Model-based approaches accounting for physical activity to personalize insulin treatment in type 1 diabetes

Doctoral Thesis

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MODEL-BASED APPROACHES
ACCOUNTING FOR PHYSICAL ACTIVITY
TO PERSONALIZE INSULIN TREATMENT
IN TYPE 1 DIABETES

A thesis submitted to attain the degree of

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ABSTRACT

Each year, around 150,000 children and adolescents are newly diagnosed with type 1 diabetes (T1D). It is one of the most widespread autoimmune diseases worldwide, in which the body is no longer able to produce insulin due to the destruction of insulin-producing pancreatic β-cells. Insulin is the hormone responsible for lowering blood glucose (BG) levels, and people with T1D therefore require insulin treatment to adequately manage their BG. This presents a daily challenge, as BG is affected by a multitude of factors such as meals and physical activity (PA).

The management of PA is particularly challenging. PA-driven changes in glucose metabolism lead to an increase in hypoglycemia risk, as an increase in glucose utilization by the exercising muscles may cause BG levels to decline. Furthermore, hypoglycemia can still occur several hours after the activity due to a rise in insulin sensitivity. To prevent hypoglycemia and maintain stable BG levels during and after PA, insulin dose reductions and additional carbohydrate intake may be required. However, the effects of PA on BG levels depend strongly on PA intensity and duration. In addition, they change dynamically over time, which makes suitable treatment adjustment to PA difficult.

In this thesis, we study the effects of PA on BG dynamics and propose a control strategy for insulin delivery to improve glycemic control in the presence of PA. We first identify the open challenges in PA management and evaluate existing treatment recommendations in an in-silico study. We use a published model of glucose-insulin regulation that includes moderate-intensity PA to test these guidelines and assess BG outcomes for a range of different PA scenarios. While the risk for acute hypoglycemia is significantly reduced, we observe that the risk for late-onset hypoglycemia remains elevated, indicating that further treatment adjustments are needed in the hours following the PA session.

Next, we present a new model of the glucoregulatory system that incorporates the acute and prolonged effects of moderate- to high-intensity PA on glucose metabolism. We propose a stepwise approach for model calibration to describe a T1D population and further demonstrate the model’s ability to capture individual-subject data from an observational study conducted under free-living conditions. The resulting model covers the relevant PA processes affecting BG levels during activity and recovery. It allows to simulate realistic full-day scenarios and could facilitate the in-silico development of treatment strategies for PA of various intensities and durations.

Finally, we address the particular need for strategies that reduce late-onset hypoglycemia and develop an approach for insulin dosing adjustments following PA. First, we propose to estimate insulin sensitivity from continuous glucose measurements using an unscented Kalman filter to quantify PA-related changes in insulin requirements. Importantly, this approach does not rely on any PA inputs, and we show that the prolonged rise in insulin sensitivity after PA can be tracked successfully. Subsequently, we introduce a bolus calculator that uses these estimates to scale meal and basal boluses. We further extend this to continuous dosing adjustments based on model predictive control, to offer approaches both
for people who cover their insulin needs with multiple daily injections and who use an insulin pump for continuous insulin delivery. Our results indicate that the presented control strategy leads to improved BG outcomes and that it reduces the risk for PA-related late-onset hypoglycemia.
Typ 1 Diabetes (T1D) wird jährlich bei rund 150,000 Kindern und Jugendlichen neu diagnostiziert. Es ist eine der weltweit am weitesten verbreiteten Autoimmunkrankheiten, bei der der Körper durch die Zerstörung von β-Zellen der Pankreas nicht mehr in der Lage ist, Insulin zu produzieren. Insulin ist das Hormon, das für das Senken des Blutzuckers (BZ) verantwortlich ist. Zur Regulierung des BZ sind Menschen mit T1D daher auf die Gabe von Insulin angewiesen. Dies stellt eine tägliche Herausforderung dar, da der BZ von einer Vielzahl an Faktoren wie Mahlzeiten und Sport beeinflusst wird.


Schließlich befassen wir uns mit dem besonderen Bedarf für Strategien, die das Auftreten von Hypoglykämie nach dem Sport reduzieren, und entwickeln eine Methode zur Anpassung der Insulindosierung. Als Erstes schätzen wir Insulinempfindlichkeit aus kontinuierlichen Glukosemessungen mit einem Unscented
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INTRODUCTION

Diabetes is one of the most common chronic diseases worldwide. In 2019, an estimated 536.6 million people age 20 and older, 10.5% of the adult population, were affected, and its prevalence is expected to rise to 12.2% by 2045 (Sun et al., 2022). Diabetes is characterized by chronically high blood glucose (BG) levels, which is associated with severe short- and long-term complications that include cardiovascular disease, kidney failure, nerve damage and blindness (American Diabetes Association, 2014). This further results in reduced quality of life and shorter life expectancy for people living with the disease (Heald et al., 2020).

5–10% of diabetes cases can be attributed to type 1 diabetes (T1D). T1D occurs mostly in childhood, and incidence rates have been increasing yearly in many countries (Ogle et al., 2022). People with T1D do not produce endogenous insulin and rely on lifelong insulin treatment to lower their BG levels. This can result in hypoglycemia, a potentially life-threatening condition, if excessive amounts of insulin are injected. Therefore, adequate insulin dosing is crucial to achieve good glycemic control and minimize diabetes-related complications from both hyper- and hypoglycemia. This requires personalization and continuous adaptation of insulin treatment for each individual (Janež et al., 2020), where factors like diet, health status, stress and activity level need to be taken into consideration.

Regular physical activity (PA) is recommended for people with T1D for its many health benefits (American Diabetes Association, 2015), as it improves cardiovascular fitness and insulin sensitivity (the glucose-lowering ability of insulin), leads to better mental and psychosocial health and potentially improves BG control (Colberg et al., 2016; Riddell et al., 2022; Pivovarov et al., 2015). However, PA-related changes in glucose metabolism cause an increase in hypoglycemia risk, and fear of hypoglycemia is a main barrier for people with T1D to exercise (Brazeau et al., 2008). Insulin dose adjustments and carbohydrate (CHO) supplementation may be needed, but high inter-patient variability in the BG response to PA requires personalization of general recommendations (Riddell et al., 2017), making it difficult to accurately adjust treatment to PA and improve glycemic outcomes for the individual.

Late-onset hypoglycemia after PA poses a particularly challenging problem for people with T1D. It is caused by a prolonged rise in insulin sensitivity (Mul et al., 2015) and can occur several hours after the activity. Consequently, nocturnal hypoglycemia, which often stays undetected, occurs regularly in people with T1D, especially following afternoon exercise (Davey et al., 2013; Gomez et al., 2015). However, targeted strategies for its prevention are still largely missing (Riddell et al., 2017).

In this thesis, we therefore address the unmet need for personalized treatment strategies to reduce the PA-related late-onset hypoglycemia risk using mathematical modelling. We will first propose a suitable model that captures glucose-insulin regulation in the presence of PA, before presenting an approach to estimate PA-induced changes in insulin requirements from BG measurements and using these estimates to adjust insulin dosing accordingly in an in-silico study.
The following sections provide the relevant background on glucose metabolism, including effects of exercise on glucose regulation, diabetes management and recommendations for treatment adjustments to PA, and a brief overview of models of the glucoregulatory system and control strategies for insulin delivery in T₁D.

1.1 GLUCOSE METABOLISM AND DIABETES

In health, BG is tightly controlled and kept within a range of 70–110 mg/dl. Glucose homeostasis is governed by a negative feedback system with the two primary regulators insulin and glucagon, where insulin corrects for elevated and glucagon for low BG levels. A schematic of BG regulation is shown in Figure 1.1.

Insulin is a hormone produced by pancreatic β-cells and secreted when BG levels are high. It stimulates the conversion of glucose into glycogen in the liver (glycogenesis) and glucose uptake by adipose tissue and muscle cells (Röder et al., 2016). Insulin-dependent glucose uptake is mediated by the glucose transporter GLUT4, which belongs to a family of membrane proteins that transfer glucose between plasma and cells via facilitated diffusion (Blanco and Blanco, 2017). GLUT4 moves to the cell membrane in the presence of high BG and insulin levels, allowing glucose to enter the cells. Insulin thus drives glucose disappearance from plasma to decrease BG levels, for example after meals, and protects against hyperglycemia.

Glucagon, on the other hand, is produced by pancreatic α-cells and secreted when BG levels are low (Röder et al., 2016). The hormone stimulates the breakdown of glycogen stored in the liver into glucose (glycogenolysis) (Adeva-Andany et al., 2016). The glucose is then released into plasma to increase BG levels, offering protection against hypoglycemia. Other counterregulatory hormones that stimulate glucose production during hypoglycemia are epinephrine, cortisol and growth hormone (Sprague and Arbeláez, 2013).

Figure 1.1 – Schematic of BG regulation in healthy individuals.
In type 1 diabetes, normal BG regulation is impaired and BG levels are chronically elevated. T1D is an autoimmune disease, which occurs mostly during childhood and is characterized by complete insulin deficiency due to the loss of pancreatic β-cells (Atkinson et al., 2014). The lack of insulin subsequently prohibits insulin-driven glucose disappearance from plasma, leading to hyperglycemia, and insulin treatment is required to lower BG levels.

Two common diagnostic criteria for T1D are the fasting glucose level and the oral glucose tolerance test (OGTT) (American Diabetes Association, 2014). A fasting BG below 110 mg/dl is expected in healthy individuals, while a BG above 126 mg/dl is a criterion for T1D. During the OGTT, 75 g of glucose dissolved in water are ingested orally and blood samples are drawn to track BG levels. Here, a two-hour BG below 140 mg/dl is expected in healthy individuals, while BG levels above 200 mg/dl are indicative of T1D.

1.2 MANAGEMENT OF TYPE 1 DIABETES

Management of T1D consists of exogenous insulin treatment and glucose monitoring to keep BG levels within a defined target range of usually 70 to 180 mg/dl. The amount of insulin required is determined based on the glucose level and other factors such as patient characteristics, meal intake and physical activity (Janež et al., 2020). One key determinant of a person’s insulin needs is insulin sensitivity (SI), which describes the effect of insulin on glucose disappearance from plasma (Bergman et al., 1979). It exhibits high inter- and intra-patient variability and individuals with lower SI require larger amounts of insulin. Thus, insulin needs are patient-specific and treatment needs to be tailored adequately to the individual person.

Insufficient amounts of insulin result in hyperglycemia (BG > 180 mg/dl), which is associated with several complications (Katsarou et al., 2017). Long-term complications from persistent hyperglycemia include retinopathy, neuropathy and cardiovascular diseases, among others. Severe hyperglycemia with ketoacidosis presents a potentially life-threatening, acute consequence from insufficient amounts of insulin. The body resorts to fat as an energy source, and toxic amounts of ketones can build up in the blood when it is broken down.

Over-dosing of insulin, on the other hand, may lead to hypoglycemia (BG < 70 mg/dl) (The Diabetes Control and Complications Trial Research Group, 1993). Hypoglycemia is associated with severe complications that reach from sweating, shaking and dizziness to unconsciousness, coma and death (Cryer et al., 2003). They occur acutely when glucose levels drop too low and hence, may be very harmful. Hypoglycemia is treated by glucose intake, usually in the form of sugary drinks or glucose tablets that are quickly absorbed.

The aim of insulin treatment is to maintain glucose levels as close as possible to normal, while avoiding hypoglycemia (Holt et al., 2021). Glycemic outcomes are evaluated by HbA1c, which gives information about the three-month average glucose level. The target for good glycemic control is an HbA1c below 7%, corresponding to an average BG of 154 mg/dl (American Diabetes Association, 2022).
1.2.1 Glucose Monitoring

Two main approaches are used for glucose monitoring to assist in maintaining target BG levels and inform insulin dosing: Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM).

When self-monitoring BG, a blood drop is obtained by a finger prick, and the glucose concentration is then read out with a BG meter (Benjamin, 2002). It is generally recommended that BG levels are monitored at minimum four times a day, during fasting and before meals and bedtime. Additional BG measurements can be useful to gain a better insight into glucose dynamics and adjust insulin treatment accordingly, for example by adding readings in the postprandial phase.

More recently, CGM devices came into practical use that continuously measure glucose levels in the subcutaneous interstitial fluid, which are then displayed by a receiver or smartphone. Real-time CGM (rtCGM) systems measure and display the glucose level at regular time intervals, most commonly every 5 min. Alternatively, intermittent scanning CGM (iscCGM) systems assess glucose levels every minute, but results can only be read out and displayed when scanning the device (Freckmann, 2020). In addition to continuous information on glucose levels, alarms for (predicted) hypo- and hyperglycemia and glucose trend arrows allow the user to react more quickly to glucose excursions (Freckmann, 2020).

CGM offers a more complete picture of glycemia compared to SMBG and is associated with a reduction in HbA1c and hypoglycemic episodes. It should therefore be considered for glucose monitoring (American Diabetes Association, 2023). In the US, CGM is used by around 50% of people with T1D (DeSalvo et al., 2021).

Furthermore, continuous glucose measurements allow for additional indicators of glycemic control beyond HbA1c such as time in range (TIR). TIR provides more timely information on glucose levels, and it is recommended that individuals spend at least 70% TIR, while time below range (TBR) and time above range (TAR) should be limited to 4% and 25%, respectively (Table 1.1) (American Diabetes Association, 2022; Holt et al., 2021).

### Table 1.1 – Recommended glucose targets (American Diabetes Association, 2022; Holt et al., 2021).

<table>
<thead>
<tr>
<th>BG [mg/dl]</th>
<th>% of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>severe hyperglycemia</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>hyperglycemia</td>
<td>&gt; 180</td>
</tr>
<tr>
<td>in range</td>
<td>70-180</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>severe hypoglycemia</td>
<td>&lt; 54</td>
</tr>
</tbody>
</table>

1.2.2 Insulin Administration

The aim of insulin treatment is to mimic the natural insulin response of healthy subjects to achieve good glycemic control in T1D. In functional insulin therapy (FIT), insulin requirements are separated into basal, meal and correction compo-
nents (Pavlicek and Lehmann, 2006). Basal insulin is used to maintain a stable baseline insulin level. This is required to repress hepatic glucose production adequately and maintain fasting BG levels. Meal and correction insulin are used to counteract the rise in BG levels from meals and to lower BG levels in case of hyperglycemia, and can be combined in a single bolus.

**Treatment options**

Insulin can be administered in different ways. One option is to use syringes or insulin pens to give manual bolus injections (American Diabetes Association, 2023). Most people following this approach rely on pens, and current models record time and amount of insulin administered. Multiple daily injections (MDI) are required to cover basal insulin needs and to correct for meals and other hyperglycemic events. Treatment consists of a combination of different insulin types, where intermediate or long-acting insulin is used for basal injections. It is administered once or twice per day and remains active for 12 to 24 h. Rapid-acting insulins, on the other hand, are active for only 3 to 5 h. They reach peak action after around 2 h and are used for meal and correction boluses (Hirsch et al., 2020).

The more advanced approach is continuous subcutaneous insulin infusion (CSII) using an insulin pump. Insulin pumps use rapid-acting insulin that is delivered continuously to maintain basal insulin levels (American Diabetes Association, 2023). The basal infusion rate can be varied over the course of the day according to a defined basal insulin profile that is tailored to an individual and their specific insulin needs (Beck et al., 2019). Meal and correction boluses, manually entered by the user, are delivered by the pump as well.

There is no consensus to guide the choice between CSII and MDI, as only a small reduction in HbA\textsubscript{1c} and severe hypoglycemia occurrences has been observed for pump therapy compared to MDI (Holt et al., 2021).

**Bolus calculation**

In FIT therapy, bolus doses to correct for meals and hyperglycemia are computed according to (Schmidt and Norgaard, 2014)

\[
bolus = \frac{CHO}{ICR} + \frac{G - G_t}{CF} - IOB.
\]

The first term represents the meal component of the bolus, which depends on the CHO content of the meal, \(CHO\ [g]\), and the subject-specific insulin-to-CHO ratio, \(ICR\ [g/U]\). The insulin-to-CHO ratio describes how many grams of CHO are covered by injection of one unit of insulin.

The second term defines the correction component that addresses glucose excursions from the target. It is calculated based on the difference between current and target BG, denoted by \(G\) and \(G_t\ [mg/dl]\), respectively, and the correction factor, \(CF\ [mg/dl/U]\). The correction factor is subject-specific and describes by how much BG levels are lowered after injection of one unit of insulin.

Finally, insulin-on-board, \(IOB\ [U]\), is covered by the third term in the bolus formula. Insulin-on-board is the amount of insulin that is still active from previous injections and is subtracted from the amount required to correct for meals and hyperglycemia to avoid over-dosing and subsequent hypoglycemia.
The treatment parameters ICR and CF need to be tailored to each person individually and are determined and continuously adapted together by the patient and physician (Davidson et al., 2008). Different values may be applied at different times of the day, since insulin sensitivity follows a diurnal pattern with lower insulin sensitivity in the morning, which results in varying insulin requirements throughout the day (Hinshaw et al., 2013).

1.2.3 Treatment Approaches

Any combination of the previously described glucose monitoring and insulin delivery methods is possible for T1D treatment (Perkins et al., 2021), and devices are chosen individually depending on a person’s needs, preferences and abilities (American Diabetes Association, 2023).

The development of CGM additionally gave rise to new technologies that integrate CGM and CSII, allowing further improvements in glycemic control. In sensor-augmented pump (SAP) therapy, the insulin pump acts as a receiver and displays CGM values (Berget et al., 2019). This makes sensor readings more accessible, and the user can react more readily to glucose excursions. Many SAP systems have hypoglycemia suspension features, where insulin delivery is suspended when glucose levels drop below a certain threshold or when hypoglycemia is predicted within a certain time window, successfully reducing exposure to hypoglycemia (Bergenstal et al., 2013; Buckingham et al., 2015).

Another advancement in diabetes treatment was the advent of automated insulin delivery (AID) or hybrid closed-loop (HCL) systems, also referred to as artificial pancreas. In HCL systems, the pump-delivered basal insulin rate is automatically adjusted based on real-time glucose measurements from CGM sensors and a control algorithm to drive BG levels towards a specified target (Lal et al., 2019; Ware and Hovorka, 2022). These systems are hybrid as the user has to count CHOs and announce meals for bolus administration. HCL insulin delivery is associated with lower mean glucose, reduced hypoglycemia and improved TIR (Weisman et al., 2017; Bekiari et al., 2018), and further improves quality of life for people living with T1D (Barnard et al., 2017). The greatest improvements are observed in overnight control, while regular user input is still required during the day to achieve good glycemic outcomes around meals and physical activity.

1.3 EFFECT OF EXERCISE ON GLUCOSE METABOLISM

Physical activity induces changes in glucose metabolism to meet the body’s increased energy demand while maintaining stable BG levels. These changes occur on different time scales and depend on PA intensity and duration (Mul et al., 2015; Romijn et al., 1993).

PA is classified into aerobic and anaerobic exercise based on whether or not energy is generated using oxygen (Patel et al., 2017). Aerobic PA includes activities that are performed continuously at light, moderate or vigorous/high intensities and can be maintained for a prolonged time period, like running or cycling. High-intensity activities like sprinting that can only be maintained on the order of seconds or minutes, as well as resistance training fall into the category of anaerobic PA.
During moderate-intensity PA, glucose from plasma represents one of the main energy sources. Glucose uptake (GU) by the exercising muscles increases acutely at the onset of an activity through contraction-stimulated recruitment and translocation of GLUT4 transporters to the cell membrane and is linear in PA intensity (Jensen and Richter, 2012). This process is insulin-independent, and PA and insulin have additive effects on GU by muscle cells from blood (Mul et al., 2015). After PA, GU returns to its baseline level typically within 30 min.

Similarly, hepatic glucose production (GP) from gluconeogenesis and glycogenolysis is upregulated during PA to compensate for the rise in glucose utilization (Petersen et al., 2004; Camacho et al., 2005). This is mainly controlled by changes in the secretion of insulin (in health) and glucagon. Specifically, a drop in insulin and increase in glucagon secretion are observed, although other counterregulatory hormones like cortisol and epinephrine are involved as well.

In health, GP is upregulated such that it matches the rise in GU during moderate-intensity PA, and BG levels remain stable throughout the activity (Camacho et al., 2005). In T1D, however, BG levels fall in most cases. Insulin treatment needs to be adjusted to achieve an appropriate reduction in insulin levels and following increase in GP, but insulin concentration is usually not sufficiently reduced at PA onset (Riddell et al., 2017). Falling BG levels and hypoglycemia may also be observed in healthy individuals during prolonged PA when liver glycogen stores deplete and GP cannot be maintained by gluconeogenesis alone (Richter and Hargreaves, 2013).

In contrast, high-intensity aerobic PA may lead to a transient rise in BG levels. Regulation of GP shifts from the pancreatic hormones to cortisol and catecholamines (Marliss and Vranic, 2002). These hormones rise considerably during high-intensity PA and induce a drastic increase in GP, and GP can exceed GU causing BG levels to rise. Anaerobic or mixed aerobic-anaerobic PA can lead to different responses in glucose levels (Riddell et al., 2017).

In addition to the insulin-independent changes in glucose metabolism, PA causes a rise in insulin sensitivity. SI increases during PA in proportion to intensity and duration, and remains elevated for up to 48h during recovery to facilitate insulin-dependent GU and drive glycogen repletion (Mul et al., 2015). In people with T1D, the prolonged rise in insulin sensitivity increases the risk for late-onset hypoglycemia and ongoing treatment adjustments might be required.

1.4 TREATMENT ADJUSTMENT TO EXERCISE

Accurate adjustment of treatment to PA in T1D to maintain stable BG levels and prevent hypoglycemia during and after the activity is challenging. PA effects on BG levels and insulin requirements are difficult to predict, since they depend on many factors, such as PA intensity and duration, but also insulin condition, nutritional status and timing of the activity (Riddell et al., 2017; Paiement et al., 2022). Consequently, many people with T1D refrain from exercising due to fear of hypoglycemia. Indeed, the majority of individuals do not reach the target of 150 min of accumulated activity per week as recommended by the American Diabetes Association (McCarthy et al., 2016).

Guidelines for treatment adjustments are developed to support people with T1D in achieving adequate glycemic control during PA, and make recommendations
for CHO supplementation and insulin dose reductions to protect against PA-induced hypoglycemia. The consensus guidelines from 2017 give a comprehensive overview of suggested actions and address exercise management for different PA modalities (Riddell et al., 2017). They provide safe glucose targets as well as insulin and carbohydrate recommendations based on PA intensity, duration and the patient’s recent nutritional and insulin history.

In preparation of PA, it is recommended to individuals on CSII to suspend basal insulin infusion at the onset of PA or, preferably, to reduce the basal rate 60 to 90 min prior to the PA session (Riddell et al., 2017). This was shown to decrease hypoglycemia during the activity, while limiting exposure to hyperglycemia after PA (Franc et al., 2015). Reductions of long-acting basal insulin before PA in MDI therapy are not generally recommended, however, since they might lead to hyperglycemia during non-exercise periods during the day (Campbell et al., 2015).

Meal boluses for CHO intake shortly before PA can be reduced both for people on CSII and MDI therapy, where bolus reductions in proportion to PA intensity and duration should be considered for sessions longer than 30 min (Riddell et al., 2017). In addition, pre-PA snacks offer the possibility to increase BG levels, and a safe BG range for commencement of aerobic PA of 126 to 180 mg/dl is suggested, or 90 to 180 mg/dl for anaerobic PA. Trend arrows on CGM devices act as an additional indicator whether it is safe to start exercising or to decide on potential actions (Moser et al., 2020).

During PA, BG should be monitored closely and carbohydrates ingested regularly to prevent hypoglycemia. CHO amounts are recommended based on PA intensity and duration and the individual’s insulin status (Riddell et al., 2017). Furthermore, glucose thresholds of CGM devices can be adjusted during exercise such that early alarms for hypo- and hyperglycemia allow to react to those excursion in time (Moser et al., 2020), and a temporary glucose target can be set for HCL systems to drive the system towards higher BG levels (Zaharieva et al., 2020).

To address the PA-induced risk for late-onset hypoglycemia, BG levels should still be monitored carefully after PA, and additional CHOs and further insulin dose adjustments might be required. Nocturnal hypoglycemia is a special concern, and the risk is elevated in particular following afternoon PA (Gomez et al., 2015; Davey et al., 2013). A bedtime snack and potential basal insulin reductions during the night both for MDI and CSII are recommended to reduce this risk (Riddell et al., 2017).

It is important to note that guidelines for PA management present general recommendations. They further need to be tailored to the individual person in a trial-and-error process to improve BG levels during and after PA. Consequently, this is mostly helpful for individuals that follow a regular and structured exercise regimen, and requires planning ahead of the PA session.

In addition, it is recognized in the consensus guidelines that PA-induced late-onset hypoglycemia is difficult to tackle, and the need for more studies to evaluate nutritional and insulin requirements to manage glycemia adequately in the recovery period is emphasized (Riddell et al., 2017). Although BG levels may rise during high-intensity PA, it does not offer protection against late-onset hypoglycemia as has been previously proposed (Maran et al., 2010). Instead, the risk for late-onset hypoglycemia is elevated for both moderate and high intensities. Finally, studies
have shown that there is no safe bedtime glucose range that guarantees protection against nocturnal hypoglycemia (Adolfsson et al., 2018).

### 1.5 Modelling of Glucose-Insulin Regulation

Mathematical models to predict BG concentrations have been applied in diabetes research for many decades. They are developed to better understand the physiology of glucose-insulin regulation, to determine physiologically relevant parameters, to evaluate treatment and control strategies in-silico and for educational purposes. Most models are compartmental models that capture the physiology of the glucoregulatory system. Their complexity varies hugely depending on their intended application. To have a complete picture of glucose-insulin regulation in T1D, components that describe BG regulation, pharmacokinetics and -dynamics of injected insulin and glucose appearance from meals are required. Depending on their level of accuracy, these knowledge-driven models can be categorized into physiological and semi-mechanistic models (Balakrishnan et al., 2011).

#### 1.5.1 Physiological Models

Physiological models are developed to gain a better understanding and provide a detailed and accurate description of the physiology of a system. In models of the glucoregulatory system, organs and tissues are typically represented by individual compartments. The compartments are connected by blood flow, allowing exchange between them, and the distributions of glucose and hormones like insulin and glucagon as well as their interactions are incorporated. Two examples are the Sorensen model from 1978 (Sorensen, 1978) and a more recent one by Kim et al. (2007).

Physiological models are generally very large. Their parameters are therefore not easily identifiable and an average quantification of the considered processes is provided.

#### 1.5.2 Semi-Mechanistic Models

Semi-mechanistic models still represent the physiological interactions of glucose-insulin regulation, but the complexity is reduced compared to physiological models by combining some of the involved tissues and organs into single compartments.

The Bergman Minimal Model (BMM) is one of the first widely applied models of glucose-insulin regulation, and was developed to determine insulin sensitivity from an intravenous glucose tolerance test (IVGTT) (Bergman et al., 1979). It is a compartmental model, defined by

\[
\begin{align*}
I(t) & \overset{k_2}{\underset{k_6}{\rightarrow}} \Gamma \\
\text{Liver} & \overset{k_5}{\rightarrow} G \\
\text{Periphery} & \overset{k_1}{\rightarrow} G
\end{align*}
\]

\[
X = (k_4 + k_6) I' \\
p_1 = k_4 \\
p_2 = k_6 \\
p_3 = k_5 (k_4 + k_6)
\]
with plasma glucose concentration $G$ and plasma insulin concentration $I$. The corresponding basal levels are $G_b$ and $I_b$, respectively. Insulin enters a remote compartment, $I'$, from where it acts on glucose via the dynamic state $X$. Since the model with parameters $k_i$ is not identifiable, a reparametrization is carried out that allows identification of all parameters $p_i$, which is required if the model’s purpose is to extract physiological properties, like insulin sensitivity in this case. Insulin sensitivity is represented by the ratio $p_3/p_2$ and describes the influence of insulin on glucose disappearance. Furthermore, the parameter $p_1$ represents glucose effectiveness, which describes the glucose lowering effect of glucose itself.

An extended version of the BMM includes sub-models for insulin kinetics after subcutaneous administration and glucose appearance after meals (Patek et al., 2016). This model is not identifiable from BG measurements alone, but is often used as a simulation model for glucose-insulin regulation in T1D.

**Insulin sensitivity estimation** Insulin sensitivity can be estimated from an IVGTT using the BMM. However, insulin sensitivity is a continuously changing quantity. It follows a diurnal pattern (Hinshaw et al., 2013), changes throughout the menstrual cycle (Brown et al., 2015) and is affected by physical activity (Wojtaszewski et al., 1997), among others. Therefore, continuous estimation of insulin sensitivity has been a topic of interest and several studies have shown that it can be tracked with an unscented Kalman filter (UKF) from CGM data (Brown et al., 2015; Boiroux et al., 2017a). This approach can be used to identify factors affecting glycemic variability and to monitor changes in insulin requirements to inform, for example, bolus calculators to improve glycemia (Boiroux et al., 2017a). However, UKFs have only been applied to estimate slow variations in SI with medium amplitude, whereas fast, larger changes that are encountered during PA have not been considered so far.

Other semi-mechanistic models are developed specifically for simulation purposes to predict BG trajectories in response to external inputs like meal intake and insulin administration. They are then used to assess treatment strategies or to develop and evaluate control algorithms for insulin treatment.

One prominent example is the Dalla Man meal simulation model (Dalla Man et al., 2007b). It is applied in the UVa/Padova simulator that was approved by the FDA to replace animal trials for preclinical testing of control strategies for insulin delivery (Kovatchev et al., 2009). The model was developed to describe physiological processes in the postprandial state, first for healthy subjects and people with type 2 diabetes. It was later extended to capture T1D by adding a model component for subcutaneous insulin kinetics (Dalla Man et al., 2007a). Another widely used model is the Hovorka model (Hovorka et al., 2002), in which the effects of insulin on glucose distribution, glucose disposal and glucose production are considered separately.

Due to the complexity of these models, parameters are usually not identifiable from easily available BG data or standard clinical tests like the OGTT. Instead, complex clinical trials are required for their identification. Results of these trials are
used to generate virtual patient populations (VPP) that capture the variability of a realistic T1D population, which can subsequently be used for in-silico evaluation of control algorithms for insulin delivery.

Besides their use in in-silico studies, simulation models are regularly used as prediction models in control algorithms (Lunze et al., 2013), where parameters with the highest inter-patient variability are adjusted to the individual for personalization of the model. In addition, simple control-oriented models are developed that focus on control performance instead of accurate BG predictions and enable easy personalization to circumvent identifiability issues and model-patient mismatch that could lead to poor control performance (Van Heusden et al., 2012).

1.6 Models of Glucose-Insulin Regulation Including Exercise

Models that capture the effects of PA on glucose metabolism are crucial to simulate BG dynamics under realistic conditions and to allow the development of improved control strategies for PA management in-silico. However, most existing models do not include PA, since this requires substantial extensions and poses new challenges as the complex physiology of PA has to be described in sufficient detail.

First, it is essential to incorporate the PA-driven changes in insulin sensitivity. It has been established that insulin sensitivity increases during PA and remains elevated for a prolonged period of time during recovery to increase GU and hence, drive glycogen repletion. This needs to be considered to study the prolonged effects of PA on BG dynamics and evaluate treatment strategies to reduce the risk for late-onset hypoglycemia. Second, the insulin-independent effects of PA on GU and GP should be incorporated as individual model components to reflect glucose regulation during exercise accurately. This allows for further extensions to describe hepatic glycogen depletion and high-intensity PA that affect GP, and thus, to cover a wider range of glucose responses to PA.

Some models that describe glucose-insulin regulation in the presence of PA have been developed. They typically focus on specific aspects of PA metabolism and are presented as extensions of existing glucoregulatory models. PA is quantified using relative oxygen consumption, $PVO_{2max}$, or heart rate, since both are proportional to energy expenditure (Howley, 2001). A summary of models and their components is given in Table 1.2.

Roy and Parker (2007) proposed a PA model based on the BMM. They incorporated exercise-driven insulin removal and the insulin-independent rise in GU and GP during the activity, where all processes are linearly dependent on PA intensity. Furthermore, they considered reduction in GP due to glycogen depletion during prolonged PA. The model was calibrated on data from healthy subjects from the literature, but validated also on data from people with T1D.

Hernández-Ordoñez and Campos-Delgado (2008) proposed a PA extension to the Sørensen model that accounted for the same exercise-induced changes in glucose metabolism, and further added an increase in peripheral insulin uptake. The model parameters of the PA components were determined from literature data of healthy subjects performing PA at different intensities and durations. Resalat et al. (2019b) used these PA components in combination with the Hovorka model to generate a virtual patient population and allow simulation of scenarios that include PA sessions.
Another PA extension of the BMM was presented by Breton (2008). The model includes a prolonged rise in insulin sensitivity and an acute, intensity-dependent increase in glucose effectiveness (SG). Glucose effectiveness describes the net effect of glucose on the glucose rate of change, but does not distinguish between its influence on GU and GP. The model parameters were determined from individuals with T1D undergoing a hyperinsulinemic clamp protocol and performing 15 min of moderate-intensity PA at 50% VO$_{2\text{max}}$. Dalla Man et al. (2009) incorporated this PA extension into their meal simulation model in an in-silico study, and added intensity- and duration-dependence for the PA-driven increase in insulin sensitivity.

Alkhateeb et al. (2021) tested various versions of the BMM to describe PA metabolism adequately. They found, similar to the previous model, that glucose effectiveness increases with PA intensity and that insulin sensitivity increases with PA duration and intensity. They evaluated the model proposals on T1D data from a 60 min PA session carried out at 60% VO$_{2\text{max}}$.

Finally, Hobbs et al. (2022) evaluated several PA models that were based on the Hovorka model to study the effect of PA intensity and duration on GU, GP and glucose transfer. They selected a model with an insulin-independent increase in GU, which rises immediately at the beginning of PA in proportion to PA intensity, but returns slowly to its baseline after the activity. Their results on insulin-dependent contributions to GU were inconclusive. Glucose transfer and GP are also intensity-dependent and increase acutely during PA. They further incorporated high-intensity exercise (HIE) by adding a component to GP that is triggered when heart rate exceeds the ventilatory threshold. The model parameters were partly derived from literature and partly personalized to the individual in a multi-day clinical study including different protocols and different PA sessions.

However, the presented models have several limitations. They do not consider all relevant processes in glucose regulation that are triggered by PA (Table 1.2) and some of them were only calibrated on data from healthy subjects, on data obtained during clamp studies in T1D, or on a single PA scenario. In those cases, it is not entirely clear how they translate to exercise metabolism in T1D under normal conditions and for PA of varying duration and intensity.

<table>
<thead>
<tr>
<th>Table 1.2 – Overview of PA models and their exercise components.</th>
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<tr>
<td>SI</td>
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<tr>
<td>Roy and Parker (2007) – ✓ ✓ ✓ –</td>
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<tr>
<td>Breton (2008) ✓ ✓ – – – –</td>
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<tr>
<td>Alkhateeb et al. (2021) ✓ ✓ – – – –</td>
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<tr>
<td>Hobbs et al. (2022) – ✓ ✓ – ✓</td>
</tr>
</tbody>
</table>

SI: insulin sensitivity, SG: glucose effectiveness, GU: glucose uptake, GP: glucose production, HIE: high-intensity exercise. Insulin-independent effects of PA on glucose metabolism can be considered for GU and GP separately, or combined in a change in SG.
Closed-loop (CL) control, both fully and hybrid, for diabetes management refers to the automated delivery of insulin to maintain stable BG levels. CL systems consist of three components: a CGM device to measure glucose levels, a control algorithm, and an insulin pump for continuous administration of insulin. The control algorithm uses the current glucose measurement to determine the insulin needed to drive BG levels towards a pre-defined target level and adapts the delivery rate of the insulin pump accordingly. The purpose of CL systems is to improve glycemic outcomes and minimize short- and long-term complications related to T1D. Furthermore, they aim to decrease the burden of daily diabetes management by minimizing required user interventions (Ware and Hovorka, 2022).

1.7.1 Control Algorithms

Three types of control algorithms are commonly applied in closed-loop insulin delivery systems: Proportional-integral-derivative (PID) control, fuzzy logic and model predictive control (MPC).

In PID controllers, the insulin dose is determined from the deviation of the current glucose measurement from a specified target level (proportional), the cumulative difference (integral), and the rate of change in this difference (derivative). In fuzzy logic control, rules based on a set of inputs like current glucose level and glucose change are applied that imitate expert reasoning to adjust insulin delivery (Lal et al., 2019).

Here, we focus on MPC algorithms. They are most often used for automated insulin delivery and show greater improvements in TIR and lower mean glucose compared to PID approaches (Pinsker et al., 2016b; Weisman et al., 2017). In MPC, a glucoregulatory model is used to predict BG trajectories from the newest CGM reading over a defined time period and find an insulin input sequence that drives BG levels to a pre-specified target. This is achieved by minimization of an objective function, while allowing for constraints on inputs and outputs that need to be satisfied. Only the first element of the controller-derived input sequence is applied, before the process is repeated when the next glucose measurement is available (Fig. 1.2).

Many MPC-based approaches have been proposed in the literature, for example by Hovorka et al. (2004), Magni et al. (2009a), Clarke et al. (2009), Breton et al. (2012), Gondhalekar et al. (2016), and Boiroux et al. (2017b). The advantage of MPC algorithms is that delays in insulin absorption are considered and that active
insulin (Ellingsen et al., 2009) and carbohydrate intake can be taken into account. Some controllers incorporate diurnal variations (Toffanin et al., 2013) and use target zones instead of a single BG target (Gondhalekar et al., 2016). Furthermore, asymmetric objective functions capture the asymmetry in severeness of acute complications arising from hypo- and hyperglycemia (Lee et al., 2016). Adaptive approaches are developed for disturbance rejection (Turksoy et al., 2013) or to tune model or treatment parameters over time (Magni et al., 2009b; Toffanin et al., 2018; Resalat et al., 2019a).

Another advantage of MPC is that additional sensor data can be integrated into the algorithm to improve BG predictions and propose better suited control actions. Heart rate, accelerometry or energy expenditure are available from wearable sensors and are used to accommodate PA (Breton et al., 2014; Jacobs et al., 2015). Psychological stress might also be a useful input for CL algorithms (Gonder-Frederick et al., 2016), since it can affect BG dynamics in people with T1D (Hanson and Pichert, 1986; Moberg et al., 1994; Riazi et al., 2004). Finally, integration of meal detection algorithms into multivariable control systems can be used to improve meal size estimation and postprandial control (Samadi et al., 2018).

1.7.2 Control and Exercise

Despite the huge advancements in diabetes technology, meals and physical activity remain two of the biggest challenges in diabetes management in general and also present the main hurdles in the development of fully automated insulin delivery systems. This is due to the slow absorption and action of rapid-acting insulins in comparison to the fast changes in glucose levels (Ruan et al., 2017) and varying BG responses to exercise (Riddell et al., 2015). Indeed, a recent meta-analysis by Eckstein et al. (2021) reveals that although TIR improves, post-exercise hypoglycemia is not reduced in CL systems compared to the standard of care.

To provide suitable glycemic control during PA and prevent PA-induced hypoglycemia, modified control algorithms may be useful, which rely on additional inputs for exercise detection (Kovatchev, 2019; Ware and Hovorka, 2022), for example heart rate or accelerometry from smartwatches, and are able to respond to different PA modalities, intensities and durations (Riddell et al., 2015). Furthermore, exercise-informed bolus calculators could aid in adjusting insulin dosing appropriately to the activity (Colberg et al., 2015). In particular, control algorithms for exercise management should counteract the anticipated drop in glucose levels during the activity and account for the increased risk for late-onset hypoglycemia to improve TIR and reduce the occurrence of PA-related hypoglycemic events.

Although PA is rarely considered explicitly in the internal models of control algorithms, some model-based approaches for automated insulin delivery during exercise have been presented. Breton et al. (2014) incorporated PA via heart rate (HR) into a control-to-range algorithm, where BG trajectories are predicted based on the BMM. The predictions are translated into hypo- and hyperglycemia risk, which are then used to attenuate the basal rate or deliver small correction boluses. During PA, the hypoglycemia risk is modulated, using a higher BG threshold and faster increase compared to non-PA periods. Applying this heart rate-informed controller led to a reduction in the BG decline during exercise in a randomized crossover study with twelve adult participants with T1D compared to a standard
control-to-range controller. TIR did not improve significantly in the post-PA period and a slight increase in the low blood glucose index (LBGI) was observed during the night. Similar results were obtained in a study with adolescents (DeBoer et al., 2017).

Resalat et al. (2016) incorporated a component describing aerobic PA into the process model of an MPC algorithm to improve BG predictions in the presence of exercise in an in-silico study. The process model consists of the Hovorka model combined with the PA model presented by Hernández-Ordoñez and Campos-Delgado (2008), increasing the effect of insulin on glucose transport, GU and GP during the session. Modelling of PA effects improved the glycemic outcome in a single-hormone MPC with insulin, which was improved further by applying a dual-hormone MPC with insulin and glucagon. This approach relies on accurately modelling the PA effect on BG and is limited to moderate-intensity PA with declining glucose levels.

PA was integrated into an MPC algorithm by Garcia-Tirado et al. (2019) using an exercise-specific input signal. A PA net effect, i.e. PA-induced glucose change, is extracted from glucose measurements after accounting for meals and insulin using a glucoregulatory model. The net effect can then be fed into the process model for BG predictions during PA, where an ensemble of different PA patterns from recent history is considered. This approach was first evaluated on virtual subjects from the FDA-approved UVa/Padova simulator (Kovatchev et al., 2009), before being tested in a randomized crossover study with eighteen participants with T1D. In this study, it was incorporated into a controller that further included an exercise detection component and a PA-informed meal bolus (Garcia-Tirado et al., 2021). Insulin delivery was gradually decreased when exercise was predicted and hypoglycemia occurrences were reduced during and after PA. However, this strategy is only suitable for people that exhibit a regular exercise behavior.

The proposed PA-informed controllers were tested on well-defined, moderate-intensity PA sessions, but their performance for different PA intensities, durations and timings still needs to be confirmed. In particular, their response to rising BG levels during high-intensity PA is not clear. This refers to the approaches proposed by Breton et al. (2014) and Garcia-Tirado et al. (2019), where this PA modality could be covered. Furthermore, prolonged effects of PA on glucose metabolism are not considered in any of the proposed control algorithms. This prohibits to address the PA-induced increase in late-onset hypoglycemia risk and systematically improve glycemic outcomes in the recovery period.

1.8 Contributions of this Thesis

Exercise management presents a huge challenge for people with T1D. Although guidelines exist, it is difficult to adjust treatment appropriately to maintain normoglycemia, since effects of PA on BG levels depend on PA intensity, duration and other factors such as previous meals. In addition, they act dynamically over time, which further complicates adequate treatment adjustment and calls for strategies that take these dynamics into account. There is a particular need for strategies that target prolonged PA effects, in order to minimize the associated risk for late-onset hypoglycemia, one of the main barriers to PA for individuals with T1D.
In-silico evaluation and development of treatment strategies could be a useful tool to improve glycemia in the presence of PA. However, models that capture the relevant exercise physiology are currently lacking. The goal of this thesis was to develop a model of the glucoregulatory system that includes acute and prolonged effects of PA on glucose metabolism for different PA intensities, and to propose a strategy for insulin dose adjustments for basal and meal insulin to minimize the occurrence of PA-induced hypoglycemia in the recovery period.

In Chapter 2, we propose the use of glucoregulatory models to evaluate existing treatment strategies for PA management in an in-silico study, which allows consideration of a wide range of scenarios. We focus on evaluating the consensus guidelines (Riddell et al., 2017) and a CHO algorithm that suggests CHO intake based on glucose levels and trends during the session (Riddell and Milliken, 2011). We rely on the published model for moderate-intensity PA by Breton (2008) and extend it with components for insulin kinetics and glucose appearance after meal intake to perform full-day simulations. We assess the guidelines’ performance in improving glycemia and identify their shortcomings on a range of PA scenarios with varying intensity, duration and timing.

In Chapter 3, we present a model of glucose-insulin regulation that covers moderate- to high-intensity aerobic PA including glycogen depletion for PA of prolonged duration. The model can predict declining BG levels during moderate-intensity PA, but also includes high-intensity PA with rising BG levels. We propose a systematic strategy to calibrate the model on population-average data from healthy subjects and afterwards adjust model parameters to a T1D population. We validate the model on independent studies of increasing complexity that cover PA of varying intensity and duration, partly in combination with meal intake and corresponding meal bolus administration, or insulin dose reductions. Finally, we personalize the model on data from individuals with T1D recorded under free-living conditions to demonstrate its applicability on the individual-subject level and its potential to evaluate individualized treatment strategies.

In Chapter 4, we propose an approach to account for PA-related changes in insulin requirements via estimation of insulin sensitivity in MDI therapy, where we focus on the prolonged changes in glucose metabolism that might require continued insulin dose adjustments during recovery. We first address the open problem of estimating rapid PA-induced changes in SI from CGM measurements using an unscented Kalman filter. Subsequently, we present a proportional control strategy to adjust meal and basal boluses based on these estimates following the PA session.

In Chapter 5, we extend this approach to CSII therapy and develop an MPC algorithm that continuously adapts the basal rate to an individual’s changing insulin requirements to improve glucose outcomes and prevent late-onset hypoglycemia in the presence of PA. We update the target basal rate based on the estimated insulin sensitivity to maintain a fixed BG target, and adjust the SI parameter of the personalized process model at every time step to make more accurate BG predictions. We evaluate the proposed control strategy on different exercise and disturbance scenarios, and compare its performance to a baseline MPC that does not take SI estimation into account.
SIMULATION-BASED EVALUATION OF TREATMENT ADJUSTMENT TO EXERCISE IN TYPE 1 DIABETES

This chapter is published as:


Author contributions:

JD developed the Python code implementing the mathematical model, conducted simulations, and created the figures. HMK and JD conceived and implemented the study and wrote the initial draft of the manuscript. SB, M-AB, and GS contributed in defining the simulation scenarios and provided clinical expertise in interpreting results. All authors contributed to the article and the interpretation of the results. All authors approved the submitted version.

2.1 ABSTRACT

Regular exercise is beneficial and recommended for people with type 1 diabetes, but increased glucose demand and changes in insulin sensitivity require treatment adjustments to prevent exercise-induced hypoglycemia. Several different adjustment strategies based on insulin bolus reductions and additional carbohydrate intake have been proposed, but large inter- and intraindividual variability and studies using different exercise duration, intensity, and timing impede a direct comparison of their effects.

In this study, we use a mathematical model of the glucoregulatory system and implement published guidelines and strategies in-silico to provide a direct comparison on a single ‘typical’ person on a standard day with three meals. We augment this day by a broad range of exercise scenarios combining different intensity and duration of the exercise session, and different timing with respect to adjacent meals. We compare the resulting blood glucose trajectories and use summary measures to evaluate the time-in-range and risk scores for hypo- and hyperglycemic events for each simulation scenario, and to determine factors that impede prevention of hypoglycemia events.

Our simulations suggest that the considered strategies and guidelines successfully minimize the risk for acute hypoglycemia. At the same time, all adjustments substantially increase the risk of late-onset hypoglycemia compared to no adjustment in many cases. We also find that timing between exercise and meals and additional carbohydrate intake during exercise can lead to non-intuitive behavior due to superposition of meal- and exercise-related glucose dynamics. Increased insulin sensitivity appears as a major driver of non-acute hypoglycemic events. Overall, our results indicate that further treatment adjustment might be required
both immediately following exercise and up to several hours later, but that the intricate interplay between different dynamics makes it difficult to provide generic recommendations. However, our simulation scenarios extend substantially beyond the original scope of each model component and proper model validation is warranted before applying our in-silico results in a clinical setting.

2.2 Introduction

Type 1 diabetes (T1D) is a common endocrine disorder that results from autoimmune destruction of pancreatic β-cells and leads to elevated blood glucose levels (hyperglycemia) if untreated. Treatment consists of exogenous insulin administration to cover dietary carbohydrate intake and needs to be tailored to each individual with continuous adjustments over time. A basal insulin level is provided either by continuous subcutaneous infusion using an insulin pump or once or twice daily injection of long-acting insulin to maintain glucose homeostasis in fasting conditions. In addition, bolus injections of rapid-acting insulin are used to compensate for meals, where the required dose depends on the size of the meal, the blood glucose level immediately preceding the meal, and potentially the insulin-on-board from previous injections.

Regular physical activity (PA) is beneficial for people with T1D and is therefore recommended in current clinical guidelines (American Diabetes Association, 2015; Colberg et al., 2016). However, physical activity leads to dynamic changes in blood glucose regulation on two different time-scales: first, increased energy requirements by working muscles lead to increased glucose uptake and corresponding faster decrease of blood glucose during the activity (Romijn et al., 1993; Camacho et al., 2005; Jensen and Richter, 2012). Second, insulin sensitivity increases during the activity and remains elevated for several hours during subsequent recovery to help replenish glycogen stores (Mul et al., 2015). Clinical guidelines recommend reducing the insulin bolus for a pre-exercise meal as well as additional carbohydrate intake before and during exercise depending on the initial blood glucose level respectively the duration of the exercise (Riddell et al., 2017; Adolfsson et al., 2018), as well as a potential reduction in basal insulin. However, accurately adjusting a person’s treatment to physical activity remains a largely unsolved problem in general (Annan, 2016), both immediately following exercise (acute hypoglycemia) and several hours later, particularly overnight (late-onset hypoglycemia). Indeed, fear of exercise-induced hypoglycemia is a major impediment for patients to exercise regularly (Brazeau et al., 2008).

Clinical guidelines for adjusting treatment to physical activity are based on evidence from a plethora of clinical trials. Similarly, newer proposals, e.g., to exploit the ability to detect glucose trends using continuous glucose monitoring (CGM) devices are thoroughly evaluated using clinical trials. On the other hand, the large heterogeneity of patient responses and many degrees of freedom to define study protocols—such as pre-exercise meals and specification of the exercise session—might make it difficult to evaluate the differences between adjustment strategies directly. These factors also pose challenges when summarizing results over different studies. In addition, preventing both acute and late-onset hypoglycemia might induce competing goals for an adjustment strategy. For example, recent proposals to use high-intensity intervals before exercise were shown to decrease
acute hypoglycemia (Marliss and Vranic, 2002; Yardley and Sigal, 2015), but can increase the risk of late-onset hypoglycemia (Aronson et al., 2019).

Furthermore, clinical guidelines must strike a balance between accuracy and ease of use by patients, and typically use discrete categories for adjustments depending on intensity and duration of exercise. This can lead to abrupt changes in treatment adjustment for very similar exercise scenarios at the ‘border’ of categories.

On the other hand, mathematical models have been used in diabetes research and care for several decades (Balakrishnan et al., 2011; Ajmera et al., 2013). Suitable models allow in-silico clinical trial simulation to improve trial design (Danne et al., 2014). Model-based in-silico evaluation of control strategies in the context of automated insulin delivery systems is also becoming increasingly important and first systems gained FDA approval for design, testing, and validation of closed-loop controllers (Dalla Man et al., 2014), which allows in-silico evaluation and optimization of control methodologies (Breton et al., 2012; Pinsker et al., 2016b) and treatment adjustments (Fabris et al., 2019; Fabris et al., 2020). Several models also consider the effects of physical activity on glucose dynamics (Breton, 2008; Dalla Man et al., 2009; Romeres et al., 2021; Alkhateeb et al., 2021).

Here, we use a mathematical model to directly compare the effect of several published exercise-related adjustment strategies in-silico. We consider a broad variety of scenarios and consider different moderate exercise intensities and durations, but also exercise times in relation to adjacent meals and to bedtime. We compare the strategies’ performances with relevant summaries such as time-in-range and acute and late-onset hypoglycemia risk. This setup thus provides insight into the individual and combined effects of different exercise modalities.

We rely on published components for our model, but did not validate the full model for the considered scenarios. Our conclusions are therefore tentative and an exact quantification of the comparisons depends on the accuracy of the underlying mathematical model. Nevertheless, our simulations are in line with clinical experience, show clear qualitative differences between the guidelines under different exercise scenarios, and point at areas requiring further clinical study. In particular, while all strategies can substantially reduce the risk of acute hypoglycemia, prolonged changes in insulin sensitivity would require additional insulin bolus adjustment for meals following exercise to avoid late-onset hypoglycemia. Moreover, the timing of exercise in relation to meals can lead to inadvertent effects, particularly when considering glucose trends.

2.3 METHODS

We rely on published models for our in-silico study of treatment adjustments to physical activity and provide a detailed description of the final model in Section 2.3.1. We consider two published treatment adjustment strategies which we outline in Section 2.3.3, and compare them using standard performance measures given in Section 2.3.4. We also propose exploiting ideas from global sensitivity analysis (GSA) and review the necessary methodology in Section 2.3.5.
2.3.1 Model

We use a published validated model for glucose-insulin regulation that captures the changes to glucose metabolism driven by short moderate-intensity exercise (Breton, 2008) to simulate the expected blood glucose dynamics with and without treatment adjustments. We augment this model with a published extension to account for the intensity- and duration dependence of exercise-driven changes in insulin sensitivity (Dalla Man et al., 2009). We allow for glucose appearance after a meal using a published model describing the appearance rate (Hovorka et al., 2004). Finally, we describe insulin kinetics after injection of a subcutaneous bolus using a published two-compartment model (Nucci and Cobelli, 2000) that we calibrated on published data for insulin aspart (Svehlikova et al., 2021) using ordinary least squares regression.

The glucose-insulin dynamics proposed in Breton (2008) are given by the system of ordinary differential equations

\[
\begin{align*}
\dot{X} & = -p_2 \cdot X + p_3 \cdot \Delta I \\
\dot{G} & = -p_1 \cdot (G - G_b) - (1 + \alpha \cdot W \cdot Z) \cdot X \cdot G - \alpha \cdot W \cdot Z \cdot X_b \cdot G \\
& \quad - \beta \cdot Y \cdot G + \frac{Ra}{V_g \cdot BW} \\
\dot{Y} & = -\frac{1}{\tau_{HR}} \cdot Y + \frac{1}{\tau_{HR}} (HR - H_{Rb}) \\
\dot{Z} & = - (f(Y) + \frac{1}{2}) \cdot Z + f(Y),
\end{align*}
\]

where a dot denotes a time-derivative and we suppress the explicit dependence on time in our notation. The state \( X [1/\text{min}] \) describes the action of insulin in a remote compartment on plasma glucose \( G [\text{mg/dl}] \), \( G_b \) is the basal plasma glucose level, and \( p_1 \) to \( p_3 \) are rate parameters. Insulin is considered as the difference \( \Delta I = I - I_b = I_t + I_c - I_b \) between plasma insulin concentration \( I [\mu \text{U/ml}] \) and the basal level \( I_b \). Plasma insulin is divided into the concentration \( I_t \) required to achieve a target glucose level \( G_t \) and a contribution \( I_c \) from insulin bolus injections.

The model considers the increase in heart rate \( HR [\text{bpm}] \) above its basal rate \( H_{Rb} \) to quantify exercise intensity, and encodes the cumulative effect delayed by a time constant \( \tau_{HR} [\text{min}] \) in a state variable \( Y \), representing energy expenditure. This impacts the glucose concentration through a state \( Z \) driven by the function

\[
f(Y) = \frac{Y}{\beta \cdot H_{Rb}} \bigg/ \left( 1 + \frac{Y}{\beta \cdot H_{Rb}} \right) \bigg)^n, \tag{2.2}
\]

defining the exercise onset when \( Y \) reaches a certain fraction \( a \) of the basal heart rate \( H_{Rb} \). The time constant \( \tau [\text{min}] \) allows for a slow decay of \( Z \) after exercise.

We follow a proposal by Dalla Man et al. (2009) and account for the dependence of the exercise-driven rise in insulin sensitivity on exercise duration and intensity using the integrated over-basal heart rate

\[
W = \int_0^t (HR - H_{Rb}) \, dt. \tag{2.3}
\]

Overall, exercise increases insulin action by the factor \( \alpha \cdot W \cdot Z \). This includes the increase in the effect \( X_b \) of basal insulin on plasma glucose, which was also
incorporated by Dalla Man et al. (2009). The insulin-independent rise in glucose clearance is given by $\beta \cdot Y \cdot G$ and is proportional to the exercise intensity.

We use an established model to describe the appearance rate $Ra$ [mg/min] of glucose in plasma after carbohydrate intake (Hovorka et al., 2004):

$$Ra = \frac{f \cdot D \cdot t \cdot e^{-t/\tau_{max}}}{\tau_{max}^2},$$  

(2.4)

where $f$ is the bioavailability of the meal, $D$ [mg] is the amount of ingested carbohydrates (CHO) and $\tau_{max}$ [min] is the time of maximum appearance rate. The parameters $V_g$ [dl/kg] and $BW$ [kg] give the glucose distribution volume and the body weight, respectively.

Finally, we use a two-compartment model described in Nucci and Cobelli (2000) to describe insulin kinetics after a subcutaneous injection:

$$\dot{x}_1 = -k_{21} \cdot x_1 + u$$

$$\dot{x}_2 = k_{21} \cdot x_1 - (k_d + k_a) \cdot x_2$$

$$\dot{I}_c = \frac{k_v}{V_i} \cdot x_2 - k_e \cdot I_c,$$

(2.5)

where the injected insulin $u$ [$\mu U$/min] passes through the subcutaneous compartments $x_1$ and $x_2$ [$\mu U$] before reaching the plasma insulin compartment; $k_{21}, k_d, k_a$ and $k_e$ are rate parameters and $V_i$ [ml/kg] is the insulin distribution volume.

We provide the parameters of this model in Table 2.1. The parameters of the glucose-insulin model were taken from the original publication (Breton, 2008), but we adjusted $\alpha$ based on the model augmentation proposed in Dalla Man et al. (2009). For the parameters of the glucose appearance rate, we used the original parameters given in Hovorka et al. (2004). Finally, we calibrated the insulin injection model to insulin aspart using ordinary least squares regression based on recently published data (Svehlikova et al., 2021). Throughout this study, we consider an ‘average’ person of $BW = 70$ kg body weight with a resting heart rate of $HR_b = 80$ bpm and basal insulin requirements of $I_b = 10 \mu U$/ml and a target glucose of $G_t = 120$ mg/dl.

### 2.3.2 Insulin Bolus Calculation

We calculate the insulin bolus $u$ [U] required to compensate a given meal according to

$$u = \frac{CHO}{ICR} + \frac{G - G_t}{CF},$$

(2.6)

where $CHO$ [g] is the amount of carbohydrates in the meal, $G$ [mg/dl] is the current glucose level (in the simulation) and $G_t$ [mg/dl] denotes the target glucose level. We round the calculated insulin dose to the nearest 0.5 U to mimic the usual practice in MDI-therapy. Throughout, we ignore a potential correction for insulin-on-board, since insulin injections are sufficiently spaced over time in all simulations.

In practice, the insulin bolus calculation is adjusted to an individual using the patient-specific insulin-to-carbohydrate ratio, $ICR$ [g/U], and a patient-specific correction factor $CF$ [mg/dl/U]. For our simulations, we consider a single ‘typical’
Table 2.1 – Model parameters. Parameter α was adjusted according to the model extension in Dalla Man et al. (2009).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose regulation</strong> (Breton, 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p_1$</td>
<td>0.0041</td>
<td>1/min</td>
</tr>
<tr>
<td>$p_2$</td>
<td>0.0155</td>
<td>1/min</td>
</tr>
<tr>
<td>$p_3$</td>
<td>$6.913 \times 10^{-6}$</td>
<td>1/min$^2$ per $\mu$U/ml</td>
</tr>
<tr>
<td>$G_b$</td>
<td>172</td>
<td>mg/dl</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$2.59 \times 10^{-4}$</td>
<td>dimensionless</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$3.39 \times 10^{-4}$</td>
<td>1/bpm</td>
</tr>
<tr>
<td>$\tau_{HR}$</td>
<td>5</td>
<td>min</td>
</tr>
<tr>
<td>$\tau$</td>
<td>600</td>
<td>min</td>
</tr>
<tr>
<td>$a$</td>
<td>0.1</td>
<td>dimensionless</td>
</tr>
<tr>
<td>$n$</td>
<td>4</td>
<td>dimensionless</td>
</tr>
<tr>
<td><strong>Meal</strong> (Hovorka et al., 2004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$f$</td>
<td>0.8</td>
<td>dimensionless</td>
</tr>
<tr>
<td>$V_s$</td>
<td>1.6</td>
<td>dl/kg</td>
</tr>
<tr>
<td>$\tau_{max}$ (slow)</td>
<td>60</td>
<td>min</td>
</tr>
<tr>
<td>$\tau_{max}$ (fast)</td>
<td>20</td>
<td>min</td>
</tr>
<tr>
<td><strong>Insulin</strong> (Svehlikova et al., 2021)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_{a1}$</td>
<td>0.0085</td>
<td>1/min</td>
</tr>
<tr>
<td>$k_d$</td>
<td>0.0247</td>
<td>1/min</td>
</tr>
<tr>
<td>$k_a$</td>
<td>0.011</td>
<td>1/min</td>
</tr>
<tr>
<td>$k_e$</td>
<td>0.0357</td>
<td>1/min</td>
</tr>
<tr>
<td>$V_i$</td>
<td>104</td>
<td>ml/kg</td>
</tr>
</tbody>
</table>

person and fix these two parameters to $ICR = 15$ g/U and $CF = 20$ mg/dl/U, which results in good glycemic control together with the model parameters in Table 2.1.

2.3.3 Treatment Adjustment Guidelines

For our simulation studies, we consider three treatment adjustment scenarios based on two sets of recommendations. First, we use the decision-tree carbohydrate intake algorithm developed in (Riddell and Milliken, 2011) that uses continuous glucose monitoring to propose ingestion of CHO during the activity based on glucose concentration and trend. Second, we use a collection of recommendations given in recent consensus guidelines (Riddell et al., 2017) that address insulin and CHO requirements before, during and after exercise. In many cases, the guidelines provide a range rather than a specific amount of recommended CHO intake, and
we reflect this in our simulations by separately considering the low and high end of the proposed range.

**Carbohydrate intake algorithm**

The carbohydrate intake algorithm was proposed by Riddell and Milliken and exploits information from real-time CGM to improve glucose levels during exercise and avoid hypoglycemia (Riddell and Milliken, 2011). Carbohydrate intake is recommended once glucose drops below 126 mg/dl and exercise is suspended if glucose falls below 70 mg/dl.

Specifically, 8 g CHO are recommended for glucose between 110 and 126 mg/dl and dropping at a rate greater than 5.4 mg/dl per 5 min (as indicated on a CGM device). For lower glucose levels between 90 and 110 mg/dl, the algorithm recommends 16 g CHO if glucose drops between 5.4–9.9 mg/dl per 5 min (indicated by one downward arrow) and increases the recommendation to 20 g CHO if it drops faster than 9.9 mg/dl per 5 min (indicated by two downward arrows). Finally, the algorithm proposes ingestion of 16 g CHO independent of the rate of glucose change for glucose levels below 90 mg/dl.

For our simulations, we allow multiple intakes of fast-acting CHO during the activity, but require a minimum time of 20 min between successive snacks.

**Table 2.2 – Consensus guidelines: recommended bolus insulin reduction for pre-exercise meal if bolus is administered within 120 min of exercise onset.**

<table>
<thead>
<tr>
<th>% VO²_max</th>
<th>HR [bpm]</th>
<th>Exercise duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–50</td>
<td>100–130</td>
<td>−25% &lt; 60 min, −50% &gt; 60 min</td>
</tr>
<tr>
<td>50–70</td>
<td>130–155</td>
<td>−50% &lt; 60 min, −75% &gt; 60 min</td>
</tr>
<tr>
<td>≥70</td>
<td>≥155</td>
<td>−75% &lt; 60 min, −75% &gt; 60 min</td>
</tr>
</tbody>
</table>

**Consensus guidelines**

A recent consensus statement provides a detailed overview on exercise management, including glucose targets, carbohydrate recommendations and insulin dose adjustments for both bolus and basal insulin for different forms of exercise (Riddell et al., 2017). Here, we restrict consideration to the recommendations pertinent to exercise between 30–120 min at moderate intensity.

For moderate-intensity exercise, the guidelines recommend a proportional reduction of the meal insulin bolus (Eq. 2.6) depending on the exercise intensity and duration if a meal was eaten within 120 min before exercise is started (Table 2.2).

Additional glucose targets and carbohydrate intake strategies are given to stabilize BG levels at the onset of exercise: exercise is only started if BG is above 90 mg/dl, and CHO intake is recommended based on the BG level and the insulin condition, such that a higher CHO intake is required if insulin concentrations are high.

The guidelines distinguish between low and high insulin conditions to modify the recommended CHO intake during exercise, but do not define these conditions
in detail. We consider a simulation in the high insulin condition if insulin is injected at most 120 min prior to exercise onset and in the low insulin condition otherwise. For our simulations, we separately consider following the low respectively high end of the recommended range of carbohydrate intake as given in Table 2.3.

The guidelines also generically recommend a meal after exercise. For our simulations, we follow clinical experience and consider the intake of 20 g CHO without insulin bolus if BG is below 90 mg/dl immediately following exercise.

Table 2.3 – Consensus guidelines: CHO intake before, during and after exercise. If BG is <90 mg/dl at exercise onset, exercise is delayed until BG>90 mg/dl. During exercise of more than 60 min under high insulin conditions, we consider CHO intake of 60–70 g/h.

<table>
<thead>
<tr>
<th>Insulin condition</th>
<th>low</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At exercise onset based on BG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90 mg/dl</td>
<td>15 g</td>
<td>25 g</td>
</tr>
<tr>
<td>90–124 mg/dl</td>
<td>10 g</td>
<td>10 g</td>
</tr>
<tr>
<td>&gt;124 mg/dl</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>During exercise based on duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 min</td>
<td>—</td>
<td>15–30 g</td>
</tr>
<tr>
<td>30–60 min</td>
<td>10–15 g/h</td>
<td>30–60 g/h</td>
</tr>
<tr>
<td>&gt;60 min</td>
<td>30–60 g/h</td>
<td>up to 75 g/h</td>
</tr>
<tr>
<td><strong>At end of exercise based on BG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90 mg/dl</td>
<td>20 g</td>
<td>20 g</td>
</tr>
<tr>
<td>≥90 mg/dl</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

2.3.4 **Performance Measures**

In addition to direct comparisons of predicted blood glucose curves, we consider time-in-range (TIR) and the low (LBGI) respectively high (HBGI) blood glucose index as three well-established measures to quantify the performance of different treatments.

The time-in-range gives the percentage of time that an individual’s glucose concentration remains in the desired range of 70–180 mg/dl. The TIR does not distinguish between low and high blood glucose excursions.

The low blood glucose index (LBGI) and the high blood glucose index (HBGI) measure the extent and frequency of low, respective high blood glucose events based on the BG risk function (Kovatchev et al., 2000), given as

\[
 r(G) = 10 \cdot 1.509^2 \cdot \left( \left[ \ln(G) \right]^{1.084} - 5.381 \right)^2.
\]

This function provides a quantitative risk score for each BG level. It has a minimum at 112.5 mg/dl, and it is customary to distinguish values below and above this minimum via
\[ rl(G) = \begin{cases} r(G) & \text{if } G < 112.5 \text{ mg/dl} \\ 0 & \text{otherwise} \end{cases} \]
\[ rh(G) = \begin{cases} r(G) & \text{if } G \geq 112.5 \text{ mg/dl} \\ 0 & \text{otherwise} \end{cases} \]  (2.8)

Given \( n \) blood glucose readings \( G_1, \ldots, G_n \), the LBGI and HBGI correspond to the average risk of the recorded events below respectively above the threshold of 112.5 mg/dl:

\[ \text{LBGI} = \frac{1}{n} \sum_{i=1}^{n} rl(G_i) \]
\[ \text{HBGI} = \frac{1}{n} \sum_{i=1}^{n} rh(G_i) . \]  (2.9)

2.3.5 Variance-Based Global Sensitivity Analysis

We use a global sensitivity analysis (GSA) approach (Sobol, 1990) to investigate how simultaneously changing model parameters and the timing of exercise is reflected in changes in the time-in-range and low blood glucose index. Our rationale is that parameters in the mathematical model are associated with physiological processes; large variation caused by parameters associated with the same process would then allow us to gauge the relative importance of different processes on the TIR and LBGI under exercise.

Global sensitivity analysis is a standard tool for evaluating identifiability and robustness of nonlinear models (Zhang et al., 2015). For a given function \( f(p_1, p_2, \ldots, p_k) \) with \( k \) inputs, GSA varies all inputs simultaneously and records the resulting responses. We can then calculate the variance \( V \) of the responses. The first-order Sobol index \( S_1(i) \) of the \( i \)th input is the proportion of \( V \) attributed to variation in \( p_i \) alone (also called the main effect), while the second-order Sobol index \( S_2(i) \) is the proportion additionally attributed to co-variation (or second-order interaction) of \( p_i \) and any other parameter. The total Sobol index \( S_T(i) \) describes the overall contribution of parameter \( p_i \) to the variation in the response, considering its main effect and all interactions of any order.

Intuitively, a large \( S_T(i) \) results if variation of input \( p_i \) yields large variation in the response; the indices \( S_1(i) \) and \( S_2(i) \) then further detail what part of this variation is caused by \( p_i \) alone respectively in conjunction with simultaneous variation of another input.

2.4 Results

We base our treatment adjustment comparisons on a simulated standard day using the model outlined in Section 2.3.1. Our standard day consists of a 24h simulation period, starting at 6:00h in the morning. We consider three typical meals: a breakfast of 50g carbohydrates at 7:00h, a lunch of 70g carbohydrates at 13:00h, and a dinner of 60g carbohydrates at 19:00h. For each meal, we set the time of maximum appearance rate to \( \tau_{\text{max}} = 60 \text{ min} \); this corresponds to a typical mixed meal. We administer an insulin bolus injection 15 min before each meal and use the bolus calculator (Eq. 2.6) to determine the required standard bolus. For simulations based on the consensus guidelines, we decrease this bolus according to Table 2.2 if
required. We modify our standard day for some of our simulation scenarios and indicate these changes in the corresponding sections.

2.4.1 Variation of Insulin Sensitivity and Meal Appearance

It is well known that insulin sensitivity varies strongly between individuals. We therefore asked how the glucose dynamics changes with changes to the basal insulin sensitivity in our simulation in the presence of exercise. For this, we simulated blood glucose trajectories for our standard day, but added a 60 min exercise session at a very moderate heart rate of 120 bpm at 15:00h. We then altered the basal insulin sensitivity by ±30% without adjusting the treatment and keeping patient-specific parameters ICR and CF constant, resulting in the dynamics shown in Fig. 2.1A. The impact of insulin sensitivity is clearly visible and within the range expected from clinical experience. Noteworthy, increasing the insulin sensitivity (i.e. increasing the parameter \( p_3 \)) shifts the glucose levels before and during exercise, but yields virtually identical BG levels after exercise (Fig. 2.1A dark blue and light blue).

Next, we considered the impact of glucose appearance from meals using the same exercise scenario. Specifically, the time \( \tau_{\text{max}} \) to maximum appearance is highly variable in practice and strongly depends on the meal composition, which is often not known precisely. We therefore altered this parameter by ±30%, corresponding roughly to meals with moderately slow respectively moderately fast glucose appearance (Fig. 2.1B). Altering glucose appearance has a strong effect on the height and width of the resulting blood glucose peak following the meal. Slower appearance, corresponding to a more complex meal composition and described by a higher \( \tau_{\text{max}} \), leads to low and broad peaks, while appearance of fast-acting CHO is characterized by high and narrow peaks. Furthermore, the decrease in BG levels after the peak is more pronounced for smaller \( \tau_{\text{max}} \), since the meal is already absorbed while the bolus insulin is still active.

Differences in insulin sensitivity and in meal absorption therefore complicate a direct comparison of treatment options based on blood glucose trajectories of different individuals and meals. In the following, we therefore fix the insulin sensitivity and use a fixed time of maximum glucose appearance of 60 min for the main meals in order to isolate the treatment effects and allow a direct comparison of different treatment adjustments to exercise.

**Figure 2.1** – Variation in blood glucose dynamics for the standard day with 60 min of exercise at a heart rate of 120 bpm (vertical lines). (A) Insulin sensitivity varied by ±30%. (B) Time of maximum glucose appearance \( \tau_{\text{max}} \) varied by ±30%.
2.4.2 Timing of Physical Activity

The effect of exercise on blood glucose depends on exercise duration and intensity but also on the timing between exercise and meals, which affects resulting BG dynamics. However, the impact of exercise performed during different phases of meal absorption on BG is not obvious and guidelines only consider insulin bolus reductions for pre-exercise meals. To further elucidate the relation between meal absorption and exercise, we examined the effect of exercise timing on blood glucose levels with and without applying treatment adjustments.

We again base our simulations on the standard day described in the beginning of this section. In addition, exercise was performed for 60 min at a heart rate of 120 bpm. We considered several starting times for the exercise session, starting at 13:30h (immediately following lunch) and spaced in 30 min steps until a latest session at 17:30h that finishes 30 min before dinner.

We compare the resulting blood glucose trajectories without adjustments, with adjustment following the carbohydrate intake algorithm, and with adjustment following the consensus guidelines with low respectively high carbohydrate intake if required. We assumed a fast glucose appearance with parameter $\tau_{\text{max}} = 20$ min for the suggested carbohydrate snacks. The resulting trajectories are shown in Figure 2.2.

Without treatment adjustment to exercise (Fig. 2.2A), exercise sessions later after lunch start at comparatively lower BG levels, as more of the meal carbohydrates

![Image of glucose levels for exercise performed at different times during the afternoon for 60 min at a heart rate of 120 bpm (A) without treatment adjustment to exercise, (B) with adjustment based on the CHO algorithm, (C) using the lower CHO recommendation of the consensus guidelines and (D) using the upper CHO recommendation of the consensus guidelines.](image-url)
are already absorbed at the time of exercise. Consequently, later exercise leads to lower minimal BG levels towards the end of the session, reaching hypoglycemia in many cases. At the same time, the overall decrease in BG level is considerably higher for exercise started more closely to lunch, because the exercise-independent decrease of blood glucose from meal absorption and the active insulin from the meal bolus combine with the increased glucose demand during exercise. While BG levels are higher at the end of exercise for these earlier exercise sessions, the meal glucose is continued to be absorbed after the activity and glucose keeps decreasing. Consequently, blood glucose trajectories are similar for all exercise scenarios by dinner time. Moreover, exercise-driven insulin sensitivity returns to baseline only slowly over the course of several hours during recovery, and the difference in exercise timing has little impact on the overnight BG curves. Nevertheless, the increased insulin sensitivity manifests in a considerably lower blood glucose of about 100 mg/dl during the night, as compared to the unperturbed target level of 120 mg/dl at the beginning of the simulation.

When applying the CHO intake algorithm (Fig. 2B), the BG trajectories fall into two broad categories. For earlier exercise, the algorithm proposes only a small amount of CHO towards the end of the session, and BG further decreases to 70 mg/dl between exercise and dinner. For later exercise, on the other hand, BG levels fall below 70 mg/dl during the activity and the algorithm correspondingly recommends a larger CHO amount which results in considerably higher BG concentrations at dinner time compared to the previous case. This difference in BG at dinner time leads to substantial changes in the calculated meal insulin bolus: adjustments for later exercise result in a higher calculated insulin bolus because they stabilize the BG level during and after exercise and yield BG levels close to the target at dinner time. This bolus amplifies the elevated effect of insulin on glucose disappearance and results in low overnight BG. In contrast, adjustments for earlier exercise also stabilize BG levels during exercise, but yield low BG levels at dinner time. The calculated insulin bolus is now reduced, resulting in an overnight BG in the normoglycemic range.

Next, we adjusted treatment following the consensus guidelines and used the low recommended CHO amount during exercise (Fig. 2C). For early exercise sessions, the guidelines result in a reduced insulin bolus for lunch. Then, BG levels can be maintained during the activity and stay in the normoglycemic range until dinner. When exercise is performed in the afternoon starting at 15:00h or 15:30h, the insulin bolus is not reduced, BG drops strongly during exercise and reaches 70 mg/dl by dinner time. For later exercise, the guidelines recommend additional intake of 20 g CHO without insulin bolus and BG consequently increases after the activity and remains high when the dinner bolus is administered. Similar to the CHO intake algorithm, the differences in BG level at dinner time and associated differences in insulin bolus maintain normoglycemia overnight for early- and mid-afternoon exercise, but result in low BG for the other scenarios.

Finally, we considered the upper end of the recommended CHO amount for the consensus guidelines (Fig. 2D). The additional carbohydrates push the blood glucose higher during exercise compared to the previous scenario and result in more similar BG levels at dinner time for the different timings. However, the insulin bolus calculation still yields slightly different recommended doses, and
while overnight BG trajectories now all remain in the normoglycemic range, higher insulin doses for later sessions result in gradually lower BG trajectories.

To summarize the performance of the treatment adjustments and allow more direct comparison, we evaluate the time-in-range (TIR) and low blood glucose index (LBGI) over a 24-hour period resulting from each scenario (Fig. 2.3). Without treatment adjustment, TIR is lower when exercise is started later, but increases again slightly for exercise starts after 16:00h. All three treatment adjustment strategies lead to substantial improvement of TIR and show similar results for the first two hours. Most notably, the consensus guidelines with low CHO intake show substantial deterioration when starting exercise after 16:00h, moving closer towards dinner time, in agreement with the trajectories in Figure 2.2.

Comparing the treatment adjustments in terms of LBGI yields a similar overall conclusion: without adjustment, LBGI continuously increases the later exercise is started. While the consensus guidelines show very similar results both for the lower and higher CHO recommendation for early exercise, using the low end of the proposed CHO intake results in higher LBGI for later exercise.

Overall, the consensus guidelines with high CHO intake give the best performance both in terms of TIR and LBGI for this simulation scenario. The qualitatively similar results for TIR and LBGI over all adjustments indicate that adjustments mainly improve TIR by avoiding hypoglycemia, without overly increasing hyperglycemia in the process.

![Figure 2.3](image)

**Figure 2.3** – (A) TIR and (B) LBGI for different exercise starting times considering no adjustment (blue), the CHO intake algorithm (orange), and the consensus guidelines with low (green) and high (purple) CHO intake.

### 2.4.3 Combination of Exercise Intensity, Duration and Timing

The two sets of treatment adjustment strategies explicitly consider duration and intensity of the exercise, but do not account for the time of exercise during the day or with respect to adjacent meals, unless exercise is performed within two hours of a meal. Given the substantial impact of this timing on the blood glucose trajectories, we next look at combinations of exercise duration, intensity, and timing, and evaluate the resulting BG trajectories with and without treatment adjustments. We now consider exercise at three moderate intensities of $HR = 120, 140$ and $160$ bpm and vary the exercise duration in 15 min increases from 30 min up to 120 min. Finally, we consider each combination of intensity and duration in three scenarios based on our standard day, where we alter the starting time of the exercise...
session to enforce a bolus insulin reduction, respectively a low and high insulin condition. We again use $\tau_{max} = 20$ min to model the fast absorption of exercise snacks.

We again consider no adjustment to treatment, the carbohydrate intake algorithm, and the consensus guidelines using the low respectively high end of the recommended CHO intake. We summarize the performance of each treatment adjustment using time-in-range, and low and high blood glucose index. Since a main focus of treatment adjustment is avoidance of exercise-induced hypoglycemia, we additionally quantify the risk of acute and late-onset hypoglycemic episodes for each scenario and calculate the LBGI of acute hypoglycemia during and up to 60 min after exercise, and the LBGI of late-onset hypoglycemia during the night from 19:00h to 6:00h the following morning. We summarize the simulation results as heatmaps shown in Figure 2.4. Note that for TIR, larger values with darker more red-pink colors indicate better time-in-range, while for the other four measures lower values with lighter more yellow colors indicate better treatment.

**Scenario 1: exercise in postabsorptive state**

For our first scenario, we modify our standard day and introduce an exercise session starting at 12:00h while postponing lunch to 14:30h. Then, the BG level is close to fasting levels at the beginning of exercise and glucose dynamics are entirely governed by exercise and corresponding treatment adjustments. The performance measures are shown in Figure 2.4A.

For this scenario, all three treatment adjustments show substantial improvements over no adjustment for TIR and hypoglycemia-related LBGI, acute and late-onset hypoglycemia risk measures. Time-in-range is high using any adjustment, showing only a slight decrease towards longer exercise duration for high CHO intake. For both TIR and LBGI, the carbohydrate intake algorithm and the consensus guidelines with low CHO intake show comparable results. Interestingly, using the consensus guidelines with high CHO intake results in higher LBGI for longer exercise duration compared to the other two adjustments. This adjustment also shows inferior HBGI control, indicating that the high CHO intake likely overcompensates for the glucose uptake from exercise, resulting in higher HBGI, while being unable to maintain a sufficient blood glucose level over longer periods.

All three strategies achieve near-prevention of acute hypoglycemia for lower intensity exercise regardless of duration, and the carbohydrate intake algorithm manages to keep acute hypoglycemia risk low also for higher intensities. Meanwhile, both variants of the consensus guidelines show increased acute risk for higher intensities, especially for durations around one hour.

Risk of late-onset hypoglycemia is substantial in this scenario for higher intensities and longer duration. All three adjustment strategies reduce this risk and we observe a clear dose-response relation with longer duration and higher intensity being more difficult to control, with the carbohydrate intake algorithm and the consensus guidelines with low CHO intake reducing the risk slightly more than following the high CHO recommendations.
Figure 2.4 – TIR, LBGI and HBGI over 24h-simulations and the corresponding acute and late-onset hypoglycemia risk for different adjustments, intensities and exercise durations. (A) Scenario 1: exercise in postabsorptive state. (B) Scenario 2: exercise with prior insulin bolus reduction. (C) Scenario 3: exercise without prior insulin bolus reduction.
Scenario 2: exercise with prior insulin bolus reduction

Next, we modify our standard day by introducing an exercise session at 14:30h, corresponding to a time shortly after lunch. The consensus guidelines then propose a reduction of the insulin bolus for lunch, and exercise is performed in a high insulin condition. The results are given in Figure 2.4B.

Again, all three treatment adjustments improve LBGI and acute hypoglycemia risk compared to no adjustment over all durations and intensities. While the CHO intake algorithm shows good overall control of TIR, applying the consensus guidelines results in a decrease of TIR for longer and more intense exercise, especially for high CHO intake. This is explained by the corresponding increase in HBGI for these scenarios, which exceeds a no treatment option substantially and indicates a likely overcompensation with too high CHO amounts.

The carbohydrate intake algorithm shows slightly elevated acute hypoglycemia risk compared to the two consensus guidelines variants, but simultaneously presents a lower risk for late-onset hypoglycemia. Notably, late-onset hypoglycemia risk is similar for no adjustment and the CHO algorithm, while it increases compared to no adjustment for the consensus guidelines and longer exercise duration. In addition, long exercise of higher intensity poses a problem for all three strategies: while acute hypoglycemia risk is well-controlled, the risk of late-onset hypoglycemia increases rapidly with intensity and duration.

Scenario 3: exercise without prior insulin bolus reduction

As our third scenario, we modify our standard day by an exercise session at 15:30h. Blood glucose is then still elevated from the preceding lunch at the beginning of exercise. However, consensus guidelines do not adjust the insulin bolus for lunch due to the larger time gap between meal and exercise, and exercise is performed in a low insulin condition. We show results in Figure 2.4C.

In this scenario, all three treatment adjustments struggle to keep time-in-range high for higher intensities and longer durations, and consensus guidelines with high CHO intake show low TIR for longer exercise even at low intensity, with corresponding high HBGI for these exercise scenarios. In contrast to the previous scenarios, HBGI is generally high, and particularly so for short duration exercise.

Reduction of LBGI compared to no adjustment is clearly visible for all strategies, but works less efficient compared to scenario 2. As before, LBGI deteriorates for all adjustments with increasing intensity and duration.

The risk of acute hypoglycemia in this scenario is very high without treatment adjustment, even for comparatively short duration of exercise. All three adjustment strategies reduce this risk to very low values, with notable increase in risk for the highest intensity. The carbohydrate intake algorithm shows good control of acute hypoglycemia risk throughout, and consistently yields the lowest risk of late-onset hypoglycemia. Meanwhile, the two consensus guideline adjustments help reduce the acute risk further, and the high CHO intake in particular is very successful for higher intensities and longer duration in this regard. On the other hand, better reduction of acute hypoglycemia results in increased risk of late-onset hypoglycemia. Overall, late-onset hypoglycemia seems difficult to control in this scenario for all adjustments, and the risk score is substantially higher compared to the two previous scenarios, and reaches very high levels for long exercise duration.
In summary, all three adjustment strategies show dramatic improvement over all measures compared to no adjustment. The consensus guidelines are successful in avoiding acute hypoglycemia when exercise is preceded by a meal, but less so in a postabsorptive state. The carbohydrate intake algorithm also performs well in this regard. While all three adjustment strategies also reduce the risk of late-onset hypoglycemia when starting exercise in a postabsorptive state, all strategies struggle to maintain a low late-onset risk score when blood glucose dynamics from a preceding meal are added. Of note in these scenarios is that all strategies show higher late-onset risk score compared to no adjustment, clearly indicating the difficulties to maintain glycemic control over a long period with multiple factors impacting the blood glucose dynamics. Indeed, preventing acute and late-onset hypoglycemia appear to be conflicting goals, with better acute control leading to worsened late-onset control.

2.4.4 Application of Guidelines to a Patient Population

To evaluate whether our conclusions generalize to a broader population, we repeat our analysis for 100 new subjects, described by different parameter sets. We allow variation in the most important parameters glucose effectiveness \((p_1)\), insulin sensitivity \((p_3)\), exercise-driven increase in insulin sensitivity \((\alpha)\) and glucose clearance \((\beta)\), and sample each parameter independently from a corresponding normal distribution with a standard deviation of 20% of the nominal parameter value. We again consider the three scenarios described previously and concentrate on an exercise duration of 90 minutes and an intensity of \(HR = 140\) bpm for brevity. The results are shown in Figure 2.5, where we observe excellent agreement with our previous conclusions for all five performance measures and all adjustments. We also considered the remaining exercise durations and again found excellent agreement with our conclusions from the ‘typical’ individual (Suppl. Fig. S2.1-S2.3), including outcomes on the individual subject level (shown for 10 randomly selected subjects in Suppl. Fig. S2.4-S2.6).

2.4.5 Sensitivity Analysis

Our final analysis aims at quantifying which physiological processes drive the time-in-range and LBGI in the presence of exercise. For this, we exploit ideas from global sensitivity analysis to decompose the observed variation in TIR, respectively LBGI, into components associated to individual model parameters. We again use our standard day and add a 60 min exercise session at 15:30h, with a very moderate intensity of \(HR = 120\) bpm.

We used the Python package SALib (Herman and Usher, 2017) for calculating the Sobol indices. We allowed each parameter to vary up to \(\pm 20\%\) around its nominal value (Table 2.1), and uniformly sampled \(N = 51,000\) random parameter sets from the resulting parameter region. For each sampled parameter set, we simulated the blood glucose trajectories without further treatment adjustments and recorded TIR and LBGI, before calculating the variation of these two responses using the standard variance estimator.

For time-in-range, we find that the glucose distribution volume \(V_g\) has the largest impact (Fig. 2.6A), with a first-order sensitivity of about 50%. In other words,
changes in the distribution volume account for about half of the variation in the observed TIR for this simulation scenario. This is not surprising, as $V_g$ largely determines the BG rise after meal intake and hence affects hyperglycemic episodes. The glucose effectiveness $p_1$ and the basal glucose concentration $G_b$ provide the second- and third-largest contribution with main effects of about 10% each. Thus, glucose-related parameters explain the vast majority of variation in TIR. In addition, we find substantial interactions between the insulin action parameters $p_2$ and $p_3$ and the insulin kinetics parameters $k_a$, $k_e$ and $V_i$ (Fig. 2.6B), as well as between $p_2$ and $p_3$ with $\alpha$, which scales the exercise-driven increase in insulin sensitivity. While these parameters only account for a smaller fraction of the observed variation in TIR individually, the substantial interactions between these parameters indicate an intricate interplay of insulin-related processes.

In contrast, the variation in low blood glucose index is mainly associated with insulin-related parameters, while the importance of the glucose distribution volume $V_g$ is much lower than for TIR (Fig. 2.6C,D). Specifically, $p_2$ and $p_3$ dominate the explained variation with first-order effects of 26% and 18%, respectively. These parameters are associated with insulin-driven glucose disappearance from plasma and thus affect hypoglycemic BG excursions. In addition, exercise-driven changes in insulin sensitivity captured by $\alpha$ contribute to this effect during and after exercise, with a large main effect of 15%. Compared to TIR, the LBGI is less affected by insulin kinetics represented by $k_d$, $k_e$ and $V_i$.

Together, these results suggest that TIR is affected mainly by glucose-related processes, likely due to hyperglycemic excursions following meals, while parameters related to insulin action explain most of the variation in LBGI.
We extended our analysis by adding the timing of the exercise session as an additional parameter, where we allowed exercise to begin any time between 13:30h and 17:30h, and sampled $N = 54,000$ parameter sets. The exercise timing then accounts for more than 20% of the variation in TIR (Fig. 2.7A,B) and its contribution is only exceeded by the glucose distribution volume $V_g$. The relative contributions of the remaining parameters are very similar to before. In other words, the timing of exercise has a larger impact on time-in-range than all patient-related parameters, with the exception of $V_g$.

For the LBGI, the relative contributions of the model parameters also remain similar to before, while the exercise timing now explains roughly the same amount of variation as $\alpha$ (Fig. 2.7C). Overall, parameters involved in insulin action and exercise timing account for the majority of the variation in low blood glucose index.

These results confirm that exercise timing is an important contributor to the blood glucose dynamics, and that exercise-induced changes in insulin sensitivity appear as a major contributor to hypoglycemic events. The comparatively small contributions of interactions to the variation of LBGI show that exercise timing and insulin sensitivity provide independent contributions to this variation in the simulated scenario (Fig. 2.7D).
Figure 2.7 – Sobol sensitivity indices for time-in-range (top row) and low blood glucose index (bottom row) for model parameters and exercise timing $t_{PA}$. (A),(C): main effect $S_1$ and total effect $S_T$. (B),(D): second-order effects $S_2$ for parameters with a minimum total effect of 5%.

2.5 DISCUSSION

In this study, we evaluated different proposed strategies for treatment adjustment to exercise in T1D in-silico using a mathematical model of glucose-insulin regulation and exercise metabolism. Simulation studies offer the opportunity to explore a broad range of possible scenarios and treatment options under identical conditions, and results can be systematically evaluated and compared. We relied on a combination of existing models describing glucose-insulin regulation during exercise, insulin kinetics and meal absorption, thus covering daily activities and allowing us to perform realistic long-term simulations.

We investigated the effect of exercise timing on BG dynamics, and tested a variety of combinations of exercise intensities and duration. For each scenario, we compared BG trajectories and corresponding measures of TIR, and LBGI and HBGI, which represent hypo- and hyperglycemia risk. Since exercise is associated with an increased risk of hypoglycemia during the activity, but also causes nocturnal hypoglycemic episodes due to a prolonged elevation of insulin sensitivity, we further studied acute and late-onset hypoglycemia risk for the different treatment adjustment strategies. Finally, we performed a global sensitivity analysis to de-
termine the impact of model parameters, and hence individual processes such as insulin action, and exercise timing on TIR and LBGI.

We applied the CHO intake algorithm by Riddell and Milliken (2011), which recommends the intake of fast-acting carbohydrates during exercise based on glucose readings and (downward) glucose trends. The aim of this algorithm is to keep glucose levels stable during the activity and avoid exercise-induced hypoglycemia. We studied glucose dynamics also after exercise when assuming no further adjustment of the remaining treatment. However, we are aware that the recommendations do not include treatment after exercise and do not target the prevention of late-onset hypoglycemia. Additionally, we used a set of consensus guidelines, which recommend treatment adjustment before, during and shortly after exercise (Riddell et al., 2017). They provide recommendations on insulin bolus reduction for pre-exercise meals, starting glucose targets and CHO requirements during the activity, and we tested both the lower and upper carbohydrate recommendations.

The consensus guidelines (Riddell et al., 2017) recognize the problem of exercise-related late-onset hypoglycemia, but cite only few related clinical studies. Due to this current lack of evidence, they do not provide differentiated guidelines for insulin dose adjustments and nutritional requirements based on intensity, duration and timing of the activity for exercise of moderate duration and intensity. Similarly, late-onset hypoglycemia is discussed in the ISPAD guidelines (Adolfsson et al., 2018), where it is further mentioned that no specific bedtime glucose guarantees the prevention of nocturnal hypoglycemia. We therefore did not apply any treatment adjustment strategy to reduce late-onset hypoglycemia but evaluated the BG outcome if detailed guidelines around the activity are followed. Treatment adjustments are nevertheless often made in clinical practice, but have to be based exclusively on experience rather than evidence-based guidelines.

Our simulation results suggest that the considered treatment adjustment strategies reduce acute hypoglycemia risk in general and can substantially reduce the increase in risk with exercise intensity and duration seen without adjustment. However, the risk for late-onset hypoglycemia remains elevated after exercise even with treatment adjustments for short and moderate exercise sessions, and can even exceed the risk after no adjustment if a correction bolus for post-exercise hyperglycemia is not reduced.

Our sensitivity analysis suggests that the prolonged rise in insulin sensitivity is the driving factor of late-onset hypoglycemia. Consequently, the increased insulin sensitivity should be considered for improving BG levels after exercise. Indeed, insulin and CHO requirements are usually adjusted for the rest of the day in clinical practice, and more targeted guidelines would be beneficial.

We could not observe clear trends regarding the risk of hyperglycemia, indicating that guidelines focus on prevention of hypoglycemia while accepting more hyperglycemic events to achieve this goal.

In our simulations, we observed that BG levels differ substantially during and after the same activity depending on timing of the exercise session in relation to meals. We hypothesize that the superimposed blood glucose dynamics of pre-exercise meal absorption, meal bolus and exercise make it difficult to derive a suitable treatment adjustment, and that the ongoing dynamic effect of exercise can lead to inadequate insulin bolus administration for post-exercise meals, where the nonlinear effect of increased insulin sensitivity affects larger insulin doses more.
Consequently, late-onset hypoglycemia is more likely to occur after adjustment, with high CHO intake and thus elevated BG levels, compared to no adjustment for some scenarios. Overall, these findings suggest that it is difficult to avoid acute and late-onset hypoglycemia simultaneously if treatment after exercise is not adjusted appropriately and that the risk for late-onset hypoglycemia increases with more complex situations.

Recently, new guidelines on glucose management for exercise have been presented (Moser et al., 2020). They combine detailed guidelines on insulin treatment adjustment and CHO requirements before and during exercise and the immediate post-exercise period with information from CGM data, and take into account dropping and rising BG trends. Most likely, a tighter control of BG levels is achieved following this strategy. For the nocturnal period after late-afternoon or evening exercise, they propose intake of carbohydrates when glucose levels drop below a certain threshold. To target late-onset hypoglycemia proactively, this strategy could be combined with insulin sensitivity tracking. It was shown that insulin sensitivity can be estimated from CGM data (Fabris et al., 2019; Fabris et al., 2020), and insulin doses could be scaled according to the exercise-driven change in insulin sensitivity compared to rest.

We first considered a single ‘typical’ person with diabetes for our analyses to allow direct comparison of different simulation scenarios and treatment guidelines. We then considered a random selection of subjects varying substantially in critical parameters and found that all results generalize to this setting.

We emphasize that it is not our aim to recommend actions for individuals, but to improve understanding of the effects of different treatment adjustments and their advantages and disadvantages. Our findings agree qualitatively with clinical observations on exercise-driven hypoglycemia (Riddell and Milliken, 2011; Metcalf et al., 2014; Campbell et al., 2013) but are still predicated on the assumption that the model captures exercise processes adequately. In particular, we did not validate the full model in this study and our simulation scenarios extend substantially beyond the range of demonstrated validity for its individual model components. Our conclusions are therefore tentative in this respect, and further validation is warranted before application in a clinical setting.

Overall, we applied in-silico simulation studies as a useful tool for the systematic analysis and comparison of treatment strategies. We found that acute hypoglycemia can be prevented in most cases following current guidelines for treatment adjustment to exercise. Late-onset hypoglycemia presents an open problem and is caused by an elevated insulin sensitivity, where the timing of exercise in relation to meals plays a crucial role. Insulin bolus reduction of post-exercise meals might also be required depending on the timing of the exercise session. Similar studies could benefit the development of new treatment adjustments and the generation of testable clinical hypotheses, and validated models capturing additional physiological effects such as high intensity exercise and glycogen depletion during prolonged exercise would allow a broader range of exercise scenarios and strengthen conclusions based on in-silico simulations.
ACKNOWLEDGEMENTS

The authors thank Jörg Stelling and Marc Pfister for helpful discussions.

DATA AVAILABILITY STATEMENT

The Python code for model implementation, analysis, and reproduction of all figures can be found in the T1D Exercise Adjustment GIT repository at https://gitlab.com/csb.ethz/t1d-exercise-adjustment.
2.6 Supplementary Material

2.6.1 Supplementary Figures

Figure S2.1 – Distribution of TIR, LBGI and HBGI and the corresponding acute and late-onset hypoglycemia risk from 24h-simulations of a patient population. Exercise is performed with $HR = 140$ bpm for different durations in the postabsorptive state (Scenario 1). No adjustment (blue), the CHO intake algorithm (orange), low (green) and high (purple) CHO recommendations are considered.
Figure S2.2 – Distribution of TIR, LBGI and HBGI and the corresponding acute and late-onset hypoglycemia risk from 24h-simulations of a patient population. Exercise is performed with $HR = 140$ bpm for different durations after a meal with insulin bolus reduction (Scenario 2). No adjustment (blue), the CHO intake algorithm (orange), low (green) and high (purple) CHO recommendations are considered.
Figure S2.3 – Distribution of TIR, LBGI and HBGI and the corresponding acute and late-onset hypoglycemia risk from 24h-simulations of a patient population. Exercise is performed with $HR = 140$ bpm for different durations after a meal without insulin bolus reduction (Scenario 3). No adjustment (blue), the CHO intake algorithm (orange), low (green) and high (purple) CHO recommendations are considered.
Figure S2.4 – TIR, LBGI and HBGI over 24h-simulations and the corresponding acute and late-onset hypoglycemia risk for 10 subjects. Exercise is performed in the postabsorptive state (Scenario 1) for (A) 60 and (B) 90 min with $HR = 140 \text{ bpm}$. 
Figure S2.5 – TIR, LBGI and HBGI over 24h-simulations and the corresponding acute and late-onset hypoglycemia risk for 10 subjects. Exercise is performed after a meal with insulin bolus reduction (Scenario 2) for (A) 60 and (B) 90 min with HR = 140 bpm.
Figure S2.6 – TIR, LBGI and HBGI over 24h-simulations and the corresponding acute and late-onset hypoglycemia risk for 10 subjects. Exercise is performed after a meal without insulin bolus reduction (Scenario 3) for (A) 60 and (B) 90 min with HR = 140 bpm.
NEW MODEL OF GLUCOSE-INSULIN REGULATION
CHARACTERIZES EFFECTS OF PHYSICAL ACTIVITY AND
FACILITATES PERSONALIZED TREATMENT EVALUATION IN
CHILDREN AND ADULTS WITH TYPE 1 DIABETES

This chapter is submitted as:
Julia Deichmann, Sara Bachmann, Marie-Anne Burckhardt, Marc Pfister, Gabor Szinnai, Hans-Michael Kaltenbach. “New Model of Glucose-Insulin Regulation Characterizes Effects of Physical Activity and Facilitates Personalized Treatment Evaluation in Children and Adults With Type 1 Diabetes.”

Author contributions:
JD developed the Python code, analyzed the data, conducted simulations, and visualized results. HMK and JD conceived and implemented the study, processed the data, and wrote the initial draft of the manuscript. SB, M-AB, MP and GS provided clinical expertise for developing the model, and interpreting the data and results. All authors contributed to the article and the interpretation of the results.

3.1 ABSTRACT

Accurate treatment adjustment to physical activity (PA) remains a challenging problem in type 1 diabetes (T1D) management. Exercise-driven effects on glucose metabolism depend strongly on duration and intensity of the activity, and are highly variable between patients. In-silico evaluation can support the development of improved treatment strategies, and can facilitate personalized treatment optimization. This requires models of the glucose-insulin system that capture relevant exercise-related processes. We developed a model of glucose-insulin regulation that describes changes in glucose metabolism for aerobic moderate- to high-intensity PA of short and prolonged duration. In particular, we incorporated the insulin-independent increase in glucose uptake and production, including glycogen depletion, and the prolonged rise in insulin sensitivity. The model further includes meal absorption and insulin kinetics, allowing simulation of everyday scenarios. The model accurately predicts glucose dynamics for varying PA scenarios in a range of independent validation data sets, and full-day simulations with PA of different timing, duration and intensity agree with clinical observations. We personalized the model on data from a multi-day free-living study of children with T1D by adjusting a small number of model parameters to each child. To assess the use of the personalized models for individual treatment evaluation, we compared subject-specific treatment options for PA management in replay simulations of the recorded data with altered meal, insulin and PA inputs.
3.2 Author Summary

Exercise represents a cornerstone of diabetes management. Yet, many people with type 1 diabetes refrain from exercising, since it increases the risk for hypoglycemia and requires adjusted insulin treatment. The effect of exercise on blood glucose levels depends on exercise duration and intensity, but also varies strongly between individuals, making accurate adjustment a challenge. Mathematical models can help to better understand exercise physiology and to devise new treatment strategies. Here, we propose a model of glucose-insulin regulation that captures the effects of exercise on glucose metabolism and personalize it to individual children with type 1 diabetes, allowing subject-specific treatment assessment.

3.3 Introduction

Blood glucose (BG) homeostasis maintains glucose levels within a tight range in healthy individuals, where the two main hormones involved are insulin and glucagon to lower and raise glucose levels, respectively. In type 1 diabetes (T1D), BG regulation is impeded by the autoimmune destruction of insulin-secreting β-cells of the pancreas (American Diabetes Association, 2014). The resulting lack of insulin leads to elevated glucose levels if untreated. People with T1D therefore rely on exogenous insulin either from multiple daily injections or an insulin pump together with BG monitoring to keep glucose levels stable within a target range of usually 70-180 mg/dl, with insulin requirements varying strongly between individuals. Tight glucose control is essential to avoid long-term complications such as cardiovascular disease and retinopathy from persistent hyperglycemia, or acute complications such as loss of consciousness and seizures from severe hypoglycemia.

Mathematical models of glucose-insulin regulation are a valuable tool for the in-silico evaluation of treatment strategies in T1D and play a critical role in the development of decision support and closed-loop insulin delivery systems (artificial pancreas) (Cinar and Turksoy, 2017; Kovatchev, 2018; Kovatchev, 2019). One prominent example is the UVa/Padova type 1 diabetes simulator (Dalla Man et al., 2014) that has been approved by the FDA for preclinical testing of control algorithms for insulin treatment. While such models are typically used with hypothetical in-silico patients, a recent approach uses a personalized model to replay recorded data of individuals with T1D with altered carbohydrate (CHO) and insulin inputs, allowing subject-specific treatment assessment for improved BG control (Hughes et al., 2021).

T1D treatment also needs to be adjusted to physical activity (PA), but complex PA-driven changes in glucose metabolism pose major challenges for accurate PA management. Changes occur on different time scales and strongly depend on duration and intensity of PA. Glucose demand increases drastically during the activity and insulin sensitivity remains elevated for several hours following exercise (Camacho et al., 2005), leading to an increased risk for both acute and late-onset hypoglycemia. Current guidelines for treatment adjustment consider only coarse categories of glycemia, PA duration and intensity, and need further tailoring to the individual person (Riddell et al., 2017; Adolfsson et al., 2018). Tailoring largely relies on trial-and-error, and while PA has numerous benefits and
represents a cornerstone in diabetes management (American Diabetes Association, 2015; Colberg et al., 2016), fear of hypoglycemia restrains many people with T1D from exercising (Brazeau et al., 2008).

Extended models that capture exercise metabolism can help evaluate PA guidelines and treatment strategies (Deichmann and Kaltenbach, 2021) and the need for such models has long been recognized (Colberg et al., 2015; Riddell et al., 2015; Tagougui et al., 2019). Roy and Parker (2007) proposed a PA extension of the Bergman minimal model (Bergman et al., 1979), considering acute, insulin-independent effects of moderate-intensity PA on glucose uptake and production. They also included effects of liver glycogen depletion for prolonged PA. In an alternative proposal, Breton (2008) studied increased glucose effectiveness and prolonged PA-driven changes in insulin sensitivity during an euglycemic hyperinsulenic clamp protocol in people with T1D. However, the effects of exercise intensity and duration on insulin action were not incorporated. Dalla Man et al. (2009) integrated the model into their simulation model of the glucose-insulin system (Dalla Man et al., 2007b) in an in-silico study and added intensity- and duration-dependence, while Alkhateeb et al. (2021) evaluated different variations of the Bergman minimal model and selected a model that features an increase in glucose effectiveness and insulin sensitivity. Other models have been proposed (Lenart and Parker, 2002; Hernández-Ordoñez and Campos-Delgado, 2008; Kim et al., 2007; Palumbo et al., 2018) and a virtual patient population has been generated (Resalat et al., 2019b) that incorporates PA (Hernández-Ordoñez and Campos-Delgado, 2008).

However, these models have been developed under very controlled conditions, e.g. in clamp studies, have not been tailored to a T1D population, do not permit varying PA intensities or prolonged duration, or cover only a subset of the relevant processes. In addition, they often do not consider insulin and carbohydrate inputs. Hence, they are not suited for (personalized) treatment evaluation under everyday-life conditions.

Recently, Romeres et al. (Romeres et al., 2020a; Romeres et al., 2020b; Romeres et al., 2021) and Nguyen et al. (2021) conducted two elegant studies in which they evaluated exercise-induced changes in glucose utilization and endogenous glucose production, and separated and quantified insulin-dependent and –independent contributions. Incorporating their findings into models of exercise metabolism could alleviate some of the persistent problems and is useful for several reasons. A more accurate representation of exercise physiology by considering insulin-dependent and –independent effects separately facilitates prediction of exercise-driven changes in glucose levels and hypoglycemic events. In turn, this could be used to develop and evaluate improved insulin treatment strategies for PA in T1D. Furthermore, the quantification of overall glucose uptake and production rates allows to develop separate model components for each process. Previously, insulin-independent changes in glucose metabolism were often summarized in an exercise-induced increase in glucose effectiveness in PA models for T1D. As discussed by Alkhateeb et al. (2021), this allows for decreasing glucose levels for moderate-intensity PA, but high-intensity PA cannot be described by such models due to rising BG levels. In addition, it is difficult to incorporate liver glycogen depletion that affects the rate of glucose production for prolonged PA.
Here, we utilize these newly available data and develop a glucose-insulin regulation model for exercise that explicitly considers insulin-dependent and -independent effects on glucose uptake and production, and allows realistic full-day simulations and personalized replay simulations. The model captures the acute and prolonged changes in glucose metabolism during PA and subsequent recovery for moderate- to high-intensity exercise, and considers CHO intake and insulin injections. We first calibrate the model for a healthy population, before adjusting relevant parameters to people with T1D. We validate the model on independent data from increasingly complex scenarios including PA, insulin and CHO intake. We show how exercise duration, intensity and time of day alter BG dynamics in full-day simulations. As a main result, we demonstrate that our model can describe real-world data of individual patients. We personalize the model on data from children with T1D recorded in a free-living observational study, using only data from sensors readily available during everyday-life. We then perform replay simulations of the original scenarios with altered meal, insulin and PA inputs to evaluate different treatment strategies and PA effects on the individual subject level.

3.4 Methods

3.4.1 Development of a Glucoregulatory Model Including Physical Activity

Our proposed model is outlined in Fig 3.1 and comprises a simple core model extended by meal intake and insulin injections. Accelerometer counts AC quantify the input for PA processes affecting glucose regulation.

![Figure 3.1 – Schematic of the glucose-insulin model.](image)

Glucose, Q₁, and insulin, I, dynamics are described using a two-compartment model (Cobelli et al., 1999). Extensions capture plasma insulin kinetics after subcutaneous injection u with basal insulin infusion rate \( u_b \) (Nucci and Cobelli, 2000) and glucose appearance with rate \( Ra \) after a meal D (Hovorka et al., 2004). PA is measured via accelerometer counts AC and leads to changes in glucose metabolism indicated by dotted lines.

We use the Cobelli two-compartment minimal model (Cobelli et al., 1999) to describe glucose-insulin regulation at rest and extend it to incorporate PA-driven changes in glucose metabolism:
We consider accelerometer (AC) counts to capture movement and link them to PA
where transfer functions $f_\tau$ provide the exercise-induced insulin-independent increase in glucose uptake (GU)
plasma and in a remote compartment, respectively. Plasma insulin $I_a$ and $a$ time spent at high intensity $t_{2008}$
Breton, glucose levels. Finally, additional nonlinearities to the model as they are further modulated by changing
sensitivity. These processes depend on PA intensity (see below) and introduce
and production (GP), respectively, while $n$ scaled with bodyweight, $BW$ [kg]. The rates $r_{GLU}$ [1/min] and $(r_{GP} - r_{depl})$ [1/min]
provide the exercise-induced insulin-independent increase in glucose uptake (GU) and production (GP), respectively, while $(1 + Z)$ captures a PA-driven rise in insulin
sensitivity. These processes depend on PA intensity (see below) and introduce
additional nonlinearities to the model as they are further modulated by changing
glucose levels. Finally, $G$ [mg/dl] is the plasma glucose concentration and $V_g$ [mg/kg] the glucose distribution volume.

Measure of exercise intensity and duration

We consider accelerometer (AC) counts to capture movement and link them to PA
intensity $Y$ [counts/min] following previous approaches (Roy and Parker, 2007; Breton, 2008; Lenart and Parker, 2002):

$$
\frac{dX(t)}{dt} = -p_2 \cdot X(t) + p_3 \cdot I(t)
$$

$$
\frac{dQ_1(t)}{dt} = -\left[p_1 + r_{GLU}(t) - (r_{GP}(t) - r_{depl}(t)) + (1 + Z(t)) \cdot X(t)\right] \cdot Q_1(t)
$$

$$
\frac{dQ_2(t)}{dt} = p_4 \cdot Q_1(t) + p_5 \cdot Q_2(t)
$$

$$
G(t) = Q_1(t)/V_g.
$$

The two glucose compartments $Q_1$ and $Q_2$ [mg/kg] represent glucose mass in
plasma and in a remote compartment, respectively. Plasma insulin $I$ [µU/ml]
promotes the disappearance of plasma glucose into liver and tissue, and suppresses
hepatic glucose production via the dynamic state $X$ [1/min]. The constants $Q_{1b}$ [mg/kg] and $X_b = p_3/p_2 \cdot I_b$ [1/min] provide the basal levels of plasma glucose
and state $X$, respectively, with the basal plasma insulin level $I_b$ [µU/ml]. The
ratio $p_3/p_2$ represents insulin sensitivity and $p_1$ describes glucose effectiveness.
The rate parameters $p_4$ and $p_5$ quantify the exchange between the two glucose
compartments. Glucose appearance from meals is described by $Ra$ [mg/min] and
scaled with bodyweight, $BW$ [kg]. The rates $r_{GLU}$ [1/min] and $(r_{GP} - r_{depl})$ [1/min]
provide the exercise-induced insulin-independent increase in glucose uptake (GU) and
production (GP), respectively, while $(1 + Z)$ captures a PA-driven rise in insulin
sensitivity. These processes depend on PA intensity (see below) and introduce
additional nonlinearities to the model as they are further modulated by changing
glucose levels. Finally, $G$ [mg/dl] is the plasma glucose concentration and $V_g$ [mg/kg] the glucose distribution volume.

Measure of exercise intensity and duration

We consider accelerometer (AC) counts to capture movement and link them to PA
intensity $Y$ [counts/min] following previous approaches (Roy and Parker, 2007; Breton, 2008; Lenart and Parker, 2002):

$$
\frac{dY(t)}{dt} = -\frac{1}{\tau_{AC}} \cdot Y(t) + \frac{1}{\tau_{AC}} \cdot AC(t).
$$

The delay $\tau_{AC}$ [min] allows initial adaptation to PA.

We also track PA duration $t_{PA}$ [min], integrated AC count $PA_{int}$ [counts] and
time spent at high intensity $t_h$ [min]:

$$
\frac{dt_{PA}(t)}{dt} = f(AC(t); a_{AC}, n_2) - [1 - f(AC(t); a_{AC}, n_2)] \cdot t_{PA}(t)
$$

$$
\frac{dPA_{int}(t)}{dt} = f(AC(t); a_{AC}, n_2) \cdot AC(t) - [1 - f(AC(t); a_{AC}, n_2)] \cdot PA_{int}(t)
$$

$$
\frac{dt_{h}(t)}{dt} = f(AC(t); a_{h}, n_2) - [1 - f(AC(t); a_{h}, n_2)] \cdot q_5 \cdot t_{h}(t),
$$

where transfer functions $f(AC; a_{AC}, n_2)$ and $f(AC; a_{h}, n_2)$, defined as

$$
f(x; p, n) = \frac{(x/p)^n}{1 + (x/p)^n},
$$

capture the transition in AC count from rest to exercise, respectively from
moderate to high intensity with corresponding AC thresholds $a_{AC}$ [counts/min]
and $a_{h}$ [counts/min]. The exponent $n_2$ defines the steepness of the transition and $q_5$

delays the switch back from the high- to moderate-intensity mode during recovery. The use of transfer functions to introduce exercise-related changes was previously proposed by Breton (2008).

**Insulin sensitivity**

Insulin sensitivity increases during exercise and stays elevated afterwards for up to 48 hours to replete liver glycogen stores (Mul et al., 2015). Previous studies have further established that the increase depends linearly on PA intensity and duration (Dalla Man et al., 2009; Alkhateeb et al., 2021), and we consequently describe this rise \( Z(t) \) by

\[
\frac{dZ(t)}{dt} = b \cdot f(Y(t); a_Y, n_1) \cdot Y(t) - \frac{1}{\tau_Z} \cdot [1 - f(Y(t); a_Y, n_1)] \cdot Z(t),
\]

(3.5)

where \( f(Y; a_Y, n_1) \) defines the minimal intensity \( Y \) considered as PA with intensity threshold \( a_Y \) [counts/min] and exponent \( n_1 \), parameter \( b \) [1/count] specifies the proportional rise, and \( \tau_Z \) [min] the time for insulin sensitivity to return to its baseline level.

**Insulin-independent glucose uptake and production**

Glucose demand by active muscles increases acutely during PA and glucose uptake from plasma is upregulated. Simultaneously, hepatic glucose production by gluconeogenesis and glycogenolysis increases to maintain plasma glucose levels (Wahren et al., 1971). These processes are linear in PA intensity (Roy and Parker, 2007). We therefore define the insulin-independent rise in GU \( r_{GU} \) [1/min] and GP \( r_{GP} \) [1/min]) rates as

\[
\frac{dr_{GU}(t)}{dt} = q_1 \cdot f(Y(t); a_Y, n_1) \cdot Y(t) - q_2 \cdot r_{GU}(t)
\]

\[
\frac{dr_{GP}(t)}{dt} = q_3 \cdot f(Y(t); a_Y, n_1) \cdot Y(t) - q_4 \cdot r_{GP}(t),
\]

(3.6)

where \( q_i \) are rate parameters.

**Glycogen depletion**

Liver glycogen stores may deplete during prolonged PA and GP cannot be maintained by gluconeogenesis alone, causing an accelerated drop in glucose levels (Gonzalez et al., 2016; Camacho et al., 2005). We follow Roy and Parker (2007) and assume that glycogen stores deplete in proportion to exercise intensity and duration. The time \( t_{depl} \) [min] to depletion determined from the integrated AC count and PA duration is then given by:

\[
t_{depl}(t) = -a_{depl} \cdot \frac{PA_{int}(t)}{t_{PA}(t)} + b_{depl}.
\]

(3.7)

After depletion sets in, we allow a drop in GP rate, \( r_{depl} \) [1/min], defined by

\[
\frac{dr_{depl}(t)}{dt} = q_6 \cdot \left[ f(t_{PA}(t); t_{depl}, n_1) \cdot r_m(t) - r_{depl}(t) \right]
\]

\[
r_m(t) = \beta \cdot \left( \frac{q_3}{q_4} \cdot Y(t) + r_{GPb} \right),
\]

(3.8)

where the transfer function \( f(t_{PA}; t_{depl}, n_1) \) indicates whether exercise time exceeds \( t_{depl} \) and \( q_6 \) is a rate parameter. The maximum decrease \( r_m \) [1/min] in GP is the
sum of the basal resting GP rate, \( r_{GPb} \), and the PA-driven GP rate at steady state, \( q_3/q_4 \cdot Y(t) \), scaled by the proportion of net hepatic glucose production attributed to glycogenolysis, \( \beta \).

**High-intensity exercise**

During high-intensity PA (> 80% \( \text{VO}_2^{\text{max}} \)), GP may (initially) exceed GU and result in rising plasma glucose levels due to an increase in catecholamines and cortisol (Marliss and Vranic, 2002). We mimic the drastic rise in GP by modulating parameters \( q_3 \) and \( q_4 \) between low- (subscript \( l \)) and high-intensity (subscript \( h \)) values

\[
q_3 = [1 - f(t_h; t_p, n_2)] \cdot q_{3l} + f(t_h; t_p, n_2) \cdot q_{3h} \\
q_4 = [1 - f(t_h; t_p, n_2)] \cdot q_{4l} + f(t_h; t_p, n_2) \cdot q_{4h},
\]

where we use the transfer function \( f(t_h; t_p, n_2) \) to smoothly transition between the two exercise regimes when time spent at a high PA intensity \( t_h \) exceeds \( t_p \) [min].

### 3.4.2 Model Extensions for Full-Day Simulations

To enable full-day simulations, we further include existing models to provide plasma insulin concentration after insulin injections and rate of glucose appearance after meals, and use these as inputs to the exercise model.

**Insulin kinetics**

We use a model with two subcutaneous compartments of insulin masses \( x_1 \) and \( x_2 \) [\( \mu \text{U} \)] and a plasma insulin compartment \( I \) [\( \mu \text{U/ml} \)] to model plasma insulin after a subcutaneous injection (Nucci and Cobelli, 2000):

\[
\frac{dx_1(t)}{dt} = -k_1 \cdot x_1(t) + u(t) + u_b(t) \\
\frac{dx_2(t)}{dt} = k_1 \cdot x_1(t) - (k_2 + k_3) \cdot x_2(t) \\
\frac{dI(t)}{dt} = \frac{k_2}{V_I \cdot BW} \cdot x_2(t) - k_4 \cdot I(t). \tag{3.10}
\]

Insulin is injected into \( x_1 \), with \( u \) [\( \mu \text{U/min} \)] and \( u_b \) [\( \mu \text{U/min} \)] defining the rates of correction and basal insulin infusion, respectively. \( V_I \) [ml/kg] is the insulin distribution volume and \( k_i \) are rate parameters. We estimated the model parameters from insulin measurements obtained after a subcutaneous injection of 0.3 U/kg insulin aspart (Svehlikova et al., 2021) (Suppl Sec 3.8.2).

**Carbohydrate absorption**

We describe the glucose appearance rate \( Ra \) [mg/min] after a meal with carbohydrate content \( D \) [mg] with an established model (Hovorka et al., 2004):

\[
Ra(t) = \frac{f \cdot D \cdot t}{\tau_m^2} \cdot e^{-t/\tau_m}. \tag{3.11}
\]

A fraction \( f \) of glucose is absorbed into plasma and the time constant \( \tau_m \) [min] characterizes the time-of-maximum appearance rate. We determine \( f \) and \( \tau_m \) individually for each meal (see below).
3.4.3 Model Calibration

We obtained parameter values from literature or physiological knowledge when feasible and estimated the remaining parameters from published data. We followed a stepwise approach for parameter estimation and calibrated a population-average model on data of healthy subjects acquired during exercise, before adjusting parameters to describe glucose metabolism and PA effects in people with T1D (Fig 3.2 and Suppl Table S3.1).

Parameter determination for healthy subjects

We used the original parameter values of the two-compartment minimal model (Cobelli et al., 1999) and explicitly included the effect of basal insulin on glucose. To calibrate the exercise model, we separated parameters into process-specific sets and individually estimated these on data sets acquired during the corresponding exercise modes using least squares regression.

We set the delay parameter $\tau_{AC}$ to 5 min (Breton, 2008; Dalla Man et al., 2009) and chose a time constant $\tau_Z$ of 600 min (Dalla Man et al., 2009) such that insulin sensitivity stays elevated for up to 48 hours in accordance with literature reports (Mul et al., 2015).

We obtained the increase in insulin sensitivity during PA (parameter $b$) from measurements of the insulin-dependent rate of glucose disappearance during rest and 100 min of cycling at 80% $\text{VO}_2^{\text{max}}$ (Wasserman et al., 1991). We converted $\%\text{VO}_2^{\text{max}}$ to accelerometer count using

\[
\%\text{VO}_2^{\text{max}} = 0.0135 \cdot AC + 1.7228,
\]  

(3.12)
estimated from simultaneous AC count (Actigraph model 7164; Actigraph, LLC; Pensacola, Florida, USA) and %VO\textsubscript{2max} measurements for different types and intensities of PA (Evenson et al., 2008).

We estimated the insulin-independent GU and GP parameters \( q_1, q_2, q_{3l} \) and \( q_{dl} \) from total GU and GP rates measured during 60 min of PA at 40\% VO\textsubscript{2max} (Wolfe et al., 1986) (Suppl Fig S3.1 (a)). We distinguished between resting and exercise-driven contributions by separating the net rate of glucose change into endogenous glucose production and glucose uptake:

\[
\begin{align*}
GP(t) &= (p_1 + X_b) \cdot Q_{1b} - \alpha \cdot [p_1 + (1 + Z(t)) \cdot X(t)] \cdot Q_1(t) \\
&\quad + [r_{GP}(t) - r_{depl}(t)] \cdot Q_1(t) \\
GU(t) &= (1 - \alpha) \cdot [p_1 + (1 + Z(t)) \cdot X(t)] \cdot Q_1(t) + r_{GU}(t) \cdot Q_1(t),
\end{align*}
\]

where we determined \( \alpha \) from measurements at rest (\( Z = r_{GU} = r_{GP} = r_{depl} = 0 \)). We assumed that the prolonged exercise-driven change in insulin sensitivity affects both GP and GU as found in Romeres et al. (Romeres et al., 2021; Romeres et al., 2020b) and subtracted its contribution to the total GU and GP rates based on the insulin sensitivity parameter defined above.

We determined the time until hepatic glycogenolysis decreases due to glycogen depletion from reported depletion times for different intensities (Gonzalez et al., 2016) (parameters \( a_{depl} \) and \( b_{depl} \)). We estimated glycogen depletion parameters \( \beta \) and \( q_6 \) from plasma glucose measurements (Ahlborg and Felig, 1982) recorded during 180 min of cycling at 58\% VO\textsubscript{2max}, where we restricted \( q_6 \) to 0.1 min\(^{-1}\) to avoid an overshoot in GP after PA and kept the remaining parameters fixed (Suppl Fig S3.1 (b)).

Finally, moderate-intensity PA is defined by AC counts above 2296 counts/min (Evenson et al., 2008) and we enforced the transition from rest to PA between 1000 and 2000 counts/min with parameters \( a_Y = 1500 \) counts/min and \( n_1 = 20 \). Accordingly, we defined \( a_{AC} = 1000 \) counts/min and \( n_2 = 100 \) to track duration and AC count immediately from the start of PA. High-intensity PA commences at 80\% VO\textsubscript{2max} (5800 counts/min) (Marliss and Vranic, 2002), and we set \( a_h = 5600 \) counts/min and \( t_p = 2 \) min for a transition between intensity regimes at 75\%-80\% VO\textsubscript{2max}.

**Adjustment of model parameters to T1D**

To re-calibrate the exercise model to persons with T1D, we relied on the study by Romeres et al. (Romeres et al., 2021; Romeres et al., 2018), where people with T1D performed 60 min of exercise at 65\% VO\textsubscript{2max} during a glucose clamp under three different glucose and insulin conditions (V1: euglycemia – low insulin, V2: euglycemia – high insulin, V3: hyperglycemia – low insulin). Plasma glucose and insulin concentrations were measured and glucose disappearance and production rates were determined from recorded data. We estimated parameters defining insulin-independent \( (p_1, q_1-q_{dl}) \) and -dependent \( (p_3, b) \) contributions to GU and GP at rest and during PA for all conditions, and defined the resulting parameters determined under condition V1 as our standard T1D model, since V1 represents physiologically ‘normal’ conditions. For further details on the estimation procedure, see Suppl Section 3.8.1. Additionally, we computed confidence intervals for all parameter estimates from profile likelihoods to determine practical identifiability (Suppl Sec 3.8.1).
We estimated the high-intensity exercise parameters $q_{3h}$ and $q_{4h}$ from interstitial glucose measurements (Jayawardene et al., 2017) of people with T1D performing 45 min of 4 min intervals at 82.5% VO$_2^{max}$ using least squares regression (Suppl Fig S3.4). We introduced the parameter $q_5 = 0.03$ min$^{-1}$ to prevent a switch to low-intensity parameters during recovery. For the remaining parameters, we used the values determined for the hyperglycemia - low insulin condition (V3) of the previously discussed data, as the high-intensity activity was recorded under comparable conditions.

3.4.4 Model Validation

We used independent data from six additional studies covering a range of exercise intensities and durations for validating our model. Importantly, several studies include pre-exercise meal intake and insulin bolus injections as well as different insulin reduction strategies. This allowed us to validate the individual model parts and their interplay in the full model. The data sets are the following:

1. In a study by Rabasa-Lhoret et al. (2001), participants with T1D performed exercise at three intensities (25%, 50% and 75% VO$_2^{max}$) for different durations (30 and 60 min). Breakfast with 75 g of CHO and varying insulin bolus sizes (25%, 50% and 100% of typical dose) was consumed 90 min prior to PA. Plasma glucose was measured.

2. In a second study conducted by Maran et al. (2010), participants with T1D performed 30 min of exercise at 40% VO$_2^{max}$. The changes in plasma glucose and insulin concentrations were recorded.

3. Participants with T1D exercised for 45 min at 67.8% VO$_2^{max}$ in a study presented by Iscoe and Riddell (2011), where the change in interstitial glucose levels was measured.

4. The effect of basal insulin suspension during exercise was studied by Zharieva et al. (2017). Exercise was performed for 40 min at 45% VO$_2^{max}$ and the change in plasma glucose concentration was assessed.

5. In a study by Dubé et al. (2013), exercise was performed for 60 min at 50% VO$_2^{max}$, 2 h after lunch including a pre-meal insulin bolus. Plasma glucose levels were monitored and participants did or did not consume a drink containing 30 g of glucose 15 min pre-exercise.

6. Healthy subjects cycled for 240 min at 30% VO$_2^{max}$ in a study conducted by Ahlborg et al. (1974) and plasma glucose was measured. For this PA duration, glycogen depletion affects GP and subsequently glucose levels.

We generated 95% prediction intervals for studies (1)-(5) based on the T1D model derived under condition V1. The predicted glucose ranges are shown in Fig 3.3 and Suppl Fig S3.6 (a)-(e) (shaded areas). However, there is a high variation in the physiological response to PA between individuals, regarding both the increase in insulin sensitivity and in the insulin-independent processes (Romeres et al., 2021). Therefore, differences in study populations require tuning of the model parameters to accurately reflect the data, and we re-estimated parameters $b$, $q_{1l}$ and $q_{2l}$. Note
Figure 3.3 – Model validation. Data (mean ± SEM, n = 6) (Rabasa-Lhoret et al., 2001) and model predictions for validation study (1). PA sessions are marked by vertical lines. PA was performed at different intensities (25%, 50% and 75% VO$_{2 \text{max}}$) for durations of 30 or 60 min. A meal was consumed 90 min prior to PA, with a meal insulin bolus of 100%, 50% or 25% of the full dose. The shaded areas show the 95% prediction intervals of the T1D model (V₁), and solid BG trajectories display the tuned model ($b = 1.83 \cdot 10^{-6}$, $q_1 = 2.93 \cdot 10^{-6}$, $q_2 = 2.93 \cdot 10^{-6}$). Meal parameters $f$ and $\tau_m = 105$ min were determined from glucose levels at rest.

that we kept the ratio between $q_{1f}$ and $q_{2f}$ constant, enforcing a fixed steady-state level in the insulin-independent rise in GU to maintain the original ratio between PA-driven changes in GU and GP. The resulting glucose trajectories are shown as solid lines (Fig 3.3 and Suppl Fig S3.6(a)-(e)). For study (6), we used the parameter values of the healthy population and kept them unchanged (Suppl Fig S3.6(f)).

Overall, we observe good agreement between data and model predictions across all validation studies for both the prediction intervals based on the original calibration and the glucose trajectories using tuned parameters.

3.5 RESULTS

3.5.1 Effect of Physical Activity in Full-Day Simulations

We evaluate our model’s performance in full-day simulations for a range of PA scenarios to confirm that it reproduces clinical knowledge. We define a standard day consisting of three meals and corresponding insulin bolus injections. We include a PA session in the morning or afternoon and consider different intensities (30%, 60% and 90% VO$_{2 \text{max}}$) and durations (30, 60 and 180 min) (Fig 3.4).

During moderate-intensity PA, BG levels decrease with increasing intensity and duration (Riddell et al., 2017) and drop even further once glycogen stores deplete (Camacho et al., 2005). In contrast, BG levels may rise (Riddell et al., 2017) during high-intensity PA, which can provide protection against acute hypoglycemia (Guelfi et al., 2005), but the risk for late-onset hypoglycemia still increases with higher PA intensity and duration (Maran et al., 2010; Jaggers et al., 2019).
58

Figure 3.4 – Comparison of glucose trajectories for different PA scenarios in a full-day simulation. PA is performed at 30%, 60% and 90% VO$_2$max for 30, 60 and 180 minutes (a) in the morning, or (b) in the afternoon. The PA session is marked by vertical lines. Meals are eaten at 7:00, 13:00 and 19:00 containing 40 g, 60 g and 50 g CHO, respectively.

Time of day also affects the risk for nocturnal hypoglycemia, which is higher for afternoon- compared to morning-PA (Gomez et al., 2015).

Our model accurately reflects the duration- and intensity-dependence in glucose trends for moderate- and high-intensity PA. As expected, BG levels increase during high-intensity PA, but drop below those of moderate-intensity PA after the activity. We also find lower nocturnal BG levels following afternoon- compared to morning-PA. Our model thus reproduces clinical observations regarding hypoglycemia risk for a range of different PA scenarios.

3.5.2 Model Personalization on Data from Children with T1D

To establish our model’s capability to describe individual subject data, we personalize the model on multi-day at-home data from five children aged 8–14 with T1D (Bachmann et al., 2016) (‘DiaActive’ study, ethics approval no. 341/12, Ethics Commission Cantons of Basel, February 14, 2013; written formal consent was obtained from the parent/guardian for each study participant). For each participant, interstitial glucose levels were measured by continuous glucose monitoring (CGM), exercise was monitored using an accelerometer, and CHO content and timing of meals as well as timing and dosing of insulin injections were self-reported in logbooks. We provide participant characteristics and discuss data preparation in Suppl Section 3.8.5.

To personalize the model to each participant, we followed a strategy presented by Hughes et al. (2021) and determined subject-specific parameter values for insulin sensitivity ($p_3$) and meal parameters ($f$ and $\tau_m$) using least squares regression. We also estimated glucose effectiveness ($p_1$) and the basal glucose concentration $G_b$. We computed the basal insulin level $I_b$ based on the basal insulin infusion rate $u_{ib}$ and kept the remaining parameter values, including all exercise-related parameters, at their previously determined population-average level (Suppl Table S3.1, V1). We confirmed local structural identifiability of the personalized parameters using the STRIKE-GOLDD toolbox (Villaverde et al., 2016). Furthermore, we established our
Figure 3.5 – Data and personalized model for study participants #3 and #5 for two days each. For each day, recorded (red) and fitted (blue) glucose data and carbohydrate inputs (green) are shown in the upper panel. Modelled insulin concentration (blue) and insulin inputs (green) including the basal insulin infusion rate (dashed) are shown in the middle panel. Accelerometer counts (dotted) and modelled PA intensity $Y$ (blue) are shown in the lower panel with periods of physical activity highlighted in grey. The remaining participants are shown in Suppl Fig S3.8.

The model’s capacity for personalization and replay simulations with altered meal and insulin inputs— but no PA—using the UVa/Padova simulator (Python implementation (Xie, 2018)) (Suppl Sec 3.8.5). Note that we forewent the deconvolution step originally proposed to address further model mismatch.

We consider two—not necessarily consecutive—24 hour periods for each of the five children. We estimate parameters $p_1$ and $p_3$ on data from the first day and keep these values for the second day to confirm that the personalized models generalize to new scenarios. We estimate basal glucose for each day, and estimate meal parameters independently for each meal to account for inaccuracies in the self-reported meal sizes and for different meal compositions.

We quantified the model fits using the root mean square difference (RMSD) and the mean absolute relative difference (MARD) (Table 3.1). We reach commonly used targets of RMSD below 25 mg/dl (Kanderian et al., 2009) and MARD below 10% (Hughes et al., 2021) in most cases.
Table 3.1 – Evaluation of personalized model fits. Unexplained glucose excursions are excluded and results for the full 24 h period are given in brackets in these cases.

<table>
<thead>
<tr>
<th>Participant</th>
<th># 1</th>
<th># 2</th>
<th># 3</th>
<th># 4</th>
<th># 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>day 1</td>
<td>11.4</td>
<td>12.1</td>
<td>3.7</td>
<td>6.6</td>
<td>9.3</td>
</tr>
<tr>
<td>day 2</td>
<td>(84.6)</td>
<td>(34.2)</td>
<td>(36.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSD [mg/dl]</td>
<td>6.7</td>
<td>10.3</td>
<td>2.9</td>
<td>5.4</td>
<td>5.9</td>
</tr>
<tr>
<td>MARD [%]</td>
<td>(22.0)</td>
<td>(7.8)</td>
<td>(15.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 1</td>
<td>9.3</td>
<td>15.8</td>
<td>11.0</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>day 2</td>
<td></td>
<td></td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.5.3  Replay Simulations Using Personalized Models

Next, we use the personalized models to demonstrate their potential in replay simulations, a promising approach for comparing and evaluating subject-specific treatment strategies in-silico, on two 24 hour episodes selected from our data.

We first consider day 1 of participant #3 with no PA and replay these data with changes in lunch size or with an altered meal bolus (Fig 3.6(a)). As expected, a larger meal or lower bolus increase BG levels, while a smaller meal or larger bolus lead to a corresponding reduction. Differences between these treatments reduce over time and virtually vanish after dinner.

For our second scenario, we use the data for day 2 of participant #5, who exercises for 41 min at almost constant intensity of 70% VO_2max in the afternoon. Likely in anticipation of the planned PA session, the participant used no insulin bolus for the preceding meal and commenced the session in hyperglycemia. We therefore ask if an alternative treatment decision might have led to a more favorable BG trajectory, and consider reducing the pre-PA meal size from 55 g to 40 g CHO or to administer an insulin bolus of 1.5 U (Fig 3.6(b)). The replay simulation indicates that a smaller pre-PA meal could have been favorable, reducing hyperglycemia before PA without increasing the risk of hypoglycemia during the activity.

We also use this scenario to study the effect of exercise intensity and duration. First, we replay the scenario with lower PA intensities (Fig 3.6(c)). Notably, BG trajectories only start to diverge substantially after the post-PA meal as insulin sensitivity remains elevated for several hours during recovery, and further measures to avoid post-PA hyperglycemia might be required. Next, we consider varying PA duration (Fig 3.6(d)). The effect of elevated insulin sensitivity is clearly visible as the BG trajectories stay separated for the remaining simulation time, and results suggest that no additional adjustments are necessary to protect against hypoglycemia for exercise up to an hour.
Figure 3.6 — Replay simulations. (a) Participant #3, day 1. Variations in meal size and insulin dose at lunch to 50% and 150% of their original size. (b)-(d) Participant #5, day 2, with a PA session marked by vertical lines. The original glucose trajectory is shown in blue. (b) Meal or bolus adjustment for pre-PA meal. (c) Alterations in PA intensity from 70% VO\(_2\text{max}\) to 55% and 40% VO\(_2\text{max}\). (d) Alterations in PA duration from 41 min to 21, 61 and 81 min, with the post-exercise meal following directly after the session.

3.6 DISCUSSION

Mathematical models are a valuable tool to develop and evaluate treatment strategies for T1D in-silico. Finding accurate individual treatment adjustments for physical activity remains a complex process that could be facilitated by in-silico treatment evaluation, but comprehensive models including all relevant aspects of exercise metabolism suitable for this task are currently lacking.

PA-driven changes in glucose metabolism act on different time scales and require different treatment adjustments. In particular, insulin-independent processes affect BG levels mainly during PA, while insulin-dependent effects are the main cause for late-onset hypoglycemia and need to be considered for several hours post-PA. BG levels often fall during moderate-intensity PA when GU exceeds GP, while a drastic rise in GP during high-intensity PA can in contrast cause rising BG levels. It is therefore crucial to incorporate all relevant exercise processes in a PA model to study PA management in-silico.

In this work, we presented a model of glucose-insulin regulation in T1D that covers acute insulin-independent changes in GU and GP during PA, and the prolonged PA-induced rise in insulin sensitivity. We considered PA of moderate to high intensities, and accounted for depletion effects during prolonged exercise. We suggested the use of transfer functions to switch between these different exercise regimes, with the aim to keep the model compact without affecting the individual PA processes. The model includes modules for insulin bolus injections and meal intake as additional inputs to capture all aspects of daily life and diabetes management, allowing simulation of realistic scenarios.

We proposed a stepwise approach for model calibration, estimating parameters of the different model components separately on corresponding population-average data from healthy subjects. While the full model is not identifiable—a common problem for models of the glucose-insulin system—this allowed us to quantify individual contributions of the different PA-related processes accurately. Next, we
adjusted the full model to a T1D population and computed profile likelihoods to determine practical parameter identifiability. We validated the model on independent data sets covering PA of different intensities and duration, and PA in conjunction with CHO intake and insulin injections. The resulting prediction intervals show the correct behavior in glucose trends, and the model accurately predicts the observed BG trajectories after tuning a small subset of parameters with high inter-patient variability to the examined patient population, demonstrating the feasibility of stepwise model identification and its potential for calibrating complex T1D models. Additionally, we evaluated the model's prediction capabilities in full-day simulations with a range of PA scenarios against clinical knowledge.

The presented model structure is consistent with literature reports studying exercise-induced changes in glucose metabolism. Studies demonstrated that glucose utilization increases with exercise intensity for healthy subjects (Romijn et al., 1993; Van Loon et al., 2001) and for people with T1D (Shetty et al., 2016). It was shown by Romeres et al. (2021) and Nguyen et al. (2021) that this increase can be separated into insulin-dependent and –independent contributions. In particular, they confirmed that insulin-mediated GU increases gradually during the activity and remains elevated for several hours post-PA, while non-insulin-mediated GU increases rapidly at PA onset and drops to its baseline level immediately after. Nguyen et al. (2021) did not find intensity-dependence for GU, but discuss that this might have been caused by PA intensities that were not sufficiently different or by varying levels of fitness between participants.

Similarly, it was shown that endogenous glucose production increases with exercise intensity to counteract the rise in GU (Romijn et al., 1993; Van Loon et al., 2001; Shetty et al., 2016; Nguyen et al., 2021; Petersen et al., 2004). In contrast to its effect on GU, insulin suppresses GP. Romeres et al. (2020a) found that the PA-driven rise in GP is consequently inhibited in people with T1D with hyperinsulinemia, and identified a delayed effect of insulin on GP (Romeres et al., 2020b). In contrast, Nguyen et al. (2021) did not find insulin-mediated changes in GP. In this work, we followed the findings of Romeres et al. (2020b), since GU and GP rates were estimated in a model-independent way, and our model is able to describe their data well when including a PA-driven, elevated effect of insulin on GP.

Furthermore, the rate of hepatic glycogenolysis during PA increases linearly with intensity (Gonzalez et al., 2016), supporting our assumption that the time until depletion occurs decreases in proportion to PA intensity. However, we estimated depletion parameters of the model only on data from healthy subjects, and data from individuals with T1D are required to validate this model part for a T1D population. Petersen et al. (2004) observed that differences in GP between healthy and T1D subjects arise from varying contributions of gluconeogenesis, and that glycogenolysis at rest and for different PA intensities is similar for both populations. Hence, we believe that our model assumptions also hold for individuals with T1D and that predictions are therefore qualitatively correct for this population.

During high-intensity PA, counterregulatory hormones such as catecholamines and cortisol are upregulated. They are associated with increased hepatic GP that exceeds GU, and thus lead to (initially) rising BG levels during exercise (Marliss and Vranic, 2002; Adolfsson et al., 2018). The rise in BG levels persists only while these hormone levels are elevated, and is followed by several hours with an increased risk for hypoglycemia (Riddell and Perkins, 2006). We incorporated the drastic rise in
GP in our model and were able to accurately reflect the resulting glucose dynamics. However, we were unable to perform an independent validation for this scenario due to lack of additional data. Moreover, we applied a fixed threshold to transition between moderate and high intensities, although we expect this transition to be different between individuals, especially when considering different age groups. In addition, the threshold might depend on the specific situation and type of PA the person is performing, where for example stress in competitive scenarios could lead to an earlier onset of high-intensity-like glucose dynamics.

Here, we only considered aerobic exercise of moderate to high intensity. We did not incorporate anaerobic exercise that is encountered for example in high-intensity interval or strength training. Anaerobic exercise can cause different trends in glucose levels for people with T1D (Riddell et al., 2015), and it would be useful to integrate this modality into a PA model. Additionally, exercise has been reported to induce changes in insulin absorption that might affect plasma insulin concentrations (Riddell et al., 2017; Mallad et al., 2015). Our model currently does not consider this effect, as exact mechanisms remain elusive and potential changes cannot be estimated from our available data sets.

Exercise was recorded with accelerometers in our patient data, and we therefore chose AC count as PA input for our model. Other models use heart rate or %VO$_{2\text{max}}$ instead, which might be better suited to quantify PA as they measure direct physiological responses to exercise. However, it would be straightforward to convert these measures and adjust the model to different inputs, since AC count, %VO$_{2\text{max}}$ and heart rate are all linearly dependent (Evenson et al., 2008; Howley, 2001).

We applied our model to evaluate subject-specific treatment strategies in-silico based on model personalization and replay simulations. First, we validated this approach for altered meal and insulin inputs—but without exercise—against the UVa/Padova simulator. We then personalized our model to several children with T1D by adjusting a small number of parameters to each child, and accurately reproduced their glucose data recorded under real-life conditions. We presented examples of replay simulations from these personalized models to study subject-specific treatment alternatives and PA effects. Our results provide a promising proof-of-principle for adjusting treatment strategies to the individual person to improve PA management. The approach only requires data easily available in everyday settings from CGM devices and activity trackers, and we therefore expect that it also applies to the challenging case of unplanned and unstructured PA typical for children.

We anticipate that our model could be used in practice to describe and simulate blood glucose levels and to predict hypoglycemia associated with PA. Model personalization allows replay of recorded data and simulation of alternative treatment strategies to improve individual patient care, which would provide entirely new possibilities for clinical assessment and treatment adjustment. In addition, more fine-grained solutions to different exercise scenarios can be provided compared to current clinical guidelines that rely on observations of glucose changes during PA. We also anticipate that our model might find application in decision support systems or meal bolus calculators to determine insulin requirements for improved glycemic control, and would in particular allow to consider PA-induced changes in insulin sensitivity that can lead to late-onset hypoglycemia. Further applications
might include the development of control algorithms for insulin treatment adjusted to glucose metabolism during and after exercise.

3.7 CONCLUSION

We proposed a model of glucose-insulin regulation that captures the acute and prolonged effects of moderate- to high-intensity PA on glucose metabolism. The model accurately predicts BG during PA and subsequent recovery and is capable of describing data from individuals with T1D. We illustrated its use in replay simulations for personalized PA management in children, which could support clinicians in tailoring treatment strategies to individuals in the future. We also anticipate that it finds applications as an ‘exercise calculator’ (Colberg et al., 2015) for clinical decision support, as well as for improving control algorithms for closed-loop insulin delivery.

We evaluated the model’s performance on several data sets, but further validation of the model and personalized replay are warranted before application in a clinical setting.

ACKNOWLEDGEMENTS

The authors would like to thank Jörg Stelling for valuable feedback and discussions.

DATA AVAILABILITY STATEMENT

All data and Python source code to use the model and reproduce its calibration, validation, and all analyses in the manuscript are available from https://gitlab.com/csb.ethz/t1d-exercise-model.

Our individual patient data as well as the Python source code are additionally available at the ETH Research Collection, a FAIR repository, under DOI 10.3929/ethz-b-00058984.
3.8 Supplementary Material

3.8.1 Calibration of Exercise Model

Parameter determination for healthy subjects

Figure S3.1 – (a) Data (mean ± SEM, n = 8) (Wolfe et al., 1986) and model fit for 60 min of PA at 40% VO$_{2}^{\text{max}}$. (b) Data (mean ± SEM, n = 10) (Ahlborg and Felig, 1982) and model fit for 180 min of PA at 58% VO$_{2}^{\text{max}}$. Glucose levels and GU and GP rates are shown. The PA session is marked by solid lines and onset of depletion by dashed lines. PA-driven changes in GU and GP are separated into insulin-dependent (id) and insulin-independent (ii) contributions.
Table S3.1 – Model parameters. Healthy: healthy subjects. V1–V3: T1D subjects under euglycemia low-insulin (V1), euglycemia high-insulin (V2), and hyperglycemia low-insulin (V3) clamp conditions (Romeres et al., 2021; Romeres et al., 2018).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy</th>
<th>T1D</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>V1</td>
<td>V2</td>
</tr>
<tr>
<td><strong>Glucose-Insulin Regulation</strong></td>
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<td>0.0126</td>
<td>0.0214</td>
</tr>
<tr>
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<td>0.0228</td>
</tr>
<tr>
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<td>2.78 · 10^{-5}</td>
<td>2.98 · 10^{-5}</td>
</tr>
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<td>0.058</td>
<td>0.058</td>
</tr>
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<td>0.0885</td>
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<td>1.289</td>
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<td>5</td>
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<td>600</td>
</tr>
<tr>
<td>$b$</td>
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<td>3.64 · 10^{-6}</td>
<td>1.59 · 10^{-6}</td>
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<td><strong>Glucose Uptake and Production</strong></td>
<td></td>
<td></td>
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<tr>
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<td>0.27</td>
<td>0.27</td>
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<tr>
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<td>6.46 · 10^{-7}</td>
<td>2.88 · 10^{-6}</td>
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<td>4.46 · 10^{-7}</td>
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</tr>
<tr>
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<td>-</td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
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<td><strong>Glycogen Depletion</strong></td>
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<tr>
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<td>-</td>
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<td>-</td>
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</tr>
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<td>$b_{depl}$</td>
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<td>1000</td>
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<tr>
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</tr>
<tr>
<td>$n_2$</td>
<td>100</td>
<td>100</td>
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</tr>
</tbody>
</table>
Adjustment of model parameters to T1D

Parameter estimation strategy

We used data by Romeres et al. (Romeres et al., 2021; Romeres et al., 2018) to re-calibrate the exercise model to people with T1D. GU and GP were studied during 60 min of exercise at 65% VO_{2max} under three glucose and insulin conditions (V1: euglycemia – low insulin, V2: euglycemia – high insulin, V3: hyperglycemia – low insulin). When studying glucose uptake, Romeres et al. found that parameter $p_2$ and the glucose distribution volume $V_g$ were similar across all study conditions, while the participants’ insulin sensitivity ($SI$, corresponding to $p_3$) and glucose effectiveness $p_1$ varied. Hence, we fixed $V_g$ and $p_2$ ($p_2$ determined from GIR required after insulin aspart injection (Heise et al., 2017)) as well as the exchange rates $p_4$ and $p_5$ (since glucose fluctuations are small), and only estimated parameters $p_1$ and $p_3$ of the glucose-insulin model. In addition, we estimated exercise parameters $b, q_1, q_2, q_3$, and $q_4$, as well as basal levels of glucose, $G_b$, and insulin, $I_b$. We fixed $\tau_Z = 600$ min, which defines the return of insulin sensitivity to its baseline, since it is difficult to estimate such a time scale correctly based on the comparatively short recovery period included in the data.

Our parameter estimation strategy entails two steps. First, we identified parameters for condition V1 from GU and GP data and used glucose and insulin measurements as known inputs. This condition represents the physiologically ‘normal’ scenario and hence, we used the resulting parameters as our baseline description of T1D populations for the remainder of this work. Second, we tested whether our model is applicable also to other glucose and insulin scenarios, and estimated parameters for conditions V2 and V3. We used the V1 parameter estimates as prior information to constrain the parameter estimation for these conditions, since they share the same study population.

Condition V1: Euglycemia - Low Insulin

We determined parameters for condition V1 using maximum likelihood estimation, minimizing the negative log-likelihood

$$-2LL(y|\theta) = \sum_{i=1}^{n} \frac{(y_i - f(t_i, \theta))^2}{\sigma^2},$$

which corresponds to a Gaussian distribution of data points $y_i$ around model predictions $f(t_i, \theta)$ at time $t_i$ with parameter set $\theta$ and residual variance $\sigma^2$. For the minimization, we used the Nelder-Mead algorithm in Python’s scipy.optimize package.

Parameters $p_1$ and $p_3$ are not identifiable in the unconstrained optimization problem (see below). However, insulin-independent and -dependent contributions to GU are similar at rest in the original study and we exploited this fact by enforcing the relation $p_1 = X_b = p_3 / p_2 \cdot I_b$ during optimization, which makes the parameters identifiable. We also detected an outlier in GU at $t = 190$ min, which we removed to improve estimation.

Conditions V2: Euglycemia – High Insulin, and V3: Hyperglycemia – Low Insulin

We used the parameter estimates $\theta_{V1}^j$ from condition V1 to constrain the estimation problem for conditions V2 and V3. For this, we added a penalty term to the log-likelihood function that corresponds to a log-normal
distribution of parameter values around the $V_1$ estimates with about 60% relative standard deviation. The penalized log-likelihood for the optimization is then

$$-2LL(y|\theta) = \sum_{i=1}^{n} \frac{(y_i - f(t_i, \theta))^2}{\sigma_{V1}^2} + \lambda \cdot \sum_{j=1}^{k} \frac{(ln(\theta_j) - ln(\theta_{V1}^j))^2}{ln(1.6)^2}.$$ 

We used the residual standard deviation $\sigma_{V1}$ from the previous estimate. We did not employ the previous constraint on $p_1$ and $p_3$, which are freely estimated during this optimization.

The resulting glucose production and uptake rates are shown in Figure S3.2. For all conditions, the model captures the exercise-driven changes in GU and GP well. Parameter values are reported in Table S3.1 and our results agree qualitatively with the assessment of exercise effects in the original study, also in terms of the differences observed between conditions.

![Figure S3.2](image)

**Figure S3.2** – Data (mean, $n = 6$) (Romeres et al., 2021; Romeres et al., 2018) and model fits of GU and GP rates during 60 min of PA at 65% $VO_2^{\text{max}}$ under (a) euglycemia - low insulin ($V_1$), (b) euglycemia - high insulin ($V_2$), and (c) hyperglycemia - low insulin ($V_3$) conditions. The PA session is marked by vertical lines. PA-driven changes in GU and GP are separated into insulin-dependent (id) and insulin-independent (ii) contributions. Note that GU and GP rates are always positive, while exercise-induced changes can have a negative effect.

**Parameter identifiability**

Next, we considered practical identifiability of parameters and computed profile likelihoods (PL) to obtain appropriate confidence intervals (CI) (Kreutz et al., 2013). The profile likelihood is the log-likelihood function evaluated for a specific parameter $\theta_j$ with values $p$ and maximized over all remaining parameters:

$$PL_j(p) = \max_{\theta \in \{\theta|\theta_j=p\}} LL(y|\theta)$$

The $(1 - \alpha)$ confidence interval for $\theta_j$ is then found from the quantiles of the $\chi^2$-distribution with one degree of freedom.

Based on the available data, some parameters are not identifiable for condition $V_1$ (Fig. S3.3 (a)). Glucose and insulin levels are constant during the study period, impeding for example the separation of insulin-dependent and –independent processes already at rest. The parameter correlations (Fig. S3.3 (b)) reveal more insights: $p_1$ and $p_3$ correlate negatively under condition $V_1$ and can compensate for each other, confirming the observed identifiability issues. The exercise parameters
$q_1$ and $q_2$, and similarly $q_3$ and $q_4$, also show strong correlations. This is expected, since the steady state values of the GU and GP rates can be maintained when the ratio of the two corresponding parameters is held constant. The profile likelihoods for conditions V2 and V3 (Fig. S3.3 (c),(d)) show more confined parameter ranges. This is due to changes in glucose or insulin concentration during the study, allowing to distinguish between insulin-dependent and -independent contributions, and was further improved by the penalty term used during optimization.

![Profile likelihoods and parameter correlations for conditions V1, V2, and V3](image)

**Figure S3.3** – (a) Profile likelihoods and (b) parameter correlations for condition V1. Profile likelihoods for conditions (c) V2 and (d) V3. 95% confidence thresholds enclosing the parameters’ confidence intervals are marked by the upper dashed lines.
High-intensity exercise

Figure S3.4 – Data (mean ± SEM, n = 12) (Jayawardene et al., 2017) and model fit of glucose levels during 45 min of PA at 82.5% VO\textsubscript{2}\text{max}. The high-intensity PA session is marked by vertical lines.

3.8.2 Parameters of Insulin Kinetics Model

We used data from a published study on insulin kinetics to estimate the parameters of the insulin input component (Svehlikova et al., 2021). Parameter values are given in Table S3.2, and provide an excellent fit to the published data (Fig. S3.5).

Table S3.2 – Estimated parameters of the insulin kinetics model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>k\textsubscript{1}</td>
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</tr>
<tr>
<td>k\textsubscript{2}</td>
<td>0.011</td>
</tr>
<tr>
<td>k\textsubscript{3}</td>
<td>0.0247</td>
</tr>
<tr>
<td>k\textsubscript{4}</td>
<td>0.0357</td>
</tr>
<tr>
<td>V\textsubscript{I}</td>
<td>104</td>
</tr>
</tbody>
</table>

Figure S3.5 – Data (Svehlikova et al., 2021) and model fit of plasma insulin after injection of 0.3 U/kg insulin aspart.
3.8.3 Model Validation

Figure S3.6 – Data (mean ± SEM) and model predictions for model validation. (a)-(e) Shaded areas show the 95% prediction intervals of the T1D model (V1), and solid BG trajectories display the tuned model. (a) Validation study 2 (n = 8; \( b = 5.97 \times 10^{-6}, q_1 = 2.69 \times 10^{-6}, q_2 = 0.2569 \)) (Maran et al., 2010), (b) validation study 3 (n = 11; \( b = 4.84 \times 10^{-6}, q_1 = 2.06 \times 10^{-6}, q_2 = 0.1968 \)) (Iscoe and Riddell, 2011) and (c) validation study 4 (n = 12; \( b = 9.10 \times 10^{-6}, q_1 = 3.23 \times 10^{-6}, q_2 = 0.3085 \)) (Zaharieva et al., 2017). Validation study 5 (Dubé et al., 2013) (d) without pre-PA snack and (e) with pre-PA snack (n = 11; \( p_3 = 1.15 \times 10^{-5}, b = 1.30 \times 10^{-6}, q_1 = 2.54 \times 10^{-6}, q_2 = 0.2426 \)). Meal parameters are \( f = 0.55 \) and \( \tau_m = 90 \) min for lunch and \( f = 1.8 \) and \( \tau_m = 20 \) min for the pre-PA CHO. (f) Validation study 6 (Ahlborg et al., 1974) with parameters determined for healthy subjects. The PA sessions are marked by solid vertical lines and onset of depletion by dashed vertical lines.

3.8.4 Definition of Standard Patient

For our full-day simulation results, we defined a standard patient with parameter values taken over from the model calibration for T1D (condition V1). However, data did not include glycogen depletion and high intensity for this condition, and we therefore used depletion parameters \( \beta \) and \( q_6 \) from healthy subjects, assuming that the contribution of glycogenolysis to overall GP during PA is similar for healthy and T1D subjects. In condition V3, GP exceeds GU during high-intensity PA by a factor of 1.6 at steady state. We assumed the same ratio here to determine high-intensity parameters \( q_{3h} \) and \( q_{4h} \).
3.8.5 Replay Simulations

In-silico performance assessment of model personalization

We tested the performance of the personalized model in replay simulations in-silico, re-creating the experiments of the original study (Hughes et al., 2021). We used the UVa/Padova simulator (Dalla Man et al., 2014) (Python implementation (Xie, 2018)) to generate individual data of 10 virtual subjects. We then personalized our model on these data and performed replay simulations with altered meal and insulin bolus inputs. We followed Hughes et al. (2021) and evaluated the replay performance using the mean absolute relative difference (MARD) between ‘true’ and replayed glucose trajectories.

Specifically, each individual received a meal containing 0.7 gCHO/kg at 12:00 in a 24h simulation using the UVa/Padova simulator. A meal bolus was injected at the same time, where the bolus dose was computed according to a personal insulin-to-carbohydrate ratio. We personalized the model on these data to each subject. We fixed the parameters at their T1D population values and only estimated \( p_1, p_3, G_b, f \) and \( \tau_m \), with \( \tau_m \) constrained between 10 and 150 min.

In the first experiment, we changed the meal size from 0 to 200% of the original meal size in steps of 20%. For each subject, we simulated ‘true’ data with the UVa/Padova simulator, and we simulated replay predictions according to our personalized models. The resulting MARD between ‘true’ and replayed data starting from meal time at 12:00 is shown in Fig. S3.7(a).

To evaluate the impact of insulin inputs, we varied the insulin bolus from 50 to 150% of the original bolus in steps of 10% in a second experiment (Fig. S3.7(b)).

In both simulation experiments, we found an acceptable MARD of less than 10% in most cases, but exceeded this threshold slightly for more extreme alterations. Note that in contrast to the replay simulations shown in Hughes et al. (2021), we did not consider further deconvolution to feed unaccounted dynamics as additional inputs into the simulation. Rather, we relied solely on adjusting model parameters to individual subjects, and accepted slightly higher MARD values in return.

Figure S3.7 – Results of the replay simulations. MARD (mean and standard deviation) between true simulated data and replay predictions for alterations in (a) meal size and (b) insulin dose.
Model personalization on T1D data

Characteristics of study participants
We selected five pediatric T1D participants for model personalization. Baseline characteristics are presented in Table S3.3.

<table>
<thead>
<tr>
<th>Participant</th>
<th>f/m</th>
<th>age [y]</th>
<th>weight [kg]</th>
<th>insulin % basal</th>
<th>treatment</th>
<th>( u_b ) reported</th>
</tr>
</thead>
<tbody>
<tr>
<td># 1</td>
<td>f</td>
<td>8</td>
<td>34.7</td>
<td>0.9</td>
<td>59</td>
<td>MDI</td>
</tr>
<tr>
<td># 2</td>
<td>m</td>
<td>13</td>
<td>58.8</td>
<td>0.9</td>
<td>54</td>
<td>CSII</td>
</tr>
<tr>
<td># 3</td>
<td>m</td>
<td>14</td>
<td>56.3</td>
<td>0.8</td>
<td>45</td>
<td>CSII</td>
</tr>
<tr>
<td># 4</td>
<td>m</td>
<td>10</td>
<td>31.6</td>
<td>0.8</td>
<td>52</td>
<td>MDI</td>
</tr>
<tr>
<td># 5</td>
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<td>10</td>
<td>38.8</td>
<td>0.6</td>
<td>48</td>
<td>CSII</td>
</tr>
</tbody>
</table>

Data preparation
The recorded study data consist of glucose measurements, accelerometer counts, timing and dosing of insulin injections and timing and carbohydrate content of meals. Glucose data were recorded continuously by a CGM device. Continuous exercise data were obtained using an Actigraph model GT3X+ accelerometer (Actigraph, LLC; Pensacola, Florida, USA) that is worn on the right hip. Acceleration is measured along three axes, and data of the vertical axis were used to quantify intensity of movement. In contrast, participants or their caregivers manually reported insulin injections and meals in logbooks. Discrepancies between the provided information and the measured glucose levels indicate partly inaccurate or incomplete logbook data. While incorrectly estimated meal sizes were compensated for by allowing arbitrary values of the bioavailability factor \( f \) in the meal model, we had to manually account for incorrect meal times and for missing meals. To this end, we shifted meal times and the corresponding insulin bolus times to adjacent glucose minima if required. On few occasions, we found small glucose peaks during the day without reported meals or other disturbances, and introduced additional snacks without insulin bolus in these cases. All meal adjustments are given in Table S3.5.

To extract PA intervals, we smoothed the AC data using a median filter with a window size of 15 min. We identified intervals exceeding 1500 counts/min for at least 10 min as PA sessions, according to the threshold for minimum PA intensity set in the model. We merged sessions that were separated by less than 10 min into a single PA period.

Finally, we needed to define the basal insulin infusion rate \( u_b \) for each individual. For study participants on multiple daily injection (MDI) therapy, we assumed a constant basal rate, which we determined from the person’s total daily insulin requirements and the contribution from basal injections. For participants on continuous subcutaneous insulin infusion (CSII) therapy, we either used the reported values for \( u_b \), or applied the same strategy as for MDI therapy if \( u_b \) was not reported (Table S3.3).
**Personalized model**

Parameter values of the personalized models for each of the five children are given in Tables S3.4 and S3.5. The resulting model fits are shown in Figure 3.5 of the main text for two participants, and in Figure S3.8 for the remaining participants. Due to missing information, we were unable to fit a small number of glucose excursions either in the early morning or late evening; these are listed in Table S3.6 and were ignored for model personalization.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Participant</th>
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<td></td>
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</tr>
<tr>
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<td>$p_3$</td>
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<td>$G_b$, $d_1$</td>
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<tr>
<td>$G_b$, $d_2$</td>
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</table>
Figure S3.8 – Data and personalized model for participants #1, #2 and #4 for two days each. For each day, recorded (red) and fitted (blue) glucose data and carbohydrate inputs (green) are shown in the upper panel. Modelled insulin concentration (blue) and insulin inputs (green) including the basal insulin infusion rate (dashed) are shown in the middle panel. Accelerometer counts (dotted) and modelled PA intensity $Y$ (blue) are shown in the lower panel with periods of physical activity highlighted in grey.
Table S3.5 – Meal information. Time (including shift from reported logbook data) and CHO amount. Parameters $f$ and $\tau_m$.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Day 1</th>
<th></th>
<th></th>
<th>Day 2</th>
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<th></th>
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<td></td>
<td>time</td>
<td>CHO [g]</td>
<td>$f$</td>
<td>$\tau_m$ [min]</td>
<td>time</td>
<td>CHO [g]</td>
<td>$f$</td>
</tr>
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<td>07:16</td>
<td>40</td>
<td>0.04</td>
<td>36</td>
<td>02:18 (+0:10)</td>
<td>10</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>10:00</td>
<td>25</td>
<td>0.70</td>
<td>25</td>
<td>07:45</td>
<td>70</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>12:13</td>
<td>65</td>
<td>0.40</td>
<td>30</td>
<td>10:00</td>
<td>25</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>15:00</td>
<td>15</td>
<td>1.00</td>
<td>10</td>
<td>12:03</td>
<td>75</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>17:43</td>
<td>50</td>
<td>0.18</td>
<td>14</td>
<td>14:10 (+1:10)</td>
<td>10</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>15:10 (+0:10)</td>
<td>10</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>17:13 (-1:00)</td>
<td>50</td>
<td>0.48</td>
</tr>
<tr>
<td>#2</td>
<td>05:30</td>
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<td>1.22</td>
<td>143</td>
<td>08:00</td>
<td>60</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>06:00</td>
<td>40</td>
<td>0.91</td>
<td>48</td>
<td>12:00 (-0:30)</td>
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<td>3.91</td>
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<tr>
<td></td>
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<td>10</td>
<td>0.79</td>
<td>12</td>
<td>17:03</td>
<td>35</td>
<td>0.80</td>
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<tr>
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<td>10:30 (+0:30)</td>
<td>30</td>
<td>0.45</td>
<td>18</td>
<td>19:00</td>
<td>50</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
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<td>1.19</td>
<td>44</td>
<td>21:15</td>
<td>30</td>
<td>2.56</td>
</tr>
<tr>
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<td>30</td>
<td>1.83</td>
<td>49</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>19:15 (-0:45)</td>
<td>50</td>
<td>1.70</td>
<td>66</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>#3</td>
<td>06:05</td>
<td>55</td>
<td>1.01</td>
<td>68</td>
<td>09:25 (+0:12)</td>
<td>65</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>10:10</td>
<td>55</td>
<td>0.18</td>
<td>22</td>
<td>11:15 (+)</td>
<td>20</td>
<td>2.16</td>
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<td>0.76</td>
<td>67</td>
<td>12:45 (+0:15)</td>
<td>35</td>
<td>1.45</td>
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<tr>
<td></td>
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<td>18</td>
<td>16:15 (+0:11)</td>
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<td>47</td>
<td>09:30</td>
<td>50</td>
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<td>14</td>
<td>13:14 (+0:07)</td>
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<td>5.16</td>
<td>67</td>
<td>20:11</td>
<td>50</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>19:26 (-0:10)</td>
<td>30</td>
<td>0.00</td>
<td>150</td>
<td>–</td>
<td>–</td>
<td>–</td>
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Table S3.6 – Timing of glucose excursions discarded for model personalization.

<table>
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<th>Day</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#1</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>from 20:00</td>
</tr>
</tbody>
</table>
ESTIMATING INSULIN SENSITIVITY AFTER EXERCISE USING AN UNSCENTED KALMAN FILTER

This chapter is published as:

Author contributions:
JD developed the Python code, conducted simulations, and created the figures. HMK and JD conceived and implemented the study, interpreted the results and wrote the manuscript.

4.1 ABSTRACT

Insulin sensitivity is an important physiological parameter for determining insulin requirements for patients with type 1 diabetes. In addition to being highly variable between patients, insulin sensitivity increases substantially during exercise and stays elevated for several hours during subsequent recovery. We propose an unscented Kalman filter for estimating insulin sensitivity from continuous glucose monitoring data that does not require the underlying model to capture exercise and relies on average values for patient-specific parameters. Using in silico full-day simulations including exercise and meals, we study how adjusting insulin doses for elevated insulin sensitivity could decrease the risk of hypoglycemia after exercise and improve time-in-range and related metrics.

4.2 INTRODUCTION

Glucose homeostasis is a fundamental physiological process in healthy individuals that maintains plasma glucose levels in a narrow range of 70–140 mg/dl despite disturbances such as meals or exercise. The two hormones glucagon and insulin, produced in pancreatic α- and β-cells, respectively, are the two main regulators to achieve glucose homeostasis by promoting glucose production respectively glucose uptake by muscles and the liver, where glucose is converted into glycogen. Type 1 diabetes (T1D) is a common endocrine disorder resulting from autoimmune destruction of pancreatic β-cells. Patients are unable to produce insulin to maintain glucose homeostasis, and require exogenous insulin to mimic the natural glucose-insulin regulation and avoid persistent elevated blood glucose (hyperglycemia) (American Diabetes Association, 2014). Basal insulin levels are provided either by continuous infusion of insulin (in continuous subcutaneous insulin infusion (CSII) therapy) or by typically two daily injections of long-acting insulin (in multiple daily injection (MDI) therapy) to maintain glucose homeostasis in fasting conditions. In addition,
meals are compensated by bolus injections of rapid-acting insulin in both forms of therapy (Janež et al., 2020), where the required dose depends on the amount of carbohydrates (CHO) in the meal, the insulin on board (IOB) from previous injections, and the current deviation from the blood glucose target. Bolus calculations also consider the patient-specific baseline insulin sensitivity that describes the decrease in blood glucose per unit of insulin administered. This parameter is highly variable between patients and is determined clinically, e.g., by a glucose tolerance test (Bergman et al., 1979).

Moreover, insulin sensitivity increases temporarily during exercise, and remains elevated for several hours during recovery, requiring additional adjustment of the basal and bolus insulin treatment (Annan, 2016). While generic clinical guidelines exist, the accurate adjustment to exercise demands precise tailoring to the patient and situation, and presents a major challenge. In particular, exercise-induced hypoglycemia (low blood glucose) can occur acutely, but also several hours after the activity due to the prolonged elevation of insulin sensitivity, where hypoglycemia is associated with acute complications such as dizziness and unconsciousness. While advances in sensors now provide blood glucose levels almost in real-time with continuous glucose monitoring (CGM) devices, insulin sensitivity is not amenable to direct measurement and needs to be inferred from the glucose measurement.

Here, we consider the problem of adjusting basal and bolus insulin calculations for increased insulin sensitivity from exercise. We use an unscented Kalman filter (UKF) (Julier and Uhlmann, 1997) to estimate the insulin sensitivity from CGM measurements and use this estimate to propose a reduction of the insulin bolus for a post-exercise meal as well as for a reduction of overnight basal insulin to avoid hypoglycemia. Kalman filters have been previously used to estimate blood glucose (Knobbe and Buckingham, 2005) and plasma insulin concentration (Eberle and Ament, 2011; Pereda et al., 2015), and to track changes in insulin sensitivity (Boiroux et al., 2017a) from CGM measurements, but not for exercise-related insulin therapy adjustments.

We use a T1D model with exercise at moderate intensity together with an established CGM model to generate full-day data for a virtual patient population. Importantly, our observer model for the UKF only contains those model parts unrelated to exercise, and the UKF can thus not use predictions of exercise effects for the state estimation. Moreover, the UKF model has to rely on average values for all parameters, including the patient-specific and highly variable baseline insulin sensitivity and meal absorption parameters that we randomly perturb for each meal in our simulations. As a proof-of-principle, we show that reducing insulin doses based on the estimated insulin sensitivity can lead to reduced hypoglycemia and improved time-in-range.

4.3 METHODS

Our goal is the estimation of a patient’s insulin sensitivity $S_I(t)$ in the presence of disturbances such as exercise. We consider this problem as a state estimation problem and propose using an unscented Kalman filter that uses information on previous insulin injections ($u$ and $u_b$), carbohydrate intake ($D$) and a noisy measurement of interstitial glucose $\tilde{G}_I$ from a CGM device. We then use the
estimated insulin sensitivity to adjust calculations for bolus insulin doses $u$ and basal insulin requirements $u_b$ (Fig. 4.1).

**Figure 4.1** – Schematic of the UKF-assisted bolus calculator: A patient model $\Sigma_p$ simulates interstitial glucose levels $G_i$ considering exercise ($A_C$), meals ($D$) and insulin ($u, u_b$). A CGM model generates noisy observations $G_i$ as input to an unscented Kalman filter with internal model $\Sigma_u$. The estimated insulin sensitivity $S_I$ is used to adjust insulin requirements in a bolus calculator.

### 4.3.1 Observer Model

Our unscented Kalman filter uses an internal model for estimating the insulin sensitivity $S_I(t)$ that comprises: (i) a component to describe glucose-insulin dynamics derived from the two-compartment Minimal Model (Cobelli et al., 1999), (ii) a two-compartment component to describe the dynamics of plasma insulin following a subcutaneous injection of size $u$ (Nucci and Cobelli, 2000), and (iii) a simple two-compartment component to describe changes in blood glucose following a meal of size $D$. We denote the model as $\Sigma_u$ to distinguish it from the model used for simulating patient data (cf. Fig. 4.1).

The glucose-insulin dynamics (Cobelli et al., 1999) are given by

$$
\begin{align*}
\dot{X}(t) &= S_I(t) \cdot p_2 \cdot I(t) - p_2 X(t) \\
\dot{Q}_1(t) &= - [p_1 + p_4] \cdot Q_1(t) + p_5 \cdot Q_2(t) + EGP_0 + Ra(t) \\
\dot{Q}_2(t) &= p_4 \cdot Q_1(t) - p_5 \cdot Q_2(t) \\
\dot{S}_I(t) &= 0 \\
G(t) &= Q_1(t)/V_g,
\end{align*}
$$

where $X$ [1/min] is remote insulin acting on plasma glucose, $I$ [$\mu U$/ml] is plasma insulin concentration, $Q_1$ and $Q_2$ [mg/kg] are glucose masses in an accessible and non-accessible compartment, respectively, and $G$ [mg/dl] is plasma glucose concentration. Insulin sensitivity is represented by state $S_I$ [ml/$\mu U$/min] and modulates the action of plasma insulin $I$. The parameter $EGP_0$ [mg/kg/min] is the glucose production rate at zero glucose and $Ra$ [mg/kg/min] is the glucose appearance rate from meals; $p_1$ to $p_5$ [1/min] are rate parameters, and $V_g$ [dl/kg] is the glucose distribution volume. We stress that this model does not entail
any processes—such as exercise—that would modify the insulin sensitivity $S_I(t)$ and the corresponding observer can therefore not rely on any predictions of such processes.

In this paper, we mainly consider MDI therapy. To describe the transfer of injected insulin from subcutaneous tissue into plasma, we introduce two compartments of subcutaneous insulin mass $x_1$ and $x_2$ [µU] and one plasma insulin compartment $I$ [µU/ml] (Nucci and Cobelli, 2000):

$$\begin{align*}
\dot{x}_1(t) &= -k_1 \cdot x_1(t) + u(t) + u_b \\
\dot{x}_2(t) &= k_1 \cdot x_1(t) - (k_2 + k_3) \cdot x_2(t) \\
\dot{I}(t) &= \frac{k_5}{V_i \cdot BW} \cdot x_2(t) - k_4 \cdot I(t),
\end{align*}$$

(4.2)

where $u$ [µU/min] is the rate of correction insulin injection, and $u_b$ [µU/min] is the rate of basal insulin infusion, which we assume to be constant to mimic MDI therapy; $k_1$ to $k_4$ [1/min] are rate parameters, $V_i$ [ml/kg] is the insulin distribution volume and $BW$ [kg] is the patient’s bodyweight.

To describe the glucose appearance rate $Ra$ after carbohydrate ingestion, we consider the following two-compartment model:

$$\begin{align*}
M_1(t) &= -m_1 \cdot M_1(t) + D(t) \\
M_2(t) &= m_1 \cdot M_1(t) - m_2 \cdot M_2(t) \\
Ra(t) &= \frac{f \cdot m_2}{BW} \cdot M_2(t),
\end{align*}$$

(4.3)

where $D$ [mg/min] is the ingested glucose, $m_1$ and $m_2$ [1/min] are rate parameters and $f$ specifies the fraction of glucose absorbed into plasma. This model is similar to the meal model proposed by Hovorka et al. (2004).

Continuous glucose monitoring does not measure the plasma glucose concentration $G$ directly, but rather the corresponding interstitial glucose $G_I$ [mg/dl], which leads to a time-delay between plasma glucose and measured glucose. We describe this transition using a model by Facchinetti et al. (2014) as

$$\dot{G_I}(t) = \frac{1}{\tau_G} (G(t) - G_I(t)), $$

(4.4)

with time constant $\tau_G = 6.7$ min.

Parameter values are given in Table 4.1. With $x = (X, Q_1, Q_2, x_1, x_2, I, M_1, M_2, G_I)$, the state vector of $\Sigma_u$ is $(x, S_I)$.

### 4.3.2 Unscented Kalman Filter

We use an unscented Kalman filter for estimation of the state vector $(x, S_I)$ based on the (discretized) observer model, glucose measurements of the state $G_I$ and information on insulin injections ($u$ and $u_b$) and meals ($D$). The UKF approach selects a set of points, called sigma points, spread around the mean of the current state estimate to propagate through the model and generate a new state estimate. We place the sigma points according to Julier and Uhlmann (1997) with $\kappa = 2$. Further, we initialize the diagonal covariance matrix $P$ with the following uncertainties for the states $(x, S_I)$: $\sigma = (1.65 \cdot 10^{-3}, 14.2, 9.3, 8511, 5833, 1.0, 10^{-3}, 10^{-3}, 11, 1.65 \cdot 10^{-4})$, amounting to around 10% of the initial state values. We define the diagonal elements of
the process noise matrix $Q$ according to $\sigma = (1.65 \cdot 10^{-4}, 1.42, 0.93, 851, 583, 0.1, 100, 50, 1.1, 1.65 \cdot 10^{-5})$, assuming a noise level of around 1% in each state. Finally, we assume a CGM measurement noise of $\sigma_{GI} = 15$mg/dl for the $1 \times 1$ noise matrix $R$.

4.3.3 Simulation Model

To evaluate the performance of the state estimation and the subsequent bolus calculation, we generate blood glucose trajectories over a full day including three meals and an exercise session for a set of patients in silico. Our simulation model uses the same components as in Eq. 4.2 and Eq. 4.3 of the observer model for insulin injections and meals. We augment the glucose-insulin dynamics by several equations describing changes in glucose uptake and production during and after exercise, and consider the exercise-driven change in insulin sensitivity explicitly. Specifically, we describe the glucose-insulin dynamics as

$$
\begin{align*}
X(t) &= S_{I,0} \cdot p_2 \cdot I(t) - p_2 X(t) \\
Q_1(t) &= -[p_1 + r_{GU} - r_{GP} + p_4] \cdot Q_1(t) \\
&\quad - (1 + Z(t)) \cdot X(t) \cdot Q_1(t) \\
&\quad + p_5 \cdot Q_2(t) + EGP_0 + Ra(t) \\
Q_2(t) &= p_4 \cdot Q_1(t) - p_5 \cdot Q_2(t) \\
G(t) &= Q_1(t)/V_g,
\end{align*}
$$

(4.5)

where $S_{I,0}$ is the (unperturbed) baseline insulin sensitivity of the patient, $r_{GU}$, $r_{GP}$ and $Z$ are exercise processes described below, and the remaining states and parameters are as in Eq. 4.1.

We capture exercise intensity $Y$ by accelerometer counts $AC$ [1/min] with delay $\tau_{AC}$ [min]:

$$
\dot{Y}(t) = \frac{1}{\tau_{AC}} (AC(t) - Y(t)).
$$

(4.6)

Exercise triggers a range of processes, which we describe via increases in glucose uptake $r_{GU}$ and production $r_{GP}$ [1/min]:

$$
\begin{align*}
\dot{r}_{GU}(t) &= q_1 \cdot f(Y) \cdot Y(t) - q_2 \cdot r_{GU}(t) \\
\dot{r}_{GP}(t) &= q_3 \cdot f(Y) \cdot Y(t) - q_4 \cdot r_{GP}(t),
\end{align*}
$$

(4.7)

with rate parameters $q_1$ to $q_4$ [1/min] and a function $f(Y) = (Y/a)^n/[1 + (Y/a)^n]$ that provides the transition between rest and exercise. Moreover, insulin sensitivity increases by a factor $(1 + Z)$ due to exercise, where $Z$ is given by

$$
\dot{Z}(t) = b \cdot f(Y) \cdot Y(t) - \frac{1}{\tau_Z} \cdot (1 - f(Y)) \cdot Z(t),
$$

(4.8)

with parameter $b$ and time constant $\tau_Z$ [min]. These extensions are comparable to exercise models presented by Breton (2008) and Roy and Parker (2007).

The resulting blood glucose $G$ is translated into interstitial glucose $G_I$ using Eq. 4.4, and we add two autoregressive noise processes to emulate measurement noise and generate the simulated measured glucose concentrations $\hat{G}_I$ as input into the state estimator:

$$
\hat{G}_I(t) = G_I(t) + cc(t) + \hat{\theta}(t),
$$

(4.9)
where the noise components $cc$ and $\hat{v}$ are

\[ cc(t) = 1.23 \cdot cc(t - 1) - 0.3995 \cdot cc(t - 2) + w_{cc}(t) \]

\[ \hat{v}(t) = 1.013 \cdot \hat{v}(t - 1) - 0.2135 \cdot \hat{v}(t - 2) + \dot{w}(t), \]  

(4.10)

with $w_{cc} \sim N(0, 11.3 \text{mg}^2/\text{dl}^2)$ and $w \sim N(0, 14.45 \text{mg}^2/\text{dl}^2)$ (Facchinetti et al., 2014).

We denote the simulation model as $\Sigma_p$ (cf. Fig. 4.1). The patient’s insulin sensitivity at time $t$ is then given by $S_{I,0} \cdot (1 + Z(t))$, where $S_{I,0}$ is patient-specific, and $(1 + Z(t))$ is the exercise-related increase. The state vector for $\Sigma_p$ is $(x, x_E)$, where $x_E = (Y, r_{GLU}, r_{GP}, Z)$ are the exercise-related states not present in the observer model, while $\Sigma_p$ lacks an explicit state for the insulin sensitivity.

The parameter values for this simulation model are given in Table 4.1. For our simulations, we consider two sources of variation between and within patients: first, we randomly draw the baseline insulin sensitivity $S_{I,0}$ independently for each patient. This means that the UKF has to correctly estimate the initial insulin sensitivity for each patient, as its internal model only uses the average value for $S_{I,0}$, but not the individual value for a patient. Second, the specific carbohydrate content and composition of a meal is usually not known exactly, which can lead to substantial differences in the resulting glucose appearance rate in plasma. To see how the UKF copes with this unknown disturbance, we randomly draw the meal-related parameter $m_2$ for each patient and each meal independently. Again, the internal model of the UKF only considers the average value of this distribution. The corresponding means and variances are also given in Table 4.1.

4.3.4 Meal and Basal Bolus Calculator

In conventional bolus calculators, the insulin dose is determined from the carbohydrate content of a meal, the deviation of the glucose level from the target and the estimated insulin on board. They are typically of the form

\[ u = \frac{CHO}{ICR} + \frac{G - G_t}{CF} - IOB, \]

(4.11)

where $u$ [U] is the insulin bolus, $CHO$ [g] is the amount of carbohydrates, $G$ [mg/dl] is the current glucose concentration and $G_t$ [mg/dl] the target glucose level. Here, we assume that insulin injections are far enough apart such that the insulin on board, $IOB$ [U], can be neglected. The two parameters $ICR$ [g/U] and $CF$ [mg/dl/U] are the insulin-to-CHO ratio and the correction factor, respectively. Both parameters are patient-specific and related to the individual baseline insulin sensitivity $S_{I,0}$. In clinical practice, both are determined empirically to tailor treatment to an individual patient.

We consider two modifications of the bolus calculator to adjust for the actual insulin sensitivity as estimated by the UKF. To determine a bolus injection for a meal, only the current insulin sensitivity needs to be considered, since changes in insulin sensitivity after exercise are much slower than insulin absorption and meal ingestion. We therefore consider a simple proportional adjustment

\[ u_{UKF} = \frac{S_{I,0}}{S_t} \cdot u, \]

(4.12)
Table 4.1 – Parameter values for the simulation and observer models. Cells $N(\mu, \sigma^2)$ are parameters drawn from a normal distribution with the indicated mean $\mu$ and variance $\sigma^2$.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simulation model $\Sigma_p$</th>
<th>Observer model $\Sigma_u$</th>
</tr>
</thead>
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<td>0.008</td>
<td>0.008</td>
</tr>
<tr>
<td>$p_2$</td>
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<td>0.015</td>
</tr>
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<td>$p_4$</td>
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<td>0.058</td>
</tr>
<tr>
<td>$p_5$</td>
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<td>0.0885</td>
</tr>
<tr>
<td>$S_{I,0}$</td>
<td>$N(1.65 \cdot 10^{-3}, 0.41^2 \cdot 10^{-6})$</td>
<td>$1.65 \cdot 10^{-3}$</td>
</tr>
<tr>
<td>$E_{GP_0}$</td>
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<td>3.469</td>
</tr>
<tr>
<td>$V_S$</td>
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<td>1.289</td>
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</tr>
<tr>
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<td>0.0021</td>
<td>0.0021</td>
</tr>
<tr>
<td>$k_4$</td>
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<td>125</td>
</tr>
<tr>
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</tr>
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<td>$m_2$</td>
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</tr>
<tr>
<td>$b$</td>
<td>$1.68 \cdot 10^{-6}$</td>
<td>-</td>
</tr>
<tr>
<td>$q_1$</td>
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<td>-</td>
</tr>
<tr>
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</tr>
<tr>
<td>$q_3$</td>
<td>$1.19 \cdot 10^{-7}$</td>
<td>-</td>
</tr>
<tr>
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</tr>
<tr>
<td>$a$</td>
<td>1500</td>
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</tr>
<tr>
<td>$n$</td>
<td>20</td>
<td>-</td>
</tr>
</tbody>
</table>

for a bolus insulin dose, where we scale the standard bolus by the ratio of current and baseline insulin sensitivity, estimated as $\hat{S}_I$ and $\hat{S}_{I,0}$ using the UKF (see below). Consequently, an increase in insulin sensitivity would lead to a reduction of the insulin bolus.

With MDI therapy, patients also need to inject long-acting insulin twice a day to achieve a stable basal insulin level. Increased insulin sensitivity can then lead to hypoglycemia during the night if the evening dose of long-acting insulin is not adjusted. However, the basal insulin level stays roughly constant throughout the night, while insulin sensitivity is slowly decreasing during recovery from exercise. We therefore consider an adjustment of the insulin dose proportional to the average deviation of the insulin sensitivity from the baseline value:

$$u_{b,UKF} = \frac{\hat{S}_{I,0}}{\frac{1}{2}(\hat{S}_I + \hat{S}_{I,0})} \cdot u_b,$$

(4.13)

where $u_b$ [U/min] is the typical basal insulin infusion rate of the patient.
4.4 RESULTS

We compare the two bolus calculation strategies in a 30 h simulation and use the following scenario:

- The UKF is started at 0:00.
- 3 meals are eaten: 60 g CHO at 7:00, 80 g CHO at 12:00 and 70 g CHO at 18:00.
- A correction bolus is computed before each meal using the standard or UKF bolus calculator.
- Moderate intensity exercise is performed at 60% VO$_2^{max}$ (AC=4317 counts/min) from 14:00 to 16:00.
- 15 g CHO are ingested after exercise without a meal bolus.
- Basal insulin is adjusted once at 22:00.

For our proof-of-principle, we simulate 25 patients based on the model $\Sigma_p$ and a basal glucose concentration of $G_b = 110$ mg/dl. Since glucose absorption after a meal is highly variable and difficult to capture correctly, we sample an individual meal absorption parameter $m_2$ for each meal. Moreover, we assign an individual insulin sensitivity $S_{I,0}$ to each patient to capture the high variability in this parameter over patients. In contrast, we use the nominal value for $m_2$ and the population average value for $S_{I,0}$ for the UKF model $\Sigma_u$.

4.4.1 Tracking of Insulin Sensitivity

First, we test whether we can track insulin sensitivity. Insulin sensitivity increases during exercise and stays elevated for a prolonged period of time. The simulations

\[ Figure 4.2 \] – Estimation of interstitial glucose $G_I$ (top), blood glucose $G$ (center), and insulin sensitivity $S_I$ (bottom), shown for one patient. Simulated noisy observed glucose concentrations from CGM $\hat{G}_I$ are shown in grey. The true state values are shown as blue lines, their estimates $\hat{G}_I, \hat{G}, \hat{S}_I$ from the UKF in red. Exercise is performed between the two bold vertical lines.
allow us to assess the ability of the UKF to track these changes, although the underlying changes in physiology are unknown to the observer.

Figure 4.2 illustrates the estimated interstitial and blood glucose dynamics and estimated insulin sensitivity for one patient. The mismatch between individual and assumed baseline insulin sensitivity is clearly visible at the beginning, and the UKF quickly settles on the patient-specific value ($\hat{S}_{I,0}$). Without an exercise model, the UKF can track the increase in insulin sensitivity during exercise only with a time-lag, but achieves to track the insulin sensitivity and the two glucose states again within a short amount of time after exercise. Then, it follows the slow decrease to the baseline value for the remaining time of the simulation.

4.4.2 Bolus Calculation

Second, we compare a standard bolus calculator as described in Eq. 4.11 with our proposed UKF bolus calculators in Eq. 4.12 and Eq. 4.13 that adjust for changes in insulin sensitivity. We assume perfect knowledge of the true baseline insulin sensitivity $S_{I,0}$ for each patient for the standard bolus calculator, but we rely on the UKF for estimating this parameter as the average value of $\hat{S}_{I}(t)$ over the three hours before the first meal for the extended bolus calculator. Our rationale is that the UKF estimate of insulin sensitivity will have settled to the patient-specific baseline over night. We evaluate the performance of each calculator from their resulting blood glucose profiles simulated using the model $\Sigma_p$.

Figure 4.3 shows the glucose levels and the size of the administered correction bolus of all patients for the standard and UKF bolus calculators. Before exercise is started, blood glucose is similar for both approaches and the amount of administered insulin is comparable. This is expected, since insulin sensitivity remains at its baseline level, which does not require any adjustments of the bolus size. Due to noise in the insulin sensitivity estimation, the glucose range of the UKF bolus calculator is slightly wider than the range observed for the standard calculator that profits from perfect knowledge of $S_{I,0}$.

![Figure 4.3](image-url)

*Figure 4.3* – Blood glucose $G$ (top), and sizes of the meal bolus $u$ (bottom), for the standard (purple) and UKF (green) bolus calculator. Solid lines represent the mean glucose levels, shaded areas show the full range. Exercise was performed between the two bold vertical lines. The three insulin bolus sizes are reported as median and interquartile range.
In the evening, insulin sensitivity is elevated after exercise and the bolus administered by the UKF bolus calculator is reduced compared to the standard bolus, leading to higher glucose levels and avoiding excursions into hypoglycemia after dinner. In addition, the basal bolus at 22:00 is reduced to 79.0% [77.0%, 80.3%] of its original size, allowing blood glucose to return to its basal level over night.

Table 4.2 and 4.3 summarize the results for both calculators, considering the blood glucose profiles from 6:00 for a full day and from 14:00 when differences between the calculators are expected to arise due to exercise. The time-in-range (TIR) improves under the UKF compared to the standard bolus calculator. The low blood glucose index (LBGI) and high blood glucose index (HBGI) are measures of the extent and number of low, respective high blood glucose events. We observe a reduction in the LBGI and time spent in hypoglycemia (glucose < 70 mg/dl) and only a small increase in HBGI for the UKF bolus calculator, indicating less exposure to hypoglycemia without increasing hyperglycemia.

<table>
<thead>
<tr>
<th></th>
<th>Standard Calculator</th>
<th>UKF Calculator</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR (80-140 mg/dl) [%]</td>
<td>71.2 [68.5, 73.9]</td>
<td>81.8 [78.2, 82.9]</td>
</tr>
<tr>
<td>TIR (70-180 mg/dl) [%]</td>
<td>95.6 [93.8, 97.1]</td>
<td>96.9 [95.6, 98.0]</td>
</tr>
<tr>
<td>time &lt;70 mg/dl [%]</td>
<td>4.4 [2.5, 6.2]</td>
<td>2.8 [1.8, 4.4]</td>
</tr>
<tr>
<td>LBGI</td>
<td>2.27 [2.0, 2.42]</td>
<td>1.35 [1.27, 1.46]</td>
</tr>
<tr>
<td>HBGI</td>
<td>0.41 [0.36, 0.46]</td>
<td>0.47 [0.41, 0.52]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Standard Calculator</th>
<th>UKF Calculator</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR (80-140 mg/dl) [%]</td>
<td>69.0 [66.6, 74.8]</td>
<td>85.2 [81.5, 88.4]</td>
</tr>
<tr>
<td>TIR (70-180 mg/dl) [%]</td>
<td>93.4 [90.6, 96.2]</td>
<td>95.8 [93.4, 97.3]</td>
</tr>
<tr>
<td>time &lt;70 mg/dl [%]</td>
<td>6.6 [3.8, 9.4]</td>
<td>4.2 [2.7, 6.6]</td>
</tr>
<tr>
<td>LBGI</td>
<td>3.16 [2.77, 3.46]</td>
<td>1.8 [1.54, 1.99]</td>
</tr>
<tr>
<td>HBGI</td>
<td>0.04 [0.03, 0.05]</td>
<td>0.11 [0.09, 0.15]</td>
</tr>
</tbody>
</table>

4.5 DISCUSSION

We considered the problem of estimating the increased insulin sensitivity of individual patients following exercise using an unscented Kalman filter. Our observer model comprises previously described model components for insulin administration, meals, and glucose-insulin regulation. However, we deliberately did not include exercise-related changes in this model, presenting a novel approach to track the prolonged rise in insulin sensitivity that does not rely on knowledge of the exercise session and its effects on glucose metabolism. We used the insulin
sensitivity estimates from the UKF to propose simple adjustments of the insulin treatment in an extended bolus calculator, where we considered both reduction in bolus insulin for meals following exercise and reduction of basal insulin to prevent hypoglycemia during the night.

We showed that this observer can successfully estimate insulin sensitivity before and after exercise in a 30-hour simulation scenario including unknown patient-specific baseline insulin sensitivity, three meals with unknown, random appearance rates, and a 2-hour exercise session of moderate intensity. Our simulations are based on a patient model that explicitly considers the changes in insulin sensitivity due to exercise. We also showed that considering the actual insulin sensitivity for insulin treatment adjustments can lead to improved glycemic control by increasing the time-in-range and reducing hypoglycemic excursions. This is particularly relevant for calculating meal bolus injections after exercise, and for adjusting the basal insulin rate over night to compensate for increased insulin sensitivity during recovery from exercise.

Our study is a proof-of-principle and thus has several limitations. First, the results are based on in silico simulations, and resulting improvements in glycemic control are conditional on the accuracy of our simulation model. We stress, however, that our observer model does not entail exercise and thus the ability to estimate insulin sensitivity does not depend on the specific patient model for the simulations. Second, we recognize that both simulation and observer model have not been validated on real patient data, even though we emulated existing models for all model components. Third, our results and preliminary further studies indicate that explicit consideration of exercise might be required in the observer model to reduce the time-lag between actual and estimated insulin sensitivity during exercise; low glucose sampling rates can aggravate this problem.

Despite these limitations, our study shows that estimating insulin sensitivity before and after exercise is possible from continuous glucose monitoring data, and that considering this estimate when calculating bolus insulin for meals and overnight basal insulin requirements has the potential to reduce exercise-related hypoglycemia.

ACKNOWLEDGEMENTS

We thank Jörg Stelling, Gabor Szinnai, Sara Bachmann, Marie-Anne Burckhardt, Marc Pfister and Eve Tasiudi for discussions.

4.6 FOLLOW-UP: APPLICATION TO PROLONGED AND HIGH-INTENSITY EXERCISE

Patient models available at the time of the study were limited to moderate intensity exercise of short duration. With our new patient model presented in Chapter 3, we are now able to extend our original study to prolonged moderate intensity exercise with glycogen depletion and to high intensity exercise, and test whether our approach allows to estimate insulin sensitivity and improve glycemic outcomes for these exercise modalities.
We perform the same 30 h patient simulations as before, but we replace the exercise session and examine the following scenarios:

- A prolonged moderate intensity activity is carried out at 60% $\text{VO}_2^{\text{max}}$ (AC=4317 counts/min) from 13:30 to 16:30. 20 g CHO are ingested 60 and 120 min after exercise commencement, and 15 g CHO are given at the end of the session.

- High intensity exercise is performed at 85% $\text{VO}_2^{\text{max}}$ (AC=6169 counts/min) from 15:00 to 15:45. No additional CHOs are provided.

The estimated insulin sensitivity for both exercise scenarios is shown in Figure 4.4 exemplary for one patient. Similar to moderate intensity exercise, the unmodelled, exercise-driven changes in insulin sensitivity are tracked successfully, but with a time-lag at exercise onset. For prolonged exercise, the time-lag becomes apparent also during the recovery period, since insulin sensitivity increases three-fold during the activity and changes afterwards are more pronounced compared to the other scenarios. For high-intensity exercise, we further observe an initial drop in the estimate before the increase in insulin sensitivity is correctly captured. This is due to a glucose rise during the exercise session that is not anticipated by the observer.

![Figure 4.4](image1.png)

**Figure 4.4** – Estimation of insulin sensitivity $S_I$, shown for one patient. (a) Prolonged moderate-intensity exercise. (b) High-intensity exercise. Exercise is performed between the two vertical lines.

The resulting glucose trajectories and administered meal boluses for the standard and UKF bolus calculators are depicted in Figure 4.5. The dinner bolus is reduced using the UKF compared to the standard bolus calculator due to the elevated insulin sensitivity for both the prolonged and high intensity exercise scenarios. In addition, the evening basal bolus is reduced to 54.1% [52.8%, 54.6%] and 78.7% [76.3%, 80.3%] of the original dose, respectively. This leads to higher overnight glucose levels and a reduced hypoglycemia risk.

This follow-up demonstrates the feasibility of estimating exercise-induced changes in insulin sensitivity from CGM data for exercise of varying duration and intensity using an UKF. Furthermore, our results indicate that corresponding scaling of insulin boluses can improve glucose outcomes and reduce exercise-related hypoglycemia for different exercise modalities.
Figure 4.5 – Blood glucose $G$ (top), and sizes of the meal bolus $u$ (bottom), for the standard (purple) and UKF (green) bolus calculator. (a) Prolonged moderate-intensity exercise. (b) High-intensity exercise. Solid lines represent the mean glucose levels, shaded areas show the full range. Exercise was performed between the two vertical lines. The three insulin bolus doses are reported as median and interquartile range.
MODEL PREDICTIVE CONTROL TO ACCOUNT FOR PROLONGED CHANGES IN INSULIN REQUIREMENTS FOLLOWING EXERCISE IN TYPE 1 DIABETES

This chapter is to be submitted as:

Julia Deichmann and Hans-Michael Kaltenbach. “Model Predictive Control to Account for Prolonged Changes in Insulin Requirements following Exercise in Type 1 Diabetes”

Author contributions:

JD developed the Python code, conducted simulations, created the figures, and wrote the manuscript. HMK and JD conceived and implemented the study, and interpreted the results.

5.1 INTRODUCTION

Blood glucose (BG) levels are tightly regulated by a hormonal network in healthy individuals to maintain BG within a safe range (Shrayyef and Gerich, 2010). One of the primary regulators is insulin, which is responsible for lowering glucose levels. In type 1 diabetes (T1D), glucose homeostasis is impaired due to autoimmune destruction of the insulin-producing β-cells of the pancreas. This results in insulin deficiency and hence, people with T1D rely on exogenous insulin to achieve adequate glycemic control (American Diabetes Association, 2014).

Treatment in T1D consists of insulin administration informed by glucose measurements, where two main forms of insulin delivery exist (Janež et al., 2020). In multiple daily injection (MDI) therapy, long-acting basal insulin is administered once or twice daily to maintain fasting BG levels and short-acting insulin is administered to correct for meals. In continuous subcutaneous insulin infusion (CSII) therapy, short-acting insulin is continuously delivered by a pump to cover basal insulin needs and administer bolus injections. Glucose levels can either be self-monitored (SMBG) sparsely throughout the day (Benjamin, 2002) or measured continuously with a continuous glucose monitoring (CGM) device that records interstitial glucose up to every 5 min (Freckmann, 2020).

Closed-loop algorithms for T1D management, also called artificial pancreas (AP), automatically adapt the delivery rate of an insulin pump based on continuously provided glucose measurements and a control algorithm. The most common control strategy for automated insulin delivery (AID) is model predictive control (MPC) (Lal et al., 2019). Several algorithms have been proposed (Hovorka et al., 2004; Magni et al., 2009a; Gondhalekar et al., 2016; Boiroux et al., 2017b) and evaluated in clinical studies (Hovorka et al., 2011; Brown et al., 2019; Deshpande et al., 2020; Breton et al., 2020; Bergenstal et al., 2021) that show improved glycemic outcomes and quality of life for people with T1D (Barnard et al., 2017). Most controllers fall into the
category of hybrid closed-loop systems, where the basal rate is controller-derived, but meals need to be announced to administer a corresponding insulin bolus.

Similarly, user-input is usually required around physical activity (PA), and PA presents one of the main challenges for AID systems (Riddell et al., 2015; Kovatchev, 2019; Ware and Hovorka, 2022). During moderate-intensity PA, BG levels often decline in people with T1D due to an increase in glucose utilization. This is intensified for prolonged activities when glycogen stores of the liver deplete and hepatic glucose production cannot be maintained. On the other hand, BG levels may rise during high-intensity PA (Camacho et al., 2005; García-García et al., 2015; Marliss and Vranic, 2002). In addition, insulin sensitivity (SI), which describes the glucose lowering effect of insulin, increases during PA and remains elevated for an extended period of time to drive the repletion of glycogen stores (Teich and Riddell, 2016). Consequently, PA increases the risk for hypoglycemia during and for several hours after the activity and requires adequate carbohydrate (CHO) supplementation and insulin reductions (Cockcroft et al., 2020). Accurate adjustment is difficult, and although the American Diabetes Association recommends people living with T1D to exercise for an accumulated 150 min per week (American Diabetes Association, 2015), fear of hypoglycemia prevents many from exercising (Brazeau et al., 2008).

Different model-based approaches have been proposed to correct for PA in AID systems in order to maintain stable BG levels and prevent hypoglycemia. Breton et al. (2014) presented a control-to-range AP, where the basal insulin rate is adjusted based on the predicted hypo- and hyperglycemic risk derived from model predictions, and the hypoglycemic risk is modulated during exercise periods using heart rate. Moreover, two MPC algorithms have been designed where PA is explicitly considered. In Resalat et al. (2016), a component for moderate-intensity exercise is included in the process model and in Garcia-Tirado et al. (2019), PA is represented by a collection of subject-specific input signals that describe the PA-induced glucose change.

Those approaches focus on counteracting PA-driven changes in BG levels during the activity, but do not account for prolonged effects of PA on BG metabolism arising from the elevated insulin sensitivity. We have recently shown that these changes in SI can be estimated from CGM data using an unscented Kalman filter (UKF), which captures the dynamic changes in insulin requirements after PA and allows to target BG control in the recovery period (Deichmann and Kaltenbach, 2021). We used these estimates to scale meal boluses and basal injections in MDI therapy, leading to improved glycemic outcomes.

In this work, we propose an MPC algorithm for CSII therapy that continuously adapts the pump-delivered basal rate based on insulin sensitivity estimates to account for the prolonged effects of PA on an individual’s insulin needs. We use a personalized glucoregulatory model as our process model, but do not include any PA components. Instead, we continually update the model parameter corresponding to insulin sensitivity to generate more accurate glucose predictions. Furthermore, we continually update the subject’s basal rate required to achieve a specific glucose target, which changes with changing SI.

We test our SI-informed MPC algorithm (pMPC-SI) in an in-silico study on a virtual patient population and compare its performance to a baseline controller (pMPC) without insulin sensitivity estimation. We consider different exercise scenarios covering moderate and high intensities, as well as varying duration and
timing of the activity. To evaluate the algorithm’s robustness, we further examine clinically relevant scenarios that include unexplained glucose excursions caused, for example, by unannounced meals.

5.2 Methods

We propose a model predictive control strategy that continuously adapts the insulin input $u$ to exercise-driven changes in insulin needs via estimation of insulin sensitivity, $S_I$, from continuous glucose monitoring data, $\tilde{G_I}$. Insulin sensitivity is estimated using an unscented Kalman filter, and is provided to the MPC algorithm to update the process model and the basal insulin infusion rate required to maintain blood glucose at the target level. Similarly, we adjust calculations of the meal bolus $u_m$ based on the estimated SI (Fig. 5.1).

![Figure 5.1 - Schematic of the control strategy.](image)

5.2.1 Control Law

Process model

Within our MPC algorithm, we predict BG trajectories using a glucoregulatory model that incorporates glucose-insulin dynamics (Cobelli et al., 1999), insulin kinetics (Nucci and Cobelli, 2000), glucose appearance (Hovorka et al., 2004) and transport of glucose from plasma to the interstitial tissue (Facchinetti et al., 2014).

The glucose-insulin dynamics (Cobelli et al., 1999) are described by

\[
\begin{align*}
\dot{X}(t) &= S_1(t) \cdot p_2 \cdot I(t) - p_2 \cdot X(t) \\
\dot{Q}_1(t) &= -(p_1 + X(t) + p_4) \cdot Q_1(t) + p_5 \cdot Q_2(t) + Ra(t) + EGP_0 \\
\dot{Q}_2(t) &= p_4 \cdot Q_1(t) - p_5 \cdot Q_2(t) \\
G(t) &= Q_1(t)/V_g,
\end{align*}
\]

(5.1)

where $Q_1$ and $Q_2$ [mg/kg] represent glucose mass in an accessible and non-accessible compartment, respectively, and $G$ [mg/dl] is plasma glucose concentration. Insulin $I$ [$\mu$U/ml] promotes glucose disappearance from plasma with rate $X$ [1/min]. Parameters $p_1$ to $p_5$ [1/min] are rate parameters, $V_g$ [dl/kg] is the

\[
\begin{align*}
\dot{X}(t) &= S_1(t) \cdot p_2 \cdot I(t) - p_2 \cdot X(t) \\
\dot{Q}_1(t) &= -(p_1 + X(t) + p_4) \cdot Q_1(t) + p_5 \cdot Q_2(t) + Ra(t) + EGP_0 \\
\dot{Q}_2(t) &= p_4 \cdot Q_1(t) - p_5 \cdot Q_2(t) \\
G(t) &= Q_1(t)/V_g,
\end{align*}
\]

(5.1)

where $Q_1$ and $Q_2$ [mg/kg] represent glucose mass in an accessible and non-accessible compartment, respectively, and $G$ [mg/dl] is plasma glucose concentration. Insulin $I$ [$\mu$U/ml] promotes glucose disappearance from plasma with rate $X$ [1/min]. Parameters $p_1$ to $p_5$ [1/min] are rate parameters, $V_g$ [dl/kg] is the
glucose distribution volume, \( EGP_0 \) [mg/kg/min] is the rate of endogenous glucose production at zero glucose. \( S_I \) [ml/\( \mu \)U/min] describes insulin sensitivity and can vary over time.

We model the rate of glucose appearance from meals, \( Ra \) [mg/kg/min], with carbohydrate (CHO) content \( D \) [mg] following Hovorka et al. (2004) as

\[
Ra(t) = \frac{f \cdot D \cdot t \cdot e^{-t/\tau_m}}{\tau_m^2 \cdot w},
\]

where \( f \) is the fraction of glucose absorbed into plasma, \( \tau_m \) [min] is the time until maximum appearance and \( w \) [kg] is body weight.

Insulin dynamics after injection (Nucci and Cobelli, 2000) are defined as

\[
\begin{aligned}
\dot{x}_1(t) &= u(t) + u_m(t) - k_1 \cdot x_1(t) \\
\dot{x}_2(t) &= k_1 \cdot x_1(t) - (k_2 + k_3) \cdot x_2(t) \\
\dot{I}(t) &= \frac{k_2}{V_i \cdot w} \cdot x_2(t) - k_4 \cdot I(t),
\end{aligned}
\]

with the basal insulin infusion rate \( u \) [\( \mu \)U/min] and meal bolus injections \( u_m \) [\( \mu \)U/min]. The injected insulin passes through the subcutaneous compartments \( x_1 \) and \( x_2 \) [\( \mu \)U], before entering into plasma, \( I \) [\( \mu \)U/ml]. Parameters \( k_1 \) to \( k_4 \) [1/min] are rate parameters and \( V_i \) [ml/kg] is the insulin distribution volume.

Glucose levels are measured in the interstitial tissue and glucose first has to diffuse from plasma. This introduces a time delay between plasma glucose and measured glucose that can be modelled as

\[
\dot{G}_I(t) = \frac{1}{\tau_G} \cdot (G(t) - G_I(t)),
\]

where \( G_I \) [mg/dl] is the glucose concentration in the interstitium and \( \tau_G \) [min] the time delay constant (Facchinetti et al., 2014).

**Model personalization**

The process model uses population-average parameter values (Suppl. Table S5.1) and is then personalized to the individual patient by adjusting a subset of parameters (Hughes et al., 2021). We determine subject-specific values for glucose effectiveness (\( p_1 \)) and insulin sensitivity (\( S_I \)) (Suppl. Fig. S5.1), since these parameters exhibit a high inter-patient variability, and define the personalized \( S_I \) as the subject’s baseline insulin sensitivity \( S_{I,0} \). We further determine the fraction of meal CHOs appearing in plasma (\( f \)), the time until maximum appearance (\( \tau_m \)) and the steady-state glucose concentration (\( G_b \)). The parameters are estimated from glucose measurements from a meal challenge, where individuals consume 0.7 g CHO per kg body weight and inject a meal bolus according to their personal treatment parameters.

**MPC problem formulation**

In our MPC formulation, the control input \( u \) is the basal insulin infusion rate, model states are denoted by \( x \) and the glucose output by \( y \). We additionally introduce \( d \) to take into account meals and meal boluses as pre-defined model inputs. At time step \( k \), model states are predicted over the prediction horizon \( N \) and the
optimal control input sequence $U^*$ over the control horizon $N_c$ is determined by minimization of an objective function $J$. The first element is applied to the system, and the optimization is repeated at the next time step, $k + 1$.

We define

$$J^*(x_k) = \min_{U} J(x_k, U)$$

with control input $U = [u_0, u_1, ..., u_{N_c-1}]$ and objective function

$$J(x_k, U) = \sum_{i=1}^{N_c} u_i^2 + \sum_{i=0}^{N_c-1} u_i^2$$

subject to

$$x_0 = x_k$$

$$x_{i+1} = Ax_i + Bu_i + Dd_i \quad i = 0, ..., N - 1$$

$$y_i = Cx_i \quad i = 0, ..., N$$

$$0 \leq u_i \leq u_{\text{max}} \quad i = 0, ..., N_c - 1$$

$$u_i \leq u_{\text{IOB},k} \quad i = 0, ..., N_c - 1$$

$$u_i = u_s \quad i = N_c, ..., N - 1$$

We define a quadratic objective function (eq. 5.6) with weight $R = 10^{-7}$ on the input component, a prediction horizon of $N = 12$ and a control horizon of $N_c = 6$ steps with step size $T = 5 \text{ min}$. Longer control horizons did not lead to substantial improvements. We refer to the steady-state glucose level and insulin infusion rate as $y_s$ and $u_s$, respectively.

Equations (5.7a) – (5.7c) represent the system dynamics to predict state trajectories and the glucose outcome from the current state estimate provided by an UKF (Julier and Uhlmann, 1997). The system equations are obtained from the discretization of the process model and linearization around the basal insulin infusion rate $u_s$ that achieves a target glucose level of $y_s = 110 \text{ mg/dl}$, which we also refer to as the nominal basal rate $u_{s,0}$.

Constraints (5.7d) and (5.7e) enforce positive control inputs that do not exceed $u_{\text{max}}$ and the currently required insulin taking into account insulin-on-board, $u_{\text{IOB},k}$. We set $u_{\text{max}} = 20 \text{ U/T}$. The value is chosen very high such that the controller should never reach this bound. $u_{\text{IOB},k}$ is determined at every time step (see below). Beyond the control horizon, $u$ is set to the basal rate $u_s$ (eq. 5.7f).

We formulate the MPC problem as a quadratic program (QP) to solve for the input sequence $U^*$. The optimized input $u_0^*$ is then discretized to be used in a pump with a delivery resolution of $0.05 \text{ U}$ using a carry-over scheme (Gondhalekar et al., 2016) before being applied. We denote this control strategy as pMPC.

**System updates based on SI estimation**

Next, we take changes in insulin requirements into account by tracking insulin sensitivity. We use an unscented Kalman filter for state estimation from CGM data based on the discretized process model, and we estimate SI by treating the parameter as an additional model state according to

$$\dot{S}_I(t) = 0,$$
which we initialize with the subject-specific baseline insulin sensitivity, \( S_I(0) = S_{I,0} \). We have shown previously that this approach allows to track exercise-driven changes in insulin sensitivity, and we refer the reader to Deichmann and Kaltenbach (2021) for more detailed information.

We refine the control law continually based on the insulin sensitivity estimate \( \hat{S}_{I,k} \). At every time step \( k \), the basal rate is updated following

\[
 u_{s,k} = \frac{S_{I,0}}{\hat{S}_{I,k}} \cdot u_{s,0}, \quad (5.9)
\]

with the nominal basal rate \( u_{s,0} \) describing the insulin infusion rate required to maintain \( y_s \) when insulin sensitivity is at its baseline level, \( S_{I,0} \), which correspond to the basal rate and SI used in the pMPC. The updates are integrated into the objective function (eq. 5.6) and constraints (eq. 5.7f).

Additionally, SI is a model parameter that enters into the system matrix \( A \) (eq. 5.7f). It becomes time-dependent, \( A_k \), as we use the estimate \( \hat{S}_I \) for continuous updates.

Consequently, MPC predictions are made using the current insulin sensitivity estimate, and the objective function is re-centered around an updated target delivery rate at every time step, allowing for a PA-adjusted insulin input to improve glucose outcomes. We refer to this SI-informed controller as pMPC-SI.

Note that we enforce \( \hat{S}_{I,k} \geq 0.5 \cdot S_{I,0} \) to impose an upper bound on the change in \( u_s \) from \( u_{s,0} \) to avoid overshoots in the basal rate caused by variations in insulin sensitivity or errors in its estimation.

**Insulin-on-board**

The insulin-on-board constraint, adapted from Gondhalekar et al. (2016), provides the upper bound for the insulin infusion rate \( u \) delivered by the controller based on the difference between required (\( IOB_{req} \)) and current (\( IOB \)) insulin-on-board:

\[
 u_{IOB,k} = \begin{cases} 
 (IOB_{req,k} - IOB_k) / T + u_{s,k} & \text{if } IOB_{req,k} > IOB_k \\
 u_{s,k} & \text{otherwise.} 
\end{cases} \quad (5.10)
\]

It defines the amount of insulin needed to bring glucose to its target level taking into consideration the insulin that is still active from previous injections. If the current IOB already exceeds the required IOB, the constraint imposes that the controller does not deliver more than the basal rate \( u_{s,k} \) or \( u_{s,0} \) in the pMPC.

The estimated insulin required to bring glucose back to the target level, \( IOB_{req} \), is calculated according to

\[
 IOB_{req,k} = \frac{S_{I,0}}{\hat{S}_{I,k}} \cdot \frac{\tilde{y}_k - y_s}{CF}, \quad (5.11)
\]

based on the difference between measured glucose \( \tilde{y}_k \) and target glucose \( y_s \) with the subject-specific correction factor \( CF \). \( CF \) is related to an individual’s SI and describes the glucose lowering effect of one unit of injected insulin. Similar to the updates in the basal rate \( u_s \), we introduce a scaling factor in the pMPC-SI to consider changes in insulin needs using the estimate \( \hat{S}_{I,k} \), such that the required insulin decreases with increasing insulin sensitivity.
Insulin-on-board $IOB$ is computed from the history of basal and bolus injections and insulin activity curves that describe the decay of insulin action over time (see Suppl. Sec. 5.5.2).

### 5.2.2 Bolus Calculation

A meal bolus is computed according to

$$u_m = \frac{S_{1,b}}{S_{1,k}} \cdot \left( \frac{CHO}{ICR} + \frac{\hat{y}_k - y_k}{CF} \right) - IOB_k$$

(5.12)

following the announcement of a meal, based on the amount of carbohydrates, $CHO$, the difference between current and target glucose and insulin-on-board (Schmidt and Norgaard, 2014). The first term corrects for the expected rise in glucose from the meal with the subject-specific insulin-to-CHO ratio, $ICR$, the second term corrects for deviations in glucose from the target, and the third term takes into account insulin from previous injections as described above. Again, we scale the bolus with the ratio of baseline and estimated insulin sensitivity within the pMPC-SI.

### 5.2.3 Patient Population

We generated a virtual patient population with 100 subjects for in-silico assessment of the control law using the model of glucose-insulin regulation presented in Chapter 3, which incorporates effects of physical activity on glucose metabolism. It considers the acute changes in glucose utilization and production to meet the increased glucose demand during exercise, as well as the prolonged rise in insulin sensitivity that drives repletion of glycogen stores during recovery.

We sampled non-exercise-related parameters of the model from a log-normal distribution around the population-average values defined in the original publication and a coefficient of variation of 25%. We sampled the basal insulin level $I_b$ and assumed that it is negatively correlated with the subject’s insulin sensitivity with a correlation coefficient of -0.75. Finally, body weight was sampled from a uniform distribution between 60 and 80 kg. We added one standard subject to the population that represents the population average.

We kept exercise-related parameters at their population-average values. The corresponding model parts are not included in the process model of the MPC or the observer model of the UKF. Hence, this allows to systematically analyze the robustness of the controller to the unmodelled effects of PA.

Furthermore, we assigned suitable values for the treatment parameters $CF$ and $ICR$ to each subject, where we determined $CF$ from BG trajectories after injection of one unit of insulin and adjusted $ICR$ based on a meal with $0.7$ g CHO per kg body weight (Suppl. Fig. S5.2).

### 5.2.4 Study Protocol

We evaluate the proposed MPC algorithm in an in-silico study on a standard day. The day consists of three meals at 6:00, 12:00 and 18:00 containing 60, 90 and 70 g of CHO. We assume a faster absorbing meal for breakfast ($\tau_m = 45$ min) and slower ones for lunch and dinner ($\tau_m = 60$ min) (Kanderian et al., 2009). Meals are
announced at time of ingestion and a corresponding meal bolus is given based on equation 5.12, where we set \( IOB = 0 \) since meals are far apart.

We use the standard day as a basis and extend it by different scenarios to evaluate the controller’s performance based on the resulting glucose trajectories of the virtual patient population. Our evaluation scenarios are described in the following sections.

**Test case**

We start with an artificial test case to assess how the controller reacts to changes in insulin sensitivity. To do so, we perform a 48 h simulation, repeating the standard day twice, and increase insulin sensitivity by 50% in each patient simulation after 24 h without informing the controller.

**Exercise scenarios**

We further evaluate scenarios with different PA intensity, duration and timing to assess how well the controller adapts to the varying BG responses to PA. The scenarios are extensions of the standard day that we incorporate into 30 h simulations, which allows us to study the BG outcomes during the day and in the night following PA:

1. Moderate-intensity PA is performed at 60% of maximal oxygen consumption, \( V_{O2}^{max} \), for 60 min in
   a) the morning starting at 9:00,
   b) the afternoon starting at 15:00, and
   c) the evening starting at 19:30.

2. Prolonged PA is performed at 60% \( V_{O2}^{max} \) for 150 min starting at 14:00. 15 g of fast-absorbing CHO (\( \tau_m = 30 \) min) are given each 50 and 100 min into the activity.

3. High-intensity PA is performed at 85% \( V_{O2}^{max} \) for 30 min starting at 15:15.

**Disturbance scenarios**

Finally, we consider scenarios with unforeseen challenges. We use the standard day with moderate-intensity PA in the afternoon (scenario 1b) and evaluate the controller’s performance under the following conditions:

4. Incorrect meal size estimation. In practice, the carbohydrate content of meals is often incorrectly estimated. Studies have shown that the average discrepancy is around 20% (Brazeau et al., 2013), mostly arising from underestimation of CHOs. We therefore perform simulations where meal sizes are consistently underestimated by 30%, meaning that the incorrect meal size is fed to the meal bolus calculator and the UKF and MPC algorithms.

5. Unexplained glucose excursions. Here, we examine the unexpected occurrence of hypoglycemia or rise in glucose. The latter can for example be caused by unannounced meals, a challenge encountered regularly in daily life. We simulate
a) a glucose drop that we mimic by delivering 1 U of insulin at 1:00 in the morning, and
b) a glucose rise that we induce by giving 20 g CHO at 1:00 in the morning.

5.3 RESULTS

We evaluate the pMPC and pMPC-SI algorithms based on time spent in the recommended target range (TIR) between 70 and 180 mg/dl and the slightly narrower range between 80 and 140 mg/dl, which is considered as the safe range for BG levels during fasting periods. Furthermore, we determine the time spent below range (TBR, BG < 70 mg/dl) and above range (TAR, BG > 180 mg/dl) as well as mean glucose concentration. Finally, we assess the low (LBGI) and high (HBGI) blood glucose indices (Kovatchev et al., 2000). They are a measure of the extent and number of low and high blood glucose events, respectively, hence representing the severeness of hypoglycemia and hyperglycemia encountered in the examined time period.

5.3.1 Test Case

We first evaluate how our SI-informed MPC algorithm performs in a test case with a step increase in insulin sensitivity.

The results are shown in Figure 5.2. Glucose trajectories are similar between pMPC and pMPC-SI for the first 24 h when insulin sensitivity is at its baseline. After the SI increase, the pMPC-SI adapts to the new value and we see a decrease in the required basal rate. Consequently, the controller-delivered insulin is reduced compared to the pMPC. In addition, meal boluses are smaller. Overall, this leads to higher glucose levels for the SI-informed MPC than for the baseline MPC, which are comparable to the glucose levels observed in the first 24 h.

Figure 5.2 – Mean results for the test case for the baseline controller pMPC (blue, dashed) and SI-informed controller pMPC-SI (red, solid). Shaded areas represent one standard deviation. Insulin sensitivity is increased by 50% after 24 h. The first row shows the resulting BG levels, and the second row the controller-delivered insulin input (lines) and meal boluses (circles, mean ± standard deviation). The glucose target and basal rate are depicted by black lines for the pMPC (dashed) and pMPC-SI (solid). The insulin sensitivity estimate is shown in the third row, with the true value represented in black. In the pMPC, SI is not estimated and the parameter is kept at its baseline value, $S_{1,0}$. 

A summary of the glucose outcome is shown in Table 5.1. While there is no difference in TIR between 70 and 180 mg/dl for the two controllers, TIR between 80 and 140 mg/dl is improved for the pMPC-SI. Furthermore, the mean glucose concentration is higher, and time below range and the LBGI reduced when using insulin sensitivity estimation. Simultaneously, time above range and the HBGI do not increase considerably, indicating that the controller reacts appropriately to the changes in insulin requirements.

Table 5.1 – Glucose outcome for the test case presented as mean (standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>pMPC</th>
<th>pMPC-SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR (70-180)</td>
<td>91.7 (6.5)</td>
<td>90.8 (7.4)</td>
</tr>
<tr>
<td>TIR (80-140)</td>
<td>67.9 (7.1)</td>
<td>74.6 (8.0)</td>
</tr>
<tr>
<td>TBR</td>
<td>3.0 (3.0)</td>
<td>0.1 (0.7)</td>
</tr>
<tr>
<td>TAR</td>
<td>5.2 (5.0)</td>
<td>9.1 (7.2)</td>
</tr>
<tr>
<td>mean BG</td>
<td>110.1 (5.9)</td>
<td>119.9 (6.7)</td>
</tr>
<tr>
<td>LBGI</td>
<td>1.6 (0.3)</td>
<td>0.7 (0.3)</td>
</tr>
<tr>
<td>HBGI</td>
<td>1.2 (0.8)</td>
<td>1.8 (1.1)</td>
</tr>
</tbody>
</table>

5.3.2 Exercise Scenarios

Next, we investigate different PA scenarios that include moderate and high intensities, short and prolonged duration and different timing of the activity.

We show resulting glucose trajectories, insulin delivery rates and estimated insulin sensitivity for moderate-intensity PA performed in the afternoon (scenario 1b) in Figure 5.3. During the activity, BG drops for both the pMPC-SI and pMPC. However, when insulin sensitivity is elevated at the end of PA, the SI-informed controller adapts and the insulin input drops toward zero. For the remaining simulation time, it stays consistently lower than the rate delivered by the baseline controller and achieves higher blood glucose levels slightly above the target level.

Figure 5.3 – BG levels, controller-delivered insulin and meal boluses, and estimated insulin sensitivity for scenario 1(b) with moderate-intensity PA in the afternoon for the baseline controller pMPC (blue, dashed) and the SI-informed controller pMPC-SI (red, solid). The PA session is marked by vertical lines. (a) Mean results for the patient population, where the shaded areas represent one standard deviation. (b) Results for one subject.
We observe similar patterns for morning (scenario 1a) and evening (scenario 1c) moderate-intensity PA (Suppl. Fig. S5.3).

For prolonged PA (scenario 2, Fig. 5.4a), the insulin delivery rate derived using the pMPC-SI drops substantially below the delivery rate of the pMPC already during the activity when the controller picks up on the change in insulin sensitivity. After exercise, the pump remains suspended when BG levels are very low. In this scenario, we see spikes in the insulin input during PA that occur when CHOs are supplemented. The PA-driven drop in glucose levels is not predicted by the process model, while a glucose rise is anticipated from the CHO intake, driving insulin delivery back towards $u_c$. The insulin input rate decreases again when glucose levels keep falling. BG levels after the activity are higher when applying the pMPC-SI and reach the target BG concentration.

During high-intensity PA (scenario 3, Fig. 5.4b), glucose levels rise. Therefore, a decrease in insulin sensitivity is initially detected incorrectly, accompanied by a slight rise in the basal rate, before the UKF estimate converges towards the correct value. Subsequently, the pMPC-SI delivers less insulin than the pMPC, leading to glucose levels closer to the target concentration.

The glucose outcome for the different exercise scenarios is summarized in Table 5.2. Time in range is comparable for the two controllers across most scenarios. We observe a slight improvement for evening PA in the pMPC-SI where no meal follows after the activity to raise blood glucose levels, and we observe a significant improvement in TIR for prolonged PA where the PA duration leads to a drastic rise in insulin sensitivity and hence, a considerable change in insulin needs following the activity.

Similarly, the time below range (<70 mg/dl) is comparable between controllers and we see improvements for the same scenarios as before. However, the LBGI is reduced in general, indicating that overall BG levels are higher when comparing the SI-informed and baseline controllers. This is supported by the elevated mean glucose level that is observed for the pMPC-SI for all scenarios.

Time above range (>180 mg/dl) and the HBGI are similar or increase only slightly with insulin sensitivity estimation across the examined scenarios. Hence, hyperglycemia occurrence does not increase with the proposed control strategy.

![Figure 5.4](image)

**Figure 5.4** – Mean results for BG levels, controller-delivered insulin and meal boluses, and estimated insulin sensitivity for the baseline controller pMPC (blue, dashed) and the SI-informed controller pMPC-SI (red, solid). Shaded areas represent one standard deviation and the PA session is marked by vertical lines. (a) Prolonged moderate-intensity PA (scenario 2). (b) High-intensity PA (scenario 3).
Table 5.2 – Glucose outcome for the exercise scenarios presented as mean (standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>1(a) moderate intensity</th>
<th></th>
<th>1(b) moderate intensity</th>
<th></th>
<th>1(c) moderate intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>morning</td>
<td>afternoon</td>
<td>evening</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pMPC</td>
<td>pMPC-SI</td>
<td>pMPC</td>
<td>pMPC-SI</td>
<td>pMPC</td>
</tr>
<tr>
<td>TIR (70-180)</td>
<td>88.4 (3.4)</td>
<td>84.7 (6.8)</td>
<td>86.6 (4.3)</td>
<td>86.1 (5.6)</td>
<td>82.8 (5.9)</td>
</tr>
<tr>
<td>TIR (80-140)</td>
<td>72.5 (6.2)</td>
<td>71.3 (5.7)</td>
<td>72.4 (6.9)</td>
<td>72.0 (6.5)</td>
<td>66.7 (6.1)</td>
</tr>
<tr>
<td>TBR</td>
<td>8.2 (1.3)</td>
<td>7.8 (1.3)</td>
<td>7.7 (0.8)</td>
<td>7.5 (1.1)</td>
<td>10.5 (1.8)</td>
</tr>
<tr>
<td>TAR</td>
<td>3.4 (3.0)</td>
<td>7.5 (6.2)</td>
<td>5.7 (4.1)</td>
<td>6.4 (5.4)</td>
<td>6.7 (5.2)</td>
</tr>
<tr>
<td>mean BG</td>
<td>105.6 (4.4)</td>
<td>118.9 (5.2)</td>
<td>107.9 (4.6)</td>
<td>117.5 (5.3)</td>
<td>109.4 (4.7)</td>
</tr>
<tr>
<td>LBGI</td>
<td>2.4 (0.4)</td>
<td>1.6 (0.5)</td>
<td>2.2 (0.4)</td>
<td>1.5 (0.4)</td>
<td>2.1 (0.3)</td>
</tr>
<tr>
<td>HBGI</td>
<td>0.8 (0.5)</td>
<td>1.5 (0.9)</td>
<td>1.1 (0.7)</td>
<td>1.4 (0.8)</td>
<td>1.3 (0.7)</td>
</tr>
</tbody>
</table>

2. prolonged PA                              3. high intensity PA

<table>
<thead>
<tr>
<th></th>
<th>pMPC</th>
<th>pMPC-SI</th>
<th>pMPC</th>
<th>pMPC-SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR (70-180)</td>
<td>69.3 (4.8)</td>
<td>84.2 (3.3)</td>
<td>91.5 (5.7)</td>
<td>91.2 (6.3)</td>
</tr>
<tr>
<td>TIR (80-140)</td>
<td>49.5 (5.3)</td>
<td>73.2 (4.8)</td>
<td>78.0 (6.9)</td>
<td>76.6 (7.6)</td>
</tr>
<tr>
<td>TBR</td>
<td>25.1 (3.9)</td>
<td>10.2 (1.3)</td>
<td>2.7 (2.1)</td>
<td>2.8 (2.3)</td>
</tr>
<tr>
<td>TAR</td>
<td>5.6 (3.9)</td>
<td>5.6 (4.0)</td>
<td>5.7 (4.1)</td>
<td>6.1 (4.9)</td>
</tr>
<tr>
<td>mean BG</td>
<td>96.7 (4.3)</td>
<td>114.5 (5.3)</td>
<td>111.8 (4.7)</td>
<td>118.1 (5.4)</td>
</tr>
<tr>
<td>LBGI</td>
<td>5.4 (0.7)</td>
<td>2.4 (0.5)</td>
<td>1.1 (0.3)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>HBGI</td>
<td>1.0 (0.6)</td>
<td>1.2 (0.7)</td>
<td>1.2 (0.7)</td>
<td>1.3 (0.8)</td>
</tr>
</tbody>
</table>

5.3.3 Disturbance Scenarios

Finally, we test whether our controller is robust against unmodelled disturbances (Fig. 5.5).

If the meal size is underestimated (scenario 4), smaller meal boluses are administered and the controller instead delivers more insulin following CHO intake to compensate for the unaccounted CHOls. This results in BG trajectories similar to scenario 1b, where correct meal sizes are used, and similar also to the results obtained when using the baseline MPC (Suppl. Fig. S5.4). We further observe that insulin sensitivity is underestimated around meal times, since glucose peaks are higher than expected from the entered CHOls.

During a hypoglycemic episode (scenario 5a), insulin delivery is attenuated to allow an increase in BG levels. Insulin sensitivity is overestimated, and consequently the meal bolus for breakfast is strongly reduced, causing a high BG peak.

Hyperglycemia (scenario 5b), on the other hand, is accompanied by a decrease in estimated insulin sensitivity and an increase in insulin delivery. A larger bolus is delivered for breakfast with respect to the current BG level compared to the undisturbed scenario, leading to a lower BG rise after the meal.

For both the hypo- and hyperglycemia cases, insulin sensitivity estimation and insulin delivery approach the original scenario by lunch time and the simulated glucose trajectories are comparable for the remaining study period.
In comparison, the pMPC algorithm does not react as strongly to the hypo- and hyperglycemic events as the SI-informed controller, which leads to longer exposure especially to hypoglycemia (Suppl. Fig. S5.4). On the other hand, the BG peaks following breakfast are closer to the undisturbed scenario, since the administered meal bolus is not scaled by the estimated insulin sensitivity.

A results summary of the disturbance scenarios applying the pMPC-SI is given in Table 5.3. Time in range as well as hypo- and hyperglycemia measures are comparable to the undisturbed case for all scenarios except scenario 5a. Here, time in range is lower due to longer time spent above and below the target range. First, hypoglycemia occurs per definition of this scenario, and hyperglycemia follows caused by a meal with inadequate meal bolus.

![Figure 5.5 – Mean BG levels, controller-delivered insulin and meal boluses, and estimated insulin sensitivity for the disturbance scenarios (4, 5a and 5b) applying the SI-informed controller pMPC-SI. Scenario 1(b) is included for comparison. The shaded areas represent one standard deviation and the PA session is marked by vertical lines.](image)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>1(b) no disturbance</th>
<th>4. incorrect meal size</th>
<th>5(a) hypoglycemia</th>
<th>5(b) glucose rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR (70-180)</td>
<td>86.1 (5.6)</td>
<td>84.3 (6.2)</td>
<td>77.3 (7.7)</td>
<td>88.0 (5.4)</td>
</tr>
<tr>
<td>TIR (80-140)</td>
<td>72.0 (6.5)</td>
<td>69.1 (6.5)</td>
<td>59.6 (6.1)</td>
<td>68.9 (8.6)</td>
</tr>
<tr>
<td>TBR</td>
<td>7.5 (1.1)</td>
<td>7.7 (1.3)</td>
<td>13.0 (4.1)</td>
<td>7.4 (1.0)</td>
</tr>
<tr>
<td>TAR</td>
<td>6.4 (5.4)</td>
<td>8.1 (6.0)</td>
<td>9.8 (5.5)</td>
<td>4.6 (5.2)</td>
</tr>
<tr>
<td>mean BG</td>
<td>117.5 (5.3)</td>
<td>117.9 (5.6)</td>
<td>119.1 (5.6)</td>
<td>118.1 (6.0)</td>
</tr>
<tr>
<td>LGBGI</td>
<td>1.5 (0.4)</td>
<td>1.7 (0.6)</td>
<td>2.4 (0.8)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>HGBGI</td>
<td>1.4 (0.8)</td>
<td>1.7 (1.0)</td>
<td>2.0 (1.0)</td>
<td>1.3 (0.8)</td>
</tr>
</tbody>
</table>
5.4 DISCUSSION

Prolonged changes in insulin sensitivity after exercise require continued adjustment of insulin treatment in T1D. Here, we proposed a strategy to account for these PA-induced changes in an MPC algorithm by estimating insulin sensitivity from glucose measurements using an unscented Kalman filter. The process model is continuously updated with the current estimate to generate more accurate glucose predictions and the objective function is re-centered around the updated basal rate required to achieve the desired glucose target. Meal boluses are scaled accordingly as well, based on our previous work (Deichmann and Kaltenbach, 2021).

While the SI-informed and baseline controllers perform similarly when insulin sensitivity is at its baseline, we observe an improved glycemic outcome when applying the pMPC-SI on days with PA compared to the pMPC. This becomes more relevant with increasing PA intensity and duration, since the SI rise becomes more pronounced, causing larger changes in insulin requirements. Furthermore, we can confirm that the pMPC-SI also performs well for high-intensity PA where glucose levels may rise during the activity instead of drop, which is usually encountered during moderate-intensity PA.

Currently, we observe a time-lag in the insulin sensitivity estimation at PA onset, since the UKF is not informed about the activity. This further leads to a delayed response of the controller to the PA session. To improve the SI estimation and following, reduce the reaction time of the controller, a PA input could be used to trigger a PA mode, in which the UKF could be more sensitive to changes in BG levels that are caused by the expected rise in SI.

In addition, our controller is only reactive to the delayed effect of elevated insulin sensitivity, while other approaches address the acute PA-driven increase in glucose utilization, and achieve to improve glycemic outcomes and protect against hypoglycemia during PA. We could similarly integrate an exercise component into our process model (Resalat et al., 2016) or use an exercise net effect input (Garcia-Tirado et al., 2019) to account for the anticipated BG drop during the activity, which would present a complementary feature to our proposed approach.

The proposed control strategy also performs well in disturbance scenarios with incorrect meal size estimation or unexpected glucose excursions, although these excursions are wrongly explained by changes in insulin sensitivity. Nevertheless, the incorrect SI estimation assists in counteracting the glucose change, since it further attenuates or increases the controller-delivered basal rate during hypo- and hyperglycemia, respectively. However, it might also cause over- or underdosing of close-by meals. In particular, we observed that a meal bolus delivered following a hyperglycemic event can be too large due to underestimation of insulin sensitivity. This might induce hypoglycemia and is currently limited by the lower bound on the SI estimate. To tackle this problem, a meal or disturbance detection algorithm would be a valuable extension of our controller.

Overall, we presented an MPC algorithm that successfully accounts for the prolonged changes in insulin requirements following exercise. This is achieved through estimation of insulin sensitivity from CGM data. The approach does not require any PA inputs, and leads to an improved glycemic outcome following a PA session.
5.5 Supplementary Material

5.5.1 Process Model

Model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
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<td>$p_1$</td>
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</tr>
<tr>
<td>$p_2$</td>
<td>0.0228</td>
<td>1/min</td>
</tr>
<tr>
<td>$S_I$</td>
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<td>ml/µU/min²</td>
</tr>
<tr>
<td>$p_4$</td>
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<td>$p_5$</td>
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<td>$k_3$</td>
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<tr>
<td>$V_i$</td>
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<td>ml/kg</td>
</tr>
</tbody>
</table>

Parameters marked by an asterisk are personalized to the individual subject

Model personalization

Figure S5.1 – Comparison of personalized and true parameter values for $p_1$ and $S_I$. 
5.5.2 Insulin-on-Board

Insulin-on-board $IOB$ is computed from the history of basal and bolus insulin injections and insulin activity curves that describe the decay of insulin action over time. The activity curves $\theta_j$ are vectors of 8 h length with $j \in \{2, 4, 6, 8\}$ and sampled at $T = 5$ min intervals (Walsh and Roberts, 2006). The subscript denotes how long insulin is active and a curve is chosen based on the current glucose measurement $\tilde{y}_k$ following

$$
\theta_k = \begin{cases} 
\theta_2 & \text{if } \tilde{y}_k > 300 \\
\theta_4 & \text{if } 200 < \tilde{y}_k \leq 300 \\
\theta_6 & \text{if } 140 < \tilde{y}_k \leq 200 \\
\theta_8 & \text{if } \tilde{y}_k \leq 140.
\end{cases}
$$

With the 8 h history of the controller-derived basal rate, $\Lambda_{basal,k}$, and the 8 h history of bolus injections, $\Lambda_{bolus,k}$, insulin-on-board is then defined as

$$
IOB_k = \theta_k^T \Lambda_{basal,k} + \theta_4^T \Lambda_{bolus,k}.
$$

5.5.3 Patient Population

![Figure S5.2 – Distributions of the treatment parameters CF and ICR of the patient population. The median and standard patient are marked in red (solid) and purple (dashed).](image)
5.5.4 Results

Figure S5.3 – Mean results for BG levels, controller-delivered insulin and meal boluses, and estimated insulin sensitivity for the baseline controller pMPC (blue, dashed) and the SI-informed controller pMPC-SI (red, solid). Shaded areas represent one standard deviation and the PA session is marked by vertical lines. Moderate-intensity PA is performed (a) in the morning (scenario 1a) and (b) in the evening (scenario 1c).

Figure S5.4 – Mean BG levels, controller-delivered insulin and meal boluses for the disturbance scenarios (4, 5a and 5b) applying the baseline controller pMPC. Scenario 1(b) is included for comparison. The shaded areas represent one standard deviation and the PA session is marked by vertical lines.
In this thesis, we studied the effect of PA on glucose-insulin regulation and the resulting changes in insulin requirements for people with T1D. We presented a mathematical model that predicts BG concentrations for different types of exercise in full-day scenarios and proposed a strategy for PA-informed insulin dose calculations. This strategy can be applied to scale meal and basal boluses in MDI therapy, but also extends to CSII with continuous adaptation of the basal rate. Our focus was on the prolonged effects of PA on glucose metabolism that require continued treatment adjustments during the recovery period, where our work improved predicted glucose outcomes and reduced the risk for late-onset hypoglycemia. Nevertheless, PA continues to be a great challenge for T1D management and several open questions remain that warrant further investigation.

6.1 CHALLENGES IN EXERCISE MANAGEMENT

PA leads to an increase in risk for acute and late-onset hypoglycemia in people with T1D. This risk can be reduced by appropriate insulin dose reductions and additional CHO intake. However, even individuals that follow PA management guidelines report low BG levels after PA (Pinsker et al., 2016a). In Chapter 2, we evaluated the performance of such guidelines for moderate-intensity PA in an in-silico study to identify their shortcomings and potential causes for hypoglycemia.

We found that the risk for hypoglycemia during and immediately after PA can be minimized by following recommendations for treatment adjustment to PA. In contrast, the risk for late-onset hypoglycemia remained elevated and increased with intensity and duration of the activity. These findings are in line with clinical observations (Campbell et al., 2013; Metcalf et al., 2014). Additionally, we observed that timing of the PA session in relation to meals affected BG outcomes, which was subsequently also reported by people with T1D in a recent survey (Paiement et al., 2022). We identified the prolonged PA-induced rise in insulin sensitivity as the main driver for late-onset hypoglycemia, which may necessitate additional treatment adjustments during the recovery period, and demands particular caution around post-PA meals when large amounts of insulin are delivered.

Simulation studies are commonly used to develop new control algorithms for insulin delivery. Here, we highlighted their potential in evaluating existing treatment recommendations. Unlike in clinical trials, a wide range of scenarios can be examined to assess a treatment strategy systematically. This allows to compare different strategies, identify open problems and develop targeted hypotheses that can be tested in clinical studies to improve treatment recommendations. However, the model we used consisted of different model components to allow simulation of full-day scenarios, but was not validated in this composition. Furthermore, the model covered only short, moderate-intensity PA. Validated models that capture PA of different intensity and duration are required to evaluate and refine guidelines.
for treatment adjustments in-silico for a broader range of PA scenarios, which gave rise to the development of our model in Chapter 3.

6.2 INDIVIDUAL TREATMENT ASSESSMENT AND A VIRTUAL PATIENT POPULATION

The glucoregulatory model presented in Chapter 3 is the first to consider all relevant processes of aerobic PA affecting glucose metabolism. We incorporated separate components for the PA-induced changes in GU and GP, while further distinguishing between insulin-dependent and -independent contributions. To overcome identifiability issues, we proposed a stepwise approach for model calibration, in which we first quantified the different PA-related processes separately. We successfully validated our model on complex data sets covering various PA scenarios, illustrating the feasibility of our calibration strategy. The resulting model captures moderate- to high-intensity PA including glycogen depletion for prolonged activities. It offers a detailed description of PA physiology, which is crucial to study the effects of PA on BG dynamics and develop insulin delivery strategies for PA management in-silico. However, further validation is required, in particular for prolonged and high-intensity PA, and we did not consider anaerobic PA.

Starting from a population-average description, we then personalized our model on data from children with T1D. These personalized models offer the possibility for replay simulations in the presence of PA. Replay simulations have been previously proposed for individual treatment evaluation in non-PA scenarios, where glucose outcomes for alternative CHO and insulin inputs can be compared (Hughes et al., 2021). In the future, replay simulators could be a valuable aid for clinicians to assess individual treatment adjustments and inform treatment decisions. Including PA in such a tool could guide the development of personalized PA management strategies. This requires rigorous validation and evaluation of the range of validity for changes in treatment before being applied in a clinical setting.

Besides its potential on the individual-subject level, a virtual patient population (VPP) based on our PA model could be used to develop PA-informed treatment approaches in-silico. In this work, we provide only a population-average quantification of the model, since the data required to determine accurate parameter distributions and correlations that reflect a realistic T1D population are currently not available. However, VPPs offer the possibility to evaluate the performance, safety and limitations of new insulin delivery strategies extensively, before applying them in clinical trials. They are commonly used during the development of CL algorithms, and PA would be a valuable extension to such simulators to allow simulations that capture everyday life and to develop targeted strategies to improve glucose control during PA.

6.3 INSULIN SENSITIVITY PROFILES FOR TREATMENT PERSONALIZATION

The rise in insulin sensitivity has emerged as the main driver of PA-related late-onset hypoglycemia and causes difficulties for people with T1D to adjust their insulin treatment appropriately during recovery. We therefore proposed a bolus calculator in Chapter 4, which accounts for the prolonged changes in insulin requirements due to PA. We quantified these changes via estimation of SI, and
demonstrated that the PA-induced increase in SI can be estimated continuously from CGM measurements with an UKF. Notably, we did not include PA in the internal model of the UKF and hence, our approach does not rely on an accurate description of the underlying PA physiology. Although UKFs have been presented in previous studies for SI estimation, they only addressed slow variations in SI, while we achieved to track SI changes on a much shorter time scale required for PA. This could also be applied to consider other effects, for example diurnal variations in SI.

We scaled insulin boluses in proportion to the SI estimate, leading to higher overnight BG levels and a reduced risk for hypoglycemia. Treatment could be further personalized by generating an individual SI profile that represents a person’s typical day and by adapting insulin dosing relative to this profile. Subsequently, our approach would extend directly to unstructured PA. Unstructured activity can accumulate throughout the day and might require, similar to structured PA, insulin dose adjustments (Colberg et al., 2016). An individual’s typical activity level would be captured automatically in the SI profile. Importantly, standard treatment is already tailored to this behavior, and the bolus calculator would propose adequate insulin dose adjustments for deviations from it.

The biggest limitation of our study is the time-lag in SI estimation at the onset of PA, which arises since the UKF is not informed about the activity. Initial results from a student project by Mucun Hou indicate that this time-lag can be reduced by increasing the process noise during PA. To identify PA periods, a PA detection algorithm is then required, for example from HR measurements. HR is easily accessible from smartwatches or other activity trackers and thus a convenient indicator for PA. In Breton et al. (2014), for example, the PA mode is triggered when a person’s HR exceeds 125% of their resting HR. However, the UKF is consequently more sensitive to changes in BG levels in general, and the effect of other disturbances, for example CHO intake, on SI estimation during PA needs to be investigated.

6.4 ACCOUNTING FOR CHANGES IN INSULIN REQUIREMENTS DURING EXERCISE AND RECOVERY

In Chapter 5, we extended our SI-informed insulin bolus calculation to allow for continuous adaptation of the pump-delivered basal rate, offering strategies for both MDI and CSII to consider the prolonged PA-driven changes in insulin needs. We integrated the SI estimate into an MPC algorithm, which led to a decrease in the insulin delivery rate post-PA. This resulted in improved BG outcomes during recovery compared to a baseline MPC without SI estimation.

Our results indicate that PA-related late-onset hypoglycemia can be reduced using an SI-informed controller for insulin delivery. However, additional safety features need to be incorporated. Currently, unanticipated glucose excursions, for example from unannounced meals, are explained by changes in SI. As a consequence, incorrect SI estimation can lead to over- or underdosing of insulin and potentially result in hypo- or hyperglycemia, respectively. To prevent this, we enforced an upper limit on the SI scaling factor for the controller’s target delivery rate and the meal bolus calculation. A meal detection algorithm could be applied to mitigate the issue of incorrectly estimated SI directly and would allow to propose
adequate control actions. Furthermore, the duration of pump suspension should be limited to prevent subsequent episodes of hyperglycemia due to insufficient amounts of circulating insulin.

Up until now, we have focused exclusively on the prolonged effects of PA on BG levels and insulin requirements after the activity, but did not consider falling BG levels during PA. To address this in our MPC algorithm, we could integrate a component that describes the acute, insulin-independent effects of PA on glucose metabolism in the process model, similar to Resalat et al. (2016). However, to keep the PA component as simple as possible, we propose to use the model extension by Breton (2008) for moderate-intensity PA to describe a PA-induced increase in glucose effectiveness, which is characterized by only one parameter. An average quantification of this PA component might be sufficient for BG predictions, as insulin-independent effects of PA display less inter-patient variability than the changes in SI (Romeres et al., 2021). Otherwise, the model could be adapted to the individual over time to improve the prediction accuracy. Taking these acute changes in glucose metabolism into account should allow the controller to react more appropriately to changes in BG during PA, and as a result, lead to earlier attenuation of insulin delivery compared to our original MPC approach. As a further extension, PA announcements by the user could be included to reduce insulin delivery already before the activity, considering BG predictions based on coarse intensity categories and an estimated duration of the activity. Nevertheless, pre-PA meal bolus adjustments and CHO supplementation will continue to be required to maintain stable BG levels during PA.

6.5 Conclusion

We presented a model of glucose-insulin regulation that captures the effects of moderate- to high-intensity aerobic PA on glucose metabolism, and covers all relevant processes that affect BG dynamics both during the activity and the recovery period. The model could thus benefit the in-silico development and evaluation of control algorithms for automated insulin delivery that target glycemic control around PA. Here, we applied the model to evaluate a control strategy for insulin delivery that is based on the estimation of the PA-driven changes in insulin sensitivity, presenting a promising approach to adjust insulin dosing in the hours following PA. Extensions that take the daily activity behavior of a person into account, and additional control elements that address the decline in BG levels and corresponding risk for hypoglycemia during PA might result in improved glycemic outcomes and a reduction in PA-related hypoglycemia in general. Alternatively, the proposed model could find application in simulators for individual treatment assessment, where the integration of our SI-informed control strategy for insulin dosing adjustments could further aid in proposing suitable treatment alternatives in replay simulations.

However, further validation of the model, replay simulations and control algorithm are necessary before application in a clinical setting, as well as additional features that guarantee the safety of the controller.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AC</td>
<td>Accelerometer</td>
</tr>
<tr>
<td>AID</td>
<td>Automated Insulin Delivery</td>
</tr>
<tr>
<td>AP</td>
<td>Artificial Pancreas</td>
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<tr>
<td>BG</td>
<td>Blood Glucose</td>
</tr>
<tr>
<td>BMM</td>
<td>Bergman Minimal Model</td>
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<tr>
<td>CF</td>
<td>Correction Factor</td>
</tr>
<tr>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
</tr>
<tr>
<td>CHO</td>
<td>Carbohydrate</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CL</td>
<td>Closed-Loop</td>
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<tr>
<td>CSII</td>
<td>Continuous Subcutaneous Insulin Infusion</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FIT</td>
<td>Functional Insulin Therapy</td>
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<td>GP</td>
<td>Glucose Production</td>
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<td>GSA</td>
<td>Global Sensitivity Analysis</td>
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<td>GU</td>
<td>Glucose Uptake</td>
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<td>HbA1c</td>
<td>Glycated Hemoglobin</td>
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<tr>
<td>HBGI</td>
<td>High Blood Glucose Index</td>
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<td>HCL</td>
<td>Hybrid Closed-Loop</td>
</tr>
<tr>
<td>HIE</td>
<td>High-Intensity Exercise</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>ICR</td>
<td>Insulin-to-Carbohydrate Ratio</td>
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<tr>
<td>IOB</td>
<td>Insulin-on-Board</td>
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<tr>
<td>iscCGM</td>
<td>intermittent scanning Continuous Glucose Monitoring</td>
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<td>IVGTT</td>
<td>Intravenous Glucose Tolerance Test</td>
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<tr>
<td>LBGI</td>
<td>Low Blood Glucose Index</td>
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<tr>
<td>MARD</td>
<td>Mean Absolute Relative Difference</td>
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<tr>
<td>MDI</td>
<td>Multiple Daily Injections</td>
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<td>MPC</td>
<td>Model Predictive Control</td>
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<tr>
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<td>Oral Glucose Tolerance Test</td>
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<td>PA</td>
<td>Physical Activity</td>
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<tr>
<td>PID</td>
<td>Proportional-Integral-Derivative</td>
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<tr>
<td>PL</td>
<td>Profile Likelihood</td>
</tr>
<tr>
<td>PVO$_2^{\text{max}}$</td>
<td>Relative Oxygen Consumption</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>QP</td>
<td>Quadratic Program</td>
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<tr>
<td>RMSD</td>
<td>Root Mean Square Difference</td>
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<tr>
<td>rtGGM</td>
<td>real-time Continuous Glucose Monitoring</td>
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<tr>
<td>SAP</td>
<td>Sensor-Augmented Pump</td>
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<tr>
<td>SG</td>
<td>Glucose Effectiveness</td>
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<td>SI</td>
<td>Insulin Sensitivity</td>
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<td>SMBG</td>
<td>Self-Monitoring of Blood Glucose</td>
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<td>SOGMM</td>
<td>Subcutaneous Oral Glucose Minimal Model</td>
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<td>T1D</td>
<td>Type 1 Diabetes</td>
</tr>
<tr>
<td>TAR</td>
<td>Time Above Range</td>
</tr>
<tr>
<td>TBR</td>
<td>Time Below Range</td>
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<tr>
<td>TIR</td>
<td>Time In Range</td>
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<tr>
<td>UKF</td>
<td>Unscented Kalman Filter</td>
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<tr>
<td>VO2max</td>
<td>Maximal Oxygen Consumption</td>
</tr>
<tr>
<td>VPP</td>
<td>Virtual Patient Population</td>
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