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RULE-BASED PID CONTROL OF BLOOD GLUCOSE LEVEL

Summary. The paper is concerned with closed loop control of blood glucose level in diabetic patients. Though recent research and clinical trials have already proved that PID and MPC controllers can be used on a daily basis, variability of physiological parameters in a single patient remains to be a challenge. In this work, the focus is on increased glucose metabolism due to physical activity. We show that a simple modification of PID control rule may lead to increased safety of diabetic patients, reducing the risk of hypoglycemic events.

STEROWANIE REGUŁOWE PID POZIOMEM GLUKOZY WE KRWI

Streszczenie. Artykuł dotyczy problemu sterowania ze sprzężeniem zwrotnym poziomem glukozy we krwi u pacjentów z cukrzycą. Chociaż ostatnie badania i próby kliniczne dowiodły, że regulatory PID i MPC mogą być powszechnie używane, wyzwaniem pozostaje uwzględnienie w sterowaniu zmienności parametrów fizjologicznych pacjenta. W pracy kładziony jest nacisk na zwiększony metabolizm glukozy spowodowany aktywnością fizyczną. Pokazuje się, że prosta modyfikacja wzmocnienia regulatora PID może prowadzić do zwiększenia bezpieczeństwa pacjentów z cukrzycą, poprzez zmniejszenie ryzyka wystąpienia hipoglikemii.

1. Introduction

Diabetes is regarded as the epidemics of the XXI century. It is estimated that one for every 11 persons in the world suffers from diabetes [1]. In Poland it is approximately 4.5% of the population [2]. The number of patients is on the rise and the burden on the health care system constantly increases. Moreover, The standard treatment protocol, involving Multiple Daily Injections (MDI) significantly reduces their lives comfort.

Currently there are several large US and European projects underway aimed at implementation of a closed loop glucose control systems for diabetic patients and there are some systems available on the market. However, (1) these systems are not widely used yet, (2) they are prohibitively expensive; (3) their performance is far from ideal; and (4) they do not take into account additional, easy-to-obtain information that should reduce both the number of hypoglycemic events, fluctuations and average level of blood glucose, and overall insulin intake. This paper is focused on the latter aspect of

the systems under consideration, namely the influence of the physical exercise on the system performance.

Diabetes is a group of metabolic diseases, of which the most frequently analyzed are Type 1 diabetes, Type 2 diabetes and gestational diabetes [3]. The first of these is associated with damage to the pancreatic beta cells and the resulting lack of endogenous insulin production. Patient survival depends entirely on the systematic monitoring of blood glucose levels (BG) and the administration of insulin. The other two have their source in insulin resistance [4], understood as reduced sensitivity of cells to insulin, so that the same effect of reducing blood sugar levels requires much higher than normal amount of insulin. In the case of Type 2 diabetes, many patients eventually need insulin injections as well.

Patients' treatment is aimed at lowering high blood sugar and maintaining it in the desired range of 80-130 [mg/dl] (4.4-7.2 [mmol/L]) in fasting state and within the range 100-150 [mg/dl] (5.5-8.5 [mmol/L]) during the day (the target level may vary depending on the patient) [5]. Standard treatment involves the injection of insulin or insulin analogues [6] administered repeatedly throughout the day, with time and injected doses dependent on the planned meals. It is required to maintain a strict diet regime, because underestimating the required amount of insulin may lead to hyperglycemia, which is harmful for the body in a longer time horizon, while overestimation leads to a very dangerous hypoglycemia. To calculate the required amount of insulin, it is necessary to determine the difference between the current and desired blood glucose level, the amount of carbohydrates in the planned meal (using the available tables and calculators) and the estimation of patient insulin sensitivity. Because of the great difficulty in correctly estimating these parameters, the amount of insulin needed is usually underestimated to protect the patient from life-threatening hypoglycemia. Unfortunately, this leads to maintaining too much BG, and thus hyperglycemia. Moreover, high variability between patients [7] and one patient [8-10] have been reported, adding to a complexity of the problem.

2. State of the art

A variety of algorithms and control structures closed loop control of BG have been developed, including PID controllers [11-14], predictive (MPC) [15-17], adaptive (Eren-Oruklu, 2009), systems with feedback and feedforward loops [18], run-to-run regulation [19], fuzzy-logic [20] and neural network controllers [21]. Much effort was put into identifying parameters and validating models (e.g. [22-24]). In addition, because physiological parameters are associated with processes occurring inside the cells, especially in the case of type 2 diabetes, these processes have also been the subject of many studies conducted in terms of using their results to develop the so called artificial pancreas. An overview of the work on combining models describing processes at intracellular and tissue levels can be found, for example, in [25].

Despite the existence of many different types of controllers mentioned above and proposed as the basis of the automatic glucose control system, actually only two have found their way into clinical trials. They are the PID [12] and MPC [17] controllers. They provide an adequate level of safety and resistance to changes in physiological parameters. Results of various trials have been recently reported, with both in the case

of strictly controlled conditions and at home, with patients of all ages [9], [12], [26-31].

Another innovation that has been proposed recently is addition of a second control signal, associated with the administration of glucagon, aimed at elimination of hypoglycemia events [32-33]. At the moment, however, these studies are in the initial phase and there are no such devices on the market.

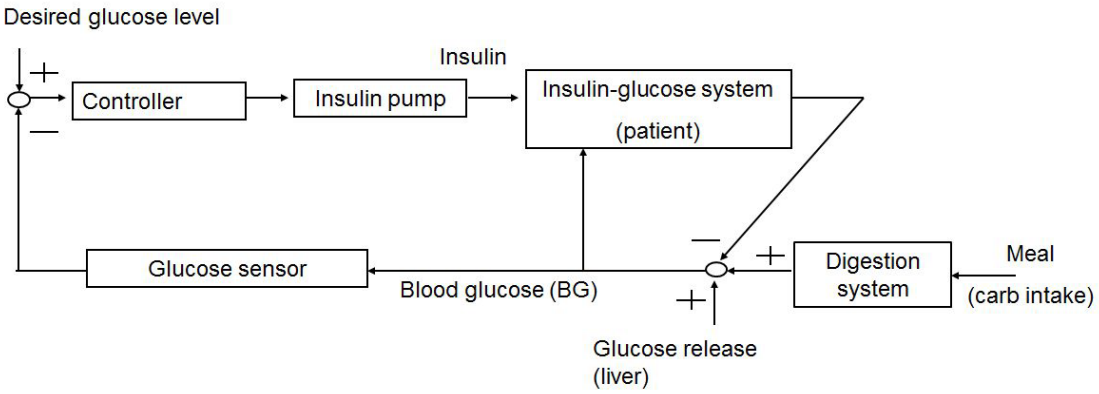


Fig. 1. A simplified block diagram of the control system

3. Mathematical model

Any control algorithm to be implemented should be first checked with numerical simulations, and these should be compared to available data. Various models of the glucose-insulin system have been proposed in the literature. The simplest of them, so called minimal model was introduced by Bergman in 1982 and has been since widely used either in its original or modified form [22, 34]. A good review of this and other models can also be found e.g. in [35]. Parameters needed for computational models were identified on experimental and clinical data [22-24]. The general block diagram is presented in Fig. 1.

A patient model consists of three subsystems (insulin-glucose, pharmacokinetics (PK), meal digestion). The first subsystem describes changes in glucose levels due to a specific concentration of insulin in the blood. It is based on the minimal Bergmann model [34], which, though developed in the previous century, proves to provide a good fit to BG measurement from current CGM devices. It consists of two differential equations, introducing as variable blood glucose levels $G(t)$ and so-called the effect of insulin $X(t)$:

$$\dot{\mathrm{G}}(\mathrm{t}) = -[\mathrm{p}_1 + p_2\mathrm{X}(\mathrm{t})]\mathrm{G}(\mathrm{t}) + \mathrm{p}_1\mathrm{G}_\mathrm{b} + \mathrm{G}_\mathrm{in}(\mathrm{t}), \tag{1}$$

$$\dot{X}(t) = -X(t) + p_3 I(t) \tag{2}$$

where $G_{in}(t)$ represents the rate of appearance of glucose in blood (the input from meals), G_b is basal glucose production, $I(t)$ is insulin concentration in blood, p_1, p_2 and p_3 are model parameters.

The second subsystem describes the pharmacokinetics of insulin and is given by a simple first order linear model:

$$\dot{I}(t) = k_1 I_{in}(t) - k_2 I(t) \tag{3}$$

where $I_{in}(t)$ represents the insulin dose injected by the control system.

The last subsystem describes the dynamics of the appearance of glucose in blood There are several models of this subsystem. However, their outputs vary enormously. Some discussion of the differences can be found in [36]. We propose to use the oldest and the simplest one, as it allows for intuitive interpretation of its parameters and easy combining of subsequent meals. It is a modification of the Lehmann and Deutsch [36, 37]. It is assumed that the rate of appearance of glucose in blood, due to the ingested glucose, is proportional to the amount of glucose in the gut, which can be described by either a solution of a single differential equation [37]

$$G_{in}(t) = k_{gabs} G_{gut}(t), \tag{4}$$

where

$$\dot{G}_{gut}(t) = -k_{gabs} G_{gut}(t) + G_{empt}(t) \tag{5}$$

with k_{gabs} and $G_{empt}(t)$ denoting a parameter and so called gastric emptying rate, respectively. The rate of appearance of glucose in blood, denoted by G_{in} is an input to the first equation in the minimal Bergman model: In [37], the time-course of the gastric emptying should follow either a triangular or trapezoidal curve, the type depending on the amount of the glucose (Fig. 2). It should be noted that these relations are a simplification, representing intravenous glucose injection in the original model. However, our studies have proven that such simplified model, when used with the Bergman minimal model (1)-(2), reproduces real-life data from CGM devices surprisingly well.

The parameters indicated in Fig. 2 may vary in a broad range. The value of v_{max} is related to the age and weigth of a patient. The increasing slope α depends on a glycemic index of the food digested, while the time T_{max} is related to the meal size.

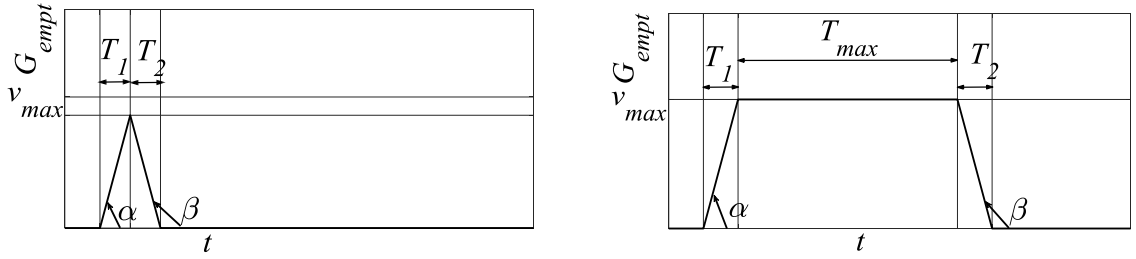


Fig. 2. The shape of the Gin(t) for a small meal (left and large meal (right)

4. Rule-based PID control

Following recent reports, one can easily show that a PID controller is sufficient to keep the BG within desired range, assuming that physiological parameters do not vary significantly.

However, the system performance significantly decreases when physiological parameters change rapidly. This might occur, for example, if a patient performs intensive physical exercise, increasing the glucose metabolism (Fig.3).

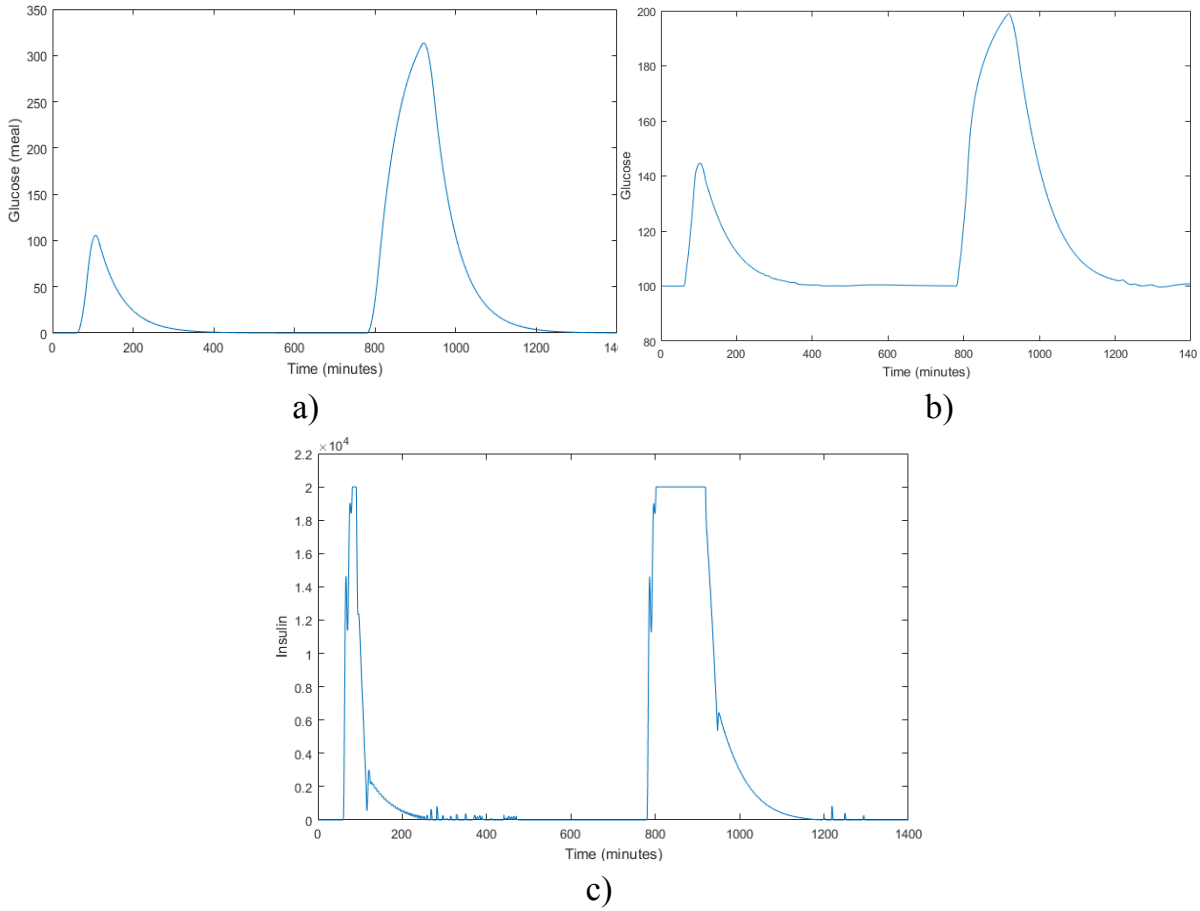


Fig. 3. Simulation results for a standard PID controller, without physical exercise: (a) glucose from the meals; (b) blood glucose; (c) insulin input

However, if the physiological parameters vary significantly, which is the case in the real world, the performance of the control system is not acceptable, as the BG fall into low levels (Fig. 4). The reason behind the significant drop in BG is in increased value of the parameter p_2, due to increased demand for energy in cells during physical effort. This should be reflected in the control algorithm. Therefore, it seems natural to decrease the gain of the controller, following the manual switch of the controller into a "physical exercise" mode. This idea could be further expanded into automatic detection of the physical effort through, e.g., communication with a pulsometer. The proposed transfer function of the PID controller is then given by

$$K_C(s) = \frac{k}{1+\alpha E}\left(1 + \frac{1}{T_I s} + \frac{sT_D}{1+sT_D/N}\right), \tag{4}$$

where α is a controller parameter and E represents the physical effort.

To avoid oscillations in the lower range of BG, which are due to large TD parameter, required in the system, an additional rule has been proposed, to switch off the derivative part of the controller for BG below the set point.

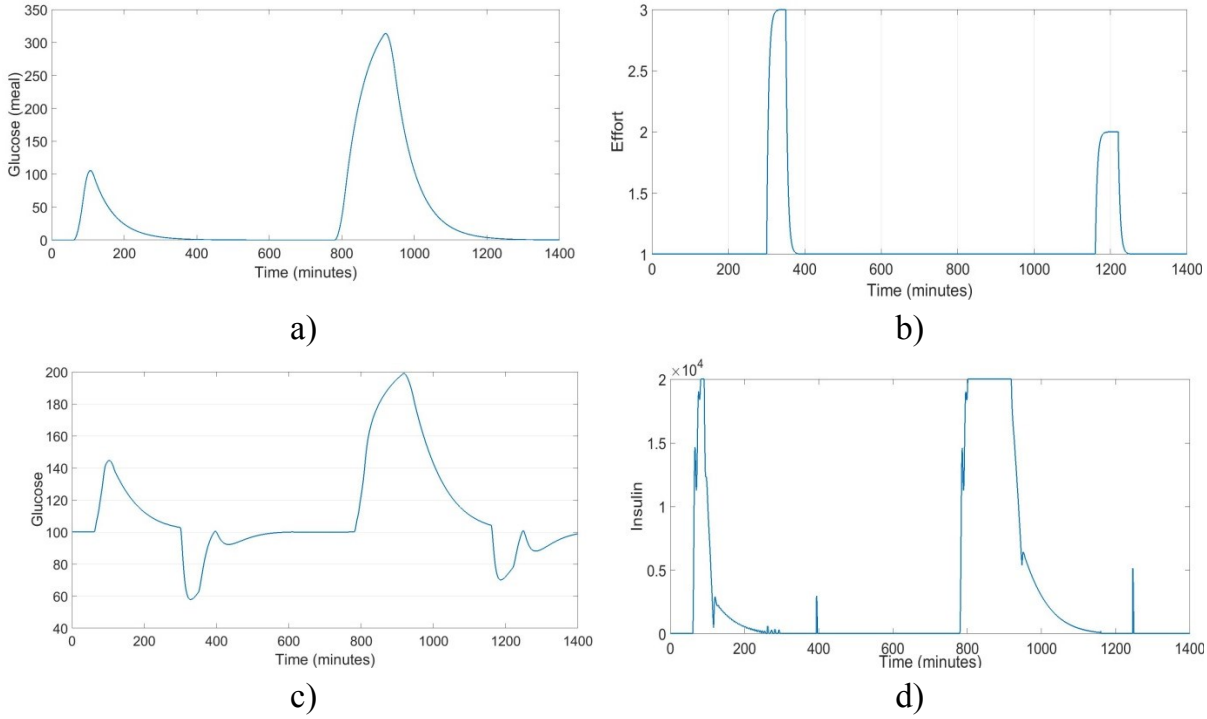


Fig. 4. Simulation results for a standard PID controller, with a physical exercise: (a) glucose from the meals; (b) physical effort; (c) blood glucose; (d) insulin input

The system performance is better than the previous one (Fig. 5). Due to additional rule that has been applied, oscillation in the low BG range disappeared and the lowest BG has been increased. Nevertheless, the effort leads to BG that is too low. That is caused by the fact that the control is bounded by 0 value (the control is the insulin dose). Of course, if the physical activity took place earlier, one could show a satisfactory system behavior. However, this would be only a theoretical scenario, as usually extensive effort does not follow the meal immediately.

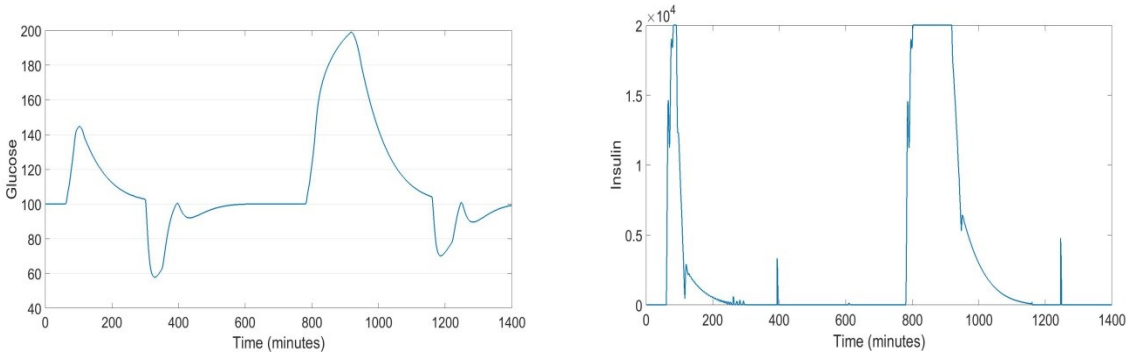
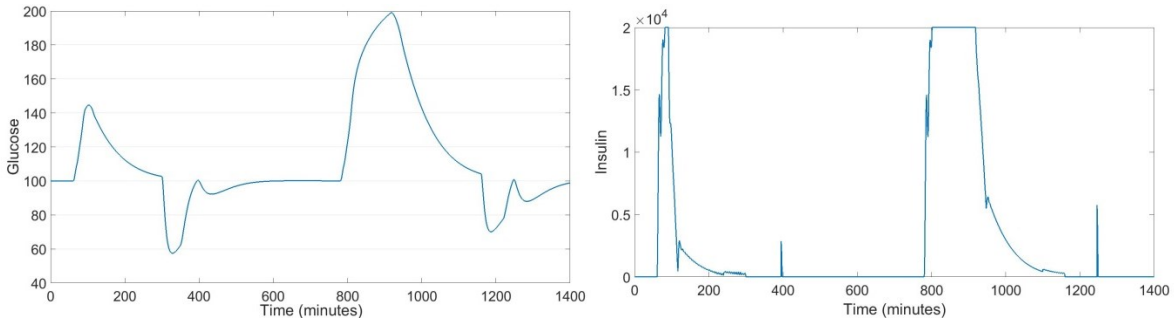


Fig. 5. Simulation results for a rule-based PID controller with a variable gain and meal and physical effort setup as in the Fig. 4, with a physical exercise: (a) blood glucose; (b) insulin input

However, if the switch in the controller setup is user-driven, it can be done in advance, thus creating an additional feedforward control. If this is used in a combination with a standard PID, the minimum BG is slightly increased (Fig. 6) but otherwise, the difference in the system performance is negligible. Better results are obtained when a combination of feedforward control and rule-based PID with a variable gain is used (Fig. 7). Once again, in such application and the setup of exercise parameters chosen for illustration, it is not possible to completely avoid the drop in BG, due to the constraints imposed on control variable. However, BG levels are kept in the range acceptable for diabetic patients.



a) b)

Fig. 6. Simulation results for a rule-based PID controller with constant parameters, meal and physical effort setup as in the Fig. 4, with a physical exercise and its prediction: (a) blood glucose; (b) insulin input

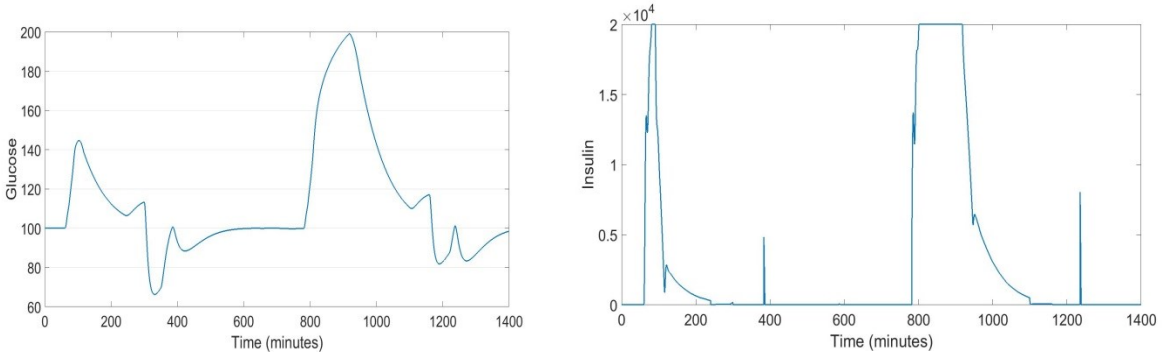


Fig. 7. Simulation results for a rule-based PID controller with a variable gain, meal and physical effort setup as in the Fig. 4, with a physical exercise and its prediction: (a) blood glucose; (b) insulin input

5. Conclusions

In the paper, a rule-based PID closed-loop control of blood glucose of diabetic patients has been proposed. It is based on two rules:

- If the BG is below set-point, the derivative part of the controller should be switched off.
- If a physical activity is planned, the controller should be set to an effort mode, in which the controller gain is significantly reduced.

The simulation results indicate that such approach yields better results than a standard PID control, reducing oscillations when BG is low and increasing the minimum BG during the exercise, thus reducing the risk of hypoglycemia. The proposed solution can be expanded by including pulsometer measurements in the controller tuning, though such option has not been tested yet.

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