Sparsity maximization approach to multiple daily injections therapy for type 1 diabetic patients

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Sparsity maximization approach to multiple daily injections therapy for type 1 diabetic patients

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Abstract

Based on sparsity maximization we propose a controller for Multiple Daily Injections (MDI) therapy for Type 1 Diabetes melitus (T1DM) individuals. Based on convex relaxations on the sparsity maximization problems and by implementing personalised linear models of patient we formulate a model predictive controller to determine insulin boluses. By relaxing the constraints of the unsafe regions after meal consumption for pre-defined time interval we obtain sufficient performance with a long enough horizon. To improve the controllers performance a case-based reasoning framework is implemented to tune the controller constraints for increasing time spent in euglycemia.

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Max van Wilsum

Chapter 1

Introduction

Diabetes mellitus is an auto-immune disorder with two possible types. Type 1 diabetic patients fail to produce their own insulin, while type 2 diabetic patients fail to utilize the insulin, i.e., it does not have any effect. Insulin is important for the human body, as it breaks down the glucose in the blood plasma. For diabetic patients, who fail to either utilize or produce their insulin, this lead to high blood glucose (BG) values (hyperglycemia). Hyperglycemia is undesirable for a diabetic patient for several reasons. First of all hyperglycemia leads to unfavorable symptoms such as blurred vision, stomach pain and generally feeling sick. However more importantly consequently high levels of blood glucose show to lead to various diseases later in life. For example it is shown that the risk of cardiovascular diseases can be linked to high BG levels [7] and thus should be prevented.

For Type 1 Diabetes melitus (T1DM) the solution to deal with the missing of insulin can be dealt with by externally administrating insulin to lower the BG values. Although by injecting insulin externally is sufficient for lowering the BG values, another problem arises. High levels of blood glucose are dangerously in the long run, but by injecting too much insulin the BG values of a T1DM patient can reach dangerous low values (hypoglycemia). Hypoglycemia can be directly linked to life-threatening situations, such as a cardiac arrest [8]. Especially at higher age the change of such life-threatening effects increases. The effect of hyperglycemia, except from being uncomfortable, takes longer to develop and such different ages require different objectives for T1DM patients.

The administration of insulin can be split up in two different approaches. The first approach to deal with administration of insulin is by using continuous subcutaneously insulin infusion (CSII), with the use of a dedicated pump, which is a so-called artificial pancreas (AP) [9]. By periodically measuring the BG values of the T1DM patient every five minutes, the insulin infusion is constantly adjusted to maximize the time in the normal glucose range (euglycemia). Another method to deal with the administration of insulin is by using syringes with insulin. Typically this treatment consist of a basal insulin injection once or twice daily (depending on the type of basal insulin), which is a more slowly acting insulin, but keeps lowering the blood glucose throughout the day. Now when meals are consumed, carbohydrates (CHO) content of the meal have an effect of increasing the BG values, thus at meal times it is important to

inject a proper insulin bolus to minimize the hyperglycemia and to not reach hypoglycemia. For this specific injection at meal times rapid-acting insulin is used, which has a greater effect on the BG but does not last for long in the blood stream. This type of treatment is referred to as Multiple Daily Injections (MDI) therapy.

For an AP the challenge in regulating the BG levels lies within the adjusting of the controller to deal with hyperglycemic events, and to cease the continuous insulin inflow to reject hypoglycemic events. The main advantage of such an AP is that it can continuously adjust the insulin inflow to the patient, and thus can achieve very good performance overall. However, lots of reasons can be made to not use one of these closed-loop controllers for dealing with type 1 diabetes. First of all, the purchase of such a pump can be expensive [10], compared to simple MDI treatment, where no such device is necessary. Secondly, a pump must be applied on the body of the patient, which can feel restricted for several reasons, and can have discomfortable side effects such as skin irritation. For these reasons T1DM patient do not always opt to use an AP, but often choose to use MDI therapy.

Deciding the size of a bolus injection, i.e., the injection of rapid-acting insulin when CHO is consumed for MDI therapy is a hard problem. As every T1DM patient reacts differently to the insulin for every patient a specific controller / bolus calculation has to be done. In the current framework of MDI generally for every meal consumed the patient has to calculate a bolus and injects themselves with a sufficient amount of insulin, even though one insulin bolus could be enough to keep the patient in the safe region of blood glucose.

1-1 Motivation

As Diabetes is such a widely known disease having a effect on so many people, lots of research is aimed towards having an as safe as possible method of injecting insulin to deal with the rising of BG caused by the consumption of CHO. While the obvious answer to restrict people as less as possible is an AP, there are reasons why people would not want such an device, even though it gives them more flexibility and less to worry about their BG levels. MDI therapy gives T1DM more control by injecting the insulin themselves, such that pump malfunctioning is something they do not have to worry about, although for every meal they are consuming they have to compensate and inject insulin through syringes, as well as measure their blood glucose levels generally with a self-monitoring of blood glucose (SMBG) device, to calculate the appropriate insulin bolus. To fill the gap between the comfort of an AP in the sense of not having to worry about the blood glucose levels, as well as having the cheap, self control MDI therapy, it makes sense to use a continuous glucose monitor (CGM) for MDI therapy and to minimize the control inputs needed to stay in the safe region of BG levels. This gives the T1DM a clear view of their blood glucose levels, and not to worry that consuming a snack between meals will give them dangerously high BG levels. Or, on the other hand, that if insulin is injected for every snack, the insulin in the body will stack and can cause hypoglycemia. Thus this creates an interesting control problem: when should insulin be injected, and how much insulin should be injected.

1-2 Problem formulation

To regulate the blood glucose values of a T1DM patients using multiple daily injections we want to minimize the total number of rapid-acting insulin injections, while maximizing the time spend with normal concentration of glucose in the blood. Suppose we can identify a Linear Time-Invariant model of a specific patient:

$$\begin{aligned} x(k+1) &= A_p x(k) + B_p u(k) + E_p d(k) \\ y(k) &= C_p x(k) + D_p u(k) \end{aligned} \tag{1-1}$$

where $x(k) \in \mathbb{R}^n$ is the state vector, $u(k) \in \mathbb{R}$ represents the short-acting insulin, $d(k) \in \mathbb{R}$ the meal disturbance vector, i.e. the amount of carbohydrates (CHO) the individual consumes and $y(k)$ is the blood glucose level. After the consumption of a meal, or a long time after the last injection of insulin, the blood glucose levels will rise outside of the bounds of the euglycemic range. There are several other factors which influence the BG levels, such as fear, anxiety, physical activities stress. The euglycemic range is defined as below 180 mg/dl and above 70mg/dl.

$$\mathcal{Y}_{safe} = \{y | y \in \mathbb{R}, 70 \leq y \leq 180\} \tag{1-2}$$

Keeping the BG in the euglycemic range is important, and in an AP the insulin infusion rate of the pump can be constantly adjusted. Individuals using MDI therapy only inject themselves through syringes when necessary. This lead to different optimization problem in contrary to the AP MPC. We want to minimize the cardinality of the input, which is equivalent to maximizing the sparsity of a vector. Maximizing the sparsity of the control input (Insulin injection) such that it adopts an impulse like behavior while maintaining euglycemia is the main idea to get a insulin bolus sufficient for MDI therapy. Maximizing the sparsity of a vector corresponds to minimizing the ℓ_0 norm.

$$\min ||u||_0 \tag{1-3}$$

We want to minimize the inputs at every instance when a meal is about to be consumed, such that the T1DM patient knows if it is necessary to inject themselves with rapid-acting insulin at the time of ingestion of CHO or in the future. So at every time instance when a meal is consumed we want to minimize the sparsity of inputs to determine if the insulin injection should be immediately injected or the patient can wait until the next meal. Here we make the assumption that we know the next time of the meal and its size. Currently machine learning algorithms are developed to identify diurnal (daily) patterns on how T1DM snack and exercise such that that information is available beforehand which makes it a reasonable assumption [11]. Basal insulin injections are not taken into account in this work, we assume that we know the long-acting insulin dose to keep the BG levels in a safe range. To sum up the control objectives we want to do the following: 1) Maximize the time in euglycemia, 2) minimize the amount of short-acting insulin injections.

However, to come to solutions for these problems we have to make a few very important assumptions, which are listed here

- Assumption 1: We assume in this work that the basal insulin dosage is known, this is important because we want to know that in fasting condition the system is in equilibrium when we solve the optimization problem.
- Assumption 2: The meals the patient is about to consume are known for a future horizon of 6 hours. To determine a single insulin bolus for the patient for a sequence of meals we have to assume that we know what the meals are that the patient is about to consume.
- Assumption 3: The parameters of the insulin dynamics and the meal dynamics are known. We make this assumption to better determine the dynamics of the glucose subsystem and to properly excite the system.
- Assumption 4: The blood glucose levels from the CGM measurements represent the real blood glucose levels and the insulin can be precisely injected as calculated, and are not needed to be rounded.

The structure of the thesis is as follows:

- In Chapter 1 we introduce the reader to the situation where T1DM patients deal with, the motivation for writing this thesis and the problem formulation.
- Chapter 2 gives insight in the background of treatment of T1DM, what type of models have been used in the past and the control methods for both MDI and the AP are shown.
- Chapter 3 introduces the Virtual patient. The equations which are used to simulate an in-silico T1DM as well as the identification of a linear time-invariant (LTI) model for predictions
- Chapter 4 contains the steps to formulate a sparsity maximization model predictive control (MPC) for MDI therapy
- In chapter 5 Case-Based Reasoning (CBR) is introduced, as well as how it is implemented to improve the controllers performance
- Chapter 6 contains all the simulations for different testing scenarios to asses the performance of the controllers.
- In the last chapter, 7, conclusions about this work and suggestions for future work are made.

Chapter 2

Background

In this chapter we give the background of Type 1 Diabetes melitus (T1DM) treatment. A bit of background on the types of insulin generally used by T1DM patients is provided. As well as the methods to deliver the insulin into the human body. Then the different control methods for calculating the appropriate insulin boluses (in case of Multiple Daily Injections (MDI) therapy) or insulin infusion rates (when using an artificial pancreas (AP)) will be explained as well with their specifications. Different types of sensors to measure the blood glucose values are also discussed. Individualized models used for prediction and simulation of a T1DM patient, their strengths and their use are explained.

2-1 Insulin and actuators

Injection of insulin is essential for a T1DM patient, and there are different types of insulin on the market. The main differences between these types of insulin is their duration and their peak appearance in the blood glucose. In this work we make use of two different types of insulin. The first is rapid-acting insulin, where different types are lispro, aspart and glulisine [12]. The idea is that these rapid-acting insulin have a very fast peak time, and a short duration of around 4 hours, this makes it ideal to inject at meal times to reject the hyperglycemic events. Another kind of insulin is the slow-acting (basal) insulin. Different types are glargine, detemir and degludec [12]. These basal insulin's have a much longer duration when compared to the bolus insulin, of around a day, and have less of a peak. This basal insulin is generally injected once or twice a day, depending on the kind of basal insulin used and how a T1DM patient react to it, to lower the blood glucose (BG) levels throughout the day. The differences between the appearance rate of a basal and bolus insulin dosage are shown in figure 2-1.

To inject the insulin into the subcutaneous space, different actuators are possible. The first method, to self-inject insulin, is a syringe. From a vial with insulin the insulin can be obtained by the syringe, and afterwards injected into the body. The main difficulty experienced with syringes is that dosing accuracy is hard. An modern alternative to the classic syringe is the

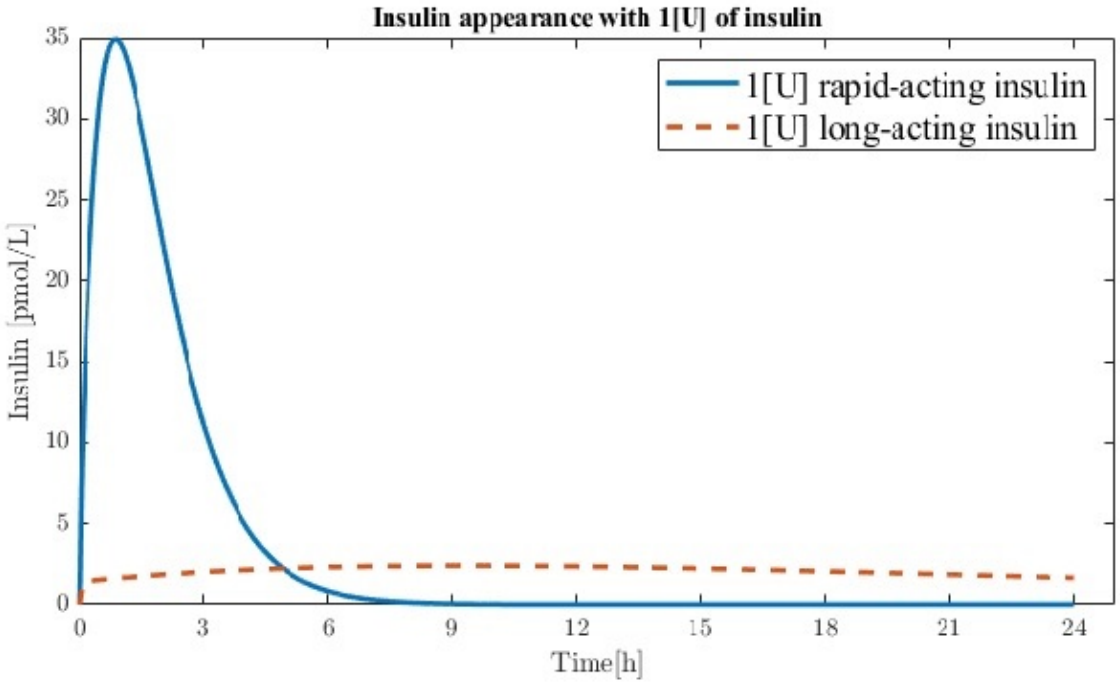

Figure 2-1: Appearance rate of 1 $[U]$ of both rapid-acting and long-acting insulin

insulin pen. The insulin pen is a three-component device: a cartridge for insulin, a short needle (disposable) and a dosing mechanism. Insulin pens are shown to have positive effect of T1DM on their treatment compared to syringes, as the dose accuracy is better, has more flexibility and over all improves glycemic control [13]. In figure 2-3 a person self-injecting themselves with a insulin pen is depicted. A more advanced method of injecting insulin are the insulin pumps. These pumps are connected with a small tube to the infusion patch which is applied to the body. A control algorithm can constantly adjust the infusion rate of insulin to the infusion set which then enters the body. Insulin pumps can achieve tighter glycemic control because of their ability to constantly adjust, and therefor can more accurately resemble the physiologic insulin deliverancy of the pancreas. While the advantages are clearly present, there are some significant negatives sides. Firstly, safety is a key point, if the pump suspends or there is a leakage in the infusion set, wrong insulin amount are injected if any at all [14]. T1DM patients can also experience skin irritation and the use of a pump involves more training from the patient, compared to insulin pens. Finally, not everyone is available to afford a pump due to the high prices [10]. In figure 2-2 a insulin pump is shown on a body.

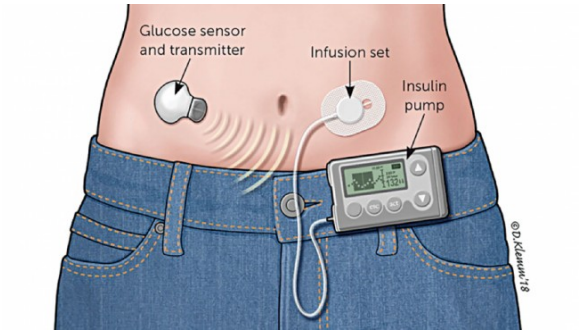

Figure 2-2: Example of a person with an insulin pump. [1]

Figure 2-3: Example of a MDI therapy patient injecting with an insulin pen. [2]

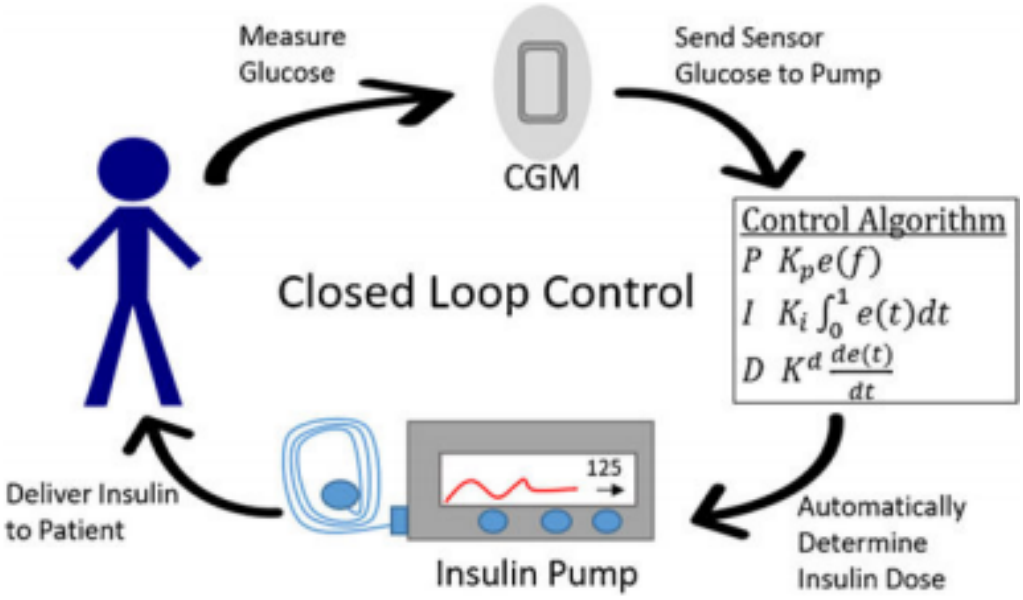

Figure 2-4: Closed loop control of diabetes using an artificial pancreas [3]

2-2 Control

In the previous years the focus for treatment of diabetes has shifted towards the use of an AP. The AP serves the same purpose as a normal pancreas, which means that it can continuously provide the necessary insulin to the body, although meal announcements to the controller are necessary. Based on the size of this meal, current blood glucose levels and a prediction model of the patient, the controller of the AP decides the infusion rates of insulin. T1DM patients can achieve in the safe region of the BG levels nearly all of the time, while only providing the controller with their meal information. This treatment of T1DM is a closed loop controller.

Different control techniques can be found in the literature to design such an closed loop controller. Negative feedback control such as PID controller is one of these control techniques

used, also, logic-based controllers are designed [9]. Model based controllers are also designed, and model predictive control (MPC) is one of the most implemented for glycemic control. Non-linear MPC+ is one of the possible MPC formulations. By implementing a cost function punishing hypo and hyperglycemic events the controller tries to keep the T1DM patient in euglycemic range [15]. Linear MPC variants are also widely available, for instance the zone MPC [16], where certain zones, such as hypo- and hyperglycemic range are punished while other zones are not. By making use of the repetitive nature of the dynamics between insulin and glucose over a days period, controller performance can be increased by using iterative learning [17]. To keep the BG levels at steady state level the controller continuously infuses rapid-acting insulin, so for AP only rapid-acting insulin is used. In figure 2-4 the closed loop control of an AP is depicted.

MDI therapy on the other hand can not constantly adjust the insulin inflow to a T1DM patient. As a meal is consumed the T1DM patient has to measure their own BG levels using a self-monitoring of blood glucose (SMBG). This device measures the BG as follows: first the patient takes a small blood sample with a finger stick using a lancet, then the blood sample is placed on a test strip and inserted into the blood glucose device to measure the patients current BG values. Another important factor for calculating the meal bolus at meal time is the current insulin on board (IOB). This means how much of the insulin injected at the previous meal is still active in the blood. If IOB is high less insulin is necessary to compensate for a meal, as the current insulin in the body can actively lower the blood glucose levels. If this is ignored it can lead to hypoglycemia as there is to much active insulin and will lower the BG values too much. Using the information of carbohydrates (CHO) contents of the meal and their current blood glucose levels and the IOB values a proper insulin bolus can be calculated to account for the meal, and bring the glucose levels to the desired safe range.

The basic insulin calculators for MDI therapy is based on the insulin-to-carbohydrate (CR) values.

$$u_{\text{insulin}}[U] = \frac{\text{CHO}[g]}{\text{CR}} \tag{2-1}$$

Here, the CR values for a specific T1DM patient is usually based on the sensitivity of the patient to insulin injected, which means that patients sensitive to insulin usually have a higher CR values compared to low insulin sensitive patients. In (2-1) the IOB and current BG levels are not taken into account.

$$u_{\text{insulin}}[U] = \frac{\text{CHO}[g]}{\text{CR}} + \frac{\text{Current BG - Target BG}}{\text{CF}} - \text{IOB} \tag{2-2}$$

In this slightly more sophisticated bolus calculator the BG and IOB levels are taken into account. Here CF is the correction factor, and is like the CR a patient specific parameter [18].

The main factor to take into account when using such an bolus calculator as (2-1) and (2-2) are the tuning of the patient specific parameters CR and CF. While there are physiological based ways to determine the CR, since the human body changes, the sensitivity to either CHO or to insulin can also vary after some time. This leads to CR values which should also change over time to account for the change in sensitivity. To create patient specific CR values

multiple approaches are available. Run-to-run algorithms, an iterative tuning method, can be implemented to adapt the CR value until it converges when a specific performance is met [19]. After every meal the BG levels are measured through SMBG, and if the BG values are too low the CR values are increased and if the BG levels are too high the CR levels are decreased. In this work the bolus calculator of the form (2-1) are used, and the CR values are specified for every meal, i.e., breakfast, lunch and dinner. Another way to implement a run-to-run method is by using case-based learning [20][21]. Where a case-base is build based on the parameters of a specific situation, in the case of a T1DM patient it can be the time of day, CHO content of a meal, the past and future activity and the IOB. Then all this information is saved as a case, and a similar case is searched based on the parameters, and the previously used CR values can be used. The run-to-run algorithm then updates the CR value if it is not satisfactory.

Other implementation of bolus-based calculators can be in the form of a model-based controller. The dynamics of the system are estimated and used to predict the blood glucose values in the future horizon. In the work of [22] low-order transfer functions are used to predict the glucose values, and an optimisation problem is formulated to minimize the glucose values with a cost function that penalizes very low glucose values highly, normal glucose levels low, and high glucose values medium. In [23] the same sort of optimisation based models are used and compared to a MPC, although with a quadratic cost function with a reference value.

These Bolus calculators all have the same focus: to keep the post prandial (after meal) glucose levels as much as possible in the euglycemic range and to prevent hypoglycemia if possible. In [24] a different approach is suggested. Here instead of focusing on minimizing every meal properly, it has a constraint on the amount of insulin injections a T1DM patient can inject. An analysis is done on after how many injections an extra injection is not necessary. This is called cardinality constrained rolling horizon control, Cardinality constrained optimization problem is shown to be a NP-hard problem, although can be simplified to be solved efficiently.

As earlier stated an essential part of MDI therapy is the dosage of basal insulin. There are some rule of thumbs for calculating the basal insulin dosage, such as that is should be 50% of the total daily insulin. Some work has been done on how to optimize these dosages as well, such as iterative learning control [25]. This shows good control, although generally this problem is hard because we cannot tune the basal and bolus insulin dosages at the same time due to thir same effect on BG levels, the iterative learning method is also implemented together with run-to-run control to achieve good control [19].

Generally for MDI therapy SMBG devices are used to measure the BG values. These provide very accurate measurements of the BG levels, although they also have multiple down sides. Firstly, they only provide a measurements when the T1DM patient wants to measure themselves, this means that in the time between measurements generally the patient has no idea about they blood glucose values, accept for the fact that the effects of being in hypo- / hyperglycemia. Secondly, the use of SMBG devices can be found cumbersome by some patients that do not like to grab the piece of equipment every time a meal with CHO is about to be consumed, as it can be quite invasive as well. The alternative to the self-measurements is the continuous glucose monitor (CGM): a device implemented on the body to read the glucose levels. There is one significant difference between the CGM and SMBG. Where the SMBG measures the blood glucose values directly from the blood, the CGM measures the interstitial glucose levels. The relations between the blood and interstitial glucose are described in [26].

Another significant aspect of the CGM is that it is more prone to sensor noise compared to the SMBG. The main advantages of the CGM are the constant updates on glucose levels and is is unnecessary to do the routine of measuring of SMBG.

Figure 2-5: Example of a Self-Measuring of blood glucose (SMBG) device to measure the blood glucose values [4]

Figure 2-6: Example of a continuous glucose monitor (CGM) applied tot the upper arm to measure blood glucose values. [5]

2-3 Models

2-3-1 Simulation

Essential for assessing the performance of different types of treatment for diabetes are models to describe the effect of both rapid-acting and long-acting insulin on the BG levels. Instead of using real patients to test the controller performances it is fast and safe to use an in-silico patient, i.e., a virtual patient that we can inject with CHO, rapid-acting and long-acting insulin. These models have evolved to more complex models to better mimic real-patient responses to insulin. The first physiological model to describe the glucose dynamics is the Bergman minimal model [27]. Which is a third-order non-linear multiple-input single-output model, with as inputs the plasma insulin concentration and the CHO consumption, and as output the BG levels in the plasma. Later, in 2002, a new model was introduced to describe the glucose kinetics, called the Hovorka model [28]. Here the complexity is increased by partitioning the distribution & transport, disposal and endogenous production of the glucose. It is a higher order model than the Bergman minimal model, and non-linear as well. The previous models were good enough to test controllers, but were not sufficient to stop the animal trials for further testing. In 2007 a new model was introduced for simulation of a T1DM patient, called the UVA/Padova simulator [29]. This simulator was accepted by the FDA for testing instead of doing animal trials. Again the complexity is increased to better simulate the response the BG levels to rapid-acting and slow-acting insulin and CHO. While the main pitfall of [29] is that blood glucose to different meals throughout the day is essentially the same, updates are from single-meal to single-day for the simulator are implemented [30].

2-3-2 Prediction

Some of the control algorithm do not need a prediction model to determine the insulin necessary to compensate a meal, such as the Run-to-run algorithm to tune the CR. Although for any optimization based controller a linear time-invariant (LTI) prediction model is a must. To create such model multiple approaches are taken. The models can be divided in three distinct different models: Low-order physiological based models and higher-order state-space models and the neural network predictor [31]. We will only discuss the first two. The low-order models generally have the following structure [32] [33].

$$\begin{aligned} Y_{bg}(s) &= G_{carb}(s)u_{carb}(s) + G_{ins}(s)u_{ins}(s) \\ G_{carb}(s) &= \frac{K_{carb}}{s(1+sT_{carb})} \\ G_{ins}(s) &= \frac{K_{ins}}{s(1+sT_{ins})} \end{aligned} \tag{2-3}$$

This gives us the parameter vector $\begin{bmatrix} K_{carb} & K_{ins} & T_{carb} & T_{ins} \end{bmatrix}$ which can be identified by a least-squares optimization problem. The model is identified by first giving a meal to a T1DM patient and injecting insulin a few hours after the meal. A benefit of the model is that the parameters have physiological meaning, but from the structure of the transfer function with the integrator it is obvious that the model needs to be reset to deal with the error. Another disadvantage is that while this model can almost perfectly describe a meal with an insulin bolus, it does not work for meals without insulin and vice versa. In [34] the models from [32] and [35], both low-order models, are compared and a new model is proposed without integrator behaviour, such that no integrator reset is necessary.

The higher-order state-space identification utilizes different methods to create prediction models. For these type of models normally at least one day of CGM measurements are used as output data, while for input data not directly the impulses of CHO and insulin boluses are given. Instead of giving the time and size of a meal and the insulin, they are transformed with physiological meaning to their respective rate of appearances. In the work of [23] these impulses are filtered with transfer functions to their rate of appearances. Then these state-space models can be identified using this input-output data. Different identification techniques are used throughout the literature. In [36] subspace identification using the n4sid and SMI routine in MATLAB is used to identify different orders of state-spaces, ranging from 3 to 6 states. Another method for identification is to use ARX and ARMAX models as in [37]. Here, second order ARX and ARMAX-based predictor are estimated. The comparison between ARX & ARMAX predictors and subspace identification based predictors is also made, while all are showing good fit for very-short term predictions, i.e., 60 minute ahead, and they get worse by increasing the horizon.

2-4 Sparsity maximisation

Obtaining impulsive like behaviour for MDI therapy can be achieved through different methods. In some work when a meal is ingested an optimization problem is formulated and solved based on minimizing the time in the unsafe regions, while only allowing the first control input

to be non-zero, to create an insulin bolus like behaviour. Another approach, as stated in [24], is by having a 24h horizon, and having a cardinalty constraint on the short-acting insulin, such that no more than a predefined number of injections can be administered.

To minimize the amount of inputs of a system, is equivalent to maximizing the sparsity of the input vector. The maximization of the sparsity can be seen as minimizing the cardinality. The minimization of the cardinality can be seen as minimizing the ℓ_0-norm of a vector. The ℓ_0-norm is defined as the number of non-zero elements in a vector. The minimization of the ℓ_0-norm of a vector is generally a NP-hard problem. This means that we can not guarantee that we can efficiently find a solution to this problem.

To deal with this relaxations are proposed to switch from the ℓ_0-norm to a ℓ_1-norm [38], Where the ℓ_1-norm is the sum of absolute values of a vector. Minimizing the ℓ_1-norm is a convex optimization problem, such that an solution can be efficiently found. Additionally, a vector of weights W is introduced with the same length of the vector of which we want to maximize the sparsity. The weight vector is initialized with all 1's. This gives us the following optimization problem.

$$\begin{aligned} \min_{u} \quad & \sum_{k=0}^{K} w_k ||u_k||_1 \\ \text{subject to} \quad & \text{constraints} \end{aligned} \tag{2-4}$$

After a solution to the minimization problem (2-4) is found, the solution can be used to re-initialise the weights, and to resolve the same optimization problem until no more further changes of the input vector. The re-weighting occurs in the following fashion

$$w_i = \frac{1}{|u_i| + \epsilon} \tag{2-5}$$

such that the weight of high inputs are lowered and vice versa. The parameter ϵ is introduced to provide stability and to make sure the divider is non-zero. The algorithm is reasonably robust to the choice of ϵ. The re-weighting can be repeated until no changes in the input vector occur anymore. It is not always necessary to re-weight the optimization problem. By the nature of the minimization of the ℓ_1-norm often immediately a sparse solution is found.

Chapter 3

Virtual Patient & Patient Models

When designing a controller for a Type 1 Diabetes melitus (T1DM) patient, a necessary component is to asses its performance. This is where the virtual (in silico) patient comes in, instead of testing the controller on real patients, a virtual patient can be simulated. The Virtual patient is a high-order non-linear model with physiological meaning to simulate the effect of insulin and meal consumption on the blood glucose levels of a T1DM patient [29]. Within the model, a lot of parameters are present, which differ from person to person, as their responses to carbohydrates (CHO) and insulin are different. Identification of the parameters are done in [39], based on measurements of insulin and glucose fluxes and concentrations. The virtual patient is implemented in MATLAB and simulink, and solved using ordinary differential equation (ODE), with a fixed step time of one minute. To simulate multiple patients, in [40] for 300 patients (100 adult, 100 adolescent and 100 children) specific parameters from a proper distribution are extracted. As the original virtual patient only contained rapid-acting insulin, long-acting insulin is incorporated in the simulator, so that patient following Multiple Daily Injections (MDI) therapy can also be simulated [41]. The virtual patient effectively contains three different systems: the glucose subsystem, the insulin subsystem and the gastro-intestinal tract. The insulin and gastro-intestinal tract respectively lower and increase the blood glucose (BG) values. As the virtual patient is a highly non-linear model, and we can not generally assume we know all the specific parameters, the linear time-invariant (LTI) variant of these models are also necessary; as well as their identification. In this chapter the different subsystem equation are introduced, as well as the identification process of their linear variant as to utilize for control.

3-1 Glucose dynamics

At the heart of the virtual patient are the glucose dynamics. These describe how the BG levels are effected by the insulin and CHO in the blood plasma. It is divided into two different utilizations of glucose: insulin dependant and insulin in-dependant. The endogenous glucose production also effects the glucose levels. The dynamics are described by the following equations.

$$\begin{aligned} \dot{G}_p(t) &= EGP(t) + RA(t) - U_{ii} - k_1 G_p(t) + k_2 G_t(t) \quad G_p(0) = G_{pb} \\ \dot{G}_t(t) &= -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t) \quad G_t(0) = G_{tb} \\ G(t) &= \frac{G_p}{V_g} \quad G(0) = G_b \end{aligned} \tag{3-1}$$

The states, $G_p(t)$ and $G_t(t)$, represent the masses of glucose in respectively the plasma and rapid equilibrating tissues in $[mg/dL]$. The blood plasma glucose concentration $G(t)$ $[mg/dL]$, is the plasma glucose divided by the distribution volume of glucose V_g $[dL/kg]$. The rate of appearance of glucose, by consumption of CHO is $RA(t)$ $[mg/kg/min]$, which is further explained in the gastro-intestinal tract section. $EGP(t)$ $[mg/kg/min]$ describes the endogenous glucose production. U_{id} and U_{ii} $[mg/kg/min]$ represent respectively the insulin-dependent and insulin-independent utilization of glucose. furthermore there are the rate parameters k_1 and k_2 $[1/min]$.

3-1-1 endogenous glucose production

Both insulin and the glucose in the blood plasma have effect on the endogenous glucose production, the equations can be written as follows

$$\begin{aligned} EGP(t) &= k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot X^L(t) \\ \dot{I}'(t) &= -k_i \cdot (I'(t) - I(t)) \quad I'(0) = I_b \\ \dot{X}^L(t) &= -k_i \cdot (X^L(t) - I'(t)) \end{aligned} \tag{3-2}$$

The first state, $EGP(t)$ $[mg/kg/min]$ represents the endogenous glucose glucose production. The second state $I'(t)$ $[pmol/l]$ is the delayed comparment for insulin action on the glucose production. $X^L(t)$ $[pmol/l]$ is the insulin action on the glucose production. $I(t)$ $[pmol/l]$ represents the plasma insulin concentration. furthermore there are four rate parameters, k_{p1} $[mg/kg/min]$, k_{p2} $[1/min]$, k_{p3} $[mg/kg/min/(pmol/l)]$ and k_i $[1/min]$.

3-1-2 glucose utilization

adipose tissue and the muscle of the body utilize the blood glucose in the blood plasma. These insulin dependant dynamics can be described as follows

$$\begin{aligned} U_{id}(t) &= \frac{[V_{m0} + V_{mx} * X(t)] G_t(t)}{K_{m0} + G_t(t)} \\ \dot{X} &= -p_{2U} * X(t) + p_{2U}[I(t) - I_b] \quad X(0) = 0 \end{aligned} \tag{3-3}$$

Where $U_{id}(t)$ $[mg/kg/min]$ is the in dependant glucose utilization and $G_t(t)$ the mass of glucose in the tissue. $X(t)$ $[pmol/l]$ represents the remote insulin, and I_b is the basal level of insulin plasma. p_{2U} is a constant, which effect the action of the insulin on the glucose utilization. Finally we have three model parameters: K_m, V_{m0} and V_{mx}.

3-1-3 Insulin dynamics

To control the glucose level of a patient, insulin is used to utilize the glucose in the blood plasma. Although after intravenous injection of insulin it does not directly effect the glucose levels, as it first needs to reach the to the blood plasma. The models to describe this insulin from injection to insulin in plasma are described by compartmental systems, and are similar for rapid and long acting insulin with small differences.

Rapid-acting insulin

Rapid acting insulin has a fast effect on the BG levels, but it also disappears fast from the body. The dynamics of only the rapid-acting insulin are described by a 4th order LTI system containing one input u_1, which is the amount of rapid-acting insulin injected using a syringe.

$$\begin{aligned}
\dot{x}_1(t) &= u_1\delta(t) - (k_d + k_{a1})x_1(t) \\
\dot{x}_2(t) &= k_d x_1(t) - k_{a2}x_2(t) \\
\dot{x}_5(t) &= k_{a1}x_1(t) + k_{a2}x_2(t) - (m_2 + m_4)x_5(t) + m_1 x_6(t) \\
\dot{x}_6(t) &= -(m_1 + m_3)x_6(t) + m_2 x_5(t)
\end{aligned} \tag{3-4}$$

x_1 $[pmol/kg]$ and x_2 $[pmol/kg]$ are respectively the amount of non-monomeric and monomeric rapid-acting insulin which is present in the subcutaneous space after injection, while x_5 $[pmol/kg]$ and x_6 $[pmol/kg]$ are respectively the total amount of rapid-acting insulin in the plasma and the liver. As can be seen there are multiple parameters, $m_{1,2,3,4}$ and $k_{d,a1,a2}$, which are rate parameters. Important to notice is that these are parameters which are different for every patient.

Slow-acting insulin

At first the UVA/Padova simulator only contained the fast acting insulin model. As for MDI also long acting insulin is used, this was incorporated in the UVA/Padova simulator [41]. Slow-acting insulin releases insulin more constant and over a longer period in the blood plasma. The slow-acting insulin follows the same logic as the rapid-acting insulin. A compartmental system, similar to (3-4) is constructed in [41], where it is implemented as addition in the UVA/Padova simulator.

$$\begin{aligned}
\dot{x}_3(t) &= -k_{sp}x_3(t) + \alpha F u_2\delta(t) \\
\dot{x}_4(t) &= -k_a x_4(t) + k_{sp}x_3(t) + (1-\alpha)F u_2\delta(t) \\
\dot{x}_7(t) &= k_a x_4(t) - (m_6 + m_8)x_7(t) + m_5 x_8(t) \\
\dot{x}_8(t) &= -(m_5 + m_7)x_8(t) + m_6 x_7(t)
\end{aligned} \tag{3-5}$$

x_3 $[pmol/kg]$ and x_4 $[pmol/kg]$ are respectively the amount of non-monomeric and monomeric slow-acting insulin which is present in the subcutaneous space, while x_7 $[pmol/kg]$ and x_8 $[pmol/kg]$ are respectively the total amount of slow-acting insulin in the plasma and the liver.

These two models of rapid-acting and slow-acting insulin together give us the dynamics of the total insulin, which is an addition of both plasma insulin values.

$$I_p(t) = \frac{x_5(t) + x_7(t)}{V_i} \tag{3-6}$$

3-1-4 Glucose rate of appearance

Depending on the amount of CHO consumed, the glucose levels in the body will rise. However, after ingestion the carbohydrates does not immediately reach the blood glucose. First the carbohydrates travel through the gastro-intestinal, the stomach, which consists of three compartment models, to a rate of appearance. To describe these dynamics from ingestion to rate of appearance (RA) of glucose in the blood plasma the following model is used [42]. Where the input, $D\delta(t)$, of the system is the amount of CHO consumed.

$$\begin{aligned}
Q_{sto}(t) =& Q_{sto1}(t) + Q_{sto2} && Q_{sto}(0) = 0 \\
\dot{Q}_{sto1}(t) =& -k_{gri}Q_{sto1}(t) + D\delta(t) && Q_{sto1}(0) = 0 \\
\dot{Q}_{sto2}(t) =& -k_{empt}(Q_{sto})Q_{sto2}(t) + k_{gri}Q_{sto1}(t) && Q_{sto2}(0) = 0 \\
\dot{Q}_{gut}(t) =& -k_{abs}Q_{gut}(t) + k_{empt}(Q_{sto})Q_{sto2}(t) && Q_{gut}(0) = 0 \\
Ra(t) =& \frac{f k_{abs} Q_{gut}(t)}{BW} && Q_{sto}(0) = 0 \\
k_{empt}(Q_{sto}) =& k_{min} + \frac{k_{max} - k_{min}}{2} \\
& (tanh(\alpha(Q_{sto} - b \cdot D)) - tanh(\beta(Q_{sto} - c \cdot d)) + 2)
\end{aligned} \tag{3-7}$$

Q_{sto1} $[mg]$ and Q_{sto2} $[mg]$ are respectively the amount of solid and liquid phase glucose in the stomach. Q_{gut} $[1/min]$ represents the glucose mass in the intestine. R_a $[mg/kg/min]$ represents the rate of appearance of glucose k_{gri} $[1/min]$ is the rate of grinding, k_{empt} $[1/min]$ is the gastric emptying rate, k_{abs} $[1/min]$ the rate of intestinal absorption, BW $[kg]$ is the body weight and finally f is the glucose fraction which appears in the plasma from the intestinal absorption.

$$\begin{aligned}
\alpha &= \frac{5}{2 \cdot (1 - b) \cdot D} \\
\beta &= \frac{5}{2 \cdot d \cdot D}
\end{aligned} \tag{3-8}$$

3-2 System identification

As the models described in the previous section of this chapter are non-linear, optimization control would become very difficult. Fortunately linear variants of these models can be constructed such that it is suitable for optimisation control. The first step to create such LTI models is to divide the system in subsystems. This gives three distinct subsystems: the insulin subsystem, the carbohydrates subsystem and the glucose subsystem. They can be interlinked the same as displayed in figure 3-1.

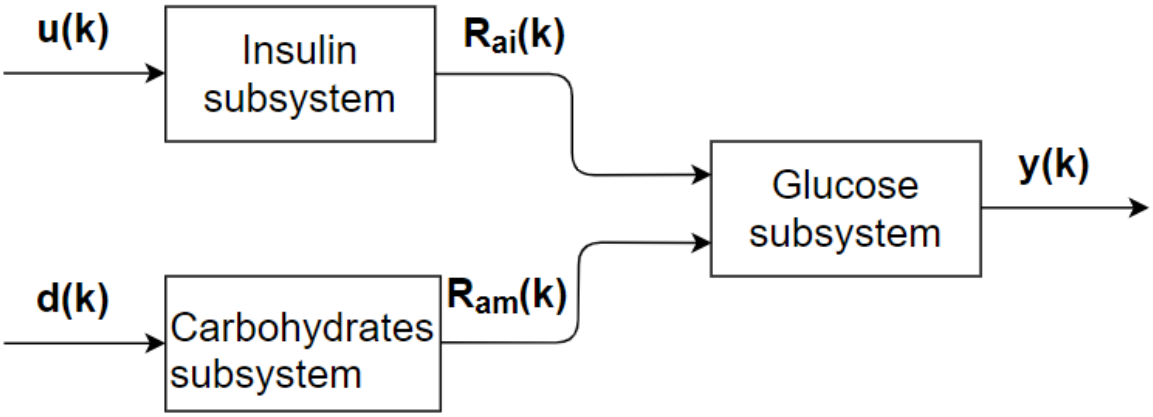

Figure 3-1: Connection of the three submodels from insulin injection and food consumption to plasma glucose levels

3-2-1 Insulin subsystem

The first subsystem is the Insulin subsystem. Notice that the equation from (3-4) and (3-5) are already LTI. In this work we assume that the parameters from this insulin subsystem are known. This assumption is made because from simulation only the identification of this subsystem is impossible and no access to a clinical environment is possible. The input to this subsystem is $u(k)[U] \in \mathbb{R}^2$ which is the long-acting insulin and the rapid-acting insulin, the output of the system is $R_{ai}(k)[mg/kg/min] \in \mathbb{R}$ representing the rate of appearance of insulin in the blood plasma.

3-2-2 Carbohydrates subsystem

In the UVA/Padova simulator, the oral glucose absorption model from [42] is implemented. It is a non-linear model which describes the dynamics from ingestion of carbohydrates to rate of appearance of glucose in the blood plasma. Parameters for the models can be obtained by parameter estimation using glucose tracers. In this work we assume the parameters for the non-linear model is available for the patient, such that we can use the non-linear model to identify a LTI variant which can describe the dynamics well. Linear models for the glucose model are more desirable, as it increases the simplicity of the optimization problem.

$$\begin{aligned} \dot{D}_1(t) &= d(t) - \frac{1}{\tau} D1 \\ \dot{D}_2(t) &= \frac{1}{\tau} D1 - \frac{1}{\tau} D2 \\ R_{am} &= \frac{1}{\tau V_g} \end{aligned} \tag{3-9}$$

This model requires 2 parameters to be estimated, namely τ and V_g. To identify these parameters we can generate input-output data from the non-linear oral glucose absorption

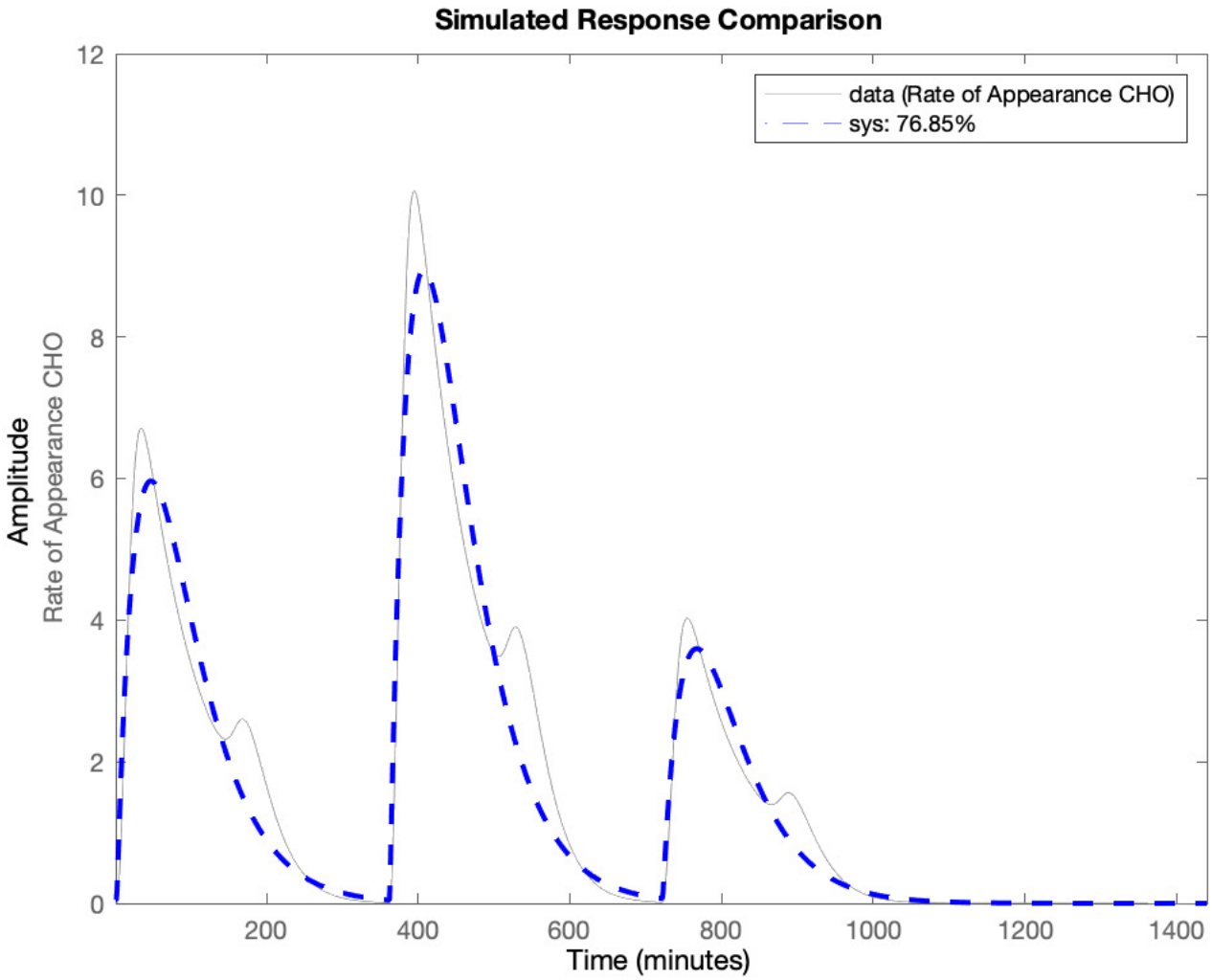

Figure 3-2: Identification of meal subsystem, the plot contains the simulated (dotted / blue) and real (solid / grey) rate of appearance of CHO $[mg/min/kg]$ values

model (3-7), and implement a grey-box parameter estimation. For this identification CHO is consumed at $Time = 0$ $[min]$, $Time = 360$ $[min]$ and $Time = 720$ $[min]$ with a respective size of 50 $[g]$, 75 $[g]$ and 30 $[g]$. As can be seen in figure 3-2 the non-linear model which is shown in grey, can be estimated relatively well by the LTI model (3-9) which is shown with the blue dotted line. With a FIT of 77% it fits the peak of glucose levels for different sizes of CHO, although the non-linearity, which is a second peak of rate of appearance, can not be accurately simulated by the model (3-9).

3-3 Glucose subsystem

The key part of simulating a T1DM individual are the glucose dynamics. We want to know how the insulin and carbohydrates effect the levels of blood glucose. Non-linear physiological models are available, such as the Bergman minimal model [27], the Hovorka model [28] and

the ones described in the previous section. For optimization purposes linear models are more desirable, and can be obtained by input-ouput data. Subspace-based model identification for prediction blood glucose using CGM measurements is done in [37], using the outputs from the insulin and carbohydrates dynamics as input of the to be identified model. We follow the same approach as done in this work except with an arx model [43], which takes on the following form :

$$\begin{aligned} A(q^{-1})G(k) = B_1(q^{-1})R_{ai}(k) \\ + B_2(q^{-1})R_{am}(k) \end{aligned} \tag{3-10}$$

Here, q^{-1} denotes the shift operator, e.g. $q^{-1}u(k) = u(k-1)$. As the insulin and glucose dynamics have the inverse effect on the glucose levels, we want to partition the inputs of the system, i.e. for the identification of the glucose dynamics the insulin injection and meal must not happen simultaneously all the time.

Glucose sub system identification

We simulate a T1DM patient for 1 day, with 1 injection of long acting insulin at the start of the day, and boluses when meals are consumed. The specific amount of long-acting insulin can be based on previous treatment. For the meals consumed we can follow a schedule consisting of breakfast, lunch and dinner, consisting of respectively $50[g]$, $75[g]$ and $30[g]$ of carbohydrates. At breakfast the insulin is injected when the meal is consumed. At lunchtime injecting 40% of the bolus 60 minutes before the consumption of the meal, and 60% after the lunch is consumed, to partitions the injection of CHO consumption and insulin injection. For the dinner the same recipe is followed except with a 30 min difference. The respective bolus for this patients are $10, 12$ and 6 units of insulin. The inputs represent the output of the two sub models: $R_{ai}(k)$ and $R_{am}(k)$. The output is the corresponding blood glucose values, with a sampling time of five minutes, as this must represent the CGM values. Using this data a 4th order A is estimated, and both B_1 and B_2 are third order, which can be represented in the following state space form.

$$\begin{aligned} x(k+1) &= \begin{bmatrix} -\alpha_1 & 1 & 0 & 0 \\ -\alpha_2 & 0 & 1 & 0 \\ -\alpha_3 & 0 & 0 & 1 \\ -\alpha_4 & 0 & 0 & 0 \end{bmatrix} x(k) + \begin{bmatrix} b_{11} \\ b_{12} \\ b_{13} \\ 0 \end{bmatrix} u(k) + \begin{bmatrix} b_{21} \\ b_{22} \\ b_{23} \\ 0 \end{bmatrix} d(k) \\ y(k) &= \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix} x(k) \end{aligned} \tag{3-11}$$

The identification is done in MATLAB as follows: We have 1 day of data from the UVA/-Padova simulator, which gives blood glucose values every minute. This output set is then reshaped such that we have a BG value every 5 minutes, i.e. 288 BG values for one day of simulation. The inputs follow the same methodology: From the linear models, which have a sampling time of one minute, we reshape to a vector of one value every 5 minutes, by only taking the input at that time exact instance, such that a $288x2$ vector with inputs is constructed. Incorporating the input and output data in MATLAB using the iddata command with a sampling time of 5, we can identify the system. With the following parameters,

$na = 4, nb = \begin{bmatrix} 3 & 3 \end{bmatrix}, nc = 0$ and $nk = \begin{bmatrix} 0 & 0 \end{bmatrix}$ with focus of identification set on prediction, which is a armax identification option in MATLAB, we use the armax command in MATLAB to estimate the 10 free parameters. Note that this creates an ARX with the chosen options. While the prediction model maximizes for the one-step ahead prediction, it yields better results than focus set on simulation, which is the other option for armax identification.

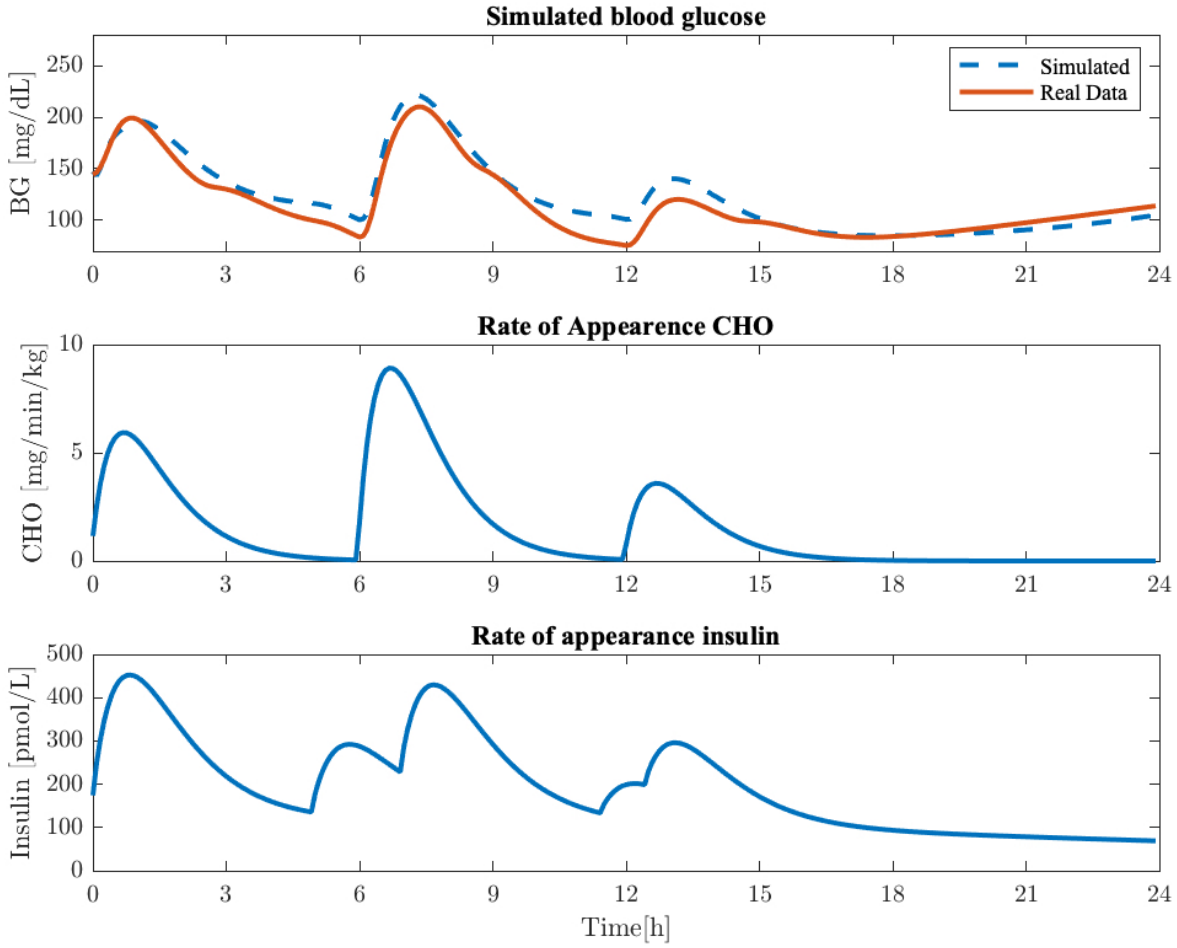

Figure 3-3: Identification of Glucose system, top plot contains the estimated (dotted) and real (solid) glucose values, the mid plot contains the rate of appearance of CHO $[mg/min/kg]$ and in the bottom plot the rate of appearance of insulin $[pmol/L]$ is plotted.

The identification of the LTI model was done for one specific patient. In figure 3-3 we can see the comparison of the data and the identified model, where in the top plot the solid orange line represents the real data straight from the UVA/Padova simulator, and the dotted blue line represent the model with the given inputs. In the middle plot we can see the rate of appearence of CHO, which is the output of equation (3-9) with the identified parameters. The bottom plot represents the rate of appearance of insulin, i.e., the output of equation (3-6) The parameters of the given patient are given in table 3-1

To see how the prediction model performs we want some validation on the model. We use the past data to determine the initial state of the system, and do a 8 hours ahead prediction with a meal and a insulin injection. We give 10.3 $[u]$ of insulin to the patient and a meal of

55 $[g]$ of CHO. The initial conditions are based on the past outputs and inputs and found using data2state command in Matlab. We also find the Variance Accounted For (VAF) for the validation data.

$$\text{VAF} = (1 - \frac{var(y - \hat{y})}{var(y)} \cdot 100\%) \tag{3-12}$$

The Variance Accounted For for this specific meal/insulin response was 98.5%

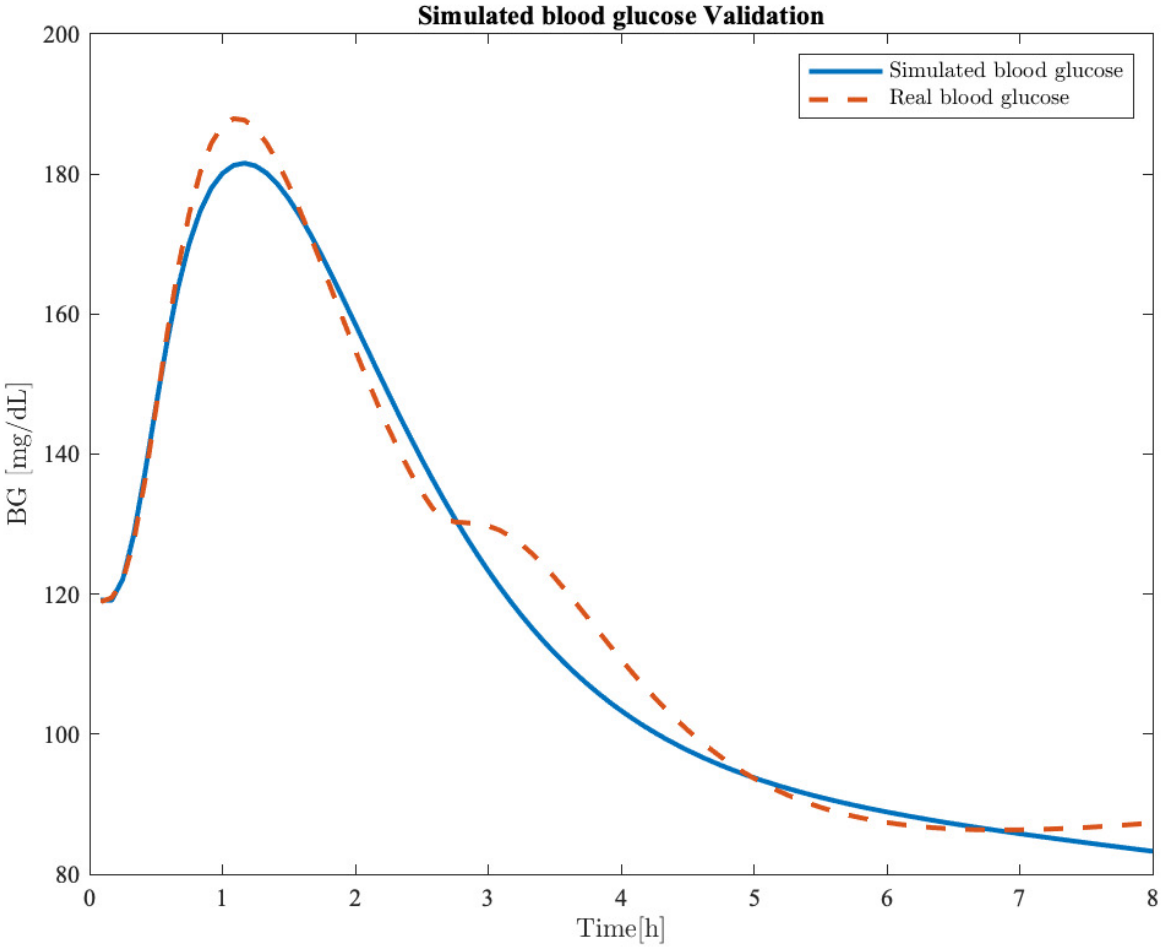

Figure 3-4: Identification of Glucose system, top plot contains the simulated (dotted) and real (solid) glucose values, the mid plot contains the rate of appearance of CHO $[mg/min/kg]$ and in the bottom plot the rate of appearance of insulin $[pmol/L]$ is plotted.

Here y is the actual data from the virtual patient, and $\hat{y}$ is the response from the ARX model.

The prediction model can, as seen in figure 3-4, find the trace of the BG levels for a meal and insulin injection fairly well. The biggest mismatch is the fact that for the prediction model the BG levels seems to drop earlier than for the virtual patient. The residuals, i.e., $y - \hat{y}$, can be found in figure 3-5, which show that the difference between the validation data and real data for the meal/insulin response is fairly low.

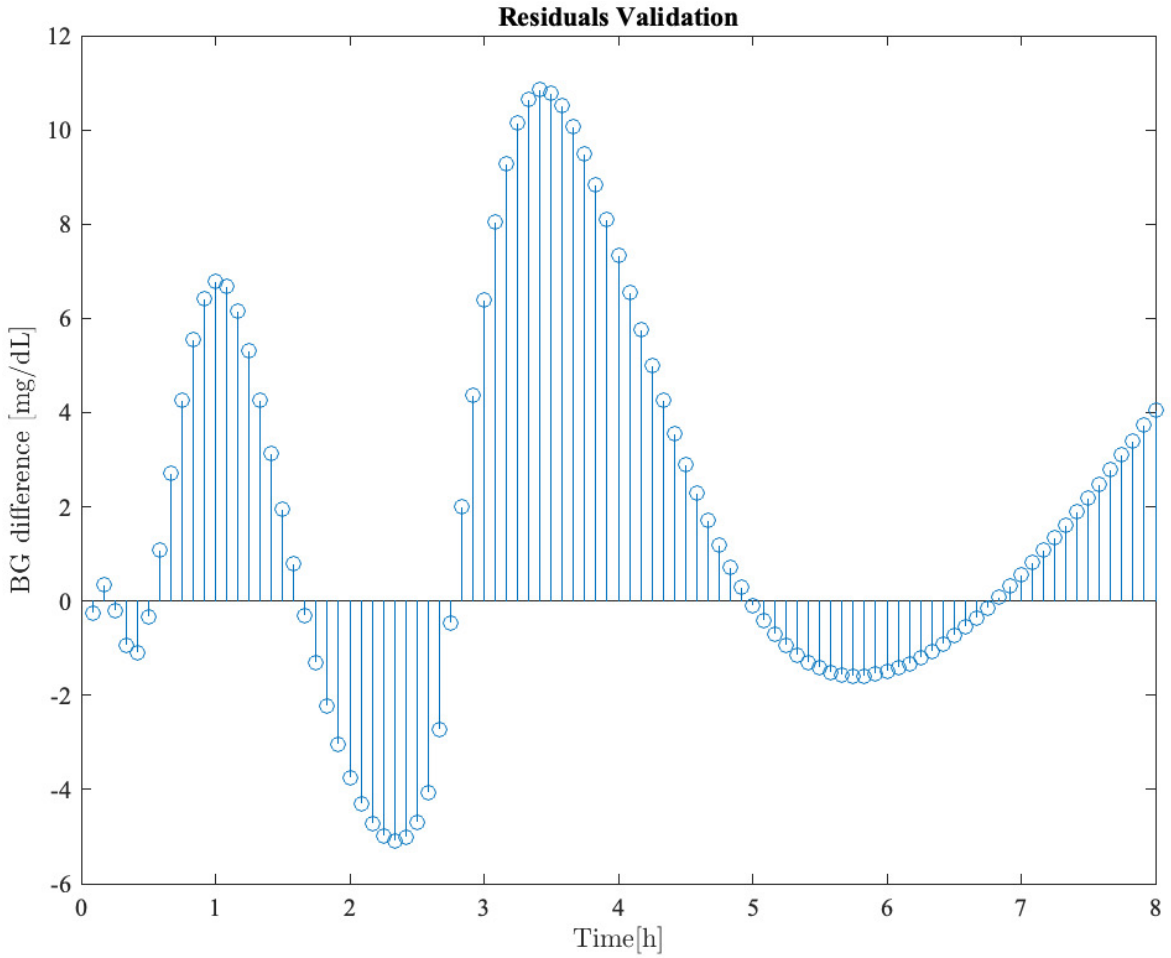

Figure 3-5: The residuals of the validation of the real blood glucose values versus the simulated blood glucose values

Unfortunately, we were not able to perform successful identification for more virtual patients than this one. Even with different sample times and detrending the data, no identified model was sufficient for a meal with the arx identification. Using other identification methods did neither yield successful results either. While the fit on the identified data works well for these models, while trying to validate these models with a longer prediction horizon one can see that these models are not useful for model predictive control (MPC). Only very short horizon prediction, i.e., one to five step ahead predictions were accurate. To better excite the system, although unphysiological, one could inject insulin when no meal is consumed, or let meals be consumed without injecting an insulin bolus.

Parameter	value	parameter	value
k_{abs}	0.036	k_{sc}	0.065
k_{max}	0.051	ka_1	0.002
k_{min}	0.011	ka_2	0.020
b	0.657	HE_b	0.6
d	0.124	I_{pb}	$Ib * Vi$
k_i	0.004	m_2	$3/5 * CL/HEb/(Vi * BW)$
k_{p2}	0.006	m_4	$2/5 * CL/(Vi * BW)$
k_{p3}	0.007	m_{30}	$2/5 * CL/(Vi * BW)$
V_g	1.830	I_{lb}	93.76
V_{mx}	0.049	$m1_{basal}$	0.1750
k_{m0}	240.5	CL_{basal}	1.0782
k_1	0.109	$m5_{basal}$	m_5
k_2	0.061	$m2_{basal}$	$3/5 * CL_{basal}/HEb/(Vi * BW)$
$p2u$	0.033	$m4_{basal}$	$2/5 * CL_{basal}/(Vi * BW)$
Vi	0.042	$m30_{basal}$	$HEb * m1_{basal}/(1 - HEb)$
m_1	0.085	F	0.8932
m_5	0.03	k	0.7412
G_b	125	k_{sp}	0.0015
EGP_b	2.953	ka	0.001
BW	59.06	f	0.90
I_b	93.76	G_{pb}	$Gb * Vg$
CL	1.162	ke_1	0.0005
k_d	0.015	ke_2	339

Table 3-1: Parameters of the identified patient

Chapter 4

Controller design

In this chapter, we will go through the design phase of the controller to maximize the sparsity of the Multiple Daily Injections (MDI) therapy. The controller uses the identified ARX model (3-11). We propose a sparsity maximization model predictive control (MPC) controller to be solved at every meal consumption to decide both if the injection of a insulin bolus is necessary to compensate for a snack aswell as deciding the amount of insulin.

4-1 Objective

First, we have to state what the main objective of the controller is. We want to find a solution with the minimal amount of insulin injections to keep the Type 1 Diabetes melitus (T1DM) patient in the euglycemic range for as long as possible. But more importantly, we want to know what are the minimal amount of injections necessary to accomplish this. To try to achieve this we propose to use the sparsity maximization as explained in the background chapter 2. Based on the convex relaxation of the ℓ_0-norm to the ℓ_1-norm we try to minimize the amount of injections to keep the blood glucose (BG) in a reasonable range for as long as possible. The objective function of the optimization problem thus looks as follows:

$$\begin{aligned} \min_{u} \quad & \sum_{k=0}^{K} w_k ||u_k||_1 \\ \text{subject to} \quad & \text{constraints} \end{aligned} \tag{4-1}$$

Where W is a vector of weights, initialized with all 1's and u is the vector of rapid-acting insulin injections.

4-2 Constraints

As can be seen in the formulation of the optimization problem 4-1, the objective function is occupied with the sparsity maximization. To achieve the desired performance of keeping

the BG levels in a safe range, we are thus required to use the constraints of the optimization problem. Within the control of the glucose values, we do not want to leave the safe regions. A logical choice for the constraints of glucose values would be an upper bound of 180 $[mg/dl]$, where hyperglycemia will occur, and a lower bound of 70$[mg/dl]$, where hypoglycemia will occur. By consuming a meal, the glucose levels will rise, and often it will rise above 180 $[mg/dl]$. By enforcing these constraints the control input should be sufficient to not let this happen. Although one has to worry about the fact that the control input can become so large that the lower bound will be violated. In this scenario the problem will become infeasible and no solution will be found. To deal with this, we propose to use dynamic constraints based on when a meal will be consumed.

Suppose a meal is consumed at the start of the control problem, we propose to relax the constraints of the upper bound of blood glucose to 280 $[mg/dl]$ for the next 180 minutes. Note that this 280 $[mg/dl]$ bound should be high enough for the specific identified models such that feasible solutions can be found. For the rest of the horizon the upper bound will be 170 $[mg/dl]$. The upper bound can also be lowered to for instance 140 $[mg/dl]$, to increase the aggressiveness of the control input.

We also want to put a constraint on the amount of insulin one could inject, u_{max}. It is important to notice that different people have different insulin sensitivity, and thus one can not generally find one maximum upper bound for a insulin injection as one can require more than double amount of insulin on the next patient. The upper bound for one injection should thus be chosen specifically for a patient. Although, with only an upper bound on the maximum amount of insulin one patient can inject, the optimization problem could decide to give multiple injections after each other. As this is an undesirable behaviour we also want to bound the amount of insulin a patient has in their blood at any time. Thus we also add a constraint on the total insulin in the blood plasma, I_p from (3-6): IOB_{max}. This would limit the amount of insulin one could subsequently inject.

In combination with the sparsity maximization we can formulate the following optimization problem, when at $k = 0$ a meal is consumed:

$$\begin{aligned}
\min_{u} \quad & \sum_{k=0}^{K} w_k ||u_k||_1 & & \\
\text{subject to} \quad & G(k) \leq 280 & k =& 0, \dots, N \\
& G(k) \leq 170 & k =& N+1, \dots, K \\
& G(k) \geq 70 & \forall& k \\
& I_p \leq IOB_{max} & \forall& k \\
& u(k) \leq u_{max} & \forall& k \\
& x(k+1) = Ax(k) + Bu(k) & \forall& k \\
& G(k) = Cx(k) & \forall& k
\end{aligned} \tag{4-2}$$

By enforcing, within the prediction horizon, that the glucose levels should be under 180$[mg/dl]$, there is no need to implement a reference value in the cost function. One would expect that because no reference cost is implemented that the controller tries to keep the blood glucose as high as possible, since less injection is necessary, Although since we have implemented the

sparsity maximization in the cost function the controller tries to find a sparse input to keep the glucose levels in the safe range for the total length of the prediction horizon. The choice of the prediction horizon should thus be larger than 180 minutes. Another important aspect in the choice of the prediction horizon in which the short acting insulin is present. The effect of the injection of short-acting insulin should be visible in the horizon to prevent over-injection of insulin. The choice of the prediction horizon should thus be larger then both the relaxation length of the upper constraint and the time after most of the insulin has disappeared. With this formulation we can calculate proper insulin boluses for a meal to keep the glucose levels in a tight range, and thus the patient does not have to worry for hypo and hyperglycemia.

4-2-1 Minimum control

In the previous section we assumed that only one meal was injected, and thus we want to keep the BG levels in a tight range after some time of injection. But suppose we have more than one meal in the future horizon, that we can know based on the habits of a T1DM patient. Now we have to find a new set of constraints as we can not just reuse the approach from the previous section.

Suppose we have a meal vector u_{meal}, where the last meal is consumed after time step K_{meal}. Then, same as in the previous section we want to make sure that after the latest meal we want to be in the euglycemic range as long as possible. To do this we we propose to use the following optimization formulation.

$$
\begin{aligned}
\min_{u} \quad & \sum_{k=0}^{K} w_k ||u_k||_1 & & \\
\text{subject to} \quad & G(k) \leq 180 & & \forall k \leq K_{Meal} \\
& G(k) \leq 280 & & K_{meal} < k \leq K_{Meal} + 36 \\
& G(k) \leq 180 & & \forall k > K_{meal} + 36 \\
& G(k) \geq 70 & & \forall k \\
& I_p \leq IOB_{max} & & \forall k \\
& u(k) \leq u_{max} & & \forall k \\
& x(k+1) = Ax(k) + Bu(k) & & \forall k \\
& G(k) = Cx(k) & & \forall k
\end{aligned}
\tag{4-3}
$$

Note that in the optimization formulation above the sampling time is 5 minutes. To show how these bounds look some bounds are shown in figure 4-1. In the upper plot the bounds can be seen for a single meal, Here $K = 8$ $[hours]$ and $N = 3$ $[hours]$. In the lower plot the bounds for a different scenario can be seen. here $K = 2$ $[hours]$, and thus the bounds for where the BG levels should be lower than 180 $[mg/dL]$ are at 5 $[hours]$. Both plots $K = 12$ $[hours]$

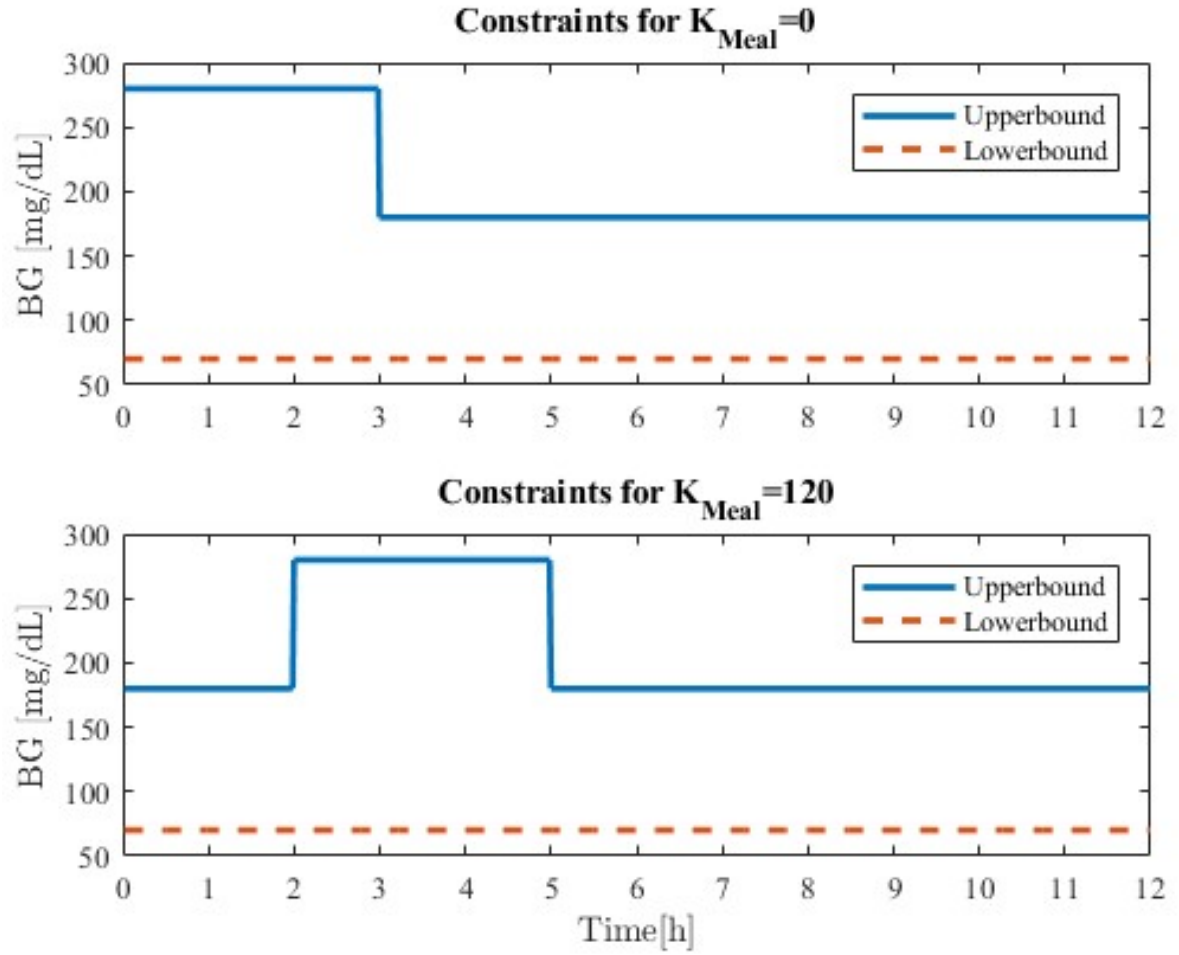

Figure 4-1: Bounds for different K_{meal} values

Finally, we have all the components to write out the algorithm for input sparsity maximization MPC for glucose control. The method is initialized at meal time with initial states determined by the past in- and outputs, using the Matlab function data2state. Furthermore, we have the next meal time K_{meal}, the bound we want to give the controller, and the carbohydrates (CHO) content to the meal to be consumed. First the weights are initialized for the input vector, as well as the constraint is set to the given bound. Then, iteratively the MPC (4-2) for a normal meal and (4-3) for a snack is solved, with the re-weighting techniques, until u_{insul} does not change anymore. This gives us either a control input at the the meal time and at the next meal time, or only at the next meal time. Note that even though an insulin injection is calculated for the next meal time, at that instance the MPC algorithm still runs. This is essential because even though we have a model for longer-prediction, we can make a more accurate prediction at that time instance itself. The optimization problem is a linear programming (LP) solved using CVX [44] [45].

Algorithm 1: Sparsity maximization

Input: X_0, K_{meal}, $Bound$, u_{meal}
Output: $u_{insulin}$
Procedure MPC with sparsity maximization
$w_i \leftarrow 1 \ \forall i$
constraint(1:$K_{meal} - 1$)$\leftarrow$ 180
constraint($K_{meal} : K_{meal} + 36$)$\leftarrow$ 280
constraint($K_{meal} + 37 : K$)$\leftarrow$ Bound
while *True* **do**
  Solve MPC (4-2) with X_0 and u_{meal}
  if $u_{insulin1}(k-1) = u_{insulin1}(k)$ **then**
    return $u_{insulin}$
    Break
  else
    $w_i \leftarrow \frac{1}{u_i + \epsilon} \ \forall i$

Chapter 5

Case Based Reasoning

Machine learning techniques to improve or design controllers are more relevant these days. By using previous outcomes for problems we can learn to solve newly encountered problems which are similair. These fit in the framework for control of a blood glucose for a Type 1 Diabetes melitus (T1DM) patient. Based on some habits of the patient we can effiently find solutions for almost the same problem, since we know what the patient is about to eat or exercise. One of these machine learning techniques is called Case-Based Reasoning (CBR) [46]. Within the framework of CBR the solution of the previous which is most similar to the newly introduced problem will be re-used, and if necessary adapted such that it can be applied. This can give flexibility to adapt the controller to adjust accordingly to a situation which is has not encountered before. Run-to-run control is a method of tuning a controller by iteratively adjusting the solution based on previous performance. It is implemented in multiple insulin bolus caluclators to adjust the insulin size of injection. In this chapter the framework and usage of a CBR is explained and implemented. As well as the implementation of run-to-run control within this framework to adjust controllers accordingly.

5-1 CBR framework

Given a new problem, in the case of a T1DM patient, a new meal, we want to use the previous insulin injection used for a similar situation to be applied. To do this a four step framework is constructed for CBR. The four steps of CBR are as follows :

1. **Retrieve** similar cases to the new case
2. **Reuse** the solution of similar case to solve the new case
3. **Revise** solution to the new case by using the results
4. **Retain** information or solution of the new case if satisfactory and useful for new cases

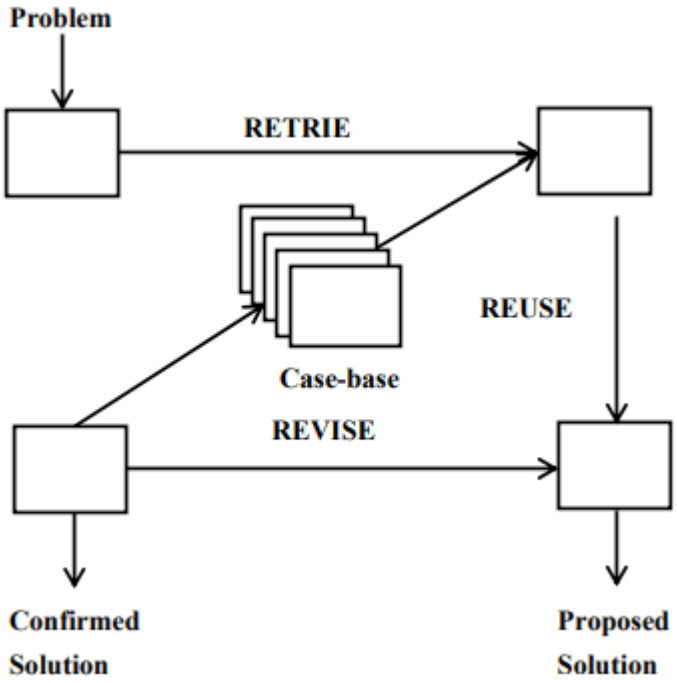

Figure 5-1: Cycle of case-based reasoning [6]

By using these four steps we can go from a new case to the solution, and save the information of the solution if it is satisfactory. Thus by solving more problems, the case-base will grow in size, and for every new accounted problem more similar cases are available and the one would expect the performance to increase. In the framework of CBR we define a case as triplet similar to [20].

$$\mathbf{C} := \{\mathbf{P}, \mathbf{S}, \mathbf{O}\} \tag{5-1}$$

In this triplet $\mathbf{C}$ is defined as the set of parameters which define the case, such that we can find similar cases to it. $\mathbf{S}$ is a solution, i.e., what type of action was taken for this case. finally we have $\mathbf{O}$, which represent the outcome of the case. If a case is retained it will be store in the case base, which is a set of all the retained cases. A case base with k is represented in the following manner

$$\mathbf{CB} := \{\mathbf{C}1, \mathbf{C}_2, ..., \mathbf{C}_k\} \tag{5-2}$$

5-1-1 Retrieve

To retrieve cases from a case-base we first have to define the parameters that define the new problem. In the work of [47] the parameters used to define a case were found by looking at the existing bolus calculators and checked the parameters used in them. We propose to use the following parameters to determine a case: carbohydrates (CHO) to be ingested, Current

blood glucose (BG) levels, insulin on board (IOB), the meal sort (lunch, breakfast, dinner), and the future exercise. Such that we have the following set of parameters

$$\mathbf{P} := \{\text{BG}, \text{CHO}, \text{IOB}, \text{Exercise}, \text{Meal}\} \tag{5-3}$$

Here, the IOB is defined as follows:

$$\text{IOB} = u_{insulin} * e^{\frac{-(t-t_k)}{\tau}} \tag{5-4}$$

For the value τ, which is the time till the insulin has no effect anymore, is set to 5. The current time is tand t_k is the time when the insulin is injected. Note that t has to be bigger than t_k

The exercise of the patient is not something we can quantify easily, So we divide the exercise up into: no exercise, low, moderate and high intensity. Note that we cannot simulate the effect of exercise in the our current virtual patient as described in chapter 3. To deal with this later we can for instance use small amounts of insulin to 'mimic' exercise.

The meal sort is the type of meal that is consumed. This is done because it is known that trough out the day the dynamics of the T1DM patient change a bit, while the prediction model does not take that into account. through this way we can adjust for the meals. In these work we assume that there are four different types of meals. The meals are sorted in breakfast, lunch, dinner and snacks, such that we have Meal := {Breakfast, Lunch, Dinner, Snack}.

Next we need to define the solution of S of the case base. The solution should be able to be re-used by the next control problem, so the option to choose the insulin injected as solution is not really feasible. Also, since the model predictive control (MPC) problem (4-2) does not have a reference in the cost function, this option is also not available. Instead we propose to adapt the MPC formulation a bit, we define a constraint in the optimization problem. This constraint is an upper bound to the BG values after 180 minutes of CHO ingestion and later.

$$\begin{aligned}
\min_{u} \quad & \sum_{k=0}^{K} w_k u_k & & \\
\text{subject to} \quad & G(k) \leq 280 & & k = 0, \ldots, N \\
& G(k) \leq Bound & & k = N+1, \ldots, K \\
& G(k) \geq 70 & & \forall k \\
& I_p \leq IOB_{max} & & \forall k \\
& u(k) \leq u_{max} & & \forall k \\
& x(k+1) = Ax(k) + Bu(k) & & \forall k \\
& G(k) = Cx(k) & & \forall k
\end{aligned} \tag{5-5}$$

and then finally we have the solution of the case base which is defined as:

$$S := \{\text{Bound}\} \tag{5-6}$$

Then finally we have to define the outcome O of the case. The outcome of the case is necessary to revise the solution of the case. In this work we have the T1DM patient equipped with the continuous glucose monitor (CGM), such that we have measurements of the BG levels over a period after an insulin injection. Thus we propose to use the maximum and minimum BG values between the consumed meal and the next meal as outcomes of the case.

$$O := \{\text{BG}_{max}, \text{BG}_{min}\} \tag{5-7}$$

To retrieve an old case we have to find which matches the parameters of the new case. The strategy to find a new case in this work will be a 1-nearest neighbour where only cases with a similar meal sort can be chosen, i.e., for breakfast only cases which are breakfast can be retrieved from the case base. The 1-nearest neighbour is perhaps most simple algorithm to find the most similar case and is based on the finding the minimum distance from the new case to the existing cases. The case from the case base with the smallest distance is chosen to be used as the solution. The distance is defined as follows:

$$Distance = \frac{|\sum_{k=1}^{4} Cb_k - Cn_k|}{K} \tag{5-8}$$

Here, C_B is the case from the case base, and Cn is the new case, the index K refers to the k'th entry of the case, i.e., for $k = 1$ refers to the BG, $k = 2$ to the CHO ,$k = 3$ to the IOB and $k = 4$ to the exercise.

5-1-2 Reuse

The reusing step is relatively simple, after we have found the most similar case, we can reuse the solution found. To use the previous solution we use the bound, which is the solution the found case, as input for the MPC (4-2). Then we let the MPC solve the new problem and use the insulin it suggest as input for the T1DM patient to self-inject.

5-1-3 Revise

After the insulin is injected, and the outcome has been found we have the ability to revise our solution. It is unnecessary to revise the solution if the solution was already found to be satisfactory, Thus we have to define when a solution is not found satisfactory. We certainly find the solution to be satisfactory if the postprandial BG levels stays within the euglycemic range

$$\text{BG}_{Max} < 180[mg/dl] \;\; \& \;\; BG_{min} > 70[mg/dl] \tag{5-9}$$

If this condition is satisfied, there is no need to revise the solution of the case. However, most of the time the the postprandial BG levels do not stay within the euglycimic range, but can still give the maximum acceptable control. We propose to only revise the solution based on the lower bound of the outcome BG_{min}. The main reason for only revising the solution based on the lower bound is because the hypoglycemia is something we want to avoid in all

possible cases. If insulin bolus is shown to reach the lower bound of the euglycimic range, any larger insulin bolus would most likely cause the the T1DM patients BG levels to reach hypoglycemia.

Run-to-Run Control

To revise the controllers bounds appropriately we propose to use run-to-run control. Run-to-run control for a MPC to tune the weights has been done before in [48] [49]. This method of control is mainly used for repetitive processes. The main idea behind run-to-run control is that based on the performance of the controller, its parameters are adjusted every iteration, if the control was not satisfactory to obtain tighter and better control overall. It fits in the framework of the MPC controller because the controller is not tuned at all, but just bounds are giving to achieve acceptable control. By using the run-to-run algorithm to revise the bounds of the MPC we expect to minimize the time in the hyperglycemic range and reject time in hypoglycemia.

We propose a Run-to-run update scheme based on BG_{min} of the outcome. For safety reasons we do not want to maximize the control input such that it reaches the lower bound of the euglycemic range, but instead we propose that the run-to-run algorithm increases the MPC's aggressiveness until the lower bound of the BG_{min} reaches 85 $[mg/dL]$. The following update scheme is used to lower the bounds to increase the aggressiveness

$$\text{Bound} = \text{Bound} - \alpha(\text{BG}_{min} - 85) \tag{5-10}$$

Here, Bound is the constraint of the MPC after 180 minutes and α is a parameter to determine the aggressiveness of the update on a bound, note that α has to be positive to lower the Bound. In case the miss-match of the controller and the prediction model is too big, it can happen that even though a lower bound is given in the MPC formulation, the lower bound is exceeded. To deal with this we could appropriately increase the lower bound with the run-to-run control. Although this would possibly work this can also result in the optimization problem becoming infeasible, instead we propose another method. We propose to also use the upper bound constraint after 180 minutes, since in the MPC the input is minimized we could achieve the same by increasing the bounds. If BG_{min} is lower than 80 we follow the updating scheme:

$$\text{Bound} = \text{Bound} - \alpha(\text{BG}_{min} - 80) \tag{5-11}$$

This is a very basic method of adapting the bounds of the control problem. Importantly is to know if the revising makes any sense. An example could be that BG_{min} is for instance 120 $[mg/dL]$, because a snack is consumed after the meal. So to revise the control problem we want to make sure that if after that meal no snack is consumed still no hypoglycemia will occur. We propose only to revise the control problem if the length of BG levels is long enough that the entire bolus effect is seen without an extra bolus, in this work we assume 240 minutes without another meal is sufficient. We only do the revising of the control problems for single meals.

5-1-4 Retain

The last phase of case based reasoning is to retain the solution. There are multiple possible approaches to this retain phase. We could for instance specify a distance in which the previous solution taken from the case base is deleted, and the new case, if satisfactory, can be implemented in the case base. This way the case base will not become too large overtime, although this will result in a loss of information for the cases deleted, as well as gives us a too be determined distance at which we will retain and reject cases. Another approach is to keep appending the case base with the newly introduced cases. This way the case base will grow and we can expect the performance to increase, although perhaps marginally. As stated in [47] this can be seen as growing the complexity of finding the distance, although the routine to find the distance is not that computationally heavy, as it is a 1-nearest neighbour algorithm. As within the T1DM patient there is inter-patient variability the most logical option is to retain the new cases, and to delete them from the case base after a certain time, for instance 6 months. As in this work for the virtual patient, we do not take inter-patient variability into account, and simulation duration wont be excessively long we retain do not consider this scenario.

Algorithm 2: Sparsity maximization with case-based reasoning

Input: $u_{meal}, BG, IOB, Exercise, Meal, Threshold$
Procedure Case-Based reasoning
P $\leftarrow \{BG, CHO, IOB, Exercise, Meal\}$
for *every Case* **do**
  Distance(i) = $\frac{|\sum_{k=1}^{4} Cb_k - Cn_k|}{K}$
for *min(Distance)* **do**
  Bound = Solution of case found
Run **algorithm 1**
if $BG_{max} > 180 \& BG_{min} > 85$ **then**
  $\underline{B}ound = Bound$ - $\alpha(BG_{min} - 85)$
if $BG_{min} < 70$ **then**
  $\underline{B}ound = Bound$ - $\alpha(BG_{min} - 80)$
Solution = Bound
if *Distance(New Case - Old case) < threshold* **then**
  Remove Old case
  Add new case to case Base

Chapter 6

Simulation & Results

For simulation purposes a single T1DM patient was used, the parameters of the patient are given in table 3-1. Based on a individually identified model, as specified in the models section, such that we have the linear models for prediction. For accurate simulation, The virtual patient, as described in the chapter 3 is used to simulate the in-silico Type 1 Diabetes melitus (T1DM) patient. The models are implemented in MATLAB and simulink [50], and are solved using runge-kutta 4 with a time step of 1 minute. To assess the performance of the controller different scenarios are simulated. For the scenarios the long-acting insulin consists of 29[U] injected at 7AM. The choice of long-acting insulin comes from [19].

6-1 Case-based reasoning

The case-based reasoning framework as introduced in chapter 5 is implemented in Simulink and Matlab. We want to see if the case-based reasoning framework improves the performance of the controller by adjusting the bounds accordingly to receive tighter control, just for a typical day with three meals. First, we need to initialize the case-base with some basic cases. We propose to use a not too tight bound such that the Case-Based Reasoning (CBR) can tighten the bounds of the optimization problem, without having to much risk of hyperglycemic events. The parameter α also has to be determined, to be safe we chose a low value for α, here we chose $\alpha = 0.1$.

6-1-1 Testing Scenario

The testing scenario is as follow: For the normal meals, i.e., the breakfast, lunch and dinner we keep the meal time fixed at 7AM, 1PM and 7PM respectively.

The amount of carbohydrates (CHO) consumed also has to have some variation in it. For breakfast let the virtual patient consume a meal which follows a normal distribution with a mean of 50 g of CHO a standard deviation of 5 [g]. Both for lunch and dinner the CHO content

of the meal will be a normal distribution with a mean of 75 $[g]$ and a standard deviation of 8 $[g]$.

In figure 6-1 we can see the results of a typical day after one week of tuning the controller. In figure 6-2 the controller after 15 weeks of tuning with the run-to-run control is depicted. The maximum glucose value for the first week is 223 while at the end of the tuning it is 200. At the beginning of the tuning the bounds are 150 while at the end the respective bounds for breakfast, lunch and dinner are 118, 120 and 117. In the first week the time spend in hyperglycemia is 250 minutes per day, while at the end time spend in hyperglycemia is reduced to just 143 minutes per day. In both cases no hypoglycemic events occurs.

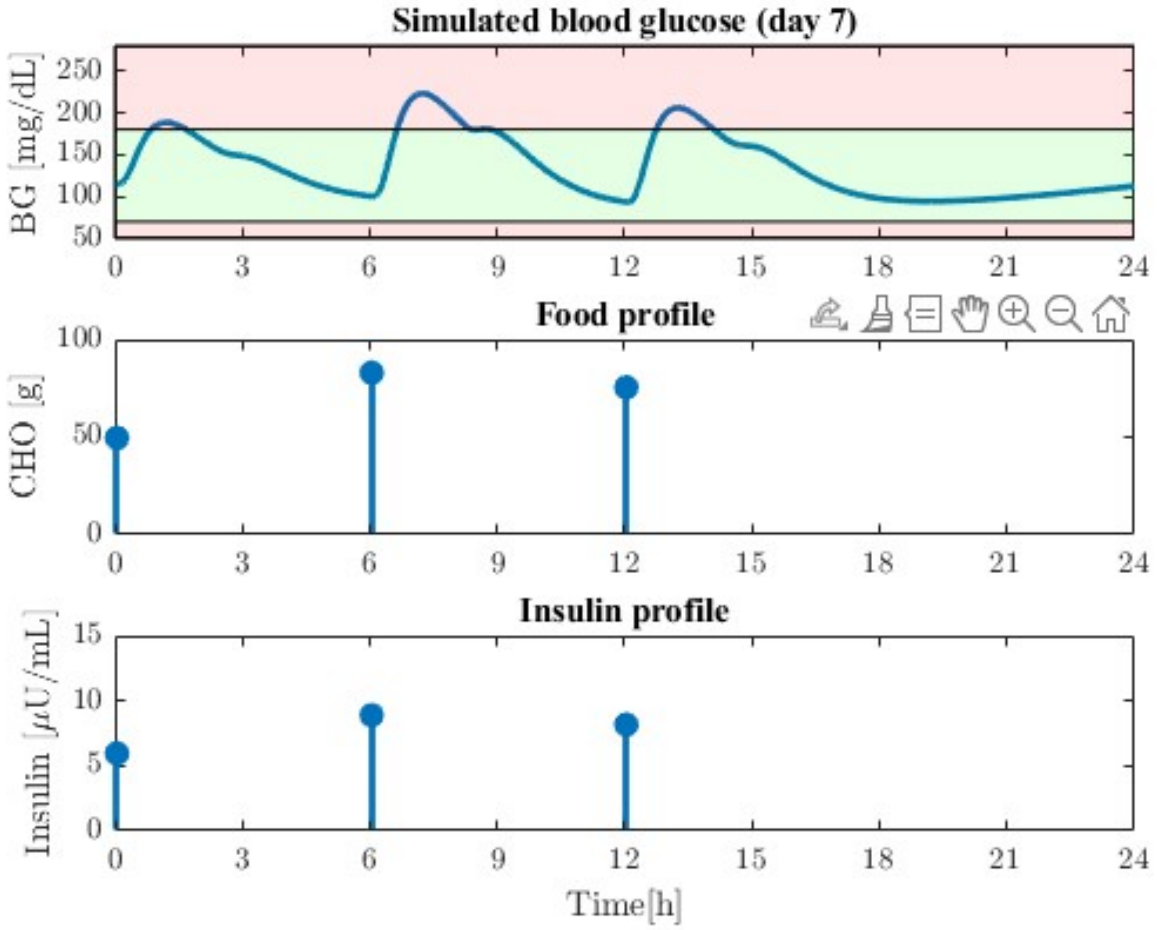

Figure 6-1: Day 7 of tuning the controller: the upper plot constraint the blood glucose values, the middle plot contains the amount of CHO consumed and the lower plot shows the insulin injected.

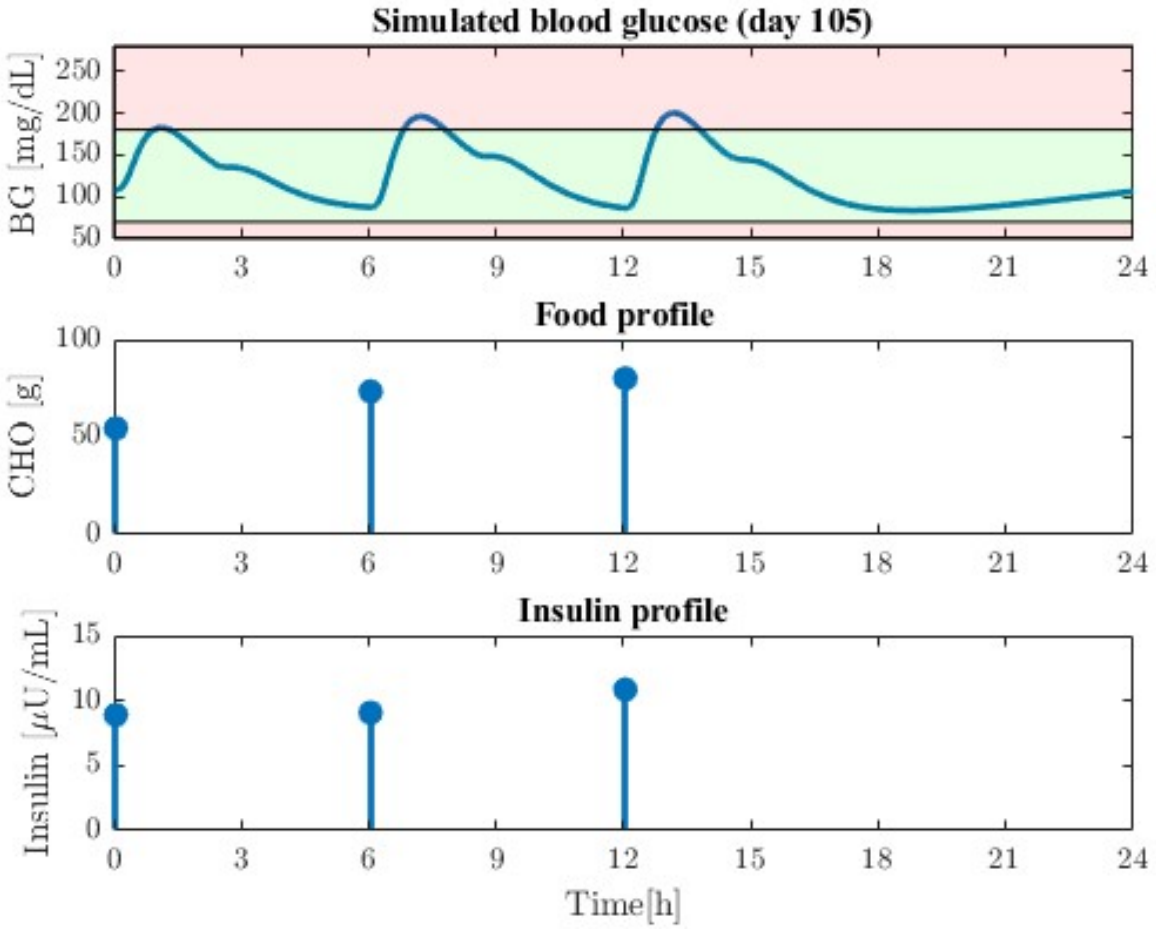

Figure 6-2: Day 105 of tuning the controller: the upper plot constraint the blood glucose values, the middle plot contains the amount of CHO consumed and the lower plot shows the insulin injected

6-1-2 Exercise implementation

To test how the case-based reasoning deals with exercise, we propose to add exercise in 4 different stages. We have three different amounts of exercise {none, small, moderate, and large}. To simulate these scenarios we implemented exercise as a small unit of insulin 120 minutes after consumption of the meal. No exercise corresponds to 0 units of insulin, small to 1 unit of insulin, moderate to 2 units of insulin and large as 3 units of insulin. The rest of the scenario is the same as described above for the meal sizes and timing.

In figure 6-3 a day at the end of the tuning process is seen where the red stem at the insulin plot corresponds to the insulin to mimic exercise. The bounds for the the cases with large exercise are at around 140 $[mg/dL]$, than for moderate 136 $[mg/dL]$ and low 128 $[mg/dL]$. While the normal cases still have the same bounds as previous. This show that the CBR can deal with cases where for example exercise is taken into account. Importantly, here the extra insulin injected for exercise is not taken into account for the model predictive control (MPC), hence the lower bounds for the optimization problem.

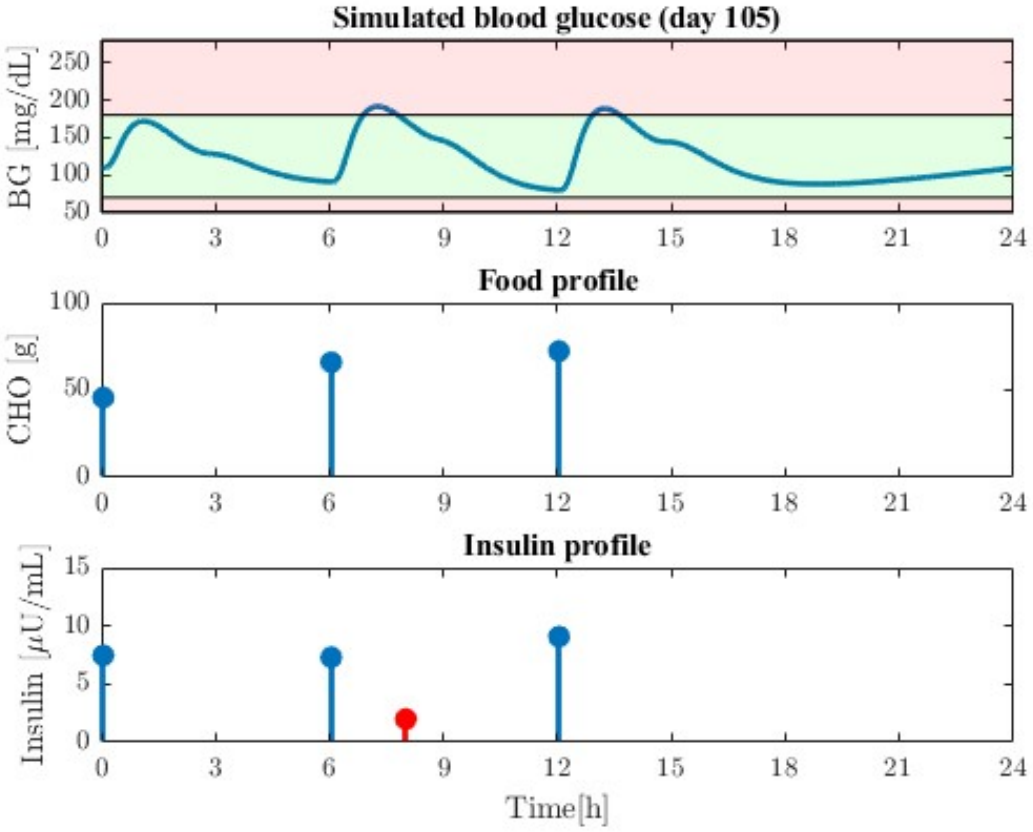

Figure 6-3: Day 105 of tuning the controller with exercise: the upper plot constraint the blood glucose values, the middle plot contains the amount of CHO consumed and the lower plot shows the insulin injected. In red the extra insulin to mimic exercise is shown.

6-2 Sparsity maximization

Now, in the previous section it was more logical that only one injection of insulin was sufficient for controlling the blood glucose levels as only one meal was consumed in the prediction horizon. Now to test if the sparsity maximization can deal with multiple meals we create a few testing scenarios where we want to see if with a minimal amount of injections a certain performance can be achieved. One can interpret these specific situations as a case in the case-base.

6-2-1 Scenario 1

The first scenario is a sequence where a few small meals are consumed in a relative small time span. Suppose at breakfast a small meal with 20 $[g]$ CHO is consumed at 7 AM, at 9AM another small meal of 10 $[g]$ CHO is consumed and finally at 10AM 30 $[g]$ CHO is consumed. The optimization problem is solved using (4-3).

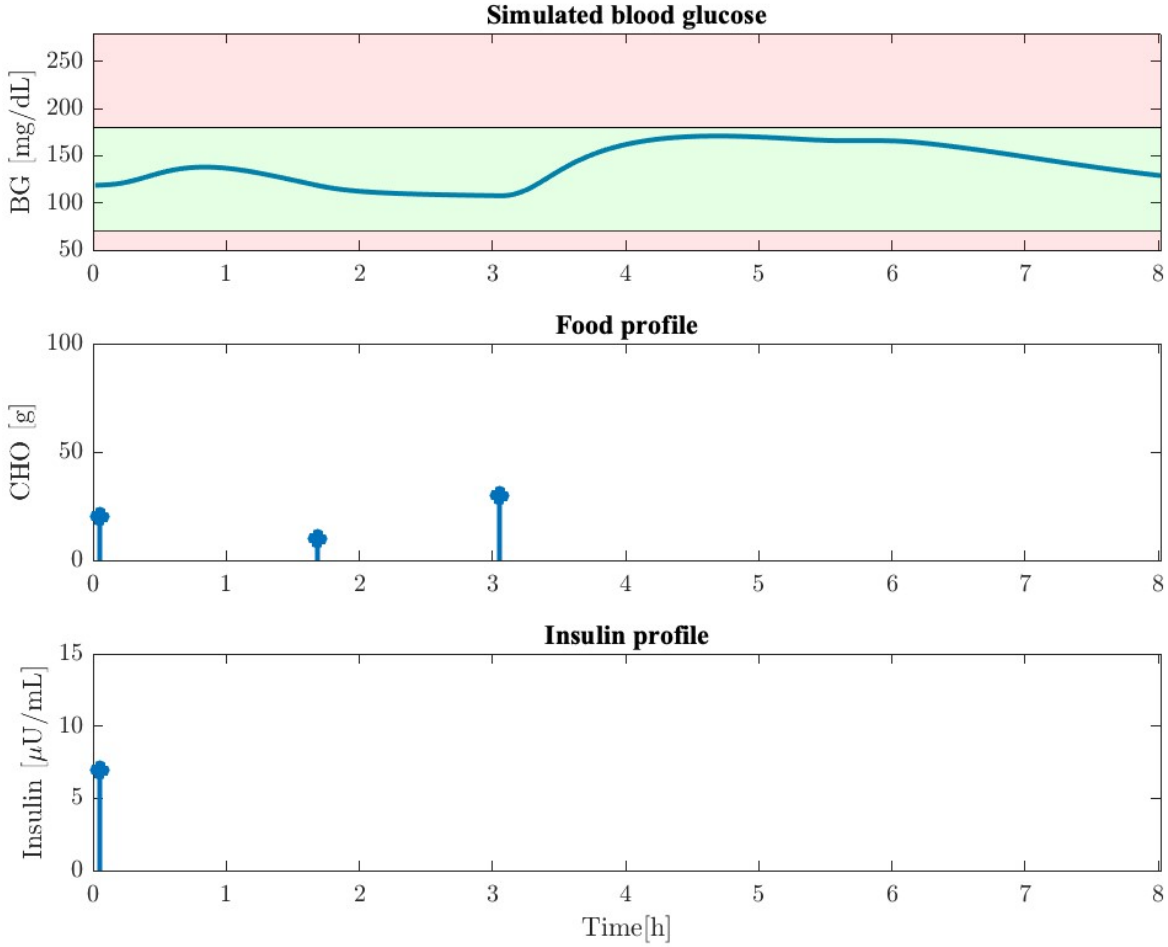

Figure 6-4: Scenario 1: the upper plot constraint the blood glucose values, the middle plot contains the amount of CHO consumed and the lower plot shows the insulin injected

As can be seen in figure 6-4, the optimization finds a single insulin injection at the first meal consumption to keep the glucose levels in the euglycemic bounds.

6-2-2 Scenario 2

The second scenario is a sequence of 2 meals, at the beginning a small meal is consumed of 13 $[g]$ of CHO, while at 2 hours and 20 minutes a bigger meal of 40 $[g]$ of CHO is consumed. The optimization problem is solved using (4-3), where the bound of glucose of 180 minutes after the last consumption is manually tuned to be 120 $[mg/dL]$.

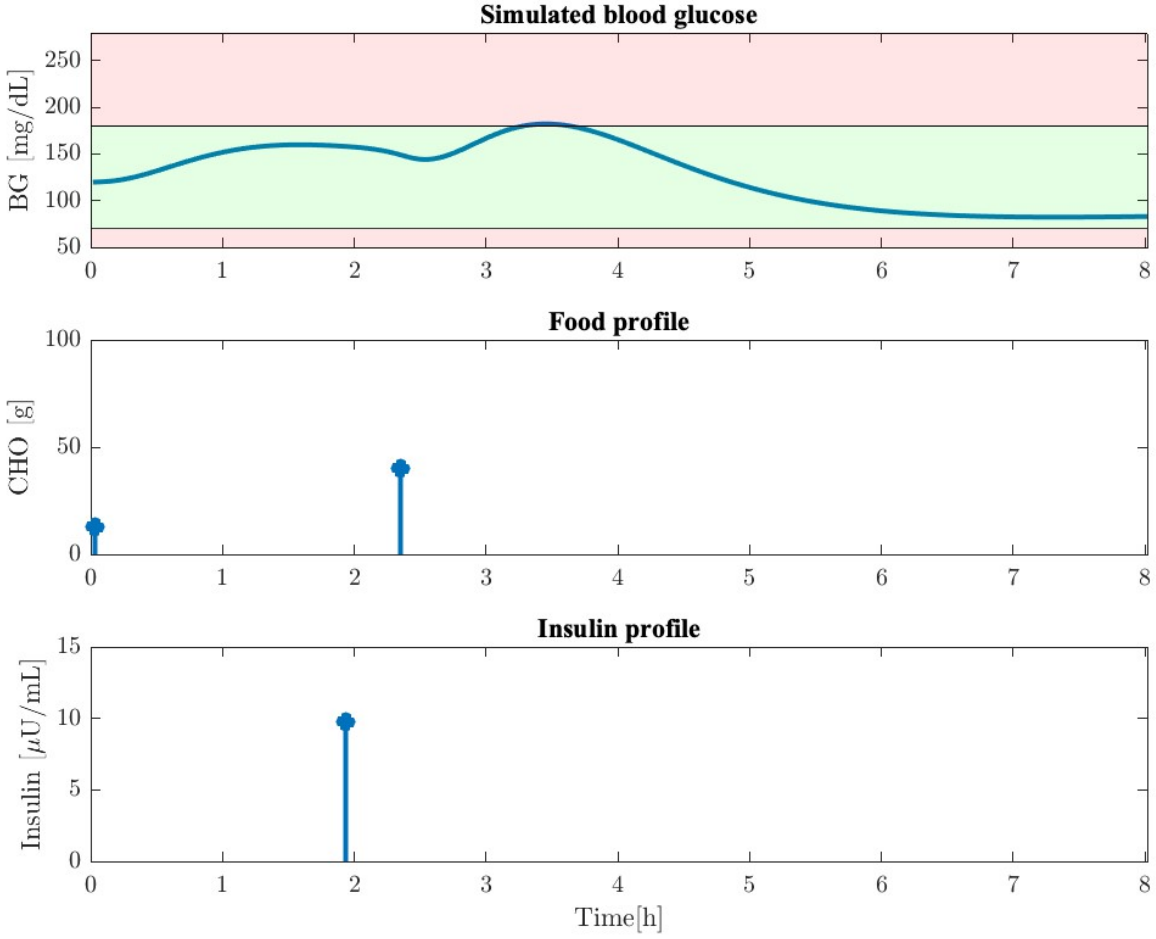

Figure 6-5: Scenario 2: the upper plot constraint the blood glucose values, the middle plot contains the amount of CHO consumed and the lower plot shows the insulin injected

In figure 6-5 the results can be seen. Only one injections just before 2 hours is found to keep the blood glucose in a safe range. If the insulin would be injected immediately the blood glucose levels would drop too low, and thus it is decided that a insulin bolus later is better.

6-2-3 Scenario 3

The third scenario is a sequence of 3 meals, at the beginning a meal is consumed of 30 $[g]$ of CHO, while at 2 hours a smaller meal of 15 $[g]$ of CHO is consumed, and finally at 3 hours a final meal of 30 $[g]$ CHO is consumed. In this scenario we bound the maximum insulin at 8 $[u]$ of insulin as no really big meal is consumed.

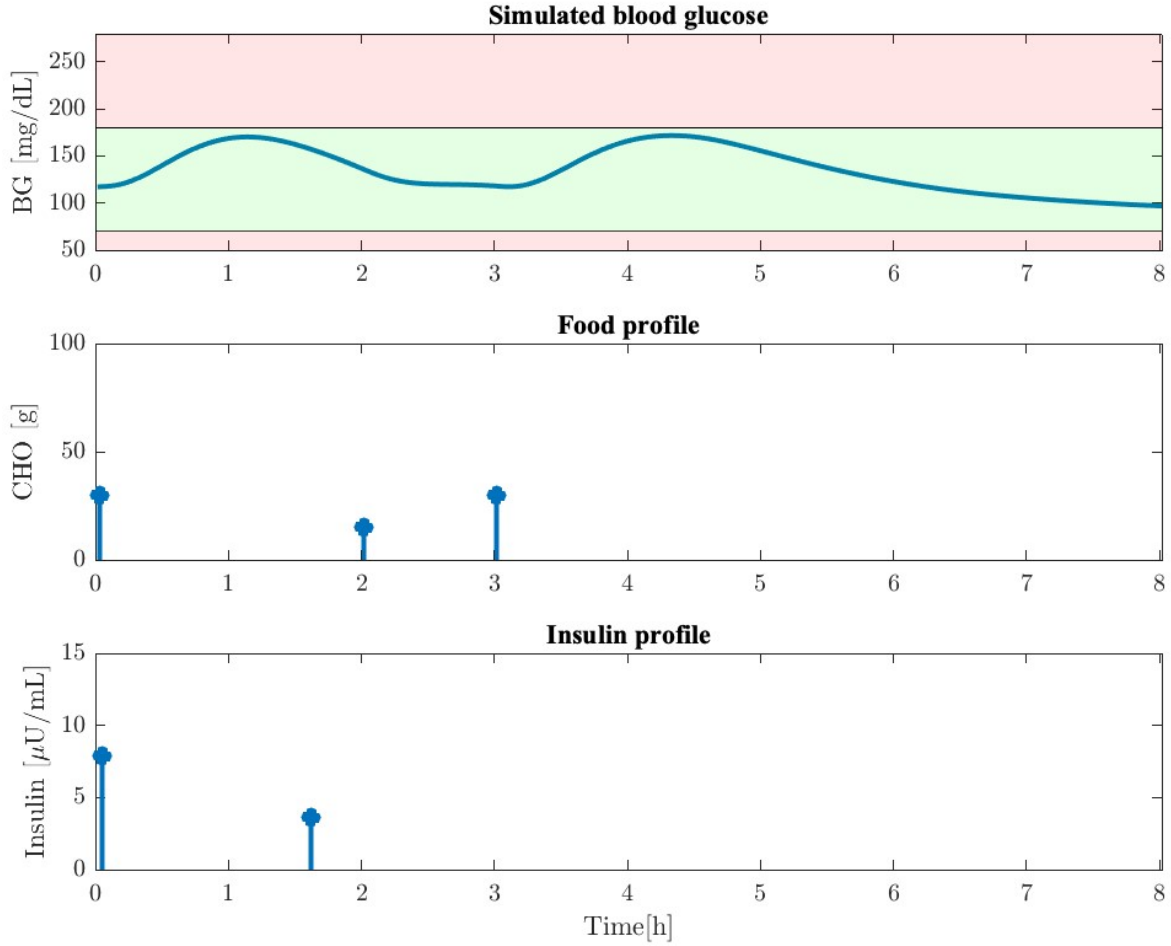

Figure 6-6: Scenario 3: the upper plot constraint the blood glucose values, the middle plot contains the amount of CHO consumed and the lower plot shows the insulin injected

Figure 6-6 shows the results of the third scenario. Here, two injections of insulin are necessary. Because the first insulin injection is not enough for the whole situation, another insulin injection around 2 hours is necessary to keep the blood glucose in safe range for the rest of the scenario.

6-3 Discussion

Case-Based reasoning and the designed controller for single meals are used to determine the proper insulin bolus after the consumption of a single consumption of CHO. As seen in the simulation the controller can be tuned interactively using run-to-run control to achieve good glycemic control. The time in the hyperglycemic range is decreased significantly from approximately 200 minutes to 100 minutes. Hypoglycemia is avoided thus we can conclude that the tuning of the MPC is conservative enough to not create too big insulin boluses.

When exercise is added, more cases are build within the CBR framework. If the controller is initialized at with safe bound, the bounds are lowered enough too lower the amount of time spent in hyperglycemia, while also avoiding the hypoglycemic events.

The sparsity maximization approach for multiple different scenarios was tested. It can be seen that the algorithm converges towards a minimal amount of injections necessary to keep the blood glucose levels in a safe range. Interesting behaviour is that the algorithm always tries to maximize the first controller input, such that lower insulin injections are necessary later in the prediction horizon. This can be explained by the fact that we use a identified model, where it is always cheaper for the cost function to inject insulin earlier than later. Although if the lower bounds are about to be violated by a insulin injection the algorithm converges towards a insulin bolus later in the horizon. Because of the way the algorithm is designed and the re-weighting, the algorithm always maximizes the input for that specific weight, and as one can see in 6-6 the first input thus becomes maximum, while the second if relatively low. So if the sparsity can not be maximized to a single insulin input, one can expect some to become their maximum allowable value without restricting the bounds.

Chapter 7

Conclusion and future work

7-1 Conclusion

We can conclude that sparsity maximization is another method to deal with calculation of insulin boluses for Multiple Daily Injections (MDI) therapy of Type 1 Diabetes melitus (T1DM) patients. The identified ARX model based on input-output data was sufficient for a model predictive control (MPC) of a single meal. Although we can also conclude that the identified model is the main bottleneck for better performance of the sparsity maximization algorithm for multiple meals.

Using case based reasoning in combination with run-to-run control is a possible way to further enhance the controllers performance, although the main reason this is necessary is because the models are not accurately enough over a longer time. A benefit of using such a case based reasoning framework is that overtime more cases are built and also the inter-patient variability could be dealt with relatively easily. However, if better methods for identification of the personalized models are possible one could always re-identify a new model.

Taking into account the assumptions made, such as that the T1DM patient was injected with the precise amount of insulin from the controller, that the CGM measurements are equivalent to the blood glucose (BG) plasma values, and that certain parameters could be assumed known, the implementation of a sparsity maximization controller is still not too realistic, but is certainly interesting to research further.

7-2 Future work

An interesting research direction to reject small meal sizes without losing the performance is to formulate the optimization problem in another way. Instead of trying to minimize the injections throughout the day at every meal instance, one could formulate a MPC in the following manner: without allowing injections what is the maximum amount of carbohydrates

one could consume without worrying of reaching hypoglycemia and will not result in a significant worse performance for the meal after it, i.e., if the postprandial glucose is too high. Within this framework one could do the optimization offline, for instance by using explicit MPC such that a T1DM patient at every time instance has the necessary information to decide how much carbohydrates (CHO) can be consumed without having to fear of hypoglycemia. Also, in this work we did not give the controller the possibility inject a meal as a control input, which could be implemented to give the controller more freedom.

In this work we use run-to-run control in a Case-Based Reasoning (CBR) framework to actively adapt the bounds to increase the performance of our controller, but only for the single meals. For this control problem the bounds are reasonable intuitive, for multiple meals the constraints for the optimization problem are less intuitive. Future research could go towards finding more intuitive and meaningful bounds for this optimization problem in general. Also, the tuning of the these bounds is not considered in this work, but it would be interesting how we can use the CGM BG values from the T1DM patient to actively adapt the bounds such that better control realised.

Further research towards better models for the glucose dynamics is always helpful. While in this work we try to keep the identification with a physiological meaning, perhaps more non-physiological methods of identification can be used to create more accurate models towards longer and multiple meal predictions of glucose.

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Glossary

List of Acronyms

AP	artificial pancreas
T1DM	type 1 diabetes mellitus
CGM	continuous glucose monitor
SMBG	self-monitoring of blood glucose
MDI	Multiple Daily Injections
MPC	model predictive control
LTI	linear time-invariant
BG	blood glucose
CHO	carbohydrates
T1DM	Type 1 Diabetes melitus
ODE	ordinary differential equation
IOB	insulin on board
CR	insulin-to-carbohydrate
CBR	Case-Based Reasoning