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Feedforward–feedback multiple predictive controllers for glucose regulation in type 1 diabetes

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ABSTRACT

Type 1 diabetic patients depend on insulin therapy to maintain blood glucose levels within safe range. The idea behind the "Artificial Pancreas" is to mimic, as close as possible, the functions of the natural pancreas in glucose sensing and insulin delivery, by using closed-loop control techniques. This work presents a model-based predictive control strategy for blood glucose regulation in diabetic patients. The controller is provided with a feedforward loop to improve meal compensation, a gain scheduling scheme to improve the controller performance in controlling the nonlinear glucose–insulin system, and an asymmetric cost function to reduce the hypoglycemic risk. Simulation scenarios with virtual patients are used to test the designed controller. The obtained results show a good controller performance in fasting conditions and meal disturbance rejection, and robustness against measurements errors, meal estimation errors, and changes in insulin sensitivity.

1. Introduction

Diabetes is a metabolic disorder characterized by the pancreas inability to maintain glucose levels within safe range (70–180 mg/dL). In type 1 diabetes mellitus (T1DM), the immune system attacks and destroys the insulin producing β-cells. Therefore, patients with T1DM need exogenous insulin delivery to achieve near-normal glucose levels. If glucose is not controlled carefully within a tight range, chronic (e.g. cardiovascular diseases, nephropathy, and retinopathy), and acute (e.g. ketoacidosis and hypoglycemic coma) complications can occur, with the latter being more life-threatening.

Since the 1970s, the idea of artificial pancreas (AP) has been addressed as a solution to replace the existing treatment, and to improve the disease management [1,2]. While no commercial AP is currently available, the components of the AP; the continuous subcutaneous insulin infusion pump (CSII), and the continuous glucose monitors (CGM), are being used in open-loop setup. Recently, the CGM technology has improved significantly, and the reliable duration of in vivo sensors continues to increase. Frequent CGM measurements provide the possibility of predicting hypoglycemic and hyperglycemic events and suggesting corrective actions. The commercial availability of CGM systems has encouraged the research into artificial pancreas. Although the sensors and pumps systems still present some limitations, their use has resulted in better clinical outcomes over conventional therapy [3].

Several studies demonstrated the feasibility of closed-loop insulin delivery systems [4–8], and a wide spectrum of closed-loop control algorithms were proposed [1,2,4,9–13]. However, there exist many factors that make it very difficult to find a general and reliable solution for the problem of glycemic control, such as inter- and intra-patients variability in insulin sensitivity, variability in patient condition, and the limitations

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of the subcutaneous (s.c.) route used for glucose sensing and insulin delivery. Therefore, the development of a reliable control algorithm to close the loop can be viewed as a dramatic step in the progress of the artificial pancreas.

This article presents a constrained model predictive control (MPC) algorithm for the blood glucose (BG) control problem in T1DM. The proposed MPC scheme employs: gain scheduling technique, feedforward control, soft output constraints with asymmetric cost function, and hard input constraints. The gain scheduling (GS) technique monitors the glucose level and assigns specific insulin dosing profile for each glycemic range, and enhances the performance of the linear MPC in controlling the nonlinear patient model. The feedforward control is used to improve postprandial performance by an anticipatory control action that prevents large hyperglycemic peaks after meals. Output constraints are used and implemented with unequal degrees of softness using an asymmetric cost function to penalize hypoglycemia more aggressively than hyperglycemia, since the former is more life-threatening. Hard constraints are imposed on insulin input due to patient's safety and pump hardware specifications concerns. Finally, state estimation is used to minimize prediction errors that result from unpredicted dynamics, and to improve noise rejection.

The designed controller is evaluated in silico; different simulations with virtual diabetic subjects have been used to test and tune the controller. The simulation scenarios aimed at testing the controller performance against many factors, such as meal disturbance, measurements errors, possible erroneous estimation of carbohydrates' amount in meals, variation in insulin sensitivity, and inter-patients variability.

The paper is structured as follows: Section 2 describes the patient model used in this work; in Section 3, the idea of the developed closed-loop algorithm – composed of MPC with feedforward control and GS scheme – is discussed; the results obtained in the simulation scenarios are presented and discussed in Section 4; and finally the conclusions are drawn in Section 5.

2. Simulation model

Several models are being used to describe the glucose–insulin system. These models range from linear models (e.g. Ackerman model [14]), to simple nonlinear models (e.g. Bergman et al. [15]), and more comprehensive mathematical models (e.g. Sorensen [16], Hovorka [17,18], and Dalla Man [19,20]). For a detailed review on available models, see [14]. The model developed by Hovorka et al. [17,18] is used in this work to represent the diabetic patients (virtual subjects). The model includes three subsystems; plasma glucose, plasma and subcutaneous insulin, and insulin action subsystems. The model shows a good trade-off between simplicity and accuracy.

2.1. Glucose–insulin model

2.1.1. Carbohydrates digestion and absorption

This model describes the carbohydrates catabolism to monosaccharides (mostly glucose) taking place during meal digestion, as well as intestinal absorption. The glucose absorption rate, $U_G(t)$, is given by

$$U_G(t) = \frac{D_G A_G t e^{-t/t_{\max,G}}}{t_{\max,G}^2} \tag{1}$$

where D_G is the amount of carbohydrates ingested, A_G is carbohydrate bio-availability and $t_{\max,G}$ is the time-of-maximum appearance of glucose in plasma [18].

2.1.2. Subcutaneous insulin absorption

Subcutaneous absorption of bolus and infused insulin is modeled by means of a linear two-compartmental system [18]:

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{\max,I}}, \qquad \frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{\max,I}} - \frac{S_2(t)}{t_{\max,I}} \tag{2}$$

where $u(t)$ represents the administration (bolus and infusion) of insulin, $t_{\max,I}$ is the time-to-maximum insulin absorption, and $S_1(t)$, $S_2(t)$ are the insulin masses in the accessible and non-accessible subcutaneous compartments. The exogenous insulin flow is thus given by

$$I_{ex}(t) = \frac{S_2(t)}{t_{\max,I}}. \tag{3}$$

2.1.3. Insulin PK/PD

Insulin pharmacokinetics is considered of first order. Plasma insulin concentration, $I(t)$, is thus described as

$$\frac{dI(t)}{dt} = \frac{I_{ex}(t)}{V_I} - k_e I(t) \tag{4}$$

where $I_{ex}(t)$ is the exogenous insulin absorption rate described above, k_e is the fractional elimination rate and V_I is the insulin distribution volume. Plasma insulin concentration is considered to have an effect on glucose transport from plasma to tissues, hepatic glucose production and peripheral glucose disposal [18]. These actions are modeled as first-order processes:

$$\begin{aligned} \frac{dx_1(t)}{dt} &= -k_{a1}x_1(t) + k_{a1}S_{IT}I(t) \\ \frac{dx_2(t)}{dt} &= -k_{a2}x_2(t) + k_{a2}S_{ID}I(t) \\ \frac{dx_3(t)}{dt} &= -k_{a3}x_3(t) + k_{a3}S_{IE}I(t) \end{aligned} \tag{5}$$

where $x_1(t)$ represents the effects of insulin on glucose distribution/transport, $x_2(t)$ represents the effect on glucose disposal and $x_3(t)$ is the effect on endogenous glucose production; k_{ai}, $i = 1, \ldots, 3$ are the deactivation rate constants and S_{IT}, S_{ID} and S_{IE}, represent respectively insulin sensitivities to transport, disposal and endogenous glucose production.