

Switching Hybrid Control of Blood Glucose in Diabetic Göttingen Minipigs

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Abstract: This paper presents the results of our recent blood glucose control trials with diabetic Göttingen minipigs. In particular, we describe our new switching hybrid control algorithm which uses different sampling intervals and insulin application strategies for daytime and night phases. The experimental results of the control application to two animals are given and compared with manual insulin treatment. Both strategies for glucose regulation result in comparable blood glucose trajectories even though meals were not announced to the controller but were taken into account in the manual protocol.

Keywords: Blood glucose control, switching control method, animal trials, diabetic Göttingen minipigs, experimental control performance evaluation

1. INTRODUCTION

1.1 Diabetes mellitus

According to the World Health Organisation, about 347 million people worldwide are currently suffering from diabetes mellitus¹. In a nondiabetic glucose metabolism, the pancreas is responsible for the stabilisation of the blood glucose concentration in the physiological normoglycemic range of 80–120 mg/dl. In the case of type 1 diabetes mellitus, the mechanism for blood glucose control is damaged, typically due to an autoimmune reaction of the body. That implies that the insulin-producing β -cells in the pancreas are completely destroyed and that the patients suffer from an absolute lack of insulin. As this hormone is responsible for a blood glucose reduction, diabetic patients suffer from elevated basal blood glucose concentrations while at the same time most glucose-consuming cells starve.

To this day, diabetic patients face the daily challenge to manually regulate their blood glucose concentration. Therefore, they have to measure their blood glucose concentration by test strips and to calculate the required amount of insulin while taking potential metabolic disturbances such as food uptake or physical activity into consideration. Acute and chronic abnormal blood glucose levels occur regularly and can induce life-threatening situations.

1.2 State-of-the-art blood glucose control

To reduce the resulting blood glucose variations and health problems, researchers have been seeking for an automatic therapy system for about five decades. The so-called 'artificial pancreas' shall reliably stabilise the blood glucose concentration in the normoglycemic range (Figure 1) by implementing a feedback controller and thus a closed-loop system. Here, the therapy system is transformed into

a continuous-time system with a continuously measuring glucose sensor and a continuous infusion insulin pump. These therapy devices are connected by a control algorithm which may include an internal patient model.

However, despite increased research efforts during the last decade, no suitable control system for everyday life has been presented so far (Chee and Fernando [2007], Lunze et al. [2013]). Recently performed closed-loop studies were mainly focusing on clinical trials under predefined conditions (Elleri et al. [2013], Hovorka et al. [2011], Nimri et al. [2012], Van Bon et al. [2012]). But the risk of an insulin overdose remains, which may induce unexpected blood glucose drops and subsequently result in acute life-threatening situations of the test persons. The major limitations are

- unreliable glucose sensor devices (Heinemann et al. [2011], Luijck et al. [2013]), due to a damped and time-delayed signal compared to the real blood glucose concentration dynamics,
- control algorithms which do not take metabolic system variations into consideration (Heinemann et al. [2011]), and

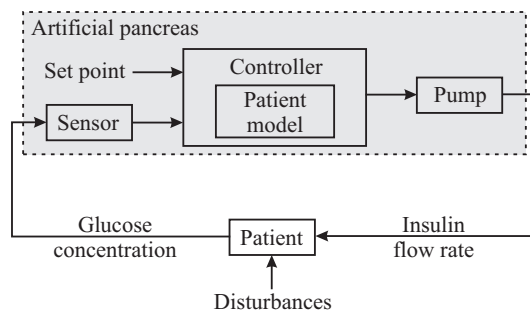


Figure 1. The artificial pancreas feedback loop, including blood glucose sensor and insulin infusion pump (actuator).

¹ <http://www.who.int/mediacentre/factsheets/fs312/en/>

- inter- and intraindividually varying uncertainties concerning the system response to insulin (Chee and Fernando [2007], Hirsch et al. [1990]).

Simulation platforms are essential for initial controller validation (Kovatchev et al. [2009]). To close the gap between *in silico* and *in vivo* control evaluations, animal trials are useful as an intermediate step (El-Khatib et al. [2009], Russel et al. [2012]). In such a setup, it is possible to test therapy systems under realistic conditions which are comparable to that in clinical trials.

1.3 Structure of the paper

The focus of the present project is the development of a control system for diabetic Göttingen minipigs which automatically calculates the required amount of insulin. This paper reports on the experimental results of the new control algorithm tested in diabetic minipigs. Towards this goal, we

- (1) shortly introduce the animal model with diabetic Göttingen minipigs and present the mathematical model of the glucose metabolism,
- (2) describe the developed control strategy and give an overview about the resulting controller structure, and
- (3) finally present the control performance protocol and the resulting blood glucose trajectories.

2. ANIMALS

2.1 Diabetic Göttingen minipigs

In literature, metabolic long-term studies focusing on diabetic secondary diseases (Gerrity et al. [2001], Grübner et al. [1992], Liu et al. [1998]) were typically carried out with Göttingen minipigs. The metabolism of these animals is comparable to humans (Larsen and Rolin [2004]). In our project, a total of $n = 8$ Göttingen minipigs was used in place of type 1 diabetes subjects. The animal trials focused on the establishment of the diabetic minipig model at the RWTH Aachen University hospital in Aachen (Germany), the verification of the developed mathematical minipig model and the test of the new control strategy in real subjects. For more information, see Lunze et al. [2011, 2012].

The entire study protocol was approved by the Animal Care and Use Committee of the State Agency for Nature, Environment and Consumer Protection, North Rhine-Westphalia, Germany.

2.2 Glucose metabolic model

Based on the well-known Sorensen model of the human glucose metabolism (Sorensen [1985]) with focus on the blood circulation, we have developed a new mathematical model for the diabetic porcine glucose metabolism. Compared to the original model, it has been reduced to 12th-order and extended by two 2nd-order systems which describe the gastro-intestinal tract and the subcutaneous insulin injection side. The parameters of the resulting model were identified either by physiological knowledge of the

minipigs or by mathematical methods based on blood glucose measurements using experimental data (Lunze et al. [2012, 2014b]).

3. CONTROL METHOD

3.1 Performance requirements and limitations

In the absence of a continuously measuring blood glucose sensor and due to the control application to diabetic animals, several performance requirements and control constraints have to be taken into consideration. Here, the infusion rate of insulin $U_{sc}(t)$ given in 'IU' (international unit) is defined to be the manipulated variable and the blood glucose concentration $G_P(t)$ given in mg/dl is the control variable.

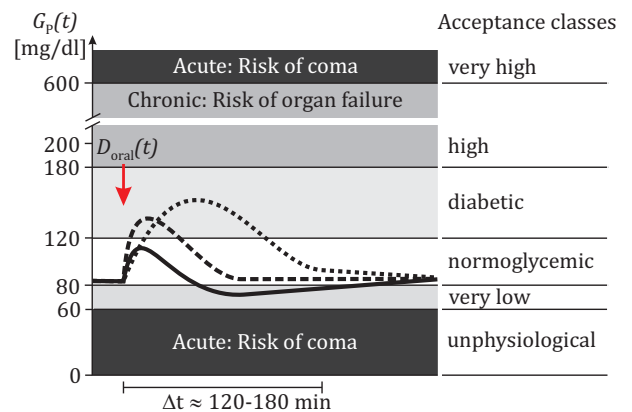


Figure 2. Classification of the blood glucose concentrations according to physiological acceptance

Performance requirements. In Figure 2, three generic blood glucose trajectories are shown which demonstrate different responses of a nondiabetic glucose metabolism to a meal uptake indicated by D_{oral} . The different blood glucose concentrations $G_P(t)$ are classified according to their physiological acceptance. Despite a good performing metabolic system including a natural feedforward-feedback mechanism (Kahn [2004]), the blood glucose concentration raises after ingestion and returns to the basal state within 120–180 min. In the case of type 1 diabetes, the extracorporeal controller has to replace the natural mechanism resulting in the following two performance requirements:

- R-1** The acceptable steady-state range of the diabetic metabolism is increased to

$$\mathcal{G}_{P,diab} = [70...180] \text{ mg/dl.} \quad (1)$$

A blood glucose drop below the critical threshold of

$$G_{P,crit} = 60 \text{ mg/dl} \quad (2)$$

has to be absolutely avoided. In the case of the animal trials, the critical threshold was reduced to 50 mg/dl, as the animals have a slightly lower normoglycemic range.

- R-2** To reduce secondary side effects of diabetes mellitus, meal-induced blood glucose peaks have to be counteracted within a short period of time. In accordance with the natural system, a settling time of the blood glucose concentration of

$$T_{\text{set}} \leq 180 \text{ min} \quad (3)$$

would be satisfying.

Control constraints. Due to the fact that currently no implantable therapy system is available, the insulin has to be applied subcutaneously and the blood glucose concentration is measured by means of blood gas analysis. The resulting control constraints are the following:

C-1 In the absence of a continuously measuring glucose sensor, the blood had to be drawn manually to measure the glucose concentration. Due to the laboratory process, the sampling time is limited to at least

$$T_0 = 15 \text{ min} + \delta T_0, \quad (4)$$

where δT_0 is an uncertainty in sampling arising to the laboratory settings and allowing small variations.

C-2 As insulin is the only manipulated variable, the controller output is physically bounded to

$$U_{\text{sc}}(t) \geq 0 \text{ IU/min.} \quad (5)$$

C-3 The applied insulin pump allowed a step size of the control input of at least

$$\Delta U_{\text{sc}}(t) = 0.1 \text{ IU.} \quad (6)$$

C-4 Additionally, the subcutaneous application of the insulin results in a time delay between insulin injection and appearance in blood. Based on the mathematical minipig model, the lag-time was defined to

$$T_{\text{sc}}^{\text{L,max}} \approx 50 \text{ min.} \quad (7)$$

C-5 Finally, the insulin sensitivity is known to have a strong impact on the blood glucose concentration. The less insulin is required to move the same amount of glucose from the blood into the muscle cells, the more sensitive the cells are. That parameter varies inter- and intraindividually.

3.2 Controller structure

Taking the aforementioned performance requirements and control constraints into consideration, a hybrid controller structure was developed. The resulting closed-loop system is shown in Figure 3, where a list of controller design decisions depicting basic ideas is given below.

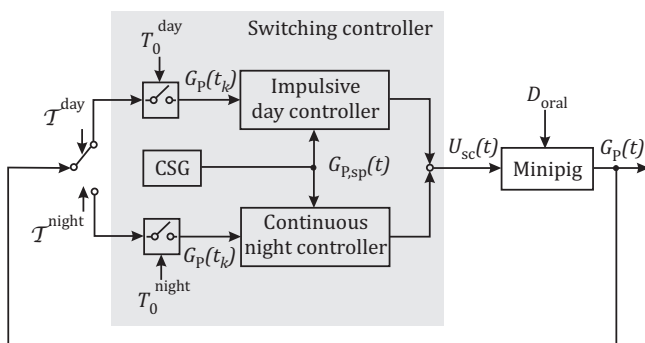


Figure 3. Closed-loop system including the switching hybrid control algorithm (CSG = command signal generator)

Switching structure. Here, we distinguish between day and night phases. As more blood glucose variations were

expected during the day due to feeding times, the blood sampling time was set to be

$$T_0^{\text{day}} = 15 \text{ min,} \quad (8)$$

and in nocturnal phases, the blood sampling time was increased to

$$T_0^{\text{night}} = 60 \text{ min.} \quad (9)$$

By that, with respect to animal welfare guidelines, the amount of blood drawn per day is reduced to a predefined volume relative to body weight. In parallel, the controller gain is changed. The control switching was synchronised with the light/dark shift in the animal housing.

Impulsive realisation. Insulin is applied as impulsive signal during the day. The employed insulin pump allows remote-controlled delivery of insulin boli. During the day, the blood sampling frequency is high compared to the manual glucose measurement process. As insulin is injected subcutaneously, which dampens the effect of insulin on the blood glucose concentration, an impulsive and a time-continuous signal have comparable effects.

Continuous realisation. Insulin is infused continuously at night. A reduced blood sampling frequency allows manual setting of the insulin basal rate at the pump.

Command signal generator (CSG). During the day, the set point is defined to be at 130 mg/dl which corresponds to values in human trials (Man et al. [2007]). At night, caused by a reduced blood sampling frequency, the controller responds to blood glucose variation not as often as during the day. Hence, the setpoint is increased to 150 mg/dl to reduce the possibility of a drop in blood glucose below the critical value of 50 mg/dl.

Basic control law. As basic control law, a PI controller was chosen to guarantee robust performance. For the control tests, the day and night controllers were implemented to be time-continuous so that small sampling time variations can be taken into consideration when calculating the next insulin dose. The controller expects the blood sampling at a predefined sampling time T_0 according to Eqns. (8) and (9).

The impulsive day controller is given exemplarily:

$$U_{\text{sc}}(t) = \sum_{k=0}^N u^{\text{day}}(t_k) \cdot \delta(t - t_k), \quad (10)$$

$$t \in \mathcal{T}^{\text{day}}, \quad k = 0, 1, 2, \dots, N \leq \infty$$

$$u^{\text{day}}(t_k) = \int_{t_k}^{(k+1)T_0^{\text{day}}} f^{\text{day}}(\tau') d\tau' + \Delta u(t_k) \quad (11)$$

$$f^{\text{day}}(\tau') = K^{\text{day}} \cdot e_k + \frac{1}{T_I} \int_{t_k}^{\tau'} e_k d\tau + u_{Ik} \quad (12)$$

$$e_k = G_{P,\text{sp}} - G_P(t_k) \quad (13)$$

$$u_{Ik} = \frac{T_0}{T_1} \sum_{i=0}^{i=k} e_i, \quad u_{I0} = u_I(t_{\text{init}}) \quad (14)$$

$$u_I(t_{\text{init}}) = \frac{1}{T_1} (G_{P,\text{sp}}(t_{\text{init}}) - G_P(t_{\text{init}})) \cdot (t_0 - t_{\text{init}}) \quad (15)$$

Here, $U_{\text{sc}}(t)$ indicates the subcutaneous insulin infusion which is the sum of insulin impulses $u^{\text{day}}(t_k)$ at control step k . $\delta(t)$ is the dirac function and e_k the control error between the current blood glucose $G_P(t_k)$ and the setpoint $G_{P,\text{sp}}$. In the case of sampling time variation, the controller takes the overestimation or underestimation of the previously injected insulin amount into consideration, called $\Delta u(t_k)$. The integral part of the controller is initialised at the time of the controller start t_0 by the difference between the blood glucose and the setpoint at time t_{init} (Eq. (15)).

3.3 Control design strategy

Initially, the controller parameters K^{day} , T_1 were chosen for the linearised glucose metabolic model by means of common loop-shaping criteria. Subsequently, the parameter values were adapted to the nonlinear model. For detailed information, see Lunze et al. [2014a].

3.4 Control performance protocol

The controller was tested during a period of 48 h including two feeding times per day which were coordinated with the daily routine in the animal housing. Control was based on venous blood glucose recordings drawn from a venous line. Insulin was injected subcutaneously using a modified commercial insulin pump (Accu-Chek[®] Combo Spirit, Roche Diagnostics, Rotkreuz, Switzerland). A commercially available glucose sensor, called CGM system, (Guardian[®] REAL Time with Enlite[®] Sensor, Medtronic Minimed, Fridley, MN, USA or G4[™] Platinum, Dexcom[™], San Diego, CA, USA), which has to be placed subcutaneously, was used for basic glucose monitoring but not for control applications.

Safety measures. In the case of a drop in blood glucose below the critical threshold

$$G_P(t_k) < G_{P,\text{crit}},$$

one of four possible interventions in Table 1 had to be carried out immediately based on the trend of the interstitial glucose concentration $\Delta G^{\text{CGM}}(t_k)$. High blood glucose concentrations were considered to be not that critical to require interventions. In the case of sensor failure, the controller test was not affected but additional blood glucose measurements were required to estimate the glucose trend.

4. EXPERIMENTAL RESULTS

Control trials. Table 2 summarizes the results of all available control trials and manual insulin protocols. Thereby, it is distinguished between low, diabetic acceptable and high glucose ranges:

$$G_{P,\text{low}} : G_P(t_k) < 70 \text{ mg/dl} \quad (16)$$

$$G_{P,\text{diab}} : 70 \leq G_P(t_k) < 180 \text{ mg/dl} \quad (17)$$

Daytime [07:00 – 19:00]:

1. **if** $\Delta G^{\text{CGM}}(t_k) \leq -2 \text{ mg/dl/min}$
then 10 ml of highly concentrated glucose solution (G-40) has to be given intravenously, the controller test had to be terminated and the blood glucose concentration had to be tightly monitored for the following 30 min manually.
2. **if** $-1 \text{ mg/dl/min} \leq \Delta G^{\text{CGM}}(t_k) \leq +1 \text{ mg/dl/min}$
then the animal gets 100 g of 'emergency' food and the controller test could be continued.

Night phase [19:00 – 07:00]:

3. see 1.
4. **if** $-1 \text{ mg/dl/min} \leq \Delta G^{\text{CGM}}(t_k) \leq +1 \text{ mg/dl/min}$
then no intervention was necessary and the controller test could be continued, but the blood glucose concentration had to be measured additionally at $t_k + 15 \text{ min}$ and the decision process was restarted.

Table 1. Safety measures procedures

$$G_{P,\text{high}} : G_P(t_k) > 180 \text{ mg/dl}. \quad (18)$$

Due to the fact that different controller sets were tested and that the blood glucose was measured discrete-time and at varying frequency, no generally valid conclusions can be drawn.

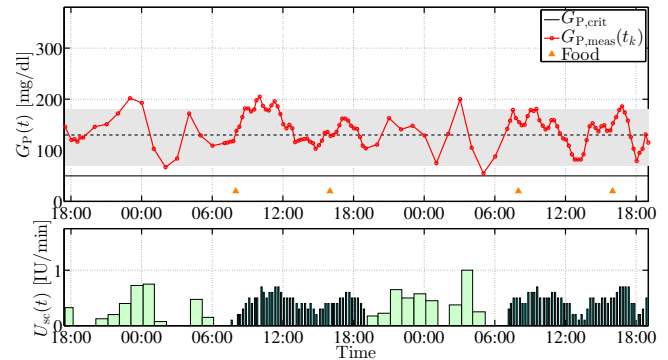


Figure 4. Control trial CT 2 with minipig No. 8 (Lunze et al. [2014a])

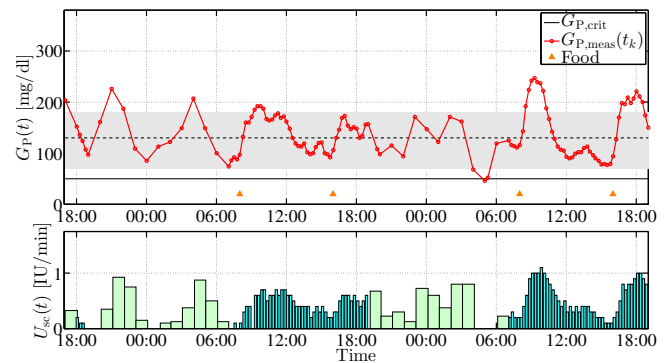


Figure 5. Control trial CT 3 with minipig No. 8

In Figures 4–8, results of clinical control trials for different animal subjects are provided. In the upper panels, $G_{P,\text{meas}}(k)$ marks the blood glucose concentration, which was obtained from blood samples via a central venous line and formed the basis for feedback control. The gray areas represent the acceptable steady-state range of the diabetic metabolism, according to $R - 1$, and the dashed lines indicate the setpoint $G_{P,\text{set}}$. In the lower panels, the subcutaneously applied insulin amounts are given. It is distinguished between boli (narrow bars) and basal rates

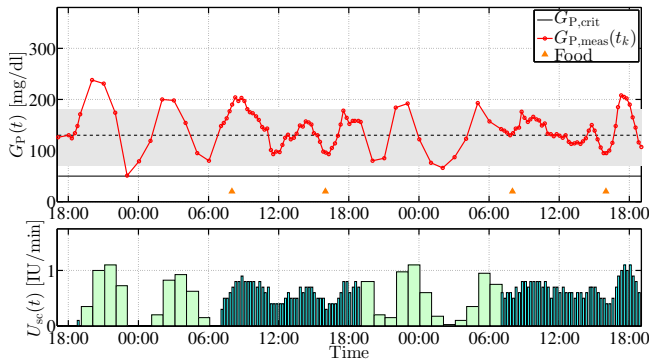


Figure 6. Control trial CT 4 with minipig No. 8

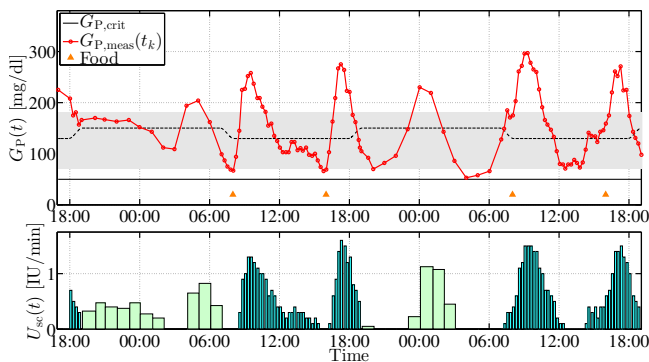


Figure 7. Control trial CT 6 with minipig No. 7 (Lunze et al. [2014a])

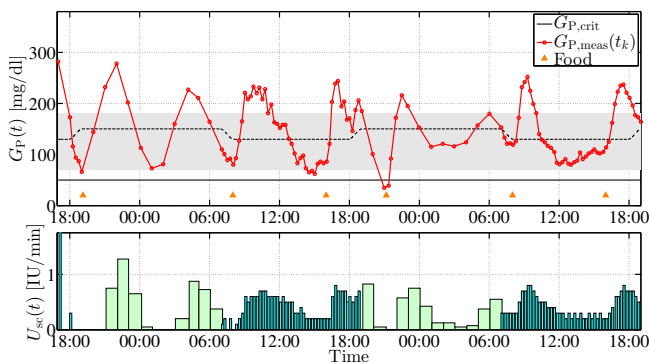


Figure 8. Control trial CT 7 with minipig No. 7

(wide bars). For easier comparison, only a fourth of each basal rate value is plotted as it corresponds to four insulin boli per hour.

Note that in the given experiments, no critical drops in blood glucose were observed. In overall, two events occurred which were counteracted by additional food, see e.g. Figure 8. However, as will be demonstrated below, the manual insulin therapy protocol including 48 h measurements also induced one critical drop in blood glucose. Furthermore, critical undershoots were avoided while overshoots above the desired range frequently happened after feeding times. For detailed information, see Lunze et al. [2014a].

Manual insulin therapy. Manual insulin therapy was administered based on determined basal rates for day-time and night shifts and additional insulin boli when thresholds were hit (see Figures 9 and 10). Note that Figure 9 shows a critical event when blood glucose level de-

Trial	MP	N	[%] of $G_P(t_k)$ in			Hypo
			$\mathcal{G}_{P,low}$	$\mathcal{G}_{P,diab}$	$\mathcal{G}_{P,high}$	
Controller tests						
CT1	8	115	8.7	73.0	18.3	1
CT2	8	125	1.6	86.4	11.5	
CT3	8	128	2.3	78.9	18.8	
CT4	8	126	1.6	84.1	14.3	
CT5	7	76	3.9	65.8	30.2	
CT6	7	128	5.4	64.1	30.5	
CT7	7	129	4.7	64.3	31.0	
48-h measurement protocol						
MT1	8	125	6.4	79.2	14.4	1
MT2	7	125	12.8	82.4	4.8	

Table 2. Evaluation of the closed-loop and the 48-h manual therapy protocols. MP indicates the minipig, N is the total number of glucose measurements per trial, CT: control trial, MT: manual therapy protocol, Hypo: $G_P(t_k) \leq 50$ mg/dl

creased below the critical threshold and additional glucose administration became necessary.

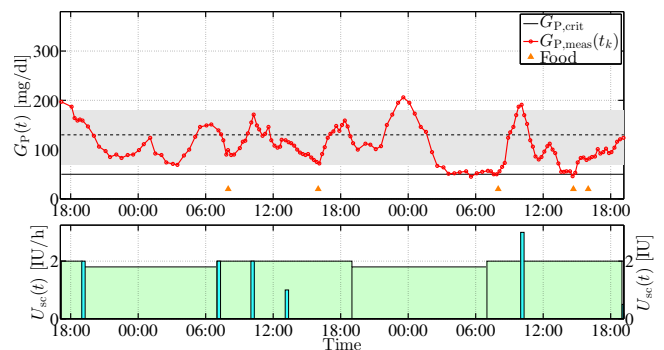


Figure 9. Manual therapy MT 2 with minipig No. 7

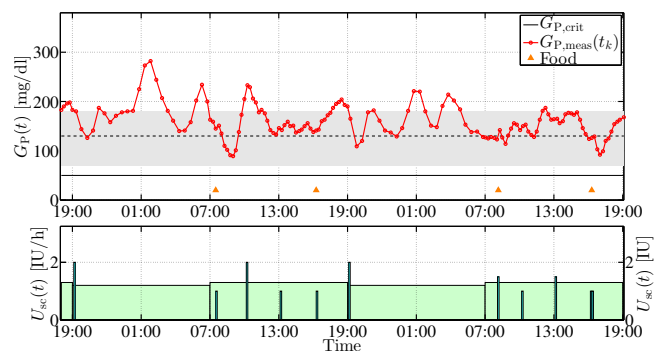


Figure 10. Manual therapy MT 1 with minipig No. 8 (Lunze et al. [2014a])

5. CONCLUSION

The experimental results obtained from 48 h time periods in our diabetic Minipigs indicate that automatic control can help to avoid critical undershoots of blood glucose levels, but did not prevent overshoots in any of our trials. A blood-glucose controller was achieved with the

proposed switching strategy, distinguishing between day and night cycles. Comparing the results of manual therapy with controller-estimated basal rates and blood glucose-dependent bolus administration, it is obvious that the control trials resulted in less critical glucose values but more values in the high range than the manual protocol (see Table 2). We conclude that the control approach mimicks the manual protocol in such a way that no better results were achieved by using manual control. In the future, more trials with more individuals are necessary to validate the results and improve the control behaviour with respect to high glucose peaks.

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