2009 American Control Conference
Hyatt Regency Riverfront, St. Louis, MO, USA
June 10-12, 2009

Robustness Properties of Optimal Insulin Bolus Administrations for Type 1 Diabetes

Harald Kirchsteiger, Luigi del Re, Eric Renard and Margot Mayrhofer

Abstract— **Type 1 diabetic patients compensate the lack of endogenous insulin by basal delivery and bolus injections at meal-times. Exact dosage of the bolus amount is critical to keep the blood glucose both below the maximum limits and above the hypoglycaemia critical values. Determination of the optimal dosage would require information which in general is not available to the patient, who uses empirical rules of thumb to choose the dosage. Although closed loop control obtained by linking insulin delivery from insulin pumps and continuous glucose monitoring systems may be considered as the ultimate solution, multiple daily insulin injections and finger stick glucose measurements remain the current mode of therapy. This paper is concerned with this conventional insulin treatment and is based on the use of model predictive techniques extended to approximate continuous control output signal by single control moves in time. The paper shows that substituting continuous measurement and insulin delivery with discrete values leads to a suboptimal control performance, but that this residual defect is not essential if compared with estimation errors of model parameters, patient inputs and/or measurements. Furthermore, the approach proposed shows in simulation sufficient robustness margins. Computations are done with an extended Bergman model tuned on available data of Type 1 diabetic patients.**

I. Introduction

With more than 246 million affected people worldwide, diabetes mellitus is one of the most widespread diseases and causes 3.8 million deaths per year, similar to HIV/AIDS [2]. Type 1 diabetes is characterized by the inability of the beta cells of the pancreas islets to produce insulin, which is essential for the uptake of glucose in the muscles and storage in the liver. Type 2 diabetic patients combine a partial defect of insulin secretion and reduced insulin sensitivity. Although Type 2 diabetic patients may finally need insulin administrations, Type 1 diabetic patients need exogenous insulin delivery from diagnosis to allow survival.

In *practice*, the common treatment for Type 1 diabetes consists of one slow acting insulin analogue injection per day to ensure a basal insulin concentration and several single shots (*e.g.* one for each meal) of a fast acting insulin analogue. The injections are usually given in the subcutaneous tissue via an insulin pen. The *insulin dosage* follows rules of thumb, *e.g.* with an amount linear to the estimated carbohydrate content of the meal. To get a feedback of the glucose control, several daily finger prick blood glucose (BG) concentration measurements should be made as well, and following insulin injections are adjusted according to these measurements.

Since the 1970s, insulin delivery can also be achieved by continuous subcutaneous insulin infusion from a portable pump, and recent research work tried to link insulin infusion to continuous glucose monitoring systems. These approaches cover standard PID-control [3], model predictive control [4-6], non-linear model predictive control [7], robust H_∞control [8] and even sliding mode control [9]. An insulin pump has the great advantage of allowing a programmable basal insulin profile with much less variability than injected long acting insulin analogs. Additionally, single boluses are given from the pump to compensate the effect of a meal.

Although great effort has been given to this topic in the last decades, there is still no system allowing closed-loop, glucose-controlled insulin delivery which is available for sale. On the one hand, this may be due to the fact that up to now, only few continuous measurement devices are approved by the FDA (U.S. Food and Drug Administration), and none of them should replace standard glucose testing via strip measurements. They typically need daily calibrations using finger prick glucose measurements and the sensor element needs to be replaced every three to five days. On the other hand, insulin pumps also have some drawbacks, like the need for a constant carriage which may be quite cumbersome for many patients, and the higher expenses.

In this paper, we consider the standard therapy for Type 1 diabetic patients and try to improve it by optimizing the time of bolus insulin injections and the amount of insulin for each meal. A gain scheduling model predictive controller, based on an extension of the widely used Bergman minimal model [10] for the diabetic patient, was adopted to attain this. The design of the controller was modified in such a way, that only single control moves in time are possible, *i.e.* the control output is zero most of the time and differs from zero only at several time points.

The paper is organized as follows: Section II introduces the mathematical models which we use for our controller and for validation, section III provides the background for control design, section IV presents the basic layout of the glucose control for Type 1 diabetes patient application, section V illustrates the main results, and final conclusions are drawn in section V.

Manuscript received September 22, 2008. The research leading to these results has received funding from the European Community´s Seventh Framework Programme FP7/2007-2011 under grant agreement n° 216592.

H. Kirchsteiger and L. del Re are with the Institute for Design and Control of Mechatronical Systems, Johannes Kepler University Linz, Austria (e-mail: harald.kirchsteiger@jku.at, luigi.delre @jku.at)

E. Renard is with the Centre Hospitalier Universitare de Montpellier (e-mail: e-renard@chu-montpellier.fr)

M. Mayrhofer was with the Institute for Design and Control of Mechatronical Systems, Johannes Kepler University Linz, Austria

II. Models Of The Glucose – Insulin System

A. Extended Bergman minimal model

The Bergman minimal model [10] was one of the first models to describe the relation between glucose and insulin, and due to its simplicity it is widely used in the control community. The model contains three compartments, represented by the following equations [11]:

$$\begin{aligned}\frac{dG(t)}{dt} &= -P_1 G(t) - X(t)\big(G(t)+G_b\big) + D(t)\\ \frac{dX(t)}{dt} &= -P_2 X(t) + P_3 I(t)\\ \frac{dI(t)}{dt} &= -n\big(I(t)+I_b\big) + \frac{U(t)}{V_I}.\end{aligned} \tag{1}$$

G is the plasma glucose concentration above the basal level G_b (mg/dl), X is a quantity proportional to the plasma insulin concentration in a remote compartment (min^{-1}), I is the plasma insulin concentration above a basal value I_b (mU/l), and $V_I = 12\,\mathrm{l}$ is the insulin distribution volume. The model inputs are appearance of ingested glucose in plasma $D(t)$ (mg/dl/min) after a meal and insulin $U(t)$ (mU/min) from an external injection, both having direct effect on the glucose and insulin concentrations in blood. The remaining parameters are [11]

$$P_1 = 0.002, \quad P_2 = 0.025, \quad P_3 = 11\cdot 10^{-3}, \quad n = 5/54. \tag{2}$$

Since a raise in the glucose concentration is usually caused by an oral ingestion of food, and not by intravenous infusion, we extend (1) with a model of the gastro intestinal tract following [12]. The trapezoidal function for the glucose rate of appearance therein is further simplified. We divided the profile into two time periods. In the first interval we assume a constant slope k_1 of the glucose absorption rate after a meal, until a peak value, defined by $D_{\max}$ (3) is reached. The parameter *CHO* denotes the carbohydrate content of the meal. In the second interval, a constant negative slope k_2, assuming $k_1 > k_2$, is supposed, which results in a triangular function *D(t)* (4), see also Fig. 1.

The parameter t_0 is the time when the meal begins, t_1 is the time when the maximum appearance occurs and was estimated with 18 minutes, and t_2 is the time when the glucose appearance reaches zero again and was estimated to 260 minutes. Both time estimations can be validated on real measurement data, *e.g.* in [13]. The remaining parameters are the glucose distribution volume V_G in dl/kg and a tuning parameter k_1.

$$D_{\max} = k_1 \frac{CHO}{V_G\,(t_2 - t_0)} \tag{3}$$

$$D(t) = \begin{cases} \dfrac{D_{\max}}{t_1 - t_0}(t - t_0) & t \in [t_0, t_1],\ t_1 > t_0 \\ -\dfrac{D_{\max}}{t_2 - t_1}(t - t_1) & t \in [t_1, t_2],\ t_2 > t_1 \\ 0 & \text{otherwise} \end{cases} \tag{4}$$

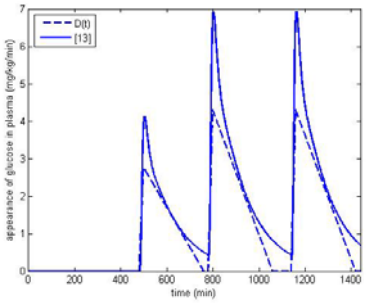

Fig. 1. Appearance of glucose in plasma after meals of 45g, 70g, and 70g of carbohydrates at 8am, 13pm, and 19pm. Solid line: rate of appearance [1], dashed line: triangular approximation

The area under the curve $\int_{t_0}^{t_2} D(t)$ is roughly proportional to the total amount of ingested carbohydrates, *CHO* (g). This simple function *D(t)* is able to approximate much more complex meal models like [1], where the rate of appearance of glucose in the gut is described with a three compartment chain and the emptying rate of the stomach is a nonlinear function depending on six parameters. In total, 10 Parameters need to be estimated from measurement data, whereas our simple approximation only depends on four parameters. Both signals are compared in Fig. 1, where the parameter k_1 was tuned to 0.65 in order to get equivalent results for the glucose concentration of the Bergman minimal model with our meal model when compared with the more complex meal model [1].

A further extension of the Bergman minimal model (1) is necessary due to the fact that insulin is usually given subcutaneously and not intravenously. This results in an additional time delay until insulin diffuses from the tissue where it is injected into the blood plasma. Following [7] the model is extended by

$$\begin{aligned}\frac{dS_1(t)}{dt} &= u_{SC}(t) - \frac{S_1(t)}{t_I}\\ \frac{dS_2(t)}{dt} &= \frac{S_1(t)}{t_I} - \frac{S_2(t)}{t_I}\\ U(t) &= \frac{S_2(t)}{t_I}\end{aligned} \tag{5}$$

where S_1 and S_2 are a two compartment chain representing the insulin, u_{SC} is the subcutaneous insulin administration, U is the appearance of insulin in plasma which is the input for (1), and t_I a time constant depending on the type of insulin analogue used (*e.g.* 55 minutes for a short acting drug).

B. Validation Model – Virtual Patient

For the validation of our control system we employ a more complex model [14] which was modified in [5] by introducing a model for subcutaneously injected insulin, similar to (5), and removing the sub-model of insulin secretion by the pancreas in order to account for Type 1 diabetics. The model consists of 13 differential equations and was used as a virtual patient for our controller *i.e.* we

assume that this model will behave like a real diabetic patient. The model was recently approved by the FDA as an alternative to animal experiments for diabetes research.

Furthermore, the parameter P_3 and the maximum value of the glucose absorption rate D_{max} of the extended Bergman model were tuned with the validation model to facilitate a good compliance between the outputs of both models, which is the plasma glucose concentration. This tuning can be seen as an initial calibration of the model to the individual patient in order to estimate the metabolic characteristics.

III. Control Design

The goal for all diabetic patients is to achieve and maintain a rather constant BG between 80 and 100 mg/dl at a basal fasting state. Too low concentrations – a state which is called hypoglycemia – have to be avoided at any time since they may cause deleterious cerebral outcomes, even if they are of only short duration. Too high concentrations – a state called hyperglycemia – over longer periods of time may cause long term complications.

In this paper, we consider concentrations between 80 and 140 mg/dl as acceptable under basal conditions, whereas concentrations below 60 and above 220 should to be avoided at any time. Values in-between 60 – 80 and 140 – 220 are also acceptable, but only for short time periods, for example after ingestion of a meal.

For a performance evaluation of the control approach, the area outside bounds AOB (6) and the minimum blood glucose are used. If the minimum BG is below 60 mg/dl, the controller is not useful and may also harm to the patient.

$$\mathrm{AOB} = \int_0^{\infty} G(t)\,dt, \quad G(t) \in \left]-\infty, 60\right] \cup \left[140, \infty\right[. \tag{6}$$

A. Model Predictive Control

A MPC solves an online finite horizon optimization problem at each sample time. A cost function (7) is minimized with respect to constraints on the input u and possibly additional output constraints.

$$\begin{aligned} \min \sum_{k=0}^{p-1} \Big\{ & \left[y(t+k\,|\,t) - r(t+k) \right]^T Q \left[y(t+k\,|\,t) - r(t+k) \right] + \\ & \Delta u^T(t+k) R \Delta u(t+k) + \rho \varepsilon^2 \Big\} \\ & s.t. \\ & y_{\min} - \varepsilon \le y(t+k\,|\,t) \le y_{\max} + \varepsilon, \;\; k = 1, \ldots p-1 \\ & u_{\min} \le u(t+k) \le u_{\max}, \;\; k = 1, \ldots, c \\ & \Delta u_{\min} \le u(t+k) \le \Delta u_{\max}, \;\; k = 1, \ldots, c \\ & u(t+k) = u(t), \; k = c+1, \ldots p \\ & x(t+1) = Ax(t) + Bu(t) \\ & y(t) = Cx(t) + Du(t) \end{aligned} \tag{7}$$

The prediction y is accomplished p (prediction horizon) samples ahead with the linear model, c represents the control horizon, $c \le p$, $r(t)$ is the reference to be tracked, Q, R, and ρ are tuning variables penalizing the tracking error, the control output increment $\Delta u(t+k) = u(t+k) - u(t+k-1)$, and the enforcement of the constraints, respectively. The optimization leads to an optimal sequence of control outputs U_{opt}, but only the first element is applied to the plant at each sample time, and at the next time step the optimization is performed again.

A valuable advantage of MPC is the easy consideration of both input and output constraints and the explicit consideration of the future predicted controlled variables with an internal model.

B. Discrete Approximation of the control output

As already stated, we want to apply our controller to optimize the standard insulin injection therapy of diabetic patients. The output of the MPC therefore cannot be continuous, but must be approximated with control outputs at single time points. Instead of applying the first element of the optimal output sequence of the controller to the plant at each sample time, the whole sequence of length $c \cdot T$, with the control horizon c and sample time T, is reduced to one control output with the size U^*_{opt} (8) at time t^*_{opt} (9).

The size of the single control move is the area of the whole optimal sequence between sample 0 and c. The optimal time for this control move can be interpreted as the barycenter in the x direction. The time t_{end} is a parameter, specifying the time range within which the continuous control output is approximated and satisfies $t_{end} \in \left[1, T, ..., pT\right]$, and t_0 is the current time instant.

$$U^*_{opt} = \sum_{t=t_0}^{t_0+t_{end}} U_{opt}(t)\,T \tag{8}$$

$$t^*_{opt} = \frac{\sum_{t=t_0}^{t_0+t_{end}} U_{opt}(t)\,t}{\sum_{t=t0}^{t_{end}} U_{opt}(t)} \tag{9}$$

Fig. 2 shows *e.g.* an optimal output sequence with control horizon 5, prediction horizon 12, sample time T=1, starting from $t_0 = 0$, and the approximated single control move with size $U^*_{opt} = 63$ at time $t^*_{opt} = 2.1429$.

Note that the calculation of U^*_{opt} and t^*_{opt} is not repeated at each sample time, but only after t_{end} samples – by setting $t_0^{(new)} = t_0 + t_{end}$ and using the new optimal output sequence of the MPC – because the information of the whole optimal input sequence from t_0 to t_{end} is already included in the previous discrete output.

C. Gain Scheduling MPC Control

For an introduction to gain scheduling, we refer to [15] and several textbooks concerning control engineering. Every gain scheduling control needs a variable which specifies the operating region of the system under control. In our application, the BG concentration is the scheduling variable. The switching between the several controllers is often difficult to manage in gain scheduling applications and may cause steps in the control output signal which as a

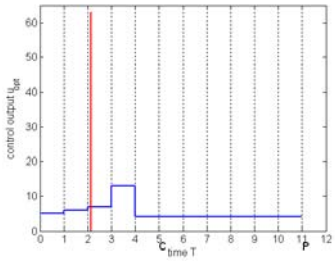

Fig. 2. Approximation of the optimal output sequence of a MPC with a single control output.

consequence can also be a reason for stability problems of the closed loop system. Here, we do not have to consider this issue, since our controller is supposed to give an output signal only at several, not concatenated time points.

IV. Application: Glucose Control

A. Control System Description

The structure of the overall control system can be seen in Fig. 3. The amount of carbohydrates is the only external input and has to be estimated by the diabetic patient because a measurement is not possible. This input is given to both models and can be seen as a measured disturbance, which has an effect on the glucose concentration that should be regulated via the insulin. The controller needs a sufficient robustness to handle the anticipated errors of this estimated quantity.

The extended Bergman model provides the gain scheduling MPC controller with continuous information on the glucose concentration and is itself updated with the actual glucose concentration from the virtual patient, whenever a strip based glucose measurement was made. This update is essential because the virtual patient model is much more complex and describes the metabolism in a more detailed way and should be done whenever a meal appears and ideally also some time after a meal. The control output is the quantity of insulin which has to be injected externally and is given to both models.

B. MPC Setup

For the purpose of control design, the extended Bergman model was linearized at eight different steady state operating points with the glucose concentrations 80, 100, 120, 140, 160, 180, 200, and 220 mg/dl and discretized with a sample time of 15 minutes to obtain the linear models required. For each of these linear models, a MPC was designed.

Since the control output cannot become negative, input constraints are considered in the MPC approach. However, we do not employ any output constraints on the glucose concentration. The setpoint for the glucose concentration was put to 100 mg/dl. This rather high value was chosen due to safety reasons, because BG shall never fall under 60mg/dl, even in the presence of errors.

The MPC approach is able to explicitly consider measured disturbance signals in the calculation of the optimal control output. It is also possible to use available future information of the disturbance for the calculation of the actual output. It was shown, that the performance of the overall control system improves significantly if the information of the carbohydrates of an upcoming meal is announced to the MPC ahead in time. Therefore we assumed that the diabetic patient knows the size of the meal 60 minutes in advance and this information is forwarded to the MPC controller. The prediction and control horizons were tuned to 400 and 240 minutes, respectively.

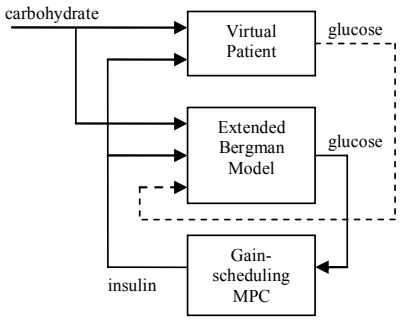

Fig. 3. Basic layout of the control system

C. Steady State Conditions

As already observed in [4], the Bergman model can only reach a steady state, when a constant, basal insulin concentration is assured. Also the virtual patient model needs a constant insulin input signal to reach steady state conditions. In a real application, this basal insulin can either be fulfilled by an insulin pump giving the basal profile or by injection of a long acting insulin analogue. Here, we assume that a constant basal insulin concentration exists due to injection of long acting insulin.

D. Test Case

All simulations that follow are performed under the same preconditions: a total simulation time of 24 hours with meals at 8am, 13pm, and 19pm containing 45g, 70g, and 70g of carbohydrates. The update of the extended Bergman model

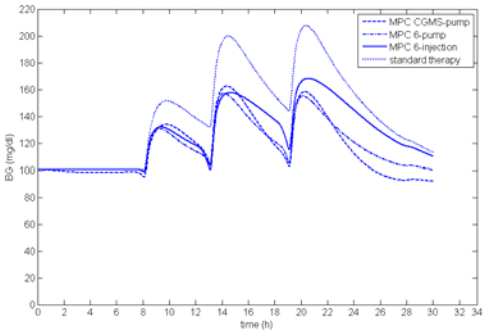

Fig. 4. Glucose concentration of the virtual patient under different controller setups: 1) MPC with continuous information on BG form the virtual patient and continuous output signal, 2) MPC with 6 measurement updates and continuous output, 3) MPC with 6 measurement updates and 3 single insulin injections, and 4) standard therapy

with the actual glucose concentration from the virtual patient model, *i.e.* real measurements, was completed six times a day: with every meal and additionally one hour afterwards.

V. Results

A. Performance Assessment

To quantify the performance of our sparse glucose measurement and insulin injection control system, we first have to evaluate a reference performance as expected when using standard rules of thumb, consisting of an insulin bolus proportional to the carbohydrate amount, but without any update of the therapy considering BG measurements. In this work we do not consider physical exercise and so do not use corrections for expected activity.

The results are then compared with a MPC using different setups, see Table 1. First a combination of perfect CGMS (the controller receives the glucose measurement directly from the virtual patient without error and time delay) and pump (the output of the MPC is not approximated with single control moves), then the setup described in the previous chapter using six single glucose measurements for updating the extended Bergman model, but without discrete approximation of the control output. Finally a MPC with discrete approximation and six measurements from the virtual patient is employed. The results are shown in Fig. 4. and point out that our approach is sensible and improves the achievable performance compared to the standard therapy. Furthermore, the approximation of the continuous control output does not entail a substantial performance degradation.

The results also show that the differences between the several configurations get higher with the amount of ingested carbohydrates.

B. CVGA

To allow a comparison and performance estimation of the different results that will follow, the Control Variability Grid Analysis (CVGA) [16] was adopted, Fig. 5. The only two quantities which are considered here are the minimum (x-axis) and maximum (y-axis) blood glucose (BG) concentrations that appear within a 24 hour cycle. Note that the x-axis is inverted and the scaling of the y-axis is not linear in order to capture a broad region. The light green area (A) is the one with the best performance, the green areas (B) are acceptable, the yellow and orange ones (C, D) may contain dangerous hypoglycemic situations and should be avoided, and the red one (E) simply indicates an erroneous control.

C. Robustness Analysis

Since the uncertainty in biomedical systems is rather large due to inter- and intra patient variability, different sources of model errors, sensor errors, and meal errors were introduced and the performance of the control system evaluated.

1) Structured Uncertainty

The parameters of the extended Bergman model (P_1, P_2, P_3, n, t_1) were changed by -30%, -20%, 0, +20%, and +30% independently from each other, which results in a total of 3125 different parameter configurations. The MPCs are still designed on the nominal, linearized extended Bergman model without any parameter variations. With all these combinations the test case was simulated, and the results in terms of the minimum and maximum glucose concentration which occur in the different simulations are shown in Fig. 5. Almost all results show up in the areas A and B, and only a few, calculated with the higher parameter variations are in the C area. These points disappear, when parameter variations are bounded within a 20% region. All C points are either caused by a 30% variation of the parameters P_1 and / or n which seem to be the most sensitive parameters.

TABLE I
Control Setups

	1	2	3	4
BG measurement	Perfect CGMS	6 strip meas.	6 strip meas.	-
Insulin delivery	Pump	Pump	3 inj.	3 inj.
Computation	MPC Bergman	MPC Bergman	MPC Bergman	Standard

The result of a single simulation can be seen in Fig. 6. Here, the parameters were changed by -20%, 0%, 20%, 20% and 30% causing a minimum BG of 96.41 mg/dl, and a maximum BG of 153.64 mg/dl. Note that the dynamics of the two systems is quite different due to the large parametric uncertainty, but the update of the extended Bergman model through measurements from the virtual patient prevents the system from diverging too far.

2) Uncertain Meal Amount

This error may happen very often in real life applications, since the diabetic patient has to estimate the content of carbohydrates of the meal by himself, which is not very easy. Here we consider an estimation error of ±20%, and ±40% respectively.

3) Uncertain Meal Time

The measured disturbance signal provided to the MPC is now moved back and forth in time 15, 30, and 45 minutes. The announcement of a meal which takes not place at all is especially dangerous, because an insulin bolus is given and the risk for hypoglycemia is increased, hover this case is not considered.

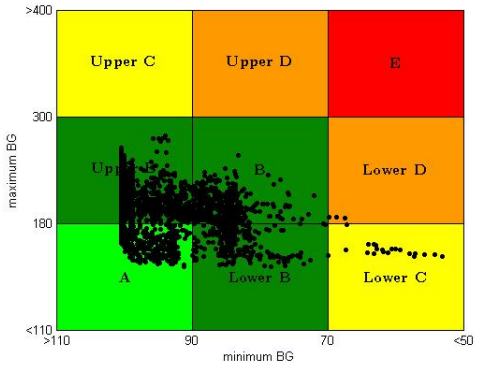

Fig. 5. CVGA of structured uncertainty analysis

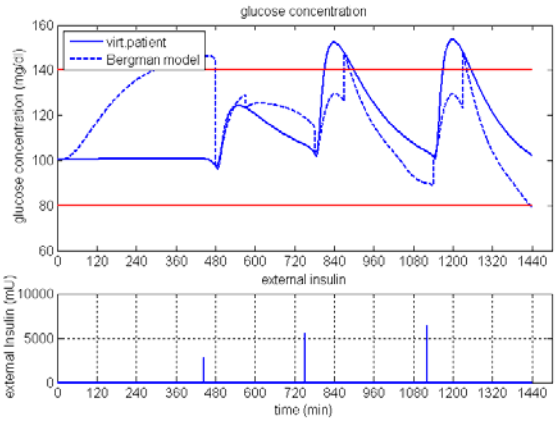

Fig. 6. Upper panel: glucose concentration of the virtual patient (solid) and of the extended Bergman minimal model (dashed). Bottom panel: calculated optimal insulin injections which are applied to both models.

4) Measurement Error

The update of the extended Bergman model with the real glucose concentration from the virtual patient is perturbed by a uniformly distributed random signal in the range of ±10 mg/dl. This error range is sensitive for commonly used self monitoring blood glucose devices [17].

5) Combination of all errors

Now, all previously described errors are applied simultaneously with a random magnitude in between boundaries to simulate the most realistic test cases in real life. The meal amount and time vary randomly between ±40% and ±45 minutes and the parameters of the extended Bergman model between ±20 percent. A Monte Carlo simulation with 1000 runs proved that in most of the cases the BG stays in the safe areas above 70 and below 300 mg/dl (green areas in the CVGA plot). The results are displayed in Table II in the form of percentage of the runs above or below a bound on the BG. All critical cases (BG between 50 and 70 mg/dl) are related to a rather large meal time delay of more than 30 minutes and can be avoided, if only delays up to 20 minutes will arise.

TABLE II
SIMULATION RESULTS WITH A COMBINATION OF ALL ERRORS

BG	Percentage of test cases
> 50	100 %
> 70	91 %
< 200	100 %
< 150	87 %

VI. CONCLUSION

We showed that it is possible to improve the common treatment of Type 1 diabetic patients by optimization of the time and quantity of single subcutaneous insulin injections. An approximation of the continuous output signal of a MPC with single control moves in time does not reduce the performance significantly in this application, but rather makes it possible to use the control advices for patients on multiple daily insulin injections. Considering the simulated test cases with different error sources that may arise in a real-life application, the gain scheduling MPC has sufficient robustness properties.

REFERENCES

[1] C. Dalla Man and C. Cobelli, "A system model of oral glucose absorption: Validation on gold standard data," *IEEE Transactions on Biomedical Engineering*, vol. 53, pp. 2472-2478, 2006.

[2] *Diabetes Atlas, Third Edition*: International Diabetes Federation, 2006.

[3] G. Marchetti, M. Barolo, L. Jovanovic, H. Zisser, and D. E. Seborg, "An Improved PID Switching Control Strategy for Type 1 Diabetes," *IEEE Transactions on Biomedical Engineering*, vol. 55, pp. 857-865, 2008.

[4] P. Dua, F. J. Doyle, and E. N. Pistikopoulos, "Multi-objective Parametric Control of Blood Glucose Concentration for Type 1 Diabetes," presented at 44th IEEE Conference on Decision and Control, and the European Control Conference 2005, Seville, Spain, 2005.

[5] L. Magni, D. M. Raimondo, C. D. Man, G. D. Nicolao, B. Kovatchev, and C. Cobelli, "Model Predictive Control of glucose concentration in subjects with type 1 diabetes: an in silico trial," presented at IFAC World Congress, 17th, Seoul, 2008.

[6] R. S. Parker, E. P. Gatzke, and F. J. Doyle, "Advanced Model Predictive Control (MPC) for Type I Diabetic Patient Blood Glucose Control," presented at American Control Conference, Chicago, Illinois, 2000.

[7] R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. O. Federici, T. R. Pieber, H. C. Schaller, L. Schaupp, T. Vering, and M. EWilinska, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiol. Meas.* , vol. 25, pp. 905–920, 2004.

[8] F. Chee, A. V. Savkin, T. L. Fernando, and S. Nahavandi, "Optimal H_∞ Insulin Injection Control for Blood Glucose Regulation in Diabetic Patients," *IEEE Transactions on Biomedical Engineering*, vol. 52, pp. 1625-1631, 2005.

[9] W. Garcis-Gabin, J. Vehi, J. Bondia, C. Tarin, and R. Calm, "Robust Sliding Mode Closed-loop Glucose Control with Meal Compensation in Type 1 Diabetes Mellitus," presented at IFAC World Congress, 17th, Seoul, 2008.

[10] R. N. Bergman, L. S. Phillips, and C. Cobelli, "Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose.," *The Journal of Clinical Investigation*, vol. 68, pp. 1456–1467, 1981.

[11] M. E. Fisher, "A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics," *IEEE Transactions on Biomedical Engineering*, vol. 38, pp. 57-61, 1991.

[12] M. Berger and D. Rodbard, "Computer simulation of plasma insulin and glucose dynamics after subcutaneous insulin injection," *Diabetes Care*, vol. 12, pp. 725-736, 1989.

[13] M. Hernández-Ordonez and D. U. Campos-Delgado, "An extension to the compartimental model of type 1 diabetic patients to reproduce exercise periods with glycogen depletion and replenishment," *Journal of Biomechanics*, vol. 41, pp. 744-752, 2008.

[14] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Meal Simulation Model of the Glucose-Insulin System," *IEEE Transactions on Biomedical Engineering*, vol. 54, pp. 1740-1749, 2007.

[15] J. S. Shamma, *The Control Handbook*: CRC Press, 1996.

[16] L. Magni, D. M. Raimondo, C. D. Man, M. Breton, S. Patek, G. D. Nicalo, C. Cobelli, and B. P. Kovatchev, "Evaluating the Efficiacy of Closed-Loop Glucose Regulation via Control-Variability Grid Analysis," *Journal of Diabetes Science and Technology*, vol. 2, 2008.

[17] T. Ghys, W. Goedhuys, K. Spincemaille, F. Gorus, and E. Gerlo, "Plasma-equivalent glucose at the point-of-care: evaluation of Rouche Accu-Chek Inform® and Abbot Precision PCx® glucose meters," *Clinica Chimica Acta*, vol. 386 pp. 63-68, 2007.