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Safety constraints in an artificial β-cell: an implementation of Model Predictive Control (MPC) with Insulin-on-Board (IOB)

Master's Thesis by Christian Ellingsen

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Abstract

Diabetes mellitus is a disease characterized by elevated levels of glucose in the blood. People with diabetes either do not produce insulin, produce too little insulin, or the cells in the body are unable to respond to the insulin signal. The consequence of this is that the glucose is unable to enter the cells and remains in the blood.

Type 1 diabetes mellitus (T1DM) is one category of diabetes mellitus. T1DM is characterized by the destruction of pancreatic β-cells that are responsible for producing insulin that are necessary for maintaining normoglycemia (normal condition with glucose concentration in the 70-100 mg/dl range) [2, 3]. People with T1DM depend upon subcutaneous or intravenous insulin injections to control their blood glucose concentration.

The short term danger in T1DM is that the glucose concentration goes lower than 60 mg/dl (hypoglycemia), which causes impaired brain functions [5]. At the same time there are several long term complications connected with high glucose concentration (hyperglycemia) over time. Examples of these are diseases such as retinopathy (blindness), nephropathy (kidney disease), neuropathy (nerve problems) and cardiovascular disease (heart and blood vessel diseases). This implies that better control of the disease would be preferable in an attempt to avoid long term complications caused by hyperglycemia and at the same time avoid the short term danger of hypoglycemia.

The development of an artificial β-cell is a challenging engineering task. The nature of the problem is that there can be a substantial mismatch between the controller model and the real patient dynamic which can cause over dose of insulin. A novel way to address this is the use of insulin-on-board (IOB) together with clinical parameters such as the insulin to carbohydrate ratio (I:C) and the correction factor (CF) to constrain the insulin delivery.

An *in silico* simulation study of T1DM subjects based on the Dalla Man et al. model [9] was performed in MATLAB® and Simulink® (The MathWorks, Inc., Natick, MA). The controllers

were developed using the MATLAB® MPC toolbox with IOB to update the maximum insulin delivery at each time step. Five different controller structures have been tested. The first two are MPC- controllers developed on linearized models of the Dalla Man et al model [9]. In this category both control with and without IOB has been evaluated. The third control structure is based on a modified IOB- controller that solely uses the IOB- calculations for the meal rejection. There is no quadratic programming (QP) problem involved in this controller structure. The two final controller structures are part of an *in silico* evaluation of a clinical trial. Here the models for the MPC- controllers are ARX-models that are developed with open-loop data of the *in silico* patients. Also here the MPC- controller has been evaluated with and without IOB.

The results for the first two control structures showed that the MPC- controller with IOB reduced the time spent in the hypoglycemic range from 14.4% to 1.5% compared to the MPC- controller without IOB. This was achieved without any significant increase of time spent in the hyperglycemic range. The modified IOB- controller approved the performance for time spent in the hyperglycemic range, without any significant increase of time spent in the hypoglycemic range. Also, in the *in silico* evaluation of a clinical trial the MPC- controller with IOB was shown to be better at preventing hypoglycemic events compared to the MPC- controller without IOB.

The weakness of the MPC- controller with IOB is that it makes the controller more conservative than the most effective treatment. It delivers the insulin in a way that corresponds to the traditional way of treating T1DM, but that does not mean that this necessarily is the most effective way to treat the disease.

The best results were achieved with a modified IOB- controller that did not include the MPC algorithm. A modified IOB- controller could therefore be used for meal rejections, while another algorithm could be used during night time and other periods with no meals, to manage basal control.

I declare that this is an independent work according to the exam regulations of the Norwegian University of Science and Technology.

Santa Barbara, July 2, 2008

Christian Ellingsen

Preface

This is my final thesis after five years of studying at NTNU, Trondheim, and they have been five fantastic years. I feel I have grown a lot as a person during these years, and I have learned a lot about how to obtain knowledge.

The Master's thesis was written at UCSB in Santa Barbara, California. The topic for my thesis has been control of diabetes, which is different to what I am used to in chemical engineering. This has been a positive challenge for me, and I feel that this has given me a wider perspective on systems engineering.

There are many I would like to thank after my six months in Santa Barbara. First of all I would like to thank Professor Sigurd Skogestad at NTNU for helping me to develop the contact with UCSB. I would also like to thank him for a useful discussion about my thesis when he was visiting UCSB. At UCSB I would like to thank my supervisor Professor Francis J. Doyle III for accepting me as a Master's student at UCSB and for all help with the thesis. I would also give special thanks to my co-supervisor Eyal Dassau for the daily follow-up during the work and the MD's at the Sansum Diabetes Research Institute, Howard Zisser and Lois Jovanovič. Last, but not at all less important, I would like to thank Matt Percival and Youqing Wang for all the discussions and their assistance with finding articles that could give me useful information about my task, and Dan Finan for helping me developing the ARX- models for the *in silico* patients.

For the leisure time in California I would like to thank Henrik Tuvnes and Eirik Tørneng for their company at the cinema, during weekend trips, at the bowling alley, downtown, at fast food joints, and more. It has been a fun time, and I will miss California.

Contents

1 Introduction

Glucose is our major source of energy, and enters the body as carbohydrates from food. In a healthy person the β-cells in the pancreas detect a rise in blood sugar. This make them start producing the hormone insulin that promotes the uptake of glucose into hepatic and muscle tissue.

Diabetes mellitus is the medical term for diseases characterized by elevated levels of glucose in the blood. It could be caused by several different factors, which lead to many categories of diabetes mellitus. People with diabetes either do not produce insulin, produce too little insulin, or the cells in the body are unable to respond to the insulin signal. The consequence of this is that glucose is unable to enter the hepatic and muscle tissue and remains in the blood.

Diabetes is emerging as a major public health concern in the modern western world. An elderly population, increasing obesity, and more physical inactivity are contributors to this. It is estimated that 18.2 million people in the U.S. have diabetes, and it is the sixth leading cause of death in the country. The disease is also expensive, and diabetes cost the US $132 billion in 2002. [1].

1.1 Type 1 diabetes mellitus (T1DM)

Type 1 diabetes mellitus (T1DM) is one of the categories of diabetes mellitus. Around 5-10 percent of all with diabetes have this variety of the disease [1]. T1DM is characterized by the destruction of pancreatic β-cells, which are responsible for producing the insulin that is necessary to maintain normoglycemia (normal glucose concentration in the 70-100 mg/dl range) [2, 3].

People with T1DM depend upon subcutaneous or intravenous insulin injections to control their blood glucose concentration. This is traditionally administered in an open-loop manner with help of insulin-to-carbohydrate ratios (I:C) and correction factors (CF). The I:C describes how much insulin the patient should inject for a certain amount of carbohydrates, and the CF corresponds to

the amount of insulin that should be given to lower the glucose concentration by a certain level (this could be recognized as the process gain in control theory). These are individual factors, and are found by performing special tests. There is an increased use of insulin pumps in the treatment of T1DM, but these are not closed-loop, as many individuals without diabetes think when they hear about insulin pumps [4].

1.2 Motivation for better control of T1DM

The short term danger in T1DM is when the glucose concentration drops below 60 mg/dl (hypoglycemia), which causes impaired brain functions [5]. This problem; however, has decreased significantly with more knowledge about insulin therapy, and the long term complications of the disease have become of greater concern.

The long term complications include the development of diseases such as retinopathy (blindness), nephropathy (kidney disease), neuropathy (nerve problems) and cardiovascular disease (heart and blood vessel diseases). These diseases are caused by high glucose concentration (hyperglycemia) over longer periods of time. A large study known as the Diabetes Control and Complications trial [6], showed that maintaining near normoglycemia by intense therapy "...effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy...". The chief adverse effect of intensive care was that it gave a two-to-threefold increase of severe hypoglycemic events. This study showed that better control of the disease would be preferable in an attempt to avoid long term complications caused by hyperglycemia and at the same time avoid the short term danger of hypoglycemia.

1.3 Previous research on diabetes control

Hovorka [7], Bequette [4] and Parker et al. [3] have written review papers that overview the previous work on diabetes control. The first glucose monitoring study was reported in 1960, and

set the stage for closing the loop [7]. This has proven to be a challenging task and after over 40 years of research, the artificial β-cell for the common T1DM patient is still to be developed.

One of the main problems in developing an artificial pancreatic β-cell has been the lack of proper technology. The total system would contain three major components: a mechanical pump, an in vivo glucose sensor, and a control algorithm [3]. The pump is the furthest developed component today, and is used by thousands of patients in an open-loop manner. Recent advances have also made available pumps that are programmable and variable-rate [3]. Glucose monitoring has seen a remarkable progress over the last decade, and a reliable real-time sensor is very close. The technical advances on the hardware part of the problem have made the control algorithm the weakest link [5].

To design a specific controller for each subject would be both time consuming and expensive, and is probably not a feasible solution. It would be preferable to have a controller that required as little information about each subject as possible. This makes it easier for the physician when a new patient is present, but gives high demands on the adaptive abilities of the controller.

Model predictive control (MPC) has received more attention lately in diabetes control. It is a controller that has an internal model that is used to predict the future behavior of the plant. The MPC- controller has some characteristics that make it especially attractive: the ability to use a linear algorithm to control a nonlinear system, inherent input constraint handling, and the prediction of future behavior based on past manipulated variable moves [3]. As with other controllers, one of the major challenges is to make the MPC- controller robust to uncertainty between the model and plant (patient).

1.4 Insulin on board (IOB) to constrain insulin infusion rate

Insulin on board (IOB) is the amount of active insulin remaining in the body from previous insulin injections. It is calculated in almost all insulin pumps available on the market today to make insulin dosing easier, more accurate and predictable for pump users [8]. For example, a

person might observe that a correction bolus of 1 insulin unit[1] is needed two hours after a meal, and could be informed by the pump that 0.3 insulin units are still active in the body. The patient would then give a bolus of 0.7 insulin units for the correction, and hopefully avoid postprandial hypoglycemia.

The objective of this work is to include IOB in an MPC- controller. I:C ratios and CF are going to be used as a measure of how much insulin the respective patient needs, and IOB- calculations are going to tell the controller how much insulin is still active from previous deliveries. From this information, a constraint on the maximum insulin delivery at the present time could be calculated. The result is a controller that uses common clinical measures to prevent over delivery of insulin.

[1] The insulin unit (U) is the basic measure of insulin, and is equivalent to 1/6000 pmol of insulin.

2 A brief review of the T1DM simulator

Dalla Man et al. [9] have developed a mathematical model that describes the physiological events occurring after a meal in normal humans. Small changes were later performed such that the model better fits T1DM characteristics. The authors of [9] also implemented the T1DM model in a MATLAB® and Simulink® (The MathWorks, Inc., Natick, MA) environment, and this simulator has been used in this work both to develop the MPC- controller and to simulate patients with T1DM. A total of ten different parameter sets that represent adult T1DM patients have been available for the author of this thesis. The "patients" values for the I:C ratio and the CF were predefined by the authors of [9], and has not been recalculated in this work.

2.1 The mathematical model

This section gives a brief description of the mathematical model for the T1DM simulator given in Dalla Man et al. [9]. The reader is referred to their article for a more detailed description of the model, but it should be noted that the changes to obtain a subject with T1DM are not included.

A schematic view of the complete mathematical model is shown in Figure 2.1. The two main sections of the model are the glucose subsystem and the insulin subsystem. There are several other sections that are not described in detail here, but the purpose of these sections is only to calculate the different inputs and outputs to the main sections. It should be noted that there is no direct connection between the glucose subsystem and the insulin subsystem (see Figure 2.1). Insulin only influences the glucose concentration through reduced glucose production in the pancreas or increased glucose utilization in muscles and adipose tissues.

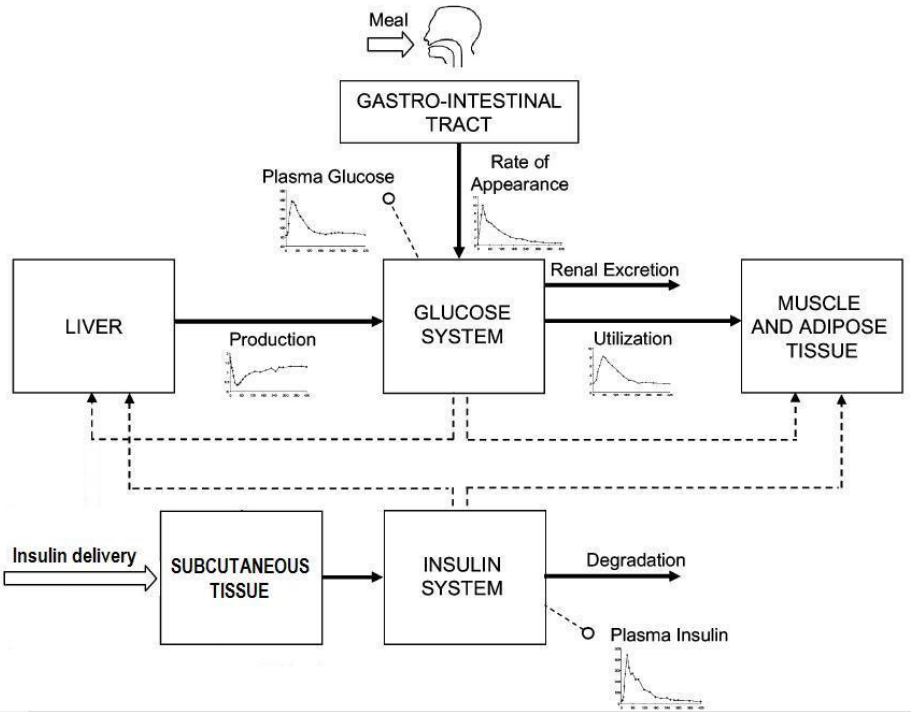

Figure 2.1: A schematic view of the mathematical T1DM model (Modified figure from Dalla Man et al. [9]. Used with permission from authors)

2.1.1 Glucose subsystem

A schematic view of the glucose subsystem is shown in Figure 2.2. It is a two compartment model that contains the glucose masses in the blood plasma and the slowly-equilibrating tissues. The equations for the glucose subsystem are:

$$\dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_t(t) \tag{2.1}$$

$$\dot{G}_t(t) = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t) \tag{2.2}$$

$$G(t) = \frac{G_p}{V_G} \tag{2.3}$$

where G_p and G_t (mg/kg) are glucose masses in plasma and rapidly-equilibrating tissues, and in slowly-equilibrating tissues, respectively, G (mg/dl) plasma glucose concentration, EGP (mg/kg/min) endogenous glucose production, Ra (mg/kg/min) glucose rate of appearance in plasma, E (mg/kg/min) renal excretion, U_{ii} and U_{id} (mg/kg/min) insulin independent and dependent glucose utilization, respectively, V_G (dl/kg) distribution volume of glucose, and k_1 and k_2 (min^{-1}) rate parameters.

There are two inputs to the model, the rate of glucose appearance and the endogenous glucose production. The former is glucose absorbed by the gut and is calculated by a nonlinear model. The latter is glucose production in the liver and is a linear function of glucose in the blood plasma and a delayed signal of insulin concentration in the blood plasma.

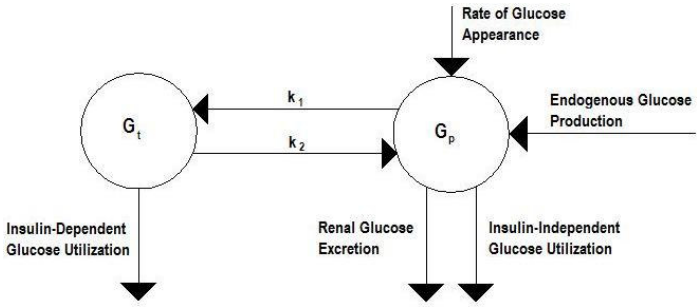

Figure 2.2: A schematic view of the glucose subsystem

The three outputs from the glucose subsystem are the renal glucose excretion, and the insulin dependent and independent glucose utilization. The former is glucose excretion by the kidney and occurs only if the plasma glucose exceeds a certain level. Insulin dependent glucose utilization is calculated by a nonlinear Michaelis-Menten equation, and is a function of glucose in the slowly-

equilibrating tissues and insulin in the interstitial fluid. Insulin independent utilization is constant and describes glucose uptake by the brain and the erythrocytes.

2.1.2 Insulin subsystem

A schematic view of the glucose subsystem is shown in Figure 2.3. It is a two compartment model that contains the insulin masses in the blood plasma and the liver. The equations for the insulin subsystem are:

$$\dot{I}_l(t) = -(m_1 + m_3(t)) \cdot I_l(t) + m_2 \cdot I_p(t) \tag{2.4}$$

$$\dot{I}_p(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t) + R_i(t) \tag{2.5}$$

$$I(t) = \frac{I_p}{V_I} \tag{2.6}$$

where I_p and I_l (pmol/kg) are insulin masses in plasma and in liver, respectively, I (pmol/l) plasma insulin concentration, R_i (pmol/kg/min) rate of insulin appearance in plasma, V_I (l/kg) distribution volume of insulin, m_1, m_2, m_3 and m_4 (min^{-1}) rate parameters.

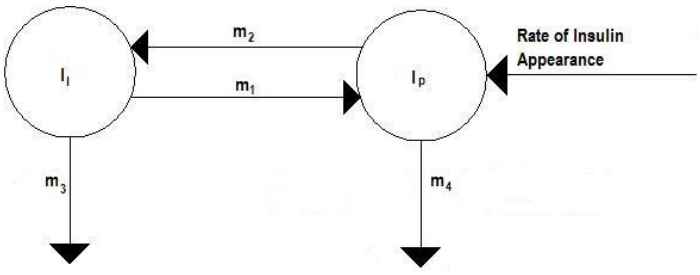

Figure 2.3: A schematic view of the insulin subsystem

There are two outputs from the insulin system, and they are both linear in describing the degradation of insulin. The only input to the insulin subsystem is the rate of insulin appearance in the blood plasma. This variable was also the most important change to the original model given in Dalla Man et al. [9]. Because persons with T1DM do not produce insulin by themselves, insulin secretion from the β-cells was removed from Equation (2.4) and the insulin rate of appearance added to Equation (2.5). The rate of insulin appearance is a linear function of non-monomeric insulin that is injected into the subcutaneous tissue, and monomeric insulin that equilibrates with the non-monomeric insulin. The equilibration process and the rate of insulin appearance into the blood stream are calculated by a subcutaneous insulin model that also was added by Dalla man et al. to modify the model in [9] to describe a T1DM patient. This model is represented in Figure 2.1 by the block called the *subcutaneous tissue*.

3 Model predictive control

Most of the reported applications of MPC are in the petrochemical industry, but it has lately started to achieve attention in other areas as well. One of these areas is diabetes control, where researchers are using MPC in an attempt to develop a controller for T1DM.

3.1 Review of concept

An MPC- controller uses an internal model to predict the effect of current and future inputs on the future outputs. There are several ways to develop the model, ranging from simple step response models to a model based on a physical understanding of the controlled process.

The controller uses the predictions to minimize a quadratic cost function with the future inputs as variable. The objective of the cost function could vary from application to application, but usually includes a cost on the output's deviation from the set points as a minimum. The optimal inputs for the next time step is given to the process, and then the cycle repeats itself as new measurements are collected.

One of the strengths for an MPC- controller is the inherent handling of constraints. If there are constraints on the inputs (and there usually are), they are simply added as inequality constraints to the quadratic cost function problem.

It is also possible to add constraints on the rate of change for the inputs. This is practical if, for example, a compressor or a pump has a maximum rate of change during a time step.

Another possibility is to add constraints on the outputs, but this is not recommended since a violation of these constraints could result in an infeasible programming problem. To avoid this problem, the output constraints could be added to the cost function itself with help of slack variables that are penalized if violated (softening of the constraints).

3.2 Theoretical details [10]

The most basic formulation of the cost function is given in Equation (3.1). Here $\hat{y}$ is a vector of the predicted outputs, r is a vector of their respective set points and Q is a weighting matrix. The notation $\| x \|_Q^2$ is called quadratic form and could also be written as $x^T Q x$. Normally Q is a diagonal matrix such that the weighting of the outputs are independent of each other. The notation $x(k+i \mid k)$ means the value of x at time $k+i$ predicted (in case of outputs) or decided (in case of reference trajectory) at time k.

$$V(k) = \sum_{i=H_w}^{H_p} \| \hat{y}(k+i \mid k) - r(k+i \mid k) \|_{Q(i)}^2 \tag{3.1}$$

The optimal inputs are simply calculated by finding the future inputs that minimizes the cost function given in Equation (3.1). This problem is a linear least-squares problem and has an analytical solution (when there are no constraints).

A controller developed with the cost function in Equation (3.1) could be rather aggressive. There are no terms that restrict the usage of the inputs, and a change from one time step to the next could be as large as the controller prefer. An extra term is commonly included in the cost function to have the ability to penalize large movements on the inputs. This is shown in Equation (3.2). Here $\Delta\hat{u}$ is a vector with the rate of change for the inputs and R is a weighting matrix.

$$V(k) = \sum_{i=H_w}^{H_p} \| \hat{y}(k+i \mid k) - r(k+i \mid k) \|_{Q(i)}^2 + \sum_{i=0}^{H_u-1} \| \Delta\hat{u}(k+i \mid k) \|_{R(i)}^2 \tag{3.2}$$

If the rate of change is weighted heavily compared to the output's deviation from their set points, the controller becomes more conservative. In the opposite case the controller would be more aggressive.

It is worth noticing that there are different "horizons" for the two terms in Equation (3.2). H_p denotes the *prediction horizon* and H_u denotes the *control horizon*. The former is how far into the future the controller should predict at each time step, while the latter is how many control moves into the future the controller should optimize to obtain the best solution. Only the inputs for the next time step would be given to the plant, but different values for H_u affects the result and it is an important tuning parameter.

If constraints are added to the inputs and/or the outputs, the problem becomes a constrained least-square problem that needs some form of iterative optimization algorithm. This does not create a significant problem as long as the constraints are linear, since the resulting quadratic programming problem is easily solved.

4 Insulin-on-board

Insulin on board is an approximation of remaining insulin in the body from previous insulin deliveries. The basal insulin requirement is not included in these calculations.[2]

Insulin pumps have become more advanced in the recent years, and are now commonly manufactured including a bolus calculator. The objective of this calculator is to help the patient with calculation of the insulin dosing. The pumps use information about the patients such as the I:C ratio and the CF together with IOB to approximate how much insulin that is proper for the patient [8]. See Appendix A for an illustration of how the IOB- calculations could be used in an insulin pump to help a patient with the insulin dosing.

4.1 The insulin action curve

The decomposition of insulin in the body varies between individuals, but also within each subject during a day. These uncertainties make it impossible to find a "correct" function for insulin action, and there are several different approaches among the different pump manufacturers. In some pumps the percentage of active insulin is assumed linear with time, while others use a nonlinear prediction [8]. The latter type of curves is a better description of the pharmacokinetic actions of insulin (see Figure 4.1 for an example of typical curves in this category), but one can argue that the overall uncertainties for insulin action is more significant than the actual shape of the curve.

Another important question, and more important than choosing the correct shape of the insulin action curve, is to choose the duration of insulin action. There are pumps that let the user choose between a value of 2 and 8 hours of insulin action.

[2] Basal insulin is the amount of insulin that is needed to keep the patient at "steady-state"." (i.e., non-meal related). The basal rate changes during a day and over time, and it is also sensitive to factors like physical activity, stress, illnesses and more.

Representative curves are given in Figure 4.1. These are also the actual curves that are implemented in the MPC- controller in this work.

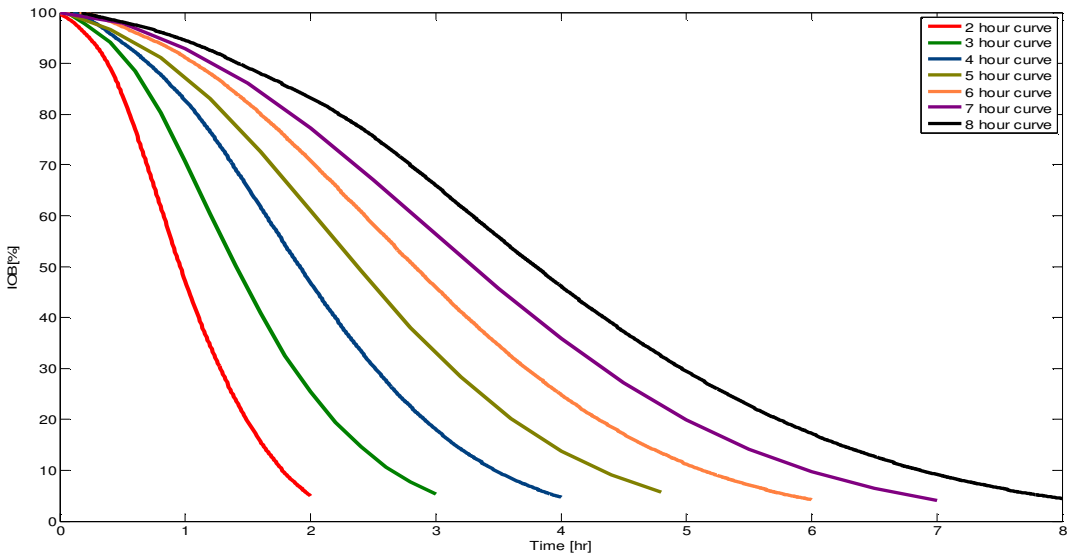

Figure 4.1: An example of nonlinear insulin action curves. These are also the curves that are implemented in the MPC- controller in this work (The data for the curves are taken from [11]).

4.2 IOB in MPC

In this work, IOB- calculations have been included in an MPC- controller to constrain the maximum allowed insulin delivery rate at each time step. The principle is just the same as what is done in modern insulin pumps, but now the calculations are performed at every sampling instant. I:C ratios and CF's are used to inform the controller how much insulin the patient need at the present time, while IOB is calculated to include insulin that is already in the body. If the need of insulin is higher than what is "on board", the MPC- controller is constrained to an allowable delivery rate.

4.2.1 Calculation of needed insulin

The I:C ratio and the CF are used to estimate the amount of needed insulin. If the blood glucose concentration is higher than the set point, the need of insulin is calculated based on the CF. The I:C ratio is used to calculate the amount of insulin needed for an announced or detected meal. This makes two categories of needed insulin, insulin needed for correction and insulin needed for meals.

Insulin needed for correction

The CF is defined as how much one insulin unit could lower the blood glucose level, and the amount of insulin needed for correction is calculated by Equation (4.1).

$$I_{CF}(k) = \begin{cases} \dfrac{y_m(k) - r(k)}{C_f} & \text{if } y_m(k) > r(k) \\ 0 & \text{otherwise} \end{cases} \tag{4.1}$$

Here I_{CF} (U) is the insulin needed for correction, y_m (mg/dl) is the current measured blood glucose value, r (mg/dl) is the desired blood glucose value, C_f (mg/dl/U) is the correction factor and k denotes the current time.

Insulin needed for meals

If the patient consumes a meal, the controller should be allowed to give a larger amount of insulin at an early stage to compensate for this. The meal could be flagged to the controller either by the patient (meal announcement) or by an algorithm that detects the meal (meal detection). The amount of insulin that is needed could then be estimated by the patient's I:C ratio. This is shown in Equation (4.2).

$$\begin{gathered}\text{IF } Meal = \text{'}YES\text{'} \\ I_{I:C}(k) = I_{I:C}(k-1) + C_{I:C} \cdot U_{Meal}\end{gathered} \tag{4.2}$$

Here $I_{I:C}$ (U) is the insulin needed to compensate for meals, $C_{I:C}$ (U/g) is the I:C ratio, U_{Meal} (g) is the amount of CHO in the meal, and k denotes the current time.

As can be seen from Equation (4.2), the calculations also include insulin that is needed to compensate for earlier consumed meals. This is important in case the MPC- controller does not want to give the insulin injection at the time of the meal, which is a likely scenario if the blood glucose level is low at the time of the meal. Hence the controller should not "forget" about the meal, but be able to compensate for it later.

The formula that keeps track of insulin delivered for earlier meals is given in Equation (4.3). In this equation there is assumed that all the delivered insulin above basal requirement after a meal is given to compensate for the meal, and not given for correction. This applies until the total amount needed to compensate for the actual meal is given.

$$\begin{gathered}\text{IF } I_{I:C}(k-1) > 0 \\ I_{I:C}(k) = \max(I_{I:C}(k-1) - (u(k-1) - B_h),\ 0) \\ \text{ELSE} \\ I_{I:C}(k) = 0\end{gathered} \tag{4.3}$$

Here u (U/h) is the infusion rate over the sampling period k and B_h (U/h) is the nominal basal insulin requirement. It should be noticed that Equation (4.2) overrides Equation (4.3).

4.2.2 Calculation of IOB

The IOB- calculations are based on the history of previous delivered insulin that covers the duration of insulin action. This is expressed as

$$I_a(k) = \left[u_a(k-1)\ u_a(k-2)\ \ldots\ u_a\left(k - \frac{T_{DA}}{T_s} \right) \right] \cdot \frac{T_s}{60\ min} \tag{4.4}$$

$$u_a(k-i) = \max(u(k-i) - B_h, 0),\ i = 1, 2, \ \ldots\ , \frac{T_{DA}}{T_s} \tag{4.5}$$

where I_a (U) is the total amount of insulin delivered above the basal insulin requirement during the time of insulin action, $u(k)$ (U/h) is the infusion rate over the sampling period k, B_h (U/h) is the nominal basal insulin requirement, T_s (min) is the sampling period, T_{DA} (min) is the duration of action and the scaling factor is to convert from an infusion rate to the total amount of insulin delivered within each sampling period.

The MPC- controller could also deliver an infusion rate of insulin that is under the basal rate. This would happen if the blood glucose values are lower than the set point or if the controller predicts that this would happen in the future. A period of under delivery of insulin would result in less insulin on board for the patient, and would normally require a small bolus of insulin when the blood glucose rises to set point again. Without this bolus, the blood glucose would be very likely to have an undesirable overshoot.

IOB, as it is defined in Equation (4.4) and Equation (4.5), does not take into account insulin infusion under the basal rate. It would therefore not allow any small bolus when the blood glucose rises to set point after being low. To compensate for this, “negative IOB” has been introduced in the controller algorithm. This is a vector that collects all insulin deliveries under

basal as a negative deviation from basal infusion rate. This is shown in Equation (4.6) and Equation (4.7).

$$I_u(k) = \left[u_u(k-1)\ u_u(k-2)\ \ldots\ u_u\left(k - \frac{T_{DA}}{T_s} \right) \right] \cdot \frac{T_s}{60\ min} \tag{4.6}$$

$$u_u(k-i) = \min(u(k-i) - B_h, 0),\ i = 1, 2,\ \ldots\ , \frac{T_{DA}}{T_s} \tag{4.7}$$

Here I_u (U) is the total amount of insulin delivered under the basal insulin requirement during the time of insulin action, while the rest of the variables are the same as in Equation (4.4) and Equation (4.5).

The IOB could then be calculated by multiplying the history of previous insulin deliveries with vectors that contains information about the insulin action. These vectors could be constructed from linear or more complicated insulin action curves (see Figure 4.1), and the duration of insulin action must be chosen. It is possible to choose different curves for the insulin delivery above the basal and the insulin delivery under the basal. The general expression is

$$I_{OB}(k) = I_a \cdot I_{fr_a} + I_u \cdot I_{fr_u} \tag{4.8}$$

where I_{OB} (U) is a scalar containing IOB, I_{fr_a} (-) is a vector containing information about how large fraction of the previous delivered insulin above basal that is left after each time step and I_{fr_u} (-) is a vector containing information about the effect of deliveries under basal.

4.2.3 Calculation of maximum allowed infusion rate

When both the needed insulin and the IOB are calculated, the maximum infusion rate for the present time step could be calculated as

$$u_{max}(k) = \max\left(\left(I_{CF}(k) + I_{I:C}(k) - I_{OB}(k) \right) \cdot \frac{60\ min}{T_s},\ B_h \right) \tag{4.9}$$

where u_{max} (U/h) is the maximum infusion rate.

5 Simulation studies with MPC

Two different MPC- controllers have been studied. The first MPC- controller is without IOB to constrain maximum insulin delivery. This is done to show how good the controller could perform in the ideal case, but also to illustrate what could happen if there is large mismatch between the model for the controller and the actual plant, or if the MPC- controller is tuned badly.

The second MPC- controller includes the constrained insulin delivery through IOB- calculations. A larger study has been performed in this case, and both model/plant mismatches have been introduced, as well as uncertainties that could occur in the real world.

5.1 Development of models for the MPC- controller

The models for the MPC- controller are linearized models of the plant at its nominal condition. The 10 different parameter sets gave the possibility to make up to 10 different linear models for the controller. If the same parameter set is chosen for both the controller model and the plant model, the “nominal” case is studied. Model/plant mismatches could simply be introduced by using different parameter sets for the controller model and the plant model.

Figure 5.1 shows a simple illustration of the plant and the MPC- controller. The MPC- controller has three inputs, the glucose measurement, the glucose set point trajectory and the glucose rate of appearance into the glucose compartment. The last input is only present if the meal is announced or detected [2]. To avoid the nonlinearities in the stomach compartment, the model for the controller was linearized without this compartment present. As a consequence of this, the meal disturbance has to be given as a filtered response into the glucose compartment and not as a step response into the stomach compartment.

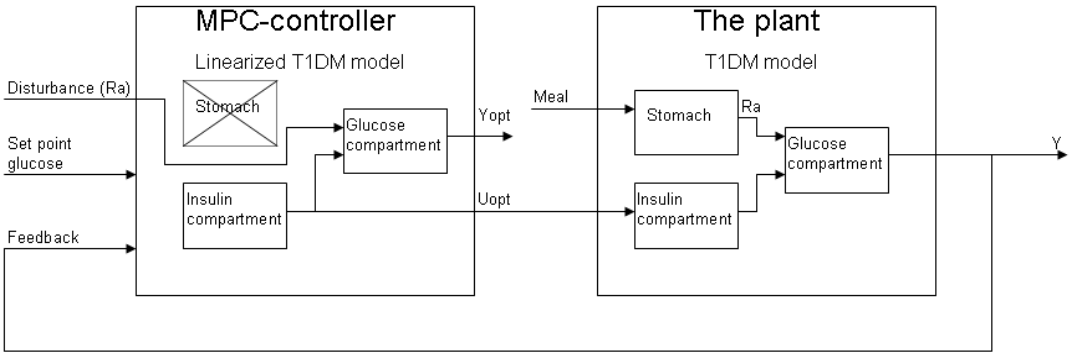

Figure 5.1: A schematic view of the MPC- controller. The model for the controller is a linearized model of the plant at the nominal condition, but not necessarily with the same parameter set. The stomach compartment is not included in the linearization of the plant in an attempt to avoid the nonlinear behavior of this compartment. Ra is the rate of glucose appearance, Yopt is the predicted future glucose concentration, Uopt is the predicted optimal insulin delivery and Y is the measured glucose concentration.

5.2 MPC without IOB

Two different cases have been simulated with the MPC- controller without IOB. The first case is the nominal case, while the second case includes some model/plant mismatch. The disturbance (meals) is measured in both cases.

5.2.1 Experimental

Meal scenario

A 24-hour period with three meals is used as the scenario for all the studies performed in this work. The simulation starts from steady state at 07:00 in the morning. The patient consumes a small breakfast with 20 grams of carbohydrates (CHO) at 08:00, then a lunch with 40 g of CHO at noon and finally a dinner with 70 g of CHO at 18:00. A summary of the scenario is given in Table 5.1.

Table 5.1: The meal scenario for all the simulations in this thesis

Event:	Time:	Time from start:
Simulation starts (steady state)	07:00	0 hours
Breakfast with 20 g of CHO	08:00	1 hour
Lunch with 40 g of CHO	12:00	5 hours
Dinner with 70 g of CHO	18:00	11 hours
Simulation ends	07:00 the next day	24 hours

Choice of patients

Two "patients" from the library with typical values for the I:C ratio and the CF were chosen for the study. Their values for the I:C ratio and CF are given in Table 5.2. For the nominal case both the linearized model for the MPC and the plant model come from Patient #1, while Patient #7 was used for the plant in the case with model/plant mismatch.

Table 5.2: I:C ratios and CF's for Patient #1 and #7

Patient #:	I:C ratio: (U/g)	CF: (mg/dl/U)
1	0.044	11.2
7	0.044	18.3

Disturbance trajectory

In the nominal case the correct disturbance trajectory (Ra in Figure 5.1) was given to the MPC-controller, while the disturbance trajectory for Patient #1 was given to the controller in the case where Patient #7 was the plant. This adds an additional factor of uncertainty to the case with model/plant mismatch.

Controller tunings

The tuning parameters were kept constant for the two cases, and are given in Table 5.3. Because this is a simple system with just one measured input and one measured output, the tuning of the

controller becomes straightforward. It can be seen from Equation (3.2) that the weight on insulin infusion rate and the weight on glucose set point tracking are relative numbers. A higher relative weighting on set point tracking compared to the weight on change in insulin infusion rate would result in more aggressive control. The tuning parameters in this section were chosen to achieve as aggressive control as possible without hypoglycemic events for the nominal case, and this is shown in the high relative weight on set point tracking compared to the weight on change in insulin infusion rate.

It was also introduced a soft constraint on glucose values under 90 mg/dl. This constraint would not make an infeasible solution for the QP solver if violated, but would give the controller a strong signal to counteract the low glucose values. The set point for the simulations was 100 mg/dl.

Table 5.3: Tuning parameters for the MPC- controller without IOB

Tuning parameter:	Value:
Sample time	5 minutes
Prediction horizon	50 sample intervals
Control horizon	5 sample intervals
Weight on change in insulin infusion rate	1
Weight on glucose set point tracing	20
Lowest allowable insulin delivery	0.5 times basal rate

5.2.2 Results

Nominal case

Figure 5.2 shows the result for the nominal case. The effort on finding good tuning parameters for the nominal case resulted in tight control without any hypoglycemic events, while the highest glucose measurement were no higher than 158 mg/dl. The dashed black lines in the upper plot

show that the future predictions follow the actual glucose measurements almost exactly. This shows that the linear prediction model is adequate for the nonlinear plant as long as the system does not drift too far from the nominal condition.

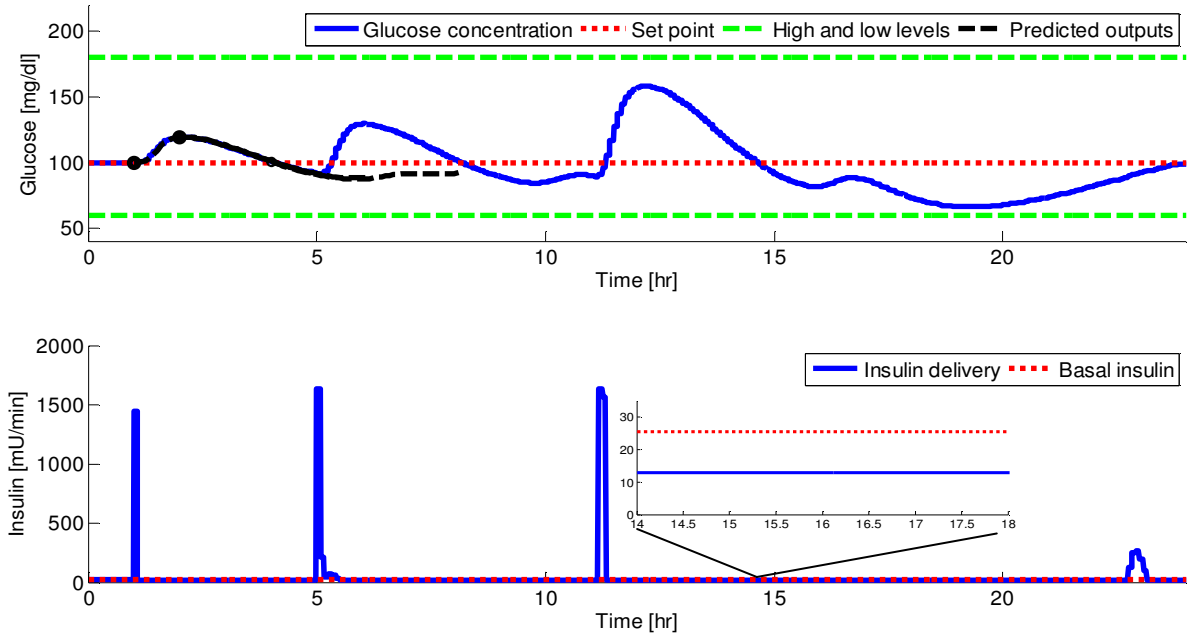

Figure 5.2: MPC without IOB to constrain maximum insulin delivery, the nominal case. Aggressive tuning results in tight control without any hypoglycemic events. The small window in the lower graph shows how the controller delivers insulin under basal requirement for a long period of time after a meal. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

A physician would be very pleased if shown the glucose trajectory in Figure 5.2. It shows a very good clinical result for the meal scenario given in Table 5.1. It is a completely different question if the physician would accept the insulin delivery in this case. A summary of the total insulin injections to compensate for each of the meals are given in Table 5.4. Basal requirement is not included in these calculations.

Table 5.4: Insulin delivered for meals in the nominal case, compared to what would be given if the insulin delivery were based on the I:C ratio

Meal:	Amount of CHO (g)	Insulin delivered (U):	Insulin required based on I:C (U):
Breakfast	20	7.1	0.9
Lunch	40	9.6	1.8
Dinner	70	15.9	3.1

Table 5.4 shows that the MPC- controller gives up to 7 times more insulin for a meal than what is recommended by the I:C ratio for the patient. These deliveries would never been approved by a physician during a clinical trial. The MPC- controller accepts these values, because it can deliver under the basal requirement for some time after the meal. This is also illustrated in the small window at the bottom plot in Figure 5.2.

It is impossible to find out if the delivery scheme proposed by this MPC- controller would work in a real case, because no doctor would approve such an aggressive controller. Another open question is if the T1DM simulator makes accurate predictions in these extreme cases.

Case with model/plant mismatch

Figure 5.3 shows the result for the case with model/plant mismatch. As can be seen from Table 5.2, Patient #7 is more sensitive to insulin than Patient #1. This causes the MPC- controller to under-predict the insulin delivery compared to the actual case. This is confirmed by the dashed black lines in Figure 5.3 that shows future predictions for some sample points. The consequence of this is over delivery of insulin, followed by a postprandial hypoglycemic event after dinner.

One could argue that the model should be improved in this case, and this is also correct. The problem is that there are so many patients with T1DM and it would be both expensive and time consuming to develop a good model for each patient. It would also demand that the common physician had good knowledge about control theory and tuning. Another problem is that patients change behavior over time.

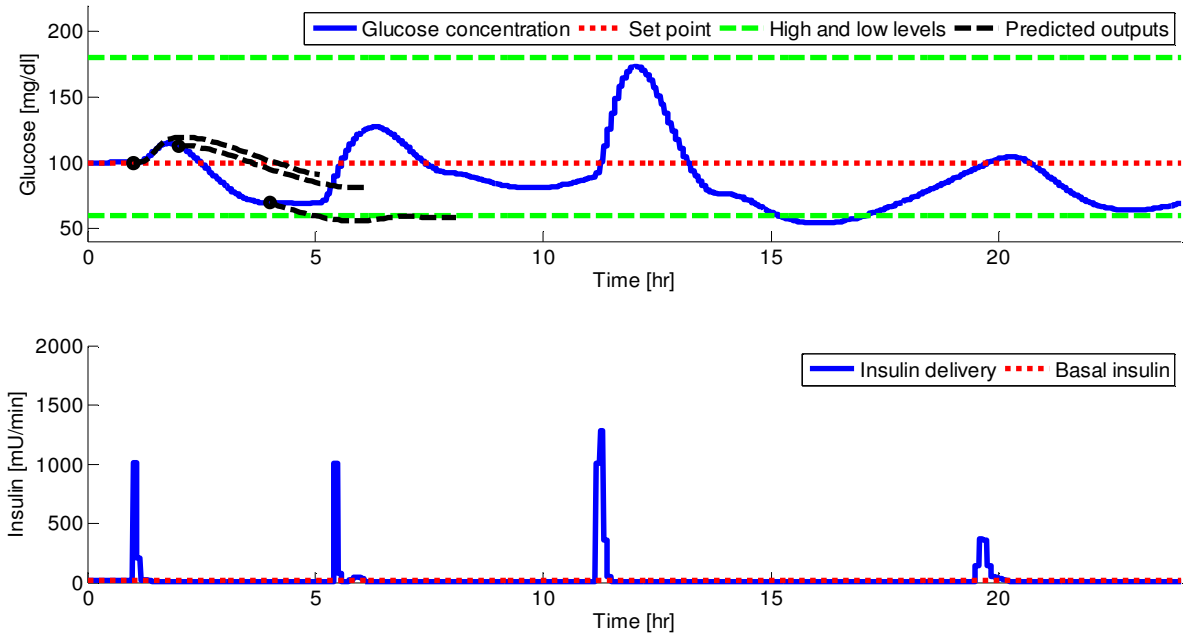

Figure 5.3: MPC without IOB to constrain maximum insulin delivery, the case with model/plant mismatch. The prediction model is less sensitive to insulin than the plant, and this causes over delivery of insulin and a hypoglycemic event. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

5.3 MPC with IOB

A more detailed study has been performed on the MPC- controller with IOB. The first part compares the performance of the constrained problem to the case where there is no constraint on maximum insulin delivery. The study also includes some simulations that are using different set point trajectories, as well as looking on the case with unmeasured meals. The main goals for this part are to check the robustness against model/plant mismatches for the constrained MPC-controller and to compare its performance to the MPC- controller without IOB.

The second part focuses on the ability of the MPC- controller with IOB to handle uncertainties in meal sizes, meal times, as well as measurement noise.

5.3.1 Experimental

Controller tunings

The basic controller tunings for the MPC- controller were kept constant through all the simulations in this section. Their values are summarized in Table 5.5.

Table 5.5: Basic controller tunings for the MPC- controllers in this section

Tuning parameter:	Value:
Sample time	5 minutes
Prediction horizon	50 sample intervals
Control horizon	5 sample intervals
Weight on change in insulin infusion rate	1
Weight on glucose set point tracing	1
Lowest allowable insulin delivery	0.5 times basal rate

For the controller configurations with IOB to constraint maximum insulin delivery, the choice of duration for the insulin action becomes a new tuning parameter. Some early preliminary studies showed that the curves with the fastest insulin action would be too aggressive for MPC- control on the T1DM simulator. It was therefore chosen to use the 6 hour curve (see Figure 4.1) as the most aggressive curve.

Different insulin action curves are used dependent on the blood glucose measurement. If the measurement is high, a fast insulin action curve is used to achieve a more aggressive control. As

the glucose values get lower, the insulin action curve changes stepwise against slower and more conservative curves. This would make the controller more aggressive on high glucose values and more conservative when the blood glucose values are closer to the set point. The specific curves that are used for different blood glucose ranges are given in Table 5.6.

Table 5.6: The active insulin action curve for different blood glucose ranges for the MPC- controllers with IOB

Blood glucose range (mg/dl):	Active insulin action curve:
<100	8 hour curve
100-140	7 hour curve
>140	6 hour curve

Section 4.2.2 explained how insulin deliveries under basal requirement were handled as "negative IOB". To avoid "negative IOB" to have influence on the controller for a long time, the fastest insulin action curve is chosen for these insulin deliveries. The "negative IOB" is an important part of the algorithm because it gives the controller the possibility to give a small stabilizing bolus when the blood glucose level is on its way back from low values. The fast insulin action curve for the "negative IOB" is chosen to avoid over dosing that could cause hypoglycemia.

Announced meals

Figure 5.4 shows an example of how an announced meal is fed to the controller. All the ten patients have completely different parameters for their meal absorption model. It is not possible to predict the actual absorption of glucose from the gut into blood stream for a real patient, and a standard absorption profile is therefore given to the controller. This mimics the real world better than giving the correct absorption profile in each case.

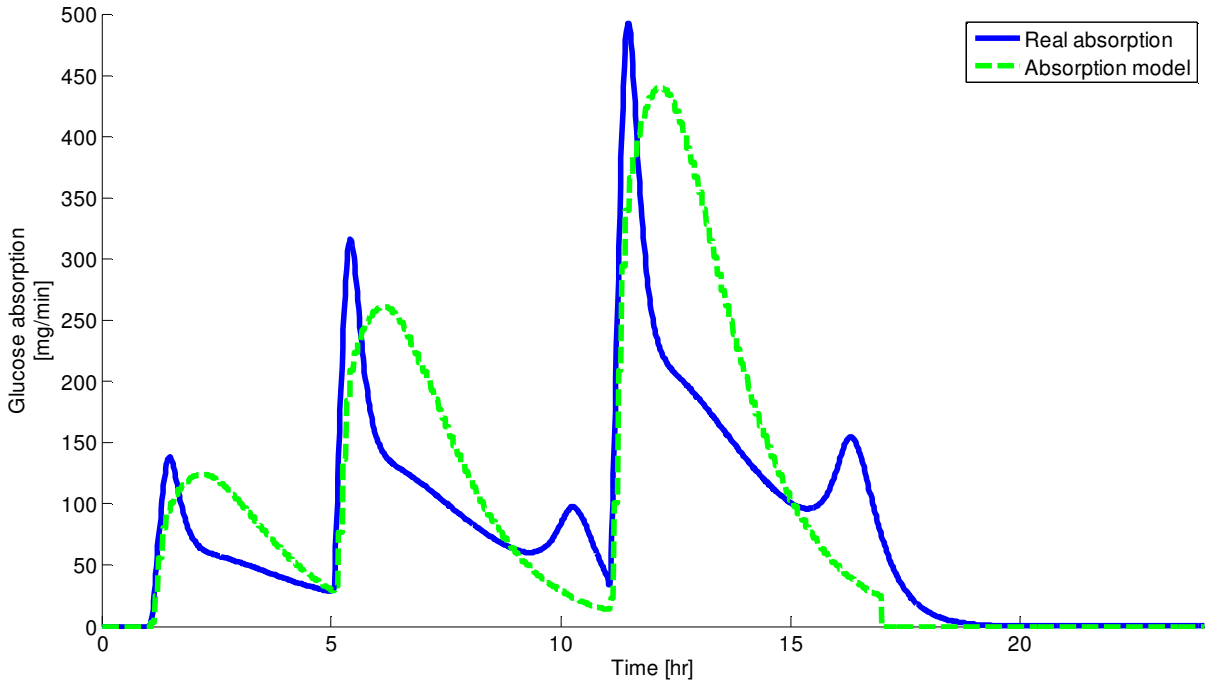

Figure 5.4: The figure shows an example on how the glucose absorption profile given to the MPC- controller could differ from the actual glucose absorption for the patient. This is done by purpose to simulate a more realistic situation.

Simulation study without measurement noise and meal uncertainties

Six different controller configurations have been studied in this category, and they are listed in Table 5.7. The goal is to see how the constrained MPC- controller performs compared to the controller without any constraint on maximum insulin delivery. A secondary objective is to see if a trapezoidal set point trajectory for meal rejection performs better than a constant set point trajectory. The trapezoidal set point trajectory is added to mimic the normal glucose profile to a meal intake, and thus avoid too aggressive control.

Model/plant mismatches has been introduced by running each of the 10 available “patients” as model for the MPC- controller against all the 10 “patients” as plant. This makes a 10 by 10 matrix and a total of 100 simulations for each configuration. The meal scenario is the same as in Table 5.1.

Table 5.7: Overview of the different controller configurations in the simulation study without measurement noise and meal uncertainties

Configuration #:	Constraint on u_{max}:	Disturbance (Meals):	Set point trajectory:
1	No	Unmeasured	Constant
2	Yes	Unmeasured	Constant
3	No	Announced	Constant
4	No	Announced	Trapezoidal
5	Yes	Announced	Constant
6	Yes	Announced	Trapezoidal

Simulation study with measurement noise and meal uncertainties

This study is performed to further check the robustness of the MPC- controller with IOB. Controller configuration #5 in Table 5.7 has been investigated further for this part, and three common uncertainties for the T1DM controller problem have been introduced. These are measurement noise, uncertainties in the meal sizes and meals that are consumed earlier or later than announced to the controller. A summary of the different cases is given in Table 5.8.

The measurement noise is assumed to have a normal distribution, with zero mean and the given error as 3 standard deviations. In Case #4 to Case#11 all the meals are subject to the same uncertainty, while in Case #12 to Case #14 all the meals are subject to a random uncertainty that have a normal distribution, with zero mean and the given error as 3 standard deviations.

The actual meal scenario is still the same as in Table 5.1, but the meal sizes and/or meal times given to the MPC- controller would differ from the actual meals.

Table 5.8: Overview of the different cases in the simulation study with measurement noise and meal uncertainties

Case #:	Measurement noise:	Announced meal sizes:	Announced meal times:
1	5 %	0	0
2	10 %	0	0
3	20 %	0	0
4	0	+ 10 %	0
5	0	+ 20 %	0
6	0	+ 40 %	0
7	0	- 10 %	0
8	0	- 20 %	0
9	0	- 40 %	0
10	0	0	- 60 min
11	0	0	+ 60 min
12	5 %	Random: ± 10 %	Random: ± 30 min
13	10 %	Random: ± 20 %	Random: ± 60 min
14	20 %	Random: ± 40 %	Random: ± 60 min

5.3.2 Results

Simulation study without measurement noise and meal uncertainties

An example simulation result is given in Figure 5.5. The plot at the upper left corner shows the glucose concentration, the set point trajectory and the boundaries for high and low glucose concentrations. Throughout this study the boundaries are defined to be 60 mg/dl for hypoglycemia and 180 mg/dl for hyperglycemia. The plot at the upper right corner shows the amount of insulin that is needed for correction, the amount of insulin that is needed for food, and the amount of insulin that is “on board”. If the IOB is higher than what is needed, the controller is not allowed to give more than the basal insulin requirement. The plot at the lower left corner shows the constraint on maximum insulin delivery, the amount that the controller is delivering

and the basal insulin requirement. The plot at the lower right corner shows which insulin action curve that is used for the different time of the simulation.

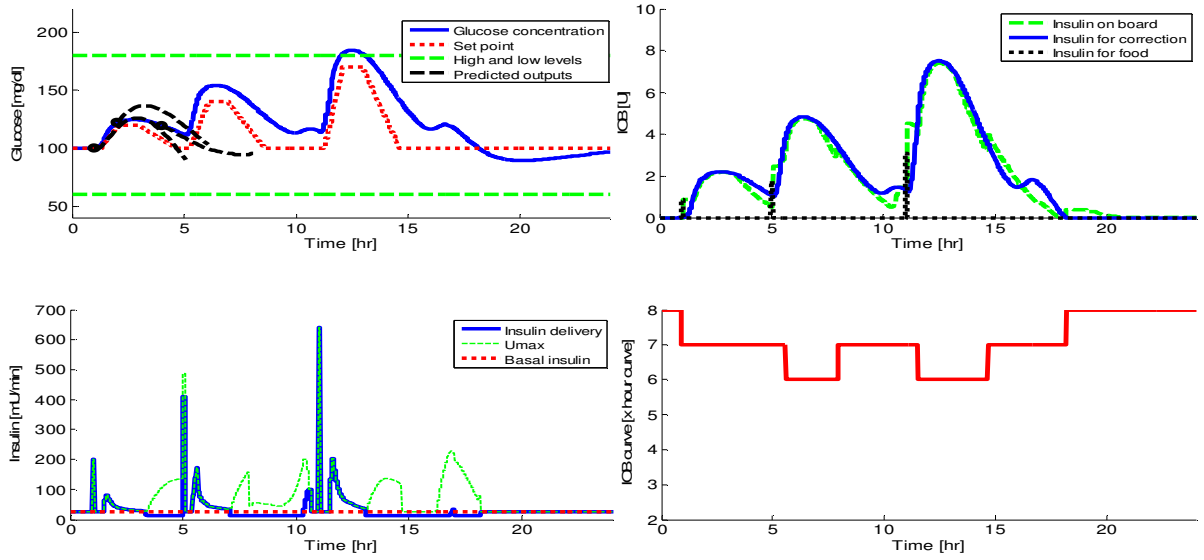

Figure 5.5: An example of a result with MPC with IOB to constrain maximum insulin delivery. The example is taken from Configuration #6 in Table 5.7 with Patient #1 as both the model for the controller and the plant. Upper left: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Upper right: Plot showing the insulin needed for correction, insulin needed for food, and how much insulin there is "on board". Lower left: Plot showing the maximum delivery of insulin the MPC- controller could give, actual delivery rate, and the basal insulin requirement. Lower right: Plot showing which insulin action curve that is used for the IOB- calculations during the simulation.

The simulation showed in Figure 5.5 is taken from Configuration #6 in Table 5.7 with Patient #1 as both the model for the MPC- controller and the plant. The result could therefore be directly compared with the result in Figure 5.2 for the MPC- controller without IOB. It is clear that the MPC- controller without IOB performs better in this exact case. It has a lower high blood glucose

value and it rejects the meals faster. The positive about the MPC- controller with IOB is that it gives the insulin in a much more traditionally and acceptable way. It does not give the large amount of insulin at the meal time and it is guaranteed that the amount of insulin delivered for a meal does not exceed the amount given by the I:C ratio. The result given in Figure 5.5 would be a tremendous improvement for a patient that stays at high blood glucose values for a long time of each day, and at the same time the insulin delivery is safe against over dosing.

The acceptable result in Figure 5.5 was also achieved without using much effort on tuning the basic tuning parameters for the MPC- controller. All that was needed was to add information about the patients I:C ratio and CF. This is an important result when it is taken into account that it is the physicians who most likely have to implement controllers on T1DM patients. They have little experience on tuning an MPC- controller, but they are much more familiar with I:C ratios and CF's. Insulin action curves are also something they know about, and by choosing different action curves they have the ability to tune the controller.

A summary of the overall results for the 6 configurations in Table 5.7 are given in Table 5.9. The two first configurations are with no meal announcement. It is clear that the MPC- controller with IOB perform much better in preventing hypoglycemia than the MPC- controller without IOB. This scenario would most likely not be present in a real artificial β-cell, because there would be algorithms that would detect meals if there is no announcement [2]. The result is still promising as a safety feature if other safety algorithms fail.

Configuration #3 and #4 are those with measured meals and the MPC- controller without IOB. The only difference between the two configurations is the set point trajectory. There are many incidents of hypoglycemia in these simulations and the patients spend a lot of the time in the hypoglycemic range. This is significantly improved for Configuration #5 and #6 where the meals are measured and the MPC- controller with IOB is used. Only 10 of the 100 simulations go into a hypoglycemic event, and the time spent in hypoglycemic range is decreased significantly. At the same time the period spent in the hyperglycemic range only increases slightly. Further investigation of the results showed that 9 out of the 10 hypoglycemic incidents for Configuration #5 and #6 came

Table 5.9: Results for the simulation study without measurement noise and meal uncertainties. The table shows how many of the hundred simulations in each controller configuration that went hypo- and hyperglycemic. Further it shows the total time of all the 100 simulations that were spent in the hypo- and hyperglycemic ranges. As a measure of performance the time spent in the blood glucose range of 60-140 mg/dl is given. The table also shows how much insulin the different controller configuration gave to each of the patients in average through the day.

Config.:	# of hypoglycemic events:	% of time < 60 mg/dl	# of hyperglycemic events	% of time > 180 mg/dl	% of time in 60-140 mg/dl range	Averagely delivered insulin (U)
1	90	33.7	4	0.08	64.1	74.5
2	16	1.9	57	3.4	76.8	52.4
3	52	19.2	11	0.5	75.2	61.7
4	48	14.4	24	1	77.5	58.7
5	10	1.5	47	2.4	76.3	50.2
6	10	1.5	52	2.8	75.8	49.8

with Patient #6. This indicate that the suggested values for the I:C ratio and the CF for this patient is too aggressive. If this was a real situation the physician would improve those parameters, or an adaptive function in the controller could improve them.

The different set point trajectories did not give any significant different results. The trapezoidal set point trajectory tends to give a little more time spent in hyperglycemic range. This could be because the controller is slightly less aggressive with the trapezoidal set point trajectory.

Simulation study with measurement noise and meal uncertainties

Table 5.10 shows the overall results for the cases in the simulation study with measurement noise and meal uncertainties. Most of the hypoglycemic event throughout these simulations comes from Patient #6.

Table 5.10: Results for the simulation study with measurement noise and meal uncertainties. The table shows how many of the hundred simulations in each of the cases that went hypo- and hyperglycemic. Further it shows the total time of all the 100 simulations that were spent in the hypo- and hyperglycemic ranges. As a measure of performance the time spent in the blood glucose range of 60-140 mg/dl is given. The table also shows how much insulin the different controller configuration gave to each of the patients in average through the day.

Case:	# of hypoglycemic events:	% of time < 60 mg/dl	# of hyperglycemic events	% of time > 180 mg/dl	% of time in 60-140 mg/dl range	Averagely delivered insulin (U)
1	10	1.6	51	2.4	76.3	50.3
2	9	1.6	47	2.1	76.9	50.6
3	9	1.8	40	1.8	78.9	51.4
4	9	1.4	47	2.3	75.8	50.1
5	9	1.3	47	2.2	76	49.9
6	6	0.8	48	2.2	77.5	49.6
7	10	1.7	49	2.5	76.6	50.4
8	11	1.8	50	2.6	77.1	50.6
9	11	1.9	52	2.7	77.5	51
10	13	1.6	64	3.2	80	52.3
11	10	1.8	32	1.7	78.7	50.7
12	10	1.5	50	2.5	76.9	50.3
13	10	1.6	48	2.2	77.7	50.7
14	9	1.8	39	1.8	79.5	51.5

The three first cases are the results with measurement noise introduced. It is interesting to discover that the number of hyperglycemic events is going down with more measurement noise, at the same time as there is only an insignificant increase in time spent in the hypoglycemic range. This is probably caused by the freedom the measurement noise gives the controller to deliver small amounts of insulin to the “patients” even at times where he/she is at target. The positive effect of these small deliveries is that they contribute as “pre-boluses” for food, and the

meals get rejected faster. At the same time the noise is not large enough to create any over delivery of insulin. This is illustrated in Figure 5.6 for Case #3 with Patient #1 as both the controller model and the plant.

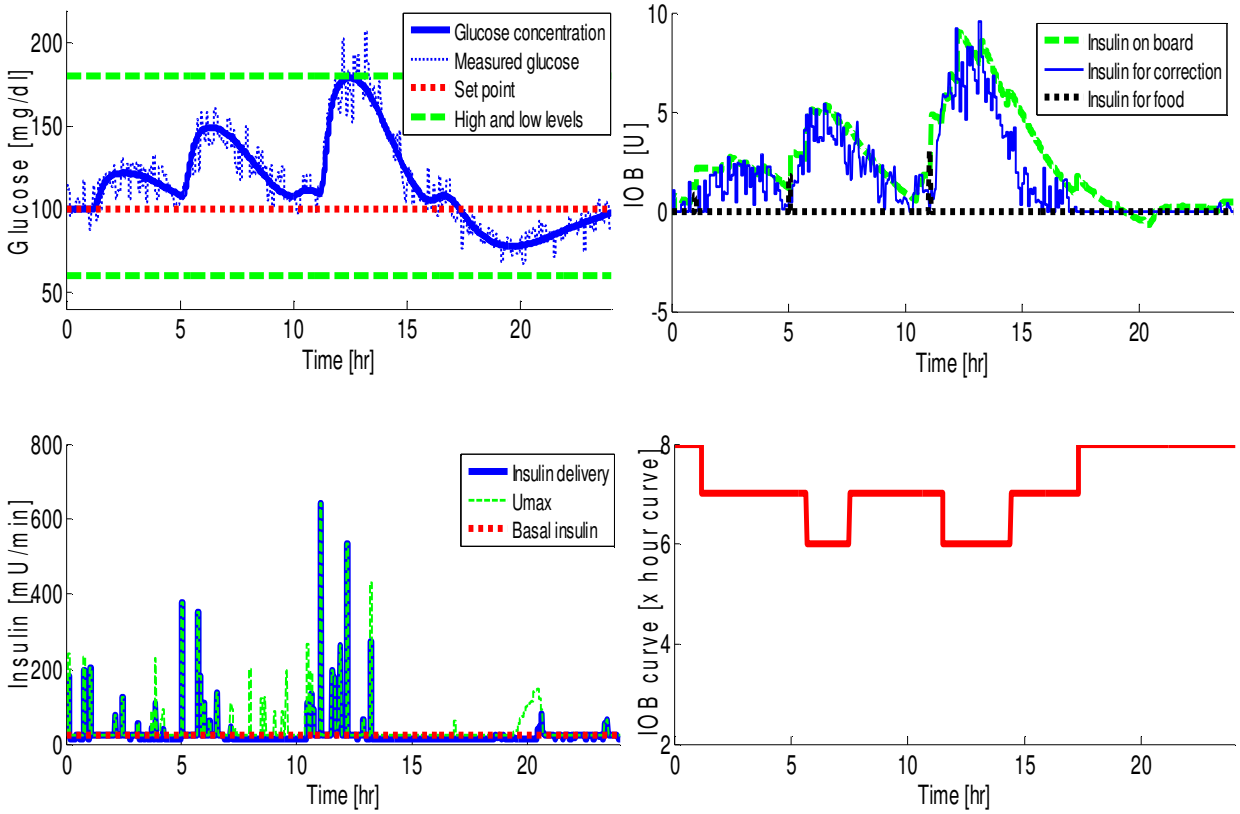

Figure 5.6: This figure shows how the measurement noise gives the controller larger freedom to deliver insulin even when the patient is at the target. The positive effect of this is that the meals get rejected faster as there is delivered larger amount of insulin ahead of the meals. The measurement noise is not large enough to cause any hypoglycemic event for this patient. The example is taken from Case #3 in Table 5.8 with Patient #1 as both the model for the controller and the plant. Upper left: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). Upper right: Plot showing the insulin needed for correction, the insulin needed for food, and how much insulin there is "on board". Lower left: Plot showing the maximum delivery of insulin the MPC- controller could give, actually delivery rate, and the basal insulin requirement. Lower right: Plot showing which insulin action curve is used for the IOB-calculations during the simulation.

Case #4 to #6 is where the meals are smaller than announced and Case #7 to #9 is where the meals are larger than announced. One would expect that when the meals are smaller than announced, there would be more hypoglycemic incidents because of over dosing of insulin. In fact the number of hypoglycemic incidents and time spent in hypoglycemic range goes down. One would also expect that when the meals are larger than announced, there would be less hypoglycemic incidents, but also here the results are slightly opposite of what is expected.

The corresponding results are given in Figure 5.7 and Figure 5.8. Figure 5.7shows the result from Case #6 with Patient #1 as model for both the controller and the plant and Figure 5.8 shows the result from Case #9 with Patient #1 as model for both the controller and the plant. Figure 5.7 clearly shows that the boluses given for the meals are larger for Case #6 than they are for Case #9 in Figure 5.8. This is also expected when it is known that the controller thinks the meals are larger in Case #6 than in Case #9.

The differences lay in what happens after the meals. In the upper plot in Figure 5.7, the first black dashed line show the prediction of the MPC- controller at the time of the breakfast. As expected, this prediction goes higher than what actually happens. But the third prediction line from the left goes lower than the actual glucose measurements, and this indicates that the controller thinks the unknown disturbance is going to continue in the future. To compensate for this the controller turn the insulin delivery to the minimum at an earlier stage than for Case #9 in Figure 5.8. Here the opposite happens. The controller correctly underestimates the contribution from the first meal, but already at the second prediction line, the controller predicts the unknown disturbance to last into the future. It therefore keeps the maximum possible delivery for a longer period of time. The difference in Figure 5.7 and Figure 5.8 is easy to see by comparing how the blue insulin delivery line follows the dashed green maximum insulin delivery line in the two cases. In Case #6 the insulin delivery is lower than the maximum insulin delivery constraint for a longer period of time than in Case #9. The consequence of the controller predictions of future disturbances is that the lowest glucose measurement is lower for the case with underestimated meals in Figure 5.8 than it is for the case with overestimated meals in Figure 5.7.

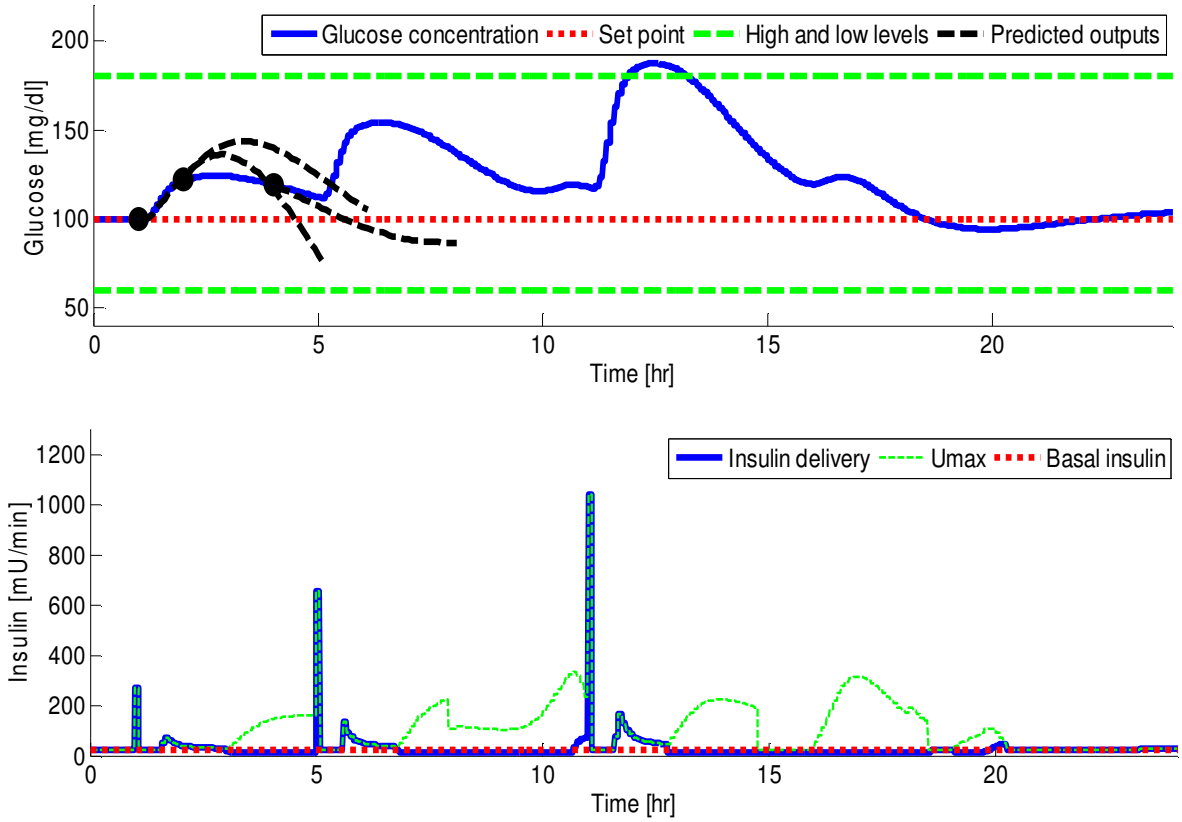

Figure 5.7: Figure showing how the MPC- controller behaves when the meals are overestimated. At the time of the meal the controller correctly predict the glucose to go higher than expected, but over time the Matlab® MPC Toolbox takes the disturbance error into account and predicts the error to last into the future. This makes the controller more conservative, and the result get opposite than expected for an overestimated meal. The example is taken from Case #6 in Table 5.8 with Patient #1 as both the model for the controller and the plant. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

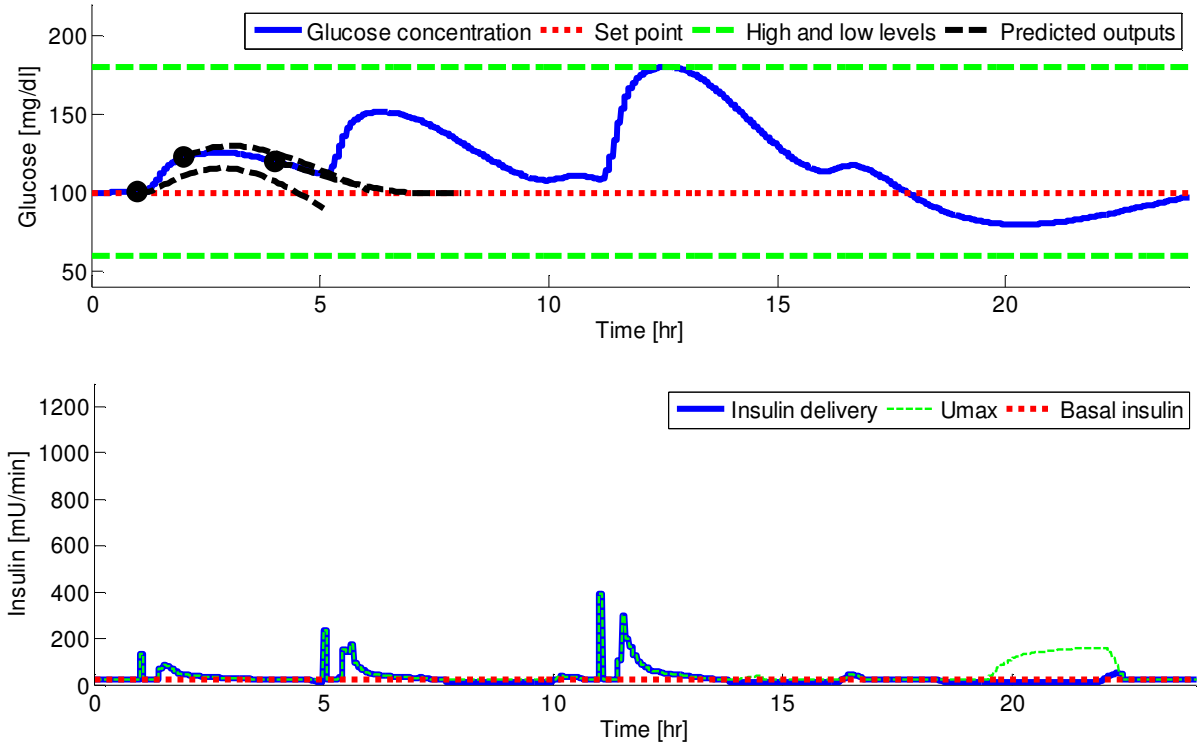

Figure 5.8: Figure showing how the MPC- controller behaves when the meals are underestimated. At the time of the meal the controller correctly predict the glucose to go lower than expected, but over time the Matlab® MPC Toolbox takes the disturbance error into account and predicts the error to last into the future. This makes the controller more aggressive, and the result gets opposite than expected for underestimated meals. The example is taken from Case #9 in Table 5.8 with Patient #1 as both the model for the controller and the plant. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

The MATLAB® MPC Toolbox has a state observer built in its controller algorithm, and if no disturbance model is added by the user, it uses an integrator as disturbance model for each output. When unmeasured disturbances are present in the system, the state observer tries to estimate the unmeasured disturbances for the future. The controller does not know that the meals were over-

or under estimated, and predicts the error to last into the future. This makes the controller more conservative when the meals are overestimated and more aggressive when the meals are underestimated.

Case #10 and #11 in Table 5.10 are when the meals are either announced later or earlier than the actual meals. If the meal is announced later the result shows a significant increase in hyperglycemic events, which was expected. There was also expected that an earlier announced meal would result in less incidences in hyperglycemic events, but it was surprising that this did not give more hypoglycemic events. If a meal could be announced as much as one hour ahead of a meal without increased danger of hypoglycemia, it would be very positive for the artificial β-cell.

Case #12 to #14 is with measurement noise, and random numbers for announced meal sizes and announced meal times. None of the cases show any alarming results and do mostly follow the result for the rest of the cases. Again there is evidence that larger measurement noise gives the MPC- controller more freedom to prevent hyperglycemia, and that without any significantly increase in hypoglycemic events.

6 Modified IOB- controller

The results achieved with the constrained MPC- controller in Chapter 5 raises the question of whether the MPC- controller with IOB is too conservative. It would therefore be interesting to see the performance of the most aggressive controller based on IOB- calculations. This is studied in this section by delivering the maximum allowed insulin delivery rate at every sample time during the daytime portion of the simulation. During the night, the MPC- controller with IOB gets turned on again. This is because the IOB- calculations are developed to handle meal rejections and not small fluctuations from basal at night.

6.1 Experimental

In this study the regular MPC- controller gets turned of during the daytime of the simulation. That means that when the simulation start at 07:00 in the morning, the controller action is solely based on the maximum insulin delivery rate defined by the IOB- calculations given in Chapter 4.2. This implies that there are no other tuning parameters than the I:C ratio, the CF, and the choice of insulin action curves. The values for these parameters and the meal scenario are still the same as given in the simulation studies in Chapter 5.

The MPC- controller with IOB is turned on 3 hours after the last meal and stays on for the rest of the simulation. The tuning parameters for the MPC- controller are the same as in Table 5.5. All the cases with measurement noise, uncertainties in meal sizes and uncertainties in meal times that are given in Table 5.8 are carried out, as well as the case without these uncertainties (denoted as Case#0). Patient #1 is used as model for the nighttime MPC- controller in all the simulations, while all the patients have been used as the plant. This gives a total of 10 simulations for each case.

6.2 Results

Table 6.1 shows the result for the modified IOB- controller. The trends in the results are the same as in the results for the MPC- controller with IOB given in Table 5.10. There is seen a slight increase in time spent in the hypoglycemic range, and this was also excepted because the modified IOB- controller is more aggressive.

An interesting observation is that there are only two "patients" that go hypoglycemic in the simulations, and that is Patient #3 and Patient #6. This shows that these patients need to recalculate their I:C ratios and CF's, or they have to choose more conservative insulin action curves for their modified IOB- controller.

As a result of the more aggressive insulin delivery, there are less hyperglycemic events and the "patients" reduce their time spent in the hyperglycemic range. At the same time they increase their time spent in the acceptable 60-140 mg/dl range. All the results make sense when it is observed that the average daily insulin delivery is slightly increased with the modified IOB-controller compared to the MPC- controller with IOB.

Also in these simulations the time spent in hypoglycemic range decreases with larger announced meals (as seen in Case #4 to Case #6). One could think that the effect of the Matlab® MPC Toolbox state observer would disappear when the MPC- controller is shut down for most of the simulation time, but Figure 6.1 and Figure 6.2 shows how the MPC- controller affect the results when it is turned on 3 hours after the last meal. Figure 6.1 is taken from Case #0 with Patient #6 and Figure 6.2 is taken from Case #6 with Patient #6. Both figures show how the insulin delivery goes under basal requirement at 14 hours when the MPC- controller gets turned on. The difference is that the MPC- controller stays under basal requirement for a longer period of time in the case where the announced meals where larger than the actual meals, and it does not give the same amount of insulin around 15 hours that is the case for the correct announced meal in Figure 6.1. The reason for this behavior is that the MPC algorithm in this application runs in the background during the day time, and therefore collects the data. This causes the controller to take into account the errors in the meal announcements. When the controller then gets turned on, the

state observer estimates the disturbance for the future, and do it wrong because there have been so many overestimated meals during the day. The effect is a more conservative controller, which was luckily a good thing for the "patient" in Figure 6.2.

Table 6.1: Results for the modified IOB- controller. Case #0 denotes the case with no measurement noise and no meal uncertainties, while the rest of the cases are those given in Table 5.8. The table shows how many of the 10 simulations in each of the cases that went hypo- and hyperglycemic. Further it shows the total time of all the 10 simulations that were spent in the hypo- and hyperglycemic ranges. As a measure of performance the time spent in the blood glucose range of 60-140 mg/dl is given. The table also shows how much insulin that was given to each of the patients in average through the day.

Case:	# of hypoglycemic events:	% of time < 60 mg/dl	# of hyperglycemic events	% of time > 180 mg/dl	% of time in 60-140 mg/dl range	Averagely delivered insulin (U)
0	2	2.2	1	0.5	80.9	52.8
1	2	2.4	1	0.5	81.5	53.2
2	2	2.7	1	0.5	82.8	53.8
3	2	3.2	1	0.4	84.3	54.9
4	2	2.1	1	0.5	81.6	52.7
5	2	1.2	1	0.5	83.2	52.7
6	1	1	1	0.4	84.3	52.8
7	2	2.4	1	0.5	80.1	52.9
8	2	2.5	2	0.8	79.3	53
9	2	2.6	4	1.4	78.6	53.3
10	1	1.1	4	1.4	82.8	53.4
11	2	2.6	1	0.4	83.1	52.8
12	2	2.4	1	0.5	82	53.3
13	2	3.1	1	0.5	82.6	54.1
14	1	1.5	1	0.4	86.5	54.8

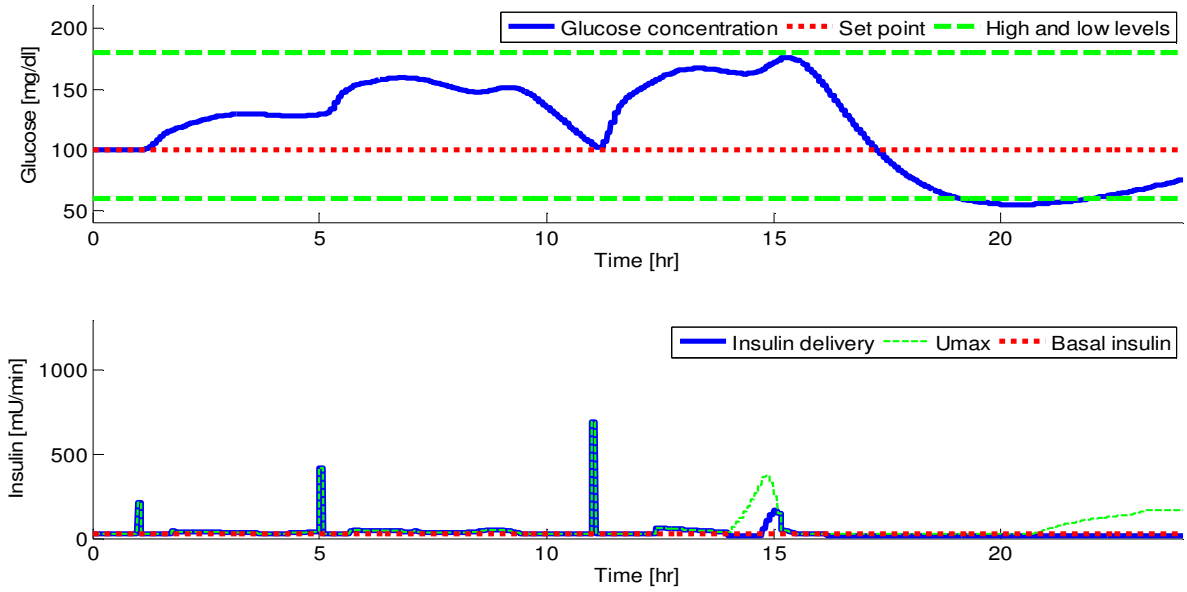

Figure 6.1: This figure shows an example of what could happen if the patient has too aggressive values for the I:C ratio and the CF. The IOB- constraint does not prevent the controller in giving too much insulin for the last meal, and a postprandial hypoglycemic event occur. The example is taken from Case #0 in Table 6.1 with Patient #6 as the plant. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and low level (definition of hypoglycemia is set to 60 mg/dl). Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

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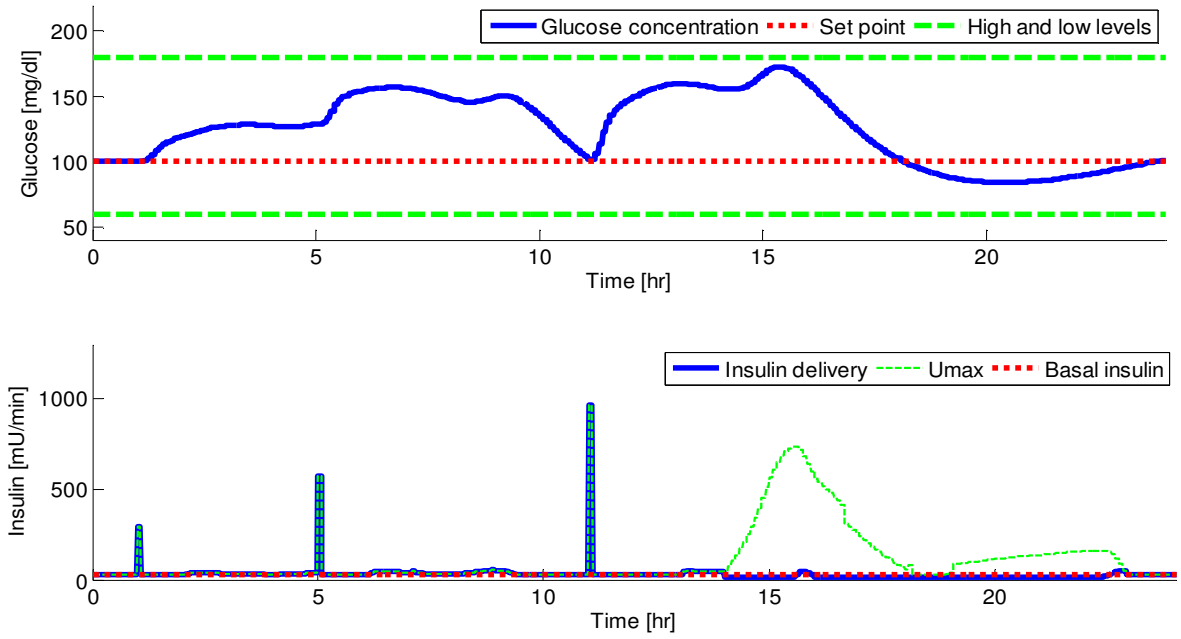

Figure 6.2: This figure shows how the Matlab® MPC Toolbox state observer affect the result when the MPC- controller gets turned on three hours after the last meal. Because the MPC-controller has run in the background during the whole day, it has collected data about the over overestimated meals during the day. This causes the state observer to predict that there is a disturbance going on that causes the blood glucose to go lower than predicted, and the controller estimates this to continue in the future. The consequence is a more conservative controller, which in this case prevent the patient to go hypoglycemic as was the case in Figure 6.1. The example is taken from Case #6 in Table 6.1 with Patient #6 as the model for plant. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

7 *In silico* evaluation of a clinical trial

The first thing necessary when making an MPC- controller for a T1DM patient is to develop the prediction model that describes the behavior of the patient. This could be done by collecting input/output data and then develop an ARX model from this data. The ARX model would then serve as the prediction model for the MPC- controller. In this section there is performed an *in silico* evaluation of a clinical trial.

7.1 Experimental

Development of ARX models

Four days with open loop data for insulin delivery, meals and glucose measurements were collected by running the T1DM simulator. The data was used to develop an ARX model for the "patient" with insulin delivery as manipulated input, meals as measured disturbance and blood glucose as measured output. This was performed for all the ten available patients. The models where then used as prediction models for the MPC- controller, and the T1DM simulator were again used as the *in silico* patients.

The ARX models are developed on data without measurement noise on the blood glucose, no noise on insulin delivery, and the correct estimations of CHO in the meals.

Controller tuning

The basic tuning parameters for the MPC- controller are given in Table 7.1. They are relaxed compared to the tuning parameters given in Table 5.5 in an attempt to get safer control in the cases without IOB, and because there is no soft constraint on low blood glucose values in this section. The insulin action curves are chosen as in Table 5.6.

Table 7.1: Basic controller tunings for the MPC controllers used in the *in silico* evaluation of clinical trial

Tuning parameter:	Value:
Sample time	5 minutes
Prediction horizon	50 sample intervals
Control horizon	5 sample intervals
Weight on change in insulin infusion rate	10
Weight on glucose set point tracing	1
Lowest allowable insulin delivery	0.5 times basal rate

Simulation studies

The meal scenario in this study is the same as before, and is given in Table 5.1. No studies with measurement noise and meal uncertainties were performed for this part.

Two different controller configurations have been evaluated. The first is an MPC- controller based on the ARX models without IOB. The second configuration is an MPC- controller based on the ARX models, but this time with IOB to constrain the maximum insulin delivery. All the ten patients are run in each configuration.

7.2 Results

The *in silico* evaluation of a clinical trial gave some good examples of how different the results could be when developing a model from clinical data. Figure 7.1 shows a closed-loop simulation of Patient #1 with an unconstrained MPC- controller. The insulin delivery in the lower plot is not especially aggressive, but the controller fails to avoid a postprandial hypoglycemic event after the dinner. This result could be avoided by relaxing the tuning parameters for the MPC- controller, but it would be better if the controller could be tuned in front of the first implementation and based on some simple clinical tests.

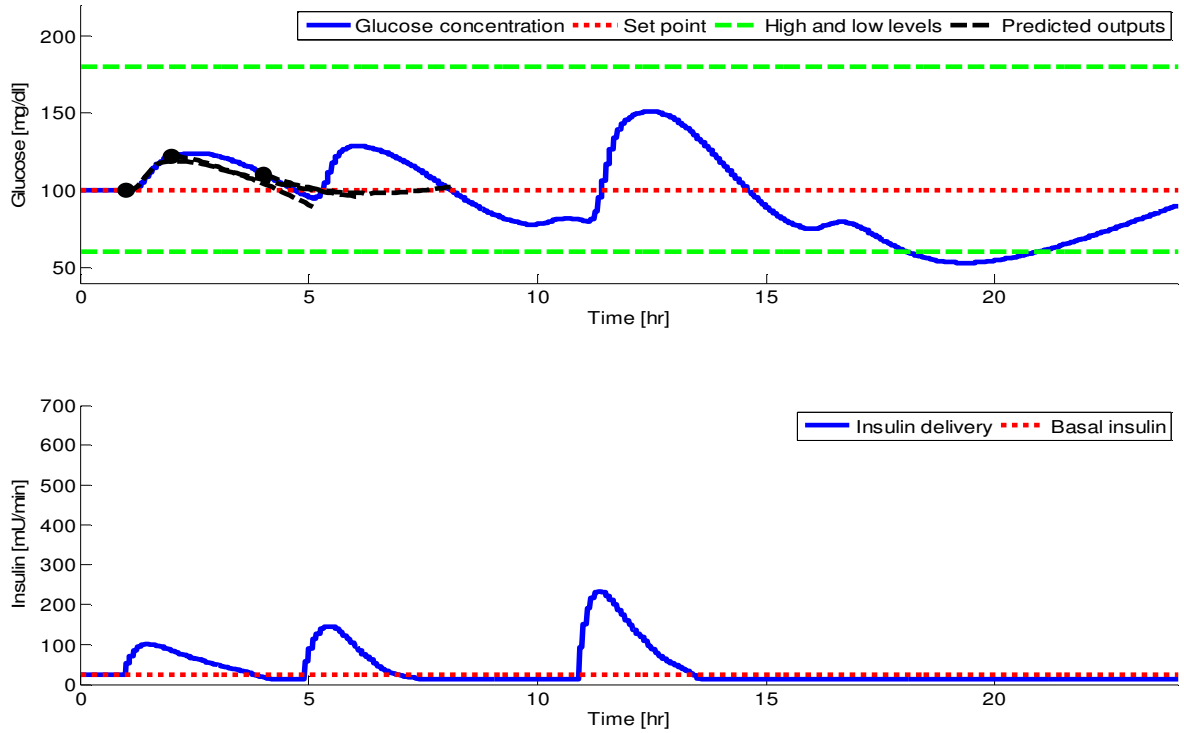

Figure 7.1: This is an example where the MPC- controller delivers too much insulin to the patient as a result of aggressive tuning of the MPC- controller and model/plant mismatch. The example is taken from Patient #1 and the unconstrained MPC- controller in the in silico evaluation of a clinical trial. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Lower plot: Plot showing the maximum delivery of insulin the MPC-controller can give, actually delivery rate, and the basal insulin requirement.

Figure 7.2 shows the same patient when using the MPC- controller with IOB. The patient avoids any hypoglycemic events by giving the controller the I:C ratio and the CF. These values are known to the patient in advance of the implementation, and were easy to implement in the controller. The controller performance is slightly reduced in the case of high blood glucose values, but the critical hypoglycemic events are avoided.

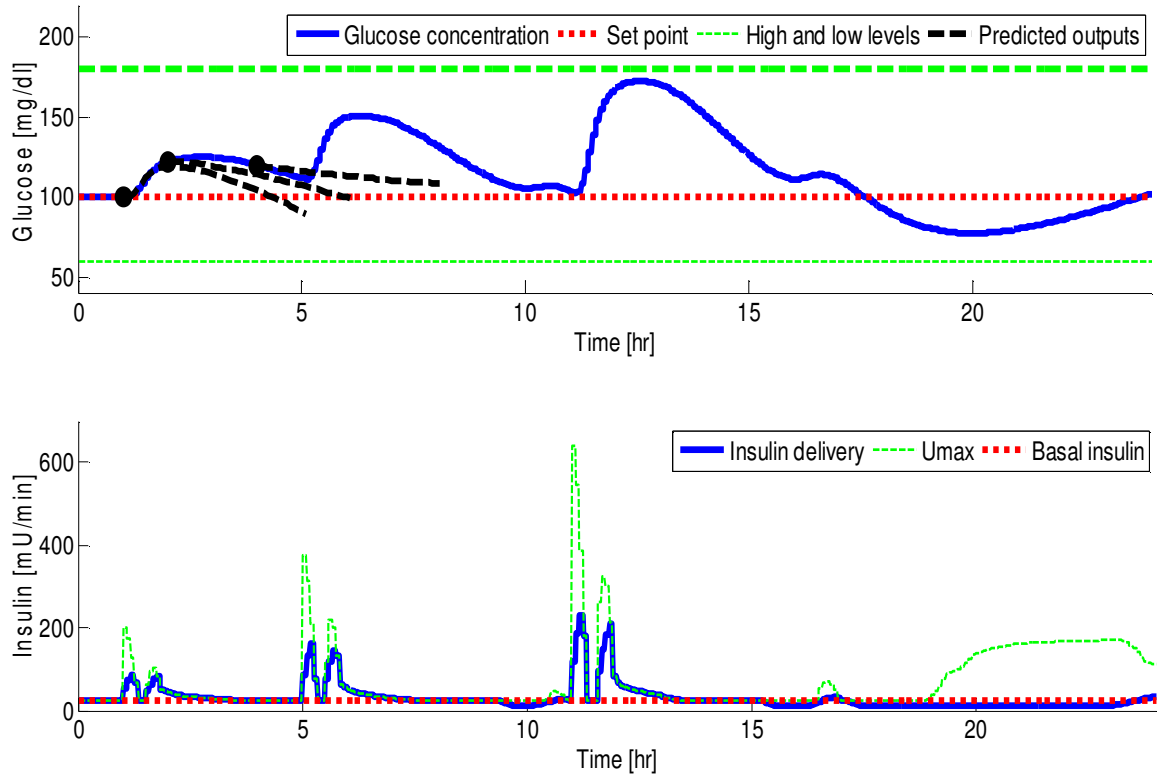

Figure 7.2: The figure is showing the same patient as in Figure 7.1 with the same tuning parameters for the MPC- controller, but this time the algorithm also include IOB to constrain the maximum insulin delivery. No hypoglycemic events are observed, and the performance is still acceptable. The example is taken from Patient #1 with the constrained MPC- controller in the in silico evaluation of a clinical trial. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Lower plot: Plot showing the maximum delivery of insulin the MPC-controller can give, actually delivery rate, and the basal insulin requirement.

Figure 7.3 shows Patient #7 and is an example of a patient that was fortunate with the tuning parameters. The figure is taken from the unconstrained MPC- controller and shows much better results than the constrained MPC- controller in Figure 7.4. The result in Figure 7.3 is also an example on a case where the controller performs well, but the insulin deliveries for the meals would be to concern for the physicians. To avoid any postprandial hypoglycemic events after the large insulin deliveries for the meals, the controller lowers the insulin delivery to half the basal

insulin requirement for a long period of time. This contradicts to the traditional way of treating T1DM, and has never been tried out in practice. The result in Figure 7.4 does not have the same performance as for the unconstrained MPC- controller, but the insulin delivery would deemed acceptable.

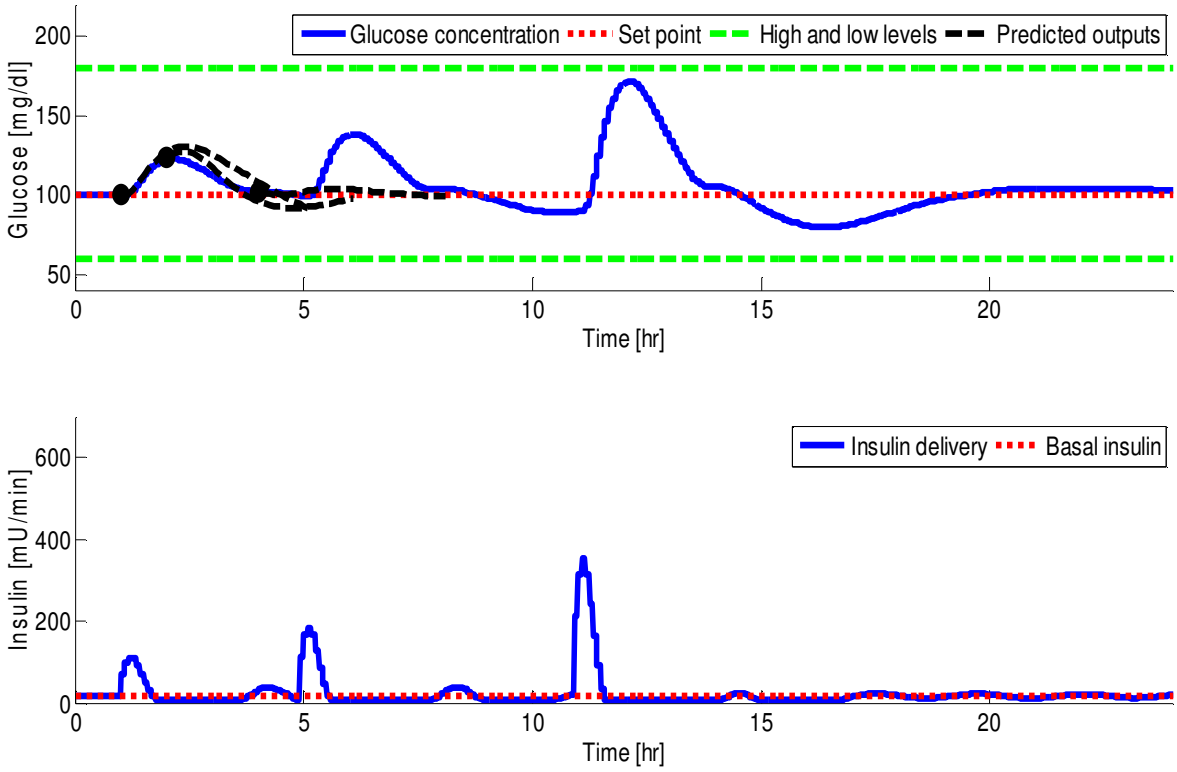

Figure 7.3: This is an example where a good performance is achieved without IOB. The controller is aggressive, but do not cause any over delivery of insulin. The example is taken from Patient #7 with the unconstrained MPC- controller in the in silico evaluation of a clinical trial. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

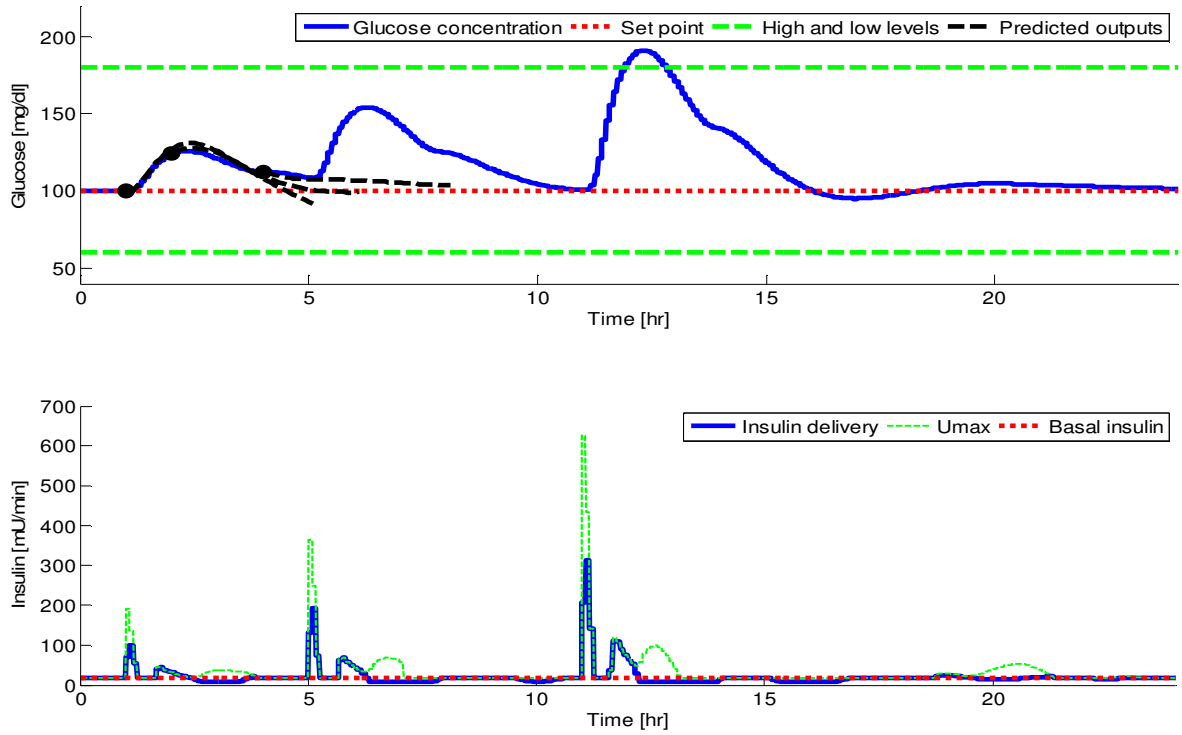

Figure 7.4: The figure is showing the same patient as in Figure 7.3 with the same tuning parameters for the MPC- controller, but this time the algorithm also include IOB to constrain the maximum insulin delivery. The performance is reduced compared to the unconstrained case, but is still acceptable. The example is taken from Patient #7 with the constrained MPC- controller in the in silico evaluation of a clinical trial. Upper plot: Plot showing the glucose concentration, the set point trajectory, the high level (definition of hyperglycemia is set to 180 mg/dl), and the low level (definition of hypoglycemia is set to 60 mg/dl). The plot also shows three prediction trajectories for the MPC- controller. Lower plot: Plot showing the maximum delivery of insulin the MPC- controller can give, actually delivery rate, and the basal insulin requirement.

Table 7.2 shows the result for all the "patients" with the MPC- controller without IOB, while the results for the constrained MPC- controller are given in Table 7.3. By comparing the values in the two tables, it could be observed that the MPC- controller with IOB prevent any hypoglycemic events Patient #1, Patient #2, Patient #8 and Patient #9. The MPC- controller with IOB also reduces the time spent in the hypoglycemic range for Patient #3 and Patient #6. These two

"patients" should recalculate their I:C ratios and CF's in order to avoid hypoglycemic events with the MPC- controller with IOB.

Table 7.2: The table gives the results for the unconstrained MPC- controller in the *in silico* evaluation of a clinical trial.

Patient #:	Hypo-glycemia:	% of time < 60 mg/dl	Hyper-glycemia:	% of time > 180 mg/dl	% of time in 60-140 mg/dl range	Delivered insulin (U)
1	Yes	11.9	No	0	82.0	55.2
2	Yes	42.8	No	0	51.6	39.2
3	Yes	16.8	Yes	0.6	75.2	154.3
4	No	0	No	0	100.0	33.1
5	No	0	Yes	1.9	89.5	56.8
6	Yes	85.6	No	0	14.4	66.5
7	No	0	No	0	94.4	35.4
8	Yes	25.9	No	0	74.1	38.8
9	Yes	8.3	No	0	86.4	85.6
10	No	0	No	0	93.9	53.5

Patient #4, Patient #5, Patient #7 and Patient #10 reduces their performance with the MPC-controller with IOB. They did not have any hypoglycemic events with the unconstrained controller, and because of the conservative nature of the MPC- controller with IOB, they increase their time in the hyperglycemic range with the constrained controller. This makes the MPC-controller with IOB to look worse than the MPC- controller without IOB from a controller engineer prospective. If one look at the performances from a clinical prospective the performance are acceptable with both the controllers for these "patients". A physician would probably consider the MPC controller with IOB as the preferable controller because it guarantee insulin deliveries that corresponds to the patient's I:C ratio and CF.

Table 7.3: The table gives the results for the constrained MPC- controller in the *in silico* evaluation of a clinical trial.

Patient #:	Hypo-glycemia:	% of time < 60 mg/dl	Hyper-glycemia:	% of time > 180 mg/dl	% of time in 60-140 mg/dl range	Delivered insulin (U)
1	No	0	No	0	79.7	45.6
2	No	0	No	0	83.1	30.7
3	Yes	9.4	Yes	4.9	75.3	131.1
4	No	0	Yes	4.9	65.7	29.9
5	No	0	Yes	5.8	80.6	50.2
6	Yes	12.7	No	0	49.1	47.1
7	No	0	Yes	3.8	83.7	31.8
8	No	0	No	0	84.2	33.1
9	No	0	No	0	90.3	61.8
10	No	0	Yes	1.3	81.3	47.1

The summary of the results from the *in silico* evaluation of a clinical trial is given in Table 7.4. Again the constrained MPC- controller shows significant better results for preventing hypoglycemia, and this without spending very much time in the hyperglycemic range.

Table 7.4: Summary of the results for the *in silico* evaluation of a clinical trial. The table shows how many of the 10 simulations in each of the cases that went hypo- and hyperglycemic. Further it shows the total time of all of the 10 simulations that were spent in the hypo- and hyperglycemic ranges. As a measure of performance the time spent in the blood glucose range of 60-140 mg/dl is given. The table also shows how much insulin the different controller configuration gave to each of the patients in average through the day.

IOB:	# of hypoglycemic events:	% of time < 60 mg/dl	# of hyperglycemic events	% of time > 180 mg/dl	% of time in 60-140 mg/dl range	Averagely delivered insulin (U)
No	6	19.1	2	0.3	76.2	61.8
Yes	2	2.2	5	2.1	77.3	53.8

8 Discussion

The simulations studies performed in this work show that the novel approach of MPC- control with IOB is a safe and reliable algorithm to prevent hypoglycemia. It is easy to understand for physicians because it corresponds with the traditional treatment of T1DM. The tuning parameters for the approach is the patients I:C ratio, CF and the choice of insulin action curves. If these tuning parameters are set conservatively enough, the controller would be safe in respect to hypoglycemia also in the worse cases of model/plant mismatch.

One could argue that the model should be improved when the model/plant mismatch is large, but because diabetes is a large and growing problem, one could not expect that this would be practical. It would be much more realistic that there were some models available for the physicians to choose. The tuning parameters should be something they are familiar with (i.e. I:C and CF), and this is the strength of MPC- controller with IOB.

The weakness of the MPC- controller with IOB is that it makes the controller more conservative than would be the most effective treatment. It deliver the insulin in a way that correspond to the traditional way of treating T1DM, but that does not mean that this is the most effective way to treat this disease. The insulin delivery for a healthy person is much more aggressive than the traditional way of treating T1DM, and in the long-term one should aim at more aggressive algorithms to treat T1DM. To achieve this, the controller must be able to give a larger delivery rate in advance of and/or during meals, and then relax the basal insulin delivery for some time after the meal to avoid hypoglycemia. This does not sound safe for all people involved in the development of the artificial β-cell, and the development should therefore take small and safe steps towards better and more aggressive controller algorithms.

Although the MPC- controller with IOB is a conservative controller; it would make a huge difference for many patients with T1DM as the majority of them have elevated blood glucose for long periods of time. This especially includes children and adolescents that are not capable of or do not want to take care of their disease. For these patients it would be a tremendous

improvement to have a controller that could bring their blood glucose values down to lower levels without danger of hypoglycemia.

For the controllers studied in this work, the modified IOB- controller had the best performance without any significant increase in hypoglycemic incidents and time spent in the hypoglycemic range. This suggest that the modified IOB- controller could be used for meal disturbances during the day and that another control algorithm could take care of the periods with less contribution from meals. There is no reason that a more complicated algorithm such as the MPC- controller with its QP solver would be necessary, as long as the modified IOB- controller guaranteed the most aggressive control achievable with the IOB- constraint.

There are many challenges that have to be overcome to achieve an artificial β-cell, and the MPC-controller with IOB can not solve all of them alone. The complete artificial pancreas would contain a set of different algorithms to secure a safe insulin delivery for the patient. It is well known that within an individual, insulin sensitivity varies over time, and also during each day. This is something the controller must be able to handle, and adaptive algorithms have to be included to achieve this. One possibility could be to use Iterative Learning Control (ILC) [12] to update values for the I:C ratio and the CF. ILC is an algorithm developed for batch processes, where information from earlier batches are used to update some parameters for the future. In T1DM, each day could be seen as a batch process, and this is something that open up for the possibility to include an ILC algorithm in the controller.

Another main problem in diabetes control is the meal disturbance. MPC- controller with IOB has shown good results in rejecting meals in this work, but the meals have been announced to the controller. This would not necessarily be the case in the real world, and there should be an algorithm included in the controller that detects any meal that is not announced. Dassau et al. [2] have proposed an algorithm that detects meals using continuous glucose monitoring (CGM). This could be used in a controller to flag a meal, and then turn on the modified IOB- controller.

9 Conclusion

The MPC- controller with IOB to constrain maximum insulin delivery shows good results on preventing hypoglycemia when there are large mismatches between the model for the MPC-controller and the actual plant (patient).

The best results were achieved with a modified IOB- controller that did not include the MPC-controller. This configuration did not give any significant increase in time spent in hypoglycemic range, at the same time as the time spent in hyperglycemic range was reduces compared to the MPC- controller with IOB. The modified IOB- controller should therefore be used for meal rejections, while another algorithm could be used overnight and during other periods without meals.

It is a complex task to achieve an artificial β-cell, and the work presented in this thesis is only part of the solution. A complete artificial β-cell must include several safety features; IOB to constrain the maximum insulin delivery should be one of them. It is essential to include adaptive algorithms that could address the dynamic nature of a T1DM patient. It would also be necessary to have an algorithm that detects meal disturbances that are not announced by the user. This algorithm would also serve as a flag for the controller to turn on the modified IOB- controller for meal rejection.

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Appendix A – Example on insulin on board calculations

The purpose of this appendix is to illustrate in more detail how the Insulin on Board (IOB) calculations are carried out. The example shows an open-loop scenario of a Type 1 Diabetes Mellitus (T1DM) "patient" that is using information about his Insulin to Carbohydrate (I:C) ratio and Correction Factor (CF), together with information about IOB in an attempt to achieve better control of his disease.

The I:C ratio and CF for our imagined "patient" is given in Table A.1, and are chosen such that they could be the values for a real patient. The "patient's" basal insulin requirement is set to 1 U/hr.

Table A.1: I:C ratios and CF's for the "patient"

I:C ratio: (U/g)	CF: (mg/dl/U)
0.1	20

Two insulin action curves are given in Figure A.1. These are the two curves that are used in the calculations executed in this appendix. Insulin action curves give information about how many percent of an earlier insulin injection that is still active in the body x hours after the injection.

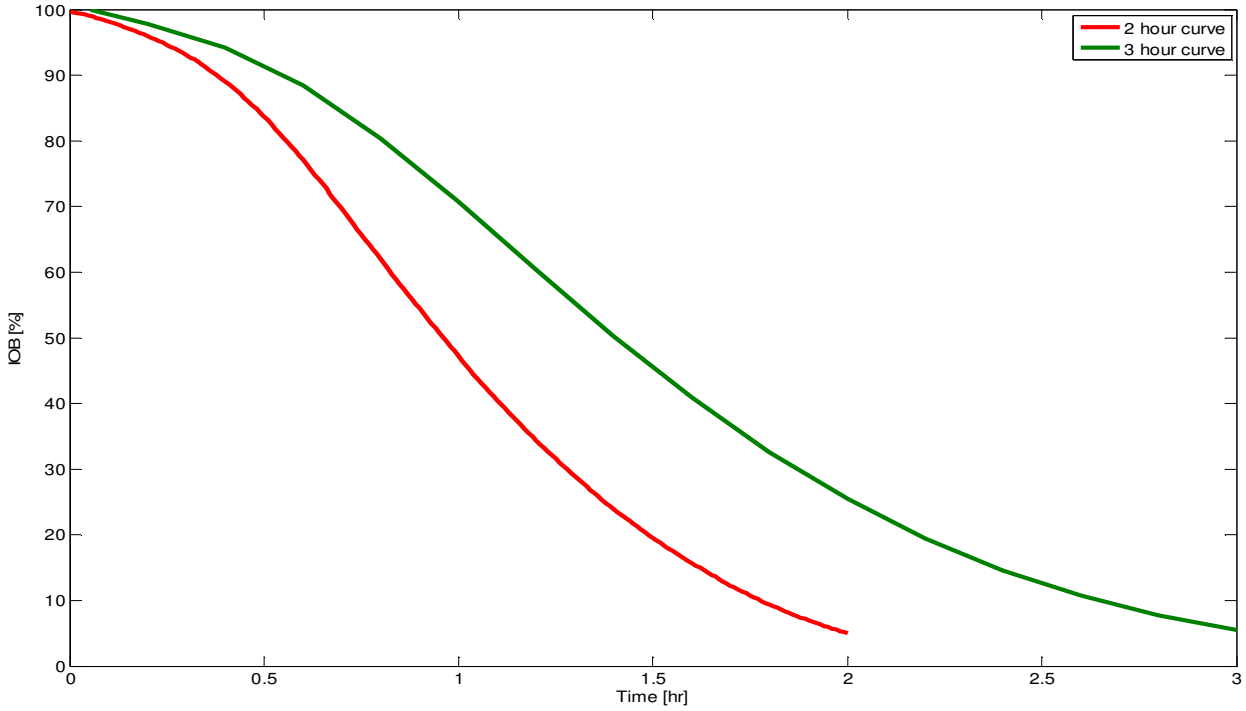

Figure A.1: The figure shows the two insulin action curves that are used for the IOB-calculations in this appendix[3].

An overview of the different events for the example is given in Figure A.2. The upper plot shows the glucose measurements the patient achieves by doing finger pricks. It also shows the desired glucose concentration and the thresholds for hypo- and hyperglycemia. The middle plot shows the insulin boluses given for food and for correction, and the basal insulin delivery. The lower plot shows how much insulin the patient calculates is needed, and how much insulin that is "on board".

The patient does the finger prick every hour, and is therefore able to make a new decision on how much insulin he should deliver at these times. This is comparable to the MPC- controller with IOB, but then the measurement is taken every fifth minute and it is therefore able to correct at an earlier stage.

[3] The data for the figure is taken from: Walsh, J., R. Roberts, *Pumping Insulin,* Torrey Pines Press, fourth ed., 2006, J., R. Roberts, *Pumping Insulin,* Torrey Pines Press, fourth ed., 2006

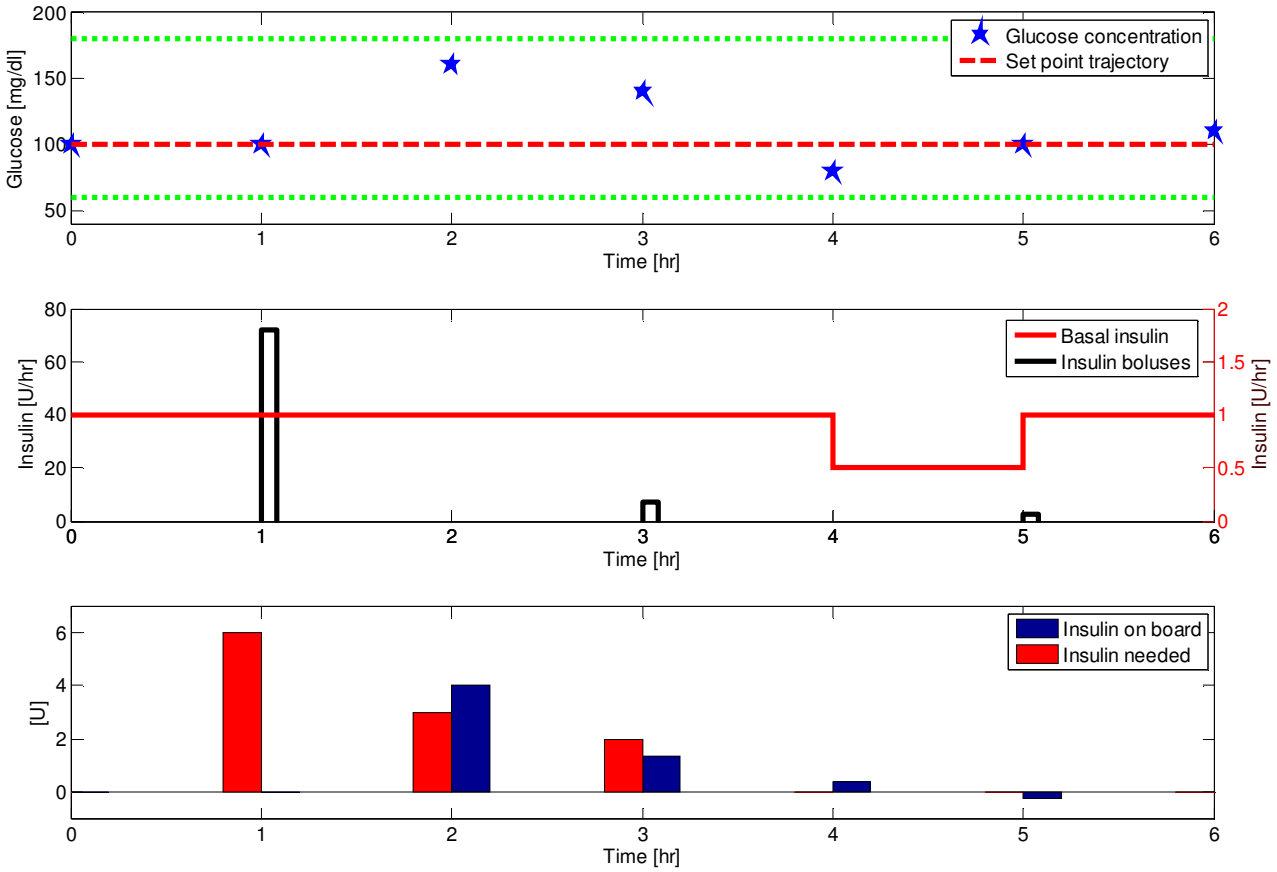

Figure A.2: The figure gives an overview of the different events for the example on IOB-calculations. The upper plot shows the glucose measurements the patient achieves by doing finger pricks. It also shows the desired glucose concentration and the thresholds for hypo- and hyperglycemia. The middle plot shows the basal insulin delivery, and insulin boluses given for food and correction. The lower plot shows how much insulin the patient calculates is needed, and how much insulin that is "on board".

Detailed description of every sampling instant

0 hours:

The "patient" does a finger prick, and the glucose reading shows 100 mg/dl. This is right on target and he does no changes to the basal infusion rate and decides not to give any extra insulin in form of an insulin bolus.

1 hour:

The "patient" is planning a meal that is containing 60 g of carbohydrates (CHO). He does another finger prick, and the glucose reading still shows 100 mg/dl. This means that he only needs to give an extra insulin bolus for the meal. By using his I:C ratio, he finds out that a insulin bolus of $0.1\ U/g \cdot 60\ g = 6\ U$ should cover for the meal. This amount is given by the pump as an increased insulin delivery of $\frac{6\ U \cdot 60\ min/hr}{5\ min} = 72\ U/hr$ for five minutes and is illustrated as the first extended insulin bolus given in the middle plot in Figure A.2.

2 hours:

The "patient" does a new finger prick to check his glucose concentration one hour after the meal. His glucose reading shows 160 mg/dl, and by using the CF the "patient" finds out that it would require an extra insulin delivery of $\frac{160-100\ mg/dl}{20\ mg/(dl \cdot U)} = 3\ U$ to lower the glucose concentration back to the normal value. This information is given to his insulin pump, but by using the 3 hour curve in Figure A.1, the pump calculates that $6\ U \cdot 66.4\ \% = 4\ U$ is already "on board". The recommendation from the pump is not to give any extra insulin bolus, and the "patient" follows this advice.

3 hours:

This is really a "patient" that likes to take control over his disease, and after 3 hours he takes another finger prick. This time the glucose reading shows 140 mg/dl. The CF says that this would an extra insulin delivery of $\frac{140-100\ mg/dl}{20\ mg/(dl \cdot U)} = 2\ U$. This time the IOB remaining from the meal bolus is $6\ U \cdot 22.8\ \% = 1.4\ U$, and the pump therefore recommends an extra insulin delivery of $0.6\ U$. This amount is given by the pump as an increased insulin delivery of $\frac{0.6\ U \cdot 60\ min/hr}{5\ min} = 7.2\ U/hr$ for five minutes and is illustrated as the second extended insulin bolus given in the middle plot in Figure A.2.

4 hours:

The "patient" knows that his insulin sensitivity changes during the day, and in anxiety that too much insulin has been delivered he does another finger prick after 4 hours. The glucose reading shows 80 mg/dl, and in a normal situation a patient would eat something that contains CHO to raise the glucose concentration. Unfortunately our "patient" is at a mountain trip for the moment, and he forgot to bring anything to eat or drink. He therefore decides to lower his basal insulin delivery to half the basal insulin requirement in an attempt to get the glucose concentration to rise. This is also what an MPC- controller with insulin as the only input would do in a situation like this.

5 hours:

The "patient" wants to see if the lowering of the basal insulin delivery really managed to raise the glucose concentration. The glucose reading shows 100 mg/dl and is right on target, but this "patient" is an experienced T1DM patient, and he knows that the glucose concentration might still be rising as a result of the under delivery of insulin that has been going on for the last hour. He therefore checks the IOB- calculations on his pump, and it tells him that there is $-0.2\ U$ of insulin "on board". Insulin pumps that are on the market today do not include anything called "negative IOB", but it has been included for the MPC- controllers that are implemented in this work. The "negative IOB" is a result of the insulin delivery under basal requirement, and is included such that the MPC- controller are able to give a small stabilizing "bolus" when the glucose concentration is on its way up again after being low. 4 hours after the first extended bolus, no insulin is "on board" from this insulin delivery. It is still $0.6\ U \cdot 22.8\ \% = 0.137\ U$ left "on board" from the second extended bolus given after 3 hours. The insulin delivery under basal requirement was delivered for the last hour, and the deliveries are divided into five minute samples and multiplied with a vector that contains information about the amount of earlier insulin doses that are still active. It is not preferable to have too much "negative IOB" because this could result in an overcorrection, and the 2 hour curve in Figure A.1 is used for all insulin deliveries under basal requirement. The under deliver of $-0.5\ U/hr$ correspond to a under delivery of $\frac{-0.5\ U/hr \cdot 5\ min}{60\ min/hr} = -0.04\ U$ per sampling instant. The "negative IOB" could then be calculated as:

$$-\begin{bmatrix}0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04 & 0.04\end{bmatrix}\cdot\frac{1}{100}\begin{bmatrix}96.7\\94.6\\91.9\\88.3\\83.7\\78.2\\72.1\\65.8\\59.4\\53.2\\47.2\\41.6\end{bmatrix}=-0.364$$

The total insulin "on board" is then $0.137\ U\ +\ (-0.364\ U) = -0.2\ U$. Insulin needed for correction is $0\ U$ because the glucose concentration is at 100 mg/dl. The "patient" decides to deliver the stabilizing insulin delivery of $0\ U - (-0.2\ U) = 0.2\ U$ in an attempt to avoid high glucose values later as a consequence of the under delivery of insulin.

6 hours:

The last finger prick show that the small stabilizing bolus prevented any high glucose concentrations as a consequence of the under delivery during the mountain trip.

Appendix B – Abstract for the Diabetes Technology Meeting

This is an abstract that is going to be submitted for the Diabetes Technology Meeting (DTM) in Bethesda, Maryland in November this year.

Safety constraints in an artificial β-cell: an implementation of Model Predictive Control (MPC) with Insulin-on-Board (IOB)

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Objective

An artificial β-cell controller should regulate both the basal insulin delivery and overcome disturbances such as meals without excessive delivery of insulin that can cause severe hypoglycemia. The nature of the problem is that there can be a substantial mismatch between the controller model and the actual patient's dynamic behavior that can result in an overdose of insulin. A novel way to address this potential risk is the use of adaptive insulin-on-board (IOB) together with clinical parameters such as the insulin to carbohydrate ratio (I:C) and the correction factor (CF) to constrain the insulin delivery.

Method

A simulation study of T1DM subjects based on the Dalla Man et al (2007) model was performed in MATLAB® and Simulink® (The MathWorks, Inc., Natick, MA). The controller was developed using the MATLAB® MPC toolbox with IOB to update the maximum insulin delivery at each time step. Ten *in silico* subjects were used to evaluate the algorithm and the controller for a given patient was evaluated against all ten patient models to evaluate the robustness of the approach.

Result

Following 100 simulation scenarios, we observed that the proposed methodology decreased the incidence of hypoglycemia from 48% (without IOB constraint) to 10% (IOB constraint implemented). It should be noted that 90% of the observed hypoglycemic incidents are related to the same *in silico* patient, suggesting incorrect I:C and/or CF values in the original publication.

Conclusion

Constrained insulin delivery by IOB calculations provides a safe and robust insulin delivery and generalizes, in an intuitive manner, the current practice implemented on most pumps. This is an essential component of any future artificial β-cell for a safe and effective therapy.