A Model Based Bolus Calculator for Blood Glucose Control in Type 1 Diabetes
Harald Kirchsteiger and Luigi del Re

Abstract—We propose a model based bolus calculator which, based on an identified model, information on the carbohydrate content of the meals and an initial single glucose measurement, computes the optimal insulin bolus dose in order to minimize the blood glucose deviations. We use a simulation model for identification of models for control and closed-loop simulations. The performance of the proposed bolus calculator is compared with a model predictive control approach which uses continuous glucose information and insulin injection. Both methods achieve comparable performance for some patients while the insulin amount, number of injections and computational complexity is significantly reduced for the bolus calculator.

Index Terms—Biomedical Systems, Blood Glucose Control, Type 1 Diabetes

I. INTRODUCTION

In the healthy human body, meal ingestion is followed by insulin secretion of the $\beta$-cells of the pancreas. The main source of energy directly available for energy producing chemical processes inside cells is glucose. The carbohydrate portion of meals is almost entirely transformed to glucose, thereby raising the blood glucose (BG) concentration. It is insulin that promotes cell uptake of blood glucose, and thereby lowers the BG concentration. Once the concentration is close to a basal state, insulin secretion is normalized and the remaining insulin is quickly cleared from the circulation. As a consequence, BG stays within a narrow range of $\approx$80 to 140 mg/dl throughout the day [1].

When there is no insulin available—as in type 1 diabetes subjects—much higher BG than usual (called hyperglycemia) result and the associated adverse long-term effects were studied thoroughly [2]. It was indeed shown in [2] that intensive insulin therapy through several daily insulin injections helps to prevent and slow down the progress of diabetes related complications. However, intensive insulin treatment implies the risk of insulin overdose which results in dangerously low BG (called hypoglycemia) and immediately impairs functionality of glucose dependent tissues such as the brain.

Artificial pancreas (AP) systems—consisting of a continuous glucose monitoring (CGM) device, a continuous insulin infusion pump and a control algorithm—are an active area of research (see e.g. [3]). Until now, no such system is commercially available. Control algorithms relying on CGM devices and insulin pumps were proposed e.g. in [4] and [5], see also [6] and the references therein.

Only a minority of type 1 diabetes patients is currently using CGM devices and insulin infusion pumps and is therefore suited for AP systems. The majority is measuring BG only several times per day (usually immediately before mealtimes) with a BG meter and injecting insulin using a syringe. For those patients, so-called bolus calculators (BC) exist, which, dependent on an individually determined insulin sensitivity and an insulin to carbohydrate ratio, estimate the amount of insulin needed to compensate a known meal disturbance. BC are now available in almost all insulin pumps [7] and also in some BG meters [8]. The use of BC can improve diabetes therapy compared to manual bolus calculation and help to avoid possible cases of hypoglycemia [9].

In this paper, we propose a novel model based bolus calculator (MBBC) and compare its performance with model predictive control (MPC). We investigate if there are benefits of the continuous insulin delivery as in AP systems compared to multiple daily insulin injections as in conventional intensive insulin therapy. For the MPC, we employ an ARX type of model. The MBBC model is a control oriented model which was first introduced in [10] and further refined in [11]. The derivation of the models for the MPC design and the model for the MBBC is described in section II. The control design is presented in section III. A presentation of the results and a discussion in Section IV conclude the paper.

II. MODELS

In this section we describe the mathematical models used for closed-loop simulation and for control synthesis.

A. Simulation model

The base model used in this study is the type 1 diabetes metabolic simulator presented in [12] which was extended in [4] with a sub-model for subcutaneous (SC) insulin injections. The inputs to the non-linear model are SC injected insulin and orally ingested carbohydrates and the output, which is to be controlled, is the plasma glucose concentration $G_p$. We do not assume to measure this quantity directly, but the SC glucose concentration $G_{SC}$ which is another output of the model. This setup is a more realistic one since SC glucose can be measured continuously using CGM systems while plasma glucose is only accessible via collection of invasive blood samples.

The simulator is parameterized to represent single virtual subjects, and the combination of all virtual subjects covers the physiologic variability observed in real patient data. The dynamics of those virtual patients are quite diverse, but single individuals have a time–invariant behavior. In our study we
synthesize and test the controllers on 10 adult virtual subjects for which parameters are available [13].

Linear models for control design were obtained by applying system identification techniques [14] on data generated with this non-linear model. The design was done individually, i.e. there are personalized models and controllers per patient. For this purpose, simulations were done with chosen meal inputs at nominal times $t_m = \{7, 13, 19\}$ h after midnight and nominal quantities $q_m = \{45, 70, 60\}$ g of carbohydrates. The times were randomly changed within an interval of $\pm 60$ min and the quantities within $\pm 20\%$ around the nominal value for the following simulated days. Insulin inputs were nominally given at the same time, but randomly changed within a time interval of $\pm 30$ min, whereas the insulin quantity $q_I$ was always proportional to $q_m$. In total, three days of date were generated to estimate the models for control.

**B. A model for MPC synthesis**

Using this dataset, first the impulse-like inputs meal carbohydrate disturbance $d(t)$ and insulin $u(t)$ are filtered with the transfer functions

$$G_1(s) = \frac{30}{(1 + 50s)(1 + 120s)}$$  \hspace{1cm} (1a)$$

$$G_2(s) = \frac{20}{(1 + 10s)(1 + 100s)}$$  \hspace{1cm} (1b)$$

to obtain the signals $R_{am}(t)$ and $R_{at}(t)$ (see Fig. 1).

The only reason for those two filters is to generate continuous signals out of the single impulses which is advantageous for the subsequent identification step. This is because insulin for example does have an effect on the BG concentration for several hours after injection which can only be captured by the model if this input is still available for output calculation or if the model has a long enough memory to internally keep this information. The same holds for the carbohydrate input. A second option would be to choose a high model order such that the exogenous input part of the model has a long enough memory, which has potentially negative effects on the numerical condition of the estimation problem.

Note that the parameters chosen in (1) result in a certain parameter set $\theta$ of the ARX-model when fitting the model to given input-output data. Since we are only interested in the overall input-output behavior, different parameter combinations might be used as well, i.e. the parameters in (1) can be changed and do not resemble physiology.

The signals $R_{am}(t)$ and $R_{at}(t)$ are used to identify ARX models [15] of 4th order (2) with $A(q) = 1 + a_1 q^{-1} + \ldots + a_4 q^{-4}$, $B_1(q) = b_1, 1 q^{-1} + b_1, 2 q^{-2} + b_1, 3 q^{-3}$, and $B_2(q) = b_2, 1 q^{-1}$.

$$\hat{G}_{SC}(k)A(q) = B_1(q)R_{am}(k) + B_2(q)R_{at}(k)$$  \hspace{1cm} (2)$$

The shift operator is denoted with $q$, i.e., $q^{-1} u_k = u_{k-1}$ and a sample time of 5 min was chosen. The orders were chosen to a) achieve a reasonable fit between measurements and model output and b) based on the coefficient of variation $CV = \frac{\text{std}(\theta)}{\text{mean}(\theta)}$

If the $CV$ is high, the estimate is rather unreliable (there is a high variation) while a low $CV$ indicates a consistent estimate of the according parameter. A comparison between simulated model output and identification data is presented in Fig. 2 for patient one and shows that the simulator can be approximated well with the linear model for control purposes which was also demonstrated in [16]. The $CV$ results in $CV = \{2.0, 4.2, 6.6, 9.4, 20.1, 21.0, 22.1, 188.7\} \times 10^{-3}$. The first four parameters (corresponding to the autoregressive part) were estimated quite accurately, whereas the following three parameters (corresponding to the carbohydrate input) are significantly higher. Finally, the last parameter which corresponds to the insulin input is again significant higher. Those results are consistent among all patients, indicating that the insulin response is much more difficult to estimate. The same conclusion can be drawn when observing the large deviation of the estimated insulin impulse response from the real response in Fig. 3.

Important for the control system are correct step/impulse responses of the model, i.e. the glucose responses when applying a single impulse of insulin or carbohydrates, respectively, once at a time, which is shown in Fig. 3. The carbohydrate response is captured quite well whereas the insulin response is a bit overestimated by the model. Both responses show some oscillating behavior which is physiologically not correct, but a consequence of the parameter optimization in the identification algorithm in order to reproduce the output as best as possible. Note the rather long time constants of the simulator which affect tuning of the horizons of the MPC.

The models (1) are discretized with a sample time of 5 min, combined with (2) (see Fig. 1) and transformed into a
The MPC requires an estimate of the current state, for which we employ a model-based state estimator. For this task it is beneficial—as will be shown in the control section—to consider the dynamics of the ARX model (2) and the impulse filters (1) separately. The discrete time state-space model for the carbohydrate impulse filter (1a) is given by

\[ \xi_m(k+1) = A_m \xi_m(k) + B_m d(k) \]  
\[ R_{am}(k) = C_m \xi_m(k) \]  
and the one for insulin by

\[ \xi_I(k+1) = A_I \xi_I(k) + B_I u(k) \]  
\[ R_{ai}(k) = C_I \xi_I(k) \]  

Using those definitions, the ARX model is given by

\[ \xi_{arx}(k+1) = A_{arx} \xi_{arx}(k) + B_{arx} \left[ R_{am}(k) R_{ai}(k) \right] \]  
\[ \hat{G}_{sc}(k) = C_{arx} \xi_{arx}(k) \]  

where \( B_{arx} = [b_{arx1} \ b_{arx2}] \) and \( A_{arx}, B_{arx}, C_{arx}, D_{arx} \) result from transforming (2) into a state-space model.

C. A model for the model based bolus calculator

Based on data from the metabolic simulator, a low-order continuous time transfer function model of the form

\[ G_{SC}(s) = \frac{K_1}{(1 + sT_1)^2 s} D(s) + \frac{K_2}{(1 + sT_2)^2 s} U(s) \]  

was identified directly in continuous time using the methodology as presented in [11] where \( D(s), U(s), \) and \( G_{SC}(s) \) are the Laplace transform of the meal disturbance input, insulin input, and SC glucose concentration output, respectively. Both inputs are assumed to have an impulse-like shape, see also Fig. 4, which means there is no more need to use the input filters (1). This modeling concept was successfully applied to real data [11].

Note that this model structure has integrating behavior and thus small modeling errors will result in a continuously growing offset error on the output. It is therefore necessary to frequently reset the model to measured values to avoid this, i.e. a measurement of the current BG concentration is required to initialize the prediction generated with the model. In the proposed control scheme, this is done whenever a new meal appears.

III. CONTROL

The variable to be controlled is the SC glucose concentration, \( G_{sc}(t) \). We denote with \( BG_{ref} \) the desired reference BG which shall be achieved using appropriate SC insulin injections in the presence of meal disturbances.

A. Optimization based control

Before the MPC and the MBBC are compared to each other, it is of interest to determine the maximum performance achievable with the given simulation-model and -scenario.

By means of an offline optimization, the optimal times \( t^*_i \) and quantities \( q^*_i \) of insulin injections are found as the solution to the following optimization problem:

\[ (t^*_i, q^*_i) = \arg \min_{t_i, q_i} J(N, t_i, q_i) \]

\[ J(N, t_i, q_i) = \sum_{k=1}^{N} \| G_{SC}(k, t_i, q_i) - BG_{ref} \|^2, \]

which penalizes the quadratic error between reference and actual SC glucose. The optimization (8) was carried out with different degrees of freedom, allowing for 3, 6, or 12 insulin injections resulting in 6, 12, or 24 optimization variables and for a simulation time of 32 hours, i.e. \( N = 32 \times 60 \).

B. Model predictive control

The MPC is synthesized based on the model (3). At every sample instant \( k \), the control signal is given as the first element of the solution to the following constrained, finite horizon \( n_{PH} \) is the prediction- and \( n_{CH} \) the control
horizon) optimization problem:
\[
\arg \min_{\Delta u} \sum_{k=0}^{n_{PH}} \left\| \hat{G}_{SC}(k) - T_{ref}(k) \right\|^2_Q + \left\| \Delta u(k) \right\|^2_R \tag{10}
\]
subject to:
\[
\begin{align*}
    u(k) &= u(k-1) + \Delta u(k) \\
    \hat{G}_{SC}(k), \quad (3) \\
    0 &\leq u(k) \leq 20 \quad k = 0 \ldots n_{CH} - 1 \\
    \Delta u(k) &= 0 \quad k = n_{CH} \ldots n_{PH}
\end{align*}
\]
where we used the notation \( \|\xi\|^2_Q \triangleq \xi^T Q \xi \) and the positive definite (diagonal) matrices \( Q \) and \( R \) are used to tune the controller for more aggressive or smooth behavior, respectively. The reference vector \( T_{ref} = [r(k) \ldots r(k + n_{PH})] \) was chosen in such a way that an exponentially decreasing tracking error between the setpoint \( BG_{ref} \) and the MPC reference results, see [17]:
\[
r(k + i) = BG_{ref} - \lambda_{ref} (BG_{ref} - \hat{G}_{SC}). \tag{11}
\]

The MPC needs the full state \( x = [\xi_{arx} \quad \xi_m \quad \xi_f]^T \) to compute the prediction, which is not directly measurable. Instead, a Kalman-filter was designed to give an estimate. The state estimator is an integral part of the control system and contributes fundamentally to the overall performance. This is especially true for the considered setup because of the following reason: The carbohydrate and insulin inputs significantly contribute to the state estimates but they are zero almost all the time. The similarity between the Kalman filter and the recursive least squares algorithm (see e.g. [15]) suggests that also in this case there is an effect similar to the well known estimator windup phenomenon which occurs if there is no excitation for a longer time to the system. In fact, simulations showed that large deviations of the state estimate follow after an impulse input to the estimator. Then, the MPC bases its decision on a wrong estimate which—in the case it results in too much insulin which is given—cannot be corrected anymore later on because insulin is the only manipulated variable and hypoglycemia will follow. The importance of observer design in the context of BG control is also mentioned in [18].

An attempt to compensate this effect is to not estimate all 8 states of the internal MPC model (3), but only the 4 contributed from the ARX model (the states \( \xi_{arx} \) in (6)). The states \( \xi_m \) and \( \xi_f \) are obtained by simulating (4) and (5) while \( \xi_{arx} \) is estimated with a Kalman–filter. This strategy makes filter tuning easier and moreover avoids large transients in the estimate \( \hat{x} \) because the inputs to the Kalman filter are already pre–filtered impulses. The dynamic system for the Kalman–filter design is
\[
\begin{align*}
    x(k + 1) &= A_{arx} x(k) + B_{KF} \begin{bmatrix} \xi_m(k) \\ \xi_f(k) \end{bmatrix} + G w(k) \tag{12a} \\
    y(k) &= C_{arx} x(k) + H w(k) + v(k) \tag{12b}
\end{align*}
\]
where \( B_{KF} = [b_{arx1} C_m \quad b_{arx2} C_I] \), \( w(k) \) denotes a certain process noise and \( v(k) \) measurement noise with given constant covariance matrices:
\[
E\{w w^T\} = Q_{KF}, \quad E\{vv^T\} = R_{KF}. \tag{13}
\]

Note that a similar overall behavior can be obtained by designing the observer for the full model (3) and proper selection of the matrices \( Q_{KF} \) and \( R_{KF} \) in such a way, that the states corresponding to the impulse filters \( (\xi_m \text{ and } \xi_f) \) are highly corrupted by measurement noise (and their estimate is therefore determined by the internal model only). However, the resulting numerical conditions make this estimation worse than the one based on separated models.

C. Model based bolus calculator

The transfer function model (7) will be utilized to generate advice on insulin dose. The focus is on a setup with bolus insulin doses and sparse BG measurements. A single BG measurement is assumed to be available at the time of the meal. Then, based on the meal carbohydrates and the personalized internal model (7), the time and quantity of the insulin bolus advice is computed. Between meals, no advice is given since no updated information on the current state of the patient is available. Of course, if additional BG measurements would be available (e.g. 2 hours after a meal) a correction insulin bolus could be computed.

Inside the controller, the model is used to predict future glucose starting at the time \( t_0 \) of the meal using information on the current BG, the carbohydrate content and the insulin bolus. Hence, the notation \( \hat{G}_{SC}(k) = G_{SC}(k; \theta, G_{SC}(t_0), d(t_0), u(t_0)), t \geq t_0 \) where \( \theta \) comprises all parameters of (7), is used for the prediction.

To compute the required insulin, the following optimization problem is solved whenever a meal occurs:
\[
\min_{u(t_0)} \sum_{k=t_0}^{t_0+n_{PH}} \left\| \hat{G}_{SC} (k; \theta, G_{SC}(t_0), d(t_0), u(t_0)) - BG_{ref} \right\|^2 \tag{14}
\]
and the resulting optimal value \( u^*(t_0) \) is rounded to the next 0.5 insulin units (dosage on insulin pens is usually adjusted in 0.5 unit steps) and applied to the patient.

Note that the optimization problem (14) is convex since it employs a linear model and a quadratic cost. Furthermore, there is only one optimization variable which enables using simple line search algorithms. The problem (14) can be solved efficiently online. Note also that the optimization is only performed at the time when there is a meal disturbance.

IV. RESULTS AND DISCUSSION

Results are presented graphically and in a table using the performance measures low (high) BG index, LBGI (HBGI) [19], time \( T_{safe} \) inside a safe region of 70 – 180 mg/dl (boundaries are also shown in the plots), total daily insulin \( I_{TD} \), and the number of insulin injections per day, \( inj \).

Results for the optimization based control are shown for one day of simulation time and patient 1. The number of injections were initially fixed with 3, e.g., one injection per meal, and then increased to 6 and 12. Fig. 5 shows the
results for $BG_{ref} = 151.3$ mg/dl which is the steady state BG concentration of this patient (the reference is 126 mg/dl later on, but for the purpose of this section we use 151.3). Surprisingly, the performance is essentially equivalent for all cases, which can also be expressed in terms of the normalized cost (9) at the optimum, which is 1.0353, and 1.0202 for the 3, 6, and 12 injections case, respectively. The slightly higher cost for the cases of 6 and 12 injections is because of numerical inaccuracies when solving increasingly more complex problems. Fig. 6 shows the result of a constrained optimization, where insulin can only be given after a meal, which is the practically more relevant case. Note that hypoglycemia after breakfast cannot be avoided because the required high insulin dose for this would cause a subsequent hypoglycemia.

There are two important conclusions from this experiments: First, one insulin bolus per meal is enough to enable effective control and second, without a meal look ahead functionality, some elevated peaks (BG > 180 mg/dl) cannot be avoided because excessive insulin quantities would result in subsequently dangerous glucose undershoots which are not controllable.

The following results for the MPC and the MBBC are all based on a $n_d = 3$ day randomly chosen meal sequence $d(t)$ with nominal times $t_m = \{7, 13, 20\}$ h and quantity $q_m = \{40, 80, 60\}$ g of carbohydrates. The nominal times were varied randomly by $\pm 60$ min and the nominal doses by $\pm 20\%$. For comparability the different control settings are evaluated with the same random sequences $d(t)$ each.

The major tuning variables of the MPC were chosen as follows: prediction horizon $n_{PH} = 120$ samples (600 min), a control horizon $n_{CH} = 6$ was realized with a blocking sequence [17] of length $[1 \ 1 \ 2 \ 2 \ 5 \ 10]$ samples, weights $Q = 100$, and $R = 5$. Those settings were giving good results for patient 1 and were kept afterwards for the other 9 patients. The desired BG setpoint was fixed to $BG_{ref} = 126$ mg/dl and the exponential reference for the MPC (11) generated with $\lambda_{ref} = 0.92$.

Fig. 7 shows results for three MPC setups: no meal disturbance lookahead for MPC_1 and MPC_3 while MPC_2 has this functionality. Furthermore, MPC_3 delivers only control signals quantized in 0.5 unit steps by rounding the result of the optimization (10).

The results obtained with the MBBC using the same horizon $n_{PH} = 600$ min are summarized and compared with MPC_3 control in Fig. 8 and Table I. As expected, the MPC performs better because it uses continuous sensing and continuously manipulated variables while the MBBC relies only on a single BG measurement at the time of the meal disturbance and applies only single insulin pulses.

Comparing the average (av.) metrics in Table I from MPC and MBBC, both the LBGI and HBGI are higher for the BC. However, when looking at the values of individual patients one can observe that they differ significantly for some (e.g. LBGI of P4 and P6) which affects the mean value, while they are in the same range or even better for others. The time in a safe region is less for the MBBC, mainly because of an initial deviation which causes a higher glucose peak for the first 3 meals, see Fig. 8. The insulin quantity and number of insulin injection is less for the MBBC.

In general, the MBBC is a potential alternative to MPC for some of the analyzed virtual patients, but not for all of them. The reduction of the total amount of insulin and the number
of injections while maintaining similar LBGI and HBGI is an appealing feature of the MBBC which is highly relevant for real patients. Furthermore, computational complexity is significantly less because an optimization problem is only solved when a meal occurs.

V. ACKNOWLEDGMENTS

The authors gratefully acknowledge the sponsoring of this work by the COMET K2 center “Austrian Center of Competence in Mechatronics (ACCM)”. The COMET program is funded by the Austrian federal government, the federal state Upper Austria and the scientific partners of ACCM.

REFERENCES


