10.24425/acs.2023.146964

Archives of Control Sciences
Volume 33(LXIX), 2023
No. 3, *pages* 681–705

Robustness of closed-loop glucose control systems

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The main purpose of this work is to provide an extensive, simulation-based comparison of robustness of PID and MPC algorithms in control of blood glucose levels in patients with type 1 diabetes and thus answer the question of their safety. Cohort testing, with 1000 simulated, randomized patients allowed to analyze specific control quality indicators, such as number of hypoglycemic events, and length of hypo- and hyperglycemia periods. Results show that both algorithms provide a reasonable safety level, taking into account natural changes of patients' physiological parameters. At the same time, we point out drawbacks of each solution, as well as general problems arising in close-loop control of blood glucose level.

Key words: artificial pancreas, closed-loop control, insulin pump, type 1 diabetes.

1. Introduction

Diabetes is described by the World Health Organization as one of four priority noncommunicable diseases that require urgent action from authorities around the world. According to the report, between years 1980 and 2014 the number of people diagnosed with diabetes rose from 108 million to 422 million [31] and that number is still on the rise. The standard treatment method involves multiple insulin injections daily, that results in significantly lower comfort of patients' lives.

In case of type 1 diabetes the treatment can be facilitated with use of insulin pumps, which administer insulin doses without the need for multiple injections. In its basic form insulin pump involves no automatic feedback to react for blood glucose levels variations. In [9] a review of currently available, more advanced (closed-loop) solutions can be found.

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This work was supported by the SUT internal grant for young researchers 02/040/BKM22/1032 (AW) and the SUT internal grant 02/040/BK_21/1022.

Received 25.01.2023. Revised 2.08.2023.

The aim of the work described in this article was to compare two types of regulation algorithms widely used in works concerning advanced automated control of blood glucose levels in patients with type 1 diabetes (so called artificial pancreas), i.e. Proportional-Integral-Derivative algorithm (PID) – used e.g. in [20,21,23,27] and implemented as shown in [13] – and Model Predictive Control (MPC) – covered e.g. in [15, 18, 24, 32] and implemented according to [5]. As was shown e.g. in [7] no extensive simulation-based comparison of those two base algorithms was made, with new works being concentrated on proposing modifications of one of the algorithms [3, 4, 11] or sensitivity analysis focused on a single algorithm and selected parameters only [25]. Moreover currently works concerning extending the system with second control signal (glucagon) are becoming more frequent ([8, 29] or in a simulation environment in [28]), while no wide-scale computational comparison was performed even for more basic control structures.

This work is focused on analysis of observing how differences between patients or changes in physiological patient's parameters (both represented by changes of mathematical model parameters) influence the quality of the closed-loop control system. An additional issue here concerns the way the controller is tuned - does it work properly if a general, not patient-specific tuning is applied? Therefore, once a specific controller has been tuned, the tuning is not changed for the whole virtual patient cohort. Such approach allows for verification of controllers' robustness, meant as possibility to use one initially tuned algorithm for wide range of type 1 diabetes patients.

All aforementioned elements were examined with use of mathematical modelling and numeric simulations, which allowed for conducting numerous trials with various values of models' parameters.

2. Materials and methods

Implementation of a proper mathematical model for performing simulations requires both description of the control object (glucose-insulin system with meal digestion subsystem) and description of the control system structure.

2.1. Mathematical modelling

The model of the patient that needed to be implemented to perform simulation testing consisted of several subsystems: glucose-insulin interaction subsystem, insulin pharmacokinetics subsystem, and meal related subsystem. Full equations of the model are provided in the Appendix A.

2.1.1. The glucose-insulin model with physical exercise

The base of the plant model are equations describing glucose-insulin interaction and insulin dynamics in the organism. In this work, so-called Bergman's minimal model [6] has been used to model glucose-insulin interaction dynamics. It consists of two first-order differential equations covering changes in time of blood glucose level $G(t)$ and effect of insulin $X(t)$.

$$\frac{dG(t)}{dt} = -(p_1 + X(t))G(t) + p_1 G_b + p_2 G_{\text{in}}(t), \tag{1}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 I(t). \tag{2}$$

The model is complemented with another first-order differential equation, describing pharmacokinetics of insulin after its external administration [6]:

Moreover, we have assumed that an intensive physical exercise or other effort may lead to increased uptake of glucose from blood. Therefore, Eq. (1) has been modified to account for exercise-dependent changes in minimal model's parameters shown e.g. in [10]:

$$\frac{dG(t)}{dt} = -\left(p_1 + P^*(t)X(t)\right) G(t) + p_1 G_b + p_2 G_{\text{in}}(t). \tag{3}$$

In Eq. (3), the additional signal value of $P^*(t)$, whose value corresponds to effort's intensity, modifies the way insulin in blood impacts the blood glucose level. When no additional effort is present value, of $P^*(t)$ is 1, what brings Eq. (3) to original Bergman's form of Eq. (1). Therefore, it can be broken up into two parts: base value (P^*_{base}) and effort-related part (P^*_{effort}), as in Eq. (4).

$$P^* = P^*_{\text{base}} + P^*_{\text{effort}}\,. \tag{4}$$

Such decomposition is used further on when changes of parameters' values are concerned.

2.1.2. The meal model

To properly simulate the blood glucose level behavior using equations from subsection 2.1.1 the signal $G_{\text{in}}(t)$ must be determined. The model used for that purpose in this work is called Lehman-Deutsch model [17]. It includes one differential equation describing gut glucose concentration, $G_{gut}(t)$. It was argued in [17] that, in reasonable simplification [26], so-called gastric emptying rate – $G_{empt}(t)$ should follow either triangular or trapezoidal curve, depending on the glycemic index of the meal and its glucose abundance. In [26] it was argued that after a small modification, such a model allows for accurate reproduction of real-life data.

2.2. Control system structure

2.2.1. Basic control loop structure

The basic closed-loop feedback control structure consists of a controller, a measuring device (glucose sensor), an actuator and the plant (glucose-insulin subsystem), as shown in Figure 1.

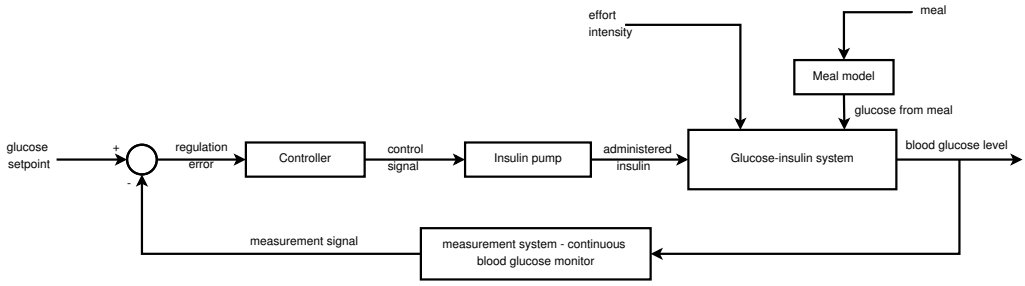


Figure 1: Basic control system structure – block diagram

The actuator of the control system is the insulin pump, responsible for administering insulin dose calculated by control algorithm. Its dynamics has been omitted in the work.

The measuring device is a glucose sensor (Continuous Glucose Measurement (CGM) device). Descriptions of sample products can be found in [2, 12]. As with the actuator, the dynamics of the sensor has been neglected. However, inaccuracies that may appear in the measurement (notably measurement noise) were taken considered in this work.

2.2.2. Controller output bounds

In any industrial application the controller output is always limited, which is related to physical constraints of the actuator. In case of a controller that should work with an insulin pump such a limitation obviously will be present. However, in this application the maximum amount of insulin that can be administered both in a single dose and throughout the day constitute additional limitations.

Preliminary simulation studies showed that, as the controller work quasi-continuously, the maximum daily amount of insulin is more critical, and yields more strict constraints for the control system than a maximum single dose.

Based on the literature survey, typical daily amounts of insulin administered to type 1 diabetes patients were taken as a point of reference. These are estimated to be around 0.5-1$[U]$ per kilogram of body mass [14]. However, the model used in this work assumes that the control system is responsible only for bolus insulin and therefore the value must be reduced to take into account that between 30% and 50% of administered insulin is a long-acting insulin [22]. As the controller should not administer the maximum possible amount of insulin all the time the

upper bound for the controllers' output adopted was 50% higher than the one calculated as pointed above. Additionally, the most strict variant was adopted, i.e. daily dose of 0.5 [U/kg] and bolus being just 50% of that value.

That resulted in the value of controller's output upper bound equal to 30 [U] per day. That divided into controller sampling periods resulted in a value that after preliminary testing was doubled (supplied insulin far from daily bound, but controllers action hindered by too small bound). Final upper bound for controller's output was 12.5 [mU].

Naturally the lower bound for the controllers' output is 0, because negative amount of insulin cannot be administered.

2.2.3. Blood glucose acceptable levels

The setpoint for control system was set at 80 $\frac{\text{mg}}{\text{dl}}$ the values separating hypoglycemia and hyperglycemia from normal levels of blood glucose must be chosen appropriately.

Taking into consideration World Health Organization's guidelines [30], as well as those put forward by American Diabetes Association [1] ranges like the ones described in [16] were implemented.

2.3. Simulation methodology

To accurately check the impact of changes in patients' parameters have on the quality of the closed-loop control system, a number of simulation scenarios were implemented, and control quality indicators were calculated for each simulation.

2.3.1. Control quality indicators

To compare different control systems in various scenarios, control quality indices must be defined. Standard control theory indices (e.g., Integral Absolute Error) may be used, but to take into account particular properties of the glucose-insulin system and health standards, problem-specific indices have been defined. They are related to hypo- and hyperglycemia in patients (Table 1). Such type of quality indicators is widely accepted as shown in [19].

Table 1: Control quality indicators

Index	Meaning	Glucose level
I_1	the number of hypoglycemic episodes in a set of simulations	below 60 mg/dl
I_2	total time of hypoglycemic episodes in a single simulation	below 60 mg/dl
I_3	total time of hyperglycemic episodes in a single simulation	above 140 mg/dl

2.3.2. A cohort of virtual patients

Since individual patients' physiological parameters vary and may also change in time for a single patient, a virtual cohort of 1000 patients has been created, for whom simulations with a predefined meal and effort scenario, described in the subsequent section, were run. For each virtual patient, model parameters were sampled from a uniform distribution, specified in Table 2. Controllers were tuned for a patient, defined by nominal parameter values, given in Table 2. Results of a set of simulations were used to calculate indices described in the preceding section.

Table 2: Nominal values and surroundings for changes of parameters

Parameter name	par_{nom}	parameter range
p_2	0.021	[0.015, 0.030]
P^*_{base}	1	[0.5, 3]
V_{max}	1/90	$[0.5\text{par}_{\text{nom}}, 1.5\text{par}_{\text{nom}}]$
$T_{\text{up\_max}}$	30	$[0.5\text{par}_{\text{nom}}, 3\text{par}_{\text{nom}}]$

Four model parameters were selected to represent heterogeneity of patient responses to meal and insulin injections. First of them is p_2 – parameter of Eq. (2) defining the rate of disappearance of insulin effect (variable $X(t)$), changes of which may account for differences in both supplied insulin and patient's reaction to insulin. The second parameter is P^*_{base}, explained in Eq. (4). By that notation a value of P^* in Eq. (3) when no additional effort takes place is meant. Its nominal value is 1, so that what was said in 2.1.1 is true for nominal values of parameters. These two varying parameters account for variability in a glucose-insulin subsystem. The remaining two varying parameters are taken from the meal model described in 2.1.2. Changing V_{max} represent variability in a digestive system across the population, while varying $T_{\text{up\_max}}$ accounts for meals with different glycemic indices.

2.3.3. Simulation scenarios

Each simulation scenario covered 24 hours. Two types of simulations were run: mass simulations for the whole cohort of virtual patients, with randomized parameters (as described in Section 2.3.2), and singular simulations, where the impact of changes of just one parameter at a time was evaluated. For singular tests, model responses were calculated only for nominal and extreme values from Table 2.

Singular simulations included two meals of different abundance (smaller – 20 g of glucose and larger – 60 g of glucose, separated in time) and no physical

effort. Thus, the impact of changing individual patient's parameters on system responses to small and large meal was evaluated.

For mass simulations all scenarios included three meals (breakfast – 20 g of glucose, lunch – 40 g of glucose, dinner – 60 g of glucose), and differ between each other only in time and intensity of the effort. Thus, a typical day for a single patient was represented, during which a physical effort could affect physiological parameters. First, a scenario with no additional physical effort was tested. Then, two other scenarios were used, each including two physical exercises throughout a day. In one of them, effort of low intensity followed small meal and effort of higher intensity followed big meal. In the other effort of medium intensity followed both small and big meal.

3. Results

Each type of simulation, described in the preceding section, was analyzed from a different perspective. For singular simulations, the focus was on transient system responses, whereas for mass (cohort) simulations the distribution of quality indicators (Table 1) were analyzed in form of histograms.

3.1. Singular simulations

The main purpose of singular simulations was to show the influence each parameter can have on the operation of the control system. Apart from that, however, another, equally important aspect can be checked. Comparing the responses of system for controllers which output has no upper limit, and those with bounds described in 2.2.2 the impact and importance of introducing such limiting can be addressed.

3.1.1. Influence of deviations of parameter p_2

First parameter to be evaluated was p_2, changes of which correspond to differences in time needed by the insulin administered to exert its action on the system. That parameter is important because it is directly related to the time constant of the control plant, which in general may lead to problems for control algorithms.

As expected, if a patient is characterized by smaller value of this parameter, than used for controller tuning, it may lead to hypoglycemic incidents for both control algorithms (Figures 2 and 3). However, for MPC those incidents are more severe. In some sense, this is the result of underestimating (indirectly) by the control algorithm of the time needed by the insulin to affect blood glucose level.

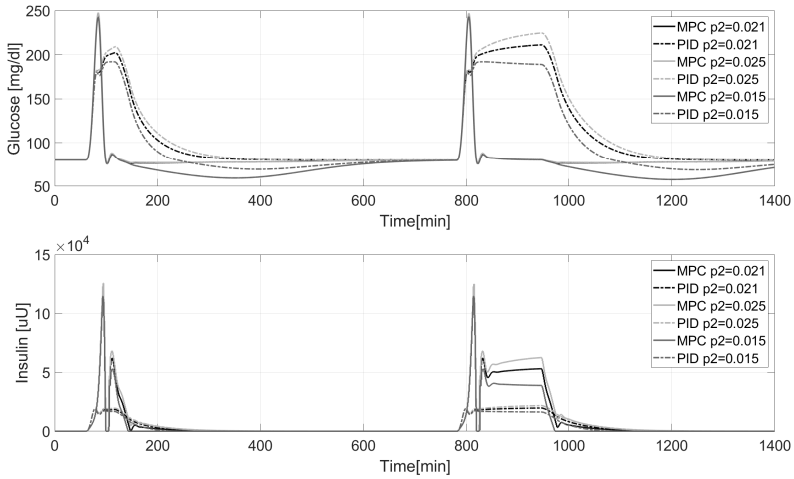


Figure 2: Responses of both control algorithms for deviations of parameter p_2 for unbounded controllers' output

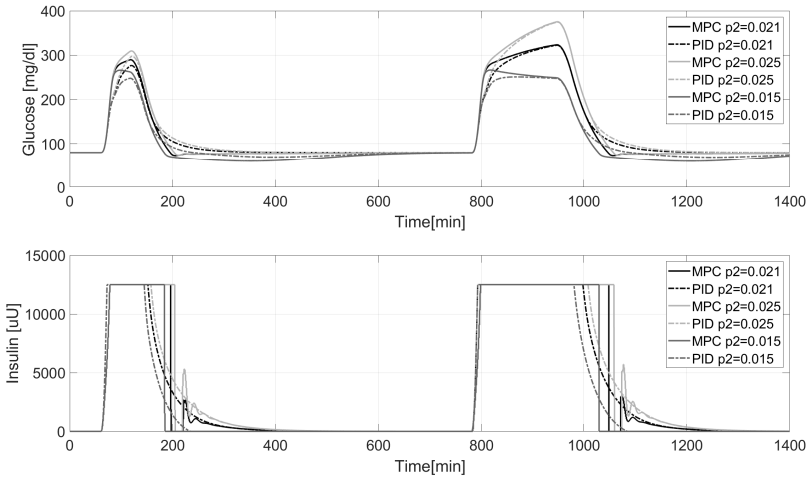


Figure 3: Responses of both control algorithms for deviations of parameter p_2 for bounded controllers' output

3.1.2. Influence of deviations of parameter P^*_{base}

One of the individual physiological characteristics that may significantly vary across the population is related to patients' insulin sensitivity, understood as the rate of glucose cellular uptake associated with insulin. In the model considered in this paper it is represented by P^*_{base}.

Figures 4 and 5 clearly indicate that the main visible consequence of different values of P^*_{base} is the peak value of blood glucose level after meal. That aspect is very similar for both control algorithms and for both unbounded and bounded controllers.

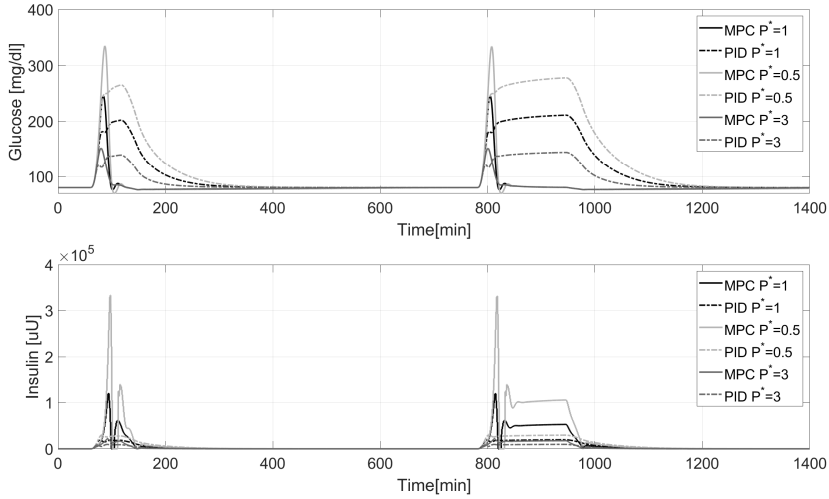


Figure 4: Responses of both control algorithms for deviations of parameter P^*_{base} for unbounded controllers' output

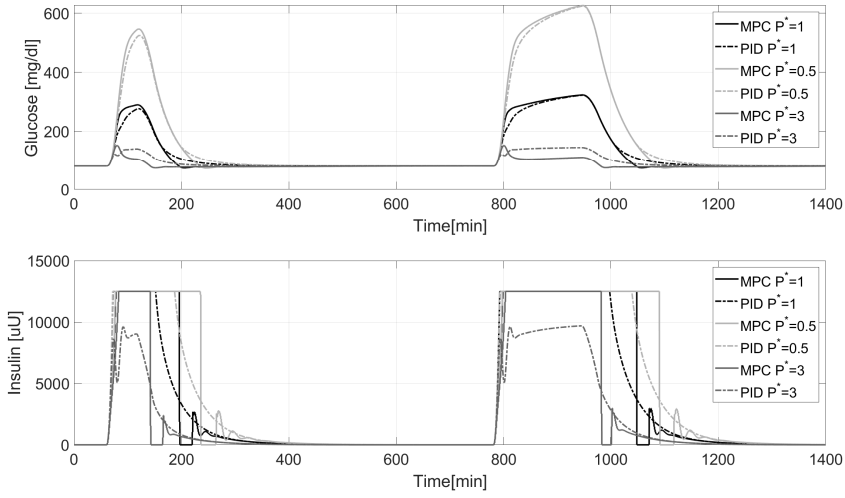


Figure 5: Responses of both control algorithms for deviations of parameter P^*_{base} for bounded controllers' output

3.1.3. Influence of deviations of parameter V_{max}

As noted before, differences in $V_{\max}$ parameter values correspond to differences in digestive system efficiency.

For this parameter, Figures 6 and 7 show significant differences in the responses of the system with nominal and changed parameter values. Not only the peak value of blood glucose level is related to $V_{\max}$'s value, but also the time required for the return of blood glucose level to desired range. A notable exception here is the MPC algorithm without upper limit on controller's output.

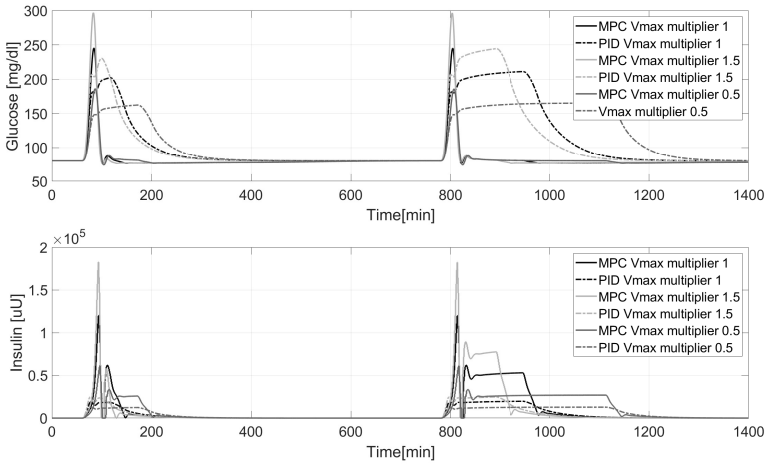


Figure 6: Responses of both control algorithms for deviations of parameter $V_{\max}$ for unbounded controllers' output

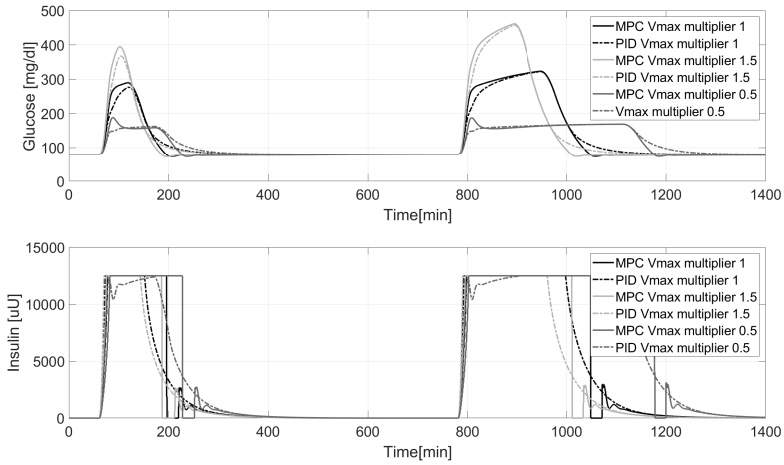


Figure 7: Responses of both control algorithms for deviations of parameter $V_{\max}$ for bounded controllers' output

3.1.4. Influence of deviations of parameter $T_{\text{up\_max}}$

Last, but not least important, parameter is $T_{\text{up\_max}}$, whose value corresponds to the glycemic index of an ingested meal. Checking its variations influence is important on the way towards universality, because of the abundance of different types of food, each of its own glycemic index value.

Figures 8 and 9 clearly show how profound an impact the glycemic index of meal has on the behavior if control systems. Not only the peak value of blood

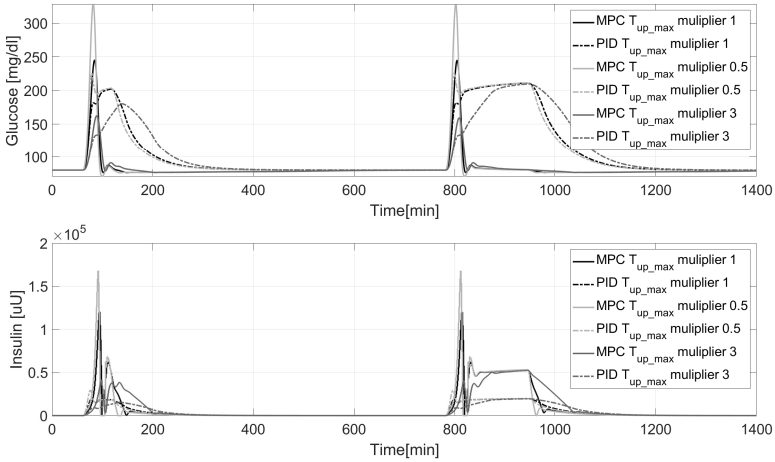


Figure 8: Responses of both control algorithms for deviations of parameter $T_{\text{up\_max}}$ for unbounded controllers' output

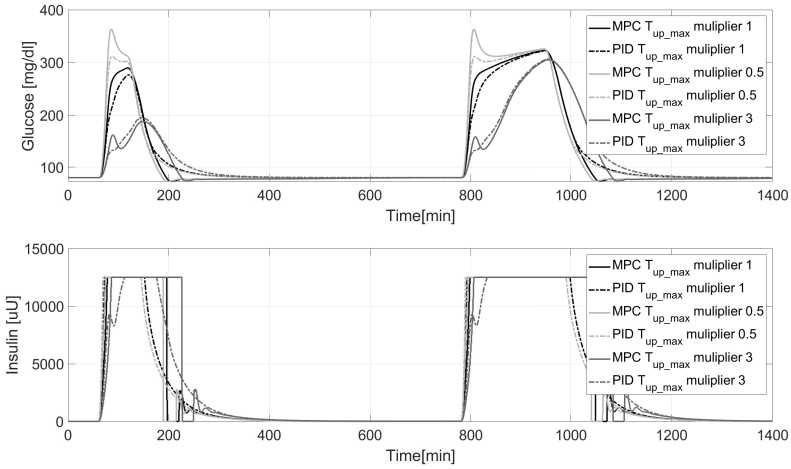


Figure 9: Responses of both control algorithms for deviations of parameter $T_{\text{up\_max}}$ for bounded controllers' output

glucose level is changing, but also the shape of response seems dependent on the actual value of T_{up_max} (most visible in results for T_{up_max} multiplier equal to 3). As in 3.1.3 the second conclusion is not relevant for the MPC algorithm without upper limit on controller's output.

3.1.5. General observations from singular simulations

Looking at all responses shown in Figures 2–9, some general conclusions concerning the operation of control systems can be drawn.

Firstly, the introduction of an upper limit for controller output has a significant impact on the system responses in every case. That concerns both algorithms, however, for the MPC the changes in behavior are far greater. The aggressive reaction of MPC controller for appearance of glucose from meal is in general halted by the limit, bringing responses for both MPC and PID closer together in terms of similarity. As the bounded output of the controller is natural in this application, this could lead to the conclusion about acceptability of both controller types.

Secondly, the same aggressiveness that allows the MPC regulator to bring blood glucose levels down quickly leads to an overshoot, that may even induce the state of hypoglycemia as shown in Figure 2.

Moreover, the general amount of insulin used by every controller, even though not calculated precisely, is clearly larger for the MPC algorithm, even with the upper limit imposed on the control signal.

3.2. Results of cohort simulations

While it is important to know the impact of the changes in parameter values on transient system responses, safety and quality evaluation should be based on some measure of hypoglycemic and hyperglycemic events across the population. To facilitate that, following the cohort simulation, empirical distributions of I_2 and I_3 quality indices (Table 1) are shown in form of histograms. For a clearer view, the histograms were drawn only for non-zero values of the quality indicators.

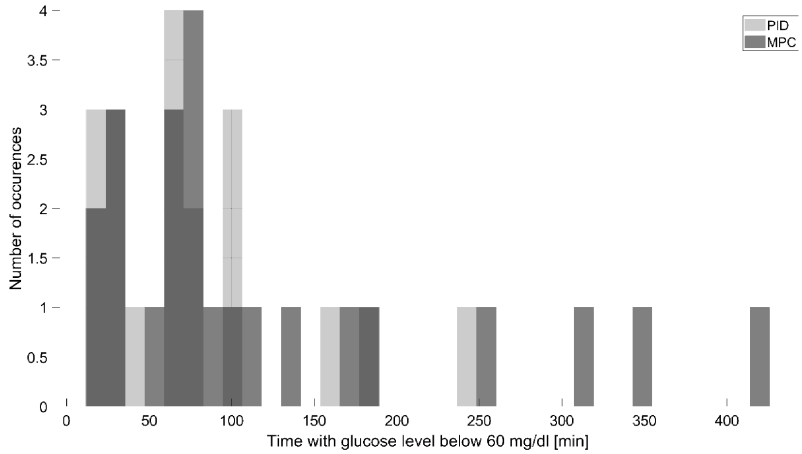
As for the I_1 quality index, it describes the total amount of hypoglycemic incidents, and together with time of hypoglycemia provides information about safety of the closed-loop control.

To foster the discussion of limiting controllers' output, cohort simulations were run for both unbounded and bounded versions.

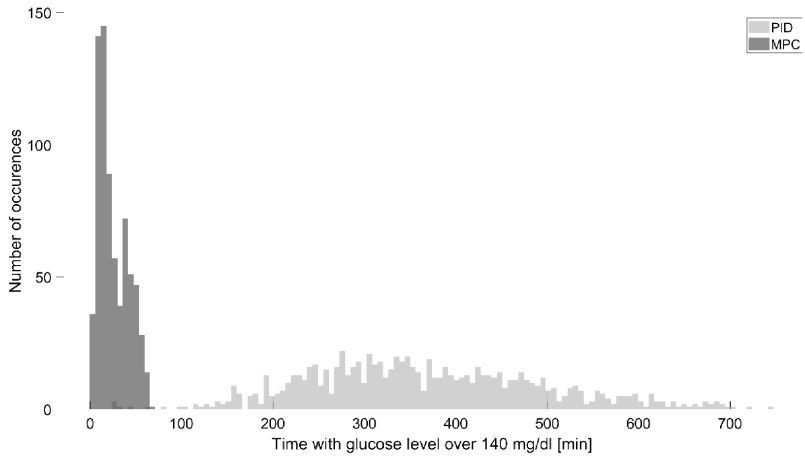
3.2.1. The scenario without physical effort

The first scenario was similar to singular simulations from 3.1, as it includes no effort. However, three meals, instead of two, constitute the glucose input.

It is worth noticing that even though there was no external event that could lower the blood glucose level, for both control algorithms, incidents of hypoglycemia were present in a few of simulations (Figures 10a, 11a). For the PID



(a) Histogram of time of hypoglycemia across simulations

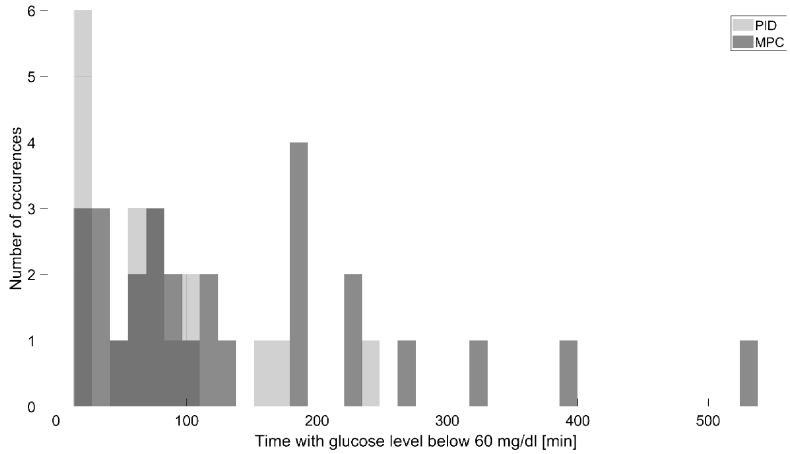


(b) Histogram of time of hyperglycemia across simulations

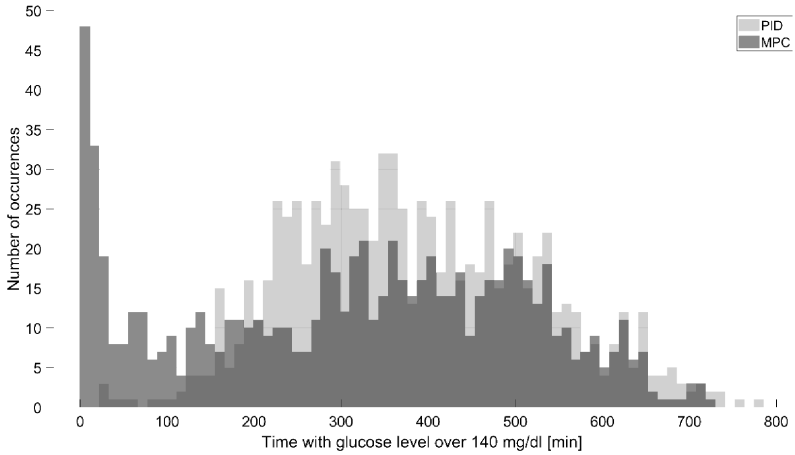
Figure 10: Histograms of quality indicators for scenario without a physical effort and unbounded controllers' output

controller, those episodes were more rare and shorter compared to the MPC controller, both for bounded and unbounded controllers' output.

The introduction of an upper limit for insulin input had several visible consequences. For time spent in state of hyperglycemia, the distributions for PID and MPC controllers, that were previously almost entirely separated (Figure 10b), came closer to each other, though the histogram for MPC controller still indicates



(a) A histogram of time of hypoglycemia across simulations



(b) Histogram of time of hyperglycemia across simulations

Figure 11: Histograms of quality indicators for scenario without a physical effort and bounded controllers' output

faster reduction of hyperglycemic states (Figure 11b). As far as hypoglycemia-related indicators are concerned, the distribution for PID controller shifted slightly towards lower values while for the MPC controller a minor shift towards larger values can be noticed. These visual observations are supported by the number of hypoglycemic incidents (Table 3) and number of simulations with such incidents (Table 4).

Table 3: The number of hypoglycemic incidents for scenario without a physical effort

Output type	Value for PID	Value for MPC
unbounded	21	31
bounded	21	41

Table 4: The number of simulations in which hypoglycemia occurred for scenario without a physical effort

Output type	Value for PID	Value for MPC
unbounded	19	23
bounded	19	28

3.2.2. A scenario with a physical effort related to meal glucose input

The second scenario included two efforts of different intensities, related to the meals glucose dose as described in Section 2.3.3. The efforts were assumed to take place after first meal (one with the smallest glucose dose) and after third meal (one with the largest glucose dose).

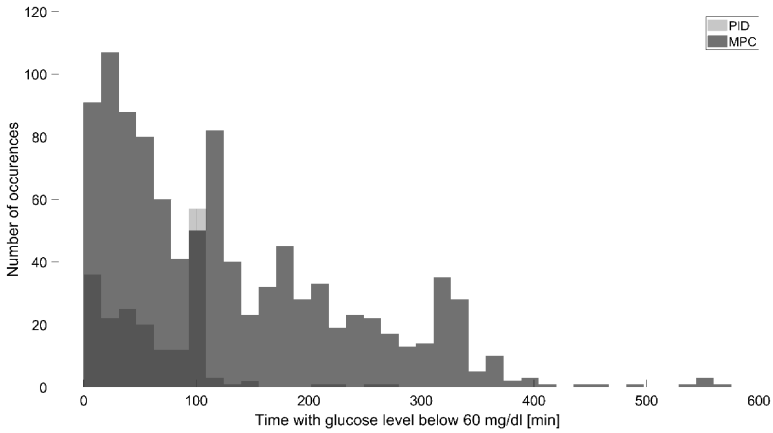
Introduction of a physical effort seems to have only a limited influence on distributions of time spent in hyperglycemia for both unbounded (Figure 12b) and bounded (Figure 13b) controllers' output. The only visible change, when compared to Figure 10b and Figure 11b, respectively, is a slight shift towards smaller values for each distribution, what is a reasonable behavior as the effort should yield a reduction of the blood glucose level.

Histograms presenting distributions of time spent in hypoglycemia are much more interesting (Figure 12a and 13a). The main impact of the physical effort can be seen, as for both control algorithms the number of simulations with hypoglycemia events dramatically increased. The rise is much more significant for the MPC controller than for the PID one, which is also clear from Table 5 and Table 6, where for MPC algorithm, more than one episode on average was present in each simulation.

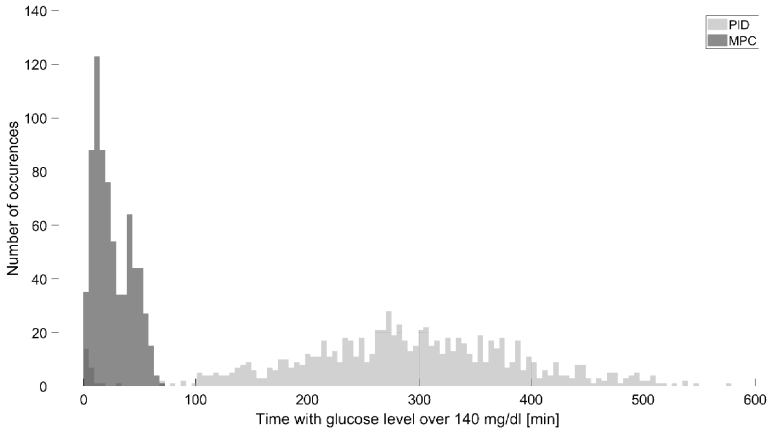
The importance of limiting controllers' output can be visible here. Both in Table 5 and in histograms (Figure 12a and 13a) it is clear that when the upper limit

Table 5: Number of hypoglycemic incidents for a scenario with a physical effort related to meal glucose input

Output type	Value for PID	Value for MPC
unbounded	206	2607
bounded	171	1541



(a) Histogram of time of hypoglycemia across simulations



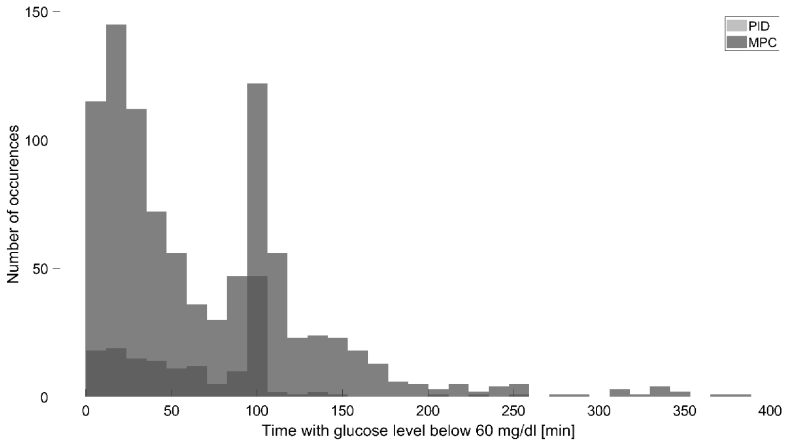
(b) Histogram of time of hyperglycemia across simulations

Figure 12: Histograms of quality indices for a scenario with physical effort related to meal glucose input and unbounded controllers' output

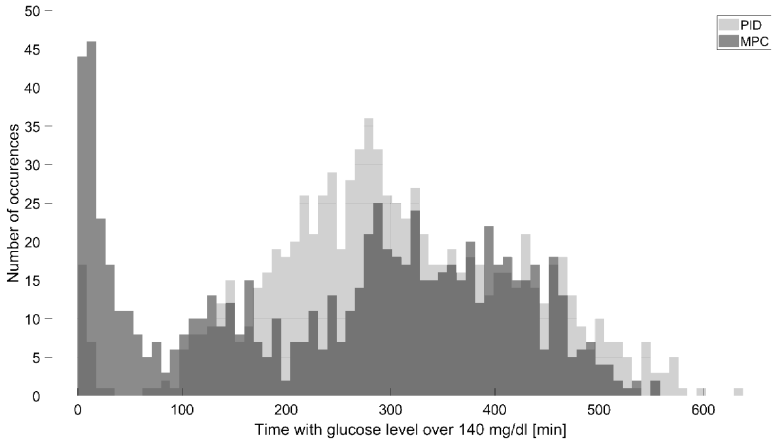
was introduced, both the time of hypoglycemia and the number of its occurrences dropped. Histograms show narrower distributions.

Table 6: The number of simulations in which hypoglycemia occurred for a scenario with a physical effort related to meal glucose input

Output type	Value for PID	Value for MPC
unbounded	194	1000
bounded	160	936



(a) Histogram of time of hypoglycemia across simulations



(b) Histogram of time of hyperglycemia across simulations

Figure 13: Histograms of quality indices for a scenario with a physical effort related to meal glucose input and bounded controllers' output

3.2.3. A scenario with a physical effort unrelated to meal

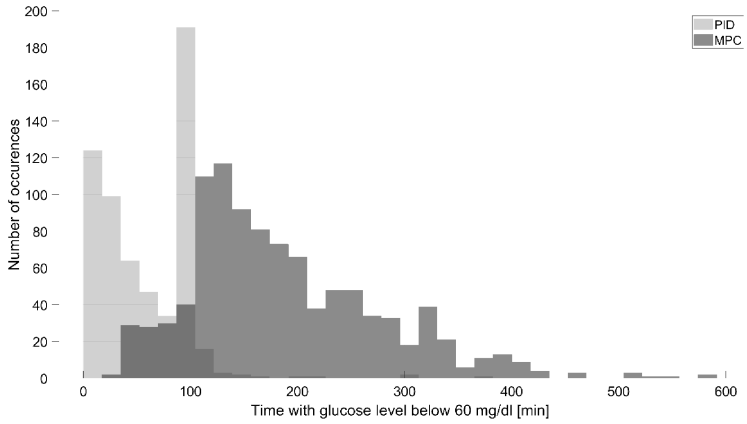
The last scenario was similar to second one, described in 3.2.2. However, the intensities of both physical efforts were the same, thus unrelated to meal glucose dose. Additionally, both efforts started sooner after the meal.

Most conclusions drawn in the preceding section, regarding influence of effort and introduction of upper bound on control system performance, hold also in this scenario (Figures 14 and 15).

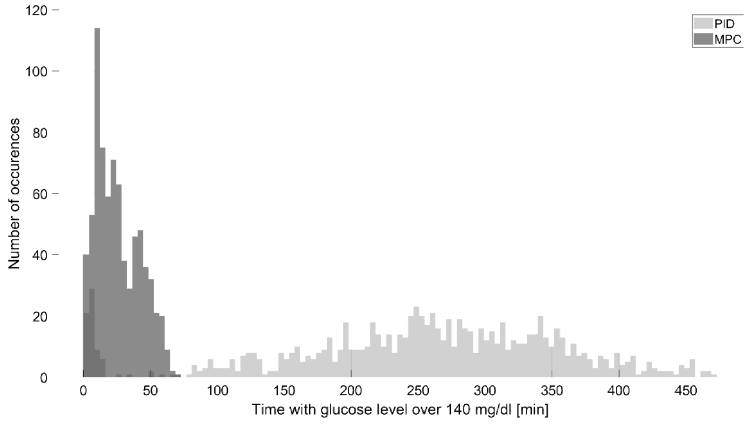
As previously, issues related to effort have small impact on the distribution of time of hyperglycemia. However, when taking into consideration hypoglycemia-related indices, a significant increase in the number of hypoglycemic incidents

Table 7: Number of hypoglycemic incidents for a scenario with a physical effort unrelated to meal

Output type	Value for PID	Value for MPC
unbounded	682	3350
bounded	508	2329



(a) Histogram of time of hypoglycemia across simulations



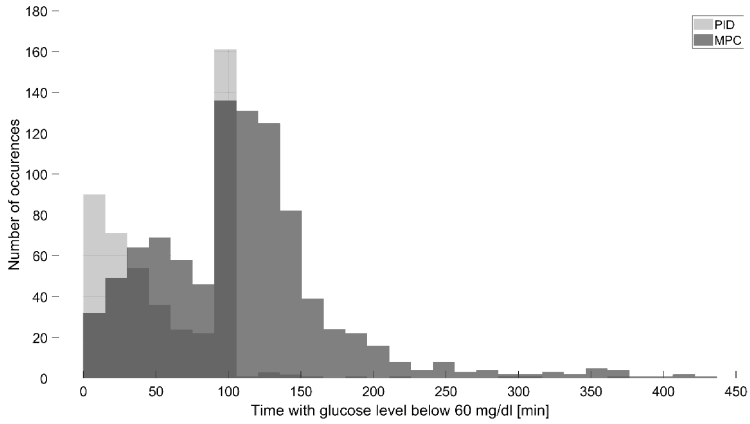
(b) Histogram of time of hyperglycemia across simulations

Figure 14: Histograms of quality indicators for a scenario with a physical effort unrelated to meal and unbounded controllers' output

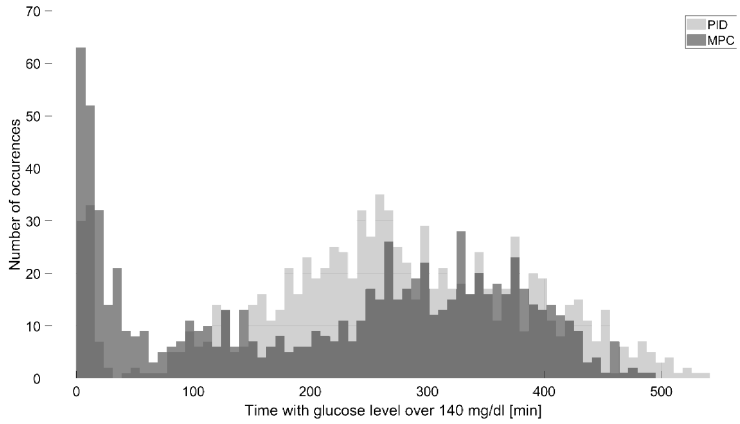
and overall number of such episodes can be observed, when compared to a scenario from the preceding section. The increase is seen for either control algorithm, but it seems that the PID controller behaviour worsened more than that of the MPC with respect to the number of hypoglycemic incidents.

Table 8: The number of simulations in which hypoglycemia occurred for a scenario with a physical effort unrelated to meal

Output type	Value for PID	Value for MPC
unbounded	586	1000
bounded	470	943



(a) Histogram of time of hypoglycemia across simulations



(b) Histogram of time of hyperglycemia across simulations

Figure 15: Histograms of quality indicators for scenario with a physical effort unrelated to meal and bounded controllers' output

4. Conclusions and discussion

Interpatient variability as well as changes of individual patient's physiological parameters constitute a major obstacle in population-wide introduction of closed-loop continuous blood glucose control systems. Simulation-based studies make it possible to check the robustness of such systems to heterogeneity in responses to insulin injection in the population of patients. A standard way to perform such studies consists in creating a cohort of virtual patients, whose parameters are sampled from a predefined distribution. Then, application-specific indices are used to compare alternative approaches to the problem and evaluate their quality. Three such indicators have been proposed in this paper.

Clinical trials, whose results were published in a variety of papers in recent years, were based on either MPC or PID control algorithms, tailored to the specific application of controlling blood glucose level in diabetic patients. However, in most cases those studies were focused on a single algorithm only, to show its applicability and safety. In many cases, the controllers have been tuned for each patient separately, in a controlled environment. Therefore, the question about being able to use a generally tuned control system, in an uncontrolled environment, remained open. This work was meant to address that problem.

In general, we have shown that both types of controllers can be used without the need for a very precise, individual tuning. However, neither of them is completely safe, in terms of eliminating hypoglycemic events. This conclusion holds also for an individually tuned controller, as patient's parameters may change in time.

Considering results shown in the work it is impossible to claim the superiority of either of algorithms. Both control structures have their shortcomings and their advantages. For the MPC controller, hypoglycemia induced by controller action is a serious issue to be dealt with, but on the other hand it allows for faster reduction of blood glucose level leading to shortening of hyperglycemia times. As for the PID-based control system, its behavior in terms of hypoglycemia may be described as more reliable, however that coincides with worse performance when reducing hyperglycemic states.

What may be stated about both control algorithms is that without some additional element of the control system (e.g. effort-related feed-forward component, dual-hormone control with glucagon apart from insulin) dealing with effort is very difficult if not even impossible. Should the controllers be tuned to minimise physical exercise-induced hypoglycemia, it would be made at the expense of significant decrease of performance in dealing with hyperglycemic states. Moreover, hypoglycemic events would not be entirely eliminated.

Results obtained for two scenarios with physical effort (sections 3.2.2 and 3.2.3) show one additional justification for the need of an additional element in the control system. As it is not only the intensity of the effort that influences

the severity of hypoglycemic incidents, but also whether there exists a relation between effort and meal that is preceding it, should that additional information be supplied to the controller it could significantly improve its behavior.

When discussing the case of explicitly limiting controllers' output maximum value in light of results shown in 3.1, it seems to be a required feature for the MPC algorithm at least. Even though without this limitation the performance of algorithms in terms of dealing with hyperglycemia is significantly better, two important drawbacks must be named. First, it is the risk involved with administering such large insulin doses, while the second is more visible in results from 3.2.2 and 3.2.3, where without upper bound imposed on the controllers output performance in states of hypoglycemia was worsened. One additional issue should be stated here. The results of simulations suggest that value of the upper bound might have been taken too conservatively, however that should have no influence on the qualitative conclusions drawn from the results.

There are many additional factors which might have a noticeable impact on the control system performance but were not included in this study. Of these, one especially important is the case of different disturbances and noises that may appear in the measurement device, that will have a direct influence on the controller.

A. Full mathematical model

The mathematical model used for creating the simulator is based on several differential equations describing different parts of system under consideration. It is based on Bergman's minimal model for glucose-insulin interaction [6], model of glucose intake from meals by Lehmann and Deutsch [17], as well as standard representation of pharmacokinetics.

The differential equations of the model used are as follows:

$$\begin{cases} \dfrac{dG(t)}{dt} = -\left(p_1 + P^*(t)X(t)\right)G(t) + p_1 G_b + p_2 G_{\text{in}}(t), \\ \dfrac{dX(t)}{dt} = -p_2 X(t) + p_3 I(t), \\ \dfrac{dI(t)}{dt} = k_1 I_{\text{in}}(t) + k_2 I(t) \\ \dfrac{G_{\text{gut}}}{dt} = -k_{\text{gabs}} G_{\text{gut}}(t) + G_{\text{empt}}(t). \end{cases} \tag{5}$$

In those equations $G(t)$ stands for glucose concentration in [mg/dl], $X(t)$ is defined in Bergman model insulin effect in unit of [min^{-1}], $I(t)$ is insulin con-

centration in [μU], G_{gut} is glucose concentration in gut in [mg/dl]. Additionally G_{gut} is connected with glucose intake from meal G_{in} [mg/dl] via relation:

$$G_{\text{in}}(t) = k_{\text{gabs}} G_{\text{gut}}(t). \tag{6}$$

Gastric emptying rate $G_{\text{empt}}(t)$ is defined, after Lehman and Deutsch and modifications in [26], in the following way:

$$G_{\text{empt}}(t) = \begin{cases} \dfrac{V_{\max}}{T_{\text{up\_max}}} t, & t < T_{\text{asc}} c\,, \\ \dfrac{V_{\max}}{T_{\text{up\_max}}} T_{\text{asc}} - \dfrac{V_{\max}}{T_{\text{down\_max}}}(t - T_{\text{asc}}), & T_{\text{asc}} \leqslant t < T_{\text{asc}} + T_{\text{desc}}\,. \end{cases} \tag{7}$$

Additionally the following relation holds:

$$T_{\text{asc}} = T_{\text{desc}} = \sqrt{\frac{D \cdot T_{\text{up\_max}}}{V_{\max}}}\,. \tag{8}$$

In that equations $V_{\max}$ is a parameter defining maximum possible value of G_{empt}, D denotes glucose dose in [mg] and $T_{\text{up\_max}} = T_{\text{down\_max}}$ maximum times of rising and falling slope of G_{empt}.

All other, not specifically defined values in the equations are parameters. Their values and corresponding dimensions are shown in Table 9.

Table 9: Base values of model parameters

Parameter name	Value	Unit
G_b	80	$\text{mg}\cdot\text{dL}^{-1}$
p_1	0.015	min^{-1}
p_2 (nominal value)	0.021	min^{-1}
p_3	$7.5 \cdot 10^{-8}$	$\text{mL}\cdot\mu\text{U}^{-1}\cdot\text{min}^{-2}$
k_1	5	$\text{mL}^{-1}\cdot\text{min}^{-1}$
k_2	0.214	min^{-1}
k_{gabs}	0.01(6)	min^{-1}
$V_{\max}$ (nominal value)	1/90	$\text{mg}\cdot\text{min}^{-1}$
$T_{\text{up\_max}}$ (nominal value)	30	min

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