Advanced Insulin Dosing Algorithms for Improving Glycemic Control in Type 1 Diabetes

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In the Name of Allāh, the Most Gracious, the Most Merciful

I humbly dedicates this thesis to …

My partner in life, Imanne, for sharing the journey.

&

My eyes to the future and dream of all possibilities,

my beloved baby girl, Maryam.

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ABSTRACT

In type 1 diabetes, insulin secretion is lost due to the autoimmune destruction of pancreatic beta cells, and life-long insulin therapy is needed to regulate blood glucose levels. Insulin therapy is currently implemented using either multiple daily injections with an insulin pen or continuous subcutaneous insulin infusion with an insulin pump. However, due to variabilities in insulin requirements, accurate insulin dosing is a challenging task for people with type 1 diabetes. As a result, most patients do not achieve their glycemic goals. Non-optimal glucose control results in acute and long-term complications that reduce life quality, and increase the risk of mortality.

In recent years, technological advances in glucose monitoring systems, insulin pumps, and insulin pens paved the way towards the development of new algorithms that facilitate type 1 diabetes management. In particular, two emerging technologies are helping to ease patients' burden: closed-loop insulin delivery systems for insulin pump users, and insulin decision support systems for multiple daily injections users.

Closed-loop insulin delivery systems, are devices that use glucose levels from a continuous glucose monitoring system to vary insulin infusions in an insulin pump in order to regulate glucose levels. Existing closed-loop systems still depend on the user input to deliver the meal-accompanying insulin boluses. However, patients, mostly adolescents, might fail to announce consumed meals which may degrade the overall performance of these systems. In the first part of this thesis, we present a novel algorithm that detects when a meal is consumed without it being announced to the

system. This is a model-based algorithm employing state estimation and hypothesis testing techniques. To validate this algorithm, We conduct a 9-hour randomized crossover clinical trial in 11 adolescents with a known history of missing to announce their meals. We show that, in this study, closed-loop insulin delivery augmented with a meal detection algorithm is efficacious compared to standard closed-loop insulin delivery.

People with type 1 diabetes are closely followed by health care professionals to regularly adjust their insulin doses to achieve their glycemic targets. This process is subjective, error-prone, and time-consuming. Decision support systems are a new concept where historical patient's data is analyzed by an algorithm to provide individualized insulin dosing recommendations. In the second part of this thesis, we present a novel algorithm that recommends individualized insulin adjustment for patients using multiple daily injections therapy. Daily glucose, insulin and meal data are fitted using a Bayesian approach to estimate patient-specific model parameters and drive a recursive control law. To validate this algorithm, we conduct an 11-day parallel randomized clinical trial in 21 adolescents in a diabetes camp. We show that the use of this algorithm is safe and results in similar glycemic outcomes compared to participants using insulin adjustments from an expert physician.

ABRÉGÉ

Dans le diabète de type 1, la sécrétion d'insuline est perdue en raison de la destruction auto-immune des cellules bêta pancréatiques. Une insulinothérapie à vie s'impose alors pour régulariser les niveaux de la glycémie. L'insulinothérapie est realisée en utilisant soit des injections quotidiennes multiples avec un stylo à insuline ou une perfusion d'insuline sous-cutanée continue avec une pompe à insuline. Cependant, en raison des variations des besoins en insuline, un dosage précis de l'insuline est une tâche difficile pour les personnes atteintes de diabète de type 1. En conséquence, la plupart des patients n'atteignent pas leurs objectifs glycémiques. Un contrôle glycémique non optimal entraîne des complications aiguës et chroniques qui réduisent la qualité de vie et augmentent le risque de mortalité.

Ces dernières années, les progrès technologiques dans les systèmes de mesure du glucose, les pompes à insuline et les stylos à insuline ont ouvert la voie au développement de nouveaux algorithmes qui facilitent la gestion du diabète de type 1. En particulier, deux technologies émergentes contribuent à alléger le fardeau des patients: les systèmes d'administration d'insuline en boucle fermée pour les utilisateurs de pompes à insuline et les systèmes d'aide à la décision en matière d'insuline pour les utilisateurs d'injections quotidiennes multiples.

Les systèmes d'administration d'insuline en boucle fermée sont des dispositifs qui utilisent le taux de glucose d'un système de mesure continue du glucose pour varier les perfusions d'insuline dans une pompe à insuline afin de réguler le niveau

de glucose. Les systèmes en boucle fermée existants dépendent toujours de la contribution de l'utilisateur pour administrer les bolus d'insuline accompagnant les repas. Cependant, les patients, principalement des adolescents, pourraient ne pas annoncer les repas consommés, ce qui pourrait dégrader les performances globales de ces systèmes. Dans la première partie de cette thèse, nous présentons un nouvel algorithme qui détecte quand un repas est consommé sans qu'il soit annoncé au système. Il s'agit d'un algorithme basé sur un modèle utilisant des techniques d'estimation d'état et de test d'hypothèse. Pour valider cet algorithme, nous menons un essai clinique randomisé croisé de 9 heures sur 11 adolescents avec un historique connu d'oubli d'indication de leurs repas. Nous montrons que, dans cette étude, l'administration d'insuline en boucle fermée avec un algorithme de détection de repas est efficace par rapport à l'administration d'insuline en boucle fermée standard.

Les personnes atteintes du diabète de type 1 sont suivies de près par les professionnels de la santé pour ajuster régulièrement leurs doses d'insuline afin d'atteindre leurs objectifs glycémiques. Ce processus est subjectif, sujet aux erreurs et prend du temps. Les systèmes d'aide à la décision sont un nouveau concept où les données historiques du patient sont analysées par un algorithme pour fournir des recommandations de dosage d'insuline individualisées. Dans la deuxième partie de cette thèse, nous présentons un nouvel algorithme qui recommande des ajustements d'insuline individualisées pour les patients utilisant une thérapie à plusieurs injections quotidiennes. Les données quotidiennes sur le glucose, l'insuline et les repas sont ajustées en utilisant une approche bayésienne pour estimer les paramètres du modèle spécifique au patient et piloter une loi de contrôle récursive. Pour valider cet algorithme, nous

menons un essai clinique randomisé parallèle de 11 jours sur 21 adolescents dans un camp de jour dédié aux jeunes diabétiques. Nous montrons que l'utilisation de cet algorithme est sûre et entraîne des résultats glycémiques similaires par rapport aux participants utilisant des ajustements d'insuline d'un médecin expert.

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CHAPTER 1

Introduction

1.1 Rationale

Type 1 diabetes is a chronic disease caused by the autoimmune destruction of the beta cells in the pancreas. The beta cells are responsible for the secretion of the hormone insulin, a necessary hormone for blood glucose levels regulation in the body. Patients with type 1 diabetes are treated with lifelong exogenous insulin therapy, in which exogenous insulin is administered to keep blood glucose levels in normal ranges.

Insulin therapy is currently implemented using either multiple daily injections with an insulin pen or continuous subcutaneous (under the skin) infusion with an insulin pump. However, insulin dosing is a complex optimization problem where several factors must be taken into account, in particular, physiological factors (sensitivity to insulin, stress, illness, etc.), and behavioral factors (eating habits, physical activities, etc.). As a result, most patients with type 1 diabetes, and especially children and adolescents, do not reach their glycemic targets. Technological advances in the treatment of diabetes, including glucose monitoring systems, insulin pumps, and insulin pens, have helped to ease the burden of diabetes management by automating certain aspects of insulin dosing.

In continuous subcutaneous insulin infusion therapy, insulin infusion is manually programmed in the insulin infusion pump. Recently, closed-loop insulin delivery systems that utilize real-time feedback of glucose levels to alter the insulin delivery in an insulin pump and achieve the target glucose level have emerged. Yet, once insulin is delivered subcutaneously, it takes up to 100 minutes to reach its maximum glucose-lowering effects. This delay is a limiting factor for achieving efficacious fully closed-loop control after meal consumption. Therefore, the current generation of closed-loop systems requires patients to announce consumed meals in order to deliver a matching insulin dose (a feed-forward approach). However, studies have shown that patients, especially adolescents, tend to forget to announce their meals. Currently, there is little understanding of the safety and effectiveness of closed-loop insulin delivery in regulating glucose after an unannounced meal. We hypothesize that a meal detection algorithm that detects when a patient consumes a meal without delivering an insulin bolus may improve glucose levels control.

In multiple daily injections therapy, one or two doses of long-acting insulin are injected every day and doses of rapid-acting insulin are injected with each meal. However, insulin requirements vary between patients and vary over time for each patient. Consequently, patients are advised by health care professionals to periodically adjust their insulin doses to achieve desired glycemic goals. With the advent of glucose monitoring systems, decision support systems that facilitate and optimize these decisions have become possible. Decision support systems are new to the field of diabetes and little is known about the safety and effectiveness of algorithmic recommendations. We hypothesize that a decision support algorithm that adjusts insulin

doses for patients using multiple daily injections may reduce the burden and improve the qualify of life of these patients.

1.2 Aims

This thesis aims to develop advanced insulin dosing algorithms for type 1 diabetes patients resulting in improved glycemic outcomes. Specifically, we aim to:

i. Investigate the safety and efficacy of controlling glucose levels during closed-loop insulin delivery after an unannounced meal.

ii. Investigate the safety and efficacy of a decision support tool for patients using multiple daily injections therapy.

Both the safety and efficacy of the developed algorithms are assessed by observing glucose metrics following a clinical study involving type 1 diabetes subjects. Safety is assessed by the absence of serious adverse events related to the algorithm. Efficacy is assessed by the ability of the algorithm to normalize glucose levels compared to a baseline. Thus, this thesis has both analytical and experimental developments, resulting in the following intermediate objectives:

- Develop an algorithm that detects when a patient consumes a meal without delivering an insulin bolus using recent glucose, insulin, and meal data. Following detection, the algorithm should improve glucose levels control.
- Design and conduct a clinical trial to evaluate the meal detection algorithm in type 1 diabetes.
- Develop an algorithm that adjust insulin doses for patients using multiple daily injections using previous day glucose, insulin, and meal data.

- Design and conduct a clinical trial to evaluate the insulin doses adjustment algorithm in type 1 diabetes.

1.3 Outline

This is a manuscript-based thesis composed of an introduction (Chapter 1), a background (Chapter 2), the thesis body including five manuscripts (Chapters 3, 4, 5, 6, and 7), and a conclusion (Chapter 8). Each manuscript-based chapter includes in addition to the manuscript a preface section with a brief summary, and the authors' contributions to the manuscript.

In *Chapter* 1, we expose the aims and the outline of the thesis. In *Chapter* 2, we introduce type 1 diabetes, its complications, and its current treatments. We then review the challenges of current treatments and discuss the role of emerging technological advances in overcoming these challenges. In *Chapter 8*, we conclude by summarizing the author original contributions, discussing the main findings, and recommending future work. These chapters are written by the author (Anas El Fathi) and critically reviewed by the author's supervisors Dr. Benoit Boulet, and Dr. Ahmad Haidar.

In *Chapter* 3, we present a review of post-meal regulation of glucose levels for closed-loop insulin delivery systems. First, we discuss how meals can be regarded as a disturbance to the closed-loop insulin delivery system. Second, we review different models from the literature describing carbohydrates absorption from consumed meals. Third, we review common control algorithms employed in closed-loop insulin delivery. Finally, we discuss meal detection techniques and learning algorithms that may enhance the prediction capabilities of closed-loop insulin delivery. Throughout

this chapter, we demonstrate concepts through simulations and discuss significant results from clinical trials.

In *Chapter* 4, we present a novel unannounced meal detection algorithm for closed-loop insulin delivery systems. This algorithm employs a linear Kalman filter and a maximum likelihood approach to estimate patients' state from previously measured glucose, delivered insulin and consumed meals. We then derive a test statistic formula using the patient's state to distinguish when an unannounced meal is consumed. We also describe a control strategy following meal detection to safely regulate glucose levels. In this chapter, we perform simulation studies to validate this algorithm.

In *Chapter* 5, we present the results of a 9-hour crossover randomized controlled trial that evaluates the efficacy of the unannounced meal detection algorithm. In this study, we recruited 11 adolescents with a history of missing to announce a consumed meal. We compared three interventions: closed-loop insulin delivery augmented with a meal detection algorithm, closed-loop insulin delivery, and conventional insulin pump therapy. At lunchtime, participants consumed a meal without the matching insulin bolus. We then evaluate glucose control in each intervention by measuring the 4-hour incremental glucose area under the curve after the lunch meal.

In *Chapter* 6, we present a day-to-day insulin dosing optimization algorithm for patients using multiple daily injections. This algorithm uses a maximum-a-posteriori method to estimate the parameters of a novel model describing the effects of consumed meals and injected insulin on glucose levels. We then combine parameter estimates, their confidence intervals, and the goodness of model-fit to generate new

insulin doses recommendations. In this chapter, we investigate the ability of the proposed model to explain real-world glucose data, using a clinical dataset of 150-day of glucose, insulin, and meal data. We also perform a 60-day simulation study to demonstrate the feasibility of this algorithm.

In *Chapter* 7, we present the results of an 11-day parallel randomized controlled trial where we evaluated day-to-day insulin doses adjustment from our algorithm. In this study, we recruited 21 participants in a diabetes camp. One group followed daily adjustments from the algorithm, and the other group followed daily adjustments from physicians. We compared glycemic outcomes between the two groups in the last week of the intervention. We also show the results of the acceptance rate of algorithmic adjustments from physicians who reviewed the algorithm recommendations. We then provide an analysis of the agreement between the algorithm and physicians on insulin doses recommendations.

A summary of publications included in this thesis, and other publications related to this work, is provided in Appendix A. This thesis includes results from two clinical trials approved by the McGill University Health Centre research ethics board. The authorization letters are included in Appendix B.

CHAPTER 2

Background

Recent technological advances in type 1 diabetes treatment contributed to the development of smarter and safer insulin dosing algorithms. In this chapter, we provide an overview of type 1 diabetes disease and its medical complications. Then, we present the current treatments and challenges of type 1 diabetes. Finally, we discuss emergent technologies for improving type 1 diabetes treatment.

2.1 Type 1 Diabetes

Type 1 diabetes is a classification of diabetes mellitus. Diabetes mellitus is a complex metabolic disorder characterized by an elevated glucose level (hyperglycemia) caused when the pancreas is unable to secrete insulin (type 1 diabetes), or when the body is resistant to the insulin it produces (type 2 diabetes) [1, 2]. Type 1 diabetes represents 5-10% of diabetes cases worldwide. As of 2017, an estimated 42.5 million adults (age 20-79 years), and 1.1 million children and adolescents (age 0-19 years) have type 1 diabetes, these incidences are increasing worldwide [3]. The cause of type 1 diabetes is still not well understood but it is attributed to interactions of genetic and environmental factors [4]. As per today, there is no immediate prospect of a cure [5].

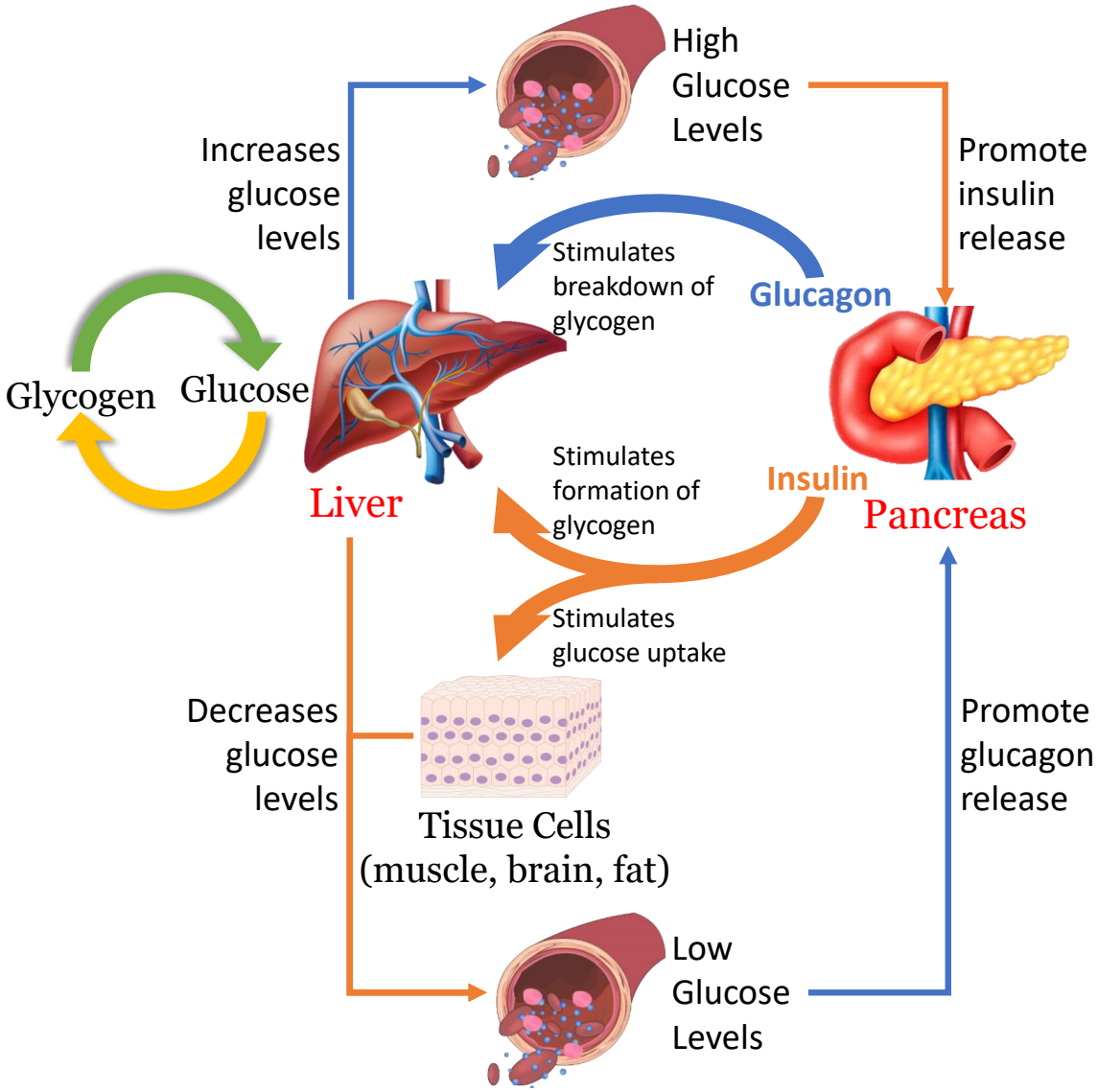

Figure 2–1: Depiction of feedback of blood glucose by actions of the pancreas and liver in a nondiabetic individual.

In nondiabetic individuals, blood glucose levels are tightly regulated by hormones secreted by the pancreas through a physiological feedback loop (Figure 2–1). In the pancreas, insulin is produced by the beta cells and glucagon is produced by the alpha cells. When glucose levels are high, insulin is released, which stimulates glucose uptake by tissue cells and the conversion of glucose to glycogen in the liver, lowering glucose levels. When glucose levels are low, glucagon is released, stimulating the breakdown of glycogen into glucose in the liver, increasing glucose levels [6].

In people with type 1 diabetes, the pancreatic beta-cells are destroyed by the autoimmune system. The loss of insulin secretion causes a break in the physiological feedback loop in Figure 2–1. Without insulin, glucose is no longer transported to or used by cells causing dangerously elevated glucose levels.

Following guidelines from the World Health Organisation, the American Diabetes Association, and Diabetes Canada, the diagnostic criteria for diabetes mellitus can be summarized in Table 2–1 [2, 7, 8]. After confirming the diabetes condition, type 1 diabetes is identified by the presence of autoimmune markers, including antibodies to the islet cell and insulin auto-antibodies [9]. Type 1 diabetes is also characterized by very low C-peptide levels. Most type 1 diabetes cases are diagnosed at a young age (less than 25) but can occur at any age [10].

Table 2–1: Criteria for the diagnosis of diabetes, either one suffices.

A fasting plasma glucose level of 7.0 mmol/L, where fasting is defined as no caloric intake for at least 8 h.
Oral glucose tolerance test: The 2-hours plasma glucose after ingestion of 75g oral glucose load above 11.0 mmol/L.
Hemoglobin A1C marker (HbA1c), a marker reflecting average plasma glucose over the previous 2–3 months, above 6.5 %.
At any time of the day, without regard to the interval since the last meal, plasma glucose is above 11.1 mmol/L.

2.2 Complications of Type 1 Diabetes

Before the discovery of insulin and its therapeutic potential by Sir Frederick Grant Banting and John James Rickard Macleod in the early 1920s, type 1 diabetes was a fatal condition. Nowadays, type 1 diabetes is treated with a life-long exogenous insulin delivery to the body. Despite current insulin therapy, type 1 diabetes is still associated with significantly decreased life expectancy due to acute and long-term complications [11, 12].

2.2.1 Acute Complications of Type 1 Diabetes

The most common acute complication of type 1 diabetes is hypoglycemia (hazardous low glucose levels). People with type 1 diabetes are more susceptible to suffer from hypoglycemia because of (i) the risk of over-delivery of insulin, (ii) the lack of the beta cells is accompanied by impaired ability to regulate the hormone glucagon, causing insufficient glucagon release during hypoglycemia [13].

Typically, hypoglycemia is defined by plasma glucose levels below 3.9 mmol/L, and its severity is defined by clinical manifestations [14]:

- Mild and moderate hypoglycemia is characterized by (i) autonomic symptoms: trembling, palpitations, sweating, anxiety, hunger and nausea (ii) neuroglycopenic symptoms: difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, and dizziness. The patient can self-treat this condition by the administration of carbohydrates.
- Severe hypoglycemia leads to coma or seizure and necessitates the assistance of other individuals. Plasma glucose level is typically less than 2.8 mmol/L.

Mild hypoglycemia episodes are frequent with type 1 diabetes patients, with a self-reported incidence rate of around 2-3 episodes per patient per week [15]. Most of these episodes are under-reported or unrecognized due to some patients suffering from impaired awareness of hypoglycemia. Data has shown a higher rate of biochemical hypoglycemia events (capillary blood glucose less than 3.5 mmol/l) in patients with hypoglycemia unawareness by up to 1.6-fold [15].

The incidence of severe hypoglycemia is around 1-2 episodes per patient per year [15, 16, 17] and is affected by risk factors such as increased duration of diabetes and impaired awareness of hypoglycemia. The risk of sever hypoglycemia causes significant anxiety for patients with type 1 diabetes and their families.

Insufficient insulin may lead to life-threatening diabetic ketoacidosis. Diabetic ketoacidosis occurs when impaired glucose utilization forces the cells to produce glucose from fatty acids yielding acidic ketone bodies as a by-product. The resulting

ketonaemia[1] causes blurred vision, tiredness, and requires complex management and hospitalization. At least one diabetic ketoacidosis events per year are reported in 5-10% of type 1 diabetes patients [18, 19].

2.2.2 Long-term Complications of Type 1 Diabetes

Of the many complex complications of diabetes, the main problem haunting type 1 diabetes patients is vascular long-term complications, which are directly correlated with increased morbidity and mortality rate. Complications usually start to develop years or decades after diabetes onset. These are microvascular complications: nephropathy (renal failure), retinopathy (blindness) and neuropathy (nerve damage), macrovascular complications consisting of cardiovascular (heart) diseases, and comorbid conditions: automimmune thyroid disease and coeliac disease [20].

The Diabetes Control and Complications Trial (DCCT, 1982-1993) established the relationship between sustained hyperglycemia and microvascular complications [21]. Subsequent observational studies by the Epidemiology of Diabetes Interventions Complications Study Research Group (EDIC, since 1994) have shown the long-lasting effects of better glycemic control, measured by HbA1c[2] levels, in reducing the rates of development and progression of microvascular and macrovascular complications [22, 23, 24] (Table 2–2).

[1] Ketonaemia refers to the presence of an abnormally high concentration of ketone bodies in the blood.

[2] HbA1c or Hemoglobin A1C is a marker reflecting average plasma glucose over the previous 2–3 months

Table 2–2: Summary of the DCCT and EDIC study.

DCCT	This was a parallel controlled clinical trial in 1441 subjects comparing intensive therapy, aimed at achieving glucose levels close to the nondiabetic range, with standard care at the time, only aimed at maintaining safe glucose levels (conventional therapy). The DCCT lasted for a mean of 6.5 years and demonstrated that strict glycemic control, with intensive therapy resulting on a median HbA1c of 7%, prevents up to 70% of microvascular complications (particularly retinopathy), compared to conventional therapy (HbA1c of 9%). The major adverse effect was a 3-fold increase of hypoglycemia in the intensive therapy group, underlying the fact that HbA1c goals should be tailored to the individual. Following DCCT, intensive therapy with the goal of achieving near-normal glycemia became the new standard of care [25].
EDIC	The EDIC is a long-term follow-up to the DCCT. After the end of the DCCT, all participants in DCCT switched to intensive therapy. EDIC demonstrated that a period of intensive glycemic control reduced the subsequent risk of a cardiovascular event by 42% and severe cardiovascular events by 57%. Subgroup analysis demonstrated that the differences in the mean HbA1c levels at the end of DCCT (7.4% vs. 9.1%) explained the majority of the treatment effect of intensive therapy.

2.3 Treatments of Type 1 Diabetes

Type 1 diabetes is a chronic disease requiring life-long insulin replacement therapy. Insulin therapy is currently implemented using either multiple daily injections via an insulin pen or continuous subcutaneous (under the skin) insulin infusion via an insulin pump. Intensive insulin therapy aiming at an HbA1c level as low as possible while avoiding hypoglycemia has the benefit of reducing the risk of acute and long-term complications [26, 27]. Self-management through self-monitoring of glucose levels, meal planning, meal macronutrient counting, and attention to physical activity are essential to achieving target levels of HbA1c [28].

In the following, we will detail (i) the forms of insulin analogs[3] used for treatment, (ii) the two principal modes of insulin administration (multiple daily injections and continuous subcutaneous insulin infusion), and (iii) glucose monitoring systems.

2.3.1 Insulin Analogs

Intensive treatment with insulin therapy imitates the physiological release of insulin as seen in non-diabetic people by following a basal-bolus insulin regimen [29]. Basal insulin mimics the relatively small but constant release of insulin which metabolizes the glucose stored in cells during fasting and regulates the production of hepatic glucose. Basal insulin requirements are affected by sleep cycle, physical activity, psychological stress, and growth hormones [30, 31, 32]. Bolus insulin is administered to mimic the response of endogenous insulin in the healthy pancreas to

[3] Analog insulin is a laboratory-grown genetically altered form of insulin to achieve the desired drug pharmacokinetics and/or pharmacodynamics.

food intake. This response occurs in a transient and rapid first phase secretion and then in a more prolonged second phase release [33, 34].

The basal-bolus regimen motivated the development of different insulin analogs characterized by different pharmacokinetics and pharmacodynamics properties. These properties determine, respectively, how insulin is absorbed into the blood circulation and how insulin in the circulation affects the body [35]. Two types of insulin analogs are of interest:

Rapid-acting insulin is a type of insulin that works over a narrow and predictable range of time. It has an onset time of 10-20 minutes after delivery, a peak-action time of 1-2 hours and a duration of action of 3-5 hours. Recently, a new faster-acting insulin is available on the market with an onset time of 4 minutes and a peak action time of 0.5-1.5 hours [36].

Long-acting insulin is a type of insulin that works over a large and predictable range of time without any peaks. It has on onset time of 1.5 hours and a duration time of over 24 hours.

2.3.2 Multiple Daily Injection

Worldwide, most patients with type 1 diabetes use multiple daily injection therapy. In this therapy, one or two long-acting insulin doses are injected daily for basal insulin, and an insulin bolus of rapid-acting insulin dose is injected with every meal, for a total of 3-4 insulin bolus injections per day, figure 2–2.

Insulin basal dose is usually related to the patient total requirement of insulin. Insulin bolus doses are mostly determined based on the meal carbohydrate content and the patient's carbohydrate ratios which specify how many grams of carbohydrate

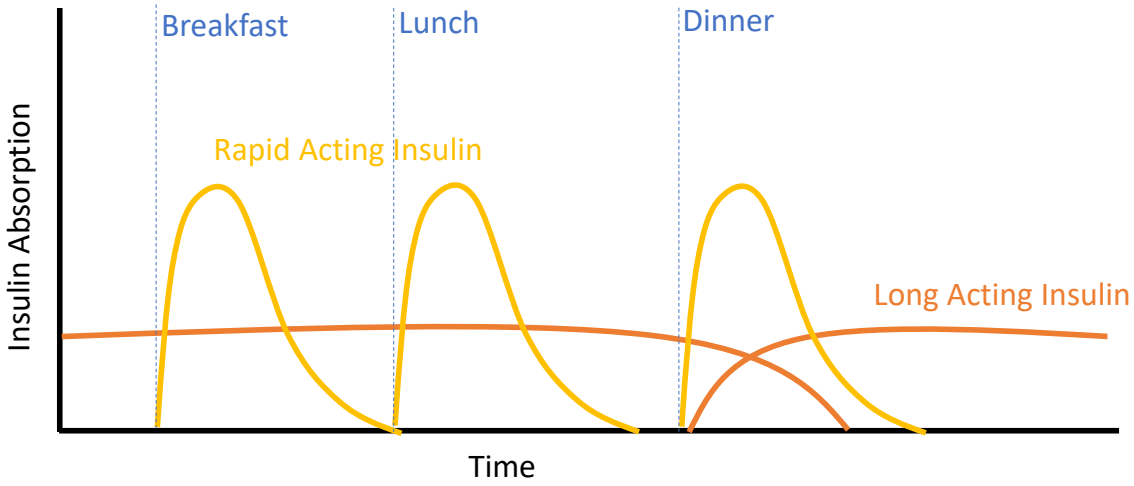

Figure 2–2: Simplified graph of multiple daily injection regimen.

are metabolized by each unit of insulin (gram per unit). Patients are required to measure their blood glucose before delivering an insulin bolus to adjust the amount of the bolus based on the current glucose level. The higher the glucose level from a target (usually 7 mmol/L), the more insulin is delivered. Some patients use a fixed dose of rapid-acting insulin at mealtimes, however, they follow a strict diet where they consume the same amount of carbohydrates in each meal.

In multiple daily injection therapy, insulin is usually delivered using insulin pens. Insulin pens were introduced in the 80s as a convenient way to deliver insulin instead of syringes. They comprise of a fine replaceable needle and a fillable insulin cartridge [37]. Recently, a new generation of smart insulin pens that can automatically log injected doses and provide Bluetooth communication with smartphones has emerged.

2.3.3 Continuous Subcutaneous Insulin Infusion

Historically, continuous subcutaneous insulin infusion therapy precedes multiple daily injection therapy, as the first pumps date to the 70's [38], however, due to its

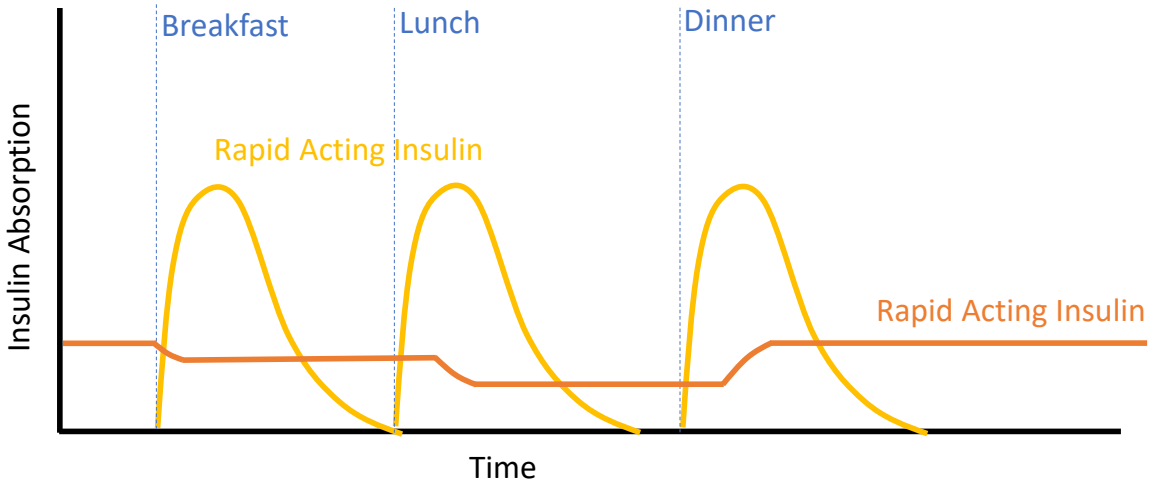

Figure 2–3: Simplified graph of continuous subcutaneous insulin infusion regimen.

cost, it took more than 20 years for insulin pump therapy to become widely used [39]. Insulin pumps are body-worn devices that can deliver insulin to the subcutaneous tissue. Connected to the pump is an infusion set, consisting of a small plastic tube and a soft cannula that is inserted under the patient's skin. Some pumps, referred to as patch pump, directly attach to the user's skin and comprise of a very short cannula embedded inside the pump. The pump's insulin reservoir is filled with rapid-acting insulin analogs.

The user can program a desired infusion rate of insulin (basal insulin) or delivers insulin boluses when needed. Patients can program up to six different basal rates to match varying insulin needs during the day, figure 2–3 [40, 41, 31]. Furthermore, most insulin pumps include other features:

- Automatic tracking of previously delivered insulin and estimation of the amount of insulin-on-board[4] . This calculation is affected by the programmed insulin action duration in the pump.
- An insulin bolus calculator to compute the insulin bolus dose using the meal carbohydrate content and/or current glucose level. This calculation is affected by the programmed carbohydrate ratios, the insulin sensitivity factor[5] and the programmed glucose target in the pump.
- An option to program temporary infusion rates when needed. For example, before or after a physical activity.

Compared to multiple daily injections therapy, continuous subcutaneous insulin infusion therapy provides more flexibility to patients to control their insulin delivery. However, it also add physical burden (carrying a pump) and an increased potential risk of ketoacidosis in the event of pump malfunction with interrupted insulin delivery [42]. Not all randomized controlled trials showed a clear advantage in reducing HbA1c levels by using a pump compared to injections. Nevertheless, meta-analysis of randomized clinical trails comparing pump therapy and multiple daily injections show a significant decrease in HbA1c (-0.55% in adults and -0.24% in children) in favour of pump therapy users [43, 44]. Also, a greater reduction in HbA1c was

[4] insulin-on-board (units) refers to the insulin that was subcutaneously delivered but not completely absorbed into blood circulation.

[5] Insulin sensitivity factor (mmol/L/units) is a number describing how much glucose is utilized by one unit of insulin.

observed when patients with poor glycemic control switched from multiple daily injections to pump therapy [42].

2.3.4 Glucose Monitoring Systems

Frequent glucose self-monitoring has been associated with decreased HbA1c and acute complications [45, 46]. Multiple devices exist for glucose monitoring, notably: blood glucose meters, continuous glucose monitoring systems, and flash glucose monitoring systems.

A blood glucose meter is a portable handheld device used to measure the capillary blood glucose. This device provides a reliable blood glucose concentration by analyzing a drop of blood obtained by pricking the finger using a lancet. Consequently, patients only use it when necessary: before consuming meals or when they are at risk of hypoglycemia.

The first commercial glucose monitoring system was introduced in 1999 by Medtronic (Medtronic, Northridge, California) [47]. These are small devices worn typically on the abdomen and contains a hair-sized wire that continuously monitors glucose levels in the interstitial fluid underneath the skin. These sensors are affected by measurement noise, delays due to diffusion processes, and time-varying systematic under/overestimation due to calibration and sensor drift [48]. Yet, they have shown greater accuracy in recent years, with a mean relative absolute difference (MARD) compared to laboratory standard is between 8% to 14% [49, 50, 51]. Most of these systems are now approved for non-adjunctive use without capillary blood glucose measurements.

The majority of glucose monitoring systems provide continuous glucose readings at one- to five-minute intervals via Bluetooth (CGMs). Glucose readings can be displayed and stored in either specialized handheld devices, smartphones or insulin pumps. Most CGMs have a lifespan of one week and need to be calibrated using blood glucose meter (usually twice a day). Recently, the new Dexcom G6 (Dexcom Inc., San Diego, California) does not require calibration (factory-calibrated) and has a lifespan of 10 days.

As opposed to CGMs, flash glucose monitoring systems (FGMs) does not transmit glucose readings, but glucose levels are retrieved on-demand when the sensor is scanned. There is only one flash glucose monitor manufactured at the moment: the Freestyle Libre (Abbott Laboratories, Abbott Park, Illinois). The Freestyle libre is factory-calibrated and has a 2-week sensor life. Recent studies have shown satisfactory accuracy with overall MARD of 11% to 14% [52, 53].

Randomized clinical trials have shown that, when compared to only using blood glucose meters, the use of glucose monitoring systems (CGMs or FGMs) is associated with an improvement in HbA1c, reduction in mild to moderate hypoglycemia, and reduced glucose variability [54, 55, 56, 57]. Nowadays, glucose monitoring systems became a must for better diabetes care [58].

2.4 Challenges of Type 1 Diabetes

Current intensive insulin therapy aims to reduce the risk of long-term complications associated with hyperglycemia [21]. Higher HbA1c levels are still the gold standard for assessing the risk of vascular diabetes complications [25]. A target of

HbA1c levels of below 7.0% is recommended for adults, while a target HbA1c levels of below 7.5% is recommended for pediatrics [59, 60, 21]. Other HbA1c targets can be set for special conditions, such as pregnancy and people with hypoglycemia unawareness.

Glucose monitoring systems are essential to guide patients and health care providers when optimizing glycemic control. Clinically meaningful outcomes derived from glucose monitoring data have been suggested as useful tools to describe overall glycemic control [61]. Common measures include:

Time-in-range Percentage of glucose readings in the range of 3.9–10.0 mmol/L per unit of time.

Hypoglycemia Percentage of glucose readings under 3.9 mmol/L per unit of time. Hypoglycemia can be categorized to at least 2 levels, mainly, level 1 when glucose readings are in the range 3.0–3.9 mmol/L, and level 2 when glucose readings are below 3.0 mmol/L.

Hyperglycemia Percentage of glucose readings above 10.0 mmol/L per unit of time. Hyperglycemia can also be categorized to multiple levels.

Mean glucose Average glucose reading in mmol/L per unit of time.

Sensor-based measures have been shown to strongly correlate with HbA1c, mainly, mean glucose, time in hyperglycemia, and time-in-range [62, 63, 64]. Other glucose sensor measures that are independent of HbA1c, such as glucose variability, may be associated with diabetes complications, but limited evidence is found in the literature [65]. An association of sensor-based measures with long-term complications is

yet to be shown in a controlled study. However, retrospective analysis of DCCT indicates that a decrease in time-in-range is associated with an increase in retinopathy risk [66]. Furthermore, the use of continuous glucose monitoring during pregnancy has been shown to be associated with reduced maternal and neonatal complications, mainly the risk of macrosomia [67].

Despite advances in insulin analogs, insulin pumps and glucose monitoring systems, achieving glycemic targets is a complex and endeavoring task. Recent results from the type 1 diabetes exchange clinic registry showed that in a cohort of $12,705$ participants in 81 American pediatric and adult endocrinology centers, only 17% of youths achieved the HbA1c goal of <7.5% and only 21% of adults achieved the HbA1c goal of <7% [68]. This can be attributed to multiple factors:

Carbohydrates counting Meal-accompanying boluses are necessary to metabolize digested carbohydrates from meals. However, providing an adequate insulin bolus relies on the ability of patients to accurately estimate the carbohydrate content of their meals, correct the insulin dose depending on the current glucose level (an extra correction bolus is provided when glucose levels are high, similarly, the insulin bolus might be reduced because of low glucose levels), and take into account the insulin-on-board. Mathematically, a meal-bolus U can be computed by:

$$U = \frac{M_{CHO}}{k_{CR}} + \max\left(\frac{G - G_t}{k_{ISF}} - U_{IOB}, 0\right) \tag{2.1}$$

where M_{CHO} is the amount of carbohydrates in the consumed meal, k_{CR} is the carbohydrate ratio, G_t is the glucose target, k_{ISF} is the insulin sensitivity factor, and U_{IOB} is the insulin-on-board.

Even though (2.1) may seem simple, patients are prone to make carbohydrate counting errors with an estimated 20% error on average [69]. It is common to underestimate or neglect insulin-on-board. It is difficult to choose an adequate glucose target and an insulin sensitivity factor. Furthermore, other macronutrients, such as protein and fat, can affect the meal absorption and requires an insulin dose adjustment (Section 3.2.2).

Physiological Factors Insulin sensitivity differs between patients and may be affected by other hormones, such as somatotropin (growth hormone), cortisol and adrenaline. As a result, physiological factors such as weight, illness, stress, menstrual cycle and puberty have a direct effect on insulin sensitivity.

In practice, women with type 1 diabetes, might use different insulin dosage during their menstrual cycle phase [70]. Adolescents in puberty and sometimes adults might increase their insulin dosage during the last hours of the nights because of the dawn phenomenon: a decrease in insulin seneitivity due to the release of growth hormones overnight, causing a sudden increase in glucose levels [71].

Physical Activity Exercise is recommended for type 1 diabetes patients [72]. It helps in lowering daily insulin dose, improving physical fitness and reducing cardiovascular risks [73]. Nevertheless, a large number of individuals with type 1 diabetes are inactive mainly because of fear of exercise-induced hypoglycemia

[74]. Glucose management during and following exercise depends on multiple factors: type of exercise (aerobic, anaerobic, mixed), intensity of exercise, and duration of exercise. During aerobic exercise glucose, levels fall in most patients. To decrease the risk of hypoglycemia, it is recommended to reduce insulin administration before exercise (reductions in basal or bolus insulin, or both), or ingest carbohydrates before the exercise, or both [75]. During anaerobic exercise, glucose levels might increase as a result of the production of glucose from stored glycogen. Both forms of exercise can cause delayed-onset hypoglycemia in the following night because of the increase in insulin sensitivity following physical activity [76, 77].

Treatment related factors Glucose control can also be affected by inherent problems caused by the insulin treatment itself. In continuous subcutaneous insulin infusion therapy, infusion set problems causing insufficient or no insulin delivery are common [78]. Insulin time-to-peak absorption can also vary depending on the age of the infusion site, where the older the site the quicker insulin is absorbed [79]. In multiple daily injections, patients will tend to only correct for high glucose levels around meal times, giving them less control during night time and fasting conditions. In all insulin therapies, patients, mainly adolescents, are susceptible to forget or intentionally omit delivering meal-accompanying insulin bolus.

2.5 Emergent Technologies for Type 1 Diabetes

With recent technological advances, new control algorithms have emerged to facilitate and automate the management of type 1 diabetes. Micro-management of

daily insulin delivery can be improved by the use of closed-loop systems that combine sensor glucose in real-time with continuous insulin delivery. Macro-management of long-term glucose control can be improved by decision support systems that guide patients in adjusting their insulin dosage.

2.5.1 Closed-loop Insulin Delivery

Closed-loop insulin delivery systems, also called artificial pancreas systems, are devices that exploit glucose feedback from a continuous glucose monitoring system to vary insulin infusions in an insulin pump in order to regulate glucose levels. The concept of closed-insulin delivery was first introduced in the 60s; at the time, both insulin infusion and glucose measurements were performed intravenously [80].

In recent years, a significant progress was made in subcutaneous insulin pumps and interstitial glucose measurements technology, resulting in commercially available systems: MiniMed 670G (Medtronic plc, Northridge, California) received approval worldwide [81]; Diabeloop (Diabeloop SA, Grenoble, France) received approval in Europe [82]; Control-IQ (Tandem Diabetes Care, San Diego, California) received approval in the United States [83]; CamAPS FX (Camdiab Ltd, Cambridge, United Kingdom) a mobile application received approval in Europe [84]. Other closed-loop insulin delivery systems were developed for research purposed [85, 86, 87] or by patients as do-it-yourself systems [88]. Most of these systems are hybrid, meaning that the user is required to enter the amount of carbohydrate in each meal in order to receive a matching insulin bolus.

Different variations exist in closed-loop systems, including: (i) Different control algorithms: proportional-integral-derivative controllers, model predictive controllers,

and controllers based on fuzzy logic [89]. (ii) Different combination of drugs in addition to insulin, such as systems combining insulin and glucagon [90, 91, 92], insulin and pramlintide [93], or insulin and other adjunctive medications [94]. (iii) The degree of automation, systems that require full carbohydrates counting (the majority), systems only requiring meal categorization [95, 96], or fully closed-loop systems [97, 98]. A detailed literature review is provided in Chapter 3.

Today, closed-loop insulin delivery is the most promising insulin therapy as it has been proven to reduce time spent in hypoglycemia (<3.9 mmol/L) by -1.7% (95%CI, -3.18 to -0.21) and to increase time-in-target (3.9 —10.0 mmol/L)[6] by 10.6% (95%CI, 4.28 to 16.87) compared to sensor augmented pump therapy [7] [100]. Yet, closed-loop systems remains new, and up-to-date diabetes education is warranted for new patients [101].

2.5.2 Insulin Decision Support System

Insulin decision support systems refer to a class of software that provides individualized insulin dosage recommendations. These systems can be targeted to health care professionals or directly to patients. For health care professionals, decision support systems take the form of remote monitoring systems that record patient daily

[6] With the raise of continuous glucose monitoring systems usage, it became more practical to assess good glycemic control with the percentage of time glucose levels are within 3.9 mmol/L and 10.0 mmol/L, also called time-in-target. Time-in-target correlates strongly with HbA1c levels [99].

[7] Sensor augmented pump therapy refers to the usage of an insulin pump and a glucose sensor. The user can adjust their insulin delivery manually in the pump using feedback from the glucose sensor.

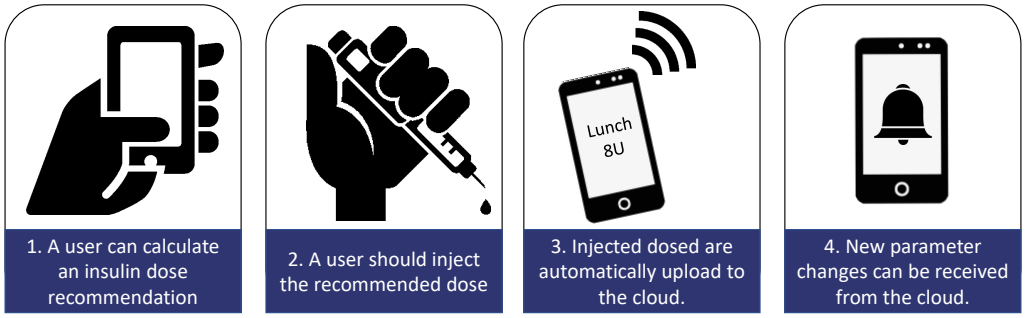

Figure 2–4: An example of an insulin decision support system that can be used by a patient. The system can be used to calculate insulin doses, doses are uploaded on the cloud and analysed by an algorithm, new parameter changes can be sent to the patient.

data, analyze trends, and in some cases provide therapeutic advice. For patients, decision support systems are mainly advanced bolus calculators that adapt to the user and suggest personalized insulin doses adjustment 2–4.

Insulin doses adjustments can be achieved by regularly adapting therapy parameters used to calculate insulin doses. Multiple rules exist in literature to estimate and adjust these therapy parameters [102, 103, 104, 105]. Therapy parameters contain, but not limited to:

Carbohydrate ratio which is a ratio that specifies how many grams of carbohydrates are metabolized by each unit of insulin (gram per unit). This ratio can be employed by patients under insulin pump or multiple daily injection therapy.

Pump programmed basal rate which is the infusion rate of insulin delivered by a pump in insulin pump therapy. Multiple basal rates can be programmed during the day.

Insulin basal dose which is number specifying the basal dose amount in multiple daily injections therapy.

Insulin sensitivity factor which is a number describing how much glucose is utilized by one unit of insulin. This factor can be employed by patients under insulin pump or multiple daily injection therapy.

The idea for insulin decision-making systems date back to the early 1980s when pocket computers began to emerge [106, 107, 108, 109]. However, serious clinical trials targeting type 1 diabetic patients have only started in the last decade. In the following, we summarize recent clinical trials investigating insulin dosing decision systems regardless of the insulin therapy (insulin pump, multiple daily injections, or closed-loop insulin delivery).

Palerm et al. [**110**] conducted one of the first clinical trials investigating the feasibility of automatic carbohydrate ratios adjustment. Over a 2 to 4 day period, sparse blood glucose levels were collected from 11 participants. Starting with their usual carbohydrate ratio, physicians made recommendations to normalize glucose levels after meals. A mathematical performance measure was then derived for use in a run-to-run algorithm [111], such that the decisions of the algorithm will match the decisions of the physician.

Charpentier et al. [**112**] conducted a 6-month randomized parallel trial in 180 adults using either insulin pumps or multiple daily injections to evaluate the

efficacy of their mobile application Diabeo. Diabeo includes a bolus calculator, automatic algorithms for the adjustment of carbohydrate ratio and basal insulin dose, or pump programmed basal rates, and data transmission to medical staff computers. They showed that (i) using Diabeo with quarterly physicians follow-up visits reduced HbA1c by -0.5% compared to only quarterly follow-up visits; (ii) using Diabeo with short teleconsultations every 2 weeks reduced HbA1c by -0.7% compared to only quarterly physician's follow-up visits. Their study was limited to participants with a baseline HbA1c $\geq 8\%$ (non-optimal control).

Bergenstal et al. [113] conducted a prospective 16-week study in adults with type 1 or type 2 diabetes using multiple daily injections to evaluate the efficacy of weekly insulin adjustments using their software DIGS. In the type 1 diabetes cohort (n=20), 14 participants completed the study. They showed that the adjustments made by their software were safe, and there was a trend in decreasing HbA1c from 8.9% at baseline to 8.3% at week 16. Their study was limited to participants with a baseline HbA1c $\geq 7.4\%$.

Kirwan et al. [114] conducted a 9-month randomized parallel trial in 72 adults using either insulin pumps or multiple daily injections to evaluate the efficacy of their mobile application (Glucose Buddy). Glucose buddy does not provide automatic insulin adjustments but transmits the patient's logs to a certified diabetes educator who made weekly insulin adjustments. Only 53 participants completed the study. They showed a decrease of -1.1% in HbA1c levels in the group using their application compared to the control group.

Reddy et al. [115] conducted a 6-week prospective study in 10 adults using multiple daily injections to evaluate the feasibility of their mobile application ABC4D. ABC4D is a bolus calculator that accounts for exercise and alcohol, and adapt parameters weekly. The algorithm is based on case-based reasoning, an artificial intelligence technique that solves newly encountered problems by applying the solutions learned from solving past similar problems [116]. They have shown the feasibility of their algorithm, and they observed a trend in decreasing post-meal hypoglycemia in the final week compared with week 1.

Messori et al. [117] conducted a 1-month prospective study in 18 adults using closed-loop insulin delivery to evaluate the efficacy of daily adjustments in carbohydrate ratios and nocturnal basal insulin. Their algorithm used a run-to-run update rule [118]. They showed a 9.7% improvement in night (00:00–08:00) time-in-target in the last week of closed-loop insulin delivery with daily adaptation compared to a baseline one-week closed-loop insulin delivery. They also observed a trend in improving overall time-in-target. This study was limited by a possible bias since it was an extension of a previous 1-month closed-loop only study.

Dassau et al. [119] conducted a 27-hour randomized crossover trial in 37 adults using closed-loop insulin delivery to evaluate the efficacy of a one-time algorithmic adjustment of pump programmed basal rates and insulin to carbohydrate ratios. They showed no difference in glucose outcomes between the two interventions (closed-loop insulin delivery before and after parameters adjustment).

Wang et al. [120] conducted an 8 × 3-hour prospective study in 10 adults using closed-loop insulin delivery to evaluate the feasibility of a learning-type closed-loop algorithm. Their algorithm employed an iterative learning control strategy to update the set-point in the cost function of the model predictive control algorithm [121]. Their strategy was feasible with an improvement in the percentage of time-in-target.

Dassau et al. [122] conducted a 12-week prospective study in 29 adults using closed-loop insulin delivery to evaluate their adaptive closed-loop insulin system. pump programmed basal rates were adjusted weekly and carbohydrate ratios were adjusted every 4 weeks. A decrease in HbA1c was observed compared to a baseline insulin pump period, but this study was not designed to measure the effect of insulin adaptations.

Breton et al. [123] conducted a 48-hour randomized crossover trial in 24 adults using either insulin pumps or multiple daily injections to evaluate the efficacy of their software DSS. DSS consisted of a combination of automated insulin titration (pump programmed basal rates, or basal dose), bolus calculation, and carbohydrate treatment advice before exercise. They showed that the use of their system reduced glucose variability from 36% to 33%, and reduced exposure to hypoglucemia from 3.8% to 1.8%.

Nimri et al. [124] conducted a study to evaluate the safety of insulin adjustments made by their software Advisor Pro. The Advisor Pro provides recommendations for insulin pump users, including recommendation in pump programmed

basal rates, carbohydrate ratios, and insulin sensitivity factors. Recommendations from their software for 3-week glucose and insulin data of 15 patients were compared with recommendations from 26 physicians. They showed that the algorithm recommendations did not differ significantly from the advice given by the physicians.

Chatzakis et al. [125] conducted a 12-month randomized parallel study in 80 children and adolescents using either insulin pumps or multiple daily injections to evaluate the efficacy of their mobile application Euglyca. Euglyca is a bolus calculator that contains a food database and account for both carbohydrates and lipids content. Physicians adjusted Euglyca parameters for participant in the experimental group each 3 months. They showed a significant decrease in HbA1c values and increase in percentages of time-in-target in the experimental group compared to the control group.

It is yet to be shown that an automatic decision support system can improve glycemic control without (or with minimal) physicians interventions. However, in studies where physicians made regular insulin adjustments using electronically logged and transmitted data, a reduction in HbA1c was observed [112, 114, 125]. Despite multiple daily injection users making up more than half of the type 1 population only a handful of studies included patients using multiple daily injections [112, 113, 114, 123, 125]. This large population is unlikely to use closed-loop systems but will still need advice and support to achieve their glycemic targets. Decision support systems remains a fairly new technology, and active research is on-going in this field.

2.6 Summary

Type 1 diabetes is a chronic disease treated with intensive insulin therapy aimed at normal glucose levels. Insulin therapy is implemented using either multiple daily injections with an insulin pen or continuous subcutaneous insulin infusion with an insulin pump. Good glycemic control assessed with HbA1c levels is essential to reduce the risk of acute and long-term complications. However, most patients do not reach their glycemic targets and are confronted with impaired quality of life and psychosocial health. Two emerging technologies are particularly helping to ease patients' burden: closed-loop insulin delivery systems, and insulin decision support systems.

CHAPTER 3

The Artificial Pancreas and Meal Control: An overview of postprandial glucose regulation in type 1 diabetes

3.1 Preface

The artificial pancreas, an insulin closed-loop delivery system that automatically regulates glucose levels, is the most promising therapy for type 1 diabetes treatments. The artificial pancreas may be regarded as a feedback system where a sensor measures glucose levels, under-skin delivered insulin is the actuator, and meals are external disturbances.

Feedback control after meal consumption is challenging because of the fast rate of glucose appearance from meals compared to the slow effects of under-skin delivered insulin. Hybrid designs with a feedforward component, requiring patients to announce upcoming meals, is an approach that trades off the patient convenience and the controller efficiency on post-meal regulation.

Model predictive controllers are at the forefront of current research, incorporating meal information, insulin constraints, and model dynamics. By incorporating model dynamics, and mainly the slow absorption of insulin, the model predictive controller can indirectly adapt its gain to avoid future hypoglycemia. Meal detection

may mitigate the risks of meal announcement omission, while learning algorithms may optimize the prediction capabilities of the artificial pancreas. In this tutorial, those concepts are reviewed with a focus on clinical implications.

3.1.1 Authors Contributions to the Manuscript

The author (Anas El Fathi) was the primary responsible for reviewing the literature and writing the manuscript. Véronique Gingras reviewed Section 3.2 Challenges of Postprandial Glucose Control. Mohamed Raef Smaoui reviewed Section 3.7.2 Machine Learning Algorithms for Postprandial Glucose Control and assisted in generating simulation results. Ahmad Haidar and Benoit Boulet provided editorial input in writing the manuscript, and provided overall supervision. All authors critically reviewed the manuscript.

The Artificial Pancreas and Meal Control: An overview of postprandial glucose regulation in type 1 diabetes

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In healthy individuals, plasma glucose concentration is tightly regulated by the action of the hormones secreted by the endocrine pancreas, principally, insulin and glucagon. Insulin is secreted by the pancreatic beta cells to signal organs to absorb glucose, and glucagon is secreted by the pancreatic alpha cells to signal the liver to produce glucose [1]. In type 1 diabetes, insulin secretion is lost due to the autoimmune destruction of the beta cells [2]. Type 1 diabetes accounts for 5-15% of the 366 million people with diabetes worldwide [3].

Type 1 diabetes is currently treated with life-long insulin-replacement therapy implemented using multiple daily injections or continuous subcutaneous (under the skin tissue) insulin infusion via a portable pump. Tight glucose control is critical for health, as a sustained elevation of glucose levels (hyperglycemia) leads to long-term complications such as heart diseases, blindness, kidney failure, and lower-extremity

amputations [4, 5]. How well the body is able to control glucose is assessed using glycated hemoglobin (HbA1c) levels, a biomarker correlated with the mean blood glucose level over a period of three months. A target of HbA1c below 7.0% is recommended for most patients with type 1 diabetes [6].

Despite advances in insulin analogs, insulin pumps, and continuous glucose sensors, most patients do not achieve acceptable glucose targets [7, 8]. A study by the Epidemiology of Diabetes Interventions and Complications reported an average HbA1c of 8.1% in 1,349 patients [7]. HbA1c higher than 7.0% is associated with a significant increase in the risk of complications [6]. For instance, an increase of only 10% in HbA1c (for example 8% to 8.8%) is associated with a 40% increase in the progression rate of diabetic retinopathy (damage to the retina) [9]. Despite the clinical efforts to control HbA1c levels, only around 27% of patients achieve HbA1c levels less than 7% [10].

Advances in continuous glucose sensors have motivated the research towards closed-loop insulin delivery systems, termed the artificial pancreas, to automatically regulate glucose levels in patients with type 1 diabetes [11]. In the artificial pancreas, the pump insulin infusion rate is repeatedly altered based on a control algorithm that relies on continuous glucose sensor readings Figure 3–1. Thus, the novelty of this approach resides in the real-time feedback of glucose levels to close the loop and establish hemostasis.

Effective closed-loop glucose control is challenged by inter- and intra-patient variability in insulin sensitivity and insulin absorption, exercise, slow absorption

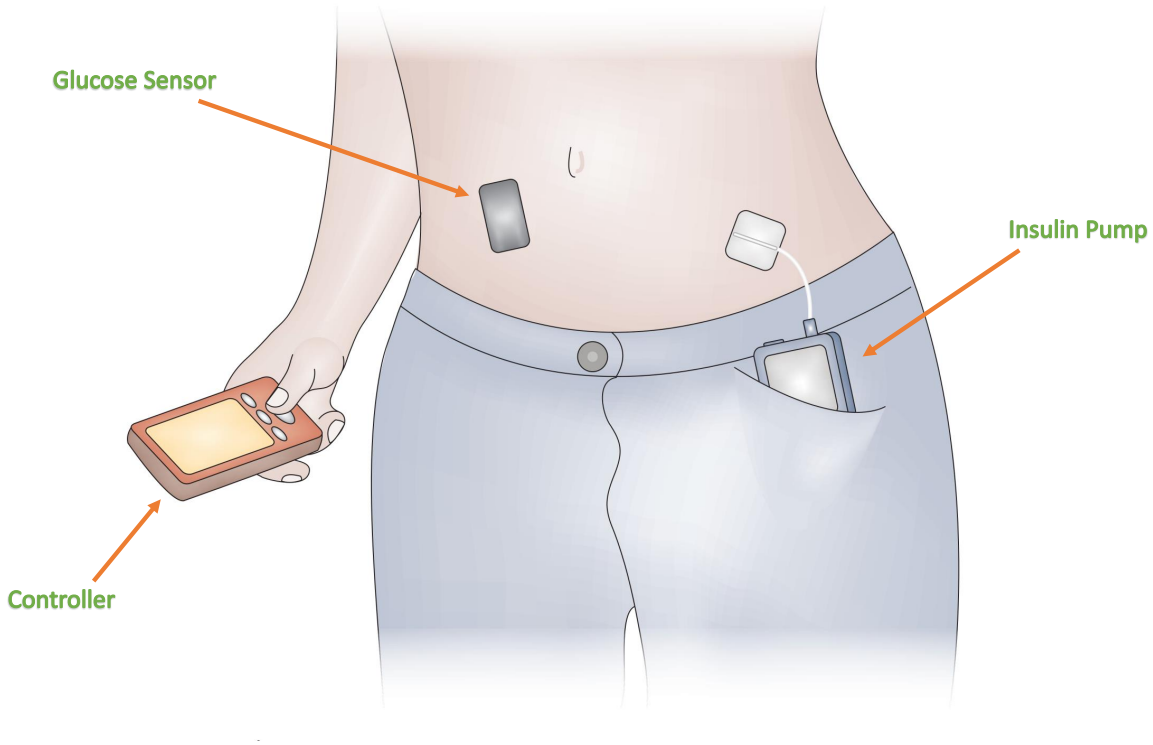


Figure 3–1: Artificial Pancreas System. A sensor measures glucose levels and transmits them to a handheld controller, which runs a control algorithm. An insulin pump delivers insulin subcutaneously. The communication is wireless. In another configuration, the algorithm may also reside in the pump. Reprinted by permission from Macmillan Publishers Ltd: [Nature Reviews Endocrinology] [11]. Copyright 2011.

of subcutaneously-infused insulin, and meals. Advanced closed-loop systems maintain glucose levels in the target range for 70-75% of the time, and the remaining time spent outside the target range is mostly due to postprandial (post-meal) hyperglycemia [12]. The purpose of this paper is to introduce the specific challenges, models, and control techniques surrounding closed-loop glucose regulation following meal ingestion.

3.2 Challenges of Postprandial Glucose Control

3.2.1 Postprandial glucose control in healthy individuals

In healthy individuals, there is little variation in plasma glucose concentrations, with fasting glucose ranging between 3.9 and 6.1 mmol/L [13], and postprandial glucose not exceeding 10 mmol/L [14]. Postprandial glucose control is ensured by the action of insulin secreted by the pancreas and the inhibition of glucagon secretion, and the resulting metabolic effects on the liver and peripheral tissues.

Plasma glucose concentration typically rises within 10 minutes following food ingestion [14]. A peak in plasma glucose concentration is observed around 60 minutes after the start of the meal and the increase rate depends on meal composition (carbohydrates type and quantity as well as other nutrients intake) and timing of the meal [14]. Other factors are also known to affect insulin sensitivity and glucose absorption in individuals such as gastric emptying, physical activity, physical or emotional stress, and growth and hormonal fluctuations (puberty, pregnancy, menopause, menstrual cycle) [15]. Plasma glucose concentrations are expected to return to the preprandial (pre-meal) level within 2 to 3 hours, although the carbohydrate and other nutrient absorption can continue for up to 5 to 6 hours postprandial [14].

3.2.2 Postprandial Glucose Control in Type 1 Diabetes

Postprandial glucose control has a major impact on the risk of long-term complications [16]. Intensive insulin therapy aims for a 2 hours postprandial glucose level between 5 and 10 mmol/L in most patients [6]. The main determinant of this postprandial glucose rise is the carbohydrate content of the ingested meal [17, 18]. Therefore, before each instance of food intake, patients need to estimate the carbohydrate content of the meal (carbohydrate counting), and self-administer an insulin bolus (dose) proportional to the carbohydrate content. Yet, carbohydrate counting is a challenging task for patients, with an estimated average error of 20% [19]. Although the meal insulin bolus is based on the amount of carbohydrate, postprandial glucose concentrations are influenced by the type of carbohydrate (glycemic index of the food consumed) [20, 21]. In addition, meals rich in lipids and protein may be absorbed 60% slower than low-fat meals [22], which results in a prolonged postprandial hyperglycemia [23, 24, 25, 26].

The considerable intra- and inter-individual variability in the metabolic effect of subcutaneous insulin infusion in patients with type 1 diabetes further complicates matters [27, 28]. For the same body weight and age, insulin sensitivity can vary by up to 6-fold between individuals. Across the daytime, a significant range of insulin sensitivity in-between meals also exists, with an increasing sensitivity from breakfast to lunch [28]. In addition, within the same individual but across days, it is estimated that there is a 31% variability in insulin sensitivity overnight and 17% variability during the day [29].

Adolescence is a period of many changes, including physiological and psychological changes. It is also a difficult period for glucose control with a low adherence to diabetes self-treatment plan [30]. The National Paediatric Diabetes Audit for England and Wales reported that more than 80% of young people were above the recommended HbA1c level for adolescents (above 7.5% [31]) [32]. The non-adherence to the standard insulin therapy includes omission [33, 34, 35] or underestimation [36] of insulin boluses for meals and snacks. Statistics shows that more than 65% of youth using insulin pump therapy miss at least one meal bolus per week [34].The reasons for insulin bolus omission remain largely unknown, but adolescents are reported to be unaware of missed boluses [34], and it is hypothesized that boluses are simply forgotten. Moreover, several studies have shown a tendency in female adolescents to skip or reduce insulin doses for weight control purposes [37, 38]. These observations suggest that the efficacy and safety of closed-loop control systems relying on patient inputs may be compromised with insulin bolus omissions in youth patients [39, 40]. An artificial pancreas design minimizing the need of user interaction with the closed-loop controller may especially benefit the young diabetes patients.

The major challenge to control postprandial glucose concentrations is the delay in rapid-acting insulin absorption compared with meal glucose absorption [41, 42]. Subcutaneously injected insulin is absorbed into the blood under the skin through the capillary membrane. The absorption rate of insulin molecules is related to the molecular size of insulin complexes [43]. Current rapid-acting insulin analogs have an onset (start of effect) between 10 and 15 minutes, with a peak action between 30 and 90 minutes [44]. However, after meal consumption, the rate of glucose appearance

is much faster than insulin absorption, leading to a rapid increase in postprandial glucose levels. This mismatch between the peak absorption of externally injected insulin and the ingested carbohydrates make it difficult to ensure tight closed-loop control of plasma glucose concentrations (for details, see Sidebar: The Relative Effect of Time-to-peak of Insulin Action and Time-to-peak of Meal Absorption) [45].

3.3 System Dynamics for Postprandial Glucose Control

Plasma glucose concentration is balanced by the rate of glucose entering the blood circulation and the rate of glucose removal from the blood. The glucose entering the blood circulation is a result of the absorption of digested carbohydrate from meals, and the endogenous glucose production. For type 1 diabetes, glucose elimination from the blood into skeletal muscle and body fat is driven by external insulin injections. Insulin also decreases the endogenous glucose production, which reduces the rate of glucose entering the blood.

This balancing mechanism is usually described by the interaction of four subsystems (Figure 3–2). Starting from the subcutaneous injection of insulin, which is the system input to regulate plasma glucose concentration, up to the measurement of interstitial glucose concentration, which is the observable variable, the subsystems are the insulin absorption kinetics, plasma glucose kinetics, and interstitial subcutaneous glucose kinetics. The fourth subsystem, glucose meal absorption kinetics, describes the dynamics of glucose appearance from the digested carbohydrates. With this representation, consumed meals are regarded as disturbance signals to the glucoregulatory system of the artificial pancreas users.

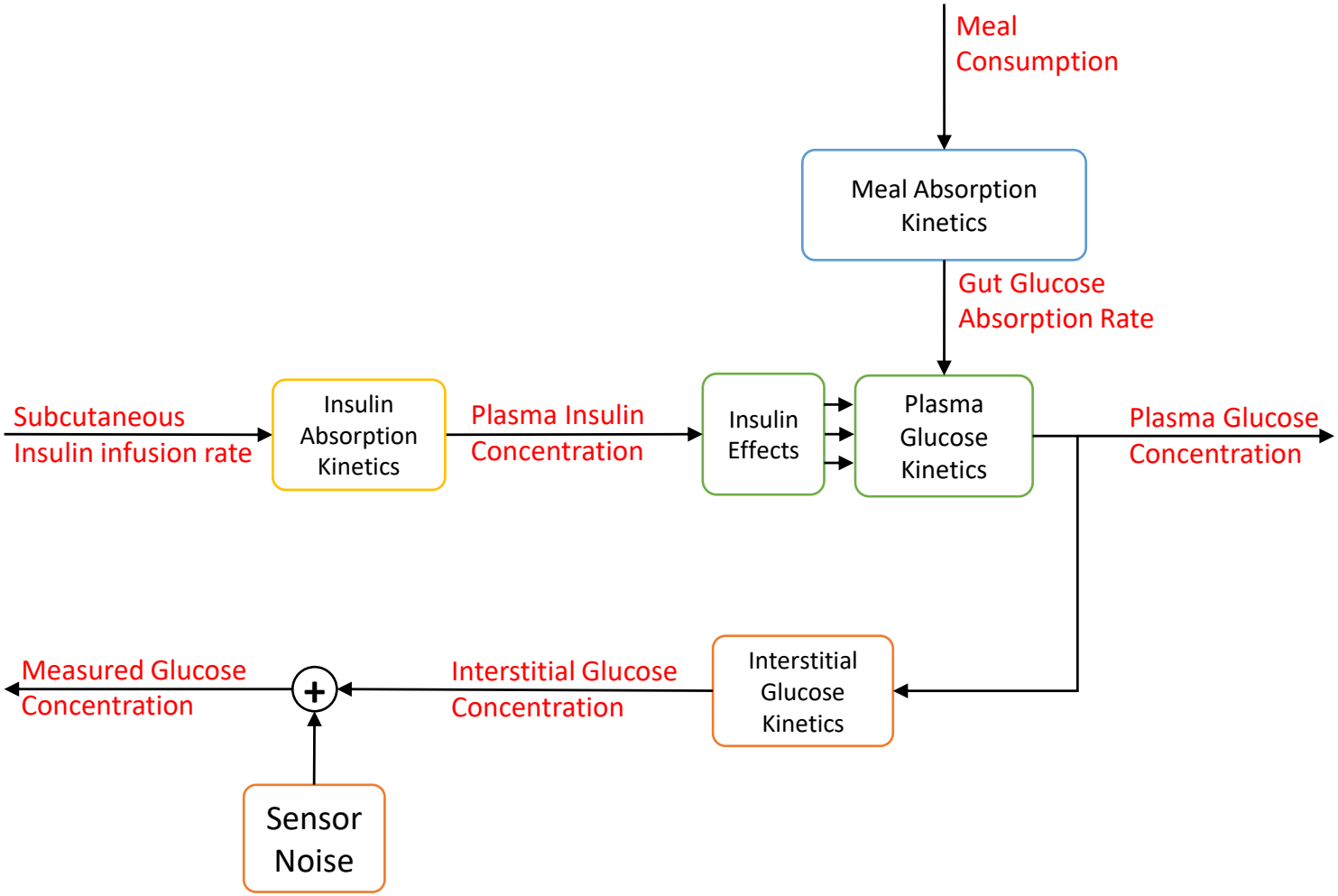


Figure 3–2: A block diagram representing the four subsystems that govern the gluco-regulatory system. Insulin is infused subcutaneously, and is absorbed slowly to the plasma. After a meal consumption, glucose is absorbed from the gut into the plasma. Both insulin absorption and meal glucose appearance affect plasma glucose levels. The measured interstitial glucose concentration is a delayed and noisy signal compared to the plasma glucose concentration.

Several mathematical models describing the glucoregulatory system of an artificial pancreas user have been proposed in the literature [41, 46, 47, 48, 49]. In this section, a representative control-relevant model, based on a compartmental approach, is presented.

3.3.1 Insulin absorption kinetics

After subcutaneous delivery, insulin is slowly absorbed following a two-compartment model

$$\begin{bmatrix} \frac{dQ_{i1}(t)}{dt} \\ \frac{dQ_i(t)}{dt} \end{bmatrix} = \begin{bmatrix} -\frac{1}{\tau_i} & 0 \\ \frac{1}{\tau_i} & -\frac{1}{\tau_i} \end{bmatrix} \begin{bmatrix} Q_{i1}(t) \\ Q_i(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} U_i(t) \tag{3.1}$$

where $Q_{i1}(t)$ and $Q_i(t)$ (units) are the insulin masses in the first and second compartment, the second compartment being the plasma space, $U_i(t)$ (unit/min) is the external insulin infusion rate and τ_i is the time constant characterizing the peak response time of the insulin absorption, which depends on the insulin analog type. Following an impulse response (such as the administration of an insulin bolus), and τ_i equals the time-to-peak of the insulin plasma concentration.

The plasma insulin concentration (insulinemia) $I_p(t)$ (munits/L) is obtained form $Q_i(t)$ as

$$I_p(t) = \frac{K_i}{\tau_i} Q_i(t) \tag{3.2}$$

where $K_i = \dfrac{10^6}{(wK_{MCR})}$ (10^{-3} min/L) is a gain inversely proportional to the metabolic clearance rate K_{MCR} (mL/kg/min) and the patient weight w (kg) [41]. In

the Laplace domain, the plasma insulin concentration $I_p(t)$ (munits/L) is expressed as

$$I_p(s) = \frac{K_i}{(1+\tau_i s)^2} U_i(s) \tag{3.3}$$

When the insulin is injected as a bolus, the input function $U_i(t)$ takes the form of a Dirac input $U_i(t) = U_{i_{Bolus}}\delta(t)$. This is equivalent to updating the first compartment by the bolus quantity

$$Q_{i1}\left(0^+\right) = \lim_{s\to\infty} s\frac{\tau_i}{1+\tau_i s} U_{i_{Bolus}} = U_{i_{Bolus}} \tag{3.4}$$

3.3.2 Plasma glucose kinetics

Bergman's minimal model assumes that plasma glucose concentration $G(t)$ (mmol/L) changes are proportional to both the remote insulin (the delayed insulin effects) $x(t)$ (1/min) and the rate of meal-glucose appearance $U_m(t)$ [50]. The minimal model dynamics are represented as [46]

$$\begin{aligned} \frac{d}{dt}G(t) &= -\left(p_1 + x(t)\right)G(t) + P_{EGP} + \frac{1}{V}U_m(t) \\ \frac{d}{dt}x(t) &= -p_2 x(t) + p_3 I_p(t) \end{aligned} \tag{3.5}$$

where $U_m(t)$ (μ mol/kg/min) is the rate of glucose appearance from ingested meal, V (mL/kg) is the glucose distribution volume, P_{EGP} (mmol/L/min) describes the rate of endogenous production of glucose, p_1 (1/min) describes glucose effectiveness (the ability of glucose to promote its own disposal), p_2 (1/min) is a time constant characterising the delay of plasma insulin effect on plasma glucose (deactivation rate

of insulin effects), and p_3 ($1/\text{min}^2$ per munits/L) is a parameter representing the activation rate of insulin effects.

A linearized form of Bergman's minimal model may be derived by assuming that the dynamics of remote insulin are faster than glucose dynamics ($x(t)$ arrives at the equilibrium point faster than $G(t)$, $x(t) \sim 0$)

$$\frac{d}{dt}G(t) = -p_1 G(t) - \frac{S_i}{\tau_i}Q_i(t) + P_{EGP} + \frac{1}{V}U_m(t) \tag{3.6}$$

where $Q_i(t)$ (units) is the insulin mass in plasma, $S_i \sim \dfrac{G_0 K_i P_3}{P_2}$ (mmol/L per units) is a positive identifiable insulin sensitivity factor (the amount of glucose level drop (mmol/L) caused by one unit of insulin), and G_0 (mmol/L) is an equilibrium point for glucose concentration. It has been suggested that this linear model (with $p_1 = 0$) may be used to asses long-term glucose dynamics in type 1 diabetes [51].

In the Laplace domain, transfer function between the insulin mass in the plasma $Q_i(s)$ and the glucose concentration in the plasma $G(s)$ is expressed as

$$\frac{G(s)}{Q_i(s)} = -\frac{S_i}{\tau_i}\frac{1}{s + p_1} \tag{3.7}$$

3.3.3 Interstitial Subcutaneous Glucose Kinetics

The Interstitial glucose concentration (where measurements are done) $G_s(t)$ (mmol/L) is obtained from the plasma glucose concentration $G(t)$ by a simple diffusion model [52]

$$\frac{d}{dt}G_s(t) = k_{sen}\left(G(t) - G_s(t)\right) \tag{3.8}$$

where k_{sen} (1/min) is the transfer-rate constant.

3.4 Meal-Related Glucose Absorption Dynamics

Identification of the kinetics of glucose appearance after meal ingestion (the disturbance dynamics) may improve the design of the control algorithm for the artificial pancreas. After food intake, the carbohydrates contained in the chyme (partially digested food in the stomach) are broken into single sugar components in the small intestine. From the small intestine, glucose is integrated to the blood circulation where it is absorbed by the rest of the organs. The profile of glucose appearance in the circulation can be described using non-parametric functions (estimated experimentally using isotope-tracer techniques [52]) [22, 47] or using parametric mathematical models [53, 54, 55]. In this section, different mathematical models to describe meal-glucose appearance are discussed.

3.4.1 Lehmann and Deutsch Meal-glucose Model

Gastric emptying $G_{emp}(t)$ (μ mol/kg/min) is the rate of expelling the chyme from the stomach to the gut. This process has been described as a piecewise-linear function by Lehmann and Deutsch [54]

$$G_{emp}(t) = \frac{K_{Bio} D_m}{T - \frac{T_{des} + T_{asc}}{2}} \begin{cases} \frac{t}{T_{asc}} & , \quad t \leq T_{asc} \\ 1 & , \quad T_{asc} \leq t \leq T - T_{des} \\ \frac{(T-t)}{T_{des}} & , \quad T - T_{des} < t \\ 0 & , \quad T < t \end{cases} \tag{3.9}$$

where D_m (μ mol/kg) represents the total amount of ingested glucose, K_{Bio} is the carbohydrates bioavailability in the meal, and T_{asc} , T_{des} and T (min) are the durations of ascending and descending rates, and total duration of gastric emptying, respectively.

Following the gastric emptying from the stomach to the gut, the glucose mass in the gut can be obtained as [47, 53, 54]

$$\frac{d}{dt}Q_m(t) = -\frac{1}{\tau_m}Q_m(t) + G_{emp}(t) \tag{3.10}$$

where $Q_m(t)$ (μ mol/kg) is the glucose mass in the gut compartment, and τ_m (min) is a time constant characterizing the appearance of glucose in the blood circulation from the gut. Moreover, the glucose gut absorption rate in the plasma $U_m(t)$ (μ mol/kg/min) is expressed as

$$U_m(t) = \frac{1}{\tau_m}Q_m(t) \tag{3.11}$$

This model have been validated on a set of 24 subject [56] and have been used in simulation and control algorithms [57, 58].

3.4.2 Two-compartmental Model for Meal-related Glucose Appearance

Meal-glucose absorption from the stomach to the gut and then to the blood circulation may be described in a two-compartment model, with identical fractional transfer rate [55]. Such a models have been popular in type 1 diabetes patient control and simulation [52, 51, 59, 60]

$$\begin{bmatrix} \dfrac{dQ_{m_1}(t)}{dt} \\ \dfrac{dQ_m(t)}{dt} \end{bmatrix} = \begin{bmatrix} -\dfrac{1}{\tau_m} & 0 \\ \dfrac{1}{\tau_m} & -\dfrac{1}{\tau_m} \end{bmatrix} \begin{bmatrix} Q_{m_1}(t) \\ Q_m(t) \end{bmatrix} + \begin{bmatrix} K_{Bio} \\ 0 \end{bmatrix} D_m(t) \tag{3.12}$$

where $D_m(t)$ (μ mol/kg/min) is the rate of glucose ingestion, Q_{m_1} and Q_m (μ mol/kg) are the glucose masses in first and second gut compartments, τ_m (min) is the time to peak of the appearance of glucose from the gut following an impulse input (instantaneous meal). In the Laplace domain, the glucose mass $Q_m(t)$ (μ mol/kg) is expressed as

$$Q_m(s) = \frac{K_{Bio}\tau_m}{(1+\tau_m s)^2} D_m(s) \tag{3.13}$$

In general, meals are assumed to be ingested instantly. In this case, $D_m(t)$ is a Dirac impulse occurring at mealtime whose area is given by $D_m = 10^6 \dfrac{Q_{CHO}}{(wM_{CHO})}$, where Q_{CHO} (g) is the quantity of carbohydrates ingested, $M_{CHO} = 180.156$ (g/mol) the molar mass of glucose, and w (kg) is the patient weight. Using the initial value theorem, the quantity of glucose in the first compartment following the meal is obtained as

$$Q_{m_1}\left(0^+\right) = \lim_{s\to\infty} s\frac{K_{Bio}\tau_m}{1+\tau_m s} D_m = K_{Bio} D_m \tag{3.14}$$

3.4.3 Three-compartmental Model with Nonlinear Gastric Emptying Rate

In addition to having a single compartment describing meal-glucose appearance from the gut, this model represents the gastric emptying from the stomach by a two compartments biphasic process of solid and liquid phase [47]

$$\begin{aligned}
\frac{d}{dt}Q_{sto1}(t) &= -K_{gri}Q_{sto1}(t) + K_{Bio}D_m(t) \\
\frac{d}{dt}Q_{sto2}(t) &= -K_{emp}(Q_{sto})Q_{sto2}(t) + K_{gri}Q_{sto1}(t) \\
\frac{d}{dt}Q_m(t) &= -\frac{1}{\tau_m}Q_m(t) + K_{emp}(Q_{sto})Q_{sto2}(t)
\end{aligned} \tag{3.15}$$

where Q_{sto1} and Q_{sto2} (μ mol/kg) are the amounts of glucose in the stomach (solid and liquid phase, respectively), $Q_{sto} = Q_{sto1} + Q_{sto2}$ is the total amount of glucose in the stomach, K_{gri} (1/min) is the rate of chyme grinding in the stomach, and $K_{emp}(Q_{sto})$ (1/min) is the rate of gastric emptying which depends on the amount of glucose in the stomach (Q_{sto}) in a nonlinear fashion

$$\begin{aligned}
K_{emp}(Q_{sto}) = k_{min} + \frac{k_{max} - k_{min}}{2}\{&\tanh(\alpha(Q_{sto} - aQ_{sto_{Full}})) \\
&- \tanh(\beta(Q_{sto} - bQ_{sto_{Full}})) + 2\}
\end{aligned} \tag{3.16}$$

where k_{max} , k_{min} are the maximum and minimum rates of gastric emptying, $Q_{sto_{Full}}$ is the total amount of ingested glucose that makes the stomach full, and α , β , a and b are tuning parameters.

This rate is maximal (equals k_{max}) when the stomach is close to empty ($Q_{sto} \sim 0$), or when the glucose quantity in the stomach is maximal ($Q_{sto_{Full}}$), otherwise this rate is decreasing to the minimal value k_{min} . This model is used in an Food and Drug Administration (FDA)-accepted type 1 diabetes patients simulator [47, 61].

3.4.4 Two-compartmental Model with Double Time-to-peak of Meal-glucose

Since different foods have different absorption profiles depending of their content (protein and fat) and complexity (glycemic index), a model has been proposed

[62] that allows double peaks in meal-glucose absorption profile. High glycemic index food produces a fast increase in the plasma glucose with a high peak, whereas low glycemic index food produces a slow and sustained increase of glucose concentration (which may continue beyond 8 hours) [22]. This model uses the same two-compartmental model described above and assumes that ingested meals $D_m(t)$ are Dirac delta functions

$$D_m(t) = \frac{10^6 Q_{CHO}}{w M_{CHO}} \delta(t) \tag{3.17}$$

$$U_{m_1}(t) = p_m \frac{K_{bio} D_m}{\tau_m} \frac{t}{\tau_m} e^{-\frac{t}{\tau_m}} \tag{3.18}$$

$$U_{m_2}(t) = \begin{cases} (1-p_m) \frac{K_{bio} D_m}{\tau_m} \frac{t-d}{\tau_m} e^{-\frac{t-d}{\tau_m}} & , \quad t > d \\ 0 & , \quad \text{otherwise} \end{cases} \tag{3.19}$$

where U_{m_1} and U_{m_2} (μ mol/kg/min) are the rate of glucose appearances from the first and second absorption channels, d (min) is a delay associated with the second absorption channel, and p_m is the portion of carbohydrate absorbed through the first channel. The total rate of glucose absorption is then expressed as the sum of the glucose appearing from the two channels

$$U_m(t) = U_{m_1}(t) + U_{m_2}(t) \tag{3.20}$$

3.5 Controller Configurations for Postprandial Glucose Control

Closed-loop glucose controllers provide insulin delivery (control actions) based on glucose sensor values. Meal consumption induce an increase of plasma glucose concentrations (the controlled quantity) moving the insulin-glucose system from its steady-state. In this respect, meals are considered as external disturbances to the glucoregulatory system for an artificial pancreas user. Yet, the information about the meal carbohydrates may be observed by the patient and provided to the main controller. The fact that meals are measured disturbances opens the door for three possible configurations for controlling postprandial glucose concentrations, either i) no meal information is provided to the controller (Feedback-only) ii) the complete meal information is provided to the controller (Feedforward-feedback), or iii) only partial meal information is provided to the controller (Partial-feedforward-feedback) (Figure 3–3).

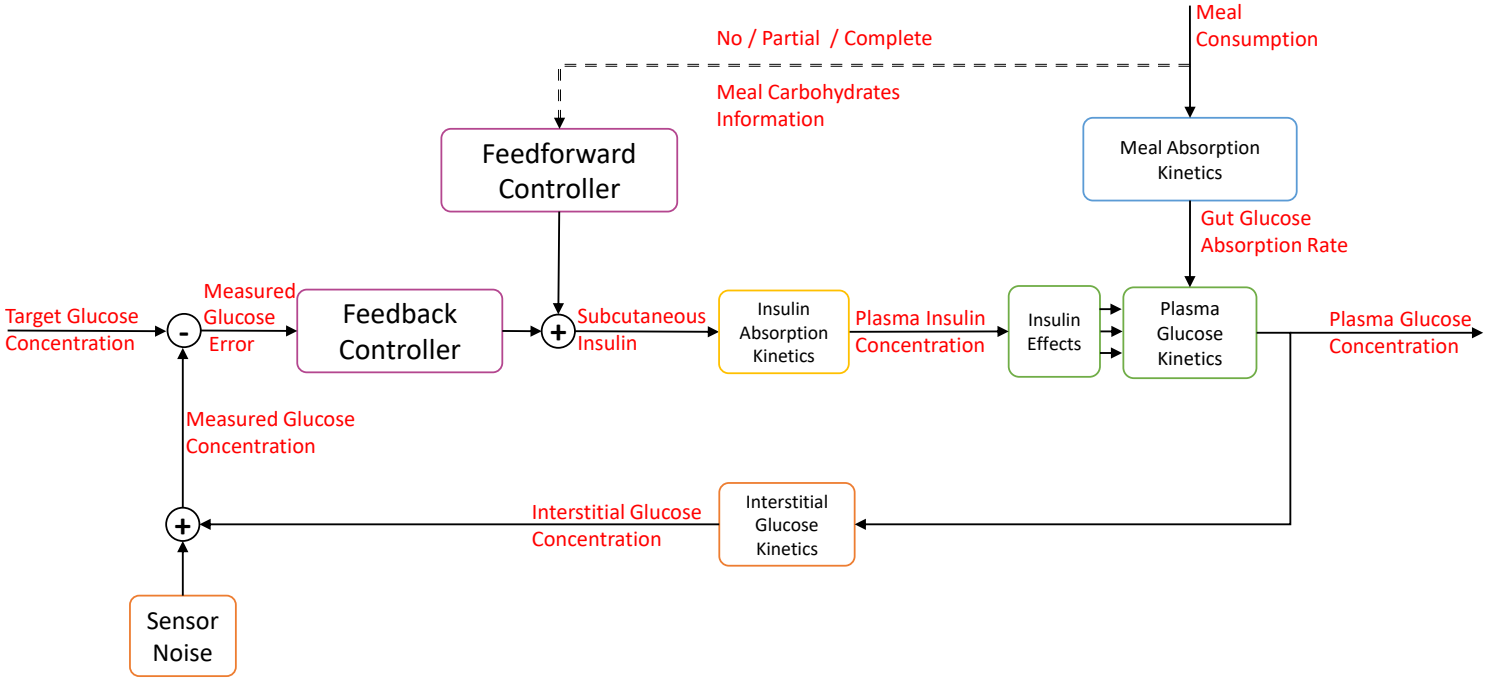


Figure 3–3: A block diagram representing control design strategies for the artificial pancreas. The feedback-only controller uses the offset between the measured glucose concentration and the target glucose to generate the subcutaneous insulin command while ignoring any information about the consumed meal (disturbance). Feedforward-feedback controller requires the complete information about the consumed meal (carbohydrate counting). This information is given to the controller to compute an insulin bolus to achieve tight postprandial glucose control. Partial-feedforward-feedback only requires qualitative information about the consumed meal (for example, only the size of the meal is provided) in order to deliver the meal-accompanying insulin bolus.

3.5.1 Feedback-only Control

Automated closed-loop control ultimately aims to relieve the patient from the burden of carbohydrate counting. Early artificial pancreas studies attempted to control postprandial glucose concentrations by relying solely on the glucose sensor readings (disturbance rejection by feedback control) [63, 64]. However, feedback-only control of postprandial glucose concentrations suffers from two major hindrances:

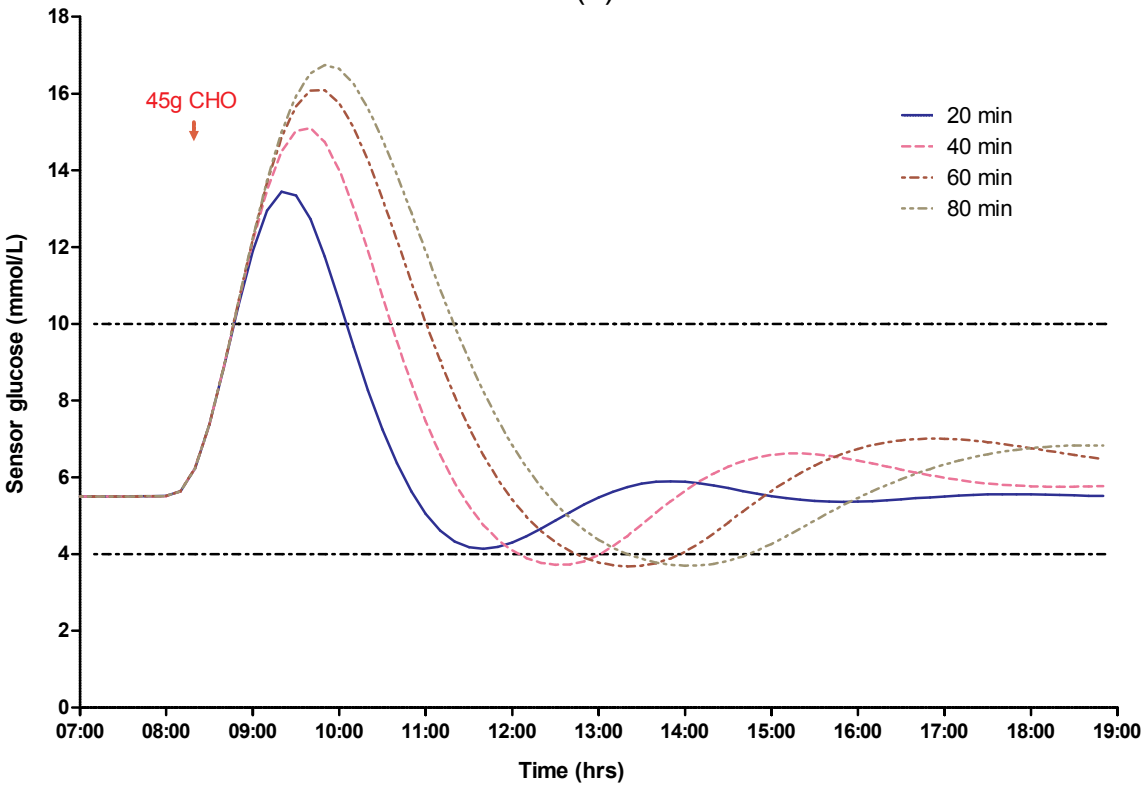
- Early postprandial hyperglycemia due to i) the rate of meal glucose appearance in the blood (the disturbance dynamics) which is faster than the absorption of subcutaneously-infused insulin (the actuator dynamics) and ii) the delay in glucose sensing in the interstitial fluid (around 15 min [65, 66]). In other words, even though a feedback controller is capable of taking corrective actions, no insulin dosing is effectively made until a deviation is observed on the controlled variable, which makes the control sluggish because of the slow dynamics of infused insulin.
- Late postprandial hypoglycemia (undesirable low glucose levels): Due to the fast increase in postprandial glucose, the closed-loop system needs to react aggressively by infusing a significant amount of insulin in the two hours after the meal ingestion, to prevent glucose concentrations from further increasing. However, due to the slow absorption of insulin delivery, this insulin continues to be absorbed and act beyond meal absorption, which may lead to late postprandial hypoglycemia. (insulin stacking [63]).

The two risks, early postprandial hyperglycemia and late postprandial hypoglycemia, are interconnected. Delivering insulin aggressively to prevent early postprandial hyperglycemia increases the risk of late postprandial hypoglycemia [63]. Conversely, delivering insulin in a conservative manner in the early postprandial period to reduce the risk of late postprandial hypoglycemia results in early hyperglycemia. This trade-off is caused by the fact that insulin-only artificial pancreas systems are positive systems where the input (insulin) and the systems states can only attain positive values [45]. This trade-off between hyperglycemia and hypoglycemia is the major barrier to adequately control postprandial glucose concentrations using a closed-loop system without feedforward control. Because hypoglycemia is a more critical issue, feedback-only control systems typically focus on eliminating hypoglycemia at the expense of hyperglycemia.

The early feedback-only algorithms tested in clinical trials showed sustained hyperglycemic levels after meal consumption and some episodes of induced postprandial hypoglycemia [64, 67]. The postprandial hypoglycemia was mainly triggered by the insulin stacking effect caused by either not considering the delay in subcutaneous insulin delivery [64], or by inaccurate modeling of the insulin subcutaneous kinetics (mainly the time-to-peak of insulin [67]). A recent pilot, non-controlled, inpatient clinical trial of a feedback-only algorithm based on multiple model predictive control has been conducted with more promising results [68], but further clinical trials are warranted for this approach.

Different approaches can be investigated to improve feedback-only postprandial glucose control. First, glucagon may be infused in the late postprandial period (in a closed-loop manner) to reduce hyperglycemia while safely avoiding hypoglycemia [69]. However, feedback-only dual-hormone systems require delivering excessive amount of glucagon to counteract high late postprandial plasma insulin concentrations [67, 70]. Second, a better control of postprandial glucose concentrations may be achievable with faster insulin analogs than the ones currently on the market (Figure 3–4). Third, other hormone analogs, such as Pramlintide and GLP-1, may be used to delay gastric emptying [71, 72] (that is, alter disturbance dynamics) to achieve better postprandial glycemic control by a feedback-only approach.

(a)


45g CHO
20 min
40 min
60 min
80 min
Sensor glucose (mmol/L)
Time (hrs)
0
2
4
6
8
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14
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(b)

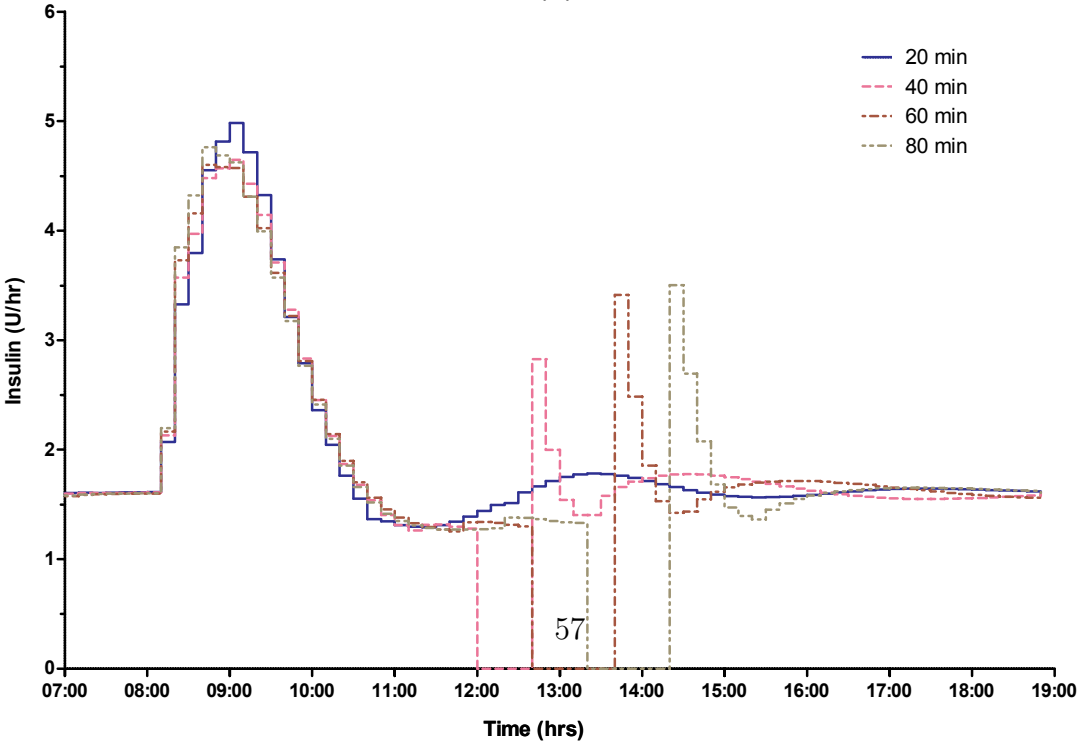
20 min
40 min
60 min
80 min
Insulin (U/hr)
Time (hrs)
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Figure 3–4 *(preceding page)*: Simulation of postprandial glucose with feedback-only control using hypothetical insulin analogs with varying insulin time-to-peak plasma concentrations τ_i. Four 12-hour experiments with varying τ_i values were conducted on a virtual patient [62] given a breakfast meal at 8 am with a 45g carbohydrate content and no insulin bolus. The control algorithm used in all experiments is a model predictive controller. The controller's aggressiveness was fixed for each τ_i value with an objective of simultaneously avoiding hypoglycemia and minimizing postprandial glucose levels. The meal information was not provided to the controller in all experiments. Postprandial glucose responses in (a) demonstrate that closed-loop systems using insulin analogs with low τ_i values achieves better postprandial control and less hyperglycemia. Faster insulin analogs have the potential to remove the burden of carbohydrate counting while achieving acceptable glucose control. In (b), the controller's insulin infusions are plotted for each τ_i experiment.

3.5.2 Feedforward-feedback Control

A feedforward controller is constructed to profit from anticipated or measured disturbances to control the process. When the disturbance dynamics are available and accurate, the feedforward control takes corrective action based on the disturbance before it affects the process. Ideally, feedforward would compensate perfectly the measured disturbance dynamics [73].

With current therapy, patients with type 1 diabetes calculate their meal insulin bolus as the carbohydrate content of the meals multiplied by the insulin-to-carbohydrate ratio (a ratio in (g/unit) that specifies how many grams of carbohydrate are covered by one unit of insulin, this ratio is typically different for breakfast, lunch, and dinner) [74]. Meal boluses are then adjusted based on i) the preprandial glucose concentrations (additional correction bolus in case of preprandial hyperglycemia) and ii) previously-infused insulin (insulin-on-board is subtracted from the correction bolus) [75]. Moreover, the timing of meal boluses may be adjusted for specific meals (for example, boluses are often delivered 15 min prior to high glycemic index meals) [76]. The most common feedforward-feedback control configuration of artificial pancreas systems (referred to as hybrid systems) adopts a similar approach: the patient calculates the carbohydrate content of the meal and provides this information to the artificial pancreas prior to meal ingestion; the artificial pancreas then computes the insulin bolus based on i) the carbohydrate content, ii) preprandial glucose concentrations, and iii) insulin-on-board.

For a linear time-invariant glucose model, the feedforward controller may be designed to cancel the effect of the disturbance $D_m(s)$ such that the overall transfer

function between the plasma glucose concentration $Q_g(s)$ and the meal disturbance is null [77]. With an insulin input $U_i(s) = C_{ff}(s) D_m(s)$, where $C_{ff}(s)$ is the feedforward controller transfer function, the transfer function yields

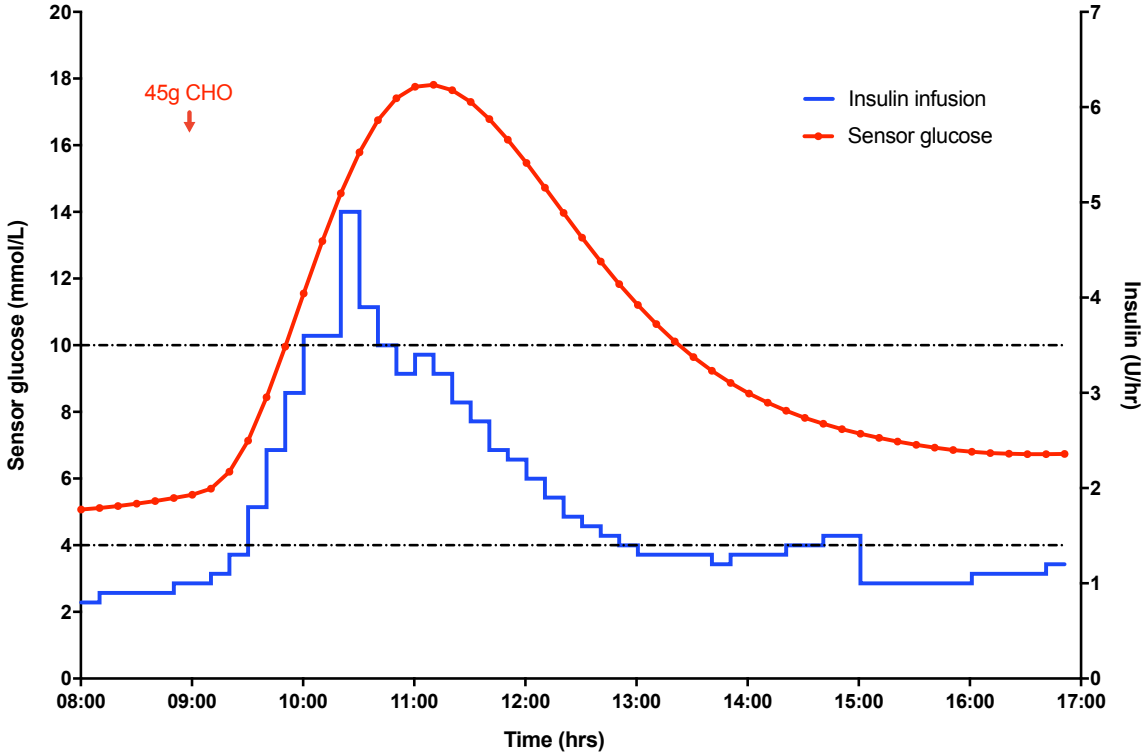
$$\frac{G(s)}{D_m(s)} = G_g(s) \left(C_{ff}(s) \frac{-S_i}{(1+\tau_i s)^2} + \frac{1}{V} \frac{K_{Bio}}{(1+\tau_m s)^2} \right) = 0 \tag{3.21}$$

or,

$$C_{ff}(s) = \frac{K_{Bio}}{S_i V} \frac{(1+\tau_i s)^2}{(1+\tau_m s)^2} \tag{3.22}$$

where S_i is the insulin sensitivity as defined before, K_{Bio} is the carbohydrates bioavailability, V is a volume distribution, τ_i and τ_m are time constant characterising the delay of insulin and meal effects to plasma glucose concentrations, and $G_g(s)$ is the transfer function from plasma insulin concentration to plasma glucose concentration ($G_g(s) = \frac{1}{(s+p_1)}$ for the model presented in section System Dynamics for Postprandial Glucose Control). Because of the input constraints (insulin infusion rate cannot be negative) and the slow dynamics of the insulin absorption (τ_i), this controller cannot be realized. Analyses of this straightforward model-based controller have been conducted for different meal sizes and shapes, but it has not been assessed clinically [78]. In practice, the feedforward controller is reduced to a simple gain multiplicator, a similar strategy to the open-loop insulin-to-carbohydrate ratio. An illustration of feedback-only performance compared to feedforward-feedback is presented in figure 3–5.

(a)


45g CHO
Insulin infusion
Sensor glucose
Sensor glucose (mmol/L)
Insulin (U/hr)
Time (hrs)
20
18
16
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12
10
8
6
4
2
0
7
6
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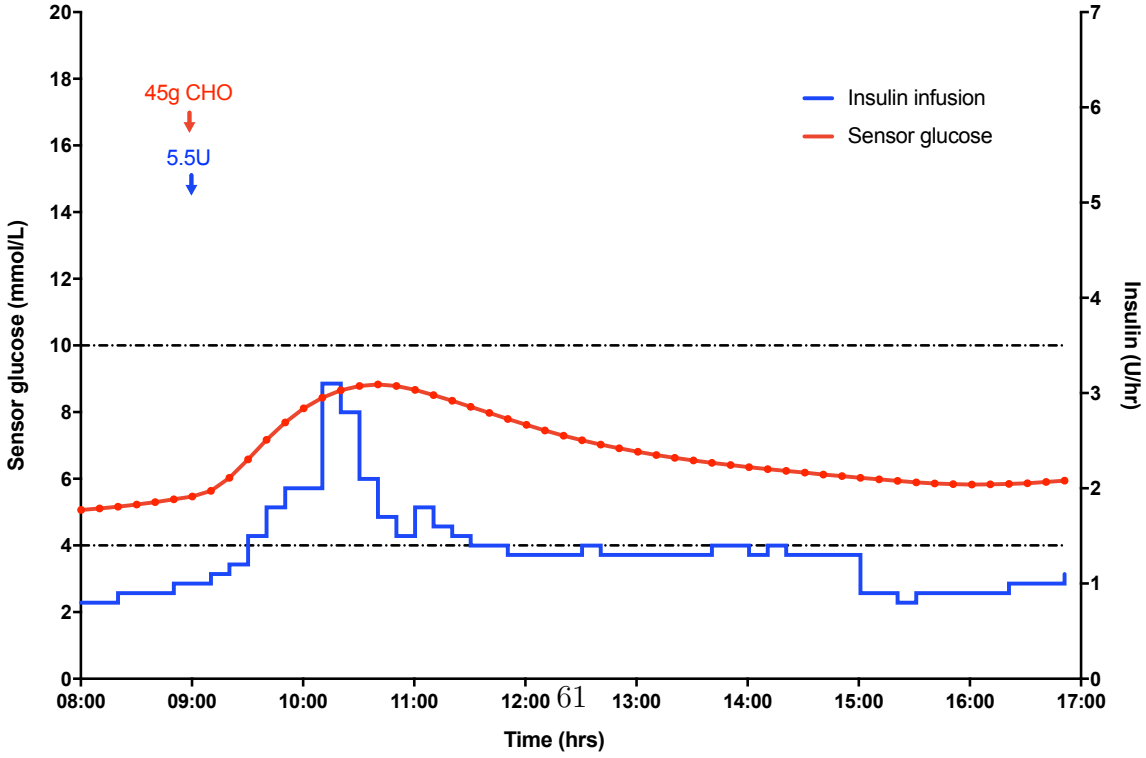
(b)


45g CHO
5.5U
Insulin infusion
Sensor glucose
Sensor glucose (mmol/L)
Insulin (U/hr)
Time (hrs)
20
18
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10
8
6
4
2
0
7
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4
3
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1
0
08:00
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Figure 3–5 *(preceding page)*: Simulation of postprandial glucose control with feedback-only vs feedforward-feedback control. In order to demonstrate and compare the performance of both control strategies, two simple in-silico experiments are conducted on a virtual patient [62] given a breakfast meal at 9 am with a 45g carbohydrate content. A model-predictive controller was used in both experiments. In the feedback-only control experiment (a), the meal information was not provided to the controller. In the feedforward-feedback control experiment (b), a bolus was calculated according to the patient's meal insulin-to-carbohydrate ratio. Although postprandial hypoglycemia has been avoided in both experiments, the increase in glucose level is much higher with the feedback-only controller, leading to hyperglycemia. With current insulin analogs, feedforward-feedback controllers are more effective in maintaining tighter glucose control.

Recent clinical trials assessing a closed-loop glucose controller based on the feedforward-feedback design have shown good results increasing the time in normoglycemia after meal consumption compared to conventional therapy [79, 80, 81, 82, 83]. Despite its success, the need of an estimate of the disturbance, which means patients not forgetting to announce the meal to the artificial pancreas and to accurately count the carbohydrate contents of the meal, remains a limitation of this strategy.

3.5.3 Partial-feedforward-feedback Control

The idea of the partial-feedforward-feedback strategy is based on keeping the meal bolus advantage while relieving the burden of carbohydrate counting. Instead of inputting the exact amount of carbohydrates contained in the meal, an indication of meal size is provided. This strategy provides two advantages; first, the control algorithm is informed that a meal will be eaten soon, which may trigger a change in controller aggressiveness to better handle the expected fast increase in glucose concentration. Second, the quantity of the soon-to-be-ingested carbohydrates may be estimated. Using learning algorithms or by applying empirical standards, a partial insulin bolus may be computed and provided by the control algorithm [84].

The most common approach is to provide a qualitative indication of the size of the ingested meal (regular, large, etc.) to compute an insulin bolus. Both a three-scale and four-scale meal size have been clinically investigated [85, 86]. The amount of the partial insulin bolus may be either computed based on patient body weight [87] or based on the insulin-to-carbohydrate ratio [85, 88]. This design has shown

comparable results with the complete feedforward-feedback approaches and better results compared to feedback-only approaches [64, 84, 85, 87].

Carbohydrate counting is prone to human errors, and this uncertainty does not give the full feedforward strategy a significant advantage over the partial feedforward one. However, partial feedforward approaches still bear the risk of a patient misjudging the meal size or simply forgetting to announce it.

3.6 Postprandial Glucose Control

MPC and PID controllers are the two most common controllers tested in randomized controlled trials [89], and their comparative merits have been debated in the literature [90, 90].In this section, MPC (adaptive and non-adaptive) and PID controllers for postprandial glucose control are discussed.

A large body of literature based on simulation studies also exist but is out of the scope of this article. Controllers tested in only simulations include H∞ -controllers [91], sliding mode controllers [92], neural network controllers [93], LPV controllers [94, 95], robust controllers [96], among others [97, 89].

3.6.1 Meal Control with PID

Proportional-integral-derivative (PID) controllers were among the first algorithms to be tested for the closed-loop control of plasma glucose concentrations [98]. The insulin command U_i is computed from the error in glucose concentration between the measured and reference glucose concentration $e_G(t)$ as

$$U_i(t) = U_{i0}(t) + K_P e_G(t) + K_I \int e_G(t)\, dt + K_D \frac{de_G(t)}{dt} \tag{3.23}$$

where $U_{i0}(t)$ is the basal inulin (insulin needs for maintaining glucose equilibrium under fasting conditions) rate specific to the individual, $e_G(t)$ is the error between the measured and reference glucose concentration, and K_p , K_D , and K_i are the PID gains.

In response to a carbohydrate meal disturbance, most of the control action and aggressiveness comes from the proportional gain K_P . The derivative gain K_D reacts to fast postprandial glucose increase and reduces postprandial hypoglycemia by adding damping to the glucose response. The integral gain K_i is needed to ensure that the target glucose is achieved in steady state [63, 99].

Because of the excessively slow dynamics of the insulin command, simple PID controllers have often induced insulin stacking, which increases the risk of hypoglycemia. Negative insulin feedback, based on an estimation of plasma insulin concentration $I_p(t)$, have been proposed to reduce the aggressiveness of the controller when insulin-on-board is high, thus reducing postprandial hypoglycemia periods [100]. Clinical studies have shown the merit of such an approach on hypoglycemia risk, yet, an overall increase of the mean glucose, especially postprandial, was observed [101, 102]

$$U_i(t) = U_{i0}(t) + (1-\gamma)\left(K_P e_G(t) + K_I \int e_G(t)\,dt + K_D \frac{de_G(t)}{dt}\right) - \gamma I_p(t) \quad (3.24)$$

where γ is a tuned constant, typically equal to 0.5.

3.6.2 Meal Control with MPC

Model predictive control (MPC) has been the most popular approach to control plasma glucose concentrations [89]. This controller provides the control action minimizing an objective function, constrained to a model describing the process evolution. The minimization of the objective function ensures the tracking of desired glucose concentrations expressed as a set-point or a zone [103, 104]. Other constraints on the control action (insulin delivery rate) which expresses physical limitations and reflect required performance (mainly avoiding hypoglycemia) [105]are usually added to the minimization problem. Finally, the use of a process model permits the incorporation of disturbance modeling and patient specific parameters, which is particularly effective for the postprandial glucose control [106].

Different implementations of MPC exists depending on the choice of the model and the objective function [57, 59, 103, 107, 108]. Since the glucoregulatory system may be regarded as an interaction of four subsystems, the following describes the state-space dynamics

$$\frac{d}{dt}X\left(t\right)=\begin{bmatrix} A_g & A_{gq} & 0_{12} & 0_{12} \\ 0_{21} & A_q & A_{iq} & A_{mq} \\ 0_{21} & 0_{22} & A_i & 0_{22} \\ 0_{21} & 0_{22} & 0_{22} & A_m \end{bmatrix} X\left(t\right)+\begin{bmatrix} 0_{11} \\ 0_{21} \\ B_i \\ 0_{21} \end{bmatrix} U_i\left(t\right)+\begin{bmatrix} 0_{11} \\ 0_{21} \\ 0_{21} \\ B_m \end{bmatrix} D_m\left(t\right) \tag{3.25}$$

where U_i is the control action (insulin injection rate), D_m is the disturbance (ingested meal), 0_{nm} is a zero matrix of size $n \times m$ and B_i , B_m A_g , A_{qg} , A_q, A_{iq} , A_{mq} , A_i and A_m denote matrices characterizing the process dynamics. Those matrices are deduced from a linear model derived from the glucoregulatory system of an artificial pancreas user presented previously, and a two-compartmental model of meal-glucose absorption as $X(t) = \begin{bmatrix} G_s(t) & G(t) & P_{EGP}(t) & Q_i(t) & Q_{i_1}(t) & Q_m(t) & Q_{m_1}(t) \end{bmatrix}^{\intercal}$, $A_g = [-k_{sen}]$, $A_{qg} = [k_{sen}]$, $A_q = \begin{bmatrix} -p_1 & 1 \\ 0 & 0 \end{bmatrix}$, $A_{iq} = \begin{bmatrix} -\frac{S_i}{\tau_i} & 0 \\ 0 & 0 \end{bmatrix}$, $A_{mq} = \begin{bmatrix} \frac{1}{V\tau_m} & 0 \\ 0 & 0 \end{bmatrix}$, $A_i = \begin{bmatrix} -\frac{1}{\tau_i} & \frac{1}{\tau_i} \\ 0 & -\frac{1}{\tau_i} \end{bmatrix}$, $A_m = \begin{bmatrix} -\frac{1}{\tau_m} & \frac{1}{\tau_m} \\ 0 & -\frac{1}{\tau_m} \end{bmatrix}$, $B_i = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$ and $B_m = \begin{bmatrix} 0 \\ K_{Bio} \end{bmatrix}$

The controlled quantity $Y(t)$ (plasma glucose concentration) and the measured quantity $Z(t)$ (interstitial glucose concentration) are obtained from $X(t)$ by

$$Y(t) = CX(t) \tag{3.26}$$

$$Z(t) = C_Z X(t) \tag{3.27}$$

where $C = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$ and $C_Z = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$

The objective function penalizes the deviation of model-predicted plasma glucose concentration $Y(t)$ from the targeted plasma glucose concentration $Y_r(t)$ (with emphasis on the terminal time to ensure stability [109]), and the incremental insulin

dose $\delta U_i(t) = U_i(t) - U_{i0}(t)$

$$J_t(\delta U_i(t)) \tag{3.28}$$
$$= \sum_{k=0}^{T-1} \left(\Gamma_y \| \frac{Y(t+k) - Y_r(t+k)}{Y_r(t+k)} \|^2 + \Gamma_u \| \frac{\delta U_i(t+k)}{U_{i0}(t+k)} \|^2 \right) + \Gamma_y^{\intercal} \| \frac{Y(t+T) - Y_r(t+T)}{Y_r(t+T)} \|^2$$

where t is the current discrete time Γ_y , $\Gamma_y^{\intercal}$ and Γ_u are unitless weighting parameters, and T is the time horizon (4 to 5 hours). The optimization problem is solved subject to the model dynamics, the insulin delivery rate limit $U_{i_{Limit}}$, and the limit on the incremental insulin delivery $\delta U_{i_{Limit}}$

$$\begin{aligned} X(t+1) &= A^d X(t) + B_i^{*d} U_i(t) + B_m^{*d} D_m(t) \\ Y(t) &= CX(t) \\ 0 \leq U_i(t+k) &\leq U_{i_{Limit}} \; k = 0 \ldots T-1 \\ |\delta U_i(t+k)| &\leq \delta U_{i_{Limit}} \; k = 0 \ldots T-1 \end{aligned} \tag{3.29}$$

where A^d , B_i^{*d} , and B_m^{*d} are obtained by discretizing the system dynamics above. At the end of each optimization cycle, only the first control action $\delta U_i(t)$ is inputted to the process.

Variants of the objective function may penalize asymmetrically positive and negative variation of the plasma glucose from the reference value, in order to emphasis postprandial hypoglycemia protection [105]. Other forms of the cost function penalize differently the incremental insulin command based on the real-time estimate of insulin-on-board, in order to avoid insulin stacking [110, 111]. In the MPC setup, an accurate model is necessary to ensure optimal dosing; underestimating insulin time-to-peak value can lead to late hypoglycemia because model inaccuracy can lead to insulin overdosing [110].

At every control cycle (5 to 10 min), when a meal information is available, the meal input is provided to the controller in the form of a Dirac delta depending on the carbohydrate content D_m (μ mol/kg). This addition is equivalent to adding D_m to the first meal compartment $Q_{m_1}(t)$

$$Q_{m_1}(t) = Q_{m_1}(t) + K_{Bio} D_{m_{Bolus}} \tag{3.30}$$

Similarly, when a mealtime insulin bolus $U_{i_{Bolus}}$ (units) is delivered to the patient (in a feedforward manner), this information is added as a Dirac delta input to U_i (t). This action is equivalent to increasing the first subcutaneous insulin compartment $Q_{i_1}(t)$

$$Q_{i_1}(t) = Q_{i_1}(t) + U_{i_{Bolus}} \tag{3.31}$$

The new updated state (that is, with meal and bolus information) is used as the initial condition for the MPC optimization problem. By doing so, the controller will consider future glucose and insulin appearances from the meal and bolus, respectively.

The MPC algorithm requires the availability of an internal state of the process $X(t)$. This internal state may be estimated by incorporating glucose measurement $Z(t)$. The state vector is updated using a state estimation technique, such as Kalman filtering, before the next optimization problem is solved. Assume i) a process noise $W(t)$ of zero-mean multivariate Gaussian type with covariance matrix $Q(t)$ and ii) a measurement noise $V(t)$ to be a zero-mean Gaussian white noise with covariance

$R(t)$, the statespace equations can be rewritten as

$$\begin{aligned} X(t) =& A^d X(t-1) + B_i^{*^d} U_i(t-1) + B_m^{*^d} D_m(t-1) + W(t) \\ Z(t) =& C_z X(t) + V(t) \end{aligned} \tag{3.32}$$

The corrected state estimation is obtained by

$$\begin{aligned} X(t|t-1) =& A^d X(t-1|t-1) + B_i^{*^d} U_i(t-1) + B_m^{*^d} D_m(t-1) \\ X(t|t) =& X(t-1|t-1) + K(t)\left(Z(t) - Z(t|t-1)\right) \end{aligned} \tag{3.33}$$

where $X(t|t-1)$ is the state prediction based on the model, $X(t-1|t-1)$ is the state of the system in the previous instant, $Z(t|t-1)$ is the predicted measurement, and $K(t)$ is the Kalman gain. The Kalman gain depends on the choice of $Q(t)$ and $R(t)$, and can be computed using the standard Kalman filtering equations [112]

$$\begin{aligned} P(t|t-1) =& AP(t-1|t-1)A^\intercal + Q(t) \\ K(t) =& P(t|t-1)C_Z^\intercal \left(C_Z P(t|t-1) C_Z^\intercal + R(t)\right)^{-1} \end{aligned} \tag{3.34}$$

where $P(t|t-1)$ is the predicted covariance matrix based on the model, and $P(t-1|t-1)$ is the covariance matrix from the previous instant. The estimate covariance matrix $P(t|t)$ provides an indication of the accuracy of the state estimate. It is obtained from the previous cycle by

$$P(t|t) = P(t|t-1) - K(t) C_Z P(t|t-1) \tag{3.35}$$

When a patient ingests a meal, the diagonal elements corresponding to the meal absorption states in the covariance matrix $Q(t)$ (column 4, row 4 in the state-space

dynamics above) may be increased to indicate uncertainty in the carbohydrate content of the meal. This allows the Kalman filter to improve the estimate of the carbohydrate content using future glucose measurements. Similarly, the process noise characteristics $Q(t)$ may be adjusted in the postprandial period to emphasize uncertainty in the meal absorption profile.

3.6.3 Adaptive Control Applications for Postprandial Glucose

Efficient postprandial glucose control may be improved by the knowledge of meal absorption dynamics (how the disturbance affects the model) and insulin sensitivity (how the controller actions reject the disturbances). Yet, on the one side, meals may be absorbed in different patterns depending on their content and complexity (food glycemic index, fat, and protein) [76]. On the other side, type 1 diabetes patients display a high variability on insulin sensitivity between patients [27, 113, 114]). An adaptive controller may be capable of taking into account these variabilities and providing better performances globally [115].

Interacting multiple model (IMM) filter was used as an indirect adaptive strategy to take into account meal and insulin variabilities [116, 117]. This strategy estimates the filter state using several competing models, run in parallel, and differ in their parameters (different rates of subcutaneous insulin absorption τ_i and rates of carbohydrate absorption profile τ_m). At each instant, every model is assigned a probability, and the filter state is estimated by mixing the model states based on their models' corresponding probabilities. Mathematically, IMM is characterized by the followings three steps:

- The interaction step: The state vector $X_{0j}(k-1|k-1)$ characterizing the model j is mixed with the state vectors of each model $X_i(k-1|k-1)$ (i is the index of the model)

$$X_{0j}(k-1|k-1) = \frac{1}{\sum_i p_{ji}\mu_i(k-1)} \sum_i p_{ij} X_i(k-1|k-1)\,\mu_i(k-1) \quad (3.36)$$

where $\mu_i(k-1)$ is the probability of model i matching the true patient dynamics, and $(p_{ij})_{ij}$ is a Markov transition probability matrix which indicate the probability of the model i transiting to model j.

- The filtering step: For each model, the glucose measurement is incorporated into the state with the use of a filtering technique (such as Kalman filter). This provides a filtered state $X_j(k|k)$ for each model. At the same time, the mixing probability is updated for each model as

$$\mu_j(k) = \frac{1}{c}\Lambda_j(k) \sum_i p_{ji}\mu_i(k-1) \quad (3.37)$$

where $\Lambda_j(k)$ is a likelihood function that characterizes the effort provided by the filter to improve (innovate) the predicted state vector based on the used model [117] and c is a normalizing factor.

- The combination step: The state vector describing best the patient model is a combination of all the state vectors weighted by their respective mixing probabilities

$$X(k|k) = \sum_i X_i(k|k)\,\mu_i(k) \quad (3.38)$$

This filter has been developed [118] and evaluated in a three-month clinical trial [81].

Adaptive generalized predictive controller strategy have also been proposed and evaluated in a series of clinical trials [84, 86, 87]. Another similar adaptive predictive controller is proposed and tested in feasibility clinical experiments [108, 119, 120]. In these controllers, the process takes the generic form of an autoregressive moving average model with exogenous inputs (ARMAX), which is a function of past plasma glucose values, insulin observations, and an exogenous input (representing other process noise and disturbances)[121, 122]. For the glucoregulatory system this model is represented as

$$Y(t) = \sum_{k=1}^{n} \alpha_k Y(t-k) + \sum_{k=0}^{m} \beta_k U_i(t-d-k) + \sum_{k=0}^{p} \gamma_k W(t-k) \tag{3.39}$$

where α_k , β_k , γ_k are system parameters (with $\gamma_0 = 1$), d is characterising the insulin delay action, $Y(t)$ are the history of plasma glucose concentrations, $U_i(t)$ are the history insulin infusion rates, and $W(t)$ are a sequence of independent zero-mean Gaussian variables. The model parameters are estimated with the Recursive Least Square method [123] by introducing the following model regressor form

$$Y(t) = \psi^{\intercal}(t)\,\theta(t) + W(t) \tag{3.40}$$

where the regressor is

$$\psi(t) = [Y(t-1)\ldots Y(t-n)\,U_i(t-d)\ldots U_i(t-d-m)\,W(t-1)\ldots W(t-p)]^{\intercal}$$

, and the parameter vector is $\theta(t) = [\alpha_1 \dots \alpha_n \beta_0 \dots \beta_m \gamma_1 \dots \gamma_p]^\intercal$. The estimated parameter vector $\theta(t)$ is computed recursively by

$$\theta(t) = \theta(t-1) + \frac{P(t-1)\,\psi(t)}{\lambda + \psi^\intercal(t)\,P(t-1)\,\psi(t)} \left(Y(t) - \psi^\intercal(t)\,\theta(t-1)\right) \tag{3.41}$$

$$P(t) = \frac{1}{\lambda}\left(P(t-1) - \frac{P(t-1)\,\psi(t)\,\psi^\intercal(t)\,P(t-1)}{\lambda + \psi^\intercal(t)\,P(t-1)\,\psi(t)}\right) \tag{3.42}$$

where $P(t)$ is a covariance matrix of the parameter vector, and λ is the forgetting factor. The online parameter vector estimation is combined with a generalized predictive control (GPC) algorithm (indirect adaptive control strategy) [124].

3.7 Other Perspectives for Postprandial Glucose Control

Beside closed-loop algorithms, other techniques were proposed to control postprandial glucose concentrations.

3.7.1 Meal Detection and Meal Size Estimation

Meal time detection and a meal size estimation algorithm may potentially improve the performance of the closed-loop controller at mealtime. In the case of a feedforward-based design, this algorithm may be used to detect an unannounced or underestimated meal, as commonly experienced by adolescents [33, 34, 35, 36]. For feedback-only design, meal detection adds a means to adjust internal gains for tighter postprandial glycemic control. Several groups developed algorithms for meal detection and meal size estimation [125, 126, 127]. These algorithms may be divided into data-driven and data-model-driven algorithms.

Early meal detection algorithms only used real-time glucose measurement to detect abrupt changes, interpreted as meal responses. The first and second derivatives

of the glucose signal may be estimated either by numerically filtering data or by a white noise driven Kalman filter [127, 128]. Using those values heuristic rules have been proposed to detect unannounced meals [129] within 30-60 minutes after meal ingestion. A Finite Impulse Response filter may be used to estimate the meal size by deconvoluting glucose measurements [129]. This strategy is prone to measurement error and patient variability. Yet, a voting scheme combining different meal detection algorithms may be utilized to increase its robustness and to reduce the risk of false positives [127].

The second category uses both a pre-defined meal digestion model and filtered glucose measurement for meal evaluation. A meal detection method based on a multiple probabilistic model of meals has been developed and tested in inpatient clinical trial with multiple large unannounced meals [68, 130]. This algorithm increases the probability of a meal by matching the glucose profile with possible shapes of glucose excursion after meal consumption [131]. Recent approaches consider meal detection as a fault detection problem in a statistical signal processing framework [132, 133]. The null hypothesis "meal is consumed but not announced" is evaluated by either a parameter-invariant approach [133] or by testing the optimality of Kalman filter (the innovation sequence is not a white noise) [132]. This hypothesis testing approach showed a high success rate and small false alarm rate compared to other approaches; however, it is only tested on simulation [132]. Unscented Kalman Filtering technique

(a powerful tool for state estimation of nonlinear systems [134]) has also been recently used to estimate the rate of ingested glucose $D_m(t)$ as part of an augmented state $X^*(t) = \begin{bmatrix} X(t) \\ D_m(t) \end{bmatrix}$ [135].

3.7.2 Machine Learning Algorithms for Postprandial Glucose Control

The increase in plasma glucose concentrations after a meal is highly variable between individuals and can vary within the same individual consuming the same meal at different times. Understanding the various factors contributing to this observed inter and intra-variability in dietary responses is desirable in algorithms that aim to predict accurate postprandial glucose responses. Machine learning approaches promise to provide improved, individualized predictions.

A comprehensive database of postprandial studies, called DISRUPT, has been produced in order to provide insights into the physiological factors that influence postprandial glucose responses [136]. The database includes postprandial measurements of insulin and glucose in addition to subject attributes of age, gender, genotype, menopausal status, body mass index, blood pressure, and a fasting biochemical profile for recorded glucose. The database allows for the analysis of the postprandial glucose responses using conventional statistical techniques to facilitate the development of accurate predictive algorithms.

A prediction algorithm based on machine learning methods was developed to predict postprandial glucose readings of elderly patients [137]. A learning component used data to relate patient meals with observed glucose readings before and after

meal consumption. The prediction model of the machine-learning algorithm relied on linear regression methods. Although the algorithm's prediction error value was lower than 20% in 73% of all tests performed on healthy subjects, additional tests in diabetes patients are necessary to assess the prediction performance of the system under greater variability.

Algorithms predicting postprandial glucose concentrations need to model the effect of different kinds of foods on glucose concentrations. Rice and potatoes, for example, produce high responses on average compared to the low responses produced by dark chocolate [138]. In addition to modeling this meal variability and composition, algorithms need to include physiological information to provide improved, personalized predictions. A machine learning algorithm has been proposed to integrate blood parameters, dietary habits, anthropometric measurements, physical activity, and gut microbiota to accurately predict the postprandial glucose concentrations [139]. The algorithm was trained in a cohort of 800 individuals with type 2 diabetes by using leave-one-out cross-validation, and validated against an independent cohort of 100 volunteers. By analyzing real-life complex meals that were consumed at different times during the day and in varying proximity to previous meals, physical activity, and sleep, the algorithm integrated the multi-dimensional clinical and microbiome patient data to accurately predict the personalized postprandial glucose responses using stochastic gradient boosting regression. Moreover, the algorithm was used to construct personalized dietary interventions that induced a lower postprandial glucose concentrations.

Machine learning algorithms adopting data-driven approaches to infer the major factors that are predictive of postprandial glucose may outperform current model-based predictions [140]. "Big Data" strategies may be important to model the complex individual response patterns of diabetes patients and support personalized diets into the clinical decision-making scheme to improve glucose control.

3.8 Future Work

With current insulin analogs (Aspart, Lyspro, Glulisine), artificial pancreas systems cannot prevent postprandial hyperglycemia, whether feedforward or feedback control configuration is used. This postprandial hyperglycemia is the main reason that patients using an artificial pancreas still spend approximately 8 hours per day (on average) in hyperglycemia [12]. More advanced controllers alone will unlikely resolve this issue, but the combination of non-insulin drugs and advanced controllers might.

Pramlintide is a hormone that delays gastric emptying (modifying the disturbance dynamics). It can be co-delivered with insulin in a closed-loop manner (multi-input control) in order to better control glucose concentrations. Pramlintide has been studied when delivered at meals time (in an open-loop manner) in addition to insulin-alone closed-loop delivery [72, 141, 142, 143], but has not been assessed when delivered in closed-loop manner. SGLT2i is a class of medications that increases the kidney filtering rate of high glucose concentrations (modifying systems dynamics), and that may be combined with advanced controllers to develop efficient feedback-only controllers that remove the burden of carbohydrate counting from the patients.

Combining SGLT2i with closed-loop systems remains an uncharted territory. Other non-insulin drugs than pramlintide and SGLT2i also exist [144].

During long-term use of the artificial pancreas, patients' insulin needs will change with time (over weeks or months).A sub-optimal insulin-to-carbohydrate ratio is equivalent to misestimating the carbohydrate content of the ingested meals, and may degrade glucose control, although closed-loop systems might be less affected by this than open-loop therapy [145, 145]. Filtering algorithms that estimate optimized insulin-to-carbohydrate ratios (using data over several days) during closed-loop operation would likely improve glucose control. Limited work has been done in this area [87, 146].

3.9 Conclusion

The artificial pancreas is a closed-loop system for glucose regulation intended for type 1 diabetes. Meal consumption is a major disturbance of the glucoregulatory system. A feedback-only approach based on the interstitial glucose measurement is a challenging task, mainly because of the long delays in insulin absorption. Combining the feedback controller with minimal feedforward disturbance information is an approach that trades off the patient convenience and the controller efficiency on postprandial regulation.

Model predictive controllers represent the forefront of current research. Incorporating meal information, bolus information, input constraints, and the model dynamics permit to bypass the insulin slow absorption in order to prevent postprandial late hypoglycemia. Meal detection may mitigate the risks of insulin bolus omission

while learning algorithms may optimize the prediction capabilities of the artificial pancreas.

3.10 Sidebar: The Relative Effect of Time-to-peak of Insulin Action and Time-to-peak of Meal Absorption

Assuming a first-order glucoregulatory model, the change in glucose concentrations can be represented in the Laplace domain as follows

$$s\delta Q_g(s) = P_{EGP}(s) - \frac{S_i}{\tau_i} Q_{ibasal}(s) + U_m(s) - \frac{S_i}{\tau_i} Q_{ibolus}(s) \tag{3.43}$$

where Q_g is the glucose mass in the plasma, P_{EGP} is the rate of endogenous glucose production, U_m is the rate of glucose appearance in the plasma due meal ingestion, Q_{ibasal} and Q_{ibolus} are the appearance of insulin in the plasma from basal and bolus delivery, respectively, and S_i and τ_i are constant representing the insulin sensitivity and time-to-peak of insulin action, respectively [52, 51].

In the postprandial period, the contributions of endogenous glucose production and basal insulin are small in comparison to meal-related glucose appearance and insulin boluses contributions. Therefore, glucose concentrations can be approximated by

$$s\delta Q_g(s) = U_m(s) - \frac{S_i}{\tau_i} Q_{ibolus}(s) \tag{3.44}$$

By using a two-compartmental model of subcutaneous insulin delivery and glucose absorption rate, glucose concentrations can be approximated by

$$s\delta Q_g(s) = \frac{K_m}{(1+\tau_m s)^2} Q_{CHO}\delta(s) - \frac{S_i}{(1+\tau_i s)^2} U_b\delta(s) \tag{3.45}$$

where $K_m = 10^3 \frac{K_{Bio}}{(wM_{CHO})}$ (K_{Bio} is carbohydrates bioavailability in the meal, w is the patient weight and M_{CHO} is glucose molar mass), $Q_{CHO}$is the quantity of consumed carbohydrates and U_b is the insulin bolus. A transformation in the time domain results in

$$\delta Q_g(t) = U_b S_i \left(\left(1 + \frac{t}{\tau_i} \right) e^{-\frac{t}{\tau_i}} - 1 \right) - Q_{CHO} K_m \left(\left(1 + \frac{t}{\tau_m} \right) e^{-\frac{t}{\tau_m}} - 1 \right) \quad (3.46)$$

This approximate model compares well to the Hovorka's model [52] (Figure 3–6), but benefits from allowing analytical analysis. For the postprandial glucose levels to come back to the preprandial levels ($\lim_{t\to\infty} \delta Q_g(t) = 0$), a sufficient and necessary condition for the bolus amount is

$$U_b = \frac{Q_{CHO} K_m}{S_i} \quad (3.47)$$

With this matching bolus, the maximum glucose excursion can be calculated as

$$\delta Q_{g_{max}} = K_m Q_{CHO} \left(\frac{1}{\alpha} - \alpha - 2\ln(\alpha) \right) e^{-\frac{\alpha+1}{\alpha-1}\ln\alpha} \quad (3.48)$$

where $\alpha = \frac{\tau_m}{\tau_i}$ is the ratio between the time-to-peak of meal absorption and time-to-peak of insulin absorption. This equation suggests that the ratio α between the times-to-peaks of meal and insulin absorptions determines postprandial glucose excursions. Moreover, the size of the meal (carbohydrate content) modulate this effect.

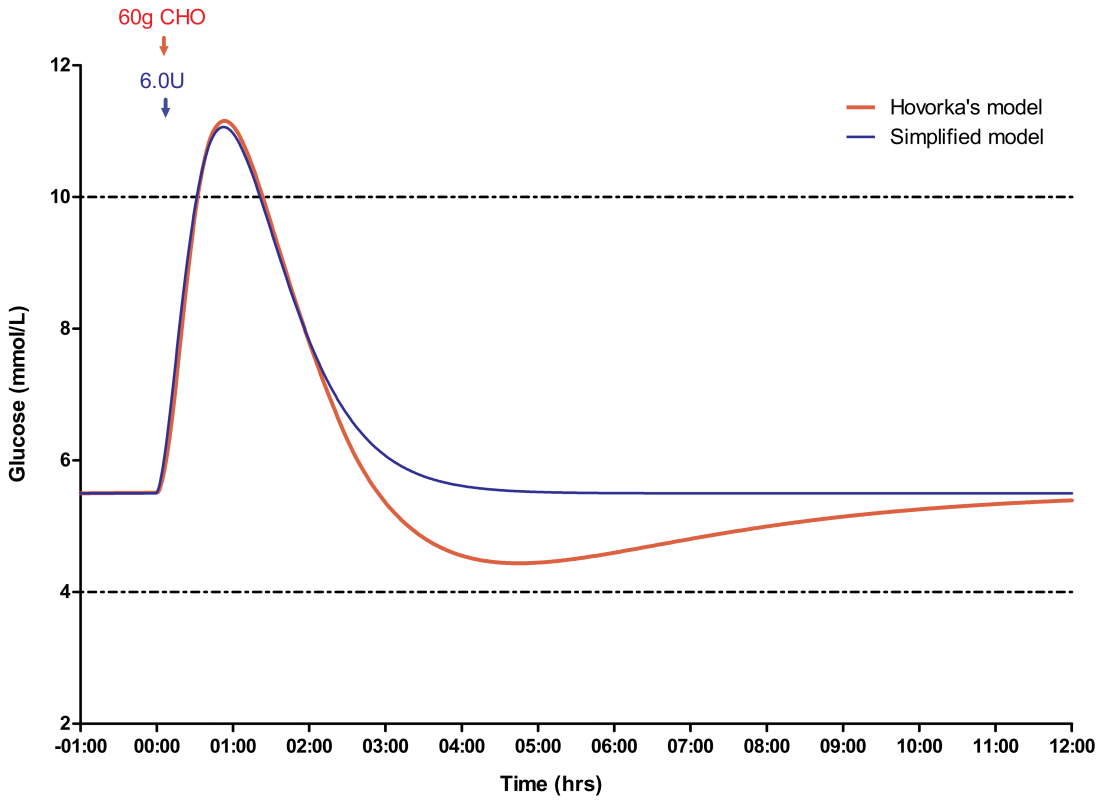

Figure 3–6: Comparison of postprandial glucose peak between the Hovorka's model and the proposed simplified model. A virtual patient with weight 45 kg (an adolescent) is receiving a constant basal insulin to keep its glucose level at 5.5 mmol/L. At time 0 the virtual patient ingests 60g of carbohydrates and delivers a bolus of 6.0U of insulin. The two plot superpose the Hovorka's model response and the simplified model response. This graph shows that immediately after meal consumption the simplified model compares well to the complete Hovorka's model. In addition, this comparison shows that the simplified model may be used to estimate the maximum peak of glucose after meal ingestion.

This result indicates that faster insulins or drugs that slows gastric emptying (for example, pramlintide) would improve glucose control. Figure 3–7 plots post-prandial glucose peaks against the ratio αbetween the times-to-peaks of meal and insulin absorptions, for different meal sizes.

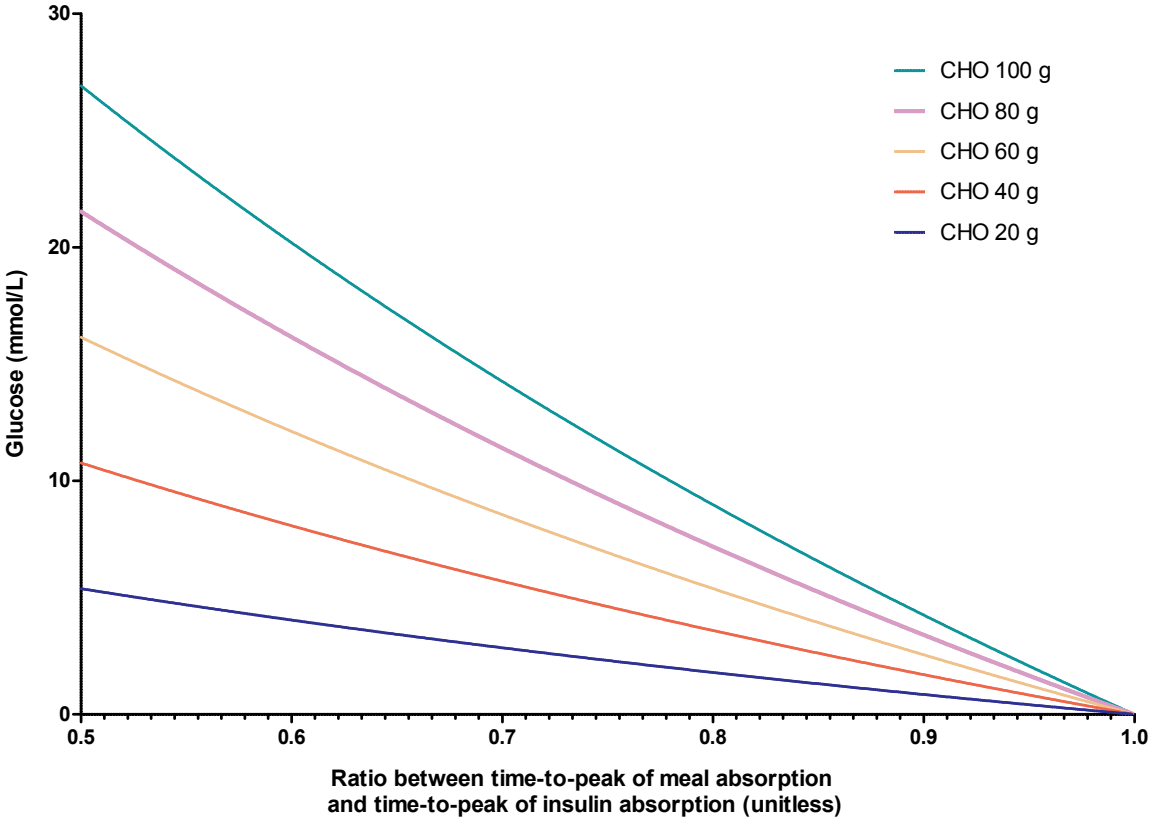

Figure 3–7: A plot of the maximum glucose peak after ingestion of different carbohydrate quantities as a function of the ratio between time-to-peak of meal absorption τ_m and time-to-peak of insulin absorption τ_i. This graph shows that, for instance, following a 60g meal the maximum peak of glucose is 5.4 mmol/L for a ratio $\alpha = \dfrac{\tau_m}{\tau_i} = 0.8$. Increasing the ratio to 0.9 (by slowing the meal digestion or by providing a faster acting insulin) may result on decreasing the postprandial glucose peak by 46% to 2.5 mmol/L.

3.11 References

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CHAPTER 4

An Unannounced Meal Detection Module for Artificial Pancreas Control Systems

4.1 Preface

In this chapter, a novel unannounced meal detection module for artificial pancreas systems is presented. This is a model-based detection algorithm utilizing a linear Kalman filter and maximum likelihood approach for patients' state and parameter estimation. A test statistic is derived to distinguish when a meal is consumed. This module was integrated into an artificial pancreas system then evaluated using simulations. Clinical data from four participants was used to show proof of concept.

4.1.1 Authors Contributions to the Manuscript

The author (Anas El Fathi) was the primary responsible for the development of the methods, interpretation of the results, and witting the manuscript. Ahmad Haidar and Benoit Boulet supervised the theoretical development. Laurent Legault supervised the conduct of the clinical study from which the data was obtained. Emilie Palisaitis coordinated the clinical study from which the data was obtained. Ahmad Haidar and Benoit Boulet provided editorial input in writing the manuscript, and provided overall supervision. All authors critically reviewed the manuscript.

An Unannounced Meal Detection Module for Artificial Pancreas Control Systems

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4.2 Abstract

The emergence of real-time glucose sensors has prompted the development of closed-loop insulin delivery systems for type 1 diabetes patients, termed the artificial pancreas. The existing closed-loop systems rely on the user's input to provide meal insulin boluses. However, patients, particularly adolescents, sometimes forget to announce consumed meals to the system. The performance of closed-loop systems after an unannounced meal may be improved with the addition of a meal detection module to the closed-loop system. We have developed a novel meal detection algorithm that detects unannounced meals using glucose measurements and insulin data. The model-based detection algorithm continually estimates an internal patient state using a linear Kalman filter. A generalized likelihood ratio test (GLRT)

statistic is computed to evaluate the consistency of the Kalman filter under the null hypothesis that all consumed meals have been announced. A threshold criterion is applied on the GLRT to distinguish if the observed glucose increase is due to an unannounced meal. Simulation results, based on nonlinear time-varying virtual patients and noisy glucose measurements, show a sensitivity of 93.23% and a false positive rate of 4.17%. We present clinical results from 11 adolescents who underwent a three-way randomized trial comparing (i) conventional pump therapy (OL), (ii) closed-loop insulin delivery (CL), and (iii) closed-loop insulin delivery with our meal detection algorithm (CL+MD) in controlling post-meal glucose levels after a meal without a bolus. Compared to OL, CL+MD decreased incremental area under the curve from the start of lunch to 240 minutes post-lunch from 24.1±9.5 h.mmol/L to 15.4±8.0 h.mmol/L (p=0.03). The CL alone did not change incremental area under the curve (19.6±10.4 h.mmol/L) compared to CSII (p=0.19). The CL+MD reduced time spent above 10 mmol/L after the missed bolus by -21.6%[-39.4 – -3.8] compared to OL (58±26.6% vs. 79.6±27.5%, p=0.02). The mean meal detection time was 41.8±16 minutes after meal consumption.

4.3 Introduction

In healthy individuals, glucose concentration is tightly regulated by the action of hormones secreted by the pancreas, primarily insulin. In Type 1 diabetes (T1D), insulin secretion is lost due to the autoimmune destruction of the pancreatic beta cells [1]. T1D is currently treated with life-long external insulin therapy. Sustained elevation of glucose levels (hyperglycemia) leads to long-term complications such

as heart disease, blindness, kidney failure, and lower-extremity amputations. Furthermore, low glucose levels (hypoglycemia) may lead to anxiety, nausea, confusion, blurred vision, and difficulty in speaking [2].

The emergence of real-time glucose sensors has prompted the development of closed-loop (CL) insulin delivery systems for T1D patients, termed the artificial pancreas (AP) [3]. In the AP, a control algorithm adjusts the insulin infusion rate based on glucose sensor readings [4]. The existing closed-loop systems rely on the user's prompt to provide meal insulin bolus. Yet, there is little understanding of the safety and efficacy of closed-loop delivery in controlling glucose levels after a missed meal bolus [5].

In conventional insulin therapy, a primary factor for poor glucose control in adolescents is the omission of insulin bolus at mealtimes. It has been observed that 65% of adolescents missed one or more mealtime bolus per week [6], which was associated with a significantly higher HbA1c (a biomarker correlated with mean blood glucose) compared to adolescents that missed less than one bolus per week (8.8% and 8.0% respectively) [7]. Another study observed that over a third of adolescents missed more than 15% of their required boluses [8]. Similarly to conventional insulin therapy, the performance of CL insulin delivery may also be affected after a missed bolus. The addition of a meal detection module which will detect an unannounced meal and signal the infusion of more insulin may improve the performance of the AP.

In the AP system when an unannounced meal is consumed, the closed-loop feedback mechanism reacts to glucose level changes by altering the pump's insulin basal

rate. Generally, a significant amount of insulin is needed to cover the glucose increase from meals, up to 20% of the patient total daily insulin dose in some cases [9]. As a result, without delivering an insulin bolus, the AP is unable of providing the needed amount of insulin in a short period of time. Thus, hyperglycemic events with unwanted high glucose levels become unavoidable [10]. Furthermore, if the feedback reacts aggressively by infusing a large amount of insulin in an attempt to prevent glucose from further increasing, then late post-meal hypoglycemia will occur due to the slow absorption of insulin delivery (since the delivered insulin continues to act beyond meal absorption) [11]. A distinct strategy is needed to mitigate hyperglycemia and hypoglycemia after a missed bolus.

Several methods have been reported in the literature for mealtime detection and meal size estimation. Without loss of generality, these methods may be divided into data-based and model-based algorithms.

The data-based algorithms rely on only real-time glucose measurement to detect abrupt changes, interpreted as meal responses. For instance, Lee et al. proposed an algorithm based on the first and second derivatives of the glucose signal and heuristic rules to detect unannounced meals within 30-60 minutes after meal ingestion [12]. Dassau et al. designed a four-way voting meal detection algorithm consisting of four different ways to compute the glucose rate of change to reduce the risk of false positives [13]. Samadi et al. proposed a fuzzy system which estimates the size of the meal using a qualitative representation of the filtered glucose sensor signal [14]. Still, data-based strategies do not consider delivered insulin and known meals

while model-based algorithms use meal and insulin absorption models alongside glucose measurements. Cameron et al. introduced a meal detection method based on multiple probabilistic meal models. This algorithm was tested in a clinical setting with unannounced meals [10]. Turksoy et al. employed an Unscented Kalman Filter (UKF) to estimate the rate of ingested glucose as part of a nonlinear model, the proposed algorithm was evaluated with clinical data [15]. Ramkissoon et al. proposed a method based on a cross-covariance criterion comparing a disturbance term estimated with a UKF and measured glucose [16]. Xie et al proposed a variable state dimension approach where a Kalman filter (KF) switches its operation between two models to detect meals and estimate their sizes [17]. Weimer et al. used a physiological parameter-invariant detector based on the confidence level of the occurrence of a meal [18].

In this paper, we describe a novel adaptive model-based meal detection algorithm. First, parameters of a linear glucoregulatory model are adapted to the observed glucose measurements. Second, the consistency of a KF is used to assess if the measurements are well explained by the model and known system inputs. Finally, a statistical hypothesis test decides if the observed glucose measurements are due to the patient consuming an unannounced meal to the system. Simulation and preliminary clinical results are presented to verify the efficacy and safety of the algorithm.

4.4 Methods

4.4.1 Kalman Filter and Consistency

A standard linear KF is represented by the following

$$
\begin{aligned}
X_{n|n-1} &= AX_{n-1} + BU_{n-1} \\
P_{n|n-1} &= AP_{n-1}A^T + Q \\
S_n &= CP_{n|n-1}C^T + R \\
K_n &= P_{n|n-1}C^T S_n^{-1} \\
X_n &= X_{n|n-1} + K_n \left(z_n - CX_{n|n-1}\right) \\
P_n &= P_{n|n-1} - K_n C P_{n|n-1}
\end{aligned}
\tag{4.1}
$$

where (A, B, C) is a set of state matrix, input matrix, and output matrix, X is the state estimate with covariance matrix P , Q and R are process and measurement noises covariance matrices, and K_n is the Kalman gain.

The innovation ν_n is defined as the difference between the measurement y_n and the predicted measurement form the model $CX_{n|n-1}$

$$
\nu_n = z_n - CX_{n|n-1} \tag{4.2}
$$

It follows that S_n is the covariance of the innovation ν_n .

A KF is said to be consistent when the probability distribution function of the true state X_n is Gaussian with mean X_n and covariance P_n [19]. Consequently, KF is consistent when the innovation sequence $\{\nu_1, \ldots, \nu_n\}$ is independent and identically distributed (i.i.d.) and follows a zero-mean Gaussian distribution with covariance S_n [19]. The consistency of a KF follows from the hypothesis that the process and measurement noises are i.i.d. zero-mean Gaussian with known covariance matrices

Q, and R. A change in the process noise, for instance, an external disturbance, may cause the KF to become inconsistent.

4.4.2 A Consistent KF for the Glucoregulatory System

An unannounced meal for the AP system may be considered as an external disturbance to the system. Under ideal conditions (linear system and Gaussian distributions), this causes the KF to become inconsistent; however, since the glucoregulatory system of a T1D patient using an AP is nonlinear and time-varying, a linear KF may not be the best choice. In fact, other nonlinear filters such as UKF have been used in the literature [15, 16]. Nevertheless, it is possible to roughly describe the dynamics of the glucoregulatory system by a linear time-invariant model [20]. Such a model can be built by linearizing the Bergman model [21]. The internal state of such a dynamical system may be represented by the quantities:

- The amount of subcutaneous insulin delivered,
- The concentration of plasma insulin,
- The amount of digested meals,
- The rate of glucose appearance from meals,
- The glucose plasma concentration,
- The interstitial glucose concentration.

The model parameters should reflect the T1D patients inter and intra-variability to provide accurate state estimation. This can be achieved by adapting some of these model parameters.

Let X_{n-N} be a known state at time $n-N$. A sequence of state propagations $\underline{X}_n = \{X_{n-N}, \ldots, X_{n-1}\}$ can be deterministically obtained by using a model with parameters p_n state matrices $(A_{p_n}, B_{p_n}, C_{p_n})$ and known insulin infusions and consumed meals $\underline{U}_n = \{U_{n-N}, \ldots, U_{n-1}\}$ A maximum likelihood estimator of the set of parameters p_n describing best the last N glucose measurements $\underline{Z}_n = \{z_{n-N+1}, \ldots, z_n\}$ is obtained by

$$p_n \in \arg\max \mathbb{P}\left(\underline{Z}_n | \underline{X}_n, \underline{U}_n, p_n\right) \tag{4.3}$$

In general, an informed a priori distribution $\mathbb{P}\left(p_n\right)$ of the set of parameters p_n may be obtained from specific characteristics of the patient and common knowledge, for instance, their total daily dose can infer about the patient sensitivity to insulin. The maximum a posteriori estimator of p_n is obtained by

$$p_n \in \arg\max \mathbb{P}\left(\underline{Z}_n | \underline{X}_n, \underline{U}_n, p_n\right) \mathbb{P}\left(p_n\right) \tag{4.4}$$

Assuming that the measurements are mutually conditionally independent when conditioned on their corresponding state and input, we have

$$\mathbb{P}\left(\underline{Z}_n | \underline{X}_n, \underline{U}_n, p_n\right) \sim \prod_{k=n-N+1}^{n} \mathbb{P}\left(z_k | X_{k-1}, U_{k-1}, p_n\right) \tag{4.5}$$

Assuming a zero-mean Gaussian measurement noise with constant covariance r^2 , we can write for $k \in [n-N, n]$

$$\mathbb{P}\left(z_k | X_{k-1}, U_{k-1}, p_n\right) \sim \exp \frac{-1}{2r^2} \left(z_k - C_{p_n}\left(A_{p_n} X_{k-1} + B_{p_n} U_{k-1}\right)\right)^2 \tag{4.6}$$

Maximum a posteriori estimation is employed to adjust the patient parameters. Then a KF routine on the glucose data using the state X_{n-N} the measurements $\underline{Z}_n$ and inputs $\underline{U}_n$ is run. By adjusting the patient parameters to fit the most recent observed glucose trend, the KF filter innovation (and the innovation covariance) is decreased unless it is hard to justify the glucose trend with the known system inputs and outputs. Large innovation values suggest the presence of external disturbances to the system, or that the measured glucose from the sensor is faulty, hence, it is not enough to rely solely on the innovation to flag the presence of unannounced meal.

4.4.3 Meal Detection and Size Estimation

A KF routine is run from time $n - N$ to n using the set of parameters p_n , glucose measurements $\underline{Z}_n$ insulin infusions and consumed meals $\underline{U}_n$ and the patient state X_{n-N} (X_{n-N} can either be the initial state or a previously estimated state). The meal input channel in the process covariance matrix Q is chosen to assume small uncertainties on the inputted meals. This means any other unknown external meal input to the T1D patient will cause the KF to be inconsistent. A hypothesis test is constructed to determine if the inconsistency of the KF is due to an external meal. We consider the two hypotheses (M is the meal detection window size):

- H_0 : No unannounced meal was consumed in the last M iterations (KF is consistent).
- H_1 : A meal of size m was consumed without informing the system at time $p \in [n - M, n]$ (KF is inconsistent).

According to the Neyman–Pearson lemma [22], the likelihood-ratio between the null and the alternative hypothesis is the uniformly most powerful test for testing

a simple hypothesis. However, for a complex hypothesis depending on unknown parameters θ (in this case $\theta = (p, m)$ the time and size of the unannounced meal) a generalized likelihood ratio test (GLRT) can be used [23]. If Θ is the parameter space of θ , the two hypotheses shall satisfy: $H_0 : \theta \in \Theta_0$, $H_1 : \theta \in \Theta_1$, $\Theta_0 \cup \Theta_1 = \Theta$, and $\Theta_0 \cap \Theta_1 = \varnothing$

We define Θ by the discrete set

$$\Theta = \{(p, m) \,|p \in [n - M, n] \,, m \in [m_{min}, m_{min} + \Delta m, \ldots, m_{max}]\}$$

where m_{min} , m_{max} are the smallest and largest detectable unannounced meal, and Δm is the minimum detectable difference in unannounced meals. With those definitions $\Theta_0 = \varnothing$ and $\Theta_1 = \Theta$.

The GLRT statistic, denoted by Λ , is written as [23]

$$\Lambda = \frac{\max \mathbb{P}\left(V_\theta | H_0\right)}{\max_{\theta \in \Theta} \mathbb{P}\left(V_\theta | H_1\right)} \tag{4.7}$$

where V_θ is a random variable with a probability distribution function depending on θ . In this case, V_θ is a random variable representing the process of KF innovations $\{\nu_{n-M}, \ldots, \nu_n\}$.

Under the null hypothesis (KF is consistent), we can write

$$\mathbb{P}\left(V_\theta | H_0\right) = \prod_{k=n-M}^{n} \frac{1}{\sqrt{2\pi S_k}} exp\left(-\frac{\nu_k^2}{2S_k}\right) \tag{4.8}$$

Similarly to [24], we show that under the alternative hypothesis $\mathbb{P}\left(V_\theta | H_1\right)$ is stated for $\theta = (p, m)$ as [Appendix 4.8.1]

$$\mathbb{P}\left(V_\theta|H_1\right) = \prod_{k=n-M}^{p} \frac{1}{\sqrt{2\pi S_k}} exp\left(-\frac{\nu_k^2}{2S_k}\right) \prod_{k=p+1}^{n} \frac{1}{\sqrt{2\pi S_k}} exp\left(-\frac{\left(\nu_k - u_k^\theta\right)^2}{2S_k}\right) \quad (4.9)$$

and

$$u_k^\theta = C\left(\prod_{r=p+1}^{k-1} A\left(I - K_r C\right)\right) BU_m, \quad k \in [p+1, n] \quad (4.10)$$

where U_m is a column vector with zeros and the value m in the meal input channel, and I is the identity matrix.

We define $\theta^* = (p^*, m^*) \in argmax\, \mathbb{P}\left(V_{\theta=(p,m)}|H_1\right)$ to be the most probable time and size of the hypothetical unannounced meal. Since the sampling distribution of Λ is non-trivial, we derive another test statistic from Λ as $\lambda = \sum_{k=p^*+1}^{n} \frac{u_k^{\theta^*}}{S_k} v_k$, and show that under the null hypothesis λ follows a zero-mean Gaussian distribution with covariance $\sum_{p^*+1}^{n} \frac{u_k^{\theta^{*2}}}{S_k}$ [Appendix 4.8.2]. Thus, a meal with parameters θ^* is flagged when λ is smaller than a criterion threshold η satisfying $\mathbb{P}\left(\lambda \leq \eta|H_0\right) < \alpha = 0.05$.

4.4.4 Insulin Bolusing Strategy

When a meal is detected, a meal size m^* and time p^* can be deduced as $\theta^* = (p^*, m^*) \in argmax P\left(V_{\theta=(p,m)}|H_1\right)$. With this information we run another KF routine, but this time with the new information about the meal m^* . A new state is obtained that contains a better estimation of the patient state. We call m the estimation of the remaining non-digested meal in the new patient state, for patient safety m is capped to 20g. An insulin bolus u is computed proportional to the remaining meal, patient carbohydrate ratio CR , glucose level G , glucose target

G_{target} , patient-specific correction factor CF and the remaining insulin-on-board (IOB).

$$u = \frac{m}{CR} + \frac{G - G_{target}}{CF} - IOB \tag{4.11}$$

Other safety rules were implemented to limit the risk of overdosing insulin. For example, the meal detection algorithm is inactive for 3 hours after any bolused meal.

4.5 Simulation Validation

We conducted a simulation experiment in the purpose of:

- Computing the sensitivity of the meal detection algorithm, that is the number of detected unannounced meals over the total number of unannounced meals.
- Computing the false alarm rate, that is the number of times the algorithm detects a meal when there was none.
- Evaluating the effects of introducing a meal detection algorithm alongside a traditional closed-loop insulin dosing algorithm on overall glycemic control.

4.5.1 Simulation Setup

The glucoregulatory system of T1D patients is nonlinear and time-varying. To simulate patients' intra- and inter-variability a simulation model presented by Wilinska et al. with time-varying parameters is implemented [25]. To account for variability between patients, model parameters are randomly sampled from a prior distribution. Moreover, the intra-individual variability is accounted for by making some

parameters oscillate periodically (with random frequencies and phases) (TABLE 4–1). The simulation is augmented with a correlated noise in glucose measurements (coefficient of variation 7% and correlation of 80%).

A simulation experiment, referred to as "CL + MD" , using 512 virtual patients randomly sampled from the distribution in (TABLE I) is conducted. The meal detection algorithm is implemented alongside a closed-loop using a model predictive controller (MPC). The simulation experiment (Fig. 4–1) consists of a 13 hours simulation where a virtual patient consumes a breakfast of 40g carbohydrates (CHO) at 7 am, and a lunch at noon consisting of either a 40g, 60g or 80g CHO.

The morning breakfast is entered into the dosing algorithm and a meal-accompanying bolus is given at breakfast. The lunch is given to the virtual patient but not announced to the insulin dosing algorithm. Since we are interested in analyzing the effects of the unannounced meal and any given bolus by the meal detection algorithm, no meal is consumed after the lunch meal. A rescue CHO of 15g is given to the virtual patient when the plasma glucose is below 2.7 mmol/L.

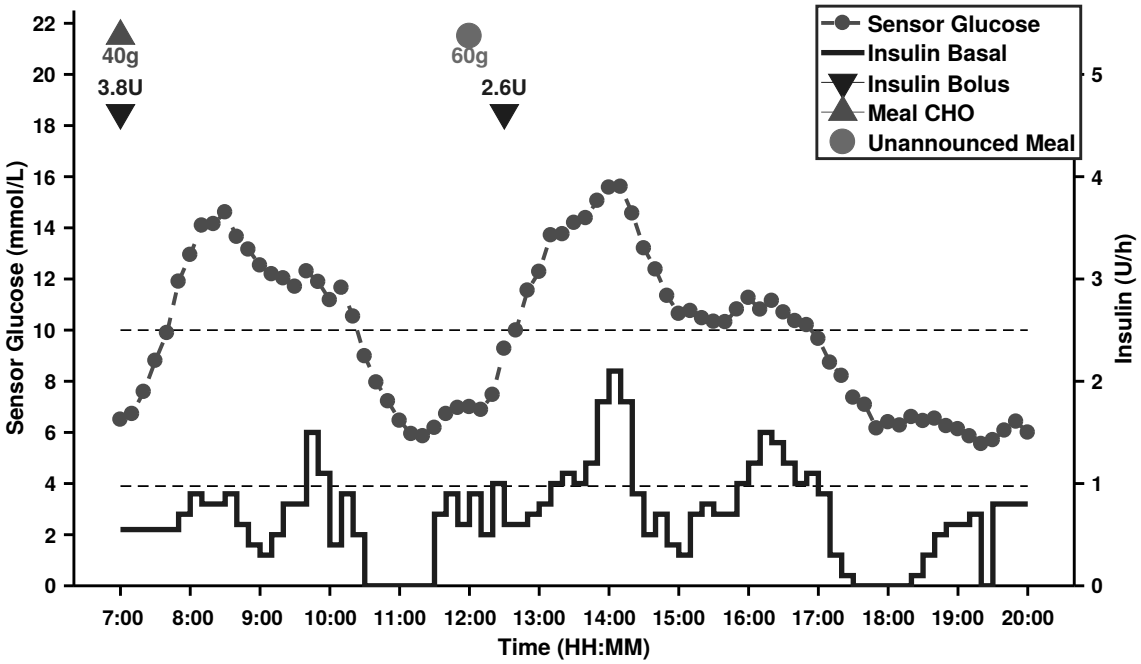

Figure 4–1: A sample simulation, the meal detection algorithm detects an announced meal and provides a bolus of 2U. Due to the model's variability, glucose levels often increase or decrease without an apparent reason, which makes it challenging for the meal detection algorithm.

Table 4–1: Hovorka's model parameters used to sample virtual patients [25]

Parameter description	**Intra- variability**	**Inter- variability**
BW Patient Weight	$BW \sim \mathcal{U}(65, 95)$	Stationary
EGP_0 Endogenous glucose production (μ mol / (kg min))	$\log(EGP_0) \sim \mathcal{N}(\log(17.0), 0.2)$	Oscillatory
F_{01} Noninsulin-dependent glucose flux (μ mol / (kg min))	$\log(F_{01}) \sim \mathcal{N}(\log(11.0), 0.1)$	Oscillatory
k_{12} Transfer rate from non-accessible (1/min)	$\log(k_{12}) \sim \mathcal{N}(\log(0.05), 0.4)$	Oscillatory
k_{a1} Activation rate (1/min)	$\log(k_{a1}) \sim \mathcal{N}(\log(0.0035), 0.4)$	Oscillatory
k_{a2} Activation rate (1/min)	$\log(k_{a2}) \sim \mathcal{N}(\log(0.055), 0.4)$	Oscillatory
k_{a3} Activation rate (1/min)	$\log(k_{a3}) \sim \mathcal{N}(\log(0.025), 0.4)$	Oscillatory
S_t Insulin sensitivity of glucose transport (L / (min mU))	$\log(S_t) \sim \mathcal{N}(\log(18.5e^{-4}), 0.4)$	Oscillatory
S_d Insulin sensitivity of glucose disposal (L / (min mU))	$\log(S_d) \sim \mathcal{N}(\log(5.1e^{-4}), 0.4)$	Oscillatory
S_e Insulin sensitivity of suppression of EGP (L / mU)	$\log(S_e) \sim \mathcal{N}(\log(190e^{-4}), 0.4)$	Oscillatory
k_a Insulin absorption rate (1/min)	$\log(k_a) \sim \mathcal{N}(\log(0.018), 0.3)$	Oscillatory
k_e Insulin elimination rate (1/min)	$\log(k_e) \sim \mathcal{N}(\log(0.12), 0.2)$	Oscillatory
τ_m Time-to-maximum of CHO absorption (min)	$\log\left(\frac{1}{\tau_m}\right) \sim \mathcal{N}\left(\log\left(\frac{1}{40}\right), 0.2\right)$	Meal Specific
V_i Insulin distribution volume (mL/kg)	$\log(V_i) \sim \mathcal{N}(\log(120), 0.1)$	Stationary
V_g Glucose distribution volume (mL/kg).	$\log(V_g) \sim \mathcal{N}(\log(150), 0.1)$	Stationary

4.5.2 Sensitivity and False Alarm

1536 simulations (3 meal sizes x 512 virtual patients) where the lunch meal is not announced to the dosing algorithm were conducted. A true positive (TP) is counted when the meal detection algorithm successfully flags a meal within 120 minutes of the lunch meal. If no meal is flagged within 120 minutes, we judge that any detection will not help reducing hyperglycemia and a false negative (FN) is then counted.

The sensitivity (the ratio of TP over the total number of unannounced meals) of the algorithm for all meals combined (40g, 60g, and 80g) is 93.23 % . Other statistics can be found in TABLE 4–2. Since the detection algorithm is driven by glucose increase, it is expected to observe that the sensitivity of the algorithm decreases with the meal size (the smallest sensitivity being for 40g meals). For unannounced moderate meals of 60g CHO, they are detected 96.29% of the times. In average, the algorithm detects a meal after a jump of glucose values above a threshold of 2.6 ± 1.2 mmol/L, and the detection time of the unannounced meal is around 40 minutes. Those values appear to be reasonable to ascertain the meal effects from the glucose increases. Similar values for detection time were observed in other studies [15-18].

A false positive (FP) is when meal detection is made in absence of an unannounced meal. In the 19968 hours of simulation (13 hours x 1536 simulations), we encountered 64 FP. The majority of FP were flagged after a 40g meal (34 out of 64 false positives) and are mostly due to the late detection of the unannounced meal (after the 120 min threshold), due to small glucose increase. Fig. 4–2 shows a case where an FP detection occurred after a late glucose increase. The delivered bolus was safe and did not cause a hypoglycemia.

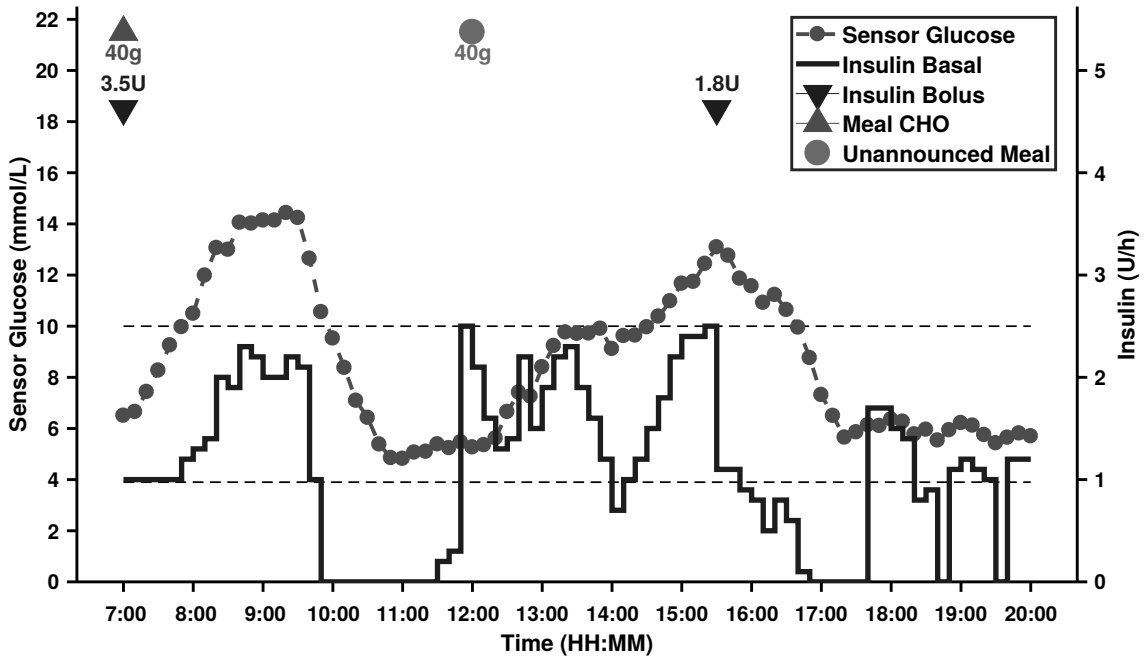

Figure 4–2: Simulation example where an FP occurred. A meal is flagged at 15:30 after 3.5 hours of having the lunch meal. The algorithm provides a bolus of 1.8U and no hypoglycemia is observed for the next 4.5 hours.

Table 4–2: Performance metrics of the meal detection algorithm

Sensitivity TP / (TP + FN)	93.23 %
Meal CHO = 40g	84.77 %
Meal CHO = 60g	96.29 %
Meal CHO = 80g	98.63 %
Number of false positives	64 (4.17 % of 1563)
Meal CHO = 40g	34 (6.64 % of 512)
Meal CHO = 60g	16 (3.13 % of 512)
Meal CHO = 80g	14 (2.73 % of 512)
Detection time	40 [30 - 50] min
Meal CHO = 40g	50 [40 - 60] min
Meal CHO = 60g	40 [30 - 50] min
Meal CHO = 80g	30 [30 - 40] min
Glucose increase at detection time	2.6 ± 1.2 mmol/L
Meal CHO = 40g	2.4 ± 1.5 mmol/L
Meal CHO = 60g	2.7 ± 1.1 mmol/L
Meal CHO = 80g	2.8 ± 1.0 mmol/L
Glucose increase 10 min before detection time	1.4 ± 1.0 mmol/L
Meal CHO = 40g	1.5 ± 1.3 mmol/L
Meal CHO = 60g	1.4 ± 0.9 mmol/L
Meal CHO = 80g	1.2 ± 0.7 mmol/L

4.5.3 Effects on Glycemic Control

Since a classification algorithm is susceptible to flag an FP, it is important to assess the impact of such an event. Also, we need to investigate the benefits, on glucose control, of adding a meal detection algorithm to a closed-loop system. Two

other simulation experiments were thus conducted to answer these two questions. Both experiments had the same structure and same virtual patients as the CL+MD experiment: 1536 simulations (3 meal sizes x 512 virtual patients) were conducted, where a virtual patient uses a closed-loop algorithm and consumes two meals, a breakfast meal and a lunch meal. However, in both experiments, the closed-loop algorithm only consisted of an MPC without a meal detection algorithm.

The first experiment, referred to as "CL + B" , simulates the scenario where the lunch was announced and bolused. The second experiment, referred to as "CL" , simulates the scenario where the lunch was not announced, and the MPC only reacted to the change in glucose levels. The two experiments serve to set base values of expected time spent in hypoglycemia and time spent in hyperglycemia as defined in [26].

Fig. 4–3 shows a significant improvement in time spent in hyperglycemia from 34.9% to 30.4% when a meal detection algorithm is added to the closed-loop algorithm, which validates the efficacy of the proposed meal detection algorithm. TABLE 4–3 compares in more details the incremental area under the curve (AUC) in the three experiments for different meals. In average, the AUC is improved by 19% from CL to CL+MD (baseline is CL+B).

Table 4–3: Incremental AUC for different meals in all experiments

AUC (h mmol/L)	**CL + B**	**CL + MD**	**CL**
CHO = 40g	8.8 ± 4.7	12.1 ± 4.4	13.7 ± 4.9
CHO = 60g	11.7 ± 5.3	17.0 ± 5.0	19.3 ± 5.4
CHO = 80g	14.1 ± 6.0	21.7 ± 5.9	24.4 ± 6.4

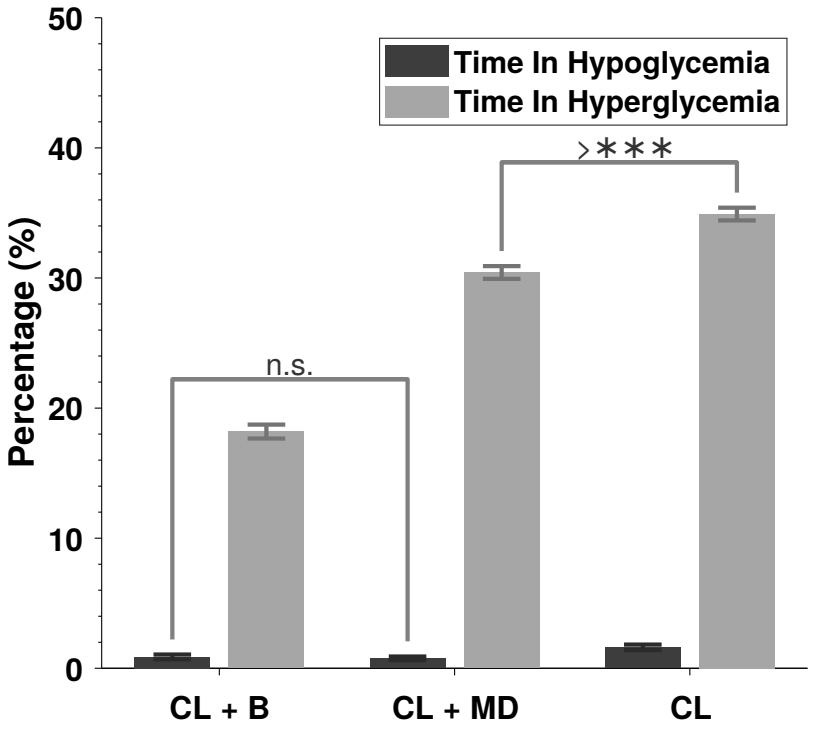

Figure 4–3: Percentage time (8 hours after the lunch meal) spent in hypoglycemia and hyperglycemia for the experiments (n=1536). CL+B: No meal detection and the lunch was announced and bolused. CL+MD: A meal detection algorithm is used, and the lunch was not announced. CL: No meal detection and the lunch was not announced. P value was computed using paired t-test.

The meal detection algorithm (CL+MD) is safe since no increase in hypoglycemia was observed (Fig. 4–3) compared to when the exact bolus was delivered (CL + B). To further investigate the safety of the meal detection algorithm when an FP is flagged, and an unnecessary bolus is delivered, we compared the time spent in hypoglycemia between simulations where an FP was flagged (n=64), and simulations where there was no FP (n=1472). The time spent in hypoglycemia when an FP is flagged (1.1 ± 0.35%) has been found non-significantly (P=0.38) different from the time spent in hypoglycemia (0.76 ± 0.08%) when there was no FP. This suggests that there is no apparent correlation between detecting an FP and causing a hypoglycemia with the developed algorithm.

The safety of the algorithm after an FP results from how we calculate the delivered insulin bolus after a meal is flagged. In fact, the size of the insulin bolus is mainly driven by the term that brings glucose levels back to the target ($\frac{(G - G_{target})}{CF} - IOB$), since the term that covers the detected consumed meal $\frac{m}{CR}$ is capped to a small CHO value (20g in this case). This dosing strategy was found to be the best compromise between: not inducing additional hypoglycemia events and decreasing the time spent in hyperglycemia.

4.6 Clinical Validation

4.6.1 Experiment Description

In this section, we will present preliminary results from an ongoing clinical study that assesses the safety and efficacy of closed-loop insulin delivery with and without a meal detection module and conventional pump therapy after a missed bolus in adolescents with T1D. The study consisted of three randomized inpatient

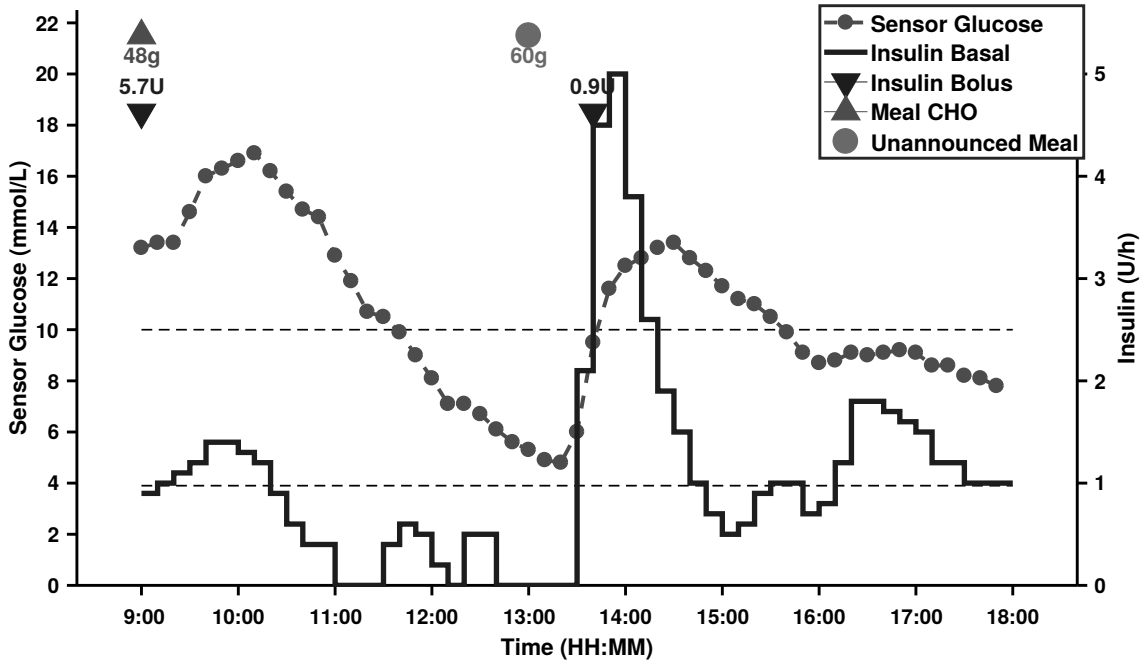

Figure 4–4: Clinical data showing the meal detection algorithm performance. An unannounced meal of 60g was consumed at 13:00. The meal was detected at 13:40, and a bolus of 0.9U was delivered.

interventions. Each patient consumed a breakfast with an insulin bolus. Then, a 60 g lunch was given to the patients without a bolus. Depending on the intervention, insulin doses were based on either a closed-loop algorithm, a closed-loop algorithm with a meal detection module, or the patients' conventional pump therapy. The interventions ended 6 hours after lunch. Fig. 4–4 shows data from an intervention where the meal detection algorithm has been used.

4.6.2 Preliminary Results

For patients' safety, if their glucose levels were sustained above 18 mmol/L, a correction bolus was delivered. When this happens, we assume that glucose levels would have stayed constant until the end of the intervention. Fig. 4–5 shows the

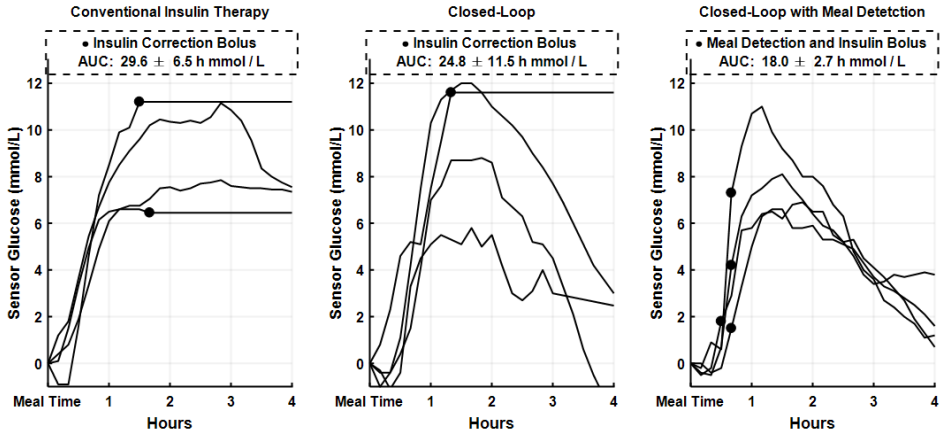

Figure 4–5: Incremental glucose after consuming a meal without bolus for four patients using conventional pump therapy, closed-loop or closed-loop with a meal detection. The diamonds indicate when a correction bolus was delivered either for safety reasons or automatically by the meal detection algorithm.

incremental AUC of four patients who completed all interventions. We observe a trend showing that the meal detection algorithm may reduce the incremental AUC after a missed bolus. In fact, AUC was decreased by 39% with the meal detection algorithm compared to 16% without meal detection (baseline is conventional insulin therapy).

To further investigate the meal detection algorithm, we used 108 hours (4 patients x 3 visits x 9 hours) of clinical data to run the meal detection algorithm offline. All the 12 unannounced meals were detected successfully, and no FP was flagged. The time of meal detection is 35 [30 - 40] minutes. Glucose increase at meal detection time is 2.89 ± 1.72 mmol/L and glucose increase 10 minutes before meal detection is 0.45 ± 0.73 mmol/L.

4.7 Conclusion

We have developed an algorithm which automatically detects unannounced meals consumed by T1D patients using glucose measurements and insulin data. The meal detection algorithm is integrated with an AP and tested in both simulation and a clinical study. Results demonstrate the potential of such an algorithm to improve post-meal glycemic control in the AP. Results of the ongoing clinical study should provide final conclusions about the safety and efficacy of a meal detection algorithm. Moreover, further testing in real life situations, such as successive meals, is warranted.

4.8 Appendix

4.8.1 Alternate Hypothesis Likelihood

When a meal of size m is consumed at time p , the hypothetical correct state predictions X^* of the KF (different from the KF state X) would be $X^*_{p+1|p} = X_{p+1|p} + BU_m$. Thus,

$$\begin{aligned}
X^*_{p+2|p+1} =& AX^*_{p+1} + BU_{p+1} \\
=& A\left(X^*_{p+1|p} + K_{p+1}\left(z_{p+1} - CX^*_{p+1|p}\right)\right) + BU_{p+1} \\
=& A\left(I - K_{p+1}C\right)X^*_{p+1|p} + AK_{p+1}z_{p+1} + BU_{p+1} \\
=& A\left(I - K_{p+1}C\right)\left(X_{p+1|p} + BU_m\right) + AK_{p+1}z_{p+1} + BU_{p+1} \\
=& A\left(X_{p+1|p} + K_{p+1}\left(z_{p+1} - CX_{p+1|p}\right)\right) + BU_{p+1} + A\left(I - K_{p+1}C\right)BU_m \\
=& X_{p+2|p+1} + A\left(I - K_{p+1}C\right)BU_m
\end{aligned} \tag{4.12}$$

By recursion we obtain, for $k \in [p+1, n]$,

$$X^*_{k|k-1} = X_{k|k-1} + C\left(\prod_{r=p+1}^{k-1} A\left(I - K_r C\right)\right) BU_m \tag{4.13}$$

It follows that the true innovation ν^*_k satisfy for $k \in [p+1, n]$

$\nu^*_k = y_k - CX^*_{k|k-1} = \nu_k - C\left(\prod_{r=p+1}^{k-1} A\left(I - K_r C\right)\right) BU_m$

Since ν^*_k follows a zero-mean Gaussian distribution with covariance S_k ν_k will follow a Gaussian distribution with the same covariance and either a zero-mean if $k \in [n-M, p]$ or a mean of $u_k^{\theta=(p,m)} = C\left(\prod_{r=p+1}^{k-1} A\left(I - K_r C\right)\right) BU_m$ if $k \in [p+1, n]$

.

We deduce that

$$\mathbb{P}\left(V_\theta | H_1\right) = \prod_{k=n-M}^{p} \frac{1}{\sqrt{2\pi S_k}} exp\left(-\frac{\nu_k^2}{2S_k}\right) \prod_{k=p+1}^{n} \frac{1}{\sqrt{2\pi S_k}} exp\left(-\frac{\left(\nu_k - u_k^\theta\right)^2}{2S_k}\right) \tag{4.14}$$

4.8.2 A Simple Test Statistic

For $\theta^* = (p^*, m^*) \in argmax P\left(V_\theta | H_1\right)$ we have

$$\begin{aligned}
\log \Lambda =& \log \mathbb{P}\left(V_\theta | H_0\right) - \log \mathbb{P}\left(V_\theta | H_1\right) \\
=& -\frac{1}{2} \sum_{k=n-M}^{n} \frac{\nu_k^2}{S_k} + \frac{1}{2} \sum_{k=n-M}^{p^*} \frac{\nu_k^2}{S_k} + \frac{1}{2} \sum_{k=p^*+1}^{n} \frac{\left(\nu_k - u_k^{\theta^*}\right)^2}{S_k} \\
=& \frac{1}{2} \sum_{k=p^*+1}^{n} \frac{u_k^{\theta^* 2}}{S_k} - \sum_{k=p^*+1}^{n} \frac{u_k^{\theta^*}}{S_k} v_k
\end{aligned} \tag{4.15}$$

Hence, $\sum_{k=p^*+1}^{n} \frac{u_k^{\theta^*}}{S_k} v_k = \frac{1}{2} \sum_{k=p^*+1}^{n} \frac{u_k^{\theta^{*2}}}{S_k} - \log \Lambda$, is a test statistic. Under the null hypothesis, the innovation sequence $\{\nu_{p^*+1}, \ldots, \nu_n\}$ is i.i.d. and follows a zero-mean Gaussian distribution with covariance $\{S_{k^*+1}, \ldots, S_n\}$. Thus, the test statistic $\lambda = \sum_{k=p^*+1}^{n} \frac{u_k^{\theta^*}}{S_k} v_k$ follows a zero-mean Gaussian with covariance $\sum_{k^*+1}^{n} \frac{u_k^{\theta^{*2}}}{S_k}$.

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CHAPTER 5

A Meal Detection Algorithm for the Artificial Pancreas: A Randomized Controlled Clinical Trial in Adolescents with Type 1 Diabetes

5.1 Preface

In this chapter, clinical results from a randomized controlled trial in adolescents with type 1 diabetes are presented to validate the efficacy of the meal detection algorithm presented in chapter 4. In this study, we recruited 11 adolescents with a history of missing to announce a consumed meal. We compared three interventions: closed-loop insulin delivery augmented with a meal detection algorithm, closed-loop insulin delivery, and conventional insulin pump therapy.

5.1.1 Authors Contributions to the Manuscript

The author (Anas El Fathi) was the primary responsible for the development of the methods and interpretation and reporting of the results. Emilie Palisaitis wrote the manuscript and coordinated the clinical study. Laurent Legault and Julia E. von Oettingen supervised the conduct of the clinical trial. Ahmad Haidar provided editorial input in writing the manuscript, and provided overall supervision. All authors critically reviewed the manuscript.

A Meal Detection Algorithm for the Artificial Pancreas: A Randomized Controlled Clinical Trial in Adolescents with Type 1 Diabetes

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5.2 Abstract

Background: Adolescents with type 1 diabetes occasionally forget to bolus at mealtime. We have developed a meal detection algorithm for the artificial pancreas that detects unannounced meals and then delivers an insulin bolus.

Methods: We conducted a randomized crossover trial in 11 adolescents on pump therapy aged 12–18 years with HbA1c$\geq$ 7.5% who have reported missing $\geq$ 1 bolus in the past 6 months. We compared (i) conventional pump therapy (CSII), (ii) our artificial pancreas (AP), and (iii) our artificial pancreas with a meal detection algorithm (AP+MDA) in controlling postprandial glucose levels after a meal without

a bolus. Participants underwent three 9-hour interventions at our research facility or at-home. Each intervention included breakfast with a carbohydrate-matched bolus and lunch without a bolus. During the AP+MDA interventions, the algorithm detects the meal and delivers a bolus.

Results: The median meal detection time by the MDA was 40 [40 – 57.5] minutes after meal consumption. Compared to CSII, AP+MDA decreased incremental area under the curve (iAUC) from the start of lunch to 4 hours post-lunch from 24.1±9.5 h.mmol/L to 15.4±8.0 h.mmol/L (p=0.03). iAUC did not differ between AP+MDA and AP (19.6±10.4 h.mmol/L, p=0.21) or between AP and CSII (p=0.33). The AP+MDA reduced time spent above 10 mmol/L (58.0±26.6%) compared to CSII (79.6±27.5% , p=0.02) and AP alone (74.2±20.6% , p=0.047). Time above 10 mmol/L did not differ between CSII and AP alone (p=0.52).

Conclusions: The artificial pancreas with a meal detection algorithm improved glycemic control after an unannounced meal in adolescents with type 1 diabetes. Free-living studies are needed to evaluate the efficacy of this meal detection algorithm in real-world settings.

5.3 Introduction

Type 1 diabetes, caused by the autoimmune destruction of the pancreas' beta cells, is treated with lifelong insulin-replacement therapy by multiple daily injections or continuous subcutaneous insulin infusion (CSII). A target of glycosylated haemoglobin (HbA1c) less than 7.5% is recommended for adolescents with type 1 diabetes by the American Diabetes Association [1]. However, despite advances in insulin analogs, insulin pumps, and continuous glucose monitoring systems, achieving

ideal glycemic targets is complex and difficult, and only 17% of youth achieve the HbA1c goal [2].

Puberty is a particularly challenging period in the management of glycemic control. As reported in the T1D Exchange registry, the average HbA1c of adolescents aged 15 to 18 year old is around 9.3% [2]. A significant factor for poor glucose control in adolescents is the omission of insulin boluses at mealtimes. In Burdick et al. [3], patient pump data indicated that 65% of adolescents missed one or more mealtime bolus per week, which was associated with a significantly higher HbA1c compared to adolescents that missed less than one bolus per week (8.8% and 8.0% respectively). Similarly, Olinder et al. [4] observed that over a third of adolescents missed more than 15% of bolus doses. O'Connell et al. [5] showed that the omission of prandial boluses in just one day in a two-week period was associated with an increased HbA1c by 0.8%.

Although artificial pancreas systems have demonstrated improved time in target compared to conventional pump therapy [6], current commercial systems and most systems in development still require user input to alert the system of a meal [7, 8, 9]. In AP systems without meal announcements, the algorithm compensates by increasing basal delivery [10]. However, this generally leads to inevitable postprandial hyperglycemia since the algorithm cannot provide sufficient insulin to cover the carbohydrates ingested by only increasing basal insulin [11]. Aggressive postprandial insulin delivery may also lead to late postprandial hypoglycemia [9, 12].

The performance of the artificial pancreas after missed boluses may be improved if the system is augmented with a meal detection algorithm. We have developed a

meal detection algorithm which automatically detects a meal with no announcement and delivers a partial insulin bolus. This study allowed for the assessment of the safety and efficacy of the artificial pancreas with and without our meal detection algorithm compared to conventional pump therapy in regulating postprandial glycemia in a clinical trial with adolescents. This study is registered with ClinicalTrials.gov, number NCT02909829.

5.4 Methods

5.4.1 Study Design

We performed a randomized, three-way, cross-over trial to compare the efficacy of our artificial pancreas with a meal detection algorithm (AP+MDA), artificial pancreas alone (AP), and conventional pump therapy (CSII) in controlling postprandial glucose levels after a meal without a bolus. Adolescents underwent three 9-hour interventions, with their order randomized, at our research facility or at home. Each intervention included breakfast accompanied by a carbohydrate-matched bolus and lunch without a bolus.

5.4.2 Participants

From January 2018 to October 2019, adolescents with type 1 diabetes were recruited from the Montreal Children's Hospital. Inclusion criteria were age between 12 and 18 years old, use of an insulin pump for at least 3 months, with a diagnosis of type 1 diabetes for at least one year, HbA1c between 7.5% and 12% , and self-reported or documented history of at least one missed bolus for meals during the previous 6 months.

5.4.3 Randomization

A block balanced randomization with a block size of six was used to determine the order of the interventions. Randomization was disclosed after the admission visit. Participants and investigators were not blinded to the allocation. Participants were blinded to insulin infusions and sensor glucose data during intervention visits.

5.4.4 Intervention Procedures

Participants chose between two intervention times and locations: from 08h00 to 17h00 or from 09h00 to 18h00 at the research facility or at home. Participants installed a glucose sensor (Dexcom G5®, Dexcom, San Diego, USA) 24–48 hours before each intervention. The glucose sensor was calibrated at the start of each intervention using capillary glucose. Participants' at-home pumps were used. Breakfast (40-50g of carbohydrates) was served at the start of the intervention, and lunch (55-65g of carbohydrates) was served 4 hours after the start of the intervention. Meals were self-selected and standardized between visits of each participant but were different between participants.

5.4.5 Insulin Delivery

During the CSII intervention, participants' usual basal rates were delivered, and the breakfast boluses were calculated using the pump's bolus calculator. During the AP and AP+MDA interventions, every 10 minutes, glucose sensor readings were manually entered into a laptop, which ran our dosing algorithm that calculated new basal insulin delivery. Study personnel delivered basal insulin manually by programming new temporary basal rates every 10 min and manually entering boluses through

the pump. During the AP+MDA intervention, the algorithm will detect the unannounced meal and compute a recommended bolus based on (i) the current glucose level and (ii) the estimated remaining carbohydrate-on-board (up to a maximum of 25g) [13].

During the AP+MDA interventions, false positives and false negatives were recorded. False positives were defined as a detected meal by the algorithm if there was no meal in the last 90 minutes. False negatives were defined as a meal that was consumed without being detected in the next 90 minutes.

5.4.6 Hypoglycemia and Hyperglycemia

Hypoglycemia was treated with 16g of oral carbohydrates if sensor glucose was below 3.3 mmol/L and associated with symptoms, or below 3.0 mmol/L irrespective of symptoms. If glucose levels were not above 3.9 mmol/L 15 minutes after treatment, another 16g of oral carbohydrates were given. A hyperglycemia event was defined when glucose reached 17mmol/L or was above 15mmol/L for 90 minutes. Hyperglycemia events were corrected with an insulin bolus calculated using the participants pump bolus calculator in the CSII intervention or the artificial pancreas bolus calculator in the AP and AP+MDA intervention. Ketones were checked for safety if blood glucose was above 20 mmol/L.

5.4.7 Statistical Analysis

The primary endpoint was the incremental area under the curve (iAUC) of the postprandial (0h–4h) glucose excursions after lunch. The study was powered to detect a minimum difference between the interventions of 2.6 h.mmol/L in the primary endpoint (equivalent to an average difference of 0.65 mmol/L for four hours).

We calculated that 12 participants would provide 80% power to detect differences between the interventions. We intended to do pairwise comparisons between the two AP interventions and the CSII interventions, and therefore did a power analysis using the sample size formula for the paired t-test with 5% significance level.

If an insulin correction bolus was delivered based on the hyperglycemia criteria, the glucose data was analysed as if the glucose would have stayed at the last glucose value before the correction bolus. We performed the following pairwise comparisons: (i) AP with CSII, (ii) AP+MDA with CSII, and (III) AP+MDA with AP, on an intention-to-treat basis. We used the two-sample t-test for outcomes with normally distributed data, and the Wilcoxon rank-sum test for outcomes with non-normally distributed data. For normally distributed outcomes, we reported means and standard deviations, and for non-normally distributed outcomes we reported medians and interquartile ranges. Normality was assessed using the Shapiro-Wilk test. We performed McNemar test to compare rates of hypoglycemia and hyperglycemia. We report nominal p values for all outcomes, and we did not do adjustment for multiple comparisons.

5.5 Results

5.5.1 Demographics

13 adolescents were admitted to the study. One dropped out after the admission visit due to lack of time to participate. Another participant dropped out after the AP and AP+MDA interventions and before the CSII intervention. Their data were excluded from analysis because they received a hypoglycemia overtreatment before

lunch during the AP intervention, which made their post-lunch data unrepresentative. Eleven participants were included in the analysis. Their mean baseline age was 14.9±1.3, HbA1c 8.3±0.6% , duration of diabetes 8.2±3.3 years, BMI 22.5±3.7 kg/m^2, daily insulin dose 0.9±0.2 U/kg, and 91% (10) female.

5.5.2 Glycemic Outcomes

As shown in Figure 5–1 and Table 5–1, the AP+MDA decreased the mean incremental area under the curve (iAUC) from the start of lunch to 4 hours post-lunch compared to CSII (AP+MDA: 15.4±8.0 h.mmol/L *vs.* CSII: 24.1±9.5 h.mmol/L, p=0.03). This improvement was not observed between AP (19.6±10.4 h.mmol/L) and CSII (p=0.33), nor between AP+MDA and AP alone (p=0.21). During the 4 hours post-lunch, the AP+MDA increased the time in target (3.9-10 mmol/L) compared to CSII by 20.46% (AP+MDA: 40.9±27.9% *vs.* CSII: 20.5±27.5% , p=0.03). There was no difference in time in target between AP (25.0±19.7%) and CSII (p=0.61), nor between AP+MDA and AP alone (p=0.07) (Table 5–1).

The AP+MDA reduced time spent above 10 mmol/L after lunch compared to CSII by 21.6% (AP+MDA: 58.0±26.6% vs CSII: 79.6±27.5% , p=0.02) and compared to AP alone by 16.3% (AP+MDA: 58.0±26.6% *vs.* AP: 74.2±20.6% , p=0.047). Mean sensor glucose was lowered with AP+MDA (11.0±2.3 mmol/L) compared to CSII (14.0±2.6 mmol/L, p=0.01) and AP alone (12.8±3.1 mmol/L, p=0.01). Sensor glucose five hours after lunch was lower in AP+MDA (8.0±3.8 mmol/L) compared to CSII (13.7±3.8 mmol/L, p<0.01) and AP alone (11.6±5.3 mmol/L, p=0.01) (Table 5–1).

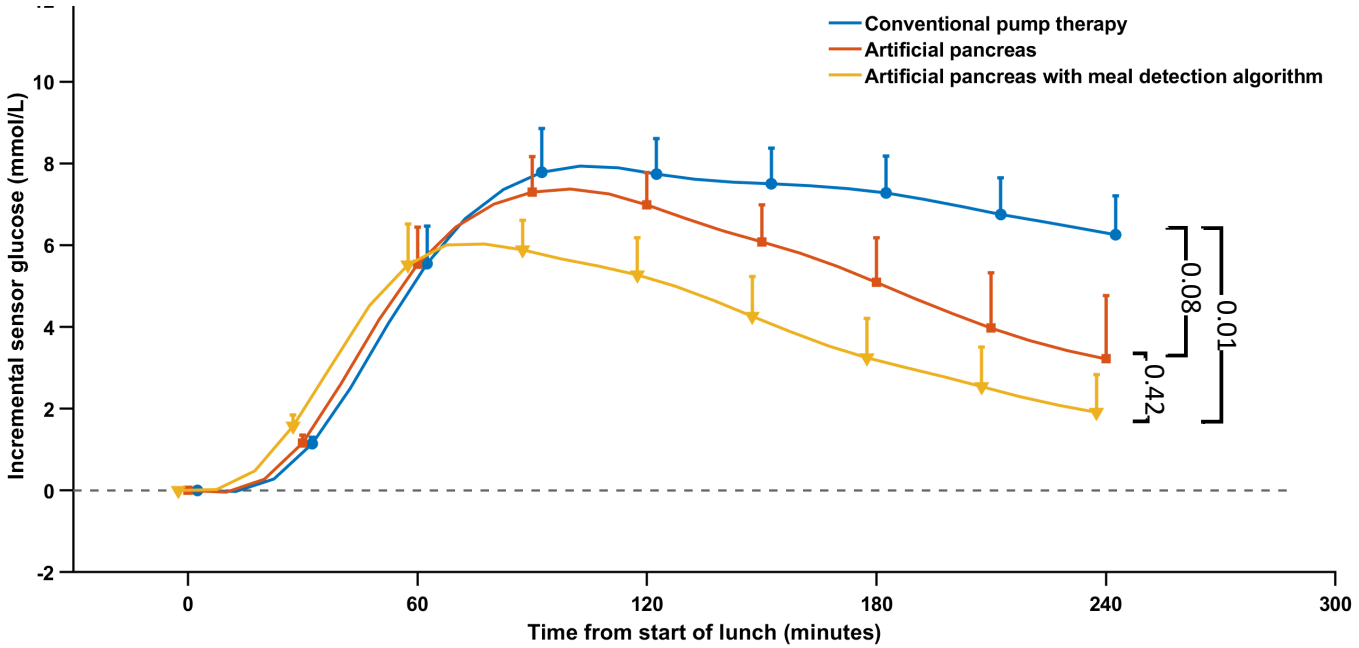

Figure 5–1: Incremental sensor glucose from the start lunch without a bolus (time=0 minutes) to 4-hours post-lunch (time=240 minutes) between all three interventions (n=11).

Table 5–1: Comparisons of conventional pump therapy (CSII), artificial pancreas (AP), and artificial pancreas with the meal detection algorithm (AP+MDA).

	CSII	**AP *vs* CSII (95%CI), p value**	**AP**	**AP+MDA *vs* AP (95%CI), p value**	**AP+MDA**	**AP+MDA *vs* CSII (95%CI), p value**
Time spent at glucose levels (%)						
3·9–10·0 mmol/L	20.5 (27.5)	4.6 (-14.5 to 23.6), p=0.61	25.0 (19.7)	15.9 (-1.7 to 33.5), p=0.07	40.9 (27.9)	20.5 (1.9 to 39.0), **p=0.03**
3·9–7·8 mmol/L	8.0 (14.3)	2.7 (-6.1 to 11.4), p=0.51	10.6 (11.8)	5.7 (-3.1 to 14.5), p=0.18	16.3 (15.1)	8.3 (1.0 to 15.6), **p=0.03**
< 3·9 mmol/L	.0 [.0-.0]	0.8 (-0.9 to 2.4), p=0.34	.0 [.0-.0]	0.4 (-2.8 to 3.6), p=0.8	.0 [.0-.0]	1.1 (-1.4 to 3.7), p=0.34
> 7·8 mmol/L	92.1 (14.3)	-3.4 (-11.6 to 4.8), p=0.38	88.6 (13.6)	-6.1 (-13.4 to 1.3), p=0.1	82.6 (14.5)	-9.5 (-16.9 to -2.1), **p=0.02**
> 10·0 mmol/L	79.6 (27.5)	-5.3 (-23.1 to 12.5), p=0.52	74.2 (20.6)	-16.3 (-32.3 to -0.2), p=0.047	58.0 (26.6)	-21.6 (-39.4 to -3.8), **p=0.02**
> 13·9 mmol/L	59.1 (30.7)	-23.1 (-55.6 to 9.4), p=0.14	36.0 (35.5)	-16.3 (-36.7 to 4.1), p=0.11	19.7 (23.1)	-39.4 (-64.9 to -13.9), **p=0.01**
> 16·7 mmol/L	37.5 [4.2-55.2]	-18.9 (-53.1 to 15.2), p=0.25	.0 [.0-9.4]	-8.7 (-23.8 to 6.3), p=0.22	.0 [.0-.0]	-27.7 (-54.7 to -0.6), **p=0.046**
Mean glucose (mmol/L)	14.0 (2.6)	-1.2 (-3.9 to 1.5), p=0.35	12.8 (3.1)	-1.8 (-3.0 to -0.6), **p=0.01**	11.0 (2.3)	-3.9 (-5.0 to -0.9), **p=0.01**
Coefficient of variation (mmol/L)	21.7 (5.6)	1.8 (-4.9 to 8.5), p=0.57	23.5 (7.9)	0.2 (-6.4 to 6.7), p=0.96	23.7 (7.1)	1.9 (-3.1 to 7.0), p=0.41

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Table 5–1 – *Continued from previous page*

	CSII	**AP *vs* CSII (95%CI), p value**	**AP**	**AP+MDA *vs* AP (95%CI), p value**	**AP+MDA**	**AP+MDA *vs* CSII (95%CI), p value**
Total Basal Insulin (U)	4.2 (1.0)	3.3 (2.7 to 4.0), **p<0.01**	7.6 (1.5)	-2.2 (-3.5 to -0.9), **p<0.01**	5.4 (1.6)	1.1 (-0.1 to 2.3), p=0.07
Total Insulin (U)	4.2 (1.0)	3.3 (2.7 to 4.0), **p<0.01**	7.6 (1.5)	1.0 (-0.1 to 2.2), p=0.09	8.6 (1.8)	4.4 (3.1 to 5.6), **p<0.01**
2-hour iAUC1 (h.mmol/L)	10.0 (4.1)	-0.5 (-4.5 to 3.5), p=0.8	9.5 (3.7)	-1.1 (-3.6 to 1.4), p=0.35	8.4 (3.5)	-1.6 (-4.8 to 1.7), p=0.31
2-hour incremental glucose increase (mmol/L)	7.7 (3.0)	-0.7 (-3.6 to 2.2), p=0.6	7.1 [5.1-8.8]	-1.2 (-3.6 to 0.1), p=0.1	5.9 [3.4-6.7]	-1.83 (-5.1 to 0.3), p=0.08
4-hour iAUC [1] (h.mmol/L)	24.1 (9.5)	-4.5 (-14.3 to 5.4), p=0.33	19.6 (10.4)	-4.2 (-11.2 to 2.8), p=0.21	15.4 (8.0)	-8.7 (-16.1 to -1.3), **p=0.03**
4-hour incremental glucose increase (mmol/L)	6.3 (3.2)	-3.0 (-6.5 to 0.4), p=0.08	3.2 (5.1)	-1.3 (-4.7 to 2.1), p=0.42	1.9 (3.1)	-4.3 (-7.1 to -1.6), **p=0.01**
Sensor glucose value at 5 hours post-lunch	13.7 (3.8)	-2.2 (-5.8 to 1.4), p=0.21	11.6 (5.3)	-3.6 (-6.2 to -0.9), **p=0.01**	8.0 (3.8)	-5.7 (-9.0 to -2.5), **p<0.01**
Participants with a hyperglycemia event [2]	5/11	NA, p=1	4/11	NA, p=0.25	1/11	NA, p=0.13
Participants with a hypoglycemia event [3]	0/11	NA, p=1	1/11	NA, p=1	0/11	NA, NA

Outcomes are mean (SD) or median (IQR). Paired differences are mean and 95% confidence interval. Outcomes are from the start of lunch to 240 minutes post-lunch, unless otherwise specified. A p value of less than or equal 0.05 is regarded as significant. NA: Not applicable.
[1] iAUC: incremental area under the curve.
[2] Hyperglycemia event: hyperglycemia requiring insulin correction as per the protocol.
[3] Hypoglycemia event: hypoglycemia requiring carbohydrate treatment.

5.5.3 Meal Detection

The median meal detection time was 40 [40 — 57.5] minutes after consumption of the meal, and there were no false positives or false negatives.

As seen in Figure 5–2, the incremental glucose was -0.15 mmol/L [-0.5 – 0.1] from mealtime to 20 minutes before detection, 1.5 mmol/L [0.9 – 1.8] from mealtime to 10 minutes before detection ($p<0.01$), and 2.6 mmol/L [2.4 – 4.8] at meal detection ($p < 0.01$). The rate of change of glucose was 6 mmol/L/h [5 – 6.5] 20 minutes before detection, 7.9 [6.6 – 11.1] mmol/L/h 10 minutes before detection ($p=0.02$), and 10.1 [7.3 – 12.5] mmol/L/h at meal detection ($p=0.6$).

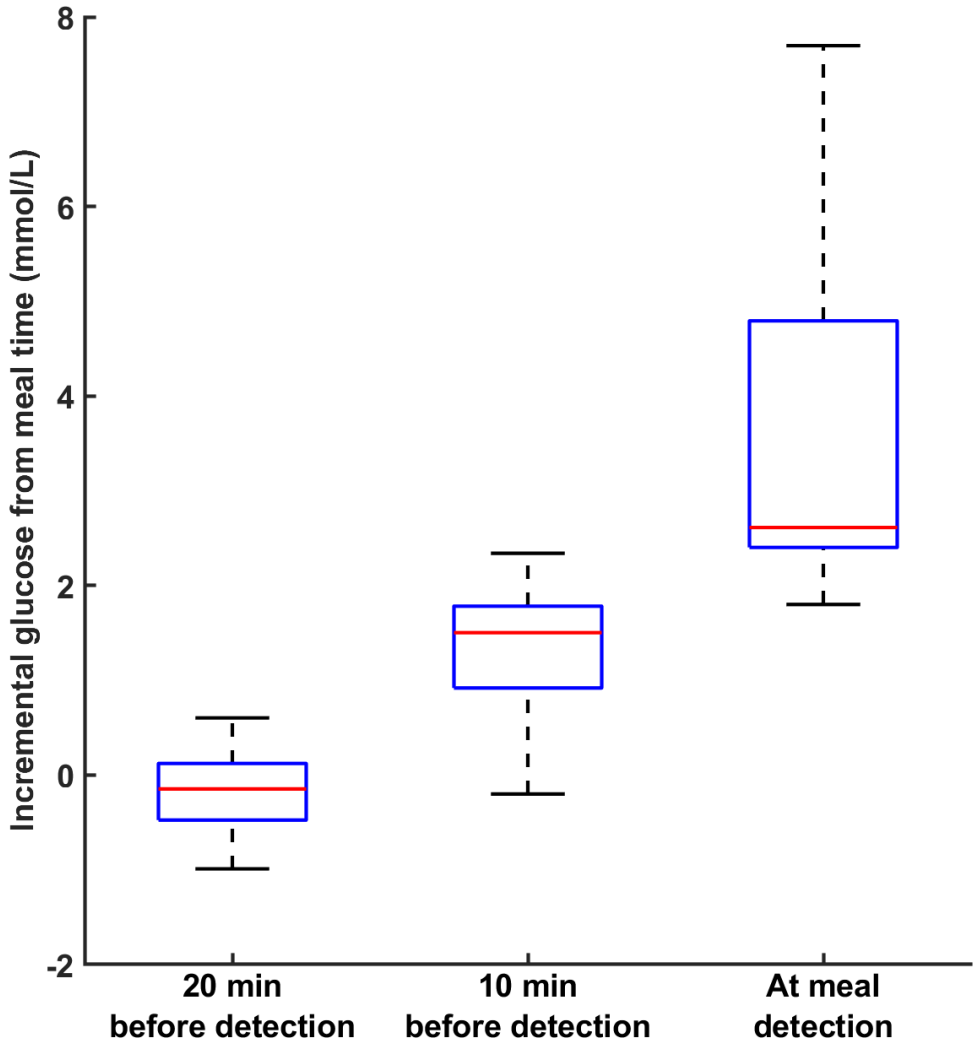

Figure 5–2: Incremental glucose levels 20 minutes before, 10 minutes before, and at meal detection (n=11). Data indicated as a boxplot (minimum, first quartile, median, third quartile, and maximum). min: minutes.

5.5.4 Insulin Delivery

The amount of basal insulin delivered in the AP arm (7.6±1.5 units) was greater than CSII (4.2±1.0 units, p<0.01) and AP+MDA (5.4±1.6 units, p<0.01). CSII and AP+MDA basal insulin delivery did not differ (p=0.07) (Figure 5–3, Table 5–1). Total insulin delivery was the largest in the AP+MDA arm, delivering 4.4 units [3.1 – 5.6] more insulin than CSII (p<0.01) and 1.0 unit [-0.1 – 2.2] more than AP alone (p=0.09) (Table 5–1).

In the AP+MDA arm, the median delivered bolus at the time of meal detection was 3.2 [2.1 – 4.4] units. The total amount of insulin delivered by the artificial pancreas after meal detection to 5 hours post-lunch was 4.4 [3.3 – 5.2] units.

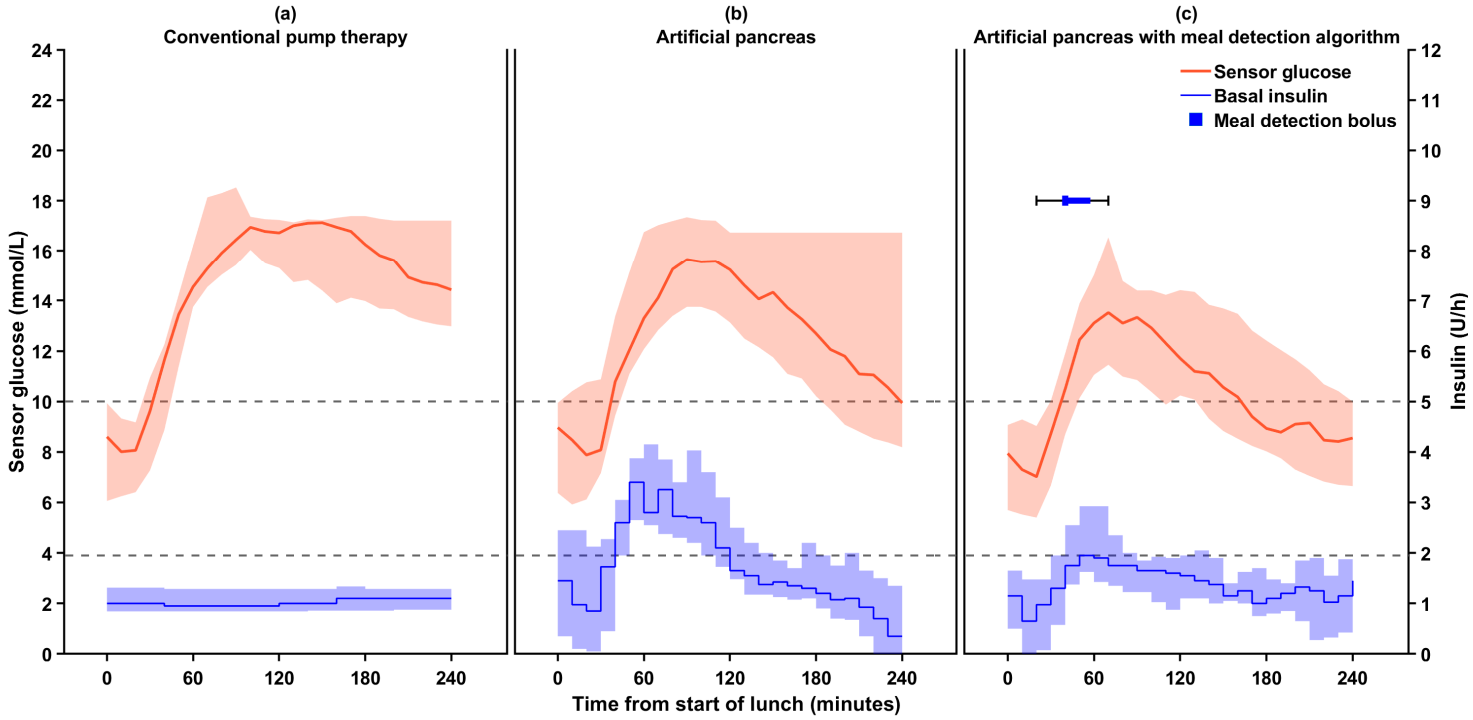

Figure 5–3: Glucose and insulin profiles the start lunch without a bolus (time=0 minutes) to 4-hours post-lunch (time=240 minutes) between all three interventions (n=11). Solid red lines and its shaded area: median sensor glucose profiles and interquartile range. Solid blue line and its shaded area: median basal insulin delivery and interquartile range. Red dot: hypoglycemia events. Blue triangle: insulin boluses are indicated as a boxplot (minimum, first quartile, median, third quartile, and maximum) of the time of the meal detection and insulin bolus delivery.

5.5.5 Hypoglycemia and Hyperglycemia Events

The median [IQR] time in hypoglycemia (<3.9mmol/L) was 0% [0 — 0] in all three arms. There were no hypoglycemia events in AP+MDA or CSII arms, and 1 hypoglycemia event in the AP arm (Table 5–1). There were 5 hyperglycemia events requiring correction boluses in the CSII arm, 4 events in the AP arm, and 1 event in the AP+MDA arm (Table 5–1). In the CSII arm, hyperglycemia events occurred at 1.5h, 1.66h, 2.0h, 2.33h, and 3.0h post meal. In the AP arm, hyperglycemia events occurred at 1.0h, 1.33h, 2.0h, and 3.0h post meal. In the AP+MDA arm, the hyperglycemia event occurred at 1.5h post meal. There were no high ketone levels.

5.6 Discussion

This study presents a randomized cross-over clinical trial evaluating the efficacy of three systems at handling a meal without a bolus in adolescents. Eleven participants underwent three 9-hour interventions with their insulin infusion controlled by (i) conventional pump therapy, (ii) the artificial pancreas alone, and (iii) the artificial pancreas with a meal detection algorithm. Breakfast was consumed with a carbohydrate-matched insulin bolus, while lunch was consumed without announcement to the systems. Compared to CSII, the artificial pancreas with a meal detection algorithm improved glycemic control after a missed bolus meal in adolescents.

Meal detection systems must be designed to detect and deliver insulin quickly after a meal to decrease postprandial hyperglycemia, but not overdeliver insulin to cause hypoglycemia. We aimed to test a meal detection algorithm that could detect meals without announcement and deliver boluses to better control glycemia postprandially.

The rate of glucose appearance in the blood from a meal is determined by the rate at which glucose is emptied from the stomach and absorbed in the intestine, the amount of extraction by the splanchnic tissues, followed by how much glucose enters the circulation [14]. A study by Pennant et al. [14] showed that in people with type 1 diabetes that did not receive prandial insulin boluses, the glucose appearance of 25% of a mixed meal glucose dose was 31.7±3.5 minutes, and 50% of the dose appeared after 54.1±4.7 minutes. Our meal detection algorithm detected the presence of a meal in between these times, after 40 [40 – 57.5] minutes.

Postprandial over-delivery of insulin may cause late hypoglycemia [15]. To avoid this postprandial hypoglycemia, the meal detection algorithm's bolus was mainly based on the sensor glucose value at the detection time. This bolus only represented, on average, 40% of the participant's usual bolus that would have been delivered at the start of the meal if it was announced. Furthermore, after detecting the meal and delivering the bolus, the basal delivery in the AP+MDA intervention became less aggressive in case of any false positives and to avoid hypoglycemia (Figure 5–3).

Delivering boluses before meals or at mealtime improves postprandial glycemia compared to postprandial boluses [15, 16]. Nevertheless, adolescents with type 1 diabetes often forget to deliver their insulin boluses on time, or even at all [4]. There are currently no recommendations regarding postprandial insulin bolusing (>30 min) (for example, if a person with type 1 diabetes only remembers to bolus >30 minutes after carbohydrate consumption). In our AP+MDA arm, the amount of additional insulin delivered by the artificial pancreas after meal detection to 5 hours post-lunch was 4.4 [3.3 – 5.2] units, which represents 53.9 [35.1 – 66.8] % of the bolus that would

have been delivered at mealtime. This artificial pancreas with the meal detection algorithm brought sensor values to 7.3 [5.7 – 8.2] mmol/L 5-hours post-meal. Therefore, at 45 minutes post-meal, we believe delivering approximately 60% of the full bolus that one would have received at mealtime may be a safe recommendation for bringing glucose back into the target range without inducing hypoglycemia.

Our artificial pancreas system makes basal insulin changes every 10 minutes. As seen by Figure 5–2, 20 minutes before meal detection, the incremental glucose was -0.15 mmol/L [-0.5 -– 0.1]. Ten minutes before detection, the incremental glucose from the meal was still only 1.5 mmol/L [0.9 — 1.8], and there was still no meal was flagged. Incremental glucose levels jump to 2.6 mmol/L [2.4 — 4.8] 10 minutes later, when the meal was detected. Therefore, if our meal detection algorithm evaluated sensor values every 5 minutes, it is possible that meal detection and its corresponding bolus could occur 5 minutes sooner. Further investigation is needed to determine if this is possible and/or has any clinical significance.

The benefits of AP alone over CSII were not apparent in the study. Participants received significantly more insulin in the AP and AP+MDA interventions compared to the CSII intervention (Table 5–1). However, the significant increase in basal insulin in the AP arm was still not sufficient to improve time in hyperglycemia (>10 mmol/L), 4-hour incremental area under the curve, or time in target (between 3.9 and 10 mmol/L) (Table 5–1, Figure 3). The average time from the start of meal to hyperglycemia events were between 1.8 and 2 hours in the AP and CSII arms, demonstrating how the artificial pancreas was not able to delay time to hyperglycemia compared to CSII following the 55-65g meal. However, glucose values did return to

target range by the end of the AP intervention (median sensor value at 5 hours post-lunch: 9.0 [8.0 -– 15.9] mmol/L), as opposed to the CSII intervention (12.1 [11.3 — 17.2] mmol/L).

Similar results regarding the handling of unannounced meals by the artificial pancreas were observed in Elleri et al.'s study [17] comparing the artificial pancreas and conventional pump therapy after a 55g meal without a bolus. In their study, although basal insulin delivery significantly increased after the meal without a bolus with the artificial pancreas, there was no difference in time in target between interventions, and postprandial hyperglycemia still was not avoided (18). This demonstrates the limitation of artificial pancreas' basal increase in response to a missed meal bolus. The improved glycemic outcomes observed in the AP+MDA arm may have been attributed to the insulin that was delivered sooner as a bolus.

Other studies illustrate the superiority of the artificial pancreas over conventional pump therapy in handling snacks without a bolus [18, 19] or meals with partial boluses [17, 18]. This suggests that the artificial pancreas's basal insulin delivery increase may be sufficient to control glycemia following a small amount of unannounced carbohydrates, but its success alone has not been shown in handling a full meal.

Other meal detection algorithms have been tested in simulations and/or using clinical data sets, achieving similar meal detection times as in this trial [20, 21, 22, 23, 24, 25, 26]. Two other meal detection algorithms have been used in clinical trials evaluating fully automated systems with no meal announcement [11, 27]. Cameron

et al. conducted a 30-hour inpatient trial with 10 participants, followed by a 54-hour hotel study with 15 participants [11]. This study demonstrated early feasibility for a fully automated system in a type 1 diabetes population with a low-HbA1c, however, it lacked randomization or a comparator arm. Dovc et al. [27] conducted a 27-h inpatient randomized crossover trial with 20 participants, comparing their fully closed-loop system with standard and faster insulin aspart. They reported a median detection time of 38.4 [32.7 — 55.8] minutes in the standard arm and 30.1 [26.9 — 54.6] minutes in the faster arm. Their fully closed-loop system demonstrated safety but did not achieve the recommended (70%) time in target. Both studies were not specifically designed to evaluate the efficacy of the meal detection algorithm.

Our study has several limitations. Firstly, the study was not conducted in a free-living setting. It is unknown how the algorithm would work in response to non-standardized mealtimes and exercise, for example. Secondly, the duration of the study (9 hours) was short. Thirdly, we used manual control to operate the artificial pancreas systems, but this was unlikely to have affected the glycemic outcomes, as insulin delivery would have been equivalent if we used an automated system. Finally, the sample size (11 participants) was small. The strengths include its three-armed randomized controlled experimental design and that the study was performed in a population that misses boluses often [4] and during lunch time at school, where they typically find it difficult to keep focused to remember to bolus [28].

In conclusion, we tested a novel meal detection algorithm for the artificial pancreas in a randomized clinical trial in adolescents. The algorithm successfully detected unannounced meals and delivered boluses, leading to a decreased incremental

area under the curve 0 to 4 hours after the unannounced meal, decreased time in hyperglycemia, without increasing hypoglycemia, compared to conventional pump therapy. Longer and larger outpatient free-living clinical trials are warranted to evaluate the external validity and efficacy of the meal detection algorithm.

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5.8 References

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CHAPTER 6

Day-To-Day Insulin Doses Optimization for People with Type 1 Diabetes on Multiple Daily Injections Therapy

6.1 Preface

Frequent insulin doses adjustment is key to achieving good glycemic control. In this chapter, new insulin doses optimization for patients with type 1 diabetes using multiple daily injections is presented. A new model-based run-to-run control law is proposed to daily adapt insulin basal dose and carbohydrate ratios. Using a model, a Bayesian approach is employed to estimate therapy parameters fitting daily records of glucose, insulin, and meal. The goodness of model-fit and confidence in parameter estimates are used to drive the run-to-run control law. Simulation results are shown to demonstrate the algorithm efficacy. Clinical data is used to evaluate the proposed model and the estimation technique.

6.1.1 Authors Contributions to the Manuscript

The author Anas El Fathi was the primary responsible for the development of the methods, interpretation of the results, and writing the manuscript. Ahmad Haidar, Robert E. Kearney, and Benoit Boulet supervised the theoretical development. Emilie Palisaitis coordinated the clinical study from which the data was

obtained. Ahmad Haidar provided editorial input in writing the manuscript, and provided overall supervision. All authors critically reviewed the manuscript.

Day-To-Day Insulin Doses Optimization for People with Type 1 Diabetes on Multiple Daily Injections Therapy

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6.2 Abstract

Goal: Multiple daily injections (MDI) therapy is the most common treatment for type 1 diabetes (T1D). It includes (i) basal insulin doses, often once daily, to keep glucose levels constant during fasting conditions and (ii) bolus insulin doses with meals to metabolize their carbohydrates. Optimal insulin dosing is critical to achieving satisfactory glycemia but is challenging due to inter- and intra-individual variability. Here, we present a novel iterative algorithm that optimizes insulin doses using previous-day glucose, insulin, and meal data. **Methods**: Our algorithm uses a maximum-a-posteriori method to estimate the parameters of a model describing the effects of meals and basal-bolus insulin doses on glucose levels. Then, it uses these parameter estimates, their confidence intervals, and the goodness of fit to generate new dose recommendations. We assessed our algorithm in three ways. First, a clinical data set of 150 days (15 participants) was used to evaluate the

proposed model and the parameter estimation method. Second, a 60-day simulation was performed to demonstrate the efficacy of the algorithm. Third, a sample 6-day clinical experiment is presented and discussed. **Results**: The model fitted the clinical data well with a root-mean-square-error of 1.75 mmol/L. Simulation results showed an improvement in the time spent in target (3.9—10 mmol/L) from 64% to 77% and a decrease in the time spent in hypoglycemia (<3.9 mmol/L) from 8.1% to 3.8%. The clinical experiment demonstrated the feasibility of the algorithm. **Conclusion**: Our algorithm has the potential to improve glycemic control in people with T1D using MDI. **Significance**: This work is a step forward towards a decision support system that improves their quality of life.

Index Terms— Type 1 diabetes, automatic adaptation, Bayesian inference, multiple daily injections, decision support system, insulin, glucose.

6.3 Introduction

Insulin is a hormone that is secreted by the pancreas to regulate blood glucose levels, and is absent in people with type 1 diabetes (T1D) due to the autoimmune destruction of the pancreatic beta cells [1]. T1D is treated with a lifelong intensive insulin-replacement therapy using multiple daily injections (MDI) or continuous subcutaneous insulin infusion via a portable pump. Intensive insulin therapy is key to reducing long-term micro- and macrovascular complications caused by sustained high glucose levels (hyperglycemia). However, most people with T1D do not achieve acceptable glucose targets, as tight glycemic control is challenging due to fear of low glucose levels (hypoglycemia) [2, 3].

MDI therapy consists of a basal-bolus insulin regimen that aims to mimic insulin secretion patterns in healthy individuals [4, 3]. Basal insulin aims to maintain glucose levels constant during fasting and overnight, accounting for about 50% of daily insulin requirements. Basal insulin is delivered in 1-2 doses/day of long- or intermediate-acting insulin; these insulins are characterized by a slow, often peak-less, absorption with a duration effect up to 24 hours [5]. Basal insulin requirements may change depending on a person's sleep cycle, physical activities, psychological stress, and growth hormones [6, 7, 8].

Bolus insulin refers to rapid-acting insulin doses given at mealtimes to metabolize meal-related glucose appearance in the blood. Insulin boluses are determined based on the carbohydrate ratios which specifies how many grams of carbohydrate are metabolized by each unit of insulin. Carbohydrate ratios change depending on the time of the day, individual's insulin sensitivity, their eating habits, and their diet [8]. People with T1D often use 3-4 carbohydrate ratios per day (i.e., one ratio per main meal).

The basal insulin dose and carbohydrate ratios, collectively referred to as the MDI therapy parameters, are specific to each individual and are periodically adjusted to improve overall glycemic control. Advances in glucose monitoring systems have made it possible for people with T1D and health care professionals to view daily glucose levels and adjust the MDI therapy parameters. However, this process is subjective, error-prone, and time-consuming. Moreover, in addition to glucose levels, one must consider insulin doses, type and amount of meals, and activity levels when

adjusting the MDI therapy parameters. The aim of this work is to develop a safe, automatic way to adjust MDI therapy parameters.

Run-to-run (R2R) algorithms are a class of algorithms that exploits the repetitive nature of a process and adjust a control signal iteratively at the end of each run to achieve a certain objective [9]. The R2R framework is well suited to our problem since incremental changes in MDI therapy parameters can be made based on daily observation of glucose profiles. This approach has been proposed for automatic daily adjustment of insulin doses, although most of the research has been focused on insulin pump users [10, 11, 12]. R2R framework was first clinically evaluated by Palerm et al. [13]. In their trial, the R2R gain was tuned to match clinically determined insulin boluses in 11 adult participants. This algorithm was expanded to adjust basal insulin for pump users [14], and was utilized in other clinical trials involving closed-loop insulin delivery systems (artificial pancreas) [15, 16]. Herrero et al. augmented the R2R framework with case-based reasoning, an artificial intelligence technique that solves newly encountered problems by applying the solutions learned from solving previous similar situations [17]. Their algorithm was evaluated in a 6-week study in 10 adults using MDI therapy. The system was safe and a trend in decreasing post-meal hypoglycemia was observed [18]. The same algorithm was also extended for basal insulin adjustments [19]. Another technique was developed by Patek et al. [20] relying on estimating glucose fluxes from individual glucose data, then retrospectively simulating the glucose trace under different insulin treatment profiles to select the optimal profile. This algorithm was incorporated in an insulin advisory system and was evaluated in a randomized clinical study [21]. In their

study, glucose variability was reduced in 24 adults using insulin pump or MDI; other glycemic outcomes were unchanged.

This paper proposes a new R2R approach for adjusting MDI therapy parameters. This approach uses a model that relates MDI therapy parameters to daily records of glucose, insulin, and meals. MDI therapy parameters are estimated in addition to other individual-specific physiological parameters using a Bayesian framework adopting the Markov Chain Monte Carlo method. The goodness of fit and confidence in parameter estimates are used to drive the R2R control law. This algorithm was utilized in an 11-day clinical study that investigated the non-inferiority of day-to-day automatic adjustments of MDI therapy parameter compared to day-to-day physician adjustments (identifier: NCT03764280 at clinicaltrials.gov). Clinical data from this study is used to assess the ability of the model to fit real-life glucose patterns. In addition, we provide simulation results comparing our R2R update rule to a baseline R2R update rule. Finally, we present a 6-day fit and insulin doses adjustment in one of the participants of the clinical study.

6.4 Methods

In this section, we present our MDI therapy optimization algorithm. First, we present the R2R update rule. Second, we present the model used for parameter estimation. Third, we present the parameter estimation method. Finally, we present the approach used to validate the MDI therapy optimization algorithm.

6.4.1 Summary of Day-to-Day Optimization Algorithm

In MDI therapy, insulin doses are determined by the therapy parameters: daily basal dose B (U) and carbohydrate ratios C_R (g/U). Let X_d be a therapy parameter

used on day d. Let $\hat{X}_d$ be a random variable describing the unknown optimal therapy parameter on day d, and $\mathbb{P}\left(\hat{X}_d|D_d\right)$ be the probability density function of $\hat{X}_d$ conditioned on the observed data D_d. The data set, $D_d = \{Y_{1:N}, U_{1:N}\}$, is observed each day and consists of measured glucose levels $Y_{1:N} = \{y_1, \ldots, y_N\}$ and inputs $U_{1:N} = \{U_1, \ldots, U_N\}$ comprising the insulin basal dose U_{ba}, the insulin boluses U_{bo}, and the meals U_m. Every day, a new MDI therapy parameter (X_{d+1}) is determined as:

$$X_{d+1} = X_d + \phi\left(\eta\left(\mathbb{E}\left[\hat{X}_d\right] - X_d\right)\right) \tag{6.1}$$

where $\mathbb{E}\left[\hat{X}_d\right]$ is the expected value of $\hat{X}_d$, η is a coefficient between 0 and 1, and $\phi(.)$ is a function defined as:

$$\phi(x) = \begin{cases} 0 & |x| < \delta x_{min} \\ \dfrac{x}{|x|}\delta x_{max} & |x| \geq \delta x_{max} \\ x & otherwise \end{cases} \tag{6.2}$$

where δx_{min} and δx_{max} are the minimum and maximum changes allowed for parameter x, respectively.

The coefficient η can be regarded as a learning rate of the update rule in (1). This coefficient depends on (i) the reliability of the MDI therapy parameter estimates and (ii) the quality of the data D_d. The greater the confidence in the estimate, the larger the value of η should be. When $\eta = 1$, the new therapy parameter in day

$d+1$ is set to $\mathbb{E}\left[\hat{X}_d\right]$. When $\eta = 0$, the therapy parameter is kept unchanged. The details of how η s calculated are described in Section 6.4.4.1.

6.4.2 Glucoregulatory Model for People on MDI Therapy

To find $\mathbb{P}\left(\hat{X}_d|D_d\right)$ using a maximum-a-posteriori method, we use a model that relates the MDI therapy parameters to interstitial glucose measurements (G_m) This model (Fig. 1) is a modified minimal model with three inputs: consumed meals (U_m), insulin bolus doses (U_{bo}), and insulin basal dose (U_{ba}) [22]. All model inputs are considered Dirac functions. A full description of model symbols is presented in TABLE 6–1.

Table 6–1: Model inputs and parameters

Symbol	**Description**	**Unit**
U_{ba}	Insulin basal dose	Units (U)
U_{bo}	Insulin bolus dose	Units (U)
U_m	Amount of carbohydrates in consumed meal	g
G_m	Sensor glucose	mmol/L
B	Optimal basal insulin dose	Units (U)
C_R	Optimal carbohydrate ratio	g/U
S_i^{ba}	Basal insulin sensitivity	mmol/L/U
τ_i	Time-to-peak of insulin action	min
K_m	Carbohydrate sensitivity	mmol/L/g
τ_m	Time-to-peak of carbohydrate absorption	min
τ_{max}	Duration effect of insulin basal dose	min
τ_s	Transfer-rate constant between plasma and interstitial glucose.	min

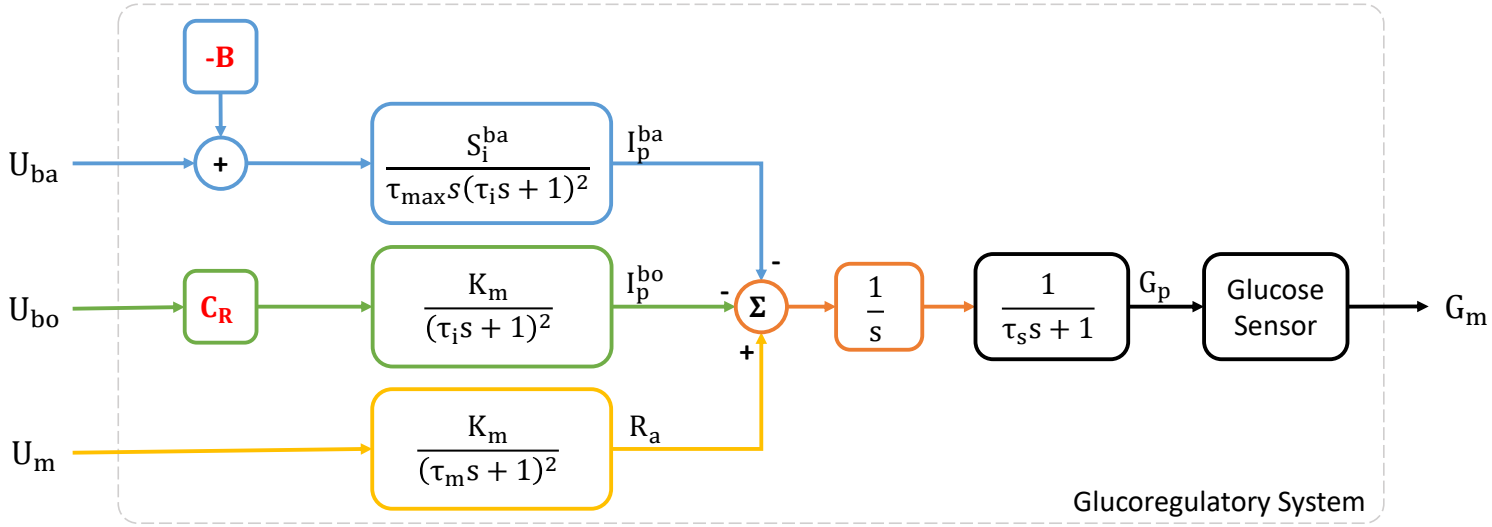

Figure 6–1: Block diagram representing the glucoregulatory system of a person with T1D using MDI therapy and a glucose sensor. Parameters are defined in TABLE 6–1.

6.4.2.1 Meals effect on Glucose

The rate of meal glucose appearance $R_a(t)$ (mmol/L/min) in the blood after an ingested meal U_m is described by the two-compartment model [23]:

$$R_a(t) = K_m \frac{U_m}{\tau_m^2} t e^{-\frac{t}{\tau_m}} \tag{6.3}$$

6.4.2.2 Bolus Insulin Dose Effect on Glucose

The rate of insulin appearance in the blood $I_p^{bo}(t)$ (U/min) after an insulin bolus dose U_{bo} is described by the two-compartment model:

$$I_p^{bo}(t) = \frac{U_{bo}}{\tau_i^2} t e^{-\frac{t}{\tau_i}} \tag{6.4}$$

At mealtimes, people with T1D deliver an insulin bolus dose proportional to the carbohydrates in the meal. The changes in post-meal plasma glucose levels are determined by the combined action of the insulin bolus and meal glucose as follows:

$$\frac{dG_p(t)}{dt} = -S_i^{bo} I_p^{bo}(t) + R_a(t) \tag{6.5}$$

where S_i^{bo} (mmol/L/U) is the bolus insulin sensitivity. The solution of (5) is:

$$G_p(t) = G_p(0) - S_i^{bo} \left(1 - e^{-\frac{t}{\tau_i}} - \frac{t}{\tau_i} e^{-\frac{t}{\tau_i}}\right) U_{bo} + K_m \left(1 - e^{-\frac{t}{\tau_m}} - \frac{t}{\tau_m} e^{-\frac{t}{\tau_m}}\right) U_m \tag{6.6}$$

The optimal carbohydrate ratio (i.e., C_R) is the ratio that leads to glucose levels eventually returning to their pre-meal glucose values. That is, $lim_{t\to\infty} G_p(t) = G(0)$

, after a bolus $U_{bo} = \frac{U_{meal}}{C_R}$ is taken. In 6.6, the unique carbohydrate ratio that satisfies this condition is:

$$C_R = \frac{S_i^{bo}}{K_m} \tag{6.7}$$

6.4.2.3 Basal Insulin Dose Effect on Glucose

Long-acting insulin doses result in a slow, sustained release of insulin into the blood circulation [24]. Models describing the pharmacokinetics of long-acting insulins exist in the literature [25, 26]. However, rather than modelling the pharmacokinetics of long-acting insulin, we modelled the effect of the quantity $U_{ba} - B$ on glucose changes, where U_{ba} is the injected basal insulin dose, and B is the unknown optimal basal dose that would maintain glucose level constant during fasting conditions [27]. Delivering insulin more than the optimal dose would lead to continuously decreasing glucose level, while delivering a dose below the optimal dose would lead to continuously increasing glucose levels. This motivates the following simple model for the basal pathway:

$$\frac{dG_p(t)}{dt} = -S_i^{ba}\left(I_p^{ba}(t) - I_{p0}(t)\right) \tag{6.8}$$

where $I_p^{ba}(t)$ (U/min) is the rate of insulin appearance into the blood circulation due to basal dose U_{ba}, $I_{p0}(t)$ (U/min) is the rate of insulin appearance into the blood that is needed to keep glucose levels steady and which results from the optimal basal dose B. The rate of insulin appearance $\left(I_p^{ba}(t)\right)$ into the blood circulation due to

a long-acting insulin dose U_{ba} can be described by the following trapezoid equation [24]:

$$I_p^{ba}(t) = \begin{cases} \left(1 - \left(\frac{t}{\tau_i} + 1\right) e^{-\frac{t}{\tau_i}}\right) \frac{U_{ba}}{\tau_{max}} & t < \tau_{max} \\ \left(\left(1 + \frac{t - \tau_{max}}{\tau_i}\right) e^{-\frac{t - \tau_{max}}{\tau_i}} - \left(\frac{t}{\tau_i} + 1\right) e^{-\frac{t}{\tau_i}}\right) \frac{U_{ba}}{\tau_{max}} & t \geq \tau_{max} \end{cases} \tag{6.9}$$

The value of the time constant τ_i in (9) is assumed to be equal to the time constant in (4). In fact, both rapid- and long-acting insulin take approximately the same time to achieve maximum effect, with the difference that rapid-acting insulin action peaks at this time, while long-acting insulin plateaus after this time for a duration τ_{max} [24]. The duration $\tau_{max}$is set to be one day, i.e., $\tau_{max} = 1440$ min. Equation (9) assumes that basal doses are always separated by the same time τ_{max} . I_{p0} (t) can be determined from (9) by replacing U_{ba} by B.

The solution of (8) for $t < \tau_{max}$ is:

$$G_p(t) = G_p(0) - S_i^{ba}(U_{ba} - B)\left(\frac{t - 2\tau_i}{\tau_{max}} + \frac{t + 2\tau_i}{\tau_{max}} e^{-\frac{t}{\tau_i}}\right) \tag{6.10}$$

Equation (10) demonstrates that glucose levels will remain constant after a basal dose U_{ba} if it is equal to B, that is, the basal dose is optimal. Equation (10) also shows that an extra 1 unit of the long-acting insulin ($U_{ba} - B = 1U$) will decrease glucose level by S_i^{ba} mmol/L after the insulin dose is completely absorbed at $t = \tau_{max} \gg \tau_i$.

6.4.2.4 Glucose Sensor Model

Glucose monitoring systems measure interstitial glucose concentrations $G_i(t)$ (mmol/L), which can be related to plasma glucose concentrations $G_p(t)$ through a diffusion model [28]:

$$\frac{d}{dt}G_i(t) = -\frac{1}{\tau_s}G_i(t) + \frac{1}{\tau_s}G_p(t) \tag{6.11}$$

Since it is not possible to estimate τ_s without directly measuring plasma glucose, we fix this value to $\tau_s = 10$ min [29]. The measured glucose is subjected to a sensor noise $\epsilon(t)$. The noise is assumed to be additive and non-white, as follows:

$$G_m(t) = G_i(t) + \epsilon(t) = G_i(t) + h(t) * e(t) \tag{6.12}$$

where $e(t)$ is a white noise with zero mean and variance σ^2, and "$*$" denotes the convolution operator. The process $h(t)$ is approximated in discrete time ($t = k\Delta t$) as a zero-mean, autoregressive model of order one [30]:

$$\epsilon_{k+1} = \alpha\epsilon_k + e_k; \quad 0 \leq \alpha < 1 \tag{6.13}$$

6.4.3 Parameters Estimation

6.4.3.1 Model Parameters and Initial Conditions

The transfer function model linking the inputs U_{ba}, U_{bo}, and U_m to the interstitial glucose concentration is given by:

$$G_i(s) = \frac{1}{\tau_s s + 1}\frac{1}{s}\left(\frac{K_m U_m}{(\tau_m s + 1)^2} - \frac{C_R K_m U_{bo}}{(\tau_i s + 1)^2} - \frac{S_i^{ba}\dfrac{U_{ba} - B}{\tau_{max}}}{s(\tau_i s + 1)^2}\right) \tag{6.14}$$

Parameters $\tau_s = 10$ and $\tau_{max} = 1440$ are assumed to be constant, parameters B, S_i^{ba}, τ_i and K_m are estimated daily, and parameters C_R and τ_m are estimated for each main meal. The sensor noise is modeled by α and σ, both parameters are estimated daily. In the following, we use p to denote the vector of parameter estimates. Initial conditions are estimated for the first day. For subsequent days, the last state of the previous day is used as initial conditions.

6.4.3.2 Maximum-a-posteriori Estimation

Using daily observed data $D_d = \{Y_{1:N}, U_{1:N}\}$, we can estimate the vector of parameter estimates p (which includes the desired MDI therapy parameters). We use a statistical approach and assume that p is a random vector with probability distribution functions (PDF) denoted by $\mathbb{P}(p)$. At the end of each day, the posterior (or updated) PDF of the parameters p given data D_d (denoted by $\mathbb{P}(p|Y_{1:N}, U_{1:N})$) is related by Bayes' rule to the likelihood function $\mathbb{P}(Y_{1:N}|U_{1:N}, p)$ and the prior probability distribution $\mathbb{P}(p)$. The maximum *a posteriori* (MAP) estimate of p (denoted by p^*) is the value for which $\mathbb{P}(p|Y_{1:N}, U_{1:N})$ attains its maximum

$$p^* = \arg\max_p \mathbb{P}(p|Y_{1:N}, U_{1:N}) \Leftrightarrow p^* = \arg\max_p \mathbb{P}(Y_{1:N}|U_{1:N}, p)\,\mathbb{P}(p) \tag{6.15}$$

The prior distributions $\mathbb{P}(p)$ aid with finding the best posterior estimates, but also mitigate against non-identifiability and makes it unlikely to attain non-physiological parameter estimates. However, in practice, non-physiological estimates may still be attained if the data is pushing strongly for non-physiologic values. Therefore, constraints were incorporated in (15) to ensure that p^* attains physiologically-plausible values. Hence, p^* is obtained by solving the optimization problem (see Appendix 6.8.1):

$$p^* = \arg\min_{p \in \mathcal{S}} J(p) + Q(p), \tag{6.16}$$

$$J(p) = \frac{1}{2\sigma^2} \| R_\alpha \left(Y_{1:N} - \hat{Y}_{1:N} \right) \|^2 + N \log \sigma - \frac{1}{2} \log \left(1 - \alpha^2 \right) \tag{6.17}$$

$$Q(p) = \frac{1}{2} \| W^{-1} (p - p_0) \|^2 + tr(\log W) \tag{6.18}$$

where $\mathcal{S}$ is the domain of physiologically-plausible parameter values defined by the set of constraints in TABLE 6–2, R_α is the inverse of the upper Cholesky decomposition of the noise covariance matrix (see Appendix 6.8.1), $\hat{Y}_{1:N} = \{\hat{y}_1, \ldots, \hat{y}_N\}$ is the glucose predictions obtained by solving (14), p is derived from p by replacing log-normally distributed parameters by their logarithms, W is the upper Cholesky decomposition of the covariance matrix of the prior distribution of p, and p_0 is the mean of the prior distribution of p. The mean and the covariance (diagonal) matrix of p can be derived from the prior distributions in TABLE 6–2. The mean of the prior distributions of MDI therapy parameters is set to the values used in the previous day.

Constraints on C_R and S_i^{ba} were derived from the formulas given by Walsh et al. for optimal carbohydrate ratio and basal insulin [8]. Constraints and prior distributions for τ_i and τ_m are derived from the literature [31, 32]. Constraints are applied to the bolus insulin sensitivity $S_i^{bo} = K_m C_R$ to make it smaller than the basal insulin sensitivity S_i^{ba} [33]. This enforces that insulin sensitivity decreases at high plasma insulin concentrations following insulin boluses, as endogenous glucose production is suppressed.

An analytical solution for the optimization problem (16) can be obtained by differentiating the inverse Laplace function of (14). However, this is overly complex due to the nonlinear dependency of the temporal solution ($Y_{1:N}$) on p and due to the constraints in (16). In gradient descent optimization, gradients (and Hessians) are approximated locally and are employed to iteratively converge towards a solution of the optimization problem. Yet, for non-convex problems, convergence is usually slow and a global optimum is not guaranteed [34]. Monte-Carlo Markov Chain (MCMC) sampling is a method where samples are drawn following a proposal distribution, then discarded while favoring samples closer to the optimum solution. MCMC has been used in the literature to solve similar problems [35, 36], yet, convergence is attained only after exploring most of the space of possible parameter values which comes with an undesirable computational time. We employed a method alternating between both gradient descent optimization and MCMC sampling. First, a Metropolis-Hasting routine explores the parameters space and constructs a sample pool around the current best solution. This is done to enable jumps in the parameters space unrelated to the gradient descent. Second, the sampling is halted, and multiple gradient descent

Table 6–2: Prior distributions of model parameters p. $\mathcal{N}(\mu, \sigma^2)$ denotes the normal distribution with mean μ and variance σ^2. $\mathcal{N}_{\log}(\mu_{\log}, \sigma_{\log^2})$ denotes the log-normal distribution where $\mu_{\log}$ and $\sigma_{\log^2}$ are means and variance of the logarithmic values of the parameter.

Parameter description	**Distribution**	**Constraints**
B Optimal insulin basal dose	B $\sim N\left(U_{ba}, (0.1U_{ba})^2\right)$ U_{ba} is the basal insulin used in a day.	$B \in [0.25, 0.75]\, TDD.$
C_R Optimal carbohydrate ratio	$C_R \sim N\left(C_{R0}, (0.2C_{R0})^2\right)$. C_{R0} is the carbohydrate ratio used for a meal	$C_R \in [2, 50]$;
S_i^{ba} Insulin sensitivity	$S_i^{ba} \sim \mathcal{N}_{\log}\left(\log\left(\frac{110}{TDD}\right), 0.005\right)$	$S_i^{ba} \in [0.8, 1.3]\, \frac{110}{TDD} \cap [0.9, 2.5]\, K_m C_R$
τ_i Time-to-peak of insulin action	$\tau_i \sim \mathcal{N}_{\log}\left(\log\left(70\right), 0.01\right)$	$\tau_i \in$ [45, 105]
K_m Carbohydrate sensitivity	$K_m \sim \mathcal{N}_{\log}\left(\log\left(\frac{15}{w}\right), 0.03\right)$, where w is the weight.	$K_m \in [0.5, 2.0]\, \frac{15}{w}$
τ_m Time-to-peak of carbohydrate absorption	$\tau_m \sim \mathcal{N}_{\log}\left(\log\left(40\right), 0.02\right)$	$\tau_m \in$ [15, 65]
σ noise standard deviation	$\sigma \sim \mathcal{N}_{\log}\left(-1, 0.05\right)$	$\log\left(\sigma\right) \in [-3, 1]$
α noise autocorrelation	$\alpha \sim N\left(0.8, 0.05\right)$	$\alpha \in [0.45, 0.95]$

optimization are carried on starting from randomly selected samples from the sample pool. This is done to benefit from the local convexity of (16) in some regions of the parameters space. Robustness assessment of this algorithm showed its reproducibility in different runs and with different sampling realizations; the coefficient of variation in parameter estimates from the same dataset was 0.01% between runs (data not

shown). A summary description of the optimization method is presented in Appendix 6.8.1.

After convergence, we achieve the solution of (16) and a pool of samples around this solution. The pool of samples is used to approximate the expectation and the uncertainty of the MAP estimate p^*. Since MDI therapy parameters X_d are a subset of the estimated parameters p, we also obtain $\mathbb{E}\left[\hat{X}_d\right]$.

6.4.4 Day-to-Day Optimization Algorithm

6.4.4.1 Run-to-run Learning Rate

Recall that, from (1), an MDI therapy parameter in day $d+1$ is obtained using the mean sample $\mathbb{E}\left[\hat{X}_d\right]$ (retrieved from the model fitting procedure) and the coefficient η. The coefficient η can be regarded as the learning rate of the update rule in 6.1, and it describes our confidence in the parameter estimates. The confidence in the parameter estimates is explained by:

i The coefficient of variation (CV) of the MDI therapy parameter estimate ($\hat{X}_d$) expressed as:

$$CV = \frac{\sqrt{\mathbb{E}\left[\left(\hat{X}_d - \mathbb{E}\left[\hat{X}_d\right]\right)^2\right]}}{\mathbb{E}\left[\hat{X}_d\right]} \tag{6.19}$$

ii The local mean absolute error (MAE) of the difference between the observed glucose levels and the predicted glucose resulting from the fit:

$$MAE = \frac{1}{L}\sum_{k=M}^{M+L-1} |y_k - \hat{y}_k| \tag{6.20}$$

where L is a time window, and M is a time characterizing the therapy parameter X_d. For instance, errors in glucose predictions after a meal are used to compute a local MAE for the carbohydrate ratio used for the meal.

The coefficient η combines CV and MAE as:

$$\eta = \frac{1}{1 + \frac{MAE}{MAE_{half}}} \cdot \frac{1}{1 + \frac{CV}{CV_{half}}} \tag{6.21}$$

where MAE_{half} and CV_{half} are tuning parameters. These values set the aggressiveness of the algorithm. We use $MAE_{half} = 1.5$ mmol/L for all therapy parameters, $CV_{half} = 0.03$ for basal insulin, and $CV_{half} = 0.05$ for carbohydrate ratios. These parameters were tuned using preliminary clinical testing in diabetes camp settings.

As a final step, the new recommendations (X_{d+1}) are subjected to other safety rules to prevent the algorithm from making unsafe recommendations. For example, if one had hypoglycemia after the lunch meal, a rule prevents recommending a smaller carbohydrate ratio (i.e., more insulin) for the lunch meal.

6.4.4.2 Accounting for Day-to-day Variability

Our method naturally accounts for inter-day variability. Even though the model structure is fixed, the method fits each day separately, which can result in different therapy parameters each day, accommodating inter-day variability. Therapy parameters update can be made every several days using running averages of the parameter estimates [37]. The number of days over which the averages are taken is denoted as P_d.

6.4.5 Method Validation

The insulin dose optimization algorithm is composed of two steps: a parameters estimation step and a dose recommendation step. The parameter estimation step was evaluated using clinical data to validate (i) the ability of the model to fit complex real data, and (ii) the physiological plausibility of the estimated parameters. The dosing recommendation step was evaluated using 30-day simulations on 100 virtual patients (VP) and compared to a baseline R2R algorithm. Furthermore, data from a 6-day clinical experiment in adolescent patients was used to demonstrate the feasibility of our algorithm.

6.4.5.1 Baseline R2R Algorithm

Results from the R2R algorithm proposed by Toffanin et al [38] have been reproduced for comparison purposes. This algorithm was designed for a closed-loop system implemented with insulin pumps. We modified the algorithm to be suited for MDI therapy by assuming one basal dose and three carbohydrate ratios. The algorithm gains were kept the same as the ones published. This R2R algorithm only uses glucose information and the time of the insulin boluses.

6.4.5.2 Simulation Environment

A simulation environment was used for algorithm assessment. This simulation environment implemented VP based on Hovorka's model [39]. Model parameters were sampled from a prior log-normal distribution with a mean taken from Wilinska et al. and between-parameter correlations from healthy individual data [40, 39]. Day-to-day glucose variability was implemented by making parameters oscillate periodically, with a random frequency and phase for each day as described in [39], and

by adding daily random glucose and insulin fluxes representing unexplained changes in plasma glucose and plasma insulin [36]. Variability in meal absorption was implemented by modeling slow and fast carbohydrate absorption rates, and by varying the time-to-peak of carbohydrate absorption for each meal [36]. The simulation includes noise in glucose measurements with a coefficient of variation of 7% and a correlation of 80% [30]. Random carbohydrate counting errors with a coefficient of variation of 20% were included.

Each VP possessed unique optimal basal dose and carbohydrate ratio. The optimal basal dose was computed from the differential equations by assuming that it will keep glucose levels constant during fasting conditions. The optimal carbohydrate ratio was determined as the value which results in 8-hour post-meal glucose levels returning to pre-meal values.

This simulation environment was validated by reproducing similar glucose outcomes from a clinical experiment (see Appendix 6.8.2). An open-access version is available at https://github.com/McGillDiabetesLab/artificial-pancreas-simulator under MIT license.

6.4.5.3 Clinical Data

Clinical data of 150 days (10 days $\times$ 15 participant) was used for validation. The data was collected from 15 adolescents, including 8 females, in a diabetes camp: age 12.5 (SD, 3.7), TDD 0.8 U/Kg (SD, 0.3), and HbA1c 8.7% (SD, 1.9). Each participant wore a Freestyle Libre glucose sensor (Abbott Diabetes Care). The Freestyle Libre is a glucose monitoring system that provides a value of interstitial glucose every 15 min. Participants had three main meals every day, whose content changed

between days and between participants. Physical activities were common throughout the camp, and snacks were permitted and not accompanied by insulin boluses. Treated hypoglycemia events and the amount of carbohydrates used for hypoglycemia treatments were recorded. The clinical data was characterized by a mean glucose level of 11.2 mmol/L (SD, 3.1) and a coefficient of variation of 38% (SD, 12). The trial was registered at clinicaltrials.gov with identifier NCT03764280.

6.4.5.4 Model Fit Assessment

The goodness of the model fit was assessed by analysis of residuals. Weighted residuals (WR) are defined at each time k as the ratio between the residuals and estimated noise standard deviation:

$$WR_k = \frac{y_k - \hat{y}_k}{\sigma} \tag{6.22}$$

The proportion of variance explained (PVE) is defined by comparing the sum of squared residuals to the data variance:

$$PVE = 1 - \frac{\sum_{k=1}^{N} (y_k - \hat{y}_k)^2}{\sum_{k=1}^{N} (y_k - \bar{y})^2}; \quad \bar{y} = \frac{1}{N} \sum_{k=1}^{N} y_k \tag{6.23}$$

Root-mean-squared-error (RMSE) is defined as:

$$RMSE = \sqrt{\frac{1}{N} \sum_{k=1}^{N} (y_k - \hat{y}_k)^2} \tag{6.24}$$

Runs test were performed to ascertain the randomness of residuals. Results are reported as median and interquartile range (IQR) or mean and standard deviation (SD).

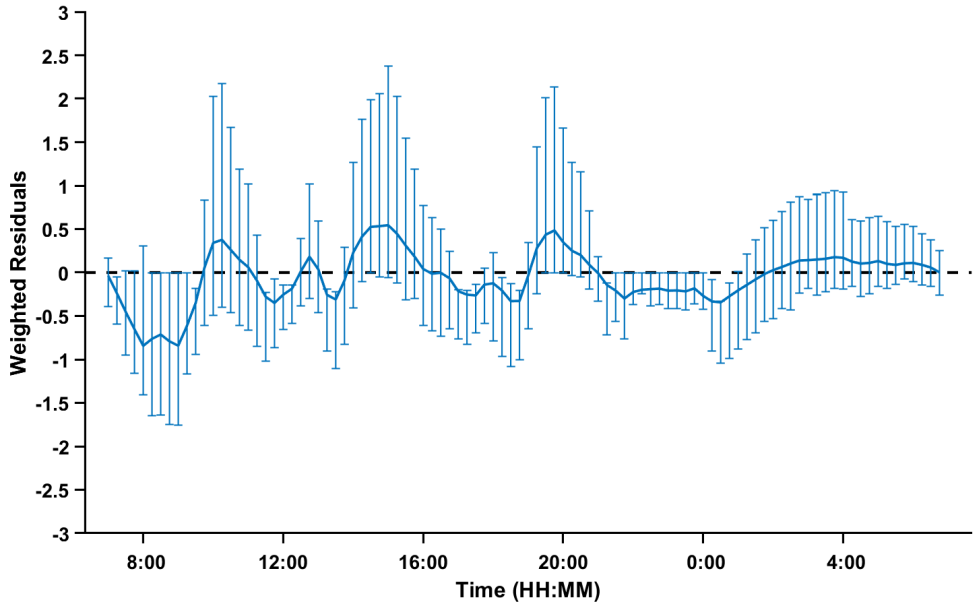

Figure 6–2: Median and interquartile range of weighted residuals of the model fit to clinical data consisting of 150 days (10 days x 15 participants).

6.5 Results

6.5.1 Assessment of Parameter Estimates using Clinical Data

A fit was performed to the 150 days of clinical data in 15 individuals using MDI therapy, and model parameters were estimated. The data consisted of measured glucose, delivered insulin doses, ingested meals (only main meals, snacks were not provided to the algorithm), and hypoglycemia treatments. Parameters for each day were estimated separately; however, data set of each individual (10 days) was fitted consecutively, such as the last state of the previous day is used as an initial condition for the following day.

Fig. 6–3 shows the median and interquartile range of the weighted residuals. Overall, the obtained residuals confirm that the proposed model provides enough

flexibility to accommodate complex real-life glucose patterns. All residuals passed the Runs test for randomness. The bias in the weighted residuals was -0.06 (IQR, -0.15–0.06), and the corresponding RMSE was 1.75 mmol/L (SD, 0.8). During the night, the RMSE was 1.26 mmol/L (SD, 0.94), while during the day, it was 1.9 mmol/L (SD, 0.85). The PVE was 77.3% (IQR, 64.6–87.7). The weighted residuals increased at mealtimes (8:00, 12:00, and 18:00). This might be caused by two reasons. First, the algorithm assumed that the meals were eaten instantaneously, while, in reality, participants spent time collecting and eating their meals, occasionally multiple times, while participating in various activities. Second, participants had snacks after meals, which were not entered into the algorithm.

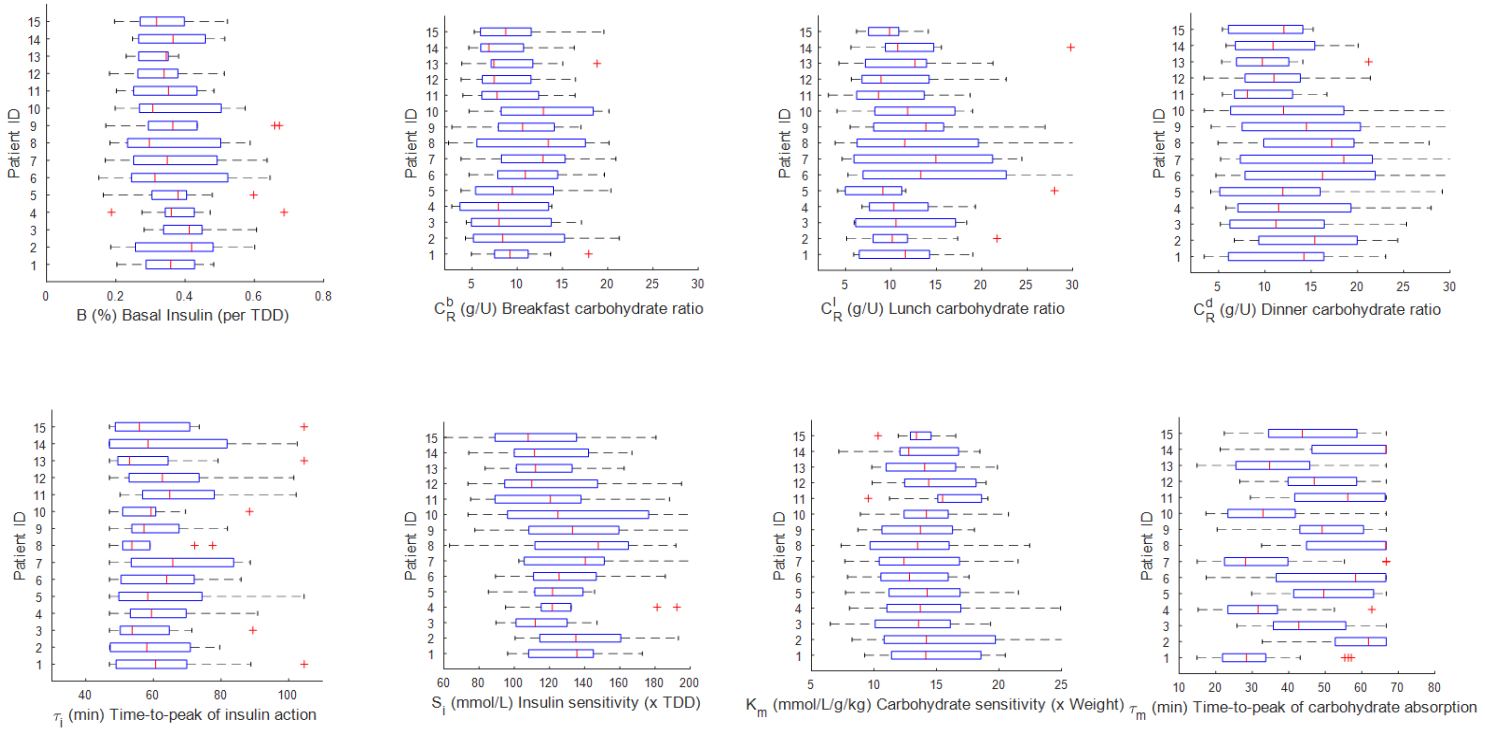

Figure 6–3: MAP estimate performed on clinical data consisting of 150 days (10 days × 15 participants). Parameters for each participant are represented by the blue horizontal box plots. Basal insulin is presented as a percentage of the patients' TDD. Insulin sensitivity (S_i) and carbohydrate sensitivity (K_m) are normalized by multiplying by patients' TDD and weight, respectively.

Fig. 6–2 shows the parameter estimates for the 15 participants over 10 days. Each participant's parameters are presented as a boxplot showing intra-individual variability between days. Coefficient of variation of all estimated parameters (n = 1492) was 4.5% (IQR, 2.8–7.0); the maximum coefficient of variation was 63%. Parameter estimates were all physiologically plausible. The average estimated carbohydrate ratio was 10.8 g/U (IQR, 6.8–15.2). Breakfast carbohydrate ratio was 9.1 g/U (IQR, 6.3–13.9) with a coefficient of variation between days of 37 % (IQR, 28–44). Lunch carbohydrate ratio was 10.5 g/U (IQR, 7.0–14.9), with a coefficient of variation between days of 53 % (IQR, 44–69). Dinner carbohydrate ratio was 12.7 g/U (IQR, 6.9–17.6) with a coefficient of variation between days of 53 % (IQR, 42–55). The observed variations in estimated carbohydrate ratios between days can be explained by differences in fat and protein contents between meals [41], as well as differences in physical activities and snacks after the meals [42]. Basal insulin represented 35% (IQR, 27–43) of total daily insulin dose. In absolute value, basal insulin was 11.0 U (IQR, 7.5–18.0). Insulin sensitivity was 4.4 mmol/L/U (SD, 2.5) with a coefficient of variation between days of 28% (IQR, 23–31). In order to evaluate the effect of the hard constraints on the parameter estimates, we re-fit the clinical data without constraints, and 97.2% of the parameter estimates were within the constraints (data not shown).

6.5.2 Simulation of Day-to-Day Insulin Doses Optimization

100 VP were created using the simulation environment described in section 6.4.5.2. Each VP consumed three main meals per day. Meals had random amounts of carbohydrates and were consumed at random times, inside pre-set intervals. For

instance, lunch was consumed between 11:30 and 13:00, and the amount was between 60 g and 100 g of carbohydrates. Up to two snacks (afternoon and bedtime) were consumed randomly, and their information was not provided to the algorithm. The total amount of carbohydrates consumed during a day was restricted to be between 140 g and 280 g. Only the main meals were accompanied by insulin boluses. The bolus doses were computed using the premeal glucose level and the carbohydrates that were counted by the VP (values were different from the true values because of the random carbohydrate counting errors). Patients had one insulin basal dose at the start of each day (7:00). Outside mealtimes, a correction bolus was delivered if glucose values stayed above 18 mmol/L for more than one hour. VP had one insulin basal dose at the start of each day (7:00). They consumed carbohydrate treatment (values were random around 16g) when blood glucose went below 2.8 mmol/L or when sensor glucose stayed below 3.9 mmol/L for more than 60 min. Sensor glucose values were sampled every 15 minutes.

The initial MDI therapy parameters in day 1 were selected to differ by 25–75% from the optimal MDI therapy parameters and such as the resulting TDD is no more than 25% of their usual TDD. This simulates the common situations with suboptimal parameters where insulin boluses are replaced by basal insulin, and vice-versa. Each day, the algorithm provided new therapy parameters that were applied in the following day.

Fig. 6–4 shows the changes in glycemic outcomes (daytime, nighttime, and overall) for 100 VP over 60 days between (i) adjustments with our algorithm every 5 days ($P_d = 5$) ; (ii) daily adjustments with our algorithm ($P_d = 1$) ; (iii) daily

adjustments with the baseline R2R algorithm; (iv) no adjustment. The same VP underwent the four arms, and, for each VP, daily variabilities and meals were the same between arms. Glycemic outcomes (time in target (3.9–10 mmol/L) and time in hypoglycemia (<3.9 mmol/L)) were computed over the last 10 days of the simulation.

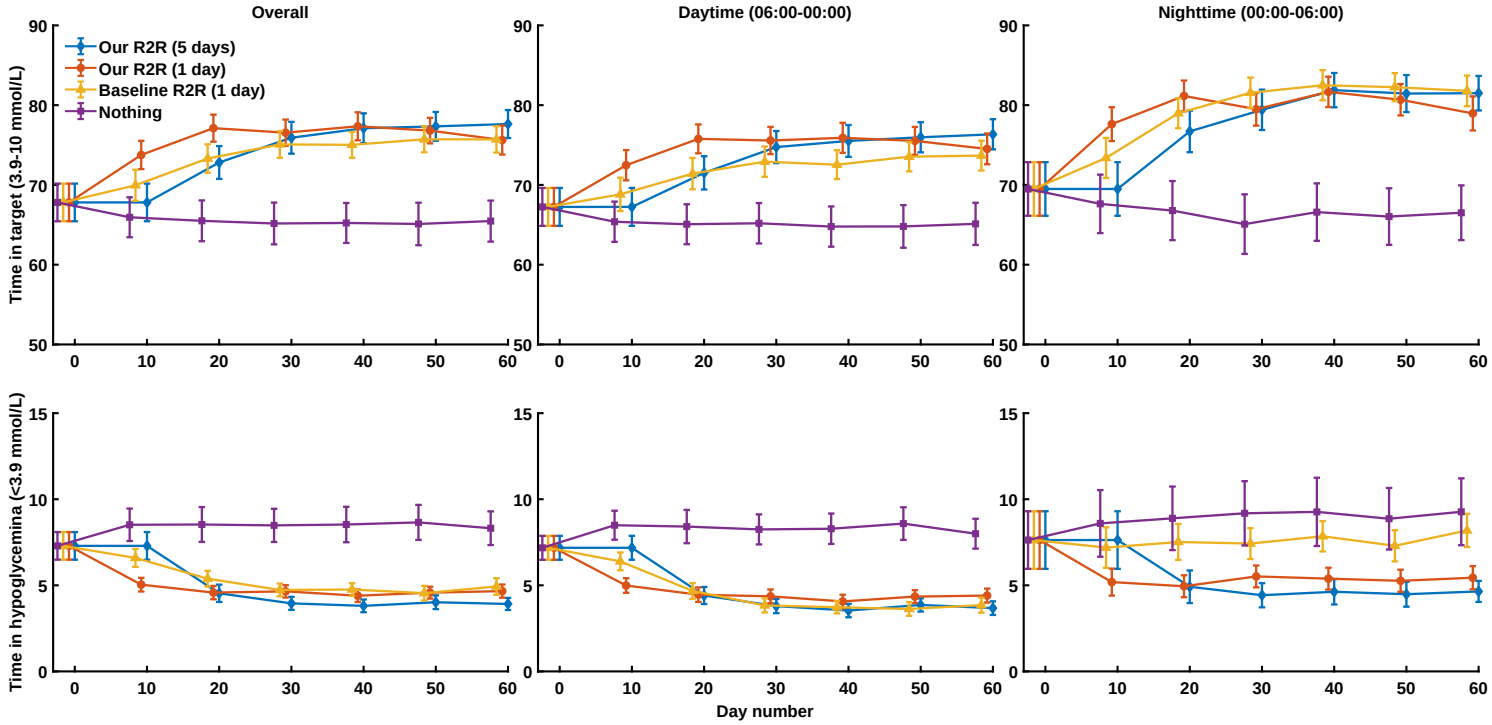

Figure 6–4: Time in target and time in hypoglycemia for 100 VP in 60-day simulations of daily therapy parameters adjustments using our algorithm, baseline run-to-run algorithm, or no adjustments. Data point represent mean values for 100 VP. Error bars represent the 95% confidence interval, where the length of each bar is (n=100) multiplied by the standard deviation.

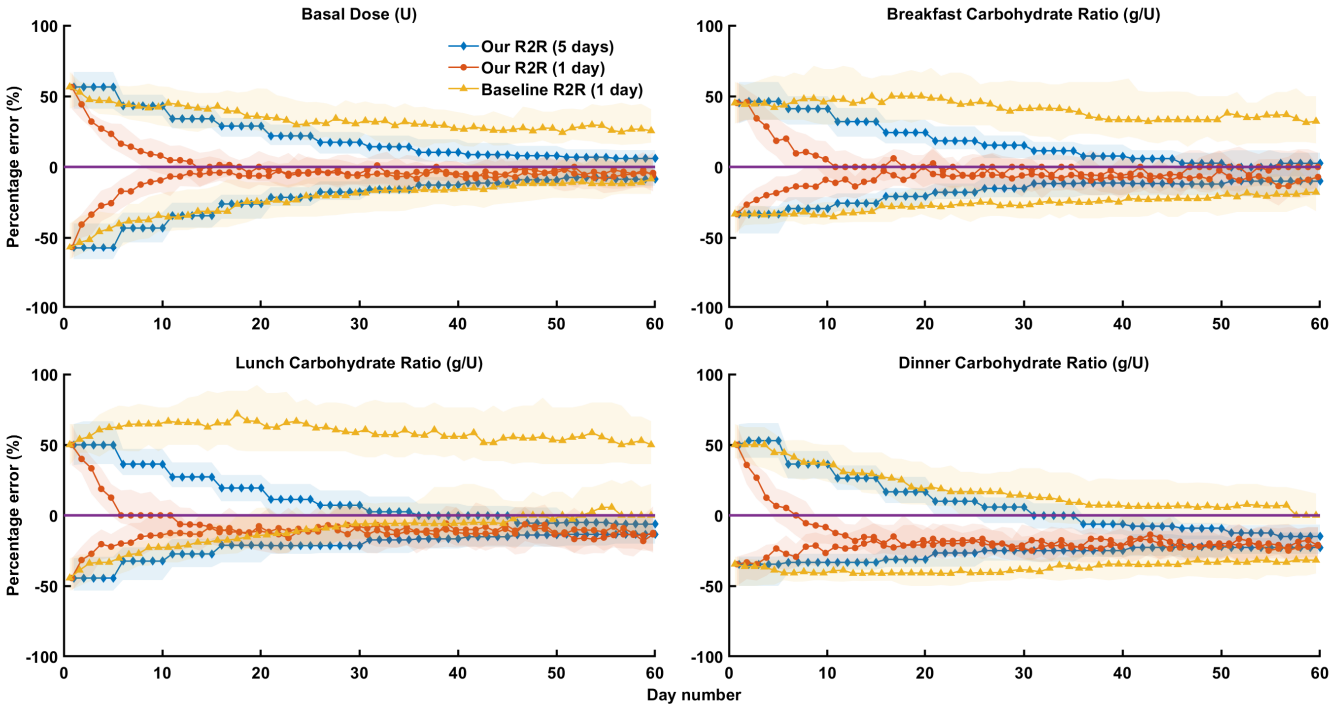

Figure 6–5: Daily percentage error in therapy parameters. Errors are calculated as a percentage difference from optimal parameter. Hard line represents the median values, and patch represents the 25%-75% percentile of parameter errors.

Compared to no adjustments, the overall glycemic outcomes in the last 10 days of the 60-day experiment were improved with our algorithm of $P_d = 5$ (time in target increased from 64.2% (SD, 13.8) to 77.0% (SD, 8.8, p<0.01); time in hypoglycemia decreased from 8.1% (SD, 5.0) to 3.8% (SD, 1.7, p<0.01)). This performance was also superior compared to the same algorithm with daily ($P_d = 1$) adjustments (time in target 74.8% (SD, 9,3, p<0.01); time in hypoglycemia 4.7% (SD, 1.8, p<0.01)), and compared to the baseline R2R ($P_d = 1$) (time in target 75.0% (SD, 8.2, p<0.01); time in hypoglycemia 4.9% (SD, 2.4, p<0.01)). The additional improvement with our algorithm of $P_d = 5$ compared to $P_d = 1$ towards the end of the simulations is likely driven by that when the algorithm of $P_d = 1$ converges closer to the true parameters it starts reacting to noise (day-to-day variability).

With $P_d = 1$ our method achieved significantly lower nocturnal hypoglycemia compared to the baseline R2R method (5.4% (SD, 3.1) vs 8.1% (SD, 4.7), p<0.01)). Even though both methods eventually converged to comparable overall time in target, our method converged much faster. This is advantageous in situations where insulin sensitivity changes rapidly such as during pregnancy or starting/stopping regular exercise.

Fig. 6–5 Shows the daily errors in the MDI therapy parameters estimates, defined as $100\frac{(X_d - X^{opt})}{X^{opt}}$, where X^{opt} is the optimal therapy parameter and X_d is the daily parameter. Positive and negative errors, indicating overestimation and underestimation, respectively, of each MDI therapy parameter are grouped together for better visualization of convergence. Our algorithm was able to reduce the initial error created in day 1 for the four therapy parameters., while the baseline R2R algorithm

maintained large errors even after 60 days. Furthermore, with our algorithm, we observe that both lunch and dinner carbohydrate ratios converged to values smaller than the theoretical optimal value. This is justified since the VP consumed snacks in the afternoon and bedtime. Our algorithm successfully adjusted for the extra carbohydrates by decreasing the carbohydrate ratios.

6.5.3 Clinical Experiment with Day-to-Day Insulin Doses Optimization

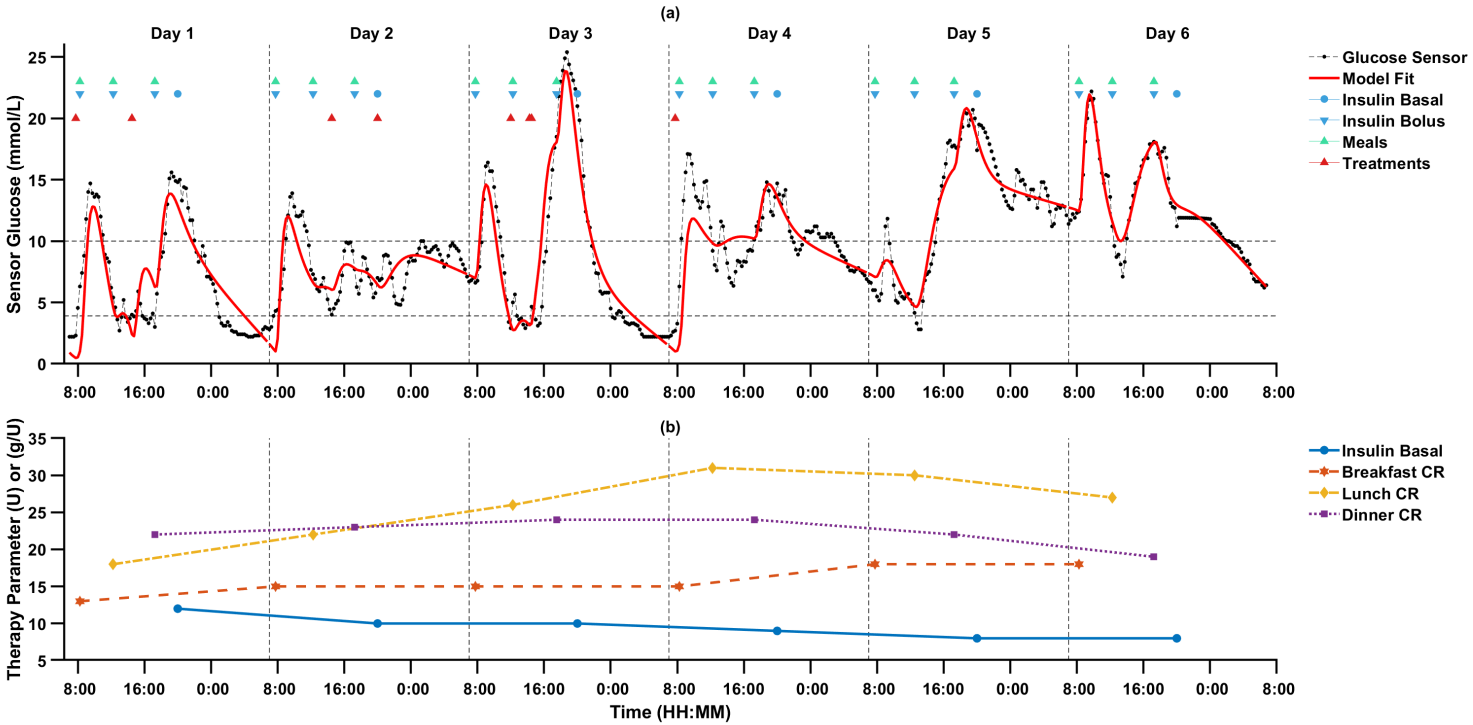

Figure 6–6: (a) Model fit of glucose sensor data for a sample patient. The black circles are sensor measurements. The red solid line represents the model fit. (b) Daily therapy parameters recommendations from the algorithm. The suggested recommendations were applied each day. CR stands for carbohydrate ratio.

Fig. 6–6 shows an example of a 6-day optimization on one of the participants in the clinical experiment. Analysis of day-to-day recommendations can be used to conceptually validate the algorithm's behavior. Overall, the algorithm recommendations were logical from day to day:

- *Day 1*: A hypoglycemia event occurred after lunch causing the algorithm to suggest an increase in carbohydrate ratios (decreasing insulin boluses). At night, a pronounced hypoglycemia event is observed, causing the algorithm to recommend a decrease in basal insulin.
- *Day 2*: Even though there was an increase in carbohydrate ratios compared to day 1, two post-meal hypoglycemia were still observed after lunch and dinner. The algorithm recommended a further increase in lunch carbohydrate ratio. There was no change in basal insulin dose. Overall day 2 was characterized by an increased time spent in glucose target range.
- *Day 3*: Despite delivering less insulin than previous days, there were multiple hypoglycemia events (afternoon and during night) and a pronounced hyperglycemia in the middle of the day. The hyperglycemia was caused by an over-treatment of hypoglycemia, and the following hypoglycemia might have been caused by an over-correction of hyperglycemia. Based on day 3 data, the algorithm recommended further decrease in insulin doses.
- *Day 4 to 6*: There were fewer hypoglycemia events but there was hyperglycemia after lunch and dinner. The algorithm slowly increased insulin doses after lunch and dinner by decreasing their carbohydrate ratios. Because of the decreasing

trend of glucose levels during the nights, the algorithm did not increase the basal insulin dose, even if they spent most of the night in hyperglycemia.

6.6 Discussion

People with T1D live with life-long burden of making important decisions about their daily insulin doses. Therefore, an effective decision support system could contribute to improving their quality of life. The proposed algorithm is a step forward towards developing a decision support system for people with T1D using MDI therapy.

Our approach utilizes an R2R update rule, yet, it stands out by that it combines glucose data with insulin and meal data via a model to guide the run-to-run algorithm. The model is characterized by (i) the separation of the basal and bolus insulin effects on glucose and (ii) the different sensitivities of insulin boluses for each meal. This provides a way to model (i) different carbohydrate ratios depending on the time of the meal [43], and (ii) variations in insulin sensitivity depending on the state of fasting or postprandial [33]. Our results showed that this model fit real-world data with different carbohydrate ratios while estimating insulin sensitivity for the basal insulin.

Through the model structure, the basal insulin dose ensures stable glucose during fasting conditions (Equation (10)) while the optimal carbohydrate ratios ensure that glucose levels return to their premeal values after 4-5 hours (Equation (6)). This model structure imposes the application of known guidelines for adjusting insulin doses [8]. For example, when glucose levels are high throughout the night but stable, equation (6) will impose a change in the dinner bolus dose by changing the optimal

carbohydrate ratio estimate instead of changing the basal dose (note that equation (10) imposes a change in basal insulin if glucose levels are increasing, not if they are high). Even though it is possible to correct high glucose levels by increasing the basal dose, the risk of hypoglycemia will increase for nights where glucose is stable but at normal levels.

In an ideal system-identification experiment, parameters should be identified using uncorrelated inputs. In our case, this can be achieved by exciting only one model channel at a time (meal, bolus, or basal channels) (Fig. 6–1). Since this is rarely the case in real life, we applied the following measures to cope with this identifiability problem: (i) the use of prior distributions to regulate parameter estimates, and (ii) the use of parameter sensitivities in the update rules of the MDI therapy parameters. The convergence of the algorithm in simulation validates the efficacy of these measures. We also choose to employ truncated prior distributions to guaranty that the posterior distribution is bounded, yet, these constraints were chosen large enough to let the data drive the parameter estimates. This is supported by the ability to fit real-world data.

Since we aimed to use insulin, meal, and glucose data in our method, as opposed to only glucose data, we needed to rely on a model. However, due to the complexity of the parameter estimation method, we used a simplified model to make implementation feasible. To assess the appropriateness of our model, we fit it with clinical data of multiple days in different individuals. The model was able to fit the data well while estimating physiologically plausible parameters with good precision. Moreover, if on a specific day the model's goodness of fit is poor (indicator of model

under-parametrization or unknown events, such as physical activities or non-recorded meals), or if we observe high uncertainty in the parameters' estimate (indicator of model over-parametrization), we prevent the algorithm from recommending large therapy changes (equation (22)), making our method robust to model inaccuracy. Effectively, the use of an adaptive R2R gain (learning rate) is key in the proposed algorithm.

Our simulations were designed to challenge our model-based algorithm by (i) providing wrong inputs to the model, mainly not entering the two daily snacks and simulating carbohydrate counting errors, (ii) simulating random glucose, meal, and insulin fluxes that our model is unable to explain [36]. These challenges led to an increased coefficient of variation of the parameter estimates and worsening of the model fit. Despite these challenging simulations, we observed an improvement in the time spent in target and the time spent in hypoglycemia. Regardless, this simulation environment does not consider all perturbations and variabilities which precludes the generalization of these results.

In the baseline R2R, each therapy parameter is updated to optimize a specific aggregate glycemic outcome (e.g., time spent in hypoglycemia after lunch, or average nocturnal glucose level [38]). However, each parameter is updated independently and the method does not consider the correlations between the effects of changing the basal insulin dose and the carbohydrate ratios, which can prevent converge to the true parameters in situations where errors in both the basal insulin dose and the carbohydrate ratios are positive (Fig. 6–5). This may explain the persist nocturnal hypoglycemia with the baseline R2R (Fig. 6–4). Our method, on the other

hand, changes all therapy parameters simultaneously and considers the correlations between their effects. This is possible since we use model fitting to estimate all parameters simultaneously using all available data (e.g., an increase in the basal insulin parameter estimate due to nocturnal hyperglycemia will also be reflected in daytime model predictions, which would in turn affect the estimate of daytime carbohydrate ratios). This may explain the convergence of our parameters (Fig. 6–5).

In simulation, day-to-day variability due to unusual days of sickness, high stress, or large carbohydrate counting errors may result in small oscillations in the MDI therapy parameters recommendations. This issue was handled by averaging recommendations from multiple days. In simulations, we choose $P_d = 5$, but in real-life this value should be at least 7 days to consider differences between the 7 days of the week.

In principle, our algorithm can be used to optimize therapy parameters for pump users. However, the identifiability issue becomes more apparent in the estimation process of pump therapy parameters compared to MDI therapy parameters. This is because pump users adjust multiple basal insulin values during the day with the aim of accommodating diurnal insulin sensitivity changes. This is a limiting factor, from an estimation problem point of view [44], since multiple model parameters would affect the same part of the day (for example, lunch carbohydrate ratio and afternoon basal rate). For closed-loop insulin delivery systems (artificial pancreas systems) where insulin delivery is automatically adjusted around usual basal rates, adjusting only one average basal rate (implemented throughout the day) might solve this identifiability issue [45].

6.7 Conclusion

We presented a novel algorithm that adjusts MDI therapy parameters for people with T1D. Our approach consists of using previous day's glucose levels, injected insulin, and consumed meals to estimate the MDI therapy parameters from a model. The estimated MDI therapy parameters, their confidence interval, and the goodness of model fit are used to generate new recommendations for the next day. The model fitted well clinical data from 15 participants with physiologically plausible model parameters. Simulation results show the effectiveness of the algorithm in improving glucose control. A sample 6-day clinical experiment demonstrated the feasibility of the algorithm.

6.8 Appendix

6.8.1 Maximum a Posteriori Probability

For a set of N observations $Y_{1:N}$ and system inputs $U_{1:N}$, we aim to derive the maximum a posteriori probability function $\mathbb{P}(p|Y_{1:N}, U_{1:N})$,where p is the vector of system parameters.

We assume that $Y_{1:N} = \{y_1, \ldots, y_n\}$ results from $U_{1:N} = \{u_1, \ldots, u_n\}$ and the initial condition y_0 as:

$$y_k = f_p(y_0, u_{1:k}) + \epsilon_k = \hat{y}_k + \epsilon_k \tag{6.25}$$

where $\hat{y}_k$ is a deterministic prediction of y_k based on the model function $f_p(.)$, and ϵ_k is a zero mean autoregressive noise governed by the parameters α and σ such as $\epsilon_{k+1} = \alpha\epsilon_k + e_k$ and $e_k \sim N(0, \sigma^2)$.

Using the chain rule, we have:

$$\begin{aligned}
\mathbb{P}\left(Y_{1:N}|y_0, U_{1:N}, p\right) &= \mathbb{P}\left(y_1|y_0, U_1, p\right) \prod_{k=2}^{N} \mathbb{P}\left(y_k|Y_{1:k-1}, y_0, U_{1:k}, p\right) \\
&= \mathbb{P}\left(y_1 + \epsilon_1|y_0, U_1, p\right) \prod_{k=2}^{N} \mathbb{P}\left(y_k + \epsilon_k|Y_{1:k-1}, U_{1:k}, p\right) \\
&= \mathbb{P}\left(\epsilon_1|p\right) \prod_{k=2}^{N} \mathbb{P}\left(\epsilon_k|\epsilon_{k-1}, p\right) \\
&= \mathbb{P}\left(\epsilon_{1:N}|p\right)
\end{aligned} \tag{6.26}$$

where $\epsilon_{1:N}$is a vector formed by ϵ_k . Since e_k is zero mean, we have $\epsilon_{1:N} \sim N\left(0, \Sigma\right)$. Using $\mathbb{E}\left[\epsilon_{k+r}\epsilon_k\right] = \dfrac{\sigma^2}{1-\alpha^2}\alpha^{|r|}$, it can de shown that $\Sigma = \sigma^2\left(R_\alpha^T R_\alpha\right)^{-1}$, with R_α defined as

$$R_\alpha = \begin{bmatrix}
\sqrt{1-\alpha^2} & 0 & \cdots & \cdots & 0 \\
-\alpha & 1 & \ddots & & \vdots \\
0 & \ddots & \ddots & \ddots & \vdots \\
\vdots & \ddots & \ddots & \ddots & 0 \\
0 & \cdots & 0 & -\alpha & 1
\end{bmatrix} \tag{6.27}$$

Finally, $\mathbb{P}\left(p|Y_{1:N}, U_{1:N}\right)$ follows from the Bayes rule:

$$\begin{aligned}\mathbb{P}\left(p|Y_{1:N}, U_{1:N}\right) &\propto \mathbb{P}\left(Y_{1:N}|y_0, U_{1:N}, p\right)\mathbb{P}\left(p\right)\\ &\propto \mathbb{P}\left(\epsilon_{1:N}|p\right)\mathbb{P}\left(p\right)\end{aligned} \tag{6.28}$$

where $\mathbb{P}\left(p\right)$ is the prior probability distribution of p.

6.8.2 Simulation Environment Validation

We validated our simulator by comparing its outcomes with the outcomes of a clinical trial in 81 individuals on multiple daily injections therapy [46]. In the trial, 2-week glycemic outcomes were reported from a FreeStyle glucose sensor. In this validation, the errors in basal rates and carbohydrate counting were identical to the ones used in section 6.5.2.

Table 6–3: Glycemic outcomes of simulations and real data

	Real data (n=81)	**Simulated data (n=100)**	**P value**
Time in 3.9–10.0 mmol/L (%)	65.42 (11.67)	64.64 (13.73)	0.51
Time <3.9 mmol/L (%)	7.75 (5.67)	8.00 (5.10)	0.65
Time >10.0 mmol/L (%)	26.67 (12.50)	27.35 (15.82)	0.58
Mean of glucose (mmol/L)	8.20 (1.10)	8.16 (1.42)	0.71
SD of glucose (mmol/L)	3.10 (0.58)	3.11 (0.74)	0.93

[1] Results are mean (SD). SD stands for standard deviation.

6.8.3 Algorithm Description

Table 6–4: Parameter estimation algorithm

```
1  Let N_T be the total number of samples, N be the number of samples in each
       iteration, T (<1) be the thinning coefficient, and B be the number of burn-
       in samples.
2  Let p be a vector parameter (a sample), p_i is an element of p, J(p) a cost
       function to minimize, and p* = arg min J(p).
3  Let S be the samples pool initialized with one initial sample p.
4  Set p^*=p.
5  While number of samples < N_T
6  ..Enter Metropolis-Hasting routine
7  ....Randomly generate m initial samples around p*.
8  ....For each initial sample p_m (parallel loop)
9  ......For iterator less than B + N/m/T
10 ........For x_i in the sample p_m
11 ..........x_i = x_i+ a random walk.
12 ..........Create a new sample p_m^New with changed x_i
13 ..........Compute the acceptance ratio α = J(p_m^New)/J(p^m)
14 ..........If β drawn from the standard uniform distribution is ≥ log α
15 ............save new sample p_m^New.
16 ......Discard the burn-in samples (B).
17 ....Combine the m chains.
18 ....Down-sample using the thinning coefficient (T).
19 ....Add new samples (N) to S
20 ....In S, discard samples with a cost far from the minimal cost.
21 ..Set p^* to the sample with minimum cost in S.
22 ..Enter Gradient Descent routine
23 ....While convergence criteria are not attained
24 ......Uniformly choose m sample from S.
25 ......For each sample p_m (parallel loop)
26 ........Run gradient descent starting from p_m.
27 ........Save sample p_m^New and cost resulting from gradient descent.
28 ......If in the new m samples, we achieved a better cost value than p*
29 ........Set new optimum p* = p_m^New.
30 ........If p* did not change or cost function stopped decreasing
31 ..........Convergence criterion is met.
32 Return p*
```

6.9 Acknowledgment

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CHAPTER 7

A Pilot Non-Inferiority Randomized Controlled Trial to Assess Automatic Adjustments of Insulin Doses in Adolescents with Type 1 Diabetes on Multiple Daily Injection Therapy

7.1 Preface

In this chapter, a clinical trial employing the algorithm in chapter 6 is presented. In this 11-day parallel randomized study in 21 adolescents with type 1 diabetes, we aimed to demonstrate the non-inferiority of algorithmic adjustments of insulin doses to adjustments made by a physician. This study was conducted in a diabetes camp, where one group was following daily recommendations from our algorithm and the other group was following daily recommendations from the camp physicians.

7.1.1 Authors Contributions to the Manuscript

The author Anas El Fathi was the primary responsible for the development of the methods, interpretation of the results, and writing the manuscript. Laurent Legault, Julia E. von Oettingen, and Preetha Krishnamoorthy supervised the clinical

trial. Emilie Palisaitis coordinated the clinical trial. Ahmad Haidar provided editorial input in writing the manuscript, and provided overall supervision. All authors critically reviewed the manuscript.

A Pilot Non-Inferiority Randomized Controlled Trial to Assess Automatic Adjustments of Insulin Doses in Adolescents with Type 1 Diabetes on Multiple Daily Injection Therapy

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7.2 Abstract

Background: Multiple daily injections (MDI) therapy for type 1 diabetes involves basal and bolus insulin doses. Non-optimal insulin doses contribute to the lack of satisfactory glycemic control. We aimed to evaluate the feasibility of an algorithm that optimizes daily basal and bolus doses using glucose monitoring systems for MDI therapy users.

Methods: We performed a pilot, non-inferiority, randomized, parallel study at a diabetes camp comparing basal-bolus insulin dose adjustments made by camp physicians (PA) and a learning algorithm (LA), in children and adolescents on MDI therapy. Participants wore a glucose sensor and underwent 11 days of daily dose adjustments in either arm. Algorithm adjustments were reviewed and approved by a physician. The last 7 days were examined for outcomes.

Results: 21 youths (age 13.3 (SD, 3.7) years; 13 females; HbA1c 8.6% (SD, 1.8)) were randomized to either group (LA (n=10) or PA (n=11)). The algorithm made 293 adjustments with a 92% acceptance rate from the camp physicians. In the last 7 days, the time in target glucose (3.9–10 mmol/L) in LA (39.5% , SD, 20.7) was similar to PA (38.4% , SD, 15.6) (p = 0.89). The number of hypoglycemic events per day in LA (0.3, IQR, [0.1–0.6]) was similar to PA (0.2, IQR, [0.0–0.4]) (p = 0.42). There was no incidence of severe hypoglycemia nor ketoacidosis.

Conclusions: In this pilot study, glycemic outcomes in the LA group were similar to the PA group. This algorithm has the potential to facilitate MDI therapy, and longer and larger studies are warranted.

Keywords: Decision support system, Multiple daily injections, Treatment adjustments, Learning algorithm.

7.3 Introduction

In type 1 diabetes (T1D), insulin is lost due to the autoimmune destruction of the pancreatic beta cells [1]. T1D is treated with lifelong insulin-replacement therapy using multiple daily injections (MDI) or continuous subcutaneous insulin infusion via a portable pump. Intensive insulin therapy aiming at tight glucose control is key

to reducing the risk of micro- and macrovascular complications caused by sustained hyperglycemia [2, 3]. However, only a minority of T1D individuals achieve acceptable glucose targets, due to fear of hypoglycemia [4].

Worldwide, MDI therapy remains the most common intensive insulin therapy for T1D. In MDI therapy, different insulin formulations are used, each characterized by a specific profile of action, aiming to mimic insulin secretion patterns in non-diabetic individuals [2, 5] . Usually, one or two long-acting insulin doses are injected daily to replace the basal secretion of insulin by a healthy pancreas, and one bolus of rapid-acting insulin dose is injected with each meal to control metabolic impact of meal-carbohydrates. Bolus insulin injections are mostly determined based on carbohydrate ratios (gram per unit) which specify how many grams of carbohydrate are handled by each unit of insulin. Insulin treatment titration in MDI therapy can be achieved by adjusting both the basal insulin dose and carbohydrate ratios.

Daily glucose profiles, insulin doses, consumed meals, and activity levels can be analyzed by patients or health care professionals to make adjustments to the basal insulin dose and carbohydrate ratios. However, this process is sporadic, time-consuming, error-prone, and subjective. A decision support system that automates this process can help achieve a more rapid treatment intensification, reduce errors, and optimize physicians and patients time.

Several groups have proposed decision support systems for individuals with type 1 diabetes [6, 7, 8, 9], but few were targeted for MDI therapy users. Breton et al. [10] conducted a randomized study in 16 pump- and 8 MDI-treated adults with T1D to evaluate an insulin advisory system comprising of an insulin titration scheme that

recommends changes in basal doses, a smarter bolus calculator, and an exercise advisor. In this 48-hour study, they showed that the use of the system reduced glucose variability compared to participants' usual care, but other glycemic outcomes were similar. Reddy et al. [11] conducted a 6-week, non-randomized study where 10 adults on MDI therapy used an advanced bolus calculator that integrated a learning algorithm to recommend meal boluses. A trend in decreasing post-meal hypoglycemia events was observed.

We have developed a learning algorithm that adjusts the basal insulin dose and carbohydrate ratios for MDI therapy, based on previous day's glucose, insulin, and meal data. In this paper, we present a randomized non-inferiority pilot study in a diabetes camp comparing glucose outcomes following insulin dose adjustments via either our learning algorithm (LA) or the camp physicians (PA).

7.4 Research Design and Methods

7.4.1 Study Design and Participants

This was an open-label, randomized, two-way, parallel study investigating the non-inferiority of automatic insulin adjustments made by a learning algorithm compared to insulin adjustments made by a physician. Both algorithm and physician adjustments were made daily. We recruited children and adolescents with type 1 diabetes using MDI therapy attending Camp Carowanis (Quebec, Canada), a camp for youth with T1D. Participants attended one of three 12-day camp sessions. Eligible participants were males and females, 8 to 21 years old, HbA1c $\leq 11\%$, and who had been diagnosed with type 1 diabetes for 1 year or longer. Participant HbA1c level was measured on the first day of each camp session by a finger stick glycosylated

hemoglobin test (A1cNow System, PTS Diagnostics, Whitestown, USA). Participants who required injections of isophane insulin (NPH) or any intermediate-acting insulin were excluded. A full list of exclusion criteria is included in the protocol (online supplementary material).

The protocol conformed to the standards set by the Declaration of Helsinki and was approved by the Research Ethics Board at McGill University Health Center. The study was registered at clinicaltrials.gov under the identifier: NCT03764280. Study participants aged 18 years or older, and parents or guardians of participants aged 17 years or younger gave written informed consent; written assent was obtained from minors.

7.4.2 Randomization and Masking

Participants were randomly assigned (1:1) to either intervention. Randomization was done in blocks of four using sealed envelopes which were opened by the participants once enrolled in the study. Participants, investigators, and camp staff were not masked to the allocation assignments.

7.4.3 Study Procedures

During each camp session (12 days), participants underwent their usual MDI therapy consisting of a long-acting insulin injection (at bedtime or in the morning) and three rapid-acting insulin injections at meals time (breakfast, lunch, and dinner). Each day, participants' insulin basal and bolus doses were evaluated by either a camp physician or by our algorithm. The insulin doses were either not changed, increased, or decreased. Daily evaluations, instead of less frequently, were imposed by the camp protocol.

At the first day of the camp, participants in both groups wore a Freestyle Libre glucose sensor (Abbott Diabetes Care, Witney, UK) for the duration of the camp. At mealtimes, the sensor reader was used to retrieve the glucose measurements over the last 8 hours, and data were downloaded every morning to be used by the algorithm and the camp physicians.

During the camp, mealtimes were standardized, but participants were free to choose their meal size and content. The camp included breakfast at 8:00 AM, lunch at 12:30 PM, dinner at 5:30 PM, a bedtime snack at 8:00 PM, and two optional snacks at 10:30 AM and 2:30 PM. If participants choose to have snacks, these snacks were given everyday irrespective of glucose levels. The mean amount of daily carbohydrates in consumed snacks was the same in both groups (32-36g). At main meals (breakfast, lunch, and dinner), participants that used carbohydrate ratios had their insulin bolus dose calculated based on the amounts of carbohydrates in their meal (calculated by the camp nutritionist), and participants that used a fixed-dose insulin regimen selected a meal with pre-specified carbohydrate content. The insulin bolus doses were also adjusted with positive or negative corrections based on mealtime glucose levels (from the Freestyle sensor). Morning, afternoon, and bedtime snacks were not accompanied by insulin boluses. Participants had morning and afternoon activities.

Glucose level (from the Freestyle sensor) was checked at each meal and snack, and we followed the camp's hypoglycemia and hyperglycemia protocols. The camp's hyperglycemia protocol was to verify ketone levels if blood glucose was more than 14.9 mmol/L. A correction bolus was given through a syringe if ketone levels were more than 1.0 mmol/L. The camp's hypoglycemia protocol was to give carbohydrates

(starting at 15g, and up to 45g) when campers felt hypoglycemic or glucose was below 4.4 mmol/L, and to treat again if glucose levels did not rise above 4.4 mmol/L after 15 min.

For the participants in the LA group, the algorithm was initialized using participant's average total daily dose over the previous three days, weight, and most recent therapy parameters. The therapy parameters consisted of the insulin basal dose and three carbohydrate ratios (for participants following a fixed dose regimen, an equivalent carbohydrate ratio value, based on the carbohydrate content of their predefined meal, was used internally by the algorithm). These parameters were cut by around 20% by the camp physicians, at the first day of the camp, before being used in our algorithm. Every morning, sensor data from the Freestyle Libre reader and previous day's meals, hypoglycemia treatments, and insulin data were used to run the algorithm. The algorithm generated a printable report with suggested insulin therapy recommendations (online supplementary material, Figure S4-S5). Reports were reviewed and approved by a physician before being implemented.

For the participants in the PA group, at-home therapy parameters were cut by around 20% by the camp physicians for the first day of the camp. For the subsequent days, we provided physicians with a report containing glucose sensor data, meals, and insulin information (online supplementary material, Figure S3). The attending camp physician made daily insulin recommendations based on this report.

Six physicians participated in reviewing the algorithm recommendations for the participants in the LA group and providing insulin recommendations for the participants in the PA group; one physician each week. Since recommendations were made

daily before the breakfast data became available, and both the algorithm and the physicians needed to see the effects of the last recommendation before making the next recommendation, the breakfast carbohydrate ratios were only evaluated once every 2 days instead of daily.

7.4.4 Automatic Adjustments of Insulin Doses

Our learning algorithm is based on a run-to-run update rule where therapy parameters (the basal dose and the three carbohydrate ratios) are updated based on their previous values and observations made during the previous day [12]. Observations consist of previous glucose, insulin, hypoglycemia treatments, and meal data. Our algorithm uses a glucoregulatory mathematical model to estimate the optimal values of the therapy parameters that would have resulted in optimal control in a specific day. The recommendation for the following day is a mixture of these optimal values and the values estimated from previous days using the run-to-run update rule. The weights of the parameters estimated in each day depends on the ability of the model to explain its data. The algorithm was implemented in MATLAB R2017b (MathWorks) and runs on a laptop.

7.4.5 Study Outcomes

The primary outcome was the percentage of time spent in the glucose target range (3.9–10 mmol/L) during the last 7 days of the study. Secondary outcomes included time spent below the target range, time spent above the target range, total insulin delivery, standard deviation of glucose, coefficient of variance of glucose, and the number of participants experiencing hypoglycemic events. Study outcomes were

also calculated for the day (07h00 to 23h00) and night periods (23h00 to 07h00). Study outcomes were calculated using sensor readings from the Freestyle Libre.

7.4.6 Statistical Analysis

The statistical analysis was calculated for the percentage of time spent in target in the last 7 days of the study. We conclude non-inferiority if the lower limit of the 95% CI for the treatments difference (LA – PA) was more than the non-inferiority threshold. We used a standard deviation of 10% and aimed to provide 80% power at the 5% significance level. We consequently calculated that 36 participants (18 in each group) are required if the non-inferiority threshold is -2 hours/day (-8.3%) and 62 participants (31 in each group) are required if the non-inferiority threshold is -1.5 hours/day (-6.4%). Therefore, we aimed to recruit between 36 and 62.

Analyses were performed on an intention-to-treat basis, in which we included data from all participants. We used the two-sample t-test for outcomes with normally distributed data, and the Wilcoxon rank-sum test for outcomes with non-normally distributed data. For normally distributed outcomes, we reported means and standard deviations, and for non-normally distributed outcomes we reported medians and interquartile ranges. Normality was assessed using the Shapiro-Wilk test. 95% confidence interval is reported when relevant. We report nominal p values for all outcomes, and we did not do adjustment for multiple comparisons.

7.5 Results

From July 2nd to August 10th, 2018, we recruited 21 campers and camp counselors, of which 10 were randomized to the LA group and 11 to the PA group. Table

Table 7–1: Baseline characteristics for study participants.

	LA group (n=10)	PA group (n=11)
Female	4 (40%)	9 (82%)
Age (years)	12.3 [8.7–14.8]	12.4 [11.2–16.4]
Weight (kg)	53 [30–64]	52 [41–67]
BMI (kg/m2)	20.3 [18.5–24.7]	22.1 [17.6–25.4]
BMI z-score	0.91 [0.05–1.38]	0.33 [-0.41–0.98]
Duration of diabetes (years)	2 [1–7]	5 [1–6.8]
Total daily insulin (unit)	27 [21–41]	37 [29–46]
Daily insulin per weight (unit/kg)	0.64 [0.53–0.89]	0.71 [0.63–0.84]
HbA1c (%)	7.8 [6.9–8.6]	7.9 [7.1–10.5]
Participants using fixed dose	3 (30%)	3 (27.3%)

1 shows the baseline characteristics of the 21 participants. There was no difference in demographics between participants in both groups. During the camp, fewer than expected campers were using multiple daily injections. Since fewer than the target number of participants were enrolled, results from this study are considered exploratory and the study is considered pilot.

7.5.1 Primary and Secondary End Points

Figure 7–1 shows the average glucose profiles in the last 7 days for both groups. Table 7–2 reports the study endpoints. The time spent in glucose target range (3.9–10 mmol/L) in the last 7 days in the LA group was similar to the PA group (39.5% (SD, 20.7) *vs* 38.4% (SD, 15.6); p=0.89), with a mean difference of 1.1% (95% CI, -15.6–17.8). The non-inferiority of the algorithm recommendations compared to the

physician recommendations within a threshold of 2 hours/day in the time spent in the target range was not significant (p=0.13), though, since fewer than the target number of participants were enrolled, this non-inferiority analysis is exploratory. The time spent in hypoglycemia (¡ 3.9 mmol/L) in the last 7 days in the LA group was similar to the PA group (4.0% (IQR, 3.2–4.3) *vs* 2.4% (IQR, 1.2–5.8); p=0.7). Primary and secondary comparisons were consistent when analyzing daytime only (7:00–23:00) and nighttime only (23:00–7:00) data (Table 2). Primary and secondary comparisons were also unchanged when analyzing 11-day data as opposed of 7-day data.

Table 7–2 details secondary endpoints of the study. Mainly, the time spent in hypoglycemia (<3.9 mmol/L) in the last 7 days in the LA group was similar to the PA group (4.0% (IQR, 3.2–4.3) *vs* 2.4% (IQR, 1.2–5.8); p=0.7). These results were consistent when analyzing daytime only (7:00–23:00) and nighttime only (23:00–7:00) data (Table 7–2). Figure 7–1 shows the average profile of glucose in the last 7 days for both LA group and PA group.

Table 7–2: Comparison of outcomes in participants adjusted by the learning algorithm (LA) and by a physician (PA). Values are averaged for 7 days for each participant.

	LA group (n=10)	**PA group (n=11)**	**Difference (LA–PA)**	**p value**
Non-inferiority primary outcome				
Percentage of time 3.9–10.0 mmol/L (%)	39.5 (20.7)	38.4 (15.6)	1.1 (-15.6, 17.8)	0.13
Day and night outcomes (24 hours)				
Percentage of time < 3.9 mmol/L (%)	4.0 [3.2–4.3]	2.4 [1.2–5.8]	0.6 (-2.0, 2.9)	0.70
Percentage of time > 10.0 mmol/L (%)	56.8 (21.1)	57.7 (18.5)	-0.9 (-19.0, 17.1)	0.91
Mean sensor glucose (mmol/L)	11.9 (2.3)	11.7 (2.7)	0.1 (-2.2, 2.4)	0.92
CV of sensor glucose (%)	41.6 (7.34)	40.9 (5.7)	0.7 (-5.3, 6.6)	0.82
Total insulin (U)	35.0 (21.3)	47.1 (23.3)	-12.0 (-32.5, 8.4)	0.23
Basal insulin (U)	12.6 (8.4)	18.2 (11.1)	-5.6 (-14.7, 3.5)	0.21
Bolus insulin (U)	22.4 (13.6)	28.9 (13.3)	-6.5 (-18.7, 5.8)	0.29
Total meals (g)	255.8 (62.9)	246.1 (53.5)	9.7 (-43.5, 62.8)	0.71
Hypoglycemia events (#/day)	0.3 [0.1–0.6]	0.2 [0.0–0.4]	0.1 (-0.1, 0.3)	0.42
Day outcomes (16 hours) (7:00-23:00)				
Percentage of time 3.9–10.0 mmol/L (%)	32.0 (19.5)	37.5 (23.0)	-5.5 (-25.1, 14.1)	0.56
Percentage of time < 3.9 mmol/L (%)	1.2 [0.0–2.9]	0.0 [0.0–1.2]	0.2 (0.0, 2.9)	0.18
Percentage of time > 10.0 mmol/L (%)	65.1 (23.3)	61.9 (23.2)	3.2 (-18.1, 24.4)	0.76
Mean sensor glucose (mmol/L)	12.9 (3.0)	12.3 (2.7)	0.6 (-2.0, 3.2)	0.61
CV of sensor glucose (%)	35.7 (8.15)	32.6 (6.6)	3.1 (-3.6, 9.9)	0.34
Hypoglycemia events (#/day)	0.0 [0.0–0.1]	0.0 [0.0–0.0]	0.0 (0.0, 0.1)	0.54
Night outcomes (8 hours) (23:00-7:00)				
Percentage of time 3.9–10.0 mmol/L (%)	42.3 (24.1)	40.2 (20.6)	2.1 (-18.3, 22.5)	0.83
Percentage of time < 3.9 mmol/L (%)	5.4 [0.5–7.6]	7.1 [1.9–12.5]	-1.9 (-8.7, 4.4)	0.50
Percentage of time > 10.0 mmol/L (%)	52.2 (23.8)	50.8 (28.1)	1.5 (-22.4, 25.4)	0.90
Mean sensor glucose (mmol/L)	10.9 (2.5)	10.3 (3.2)	0.5 (-2.1, 3.1)	0.69
CV of sensor glucose (%)	40.4 (10.5)	38.1 (8.9)	2.3 (-6.6, 11.2)	0.59
Hypoglycemia events (#/day)	0.0 [0.0–0.0]	0.0 [0.0–0.1]	0.0 (0.0, 0.0)	1.00

Values reported as mean and standard deviation or as median and interquartile range.
Values reported as mean or median with 95% confidence interval.
p value is for non-inferiority with a threshold of -8.3%. We report p value for superiority for other outcomes.
CV stands for coefficient of variation.
Only treated hypoglycemia events are counted.

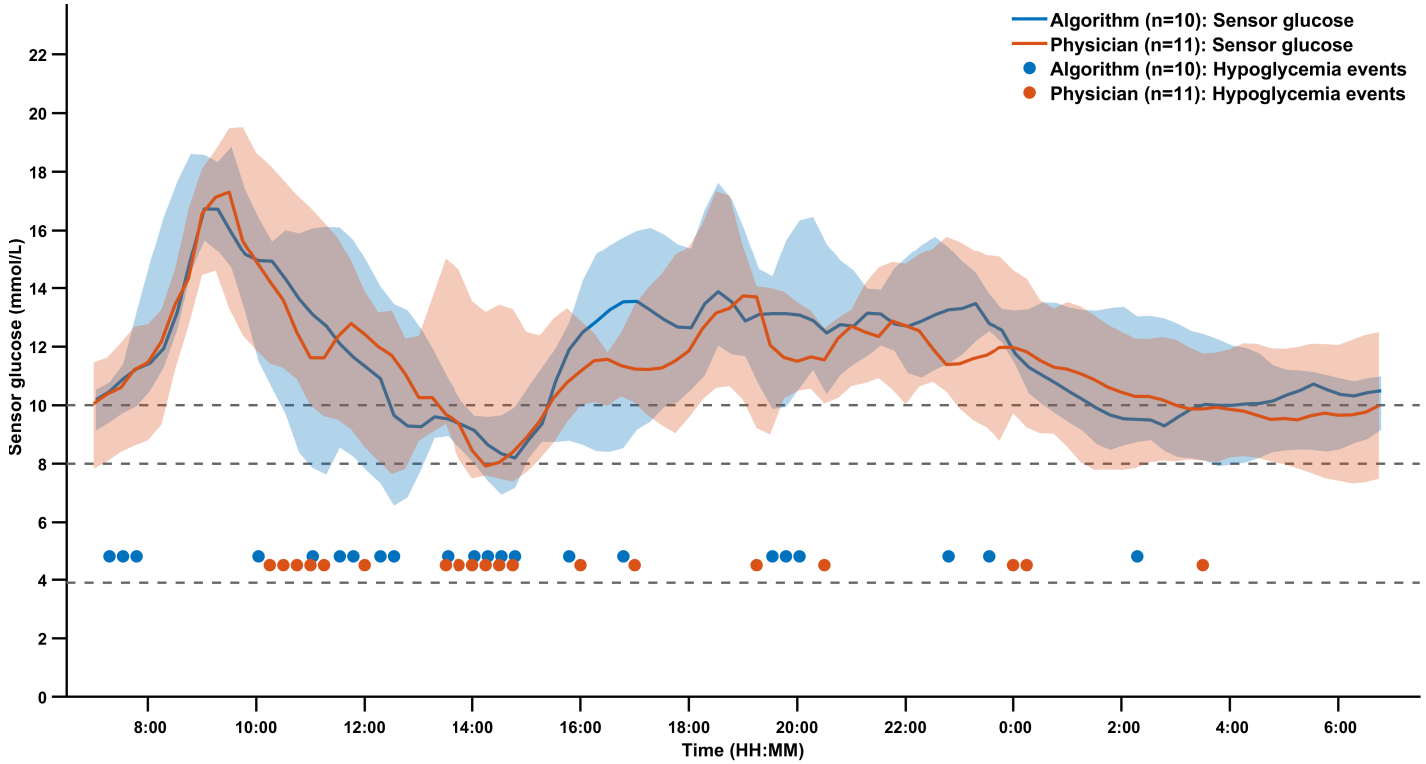

Figure 7–1: Comparison of sensor glucose in the last 7 days between the learning algorithm (LA) group and the physician adjusted (PA) group.

Similar and large variability between days could be observed in the two groups (Online supplement material, Figure 7–4): between-day variability (reported as a coefficient of variation) in time in target form day 5 to 11 in the LA group was 43.0% (IQR, 31.5–58.2) and in the PA group was 51.1% (IQR, 40.6–65.6; p=0.39).

No episodes of severe hypoglycemia or hyperglycemia with diabetic ketoacidosis occurred in either group. One adverse event occurred in the PA group but was unrelated to the study: a volleyball net fell on one of the participants.

7.5.2 Comparison Between Days (2-to-4) and Days (9-to-11)

Table 7–3 shows the comparison of outcomes between days 2-to-4 and days 9-to-11 in both groups. Four participants (two in the PA group and two in the LA group) were excluded from this analysis because of lack of glucose data points in days (2-to-4). Neither the LA group (n=8) nor the PA group (n=9) showed an improvement in the time in target between the start and the end days; however, the number of treated hypoglycemic events per day was decreased in both groups; by -1.0 (95% CI, -1.3– -0.5) (p=0.02) in the LA group and by -0.7 (95% CI, -1.0)– -0.2) (p=0.03) in the PA group.

Table 7–3: Comparison between days 3-to-5 and days 9-to-11 for both learning algorithm (LA) group and physician adjusted (PA) group.

	LA group (n=8)			**PA group (n=9)**		
	Days (3-4-5)	**Days (9-10-11)**	**p value**	**Days (3-4-5)**	**Days (9-10-11)**	**p value**
Time 3.9–10.0 mmol/L (%)	50.6 (20.6)	41.0 (21.6)	0.09	45.1 (17.3)	34.2 (19.2)	0.24
Time $<$ 3.9 mmol/L (%)	7.4 (9.3)	4.9 (3.6)	0.50	12.1 (12.4)	3.9 (4.0)	0.14
Time $>$ 10.0 mmol/L (%)	42.0 (22.2)	54.1 (19.9)	0.16	42.8 (22.5)	61.9 (22.5)	0.15
Total insulin (U/day)	32.4 (20.0)	34.9 (20.6)	0.20	48.2 (21.2)	52.9 (24.9)	0.24
Total meals (g/day)	244.4 (68.5)	273.5 (80.3)	0.07	242.8 (46.2)	250.4 (61.8)	0.46
Mean sensor glucose (mmol/L)	9.9 (2.2)	12.0 (2.5)	**0.05**	9.8 (3.0)	12.4 (3.3)	0.12
CV of sensor glucose (%)	43.2 (11.3)	42.9 (10.7)	0.95	48.0 (12.2)	39.6 (6.8)	0.11
Hypoglycemia events(3) (#/day)	1.2 [0.5–1.7]	0.2 [0.0–0.5]	**0.02**	0.7 [0.3–0.8]	0.0 [0.0–0.1]	**0.03**

Values reported as mean and standard deviation or as median and interquartile range.
CV stands for coefficient of variation.
Only treated hypoglycemia events are counted.

Table 7–4: Parameter changes from day 1 to 11 in the algorithm group (LA) and the physician adjusted group (PA).

	LA group (n=10)				PA group (n=11)			
	Basal Dose	**Break-fast CR**	**Lunch CR**	**Dinner CR**	**Basal Dose**	**Break-fast CR**	**Lunch CR**	**Dinner CR**
Mean baseline values at day 1	15.0U	11.8 g/U	14.0 g/U	14.8 g/U	20.4U	10.6 g/U	12.0 g/U	12.0 g/U
Mean change	-13%	8%	25%	3%	15%	5%	-12%	-7%
Minimum change	-46%	-10%	-36%	-28%	-44%	-60%	-58%	-69%
Maximum change	20%	58%	200%	50%	200%	114%	67%	88%
Proportion of participants who had their parameters increased	10%	30%	60%	50%	45%	45%	18%	27%
Proportion of participants who had their parameters decreased	60%	20%	30%	40%	45%	36%	82%	64%
Mean of change in participants who had their parameters increased	20%	33%	53%	21%	55%	35%	48%	55%
Mean of change in participants who had their parameters decreased	-25%	-9%	-22%	-17%	-21%	-29%	-25%	-35%
Proportion of participants with changes $\geq \lvert 10\% \rvert$	50%	30%	80%	70%	64%	55%	100%	73%
Proportion of participants with changes $\geq \lvert 20\% \rvert$	40%	20%	40%	20%	36%	36%	64%	73%
Proportion of participants with changes $\geq \lvert 30\% \rvert$	30%	10%	40%	10%	18%	36%	27%	64%
Proportion of participants with changes $\geq \lvert 40\% \rvert$	10%	10%	20%	10%	18%	18%	18%	45%

Table 7–5: Glycemic outcomes before and after daily changes in basal doses and carbohydrate ratios.

	Before	**The day after**	**Before**	**The day after**
Days where basal dose increased	**LA group (n=13)**		**PA group (n=26)**	
Basal dose (U)	19.0 [4.8–22.0]	21.0 [5.8–24.3]	16.5 [9.0–19.0]	18.0 [10.0–20.0]
Night mean sensor glucose (mmol/L)	12.3 [10.4–14.7]	8.6 [6.4–11.7]	13.2 [11.6–17.0]	11.6 [8.1–16.0]
Night hypoglycemia events (no.)	0	1	0	2
Days where basal dose decreased	**LA group (n=26)**		**PA group (n=19)**	
Basal dose (U)	12.5 [9.0–26.0]	11.5 [8.0–22.0]	20.0 [17.3–24.3]	17.0 [15.3–20.3]
Night mean sensor glucose (mmol/L)	7.2 [4.2–8.5]	8.0 [6.4–12.3]	4.6 [3.7–6.6]	7.6 [6.2–10.2]
Night hypoglycemia events (no.)	7	4	5	2
Days where carbohydrate ratios increased	**LA group (n=55)**		**PA group (n=40)**	
Carbohydrate ratio (g/U)	14.0 [10.0–18.0]	17.0 [12.0–21.8]	6.2 [5.0–10.5]	7.3 [6.0–11.5]
2-hour iAUC (h.mmol/L)	0.3 [0.0–3.9]	1.9 [0.1–4.8]	1.5 [0.0–4.0]	1.7 [0.4–4.3]
Hypoglycemia events 1 to 4 hours after meal (no.)	17	9	11	8
Days where carbohydrate ratios decreased	**LA group (n=54)**		**PA group (n=59)**	
Carbohydrate ratio (g/U)	15.0 [10.9–20.0]	14.0 [9.4–17.0]	10.0 [7.5–15.7]	8.2 [6.7–13.4]
2-hour iAUC (h.mmol/L)	1.2 [0.1–3.3]	1.0 [0.2–2.3]	4.6 [0.7–7.0]	1.9 [0.0–7.6]
Hypoglycemia events 1 to 4 hours after meal (no.)	2	5	1	7

7.5.3 Analysis of Algorithm's and Physicians' recommendations

The physicians evaluated 328 therapy parameters (insulin basal dose or carbohydrate ratios), of which they made 162 (49.4%) changes (increase or decrease). The algorithm evaluated 292 therapy parameters, of which it made 181 (62.0%) changes. Figure 7–2 shows daily parameter changes for all participants over the duration of the study.

Figure 7–3 shows the mean of the relative daily changes in each therapy parameters.

In both groups, most changes were applied in the initial days and there was a trend toward less parameter changes by the end of the study.

Table 7–4 provides a summary of parameter changes from day 1 to day 11. There was a large variability between participants in the adjustments. The magnitude of overall adjustments made by the algorithm and physicians were comparable, yet, they differed slightly from one therapy parameter to another. Table 7–5 reports glycemic outcomes before and after daily changes in the basal doses and the carbohydrate ratios. Daily changes made by the algorithm and physicians were justified and had immediate effects on glycemic outcomes.

Out of the 292 algorithm decisions (no change, increase, or decrease), the camp physicians approved 268 (91.8%) decisions and overrode 24 (8.2%). Out of those 24 overridden decisions, 6 were overridden in the same direction as the algorithm recommendations but with different magnitudes, 14 were reverted to their original values before the algorithm recommendations, 3 were changed when the algorithm did not make a change recommendation, and 1 was changed in the opposite direction

of the algorithm recommendation. Table 7–6 shows a summary of the acceptance rate of algorithm recommendations per physician.

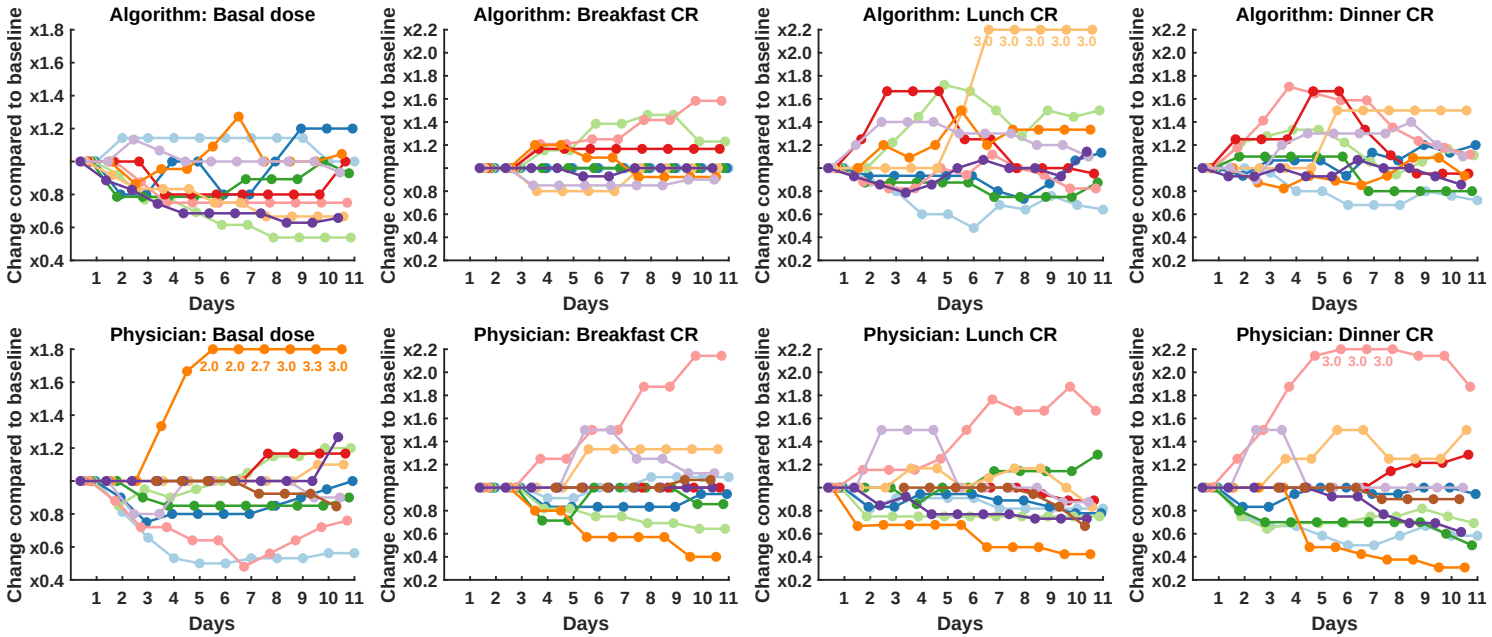

Figure 7–2: Therapy parameter (basal dose and carbohydrate ratios) changes compared to their initial values. Each color represents a different participant. For participants with fixed dose, we use the equivalent carbohydrate ratio using the size of their meals. CR stands for carbohydrate ratio.

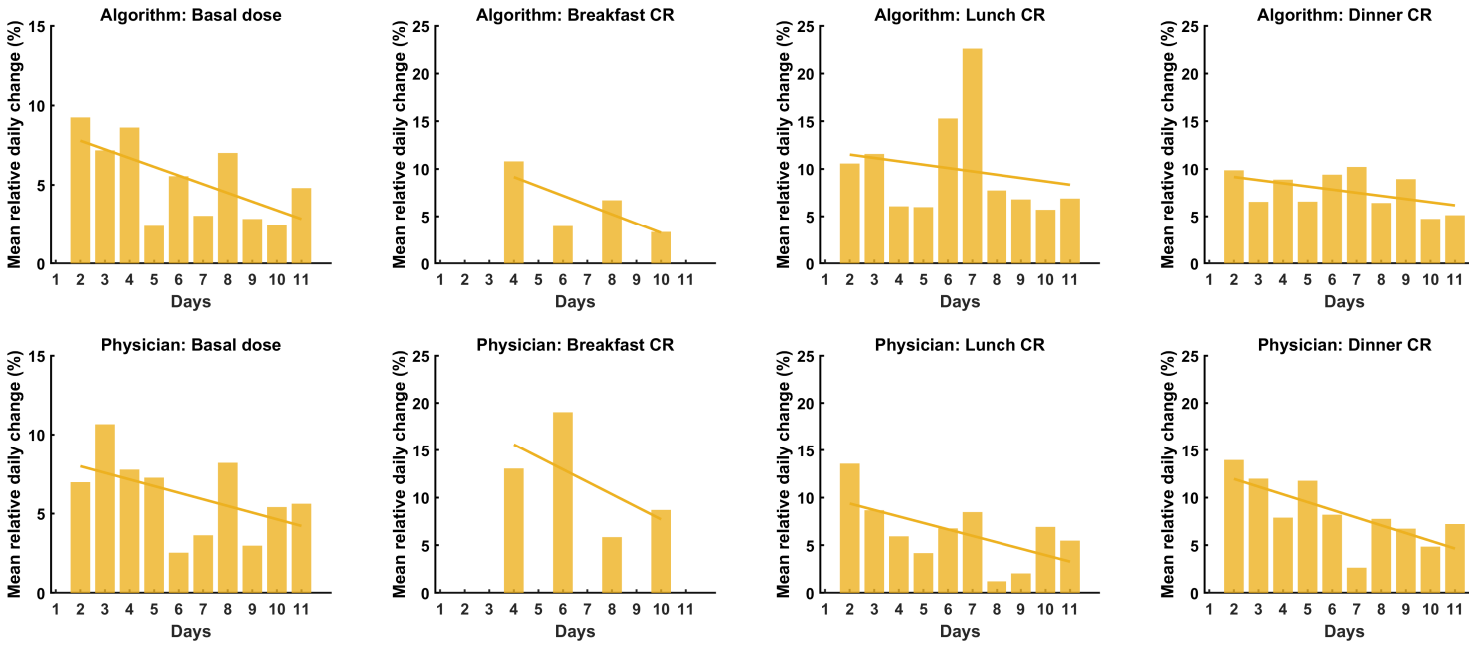

Figure 7–3: Relative daily changes in therapy parameters. For participants with fixed dose, we use the equivalent carbohydrate ratio using the size of their meals. CR stands for carbohydrate ratio.

Table 7–6: Physician acceptance rate of algorithm recommendation in the learning algorithm (LA) group.

Physician	**1**	**2**	**3**	**4**	**5**	**6**	**Overall**
Number of adjustments made by algorithm	24	35	55	90	36	52	292
Approved adjustments by physician	21 (87.5%)	28 (80.0%)	54 (98.2%)	86 (95.6%)	34 (94.4%)	45 (86.5%)	268 91.8%

7.5.4 Retrospective Analysis of Algorithm Agreement with Physicians

In this analysis, we run the algorithm retrospectively on the participants in the PA group. In total, we compared 328 recommendations (no change, increase, or decrease) made by physicians to what the learning algorithm would have recommended given similar data. We counted a recommendation agreement when a similar trend in the recommendations (no change, increase, or decrease) was observed between the algorithm and the physician. Disagreement is counted when opposite recommendations (increase vs decrease or vice-versa) were taken. A partial agreement was counted when either the algorithm or the physician recommends a change while the other did not.

Table 7–7 shows the agreement results. Most recommendations made by the algorithm were on agreement (54.3%) or partially in agreement (43.3%) with the physicians.

Table 7–7: Agreement between physicians and learning algorithm recommendations.

	Agreement	**Disagree-ment**	**Partial agreement**
Basal insulin (U) (n=96)	57.3% (55)	2.1% (2)	40.7% (39)
Breakfast carbohydrate ratio (g/U) (n=38)	57.9% (22)	0.0% (0)	42.1% (16)
Lunch carbohydrate ratio (g/U) (n=99)	52.5% (52)	2.0% (2)	45.5% (45)
Dinner carbohydrate ratio (g/U) (n=95)	51.6% (49)	4.2% (4)	44.2% (42)
All recommendations (n=328)	54.3% (178)	2.4% (8)	43.3% (142)

7.6 Conclusions

We evaluated a learning algorithm that automatically adjusts basal-bolus insulin doses for MDI therapy in children and adolescent with T1D in a diabetes camp. We aimed to show that daily insulin adjustments from our algorithm are non-inferior to insulin adjustments made by physicians. Glycemic outcomes were similar, but the recruitment target was not met and thus the study did not have enough statistical power to confirm the non-inferiority within a 2-hour margin. Nevertheless, a trend was observed. This study is a step forward toward larger and longer studies.

Intensive insulin therapy combined with glucose self-monitoring are key to improving glucose control [13, 14], but adherence to the therapy is a challenging and burdensome task, especially for adolescents [15]. Decision support systems might improve this by processing large datasets of glucose, insulin, and meals, then prompting patients with frequent insulin doses adjustments [6, 11]. Even if these systems may not be more proficient than an expert endocrinologist, demonstrating non-inferiority to physicians is important since algorithmic adjustments can be done more frequently

than physician adjustments in routine clinic visits, allowing a more rapid treatment intensification which may prove to be associated with better glucose outcomes and long-term studies.

Overall acceptance of our algorithm recommendations was high but differed between physicians (from 80% to 98.2%). Disagreement between physicians in insulin adjustments is common, which was recently demonstrated by Nimri et al. with physicians adjusting insulin pump therapy parameters [6]. In that multi-center study with 26 physicians, complete disagreement in adjustments in basal rates, carbohydrate ratios, or insulin sensitivity factors was around 10% . When run retrospectively, our results show that our algorithm rarely disagreed with the physician adjustments, with a disagreement rate of 2.7% in average.

Daily changes made by the algorithm and physicians had positive effects on glycemic outcomes of the following day. For example, in days where participants had a high night glucose, basal dose was increased, resulting in lower night glucose. However, the overall glycemic outcomes (e.g. time in range) was not improved from the start to the end of the study in both groups. This might be attributed to the large day-to-day variability in insulin needs caused by changes in physical activity, food, and weather, all of which can have a significant impact on glycemic control [16, 17, 18]. Nonetheless, both the algorithm and physicians reduced the number of hypoglycemia events, which were high at baseline likely due to a mismatch between insulin doses and the intense levels of physical activity at camp. It is yet to be seen how the algorithm performs with individuals with high baseline A1c in longer outpatient studies.

The learning algorithm runs daily, however, all previous days are implicitly included in the algorithm recommendations. Each day, the algorithm combines the last 24-hour data with the most recent therapy parameters (which were learned from previous days) to generate recommendations for the next day. The following day, the new therapy parameters embodies the information of all previous days and are updated based on the new 24-hour data. This iterative process ensures that lessons from previous days are carried to future recommendations.

Even though the learning algorithm was tested in camp settings, it is designed to work in unrestricted real-world settings. At the camp, the meals were given approximately at the same time every day, but the algorithm can accommodate variable daily eating schedule because it uses a mathematical model that accounts for all meals and insulin doses irrespective of their time. Similarly, at the camp, carbohydrates counting was performed by the camp nutritionist, but carbohydrate counting errors are common in real-life. The ability of the algorithm to mitigate carbohydrate counting errors depends on their nature. If the errors are consistently underestimated or overestimated, the algorithm will learn matched carbohydrate ratios. However, if the errors are large and random, this will jeopardize the ability of the algorithm to learn the optimal carbohydrate ratios.

One particularity of our study is the use of flash glucose monitoring systems instead of continuous glucose monitoring systems. Flash glucose monitoring systems are cheaper, and factory-calibrated. Recent literature showed good user acceptance, satisfactory accuracy (mean absolute relative difference between 11% to 14%), and clinical benefits [19, 20]. Even though the sensor was only flashed at mealtimes,

collected glucose data points over the last 8 hours were enough to generate insulin recommendations.

Our study has several limitations that preclude the generalization of our results. First, this was a short study of 11 days in a setting with large day-to-day variability. Second, every day, the same physician approved the algorithm recommendation in the LA group and made recommendations in the PA group. Third, the camp setting is a controlled environment under which participants were closely observed by camp staff. Fourth, we excluded patients using intermediate-acting insulin (NPH). Fifth, this study only enrolled 21 participants, which was under the targeted sample size. Sixth, we performed daily updates of insulin basal dose and carbohydrate ratios, as required by the camp protocol, but daily updates are unjustified outside camp settings. Our next 3-months outpatient study will implement weekly adjustments by averaging the daily recommendations (clinicaltrials.gov identifier NCT04123054).

Our result suggests that the use of our learning algorithm to make daily adjustments of MDI therapy parameter may be safe and non-inferior to a physician. Longer and larger studies are warranted.

7.7 Acknowledgments

We are grateful to all study participants. We thank the staff at Camp Carowanis, a Diabetic children's foundation at Sainte-Agathe-des-Monts, Canada, for their support and assistance during the study. We thank collogues Joanna Rutkowski and Sophie Giudicelli who helped collecting the data.

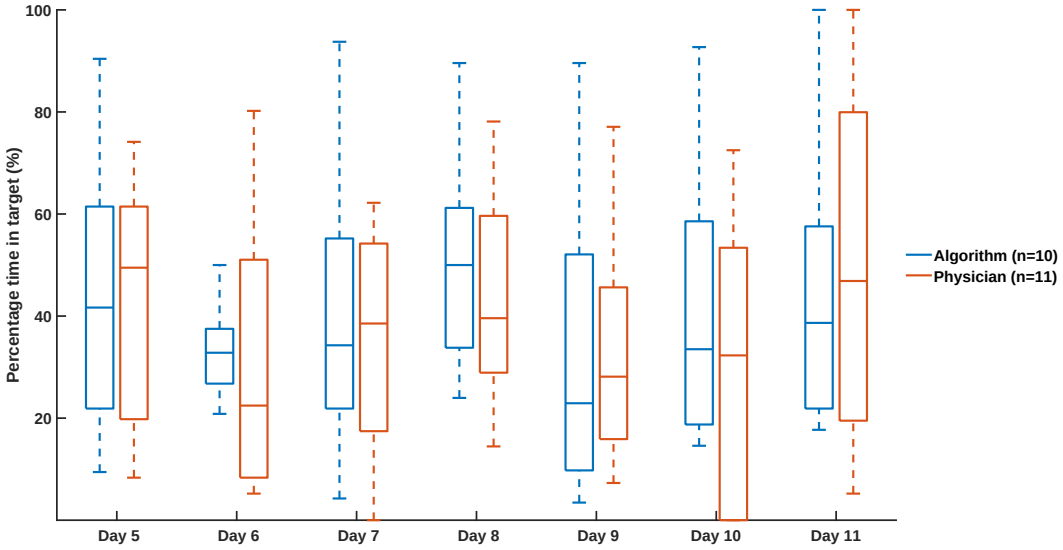

Figure 7–4: Percentage time in target in the learning algorithm group and the physician adjusted group.

7.8 Supplementary Material

7.8.1 Additional Figures for Results

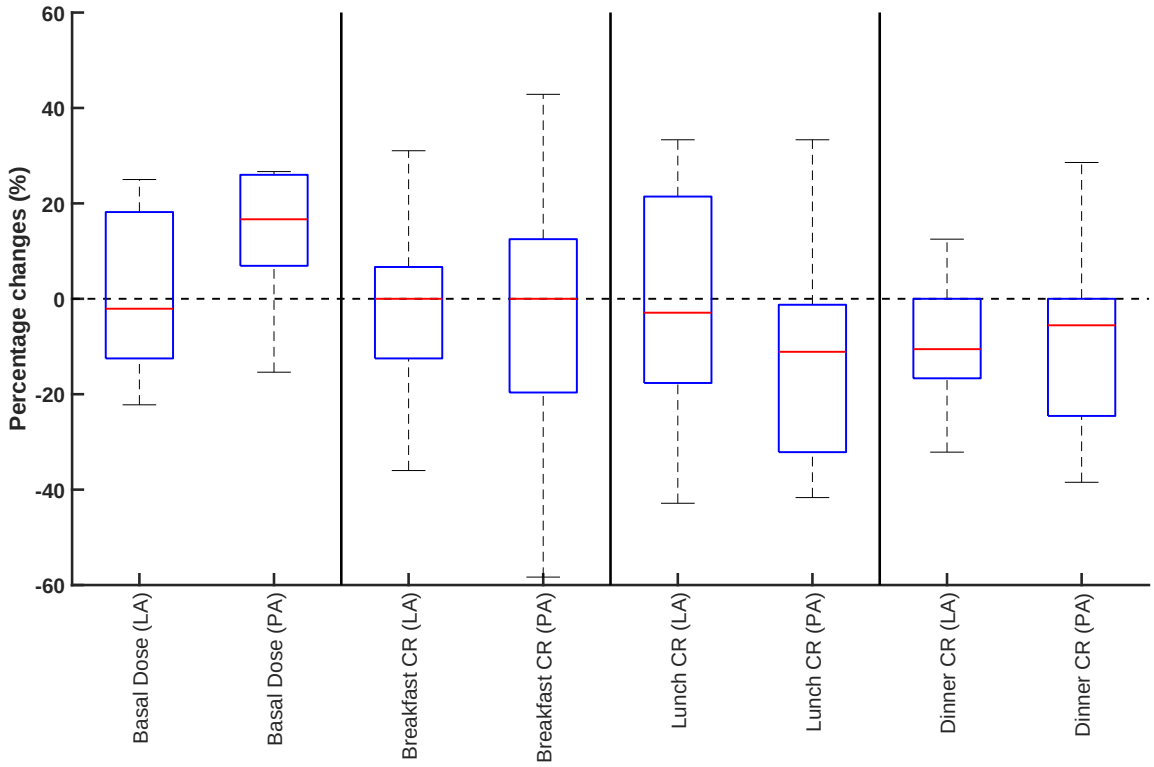

Figure 7–5: Percentage changes in parameters between day 5 and day 11 in both learning algorithm (LA) and physician adjusted (PA) groups.

7.8.2 Physicians Report

Figure 7–6 is an example of report for physicians. "Current" refers to the dose/ratios used on this day. "Recommended" refers to the physician recommendation for the following day based on this day data. In the graph, the blue circle represents the basal dose, the blue triangles represent the prandial bolus, and the red triangles represent the carbohydrate amount of the meal.

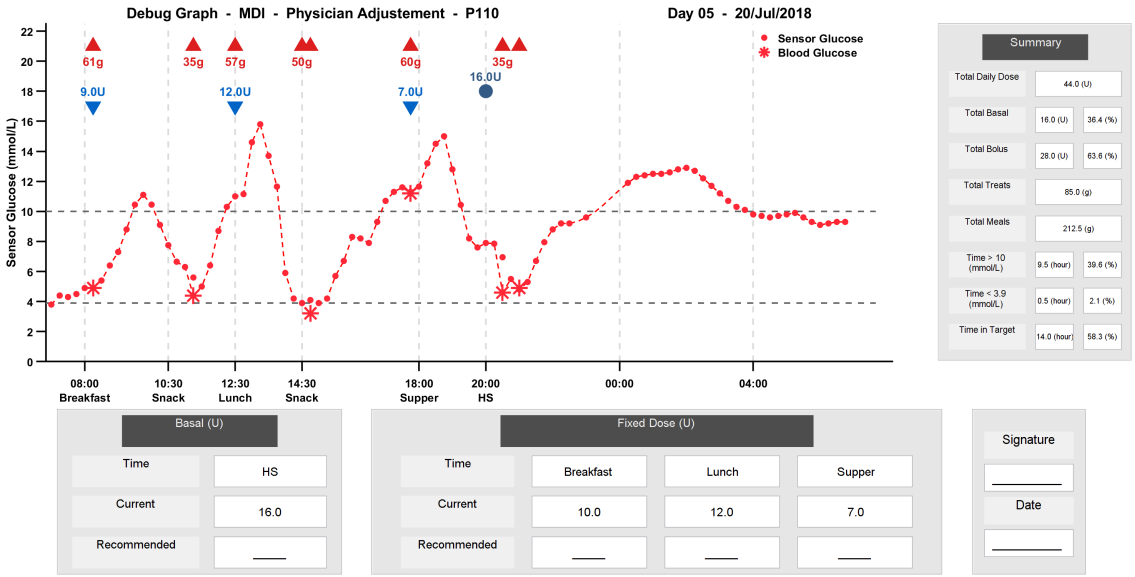

Figure 7–6: Example of physicians report.

7.8.3 Algorithm Report 1

Figure 7–7 is an example of the algorithm report. "Current" refers to the dose/ratios used on this day. "Recommended" refers to the algorithm recommendation for the following day based on this day data. "Used" refers to the physician's approved values. In the graph, the blue circle represents the basal dose, the blue triangles represent the prandial bolus, and the red triangles represent the carbohydrate amount of the meal.

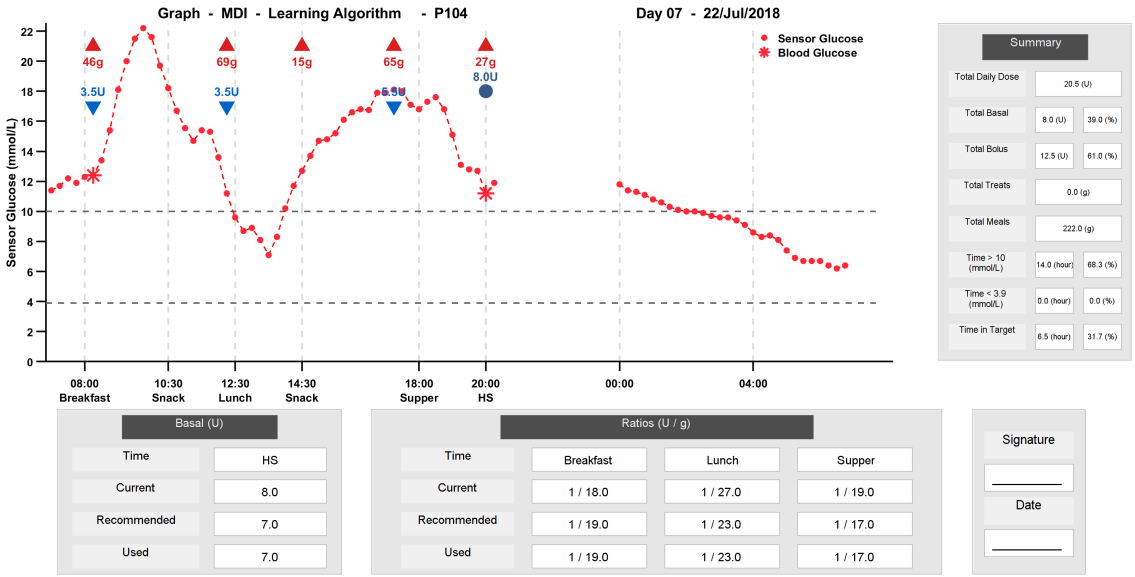

Figure 7–7: Example of algorithm report.

7.8.4 Algorithm Report 2

Figure 7–8 is an example of the algorithm report where the algorithm recommendation was overridden. "Current" refers to the dose/ratios used on this day. "Recommended" refers to the algorithm recommendation for the following day based on this day data. "Used" refers to the physician's approved values. In the graph, the blue circle represents the basal dose, the blue triangles represent the prandial bolus, and the red triangles represent the carbohydrate amount of the meal.

In this example, the algorithm recommended no change in the basal dose (4 u) but the physician changed this value to 5 u. Another physician may have opted to agree with the algorithm.

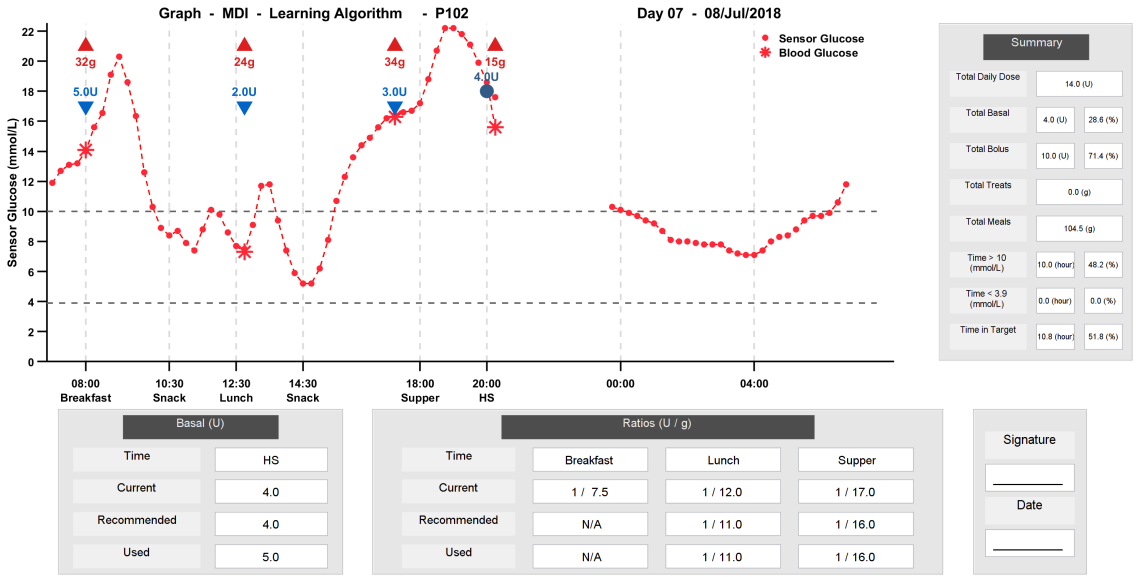

Figure 7–8: Example of algorithm report with override.

7.9 References

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CHAPTER 8

Conclusion and Future Work

In this thesis, modeling, parameter estimation, and control techniques have been exploited to develop advanced insulin dosing algorithms for improving glycemic control in people with type 1 diabetes. Specifically, we aimed to: (i) improve the safety and efficacy of closed-loop insulin delivery after a missed meal-accompanying insulin bolus; (ii) automate insulin doses' adjustments by daily adapting carbohydrate ratios and basal doses for patients using multiple daily injections. In this chapter, we summarize and discuss the main findings of this thesis, then we conclude by recommendations for future work.

8.1 Summary of Original Contributions

Here, we outline the original contributions of this thesis and their significance. A list of publications included in this thesis, or related to the work towards this thesis, is included in Appendix A.

- We developed a novel probabilistic method to detect unannounced meals from recently measured glucose, delivered insulin and consumed meals. The method

combines state estimation and a generalized likelihood test to express the probability of unannounced meals. We have shown a relatively fast detection time, with high sensitivity, and a low false-positive rate.

- We conducted a 9-hour crossover randomized controlled trial in 11 adolescents to assess the efficacy of closed-loop insulin delivery augmented by a meal detection algorithm compared to closed-loop insulin delivery only, and usual care, after an unannounced meal. We have shown that the use of a meal detection algorithm improves the performance of closed-loop insulin delivery systems. To our knowledge, this is the first clinical study to show the benefits of adding a meal detection algorithm to a closed-loop insulin delivery system.
- We proposed a novel glucoregulatory model, inspired by the Bergman minimal model, for patients using multiple daily injections. We have shown that this model can explain a 150-day of real-world data by estimating optimal basal doses and optimal carbohydrate ratios for each day.
- We developed a novel method for insulin doses adjustment using daily glucose, insulin, and meal data. This method combines estimated parameters of a proposed glucoregulatory model with a run-to-run update rule. The algorithm is characterized by an adaptive learning rate based on confidence about estimated parameters. We have shown that, in a simulation study, this algorithm outperforms classical run-to-run algorithms.
- We conducted an 11-day parallel randomized controlled trial in 21 children and adolescents using multiple daily injections to assess the non-inferiority of algorithmic insulin adjustments to adjustments made by physicians. In this study

conducted in a diabetes camp, we have shown similar glycemic outcomes in participants using the algorithm's recommendations compared to participants using the physicians' recommendations. This algorithm has the potential to improve glycemic control in type 1 diabetes patients using multiple daily injections.

Since both algorithms are titrating insulin doses and are intended for medical use by people with type 1 diabetes, they are considered Software as a Medical Device. Software as a Medical Device is regulated by the Food and Drugs Act authorities (Health Canada in Canada, Food and Drug Administration in the United States, the European Medicines Agency in Europe). The experimental results presented in this thesis can serve as the first step towards future approval by authorities.

8.2 Discussion of Findings

8.2.1 Meal Detection for Closed-Loop Insulin Delivery

Thanks to advances in glucose monitoring systems and insulin pumps, closed-loop insulin delivery is becoming the new standard for continuous subcutaneous insulin infusion therapy. Yet, these systems are still considered hybrid since meal-related boluses are delivered manually upon user request. A step towards achieving a fully automatic system will require the incorporation of a meal detection algorithm.

Ideally, a closed-loop insulin delivery system should react to the mismatch between actual glucose and the target glucose without user intervention. However, as discussed in Chapter 3, safe and efficacious control in a fully closed-loop mode is unlikely to be compatible with the current system delays associated with the subcutaneous route. Because of the delay between insulin delivery and the maximum

glucose-lowering effect of insulin (around 100min) [126], and since any delivered insulin can not be removed (system with positive-only inputs [127]), most closed-loop systems implement mechanisms to become more conservative the more insulin is delivered. For PID-based controllers, this can be implemented through negative feedback of insulin-on-board [128]. For MPC-based controllers, this can be implemented by weighting the insulin control action with insulin-on-board [129]. Consequently, when a meal is consumed without an insulin bolus, current systems will not react aggressively enough to eliminate the risk of hyperglycemia. Simulation results in Chapter 4 showed that both the risk of early hyperglycemia and late hypoglycemia is increased after a missed meal-accompanying insulin bolus.

We theorized that the control strategy needed in the case of a missed insulin bolus is distinct from the nominal control strategy. As a result, a switching approach based on a probabilistic rule that detects when an unannounced meal is consumed was developed. The proposed probabilistic approach had the advantage of designing the detection threshold to minimize the probability of making false positives. However, in Chapter 4, we argued that due to glucose variability, all switching strategies are prone to false positives (situations where a hypothetical meal is detected while no meal is consumed in reality). Consequently, our control strategy following the meal detection was rather conservative, and mainly driven by the glucose levels at the detection time, rather than the estimated meal size. We have also shown that, in simulations, after a false positive, the closed-loop controller is able to avoid hypoglycemia by insulin suspension.

Typically, using glucose levels only might be misleading to detect meals without boluses because, for instance, a long suspension of insulin can cause glucose levels to increase even without a consumed meal. Our algorithm employs a glucoregulatory model that implicitly considers interactions between previously delivered insulin, consumed meals, and observed glucose levels. Using simulations, we showed a sensitivity between 93% and 98%, depending on the carbohydrates in the consumed meal, and we observed a detection time of 40 min (IQR, [30 – 50]). Yet, since the meal detection algorithm still relies on the availability of glucose measurements, missing or unreliable measurements may result in algorithm malfunction. Although, since it is intended to run with a closed-loop system, the same safety rules applicable to a closed-loop system (Healthy communication with the sensor, filtering of readings dropouts, ...) can be applied.

Different statistical measures can be used to evaluate the performance of a detection algorithm (binary classification test). The specificity measure of a detection algorithm is the ratio of true negatives compared to all negative detections (false positives + true negatives). In our context, a false positive is defined by an instance where the algorithm did not flag an announced meal when an unannounced meal is consumed. A true negative is defined by any instance where the algorithm did not flag an announced meal when either all consumed meals were announced or there was no consumed meal. Since the frequency of unannounced meals is relatively low, the specificity is inherently biased toward the high end. In the simulations conducted in Chapter 4, we reported the count of false positives instead of the specificity to avoid

this problem. Other measures that do not take the true negative rate into account, such as F-score, could have been used instead.

In Chapter 5, we compared the efficacy of closed-loop insulin delivery augmented with a meal detection module after a missed meal-accompanying insulin bolus with standard closed-loop insulin delivery and with open-loop insulin delivery (continuous subcutaneous insulin infusion without real-time glucose monitoring). This was a randomized crossover clinical trial in 11 adolescent patients. We have shown that closed-loop (with or without meal detection module) was able to bring back glucose levels to normal levels after 5 hours of the missed bolus. However, closed-loop insulin delivery only was not able to reduce the risk of hyperglycemia (measured by the 4-hour incremental area under the curve after the missed bolus) compared to open-loop insulin delivery, while closed-loop insulin delivery with the meal detection module did. These results support the efficacy of a switched control strategy using the meal detection module.

In the clinical experiment, all unannounced meals were detected and the time of meal detection was similar to simulation results: 40 min (IQR, [40 – 57.5]). Still, this clinical experiment was limited to relatively large 60g-meals, which might have facilitated meal detection. It should be noted that adding a meal detection algorithm to current closed-loop systems does not guarantee a fully closed-loop insulin delivery system. Recent clinical studies incorporating a meal detection approach with a fully closed-loop insulin delivery system lacked a comparative arm, or did not achieve satisfying glycemic outcomes [98, 97]. However, the addition of a meal detection

algorithm does improve the efficacy and safety of current systems. Therefore, larger and longer clinical studies are warranted.

8.2.2 Insulin Doses Adjustment for Multiple Daily Injections

Multiple daily injections therapy remains the most common treatment for type 1 diabetes. Long-term management of this therapy requires continuous adaptation of insulin dosages. This can be accomplished by continuously evaluating the efficacy of previously delivered insulin doses in achieving glycemic targets. Currently, this optimization is conducted by physicians and patients, and it remains subjective, error-prone, and time-consuming. With advances in glucose monitoring systems and novel connected insulin pens, research is under steady progress to develop insulin decision support systems to automate this process.

Most current research in decision support systems is based on the run-to-run approach where a control signal is adjusted iteratively at the end of each run to achieve a certain objective [130]. Generally, the objective of the previously proposed run-to-run algorithms is to optimize a specific glycemic outcome (e.g., time spent in hypoglycemia after lunch, or average nocturnal glucose level [118]). This results in each parameter being updated independently ignoring correlations between parameters. In Chapter 6, we proposed a unique approach where the run-to-run update rule is combined with a glucoregulatory model. Using the model, we predict the optimal values of the therapy parameters that would have resulted in optimal control on a specific day. By fitting our model to all available data, optimal values are simultaneously estimated.

The proposed model structure is based on a Bergman minimal model [131], however, it was modified to incorporate clinical knowledge required in insulin therapy titration. First, it is known that different carbohydrate ratios are needed for different times of the day [132]. It is also known that the insulin sensitivity following meals can be different between meals and even different from night insulin sensitivity [133]. This motivated the separation between the insulin bolus and the insulin basal channels in this model. Second, it is known that the optimal basal insulin dose should ensure a stable glucose levels during fasting conditions and a change in this dose is reflected by a new equilibrium glucose level [134]. This was enforced in the model by neglecting glucose effectiveness in promoting its disposal [134]. Finally, it is known that the optimal carbohydrate ratios should ensure that glucose levels return to their pre-meal values after 4-5 hours. This was enforced in the model by matching the glucose absorption from the meal model to the bolus insulin absorption model. In Chapter 6, we have shown that this model can explain real-world data of multiple days in different individuals.

Each day, the recommendations for the following day are a mixture of the predicted optimal values and the values estimated from the previous days using the run-to-run update rule. This iterative process ensures that previous days' data are carried to future recommendations. In addition, in each day, the run-to-run gain (learning rate) is adapted using the quality of the data: if on a specific day the model's goodness of fit is poor (indicator of model under-parametrization or unknown events, such as physical activities or non-recorded meals), or if we observe high uncertainty in the parameters' estimate (indicator of model over-parametrization), we

prevent the algorithm from relying on its predictions, making our method robust to model inaccuracy.

In Chapter 7, we evaluated this algorithm in a clinical randomized parallel study comparing adjustments made by our algorithm to adjustments made by physicians in adolescents with type 1 diabetes. Even though we did not achieve significant non-inferiority at the desired threshold since fewer than the target number of participants were enrolled, there was no difference in the glycemic outcomes between patients in the two groups. Furthermore, a positive trend in improving glycemic outcomes could be observed when analyzing the immediate effects of parameter changes suggesting that our experiment might have been limited by the large variability between days in the camp settings.

Algorithm recommendations were generally accepted by physicians, and recommendations were different between participants suggesting treatment personalization. The overall magnitude of adjustments made by the algorithm and physicians were comparable. We also showed that when we re-run our algorithm on participants' data from the physician adjusted group, the algorithm proposed recommendations in alignment with the physicians' recommendation. Our result suggests that the use of this algorithm to make daily adjustments of insulin doses for patients using multiple daily injections is safe.

8.3 Limitations

The generalization of the above findings is limited to the experiments where the algorithms were validated.

- The meal detection algorithm classification performance was evaluated in a 13-hour simulation experiment with one missed meal, and with a carbohydrate content between (40g – 80g). The detection rate was not validated for small meals (less than 40g), consecutive missed meals, and meals with different macro-nutrient content (different fat and protein compositions).
- The meal detection algorithm was tuned to keep the rate of false positives around 5%, and such as the control strategy following a false positive does not result in increased hypoglycemia risk. Other criteria based on other statistical measures were not investigated.
- The clinical trial where the meal detection algorithm was evaluated was supervised by our clinical team and was conducted in a hospital setting. The trial was of short duration (9 hours) with a small number of participants (11). A standardized meal of around 60g of carbohydrates was used in all visits.
- The insulin dosing algorithm for people using multiple daily injections is a model-based algorithm that requires glucose, insulin, and meal data. Other algorithms may only rely on glucose data. Also, we used a simplified model to make implementation feasible, the effects of different models were not investigated.
- The ability of the insulin dosing algorithm to improve glycemic outcomes was only shown in a simulation experiment that is limited in its variabilities.
- The clinical trial where the insulin dosing algorithm was evaluated was supervised by our clinical team and was conducted in a camp setting. The trial was of short duration (11 days) with a small number of participants (21). In this

trial, we performed daily updates of insulin basal dose and carbohydrate ratios, as required by the camp protocol, but daily updates are unjustified outside camp settings.

8.4 Future Work

In light of the present work, several recommendations can be formulated for future work.

8.4.1 Hypoglycemia Treatments Detection

Previous records of hypoglycemia can unveil patterns that may help to improve glycemic control. However, not all patients record their hypoglycemia events since (i) these are frequent events for type 1 diabetes patients, (ii) there is no clear immediate benefit of recording these events (the possible benefit is only seen when patterns of hypoglycemia events can be observed from multiple days), (iii) there is no automatic way to record these events.

In Chapter 4, we presented an unannounced meal detection algorithm. This algorithm can be adapted to serve as a hypoglycemia treatment detection algorithm. Automatic hypoglycemia detection can become a basis for another algorithm that detects dangerous patterns in glucose data. In figure 8–1, we show a one-week real-world data where possible hypoglycemia events can be detected.

8.4.2 Longer and Larger Clinical Studies

The large day-to-day variabilities observed in glucose data suggests that bi-weekly or weekly insulin adjustments are better suited for people with type 1 diabetes, rather than daily adjustments.

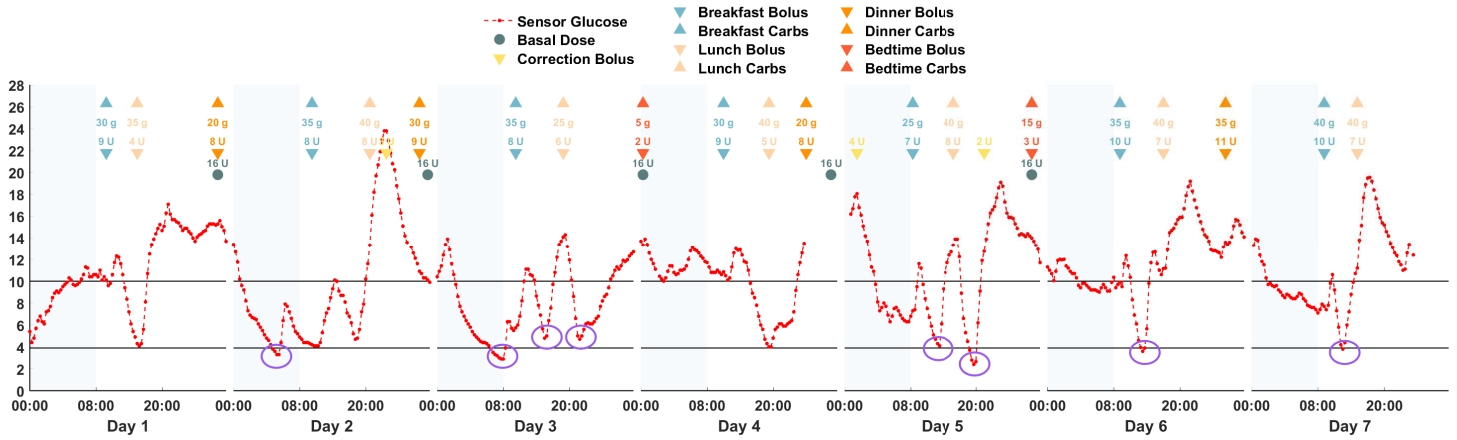

Figure 8–1: Example of one week data in a real-life settings. Possible hypoglycemia events are highlighted with violet ellipses.

A six-month randomized parallel trial in 180 patients with type 1 diabetes to evaluate the efficacy of the Diabeo mobile application, a bolus calculator with insulin adaptations, showed an improvement in HbA1c [112]. Yet, because of physicians' quarterly follow-up, or bi-weekly teleconsultations, the efficacy of automatic insulin adjustments alone could not be assessed. Similarly, a 6-month randomized parallel trial in 181 patients with type 2 diabetes to evaluate the d-Nav Insulin Guidance System, a handheld device that is used to automatically individualize the treatment (not necessarily insulin doses), showed improvement in HbA1c [135].

In Chapter 6, we argued that our method can account for day-to-day variability by averaging recommendations over several days. The positive results in Chapter 7 motivated the integration of our method in a new bolus calculator that provides weekly insulin adjustments branded the "iBolus". We are conducting a 3-month parallel randomized trial in 84 adults using multiple daily injections to investigate the superiority of algorithmic adjustments compared to patients' usual therapy (clinicaltrials.gov identifier NCT04123054).

In Figure 8–1, we show a one-week data from this study. In Table 8–1, we show an example of how weekly insulin adjustments can be generated using our algorithm. Each day, the optimal therapy parameters (basal dose and carbohydrate ratios) for this day are estimated. Each week, a new recommendation in all therapy parameters is provided based on the individual days.

Table 8–1: Results of weekly insulin adjustments from the one-week data in Figure 8–1. CR stands for carbohydrate ratio. U stands for insulin units.

	Basal Dose (U)	**Breakfast CR (g/U)**	**Lunch CR (g/U)**	**Dinner CR (g/U)**	**Bedtime CR (g/U)**
Used parameters	16	4	7	4	20
Day 1	17.7	4.7	5.3	5	
Day 2	15.2	4.3	5.8	4.3	
Day 3	16	4.9	6.6		
Day 4	17.2	5	7.7	4	15.5
Day 5	19.1	4.7	7.7		15
Day 6	16	5	5.7	4.3	
Day 7	16.6	5	6		
Recommendations	17	4.5	6.5	4.5	17

8.4.3 Adaptive Bolus Calculator

We have developed an automatic dose adjustments algorithm for multiple daily insulin. This algorithm can be used as basis for an adaptive bolus calculator that learns from patients data. A complete adaptive bolus calculator may include other functionalities:

- Fat and protein content in meals significantly affects glucose excursions after meals [136]. General recommendation on insulin dosing following a meal with fat/protein is available in the literature [137]. However, it is possible to learn individualized recommendations resulting in better control. Developing such an algorithm will require: (i) Developing a model of glucose including the effects of fat and protein. (ii) Developing an adaptive control algorithm, this algorithm may incorporate machine learning concepts to learn patient-specific glucose trends. (iii) Clinical evaluation of the algorithm.
- Physical activities are an important challenge for type 1 diabetes patients because of the risk of hypoglycemia after physical activities. Even though exercise is recommended, patients must carefully manage their glucose when they exercise. General recommendation on insulin dosing before exercise exist [75]. However, it is again possible to learn individualized recommendations resulting in better control [123].

8.4.4 Fully Closed-loop Systems

The ultimate goal of type 1 diabetes treatments is to provide optimal control of glucose without burdening patients. Currently, patients are required to count the carbohydrates content in their meals and announce it to the system. In closed-loop

insulin delivery, the main limitation of achieving fully automated control with the current insulin pumps and glucose sensors is the mismatch between time-to-peak of meal absorption and time-to-peak of subcutaneously delivered insulin. To overcome this limitation, multiple approaches can be investigated:

Faster insulin absorption Faster insulin may enable both a reduction of hyperglycemia by faster reduction of glucose and reduction of hypoglycemia by faster insulin clearance. Manufacturing of faster insulin analogs is an active area of research [138, 36].

Slower carbohydrate digestion Adjunctive therapy in the form of other medications can achieve slower meal-related glucose absorption [93, 139, 140]. By slowing glucose absorption from meals, the glucose peak after meal consumption can be delayed, giving more time for insulin to reach its peak glucose-lowering effects.

Glucagon responsiveness Glucagon is a hormone that triggers the liver to release its glucose reserve. By delivering glucagon, it might be possible to tune the closed-loop algorithm more aggressively (deliver more insulin) [87]. Also, if a meal detection is utilized, a more aggressive control strategy can be used.

A fully-closed loop system might become feasible with the arrival of new drugs, theoretical research in both modeling and control is warranted.

8.4.5 Adaptive Artificial Pancreas

Not all type 1 diabetes patients reach glycemic targets, partly due to the large day-to-day variability in insulin needs. Although closed-loop insulin delivery provides good glycemic control, these systems may need to adapt to long-term variations in

insulin requirements. Furthermore, most closed-loop systems are initialized using the open-loop therapy parameters (basal rates, carbohydrate ratios, insulin sensitivity factors), improper initialization due to non-optimal parameters may degrade the overall performance of closed-loop insulin delivery. Other specific parameter for closed-loop insulin delivery can also be adapted, such as the controller gain [121].

Adjusting these parameters may improve the overall performance of theses systems while abrupt changes in glucose levels should be handled by the closed-loop controller. Algorithms that adjust and optimize insulin dosing for closed-loop insulin delivery exist but are yet to show a clear advantage in clinical trials [119, 122, 117]. Such an algorithm can be extended from the proposed insulin doses algorithm for multiple daily injections therapy users [141].

8.4.6 Infusion-set Failure Detection

Infusion sets for pumps are usually required to be replaced every 2-3 days in order to avoid skin and infusion problems [78]. However, little is known about the true life expectancy of infusion sets, and few clinical studies investigated increasing infusion sets survival [142]. A smart algorithm that analyzes glucose profiles and detects the optimal time for infusion set may reduce the burden on patients using an insulin pump (continuous subcutaneous insulin delivery, or closed-loop insulin delivery) [143, 144, 145]. Such an algorithm can be extended from the proposed unannounced meal detection algorithm.

APPENDICES

APPENDIX A

Achievements

A.1 Publications Included in this Thesis:

List of publications included in this thesis. (∗) indicates shared co-first authorship.

A.1.1 Journal Publications

- A. El Fathi, M. R. Smaoui, V. Gingras, B. Boulet, and A. Haidar (2018). "The Artificial Pancreas and Meal Control: An Overview of Postprandial Glucose Regulation in Type 1 Diabetes." IEEE Control Systems, vol. 38, no. 1, pp. 67-85, 2018.
- A. El Fathi, R. E. Kearney, E. Palisaitis, B. Boulet, and A. Haidar. "Day-to-Day Insulin Dose Optimization for Patients with Type 1 Diabetes on Multiple Daily Injections Therapy" IEEE Transaction on Biomedical Engineering. Revision submitted February 2020.
- A. El Fathi(∗), E. Palisaitis(∗), J. E. Von Oettingen, P. Krishnamoorthy, R. E. Kearney, L. Legault, and A. Haidar. "A Pilot Non-Inferiority Randomized Controlled Trial to Assess Automatic Adjustments of Insulin Doses for Individuals with Type 1 Diabetes on Multiple Daily Injections Therapy" Pediatrics Diabetes. Revision Submitted April 2020.

- E. Palisaitis(∗), A. El Fathi(∗), J. E. Von Oettingen, L. Legault, and A. Haidar. "A Meal Detection Algorithm for the Artificial Pancreas: A Randomized Controlled Clinical Trial in Adolescents with Type 1 Diabetes" Diabetes Care. Submitted July 2020.

A.1.2 Conference Publications

- A. El Fathi, E. Palisaitis, B. Boulet, L. Legault, and A. Haidar. "An Unannounced Meal Detection Module for Artificial Pancreas Control Systems." in 2019 American Control Conference (ACC), 2019: IEEE, pp. 4130-4135.

A.2 Other Publications

List of other publications directly linked to my work towards this thesis. (∗) indicates shared co-first authorship.

A.2.1 Journal Publications

- M. Tsoukas,, J. Rutkowski, A. El Fathi, J. F. Yale, S. Bernier-Twardy, A. Bossy, E. Pytka, L. Legault and A. Haidar (2019). "Accuracy of FreeStyle Libre in adults with type 1 diabetes: the effect of sensor age." Diabetes Technology & Therapeutics, Oct 15 2019.
- E. Palisaitis,(∗), A. El Fathi(∗), J. E. Von Oettingen, P. Krishnamoorthy, R. Kearney, P. Jacobs, J. Rutkowski, L. Legault and A. Haidar (2019). "The Efficacy of Basal Rate and Carbohydrate Ratio Learning Algorithm for Closed-Loop Insulin Delivery (Artificial Pancreas) in Youth with Type 1 Diabetes in a Diabetes Camp." Diabetes Technology & Therapeutics, Oct 25 2019.
- A. Haidar, M. Tsoukas, S. Bernier-Twardy, J. F. Yale, J. Rutkowski, A. Bossy, E. Pytka, A. El-Fathi, N. Strauss, and L. Legault. "A novel dual-hormone

insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomised controlled crossover trial" Diabetes Care, vol. 43, no. 3, pp. 597-606, Mar 2020.

- S. Major, A. El Fathi, E. Palisaitis, R. E. Kearney, J. E. Von Oettingen, P. Krishnamoorthy, L. Legault, A. Haidar. "Postprandial Hyperglycemia Following Insulin Suspensions by the Artificial Pancreas: Implications for Bolus Calculators" Diabetes Obesity & Metabolism. Accepted for publication March 2020.
- J. N. Myhre, M. Tejedor, I. Launonen, A. El Fathi, F. Godtliebsen "Policy Gradient Methods for Controlling Blood glucose in Patients with Type 1 Diabetes Mellitus" Applied Soft Computing. Submitted January 2020.
- A. Jafar, A. El Fathi, A. Haidar. "Using Reinforcement Learning to Automatically Adapt Carbohydrate Ratios and Programmed Basal Rate in the Artificial Pancreas" IEEE Journal of Biomedical Health Information. Revision submitted March 2020.

A.2.2 Conference Publications

- A. Haidar et al., "Alleviating Carbohydrate-Counting Burden in Type 1 Diabetes (T1D) Using the Artificial Pancreas (AP) and Sodium Glucose-Linked Transporter 2 Inhibition," Canadian Journal of Diabetes, vol. 43, no. 7, p. S10, 2019.
- C. Bailey, et al. "The Official Journal of ATTD Advanced Technologies & Treatments for Diabetes Conference Berlin, Germany—February 20–23, 2019." Diabetes Technology & Therapeutics 21.S1: A-1.

- E. Renard, et al. "Abstracts from ATTD 2017 10th International Conference on Advanced Technologies & Treatments for Diabetes Paris, France—February 15–18, 2017." Diabetes Technology & Therapeutics 19.S1 (2017): A-1.

A.2.3 Patents

- A. El Fathi, A. Haidar "Method and System for Determining Glucose Change in a Subject," U.S. Provisional Patent Application No. 62/871,931. Filed July 2019.

A.2.4 Symposiums and Talks

- "Camp Carowanis: Étude pour les injections multiples", Café scientifique of Haidar Artificial Pancreas Lab, Canada, Quebec, Montréal. September 2018. Main Audience: General Public.
- "An Unannounced Meal Detection Module for Artificial Pancreas Systems", BME Symposium. May 2019. Main Audience: Graduate Students.
- Youtube video about the clinical studies conducted in Camp Carowanis: McGill Artificial Pancreas System - Camp Carowanis 2018. Target Audience: General Public.

APPENDIX B

Authorization Letters to Conduct Research

We attach the authorization letters received from the McGill University Health Center research ethics board to conduct the clinical trials presented in Chapters 5 and 7.

Centre universitaire de santé McGill | McGill University Health Centre

2017-07-25

Professor Ahmad Haidar
3775 University Street
Room 304
Montreal, Quebec
H3A 2B4

email: ahmad.haidar@mcgill.ca

Re: MUHC Authorization Missed Bolus / 2017-2786

"An Open-label, Randomized, Three-way, Crossover study to Assess the Safety and Efficacy of Closed-loop Delivery with and without Meal Detection Module and Conventional Pump Therapy in regulating Glucose Levels after a Missed Bolus in Adolescents with Type 1 diabetes in Inpatient settings"

Dear Professor Haidar,

We are writing to confirm that the study mentioned above has received all required institutional approvals.

You are hereby authorized to conduct your research at the McGill University Health Centre (MUHC) as well as to initiate recruitment.

Please refer to the MUHC Study number in all future correspondence relating to this study.

In accordance with applicable policies it is the investigator's responsibility to ensure that staff involved in the study is competent and qualified and, when required, has received certification to conduct clinical research.

Should you have any questions, please do not hesitate to contact the support for the Personne mandatée at personne.mandatee@muhc.mcgill.ca.

We wish you every success with the conduct of the research.

Sincerely,

Sheldon Levy

Sheldon Levy
for:
Marie Hirtle, LL.B. LL.M.
Personne Mandatée
Centre Universitaire de Santé McGill

Centre universitaire de santé McGill | McGill University Health Centre

2018-05-31

Dr. Laurent Legault
1001 Decarie Boulevard
Room A04.6320
Montreal, Quebec
H4A 3J1

c/o: Ahmad Haidar

email: ahmad.haidar@mcgill.ca

Re: MUHC Authorization (MDI Camp Study / 2019-4579)

> "An Open-Label, Randomized, Two-Way, Parallel Study to Compare the Efficacy of MDI Treatment with Physician Adjusted and Optimization Algorithm adjusted Basal-Bolus Parameters in Children and Adolescents with Type 1 Diabetes at a Diabetes Camp"

Dear Dr. Legault,

We are writing to confirm that the study mentioned above has received research ethics board approval and all required institutional approvals, namely:

- Contracts

You are hereby authorized to conduct your research at the McGill University Health Centre (MUHC) as well as to initiate recruitment.

Please refer to the MUHC Study number in all future correspondence relating to this study.

In accordance with applicable policies it is the investigator's responsibility to ensure that staff involved in the study is competent and qualified and, when required, has received certification to conduct clinical research.

Should you have any questions, please do not hesitate to contact the support for the Personne mandatée at personne.mandatee@muhc.mcgill.ca.

We wish you every success with the conduct of the research.

Sincerely,

Sheldon Levy

MUHC REB Coordinator
for MUHC REB Co-chair mentioned above

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REFERENCES

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