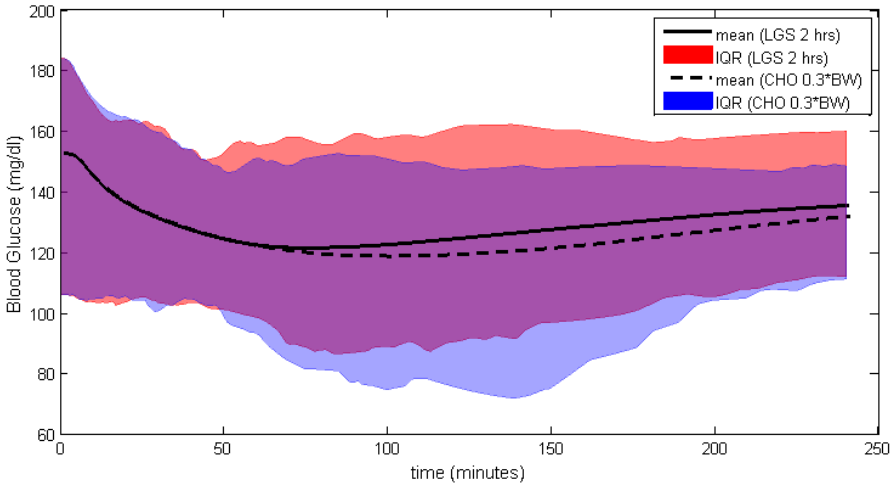

Figure 5. 14: Comparison of S2-c and S2-e

d. Comparison with HR CTR

As shown in the previous section, "LGS 2 hours" is the better strategy. We compare it to the state of the art "HR CTR controller". We observed a higher performance in hypoglycemia prevention but also a rebound in the post-exercise period. This rebound might be acceptable because we can correct it by giving a small bolus. This result is very promising since the HR CTR algorithm applies the aggressive breaks on insulin injections all the time, even without the presence of hypoglycemia risk. "LGS 2 hours" applies the action of suspending the injections only when hypoglycemia is predicted. The fact that our hypoglycemia detction algorithm produces false and true positives, even though minimal (10 to 15 %), validates more the superirority of the glycemic control.

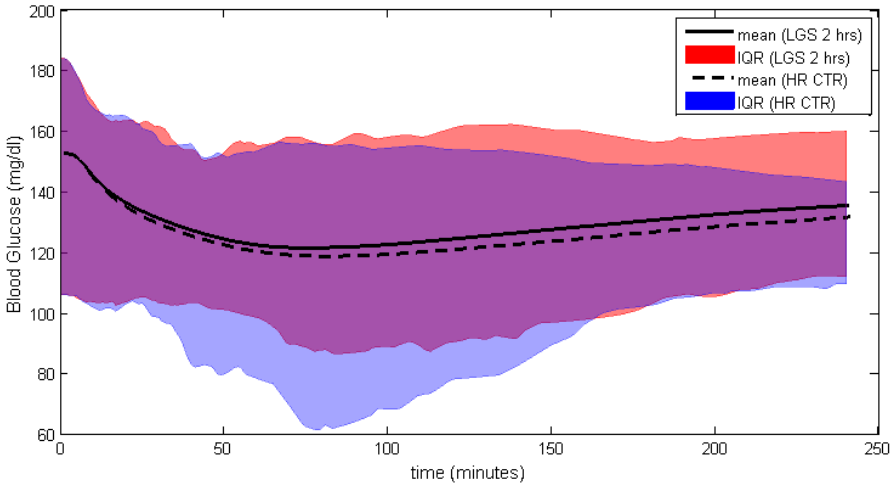

Figure 5. 15: Comparison of S2-c and S1

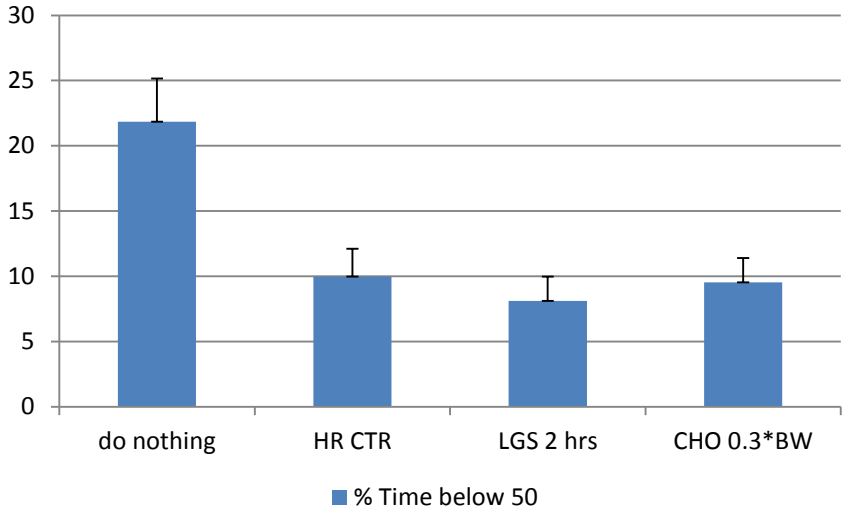

Figure 5. 16: Percentage time below 50 for the 4 different strategies

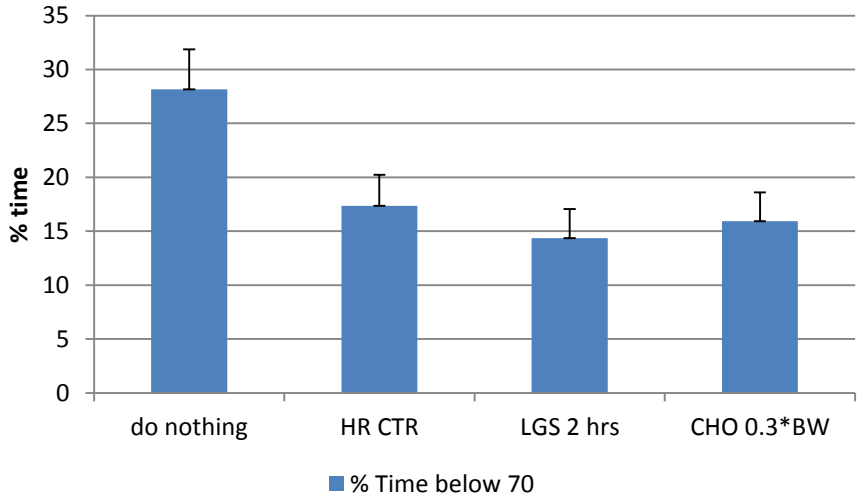

Figure 5. 17: percentage time below 70

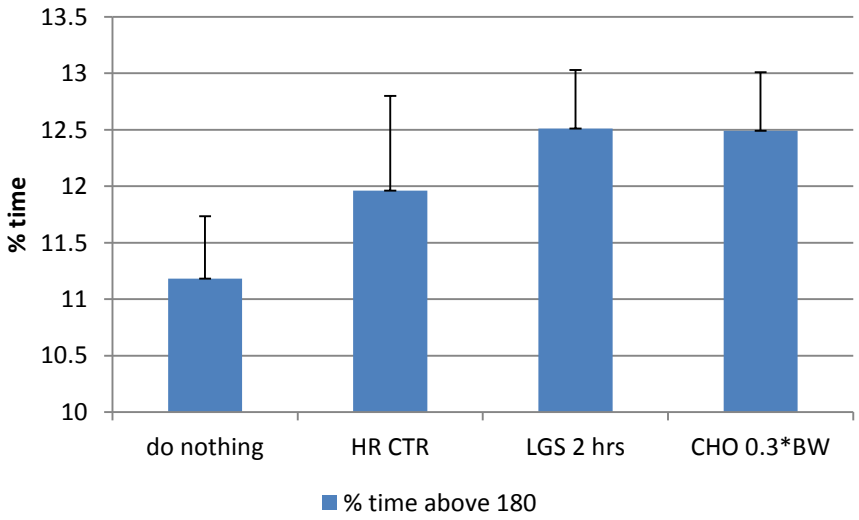

Figure 5. 18: Percentage time above 180 mg/dl

Despite the "LGS 2 hours" great results in preventing hypoglycemia, we recognize that those results have limitations. In fact, the models used are only valid for mild to moderate exercise. However, in real life, people might have higher intensities which will result in

the release of counter-regulatory hormones. Those hormones are known to cause hypoglycemia in the post-exercise period. The “LGS 2 hours” suspend might aggravate the situation in this case.

We combined the HR CTR with the “LGS 2 hours” strategy: when the exercise starts, the more aggressive breaks of HR CTR are applied to the insulin injections. In addition, if hypoglycemia was detected by the classifier at the beginning of exercise, we stop the injections of insulin for the next 75 minutes.

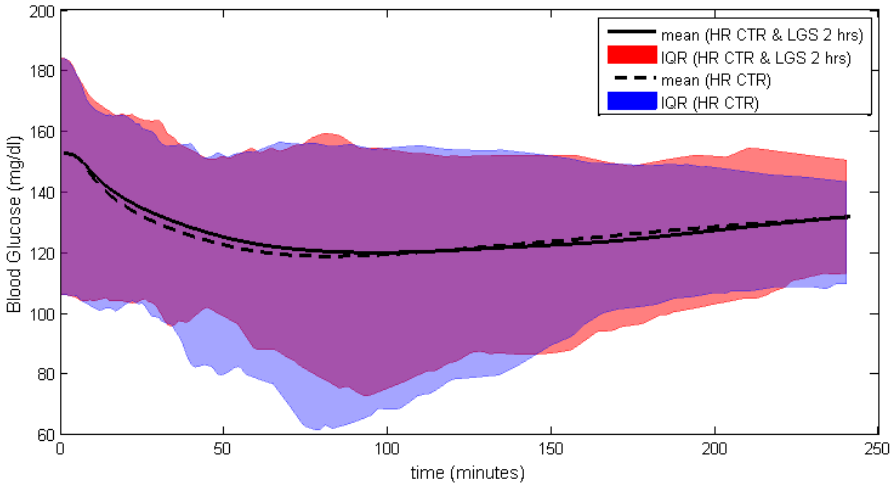

Figure 5. 19: Comparison of the combination of S2-c/HR CTR and HR CTR

As shown in Figure 5.19, the combination of both strategies results in better prevention of hypoglycemia with very minimal rebounds within the 3 hours window following exercise.

This result is promising due to the fact that patients might not have sensors to automatically detect exercise. In that case, they can use the comination HR CTR and LGS 2 hours to prevent exercise. They will have to indicate to the DSS when they are starting exercise and then follow the recommendations.

5.4. Conclusion

We were able to build an exercise detection module using off the shelf commercial devices. Based on heart rate, accelerometer data or both, we are able to automatically detect the timing and the duration of the physical activity. This module has been integrated with the DiAs artificial pancreas system. The accelerometer detection algorithm has been used in camp studies on adolescent with T1DM at Stanford University and the University of Virginia. The heart rate detection algorithm is currently deployed in an ongoing study on adolescent with T1DM at the University of Virginia and Virginia Commonwealth University. Even though this module has limitations in terms of detecting the type and intensity of exercise, it is capable of the detection of the start and the duration of any physical activities. Such an output is all we need for the DSS since that is what the actions/strategies algorithms need as an input.

We were able to define different set of strategies for a better glycemic control when T1DM patients are exercising. Using the University of Virginia FDA approved simulator, we were able to test the different hypotheses on an in silico type 1 diabetes adult population. We used the models and the classifier presented in chapter 3 and 4 to predict hypoglycemia during and immediately after exercise. The best action was identified and compared to the state of the art HR CTR controller. The low glucose suspend for 2 hours (LGS 2 hours) showed superiority in terms of hypoglycemia prevention without creating huge rebounds in the post exercise period.

The models used in the design of the DSS do not take into account the timing (morning, afternoon) and the type (aerobic, strength). It is also only valid for a mild to moderate exercise for a duration of 30 to 45 minutes. However, we believe that the methods used in this chapter can be replicated to other types and intensities of exercise. In the case of the

presence of hyperglycemia risk (i.e. intermittent high intensity exercise), a new set of actions can be added to the pool to either increase the basal insulin injections or give a small bolus correction at appropriate times.

Conclusion and contributions

The achievement of a decision support system (DSS), i.e. a system that gives insulin dose adjustments and carbohydrate treatment advice during and immediately after exercise, would greatly reduce the burden of diabetes management for patients with T1D who are engaging in a physical activity. Our contributions to the DSS focus on developing mathematical and engineering-relevant models to explain the glucose dynamics during exercise and predict associated risk for hypoglycemia. We then identified the best set of actions to be taken for a better glycemic control.

More specifically.

1. We conducted a meta-analysis of available sets of data collected during four different studies with T1D patients. We were not only able to identify the main parameters that explain the glycemic drop induced by exercise but also quantify their effects on the glucose dynamics. The blood glucose at the beginning of exercise and the body exposure to insulin have already been used by healthcare providers to educate patients in their management T1D. The results of the meta-analysis provide evidence-based information about these main clinical factors.

2. Using the same sets of data from four different clinical studies, we conducted a stepwise logistic regression to develop an exercise classifier. Based on the model we developed, we were able to predict exercise-induced hypoglycemia in T1D with a higher accuracy than 85%. The classifier was validated in the University of Virginia/University of Padova FDA approved T1D simulator and also using clinical data collected recently in a clinical trial at Virginia Commonwealth University clinical investigations services unit and University of Virginia clinical research unit. The classifier was used as the foundation for a decision support system to ensure safety for T1D patients during and immediately after a physical activity.

3. Towards the effort of designing and implementing a DSS, we used off the shelf commercially available wearable sensors for automatic detection of physical activity. Based on heart rate signal and triaxial accelerometer data, we developed an algorithm to inform the DSS of the presence of exercise. Once the patient starts a physical activity, we run the exercise classifier to predict the glycemic state. If low glucose is predicted, an action is needed.

   We defined a set of strategies to prevent events of severe hypoglycemia induced by exercise. Those strategies can be presented in 3 main categories: the low glucose suspend (LGS: we shut down insulin delivery), the carbohydrate treatment (fixed amount and a variable amount as a function of the body weight) and a combination of both. As a point of reference, we used the state of the art HR CTR algorithm that has been tested successfully in clinical trials. We ran simulations on a T1D adult *in silico* population and we were able to define the best control strategies within each category: the best LGS duration is 2 hours

starting at the moment of the hypoglycemia detection and the best carbohydrate treatment is based on the amount of 0.3 grams per Kg.

We finally were able to achieve an almost ready prototype of a decision support system that will help patients with T1D have better glycemic control when they engage in a physical activity. We have the intention to finish the implementation of the DSS and deploy it in clinical trials in the near future.

4. We recognize some limitations in our work. In fact, the DSS's low glucose prediction algorithm and safety actions are only valid for adults and more specifically for a mild to moderate exercise. In addition, we did not take into account either the type or the duration of the activity. However, we believe that this work presents a framework and an approach that can be used to cover the other different cases (i.e. long moderate exercise, short intermittent exercise, resistance training, children, adolescents). Once the data is collected, the exercise classifier can be developed and tested. Then, the simulator can be used to compare the different sets of preventative actions that need to be taken to avoid severe exercise-induced hypoglycemia.

General context

The work we have achieved falls in a more general context influenced by the abundance of affordable wearable sensors, the use of smartphones/tablets as medical devices and the emergence of the telehealth and telemedicine space.

In recent years, wearable sensors technologies have been commercialized and adopted by a wide variety of users. These devices are affordable and can measure different physiological signals (i.e. heart rate, EKG, galvanic skin temperature). Currently, people

are using them to keep track of their fitness level and have more incentives to stay active. Many professional athletes are also using these sensors to monitor their health and improve their performance. During the course of this work, we explored expanding the application of this technology to the clinical space. Based on the physiological signals collected through a chest band or an arm band, we detect the presence of exercise. As a second step, we determine whether we need to take an action of modifying the insulin doses or suggesting a carbohydrate treatment. In one hand, it is true that the reliability and accuracy of these sensors have to be put to tests. In the other hand, the wide and ubiquitous acceptance of the general market leaves no choice but try to integrate the fitbit, bodymedia armband, Zephyr, Nike+ sportsband and many others into clinical applications.

In the efforts that lead to the implementation of DSS, we will be integrating the different sensors, glucose meters/monitors and insulin pumps in a mobile platform. The University of Virginia "DiAs" system, as an example, is also a mobile artificial pancreas that is based on an android smartphone. We have been witnessing the increased use of tablets and smartphones (Android or iOS) in real time critical clinical applications. In this context, it is very interesting to see how far the research & development community can push the limits in these efforts and how far regulation authorities are willing to compromise. On another note, the huge amount of data available through the different devices is not negligible. Hence, the various applications of big data analytics in the healthcare space to improve patients' lives and move closer towards personalized care where the diagnosis, prevention and treatment are tailored to each specific patient. The abundance of data, coupled with the sophisticated analysis techniques, leave a big question mark about the privacy and security of patient information. In this area as well,

the tradeoff of sharing more or less is in the center of the equation between the different stakeholders, including the patients themselves.

Finally, there has been a shift in the healthcare industry in the United States from a fee for services delivery model to a quality of care model. This has led the medical centers and clinics to use more innovative healthcare service delivery plans and to adopt more information technology inside and outside the hospital setting. Healthcare professionals and researchers have also been focusing more and more on population health management. In fact, remote patient monitoring is the perfect example as one of the major activities developed by healthcare service providers to improve population health outcomes. The results have been encouraging since these programs succeeded in reducing readmission rates, patient compliance, morbidity rates, preventative care and many other outcomes. However, these programs have been running on a grant-based financial model and very few have studied their financial self-sustainability. Certainly, one of the solutions to the problem is using the accountable care organization model to receive reimbursements based on quality of care metrics. However, this also leads to the very basic question of how can those metrics be defined, measured and tracked so patients are the winners in the equation.

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