GPC for Diabetes Control without Meal Announcement — Control Loop Design and Control Performance Study

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Abstract: This paper presents a performance study of a Generalized Predictive Controller (GPC) for glucose regulation in Type 1 Diabetes Mellitus (T1DM). The performance study is based on the simulation experiments using T1DM subject simulator reported in literature. The GPC algorithm is designed and tuned, while no meal announcement is considered. The comparison with the PID control results reported in the literature is provided.

Key–Words: Generalized Predictive Control, Type 1 Diabetes Mellitus, Artificial Pancreas

1 Introduction

Patients with type 1 diabetes mellitus (T1DM) deal with this disease by taking several daily fingerstick blood glucose measurements and insulin injections. In recent years the insulin is also administered with a manually controlled pump.

In many cases, it is difficult to determine the correct insulin amount or rate and correct timing of injection to prevent hypoglycemia or hyperglycemia. This is true for changing daily life conditions (e.g. stress, illness or exercise) as well as for ordinary days (e.g. patient mistakes – human errors). Closing the glucose control loop with a fully automated device will dramatically improve the management of diabetes and the quality of life of the patients [2, 6, 9, 8, 7].

The artificial pancreas is a closed-loop control system for maintaining normoglycemia [12]. It is called so due to its potential to enforce glucose regulation as done by the pancreas in healthy subjects [1]. The system consists of three main parts. First, a subcutaneous insulin delivery systems (insulin pumps), which are widely used for over a decade. Second, a continuous glucose monitoring (CGM) systems. Recent advances in CGM systems have opened the way to the commercial realization of the artificial pancreas. The third main part is a control algorithm which computes the required insulin amount.

Development of the control algorithm has been accelerated in recent years by means of simulation experiments. These simulations are based on the complex mathematical models which describe the T1DM subject in detail. In this work, we are particularly interested in the model by Chiara Dalla Man and co-workers [15, 14], which we have studied and implemented in Matlab-Simulink software [16], similarly as in original T1DM simulator. We also refer to other types of complex models: [5, 10, 3] and its references.

A proportional-integral-derivative (PID) type of controllers have been used in early closed-loop control studies. The control performance has been improved using a gain scheduling and by adding a feedforward disturbance compensation [2]. In this case a meal ingestion is the disturbance which cause the increase of blood glucose level. Feedforward action therefore requires a meal announcement.

In recent years, a significant attention has been given to the application of model predictive control (MPC) strategy in diabetes control [1, 12]. For example, the linear GPC (optimization without constraints) has been reported in [11, 2]. Results of application of a nonlinear MPC has been reported in [5, 13]. Commonly, the disturbance measurement in form of meal announcement is considered in mentioned control algorithms.

In this paper we are interested in the control requirements formulation in the glycemic control problem when the MPC strategy is used and no meal announcement is considered.
2 T1DM Subject Control Model

In this section a T1DM control model is stated. The model is inferred from modified minimal model of glucose kinetics proposed in [17].

2.1 Modified Minimal Model

The differential equations corresponding to the glucose minimal model have the form

\[
\begin{align*}
G(t) &= -\left(p_1 + X(t)\right) G(t) + p_1 G_b + Ra(t) \quad (1a) \\
\dot{X}(t) &= -p_2 X(t) + p_3 (I(t) - I_b) \quad (1b)
\end{align*}
\]

where \(G(t)\) is the plasma glucose concentration \([\text{mmol/l}]\); \(I(t)\) is the plasma insulin concentration \([\text{mU/l}]\); \(X(t)\) represents the remote insulin \([\text{min}^{-1}]\) (it does not represent a physiological, measurable quantity); \(G_0\) is the basal glucose concentration \([\text{mmol/l}]\); \(I_b\) is the basal insulin concentration \([\text{mU/l}]\); and \(p_1\) \([\text{min}^{-1}]\), \(p_2\) \([\text{min}^{-1}]\), \(p_3\) \([\text{min}^{-1} \text{per mU/l}]\) are model parameters. \(Ra(t)\) is a glucose rate of appearance in plasma and represents the disturbance, which is in this context caused by the meal ingestion. This signal is neglected in further steps, since the disturbance is not considered in the controller design.

Neglecting \(Ra(t)\), the nonlinear system (1) can be approximated at the basal state \(x^b = [G_b \ 0]\), which is an equilibrium, by a linear system in the form

\[
\begin{align*}
\dot{x}_1(t) &= -p_1 \ x_1(t) - G_b \ x_2(t) + 0 \ \Delta I(t) \quad (2a) \\
\dot{x}_2(t) &= 0 \ x_1(t) - p_2 \ x_2(t) + p_3 \ \Delta I(t) \\
\Delta G(t) &= \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} \quad (2b)
\end{align*}
\]

where the state vector \(x^T = [x_1(t) \ x_2(t)], x(0) = 0\). Further, the system output is the glucose deviation from the basal state \(\Delta G(t) = G(t) - G_b\) and the insulin deviation from the basal value \(\Delta I(t) = I(t) - I_b\) acts as the system input. Transfer function of the system (2) has the form

\[
\frac{\Delta G(s)}{\Delta I(s)} = \frac{-G_bp_3}{s^2 + (p_1 + p_2)s + p_1 p_2} \quad (3)
\]

None of the signals (plasma concentrations) used in model (2) can be directly measured in the T1DM subject real-life conditions. Therefore, none of them can be used in the control algorithm. An additional sub-models have to be considered in the subcutaneous–subcutaneous route controller design. Particularly, a subcutaneous insulin and glucose kinetics (insulin is administered subcutaneously and also glucose level is measured subcutaneously).

We consider that the insulin subcutaneous kinetics can be reasonably approximated [5, 13] by the second order transfer function in the form

\[
\frac{\Delta I(s)}{\Delta v(s)} = \frac{k_d}{s^2 + k_1 s + k_{d0}} \quad (4)
\]

where \(\Delta v(s)\) \([\text{pmol kg}^{-1} \text{ min}^{-1}]\) is the subcutaneous insulin infusion rate deviation from the basal insulin infusion rate and \(k_d\) \([\text{kg mU}^{-1} \text{ l}^{-1} \text{ pmol}^{-1} \text{ min}^{-1}]\); \(k_{d0}\) \([\text{min}^{-2}]\), \(k_1\) \([\text{min}^{-1}]\) are the transfer function coefficients. Subcutaneous glucose \(G_M\) \([\text{mg/dl}]\) is, at steady state, highly correlated with plasma glucose; dynamically, instead, it follows the changes in plasma glucose with some delay [13]. This dynamics can be modeled with the first order transfer function

\[
\frac{\Delta G_M(s)}{\Delta G(s)} = \frac{k_{d0}}{s + k_1} \quad (5)
\]

where \(\Delta G_M\) \([\text{mg/dl}]\) is the deviation of subcutaneous glucose concentration from basal state and \(k_{d0}\) \([1 \text{ mg dl}^{-1} \text{ mmol}^{-1} \text{ min}^{-1}]\), \(k_1\) \([\text{min}^{-1}]\) are the parameters.

Linear continuous-time T1DM subject control model considered here consists of transfer functions (3), (4) and (5). This indicates, that the reasonable model is the fifth-order system. The model input is the subcutaneous insulin infusion rate \(\Delta v(s)\) \([\text{pmol kg}^{-1} \text{ min}^{-1}]\) and the model output is the subcutaneous glucose concentration \(\Delta G_M\) \([\text{mg/dl}]\). The model parameters are in general unknown, and have to be identified. For the identification, however, a discrete-time transfer function is considered.

2.2 Identification

We consider the general discrete-time transfer function in the form

\[
\frac{\Delta G_M(z^{-1})}{\Delta v(z^{-1})} = B(z^{-1}) A(z^{-1}) = B(z^{-1}) A(z^{-1}) = B(z^{-1}) A(z^{-1}) = b_1 z^{-1} + b_2 z^{-2} + b_3 z^{-3} + b_4 z^{-4} + b_5 z^{-5} \quad (6)
\]

The data, on which the identification has been carried out, have been generated using T1DM subject simulator. Simulator is based on the detailed model by [14]. For more information see also [12, 1, 16]. T1DM simulator data are shown in Fig. 1.

The experiment for obtaining the data is as follows: Subject is in the steady state (fasting) with glucose concentration approximately at a desired level \((t = 0 \text{ min})\). We refer to this glucose concentration as a basal glucose \(G_b\) since the corresponding basal insulin has to be administered exogenously to maintain this glucose concentration. At a time \(t = 60 \text{ min}\) a basal insulin rate step increase causes a decrease of the subcutaneous glucose concentration.

The T1DM simulator parameters reported mainly in [15] (summarized in [16]) have been used. A basal
subcutaneous insulin rate \( v = 0.375 \) [pmol kg\(^{-1}\) min\(^{-1}\)] has been used. In this particular case this rate corresponds to a basal glucose plasma concentration \( G_B = 130.2478 \) [mg/dl] = 7.236 [mmol/l]. Therefore, also a basal subcutaneous glucose concentration is \( G_{Mb} = 130.2478 \) [mg/dl]. The subcutaneous insulin rate increases to \( v = 0.375 + 0.1 \) [pmol kg\(^{-1}\) min\(^{-1}\)]. A sampling period \( T_s = 15 \) min has been used.

The discrete-time transfer function has been identified using least-squares method (MATLAB ARX routine). Identification results are summarized in the Table 1. Graphical comparison of the identified transfer function output with the simulator data is in the Fig. 1 (the basal glucose \( G_{Mb} \) is added to the actual model output \( \Delta G_M(t) \)).

### 3 GPC Design

In this section, an unconstrained generalized model predictive control algorithm is described.

As it has been mentioned above, the control model is considered in the form

\[
y(z^{-1}) = \frac{B(z^{-1})}{A(z^{-1})} u(z^{-1})
\]

where \( y(z^{-1}) = \Delta G_M(z^{-1}) \) and \( u(z^{-1}) = \Delta v(z^{-1}) \) to simplify the notation.

Consider an incremental control law \( \Delta u(k) = u(k) + u(k+1) \), which implies \( u(z^{-1}) = \frac{1}{(1-z^{-1})} \Delta u(z^{-1}) \).

![Fig. 1: Identification of the discrete-time transfer function — graphical comparison of the nonlinear T1DM simulator data and the identified ARX model.](image)

Substituting to (7) leads to

\[
\sigma(z^{-1}) y(z^{-1}) = B(z^{-1}) \Delta u(z^{-1})
\]

where \( \sigma(z^{-1}) = A(z^{-1})(1-z^{-1}) \). Equation (8) can be written in the difference equation form

\[
y(k) + \sigma_1 y(k-1) + \cdots + \sigma_{ns} y(k-ns) = b_1 \Delta u(k-1) + \cdots + b_{nb} \Delta u(k-nb) + \bar{w}_k
\]

where \( ns \) and \( nb \) are the orders of polynomials \( \sigma(z^{-1}) \) and \( B(z^{-1}) \) respectively.

Future outputs have the form

\[
y(k+N_p) + \sigma_1 y(k+N_p-1) + \cdots + \sigma_{ns} y(k+ns+N_p) = b_1 \Delta u(k-1+N_p) + \cdots + b_{nb} \Delta u(k-nb+N_p) + \bar{w}_k
\]

where \( N_p \) is the prediction horizon. The matrix shorthand notation of equations (10) has the form

\[
A_f y_f + A_p y_p = B_f u_f + B_p u_p
\]

where

\[
y_f = \begin{bmatrix} y(k+1) & y(k+2) & \cdots & y(k+N_p) \end{bmatrix}, \quad y_p = \begin{bmatrix} y(k) & \cdots & y(k-ns-1) \end{bmatrix},
\]

\[
u_f = \begin{bmatrix} \Delta u(k) & \Delta u(k+1) & \cdots & \Delta u(k+N_p) \end{bmatrix}, \quad u_p = \begin{bmatrix} \Delta u(k-1) & \cdots & \Delta u(k-nb-1) \end{bmatrix}
\]

and \( A_f, A_p, B_f, B_p \) are suitable matrices. Therefore, the controlled system output is predicted using

\[
y_f = A_f^{-1} B_f u_f + A_f^{-1} B_p u_p - A_f^{-1} A_p y_p
\]

\[
y_f = G_f u_f + G_p
\]

where matrices \( G_f \) and \( G_p \) have been introduced.

In order to derive a GPC control law the following quadratic cost function is considered

\[
J = (y_f - w_f)^T A_f (y_f - w_f) + u_f^T A_p u_f
\]

where \( w_f = \begin{bmatrix} w(k+1) & w(k+2) & \cdots & w(k+N_p) \end{bmatrix} \) is the vector of future values of reference signal (or set-point) and \( A_f \geq 0, A_p \geq 0 \) are weighting matrices. The control law is based on the solution of finite-horizon optimal control problem where the cost function is minimized with respect to the input \( u_f \).
Gradient of the cost function (13) with respect to vector \( u_f \) has the form

\[
\nabla_{u_f}(J) = 2G_f^T\Lambda_f (G_f u_f - w_f + G_p) + 2\Lambda_u u_f
\]

which leads to the optimal solution in the form

\[
u_f = -\left(G_f^T\Lambda_f G_f + \Lambda_u\right)^{-1}G_f^T\Lambda_f A_f^{-1}B_p u_p + \left(G_f^T\Lambda_f G_f + \Lambda_u\right)^{-1}G_f^T\Lambda_f A_f\gamma_p + G_f^T\Lambda_f w_f\]

The control law is obtained by applying to the system only the first element of the optimal solution (15).

In this algorithm we assume that the prediction horizon \( N_y \) and the control horizon (often denoted as \( N_u \)) have the same length.

The subcutaneous insulin rate \( \nu \) is constrained to be non-negative. Therefore, if the calculated insulin rate \( \nu \) is negative, a zero value is applied. In the algorithm it is possible to tune the weighting matrices \( \Lambda_u, \Lambda_y \) and prediction horizon \( N_y \). The vector of future values of reference signal has also influence on the control algorithm performance. The major advantage of this input–output GPC scheme is the ease of implementation since the real-time optimization is avoided.

4 Main Results

In this section, the simulation experiments are presented. The experiments have been carried out using T1DM subject simulator as described in section 2.2.

A typical day life of the T1DM subject receiving a mixed meal is simulated, with 45g of glucose over 15 minutes ingested at 8 a.m. (breakfast, \( t = 480 \) [min]), 70g over 15 minutes at noon (lunch, \( t = 720 \) [min]), and 70g over 15 minutes at 8 p.m. (dinner, \( t = 1200 \) [min]).

Insulin is administered subcutaneously. The resultant insulin infusion rate consists of two components: a basal insulin rate and insulin infusion rate computed by control algorithm. The basal insulin is the same as in the identification process in section 2.2, \( \nu_b = 0.375 \) [pmol kg\(^{-1}\) min\(^{-1}\)].

It has been mentioned above, for a given sampling period \( T_s \), the control tuning parameters are weighting matrices \( \Lambda_u, \Lambda_y \) and prediction horizon \( N_y \). In all of the following experiments, the sampling period \( T_s = 15 \) [min] and the prediction horizon \( N_y = 36 \) have been used. The weighting matrices have been used in the form \( \Lambda_u = I \cdot \gamma_1 \) and \( \Lambda_y = I \cdot \gamma_2 \), where \( I \) is the identity matrix with appropriate dimensions and \( \gamma_1 > 0, \gamma_2 > 0 \) are tunable parameters. Parameter \( \gamma_2 \), however, is fixed to \( \gamma_2 = 1 \). Only the parameter \( \gamma_1 \) has been tuned.

The set-point in all of the experiments is \( G_{sp} = 130 \) [mg/dl], which corresponds to the basal steady state \( G_b \) as in section 2.2. The control algorithm input is the control error \( e_c = G_M - G_{sp} \), where \( G_M \) [mg/dl] is the subcutaneous glucose concentration measured by CGM device. The control error actually corresponds to the \( \Delta G_M \), which is the output of model considered in section 2.2. This implies, that the straightforward choice of the vector of the reference signal future values is \( w_f = 0 \).

In the first experiment, \( w_f = 0 \) has been used. The control performance for different values of parameter \( \gamma_1 \) has been studied. Following values of \( \gamma_1 \) have been used \( \gamma_{1_a} = 200000, \gamma_{1_b} = 500000, \gamma_{1_c} = 750000 \). Results of the first experiment are shown in the Fig. 2.
Clearly, the choice of the vector of future values of reference signal \( w_f \) has an influence on control action, see equation (15). Therefore, in the second experiment, the vector \( w_f \) is computed for every sampling period.

The vector \( w_f \) is obtained as a sampled solution of differential equation in the form

\[
\dot{x} = -\frac{1}{T_e} x \quad x(0) = \Delta G_M(k)
\] (16)

where \( T_e \) [min] is the time-constant of system (16). The initial condition of system (16) depends in every sampling period on actual value of \( \Delta G_M \) (or regulation error). Similar approach has been used in [5].

In the second experiment, however, the weighting matrix \( \Lambda_u \) is fixed with \( \gamma_1 = 750000 \). The control performance for different values of the time-constant \( T_e \) has been studied. Following values of the time-constant \( T_e \) have been used: \( T_{e_0} = 500, T_{e_0} = 1000, T_{e_0} = 7500 \). Results of the second experiment are shown in the Fig. 3.

Based on the PID controller description in [14], we have used PID controller in the simplest discrete-time form, with sampling period \( T_s = 15 \) [min]. The parameters of the PID controller are: proportional gain \( K_P = 0.032 \) [pmol/kg/min per mg/dl], integral time constant \( T_I = 450 \) [min\(^{-1}\)], and derivative time constant \( T_D = 66 \) [min\(^{-1}\)] (with a derivative action filter coefficient \( N = 0.02 \)). Results of the third experiment are graphically compared with the second experiment in the Fig. 3.

### 5 Conclusions

As mentioned above, in recent papers a successful application of MPC control theory in T1DM control has been reported. In many cases, the measurement of disturbance signal is considered in the form of meal announcement. In this paper, the application of GPC without meal announcement, with satisfactory results, has been presented.

The fifth-order ARX model has been inferred and used in GPC design. Results reported in the paper [11] in Table 1. also indicate that the suitable order of ARX model is five or four.

Recall that the same sampling period \( T_s \) and predication horizon \( N_f \) have been used in all experiments. It has been shown that for the constant future set-point, when \( w_f = 0 \), the GPC algorithm can be tuned satisfactory using a ratio of weighting matrices \( \Lambda_u \) and \( \Lambda_c \). However, while the maximal values of glucose concentration have depended directly on this ratio, the risk of hypoglycemia has been almost the same in all cases, see results in Fig. 2. Therefore, the vector \( w_f \) has been generated at each time step as described above. This modification of the control algorithm allows to significantly reduce the risk of hypoglycemia, while the effect of maximal glucose concentration is negligible, see the results in Fig. 3.
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