

# Close-to-reality evaluation of a PID control algorithm for blood glucose regulation in diabetic Goettingen minipigs

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**Abstract**—Diabetes mellitus is a widespread metabolic disease, which currently requires manual treatment. Until now, no commercial closed-loop insulin therapy system has been presented yet due to many control restrictions. To reduce safety risks for the patients, adequate control methods should be tested in animal trials, prior to clinical studies, which can be regarded as an intermediate step between *in silico* and *in vivo* control performance evaluation. In this paper, diabetic Goettingen minipigs serve as proxy for the human metabolism.

After having developed a physiological and mathematical minipig model based on preceding animal trials, this paper describes a control algorithm which has been designed with the focus on real-life application. In particular, several control restrictions and requirements are taken into consideration such as delayed insulin effect on blood glucose concentration and fast response to blood glucose rise. The control robustness is evaluated with respect to three individual minipig models simulating three meals with different glucose content. It is shown that the controller responds to the disturbances similarly as a natural pancreas. Although blood glucose undershoots could not be completely avoided, no critical blood glucose drop appeared.

## I. INTRODUCTION

According to the World Health Organisation, in 2011 approximately 347 Mio. people world wide were suffering from the glucose metabolic disease diabetes mellitus with increasing trend. Diabetes mellitus is characterized by reduced or lost intracorporal insulin production which leads to an increased fasting blood glucose concentration. In particular, type-1 diabetes patients are suffering from an absolute insulin deficit requiring an extracorporal insulin therapy.

Nowadays, the treatment of type-1 diabetes patients targets to stabilise their blood glucose concentration manually in a normoglycemic range of 80 - 120 mg/dl. Based on discrete blood glucose measurements and discrete subcutaneous insulin injections this therapy method is highly challenging. Metabolic disturbances like carbohydrate ingestion or physical activity have to be manually compensated by the patient (Fig. 1). To improve the regulation mechanism, a research aim is the development of a closed-loop insulin therapy system which is also known as 'artificial pancreas'. Here, a control algorithm connects a continuously measuring blood glucose sensor to a continuously injecting insulin pump such that the diabetic patient as metabolic system is controlled (Fig. 2).

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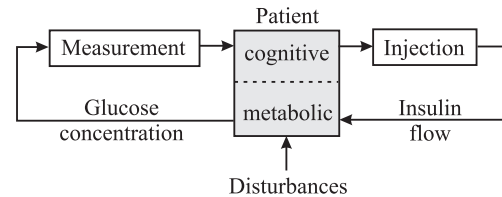


Fig. 1. In the manual insulin therapy, the patient combines the cognitive system as control unit and the metabolic system which has to be controlled.

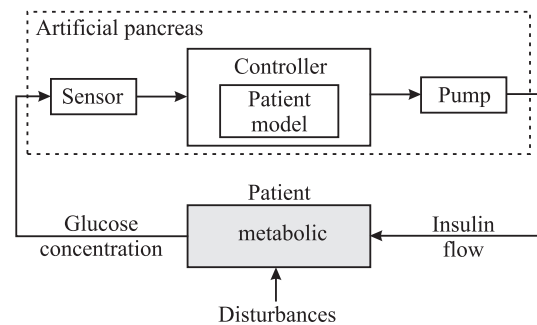


Fig. 2. Above: In the manual insulin therapy, the patient combines the cognitive system as control unit and the metabolic system which has to be controlled. Below: The artificial pancreas with the patient remaining as the metabolic system which has to be controlled. (both adapted from [1])

During the last 4 decades, several ideas concerning glucose sensors, insulin pumps and control algorithms were published as reviewed e.g. in [1], [2], [3], [4]. Until now, however, no automatic closed-loop insulin therapy system is commercially available. Some initial semi-closed-loop approaches were successfully applied in clinical studies but not in daily routine [5], [6], [7]. There are various reasons for the lack of automatic therapy approaches:

- No reliably measuring blood glucose sensor is commercially available. The currently approved glucose sensors measure the interstitial glucose concentration which is delayed up to 20 min compared to the blood glucose concentration [4], [8].
- The peak action of insulin effecting the blood glucose concentration is delayed up to 90 min. That time delay is caused by the commercially available insulin pumps which inject the insulin subcutaneously [4].
- Many of the control algorithms have not yet been tested *in vivo* but only in connection with a simulation platform which is approved by the Food and Drug Administration (FDA) of the United States for control performance evaluation [9], [10].

Although tested on a simulation platform, many of the published control algorithms have never been applied to real patients under normal life conditions in a closed-loop approach. Since the simulatory studies of the autonomous control mimic the natural metabolic response only in a limited way, there exists a potential risk to the health of the test subjects.

In consequence, animal trials are useful for the development of an autonomous diabetes treatment system. Based on recent results of a physiological animal model with Goettingen minipigs [11], [12], [13], a PID control algorithm was developed and will be presented in this paper. The controller response to blood glucose rise is evaluated with the focus on real-life conditions like e.g. delayed blood glucose measurements due to a manual protocol, and delayed insulin effect.

Until today, several control algorithms were developed which can be divided into black-box and grey-box model-based control methods [1], [4]. All of these control approaches require continuous blood glucose measurements which are not available due to the lacking blood glucose sensor. Hence, the presented PID control algorithm is designed taking time-discrete measurements into consideration.

The paper is structured as following. Section II introduces the mathematical model of diabetic Goettingen minipigs. Subsequently, the PID control algorithm is explained in Section III. Section IV evaluates and discusses the control performance with respect to robustness and the paper closes with a summary and formulations of future research steps in Section V.

## II. MATHEMATICAL MINIPIG MODEL

### A. Main idea

To close the gap between *in silico* and patient studies of control algorithms, animal trials are useful as an intermediate step. They give the possibility to test control performance and robustness *in vivo* with real inter- and intra-individual differing subjects. In particular, Goettingen minipigs have proven to be suitable for the investigations of the glucose metabolism [11], [13], [14] as these animals are omnivores and their normoglycemic level is comparable to that of humans.

In the following paragraph, the mathematical model of the diabetic metabolism in Goettingen minipigs is introduced. It is developed based on measurement data from recent animal trials and is used for the PID control design in Section III.

### B. Animal trials

In  $n = 5$  Goettingen minipigs, an acute diabetes mellitus has been reliably induced by the application of the  $\beta$ -cell toxin Streptozocin and, subsequently, the metabolic system has been successfully identified in  $n = 3$  animals. Via two central venous lines, blood samples could be drawn frequently to monitor the blood glucose trajectory which was effected by several extracorporal glucose and insulin impulses. For detailed information, see [13].

### C. Glucose metabolic model

The mathematical model of the glucose metabolism in diabetic Goettingen minipigs was developed based on human model approaches. The *minimal model* of Bergman [15] consisting of three nonlinear differential equations was extended by two subsystems of Dalla Man's model [16], [17] resulting in the following 8<sup>th</sup> order model. The kernel model describes the blood glucose (BG) concentration  $G(t)$  relative to the basal value  $G_b$ , the plasma insulin concentration  $I(t)$  and the insulin effect compartment  $X(t)$

$$\begin{aligned}\dot{G}(t) &= -p_1 G(t) - X(t)(G(t) + G_b) + D_g(t) \\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t) \\ \dot{I}(t) &= -n I(t) + U_I(t).\end{aligned}\quad (1)$$

Furthermore, the dynamics of the subcutaneous insulin injection is given by a second-order system calculating the amount of nonmonomeric (inactive) insulin  $I_{sc,1}(t)$  and monomeric (active) insulin  $I_{sc,2}(t)$  which affect the insulin appearance rate in blood  $U_I(t)$

$$\begin{aligned}\dot{I}_{sc,1}(t) &= -(k_d + k_{a1})I_{sc,1}(t) + U_{sc} \cdot \delta(t) \\ \dot{I}_{sc,2}(t) &= k_d I_{sc,1}(t) - k_{a2} I_{sc,2}(t) \\ U_I(t) &= \frac{k_{a1} I_{sc,1}(t) + k_{a2} I_{sc,2}(t)}{V_I \cdot BW}.\end{aligned}\quad (2)$$

The gastro-intestinal tract is described as a series of three first-order systems modelling the solid and liquid carbohydrate phase in the stomach,  $Q_{sto,1}(t)$  and  $Q_{sto,2}(t)$ , respectively. The third equation describes the glucose amount in the gut  $Q_{gut}(t)$  which affects the glucose appearance rate in blood  $D_g(t)$

$$\begin{aligned}\dot{Q}_{sto,1}(t) &= -k_{gri} \cdot Q_{sto,1}(t) + D_{oral} \cdot \delta(t) \\ \dot{Q}_{sto,2}(t) &= -k_{empt} \cdot Q_{sto,2}(t) + k_{gri} \cdot Q_{sto,1}(t) \\ \dot{Q}_{gut}(t) &= -k_{abs} \cdot Q_{gut}(t) + k_{empt} \cdot Q_{sto,2}(t) \\ D_g(t) &= \frac{f \cdot k_{abs} \cdot Q_{gut}(t)}{V_G \cdot BW}.\end{aligned}$$

The initial conditions are given by

$$\begin{aligned}G(0) &= G_b, & X(0) &= 0, & I(0) &= 0 \\ I_{sc,1}(0) &= 0, & I_{sc,2}(0) &= 0 \\ Q_{sto,1}(0) &= 0, & Q_{sto,2}(0) &= 0, & Q_{gut}(0) &= 0.\end{aligned}$$

Table I shows the parameter set for the nominal model [13].

## III. PID CONTROL ALGORITHM

### A. Control aim

To improve the blood glucose regulation in patients with type-1 diabetes, a closed-loop insulin therapy system is requested, see Fig. 2. In nature, blood glucose rise is responded by a pancreatic insulin release rate which is comparable to a proportional, integral and derivative system response (see Section III-C.1). Thus, in this paper, a PID control algorithm is used as regulation mechanism which was developed based on the mathematical minipig model, see Fig. 3. The blood glucose concentration was chosen as control variable  $y(t) = G(t)$ , the subcutaneous insulin infusion rate as

TABLE I  
PARAMETER VALUES FOR THE NOMINAL AND INDIVIDUAL MINIPIG  
MODELS

name	Parameter description	Value nominal	Unit
$BW$	body weight	60	kg
$G_b$	basal BG concentration	300	mg/dl
$V_G$	glucose distribution volume	1.4036	dl/kg
$p_1$	time constant of glucose disappearance	0.0105	1/min
$p_2$	time constants for...	0.0459	L/mIU min <sup>-2</sup>
$p_3$	... insulin fluctuation to...	$2.15 \cdot 10^{-5}$	L/mIU min <sup>-2</sup>
$n$	... remote compartment	0.1296	1/min
$V_I$	insulin distribution volume	0.2772	L/kg
$k_{gri}$	grinding rate constant	0.0494	1/min
$k_{empt}$	gastric emptying	0.0548	1/min
$k_{abs}$	glucose absorption in blood	0.0484	1/min
$f$	glucose fraction	0.2523	-
$k_d$	insulin dissociation rate	0.0253	1/min
$k_{a1}$	insulin absorption rate in blood	0.0043	1/min
$k_{a2}$	insulin absorption rate in blood	0.0244	1/min

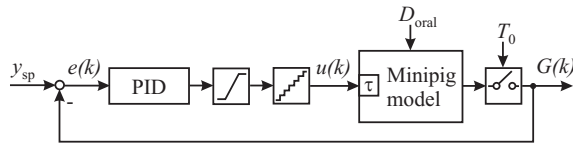


Fig. 3. Closed-loop system with PID control algorithm and minipig model including the control restrictions explained in Section III-B.

regulating variable  $u(t) = U_{sc} \cdot \delta(t)$  and the orally uptaken glucose amount  $d(t) = D_{oral} \cdot \delta(t)$  as disturbance variable.  $\delta(t)$  denotes the dirac pulse. Before introducing the PID controller, control limitations are discussed which have to be taken into consideration.

### B. Control limitations

Therapy devices for an optimal emulation of the natural blood glucose regulation are still lacking. Thus, a potential control algorithm has to stabilise the blood glucose concentration while satisfying several performance restrictions and requirements given by the real-life application.

1) *Restrictions:* The closed-loop system is characterized by the following constraints, see also Fig. 3:

L1 The controller output  $u(t)$  is physically bounded at

$$u(t) \geq 0.$$

A negative controller output  $u(t) < 0$  would have to be realised by injecting the counteracting hormone glucagon to re-increase the blood glucose concentration. In this scenario, glucagon is not included.

L2 The regulating variable has to be quantized to 0.1 I.U. steps. In this scenario, the manually adaptable insulin boli were injected by a customized pump (Roche Diagnostics, Accu-Chek<sup>®</sup> Spirit Combo) which does not allow smaller step sizes.

L3 Due to subcutaneous insulin injection by an insulin pump, the insulin effect on blood glucose concentration is delayed up to  $\tau = 90$  min [1], [4] compared to injection time (see model Eqs. (2), (3)).

L4 Blood glucose concentration as control variable has to be measured manually. A realistic measurement frequency  $T_0^{-1}$  of 4 samples per hour was chosen allowing slight time shifts.

2) *Requirements:* An adequate control performance for real-life conditions has to satisfy the following requirements:

R1 Undershoots of the control variable have to be avoided. As insulin is the only regulating variable, an undershoot cannot automatically be counteracted.

R2 The normoglycemic range is defined to

$$80 \text{ mg/dl} \leq G(t) \leq 120 \text{ mg/dl}.$$

Blood glucose concentration below the critical threshold of  $G_{crit} = 70$  mg/dl could lead to life-threatening events such as loss of consciousness so that it has to be avoided. The blood glucose range between 70 and 80 mg/dl is satisfying but not desirable.

R3 Metabolic disturbances have to be counteracted within a short period of time so that the duration of an unnormal blood glucose level is reduced. Here, the time range is set to 180 min.

R4 During animal trials, the control protocol will be performed manually. Hence, the control algorithm should be able to satisfy the performance requirements despite varying sampling time.

R5 The control algorithm should be able to adapt to inter- and intra-individual differences of the glucose metabolism. As proven by clinical studies [18], [19], [20] (p. 946ff) the insulin sensitivity shows diurnal variation and is effected by several other factors, e.g. psychological stress.

R6 To reduce the patients manual input to the control algorithm, announcements of carbohydrate ingestion or physical activity to the controller were not considered.

Requirements are ordered according to priority: the smaller the number, the more important is the requirement.

### C. Control design

1) *PID control algorithm:* According to literature, the natural insulin response of nondiabetic subjects to carbohydrate ingestion is multiphase [20], [21]. The sudden glucose step is initially responded by a fast pancreatic insulin release within 4 min followed by a slow second release phase which starts 10 min after glucose uptake. That response can be divided into a proportional, integral and derivative behaviour.

Based on that fact and on the control restrictions and requirements listed above, a black-box model-based control method was initially chosen for the regulation of the diabetic blood glucose trajectory. The PID control algorithm seemed to be the most suitable control approach as it responds to control error  $e(t) = y_{sp} - G(t)$  similarly to the natural pancreas, can be discretized, does not need any disturbance

information, and the control gain can be adapted individually a-priori or during the control application.

Since the control variable is time discrete and the regulating variable has to be quantized, the PID control algorithm is applied in the following recursive form

$$\begin{aligned} u(k) &= \Delta u(k) + u(k-1) \\ \Delta u(k) &= K \left( 1 + \frac{T_D}{T_0(k)} \right) e(k) \\ &\quad - K \left( 1 + 2 \frac{T_D}{T_0(k-1)} - \frac{T_0(k-1)}{T_I} \right) e(k-1) \\ &\quad + K \frac{T_D}{T_0(k-2)} e(k-2). \end{aligned}$$

The sampling time

$$T_0(k) = 15 \text{ min} \pm x \cdot 33 \% \quad (4)$$

was changed randomly for each time step  $k$  with  $x$  uniformly distributed, and the mean blood glucose value of the normoglycemic range in nondiabetic subjects was chosen as setpoint  $y_{sp} = 100 \text{ mg/dl}$ .

As no measurement data of the natural insulin release rate were available for Goettingen minipigs, simulation data generated by the complex model of nondiabetic humans proposed by Sorensen [22] were used. Based on the calculated insulin release rate, the control gain  $K$  and the time constants  $T_I$ ,  $T_D$  were determined to

$$K = f(BW, G_b) = -0.007 \frac{BW}{60 \text{ kg}} \cdot \frac{G_b}{300 \text{ mg/dl}} \quad (5)$$

$$T_I = 120 \text{ min}, \quad T_D = 30 \text{ min}. \quad (6)$$

The control gain was defined as function of the normalised body weight  $BW$  and basal blood glucose concentration  $G_b$  which is considered to be the nearly stationary blood glucose level three hours after the insulin injection has been stopped (see [13]).

2) *Control performance parameters:* The most important model parameters, which differ intra- and inter-individually are the subject's body weight  $BW$ , the basal blood glucose concentration  $G_b$  and the insulin sensitivity, which is lumped into the parameter  $P_2$ . The control response depending on the three model parameters

$$P = [BW, G_b, P_2]$$

was simulatively studied by changing the parameter values within a predefined range

$$P \in P_{\text{nom}} \left( 1 + [-\sigma_{\text{max}}^P, -\frac{1}{2}\sigma_{\text{max}}^P, 0, +\frac{1}{2}\sigma_{\text{max}}^P, +\sigma_{\text{max}}^P] \right).$$

Here,  $\sigma_{\text{max}}^P$  is the assumed maximum parameter deviation from the nominal value  $P_{\text{nom}}$  given in Table I

$$\sigma_{\text{max}}^{BW} = 16.67 \%, \quad \sigma_{\text{max}}^{G_b} = 30 \%, \quad \sigma_{\text{max}}^{P_2} = 20 \%.$$

To evaluate the control performance with respect to the varying patient models, two analysis parameters were taken into consideration:

- absolute and relative maximum undershoot  $y_{\min}(t_{\min})$  and

$$e_{\min}(t_{\min}) = \frac{y_{sp} - y_{\min}(t_{\min})}{y_{sp}},$$

respectively,

- mean blood glucose deviation  $\bar{y}_{10\%}$  from the setpoint range of  $y_{sp} \pm 10 \%$

$\bar{y}_{10\%} =$

$$\frac{1}{N} \sum_{t=180}^{t_{\text{end}}} \begin{cases} |y(t) - y_{sp} + 10 \%| & \text{if } y(t) > y_{sp} + 10 \% \\ |y(t) - y_{sp} - 10 \%| & \text{if } y(t) < y_{sp} - 10 \% \\ 0 & \text{else} \end{cases}$$

in the time interval  $t = [180 \dots t_{\text{end}}]$  min after glucose consumption. The system output  $y(t)$  is quasi-continuous with a time step of 0.1 min, and  $N = 10 \cdot (t_{\text{end}} - 180)$  is the total number of simulation data.

#### IV. CONTROL PERFORMANCE EVALUATION

In the following paragraphs, the control algorithm will be evaluated with respect to the introduced control performance parameters and with the focus on real-life applicability. Its response behaviour will be tested with the introduced nominal and three additional individual minipig models.

##### A. Maximum undershoot

For control performance analysis, at  $t = 0$  min the glucose amount of

$$D_{\text{oral},1} = \frac{BW}{60 \text{ kg}} 69 \text{ g} \quad (7)$$

normalised to body weight was defined as oral input.

In the upper panel of Fig. 4, for each constant insulin sensitivity value of  $P_2$ , the relative maximum undershoot  $e_{\min}$  is given and in the lower panel the corresponding time  $t_{\min}$  is shown, both depending on the body weight  $BW$  and the basal blood glucose concentration  $G_b$ . The lighter the color the larger is  $P_2$ . From the physiological point of view, a high value of  $P_2$  causes a small insulin amount remaining in the effect compartment  $X(t)$  (see (1)) which indicates a low insulin sensitivity of the insulin-dependent glucose consuming organs. Comparison of both plots in Fig. 4 shows that the larger  $P_2$ , the lower is the relative undershoot  $e_{\min}$  but the later does the undershoot occur (cf.  $t_{\min}$ ). Despite the individualised controller gain  $K$  (see (5)) the relative undershoot is still changing with body weight  $BW$  and basal blood glucose concentration  $G_b$ .

Thus, the controller stabilises the blood glucose concentration within the normoglycemic range according to the requirement [R2] for each combination of  $BW$  and  $G_b$ , but it does not stabilise the blood glucose concentration reliably within the required time range of  $t = 180$  min (cf.  $t_{\min}$ ) after meal uptake according to requirement [R3]. Blood glucose undershoots cannot be avoided entirely violating requirement [R1] (cf.  $e_{\min}$ ).

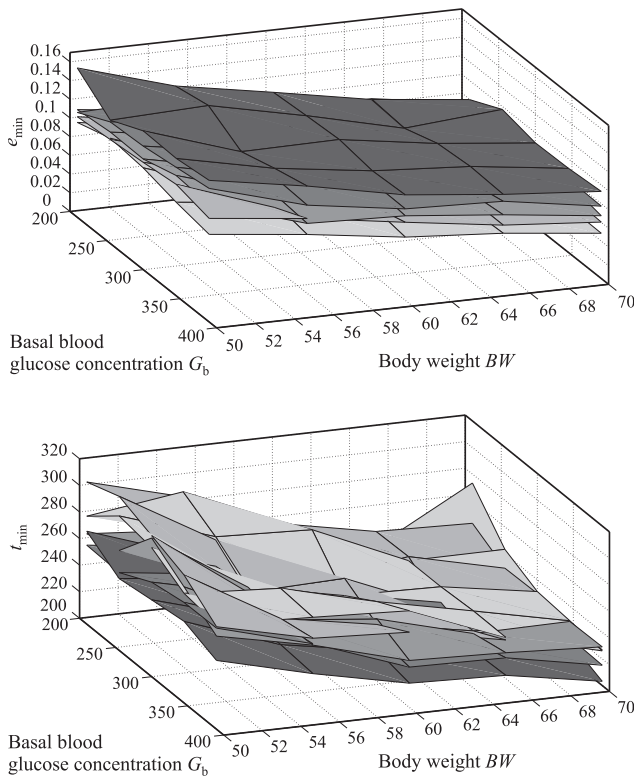


Fig. 4. Relative maximum undershoot of blood glucose concentration  $e_{\min}$  (above) and corresponding time  $t_{\min}$  (below) after glucose ingestion depending on the subjects' basal blood glucose concentration  $G_b$  and body weight  $BW$  with increasing insulin sensitivity  $P_2$ . The lighter the color the larger is  $P_2$ .

### B. Mean blood glucose deviation

To evaluate the control dynamics, the mean blood glucose deviation  $\bar{y}_{10\%}$  from the setpoint range  $y_{sp} \pm 10\%$  is investigated after glucose input  $D_{\text{oral},1}$  for  $t = [180 \dots 900]$  min. In general, for each parameter combination of  $BW$ ,  $G_b$  and  $P_2$ , the blood glucose concentration remains above the critical threshold  $G_{\text{crit}}$  which satisfies requirement [R2] (data not shown). But in particular, the mean blood glucose deviation from setpoint range was  $\bar{y}_{10\%} = 2$  mg/dl in total. Thus, control requirements [R1] and [R3] are slightly violated.

### C. Close-to-reality application

1) *Fast glucose response:* To evaluate the control performance in a more realistic way, the algorithm was applied to the three individual minipig models. After stabilising the blood glucose concentration at the desired level of  $y_{sp} \pm 10\%$ , a unique uptake of  $D_{\text{oral},2} = 69$  g glucose was assumed at time  $t = 0$  min (data not shown). In everyday life, meals were taken every 3-4 hours during day time. Hence, at  $t = 180$  min the latest, blood glucose concentration should be back at setpoint or within the setpoint range of  $y_{sp} \pm 10\%$  to satisfy requirement [R3].

For  $t > 180$  min, the simulated blood glucose concentration for all three minipig models remained in the normoglycemic range and left the setpoint range only slightly.

2) *Variation of sample time:* Due to a manual control protocol, a varying sampling time  $T_0$  (cf. (4)) was assumed as additional control restriction with the same sampling time vector applied to all three models (data not shown). Despite large sampling time and quantized insulin injections, the PID control algorithm stabilises the blood glucose concentration within the setpoint range. Hence, control performance requirement [R4] is satisfied.

3) *Realistic meal times:* Following the glucose consumption protocol of Dalla Man et al. [17], the control performance was additionally tested with three meals:

- 1) Breakfast at 8:00 o'clock:  $G_{\text{oral}} = 45$  g glucose,
- 2) Lunch at 12:00 o'clock:  $G_{\text{oral}} = 70$  g glucose,
- 3) Dinner at 18:00 o'clock:  $G_{\text{oral}} = 70$  g glucose.

Figure 5 shows the simulation results with the blood glucose trajectory in the upper panel, which was sampled at varying time  $T_0$  marked by small symbols, and the quantized subcutaneous insulin injections in the lower panel. The vertical dashed lines mark the meal times and in the upper panel, the normoglycemic and setpoint range are grey coloured. The critical blood glucose value  $G_{\text{crit}}$  is marked by a thick dashed line.

As can be seen, all blood glucose rises are promptly responded by increased insulin injections without meal announcement according to requirement [R6]. Furthermore, no blood glucose trajectory violates the critical threshold of  $G_{\text{crit}}$  which corresponds to requirements [R2] and [R5]. A variation in sampling time also has no effect on general closed-loop system stability (satisfaction of [R4]). However, the blood glucose concentration cannot be stabilised in the setpoint range after one meal before being affected by a subsequent carbohydrate ingestion (violation of [R3]) and undershoots were not completely prevented (violation of [R1]). Hence, the PID control algorithm approach seems to be robust with respect to inter- and intra-individual variations. However, due to quantized controller output and the discretised controlled variable, it does not satisfy all control performance requirements.

## V. CONCLUSIONS

In conclusion, a PID control algorithm satisfies 3 of 6 control requirements ([R2], [R4], [R6]), given that the blood glucose concentration is sampled frequently every 10–20 min. The controller response is robust with respect to variation of  $BW$ ,  $G_b$  and  $P_2$  such that no violation of  $G_{\text{crit}}$  is observed. Nevertheless, it is not possible to stabilise the blood glucose concentration reliably in the setpoint range earlier than  $t = 180$  min after glucose uptake.

In future, the controller should be extended such that the control requirements [R1], [R3] and [R5] are also reliably satisfied while reducing the blood glucose sampling frequency to a minimum. Additional robustness analysis with respect to insulin and glucose absorption variability should be performed as well. Subsequently, the control performance will be evaluated in animals before it can be tested in clinical trials within an autonomous closed-loop insulin therapy system in the long run.

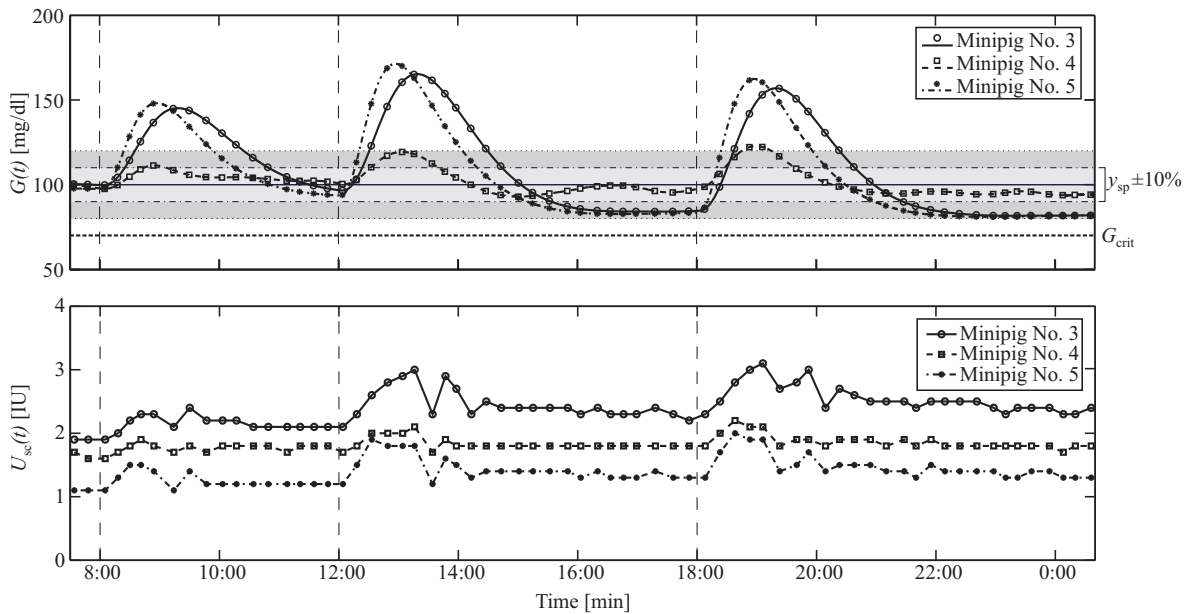


Fig. 5. Control application on all three minipig models during three meal times with different carbohydrate amounts. Above: Trajectory of blood glucose concentration  $G(t)$  in mg/dl. Below: Quantized subcutaneous insulin injections  $U_{sc}(t)$  in I.U. The vertical dashed lines mark the meal times. In the upper graph, normoglycemic and setpoint range are grey colored, the critical value  $G_{crit}$  is marked by a thick dashed horizontal line.

## REFERENCES

- [1] K. Lunze, T. Singh, M. Walter, M. D. Brendel, and S. Leonhardt, "Blood glucose control algorithms for type 1 diabetic patients: a methodological review," *Journal of Biomedical Signal Processing and Control*, vol. 8, no. 2, 2013.
- [2] R. S. Parker, F. J. I. Doyle, and N. A. Peppas, "The intravenous route to blood glucose control. a review of control algorithms for noninvasive monitoring and regulation in type i diabetic patients," *IEEE Engineering in Medicine and Biology Magazine*, vol. 20, no. 1, pp. 65–73, 2001.
- [3] R. Bellazzi, G. Nucci, and C. Cobelli, "The subcutaneous route to insulin-dependent diabetes therapy. closed-loop and partially closed-loop control strategies for insulin delivery and measuring glucose concentration," *IEEE Engineering in Medicine and Biology*, vol. 20, no. 1, pp. 54–64, 2001.
- [4] G. Chee and T. Fernando, *Closed-Loop Control of Blood Glucose*, ser. Lecture Notes in Control and Information Sciences. Springer Verlag, Berlin, Deutschland, 2007, no. 368.
- [5] R. Hovorka, K. Kumareswaran, J. Harris, J. M. Allen, D. Elleri, D. Xing, C. Kollman, M. Nodale, H. R. Murphy, D. B. Dunger, S. A. Amiel, S. H. Heller, M. E. Wilinska, and M. L. Evans, "Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies," *British Medical Journal*, vol. 342, no. d1855, 2011, online publication.
- [6] D. Elleri, J. M. Allen, M. Nodale, M. E. Wilinska, J. S. Mangat, A. M. F. Larsen, C. L. Acerini, D. B. Dunger, and R. Hovorka, "Automated overnight closed-loop glucose control in young children with type 1 diabetes," *Diabetes Technology & Therapeutics*, vol. 13, no. 4, pp. 419–424, 2011.
- [7] A. C. Van Bon, L. D. Jonker, R. Koebrugge, R. Koops, J. B. L. Hoekstra, and J. H. DeVries, "Feasibility of a bihormonal closed-loop system to control postexercise and postprandial glucose excursions," *Journal of Diabetes Science and Technology*, vol. 6, no. 5, pp. 1114–1122, 2012.
- [8] O. Schnell, *Insulinpumpen und Sensoren: Aktuelle Entwicklungen*, 1st ed. UNI-MED Science, Bremen, Germany, 2007.
- [9] B. P. Kovatchev, M. Breton, C. Dalla Man, and C. Cobelli, "In Silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes," *Journal of Diabetes Science and Technology*, vol. 3, no. 1, pp. 44–55, 2009.
- [10] J. D. R. F. International, "emerging technologies e-newsletter, may 2008," 2008. [Online]. Available: <http://www.jdrf.org>
- [11] K. Lunze, M. D. Brendel, and S. Leonhardt, "Preliminary results of a type-1 diabetes swine model," in *5th European IFMBE Conference, Budapest, Hungary*, September 14 – 18 2011, pp. 307–310.
- [12] K. Lunze, M. Walter, and S. Leonhardt, "Glucose-insulin model of glucose metabolism in acute diabetic swine based on luenberger observer," in *The 2012 American Control Conference, Montreal, Canada*, June 27 – 29 2012, pp. 5586–5591.
- [13] K. Lunze, T. Singh, and S. Leonhardt, "Modeling of glucose-insulin system dynamics in diabetic goettingen minipigs," in *8th IFAC Symposium on Biological and Medical Systems, Budapest, Hungary*.
- [14] M. O. Larsen and B. Rolin, "Use of the goettingen minipig as a model of diabetes, with special focus on type 1 diabetes research," *Institute for Laboratory Animal Research Journal*, vol. 45, no. 3, pp. 303–313, 2004.
- [15] R. N. Bergman, L. S. Phillips, and C. Cobelli, "Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and  $\beta$ -cell glucose sensitivity from the response to intravenous glucose," *Journal of Clinical Investigations*, vol. 68, pp. 1456–1467, 1981.
- [16] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose-insulin system," *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 10, pp. 1740–1749, 2007.
- [17] C. Dalla Man, D. M. Raimondo, R. A. Rizza, and C. Cobelli, "GIM, simulation software of meal glucose-insulin model," *Journal of Diabetes Science and Technology*, vol. 1, no. 3, pp. 323–330, 2007.
- [18] R. N. Bergman, "Toward physiological understanding of glucose tolerance," *Diabetes*, vol. 38, pp. 1512–1527, 1989.
- [19] R. Basu, C. D. Man, M. Campioni, A. B. and G. Klee, F. Toffolo, C. Cobelli, and R. A. Rizza, "Differences in glucose turnover, insulin secretion, insulin action and hepatic insulin extraction," *Diabetes*, vol. 55, pp. 2001–2014, 2006.
- [20] A. C. Guyton and J. E. Hall, Eds., *Textbook of Medical Physiology*, 12nd ed. Saunders, Elsevier, Philadelphia 2010, 2011.
- [21] G. M. Steil, K. Rebrin, C. Darwin, F. Hariri, and M. F. Saad, "Feasibility of automating insulin delivery for the treatment of type 1 diabetes," *American Diabetes Association*, vol. 55, pp. 3344–3350, 2006.
- [22] J. T. Sorensen, "A physiological model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes," Ph.D. dissertation, Dept. Chem. Eng., Massachusetts Institute of Technology (MIT), Cambridge, MA, USA, 1985.