Modeling of Glucose-Insulin System Dynamics in Diabetic Goettingen Minipigs

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Abstract: Development of an artificial pancreas which regulates blood glucose in a closed loop framework is the ultimate goal in the treatment of diabetes. Development of a model which captures the glucose-insulin dynamic is a mandatory step prior to the *in vivo*-test and validation of a feedback controller. Towards this end, the focus of this paper is on the development of a glucose-insulin model for diabetic Goettingen minipigs, which will serve as a proxy for human testing of a blood glucose regulator. This paper presents an eighth-order model to capture the glucose-insulin dynamics in diabetic Goettingen minipigs. Comparison of the measurement data with the calculated evolution of the blood glucose trajectories illustrate satisfactory results providing a basis of optimism for the ultimate implementation of a closed loop controller.

Keywords: Diabetes type 1, Goettingen minipigs, Glucose-insulin system, Compartment models, Oral glucose tolerance test.

1. INTRODUCTION

Increasing sedentary lifestyle in the developed world and the enormous growth in the middle classes in developing countries with its accompanying increase in caloric intake has lead to an unprecedented growth in diabetes mellitus making it among the leading chronic diseases in the world. According to the World Health Organization (WHO) [1] in 2011, approximately 346 million people world wide were suffering from diabetes mellitus. It is projected that the number of diabetes deaths will double between 2005 (approx. 3.4 million) and 2030.

Diabetes mellitus is characterized by reduced or ceased insulin production in the β-cells of the pancreas. Correspondingly, it is distinguished between type 2 and type 1 diabetes, respectively. In this paper, type 1 diabetes is in focus of the study where patients are completely dependent on the external administration of insulin.

Nowadays, type 1 diabetic patients have to control their blood glucose level by periodically monitoring their blood glucose levels. Generally, blood glucose concentration is measured by a chemically active test strip, 3 to 8 times a day. Based on external and internal disturbances, which include physical activity and psychological stress, and based on measured glucose, the patient has to determine the required amount of insulin, and inject it by a pen or pump. In essence, the patient is the controller as well as the metabolic system, which has to be controlled. Due to discrete sampling rate and poor knowledge of system disturbances, the manual insulin therapy can usually not keep the blood glucose concentration within the desired physiological range of 70 to 180 mg/dl.

[1] http://www.who.int/diabetes/en/, January 1st 2012

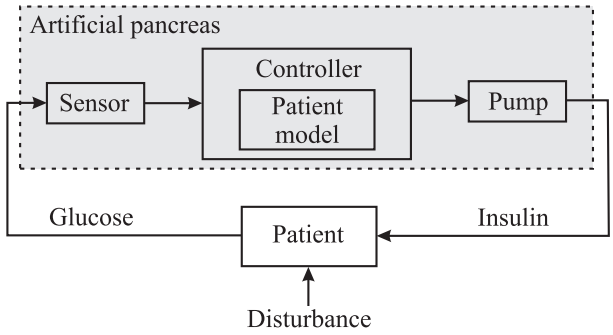

Fig. 1. The closed-loop blood glucose control system with the patient remaining as system which has to be controlled

To improve insulin therapy, since the 1970's, various research groups around the world have invested significant efforts to develop an automated closed-loop blood glucose system which is better known as artificial pancreas. The aim is to couple a sensor which continuously monitors the blood glucose concentration with a continuously injecting insulin pump based on a control algorithm to regulate the blood glucose within a tolerable range as shown in Fig. 1. Here, the patient remains as the metabolic system which has to be controlled.

Until today, the continuously injecting insulin pump is the sole commercially available device for automated insulin therapy. A reliable blood glucose sensing device is still being sought. Finally, the application of published blood glucose control algorithms is limited to clinical studies under controlled conditions, which do not represent most normal life situations, Parker et al. (2001), Chee and Fernando (2007). The closed-loop system includes the

hormone insulin as the actuating variable which decreases the blood glucose concentration, but it neglects including the counter-hormone glucagon. In the natural control loop, glucagon is responsible for the increase of blood glucose concentration. Since, the clinical studies of the autonomous control is a limited emulation of the natural regulatory mechanism, there exists a potential risk to the health of the test subject. To reduce the wide chasm between *in silico* (virtual) and *in vivo* studies of such control algorithms, animal trials are supposed to be used as an intermediate step. Our preliminary study, Lunze et al. (2011) and previously published results by other research groups, El-Khatib et al. (2007a), Larsen and Rolin (2004), have shown that the glucose metabolism of diabetic Goettingen minipigs are similar to the human ones.

Hence, to identify the effect of several external glucose and insulin impulses on the evolution of blood glucose concentration, animal trials were performed as will be outlined in Section 2. By extending the existing *minimal model* of Bergman et al. (1981) and exploiting results from Lunze et al. (2012), and by adapting the model parameter to swines, a mathematical description of the glucose insulin metabolism in diabetic Goettingen minipigs is developed in Section 3. Comparison of the measurement data and model output illustrates that the new glucose-insulin model is detailed enough to permit control design. Experimental results are given in Section 4 and the paper closes with conclusions and an outlook for future investigations.

2. ANIMAL TRIALS

2.1 Diabetic animal model

To permit periodic drawing of samples from the 5 Goettingen minipigs, two central venous lines were implanted to each of the minipig. The blood glucose measurements were the basis for blood glucose monitoring and served as the reference for a subcutaneously installed glucose sensor (Medtronic minimed, Guardian® REAL-Time). A customized insulin pump (Roche Diagnostics, Accu-Chek® Spirit Combo) was installed as well for manual insulin therapy treating with a short-acting preparation (Lilly, Humalog®).

To artificially induce diabetes mellitus in the Goettingen minipigs, Streptozocin (STZ), which is selectively toxic for the insulin-producing β-cells in the pancreas, was infused following Strauß (2009). Approximately seven days after infusion including an initial intensive care phase, the swine completely recovered and could participate in glucose metabolic tests, see also Lunze et al. (2011).

The animal trial was reviewed and approved by the State office of nature, environment and consumer protection, North Rhine-Westphalia, Germany.

2.2 Identification tests for glucose-insulin metabolism

Blood glucose concentration is affected by external and internal disturbances. To identify the system dynamics of the glucose-insulin metabolism in the Goettingen minipigs, several animal tests were performed following the time line given in Fig. 2. Initially, insulin injection was stopped 3 hours before the glucose tolerance tests (GTTs) were

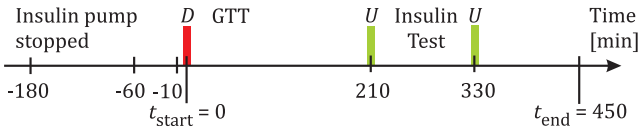

Fig. 2. Schematic presentation of the time table for GTT and Insulin test

initiated. Thus, the impact of the remaining short-acting insulin could be reduced to a minimum. Subsequently, a GTT with one of the two predefined amounts of glucose was initiated either orally (including some chow with 23 % glucose extra)

$$D_{\text{oral},1} = (1\,\text{g Glucose} + 1\,\text{g Chow})/\text{kg Body weight} \quad (1)$$

$$D_{\text{oral},2} = (2\,\text{g Glucose} + 1\,\text{g Chow})/\text{kg Body weight} \quad (2)$$

or intravenously

$$D_{\text{iv},1} = 0.25\,\text{g Glucose/kg Body weight} \quad (3)$$

$$D_{\text{iv},2} = 0.5\,\text{g Glucose/kg Body weight.} \quad (4)$$

Approximately 210 minutes later and in an interval of 120 minutes, two predefined amounts of insulin were administered intravenously or subcutaneously

$$U_{\text{iv},1} = U_{\text{sc},1} = 2\text{ IU}, \qquad U_{\text{iv},2} = U_{\text{sc},2} = 3\text{ IU}.$$

In total, the blood glucose concentration of the animals was monitored during the time interval $[t_{\text{start}} ... t_{\text{end}}]$ which corresponds to approximately 7.5 hours, with a sampling rate of 1 measurement per 15 minutes in each test. Additionally, blood glucose was measured at times $t = -60$ min and $t = -10$ min.

In Figure 3, two average measurements of 7 blood glucose trajectories each taken from 4 diabetic minipigs in total are shown by the solid lines. The grey areas represent the mean $\mu \pm$ one standard deviation σ. At $t = 0$, the blood glucose is affected by the externally administered glucose and subsequently, by the two insulin boli that were injected. On the left panel, the blood glucose trajectory variation induced by intravenous GTT (see Eq. (3)) and intravenous insulin injection ($U_{\text{iv}} = 2$ IU) is shown. On the right panel, the resulting blood glucose variation due to oral GTT (see Eq. (1)) and subcutaneous insulin injection ($U_{\text{sc}} = 2$ IU) is plotted. The time ranges at which the two insulin amounts were injected are marked by the dark grey vertical areas at approximately $t = 210$ min and $t = 330$ min.

3. MATHEMATICAL GLUCOSE-INSULIN MODEL

3.1 Blood glucose metabolism in swine

According to several publications El-Khatib et al. (2007b), El-Khatib et al. (2007a), Larsen and Rolin (2004), Swindle (2007), the behaviour of glucose metabolism in Goettingen minipigs is similar to that in humans. Subcutaneously injected insulin follows the same kinetics and system dynamics. That behaviour could be verified during the trials (see Fig. 3). The intestinal transit times are assumed to be twice as long as in humans and the nondiabetic fasting level of blood glucose is slightly lower compared to the normoglycemic range in humans. Hence, to mathematically describe the behaviour of the glucose metabolism in

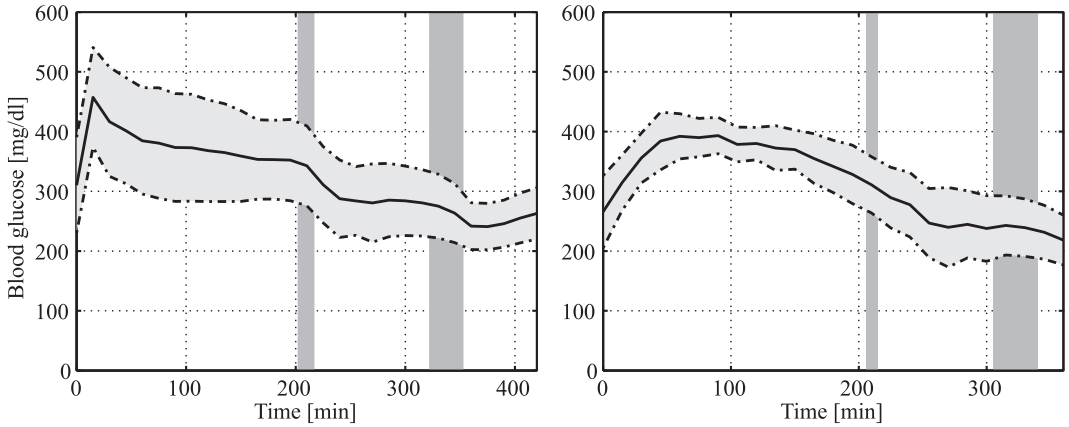

Fig. 3. Mean blood glucose trajectory $\mu(t)$ (–)(± 1 standard deviation $\sigma(t)$ (-.)) affected by glucose administration at $t = 0$ and and insulin infusions, marked by vertical grey areas. (left) intravenous GTT at $t = 0$ and intravenous insulin injection, (right) oral GTT at $t = 0$ and subcutaneous insulin injection.

Goettingen minipigs, existing compartment models for the human system can be used as a basis.

3.2 Extended minimal model

In the early 1980's, Bergman proposed the well-known 3rd order *minimal model* which describes the response of blood glucose concentration on intravenous GTTs, see Bergman et al. (1981). The glucose-insulin model for the diabetic Goettingen minipigs, which will be presented in this paper, is based on the extended version of the *minimal model* given by Lynch and Bequette (2002). Two submodels for the gastro-intestinal tract and the subcutaneous insulin dynamics proposed by Dalla Man et al. (2007a), Dalla Man et al. (2007b), referred to as *Dalla Man-model*, were added to improve the model behaviour with respect to external system inputs.

In Figure 4, the flow diagram of the resulting model for the glucose-insulin metabolism in diabetic Goettingen minipigs is shown. As external input, the intravenous and subcutaneous insulin injections are labeled as $U_{\mathrm{iv}}(t)$ and $U_{\mathrm{sc}}(t)$, respectively. The oral and intravenous glucose administration are defined as external disturbances marked by $D_{\mathrm{oral}}(t)$ and $D_{\mathrm{iv}}(t)$, respectively. The submodels from the *Dalla Man-model* are marked by the grey boxes.

3.3 Blood glucose model

According to the *minimal model*, blood glucose concentration $G(t)$ in mg/dl is given by

$$\dot{G}(t) = -p_1 G(t) - X(t)(G(t) + G_{\mathrm{b}}) + \frac{D_{\mathrm{iv}}}{V_{\mathrm{G}} \cdot m_{\mathrm{BW}}} + D_{\mathrm{g}}(t)$$

with the initial condition

$$G(0) = G_0.$$

The blood glucose concentration depends on the glucose disappearance to non-accessible compartments with the time constant p_1 and on the insulin-dependent glucose consumption represented by a nonlinear term with insulin concentration in a remote compartment $X(t)$. The blood glucose variation is calculated as the difference from the basal value G_{b}. Capturing the intravenous pathway, the

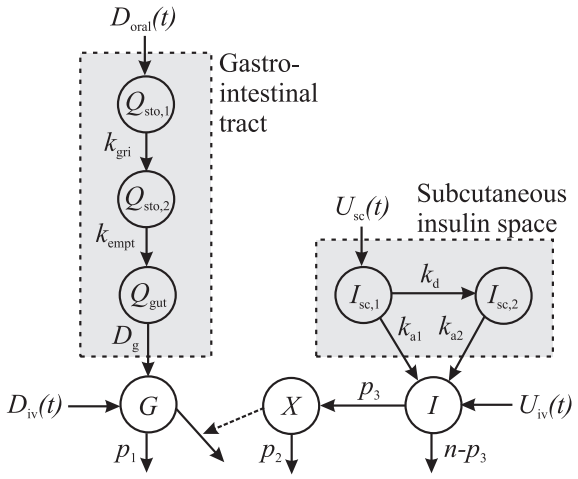

Fig. 4. Flow diagram of the glucose-insulin metabolism in Goettingen minipigs approximated by the extended *minimal model*

glucose uptake is represented by $D_{\mathrm{iv}}(t)$ normalized to the subject's body weight m_{BW} and the glucose distribution volume V_{G}. Corresponding to the gastro-intestinal tract, the glucose appearance is given by the rate $D_{\mathrm{g}}(t)$. Further information about the gastro-intestinal tract model are given below.

3.4 Insulin submodels

The intracorporal insulin concentration is assumed to be available in two compartments. $I(t)$ describes the insulin concentration in blood and $X(t)$ represents the insulin concentration in a remote compartment, both in mIU/L:

$$\begin{aligned} \dot{X}(t) &= -p_2 X(t) + p_3 I(t), & X(0) &= 0, \\ \dot{I}(t) &= -nI(t) + \frac{U_{\mathrm{iv}}(t)}{V_{\mathrm{I}}} + U_{\mathrm{I}}(t), & I(0) &= 0. \end{aligned} \quad (5)$$

The parameters p_2, p_3 and n are time constants for insulin fluctuation from blood to remote space in which the decay rate of unused active insulin molecules is also taken into account. Insulin can be administered either intravenously included by system input $U_{\mathrm{iv}}(t)$ or subcutaneously represented by the insulin appearance rate in blood $U_{\mathrm{I}}(t)$. V_{I} is

the distribution volume of insulin in blood. According to Dalla Man et al. (2007a), the systems dynamic of subcutaneously injected insulin can be modeled by the following second order system

$$\begin{aligned}
\dot{I}_{\mathrm{sc},1}(t) &= -(k_\mathrm{d} + k_\mathrm{a1}) I_{\mathrm{sc},1}(t) + U_\mathrm{sc}(t), & I_{\mathrm{sc},1}(0) &= 0,\\
\dot{I}_{\mathrm{sc},2}(t) &= k_\mathrm{d} I_{\mathrm{sc},1}(t) - k_\mathrm{a2} I_{\mathrm{sc},2}(t), & I_{\mathrm{sc},2}(0) &= 0,\\
U_\mathrm{I}(t) &= \frac{k_\mathrm{a1} I_{\mathrm{sc},1}(t) + k_\mathrm{a2} I_{\mathrm{sc},2}(t)}{V_\mathrm{I}}.
\end{aligned}$$

$I_{\mathrm{sc},1}(t)$ is the concentration of nonmonomeric insulin and $I_{\mathrm{sc},2}(t)$ of monomeric insulin in the subcutaneous space. The injection of insulin is accounted for by the model input $U_\mathrm{sc}(t)$ in mUI/min. k_a1 and k_a2 are the rate constants for insulin absorption in blood and k_d is the dissociation rate.

3.5 Gastro-intestinal tract

System dynamics of orally uptaken glucose is affected by the stomach, the intestinal transit times and the absorption rate in blood. Hence, the model approach for the gastro-intestinal tract given by Dalla Man et al. (2007b) is a third order system

$$\begin{aligned}
\dot{Q}_{\mathrm{sto},1}(t) &= -k_\mathrm{gri} \cdot Q_{\mathrm{sto},1}(t) + D_\mathrm{oral}(t),\\
\dot{Q}_{\mathrm{sto},2}(t) &= -k_\mathrm{empt} \cdot Q_{\mathrm{sto},2}(t) + k_\mathrm{gri} \cdot Q_{\mathrm{sto},1}(t),\\
\dot{Q}_\mathrm{gut}(t) &= -k_\mathrm{abs} \cdot Q_\mathrm{gut}(t) + k_\mathrm{empt} \cdot Q_{\mathrm{sto},2}(t),\\
D_\mathrm{g}(t) &= \frac{f \cdot k_\mathrm{abs} \cdot Q_\mathrm{gut}(t)}{V_\mathrm{G} \cdot m_\mathrm{BW}}
\end{aligned}$$

with the inital conditions

$$Q_{\mathrm{sto},1}(0) = 0, \qquad Q_{\mathrm{sto},2}(0) = 0, \qquad Q_\mathrm{gut}(0) = 0.$$

The rate constants describe grinding k_gri, gastric emptying k_empt and absorption in blood k_abs. f is the fraction of glucose which finally appears in blood in relation to distribution volume of glucose V_G and the subject's body weight m_BW. $D_\mathrm{oral}(t)$ in mg/min represents the ingestion rate of orally uptaken glucose as system input and $D_\mathrm{g}(t)$ is the appearance rate of glucose in blood.

4. RESULTS

4.1 Parameter identification

Goettingen minipigs show similar but nevertheless different static and dynamic behaviour concerning the glucose metabolism compared to humans. Therefore, values of some model parameters were slightly changed as shown on top in Table 1 and other parameters were adapted individually as listed on the bottom in Table 1. For off-line parameter identification in MATLAB, the method "leave one out crossvalidation" and a nonlinear least-squares fit were chosen, as the number of test procedures were few and the model is nonlinear. The measurement data for each minipig was divided into validation data and test data.

To reduce the solution space of the optimisation procedure due to high number of unknown parameters and low number of measurement data, parameter identification was split into $k = 3$ steps with different validation data:

(1) $P_1 = [p_1, p_2, p_3, n, V_{\mathrm{I},i}, V_\mathrm{G}]$: data sets including intravenous glucose and insulin application,
(2) $P_2 = [k_\mathrm{gri}, k_\mathrm{abs}, k_\mathrm{empt}, f_i]$: data sets including oral glucose uptake and diverse insulin administration,
(3) $P_3 = [k_\mathrm{a1}, k_\mathrm{a2}, k_\mathrm{d}]$: data sets fincluding diverse glucose application and subcutaneous insulin injection

with $i = 2, 3, 4, 5$ the number of the pig. For each adaption step k, with $k = 1, 2, 3$, the resulting values of the relevant parameter set P_k were defined as mean value of all relevant optimisation results with the appropriate validation data sets and were subsequently applied. Concerning the individual parameters, the mean of all calculated values based on the corresponding measurement data with one pig was determined adequately.

4.2 Adapted parameters

With respect to blood glucose behaviour, the parameters p_1, p_2, p_3, n and V_G were slightly adapted. In the gastro-intestinal tract, the grinding and absorption time constants k_gri and k_abs are assumed to be the same as in humans according to Larsen and Rolin (2004). Applying the optimisation procedure, these parameter values were solely slightly changed and thus, they are reasonable. Additionally, the emptying parameter k_empt was reduced to a constant value for model simplification. Although gastro-intestinal transit time is assumed to be slightly greater in pigs, parameter optimisation resulted in slightly faster dynamics which may be caused due to simplification.

The kinetics of subcutaneously administered insulin is slightly slower than in humans, as the maximum effect of insulin on blood glucose concentration was observered 60-90 min after insulin administration in the trials. The subcutaneous dynamics itself is faster compared to humans as the effect of insulin on blood glucose concentration could not be observed as long as in humans. Parameter optimisation resulted in highly increased time constants for k_a1, k_a2 and k_d compared to humans behaviour. These results correspond to experimental observations but do not confirm the statements given in Larsen and Rolin (2004).

4.3 Individualised parameters

Some model parameters were individualised, as the model behaviour is very sensitive to the variation in their value. Hence, the distribution volume of insulin V_I taken from Lynch and Bequette (2002) and fraction of glucose absorption f were adapted individually. As it is quite difficult to determine the basal blood glucose concentration G_b in diabetic subjects, the initially measured blood glucose level was defined as the basal value

$$G_0 = G_\mathrm{mess}(0) = G_\mathrm{b}.$$

4.4 Glucose absorption

The maximum amplitude of blood glucose concentration caused by orally uptaken glucose at $t = 0$ seems to depend on the initial blood glucose level G_0

$$\Delta G_\mathrm{max} = G_\mathrm{max}(t) - G_0 = f(G_0).$$

In Figure 5 the maximum difference of glucose ΔG_max is shown depending on the initial blood glucose values G_0

Table 1. Parameter values for submodels

Parameter	Value		Unit	Source
	Original	Adapted		
Adapted model parameters				
p_1	0.02873	0.0081	1/min	adapted from Lynch and Bequette (2002)
p_2	0.02834	0.0341	1/min	adapted from Lynch and Bequette (2002)
p_3	$5 \cdot 10^{-5}$	$8.32 \cdot 10^{-5}$	1/min	adapted from Lynch and Bequette (2002)
n	0.093	0.2139	1/min	adapted from Lynch and Bequette (2002)
V_G	1.8	0.1788	dl/kg	adapted from Dalla Man et al. (2007b)
k_{gri}	0.0558	0.1015	1/min	Dalla Man et al. (2007b)
k_{abs}	0.057	0.1015	1/min	Dalla Man et al. (2007b)
k_{empt}	0.0378	0.1047	1/min	adapted from Dalla Man et al. (2007b)
k_{a1}	0.0018	0.0082	1/min	adapted from Dalla Man et al. (2007a)
k_{a2}	0.0182	0.0998	1/min	adapted from Dalla Man et al. (2007a)
k_d	0.0164	0.0568	1/min	adapted from Dalla Man et al. (2007a)
Individualised model parameters				
V_I	[6, ..., 10]	12	L	adapted from Lynch and Bequette (2002)
f	[0.12, ..., 0.42]	0.9	dimensionless	adapted from Dalla Man et al. (2007a)

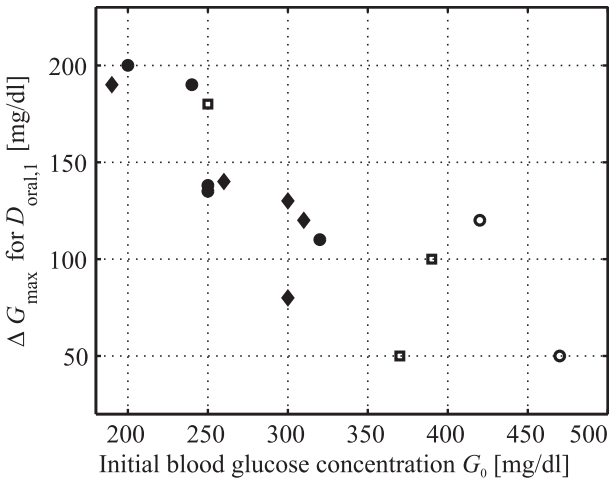

Fig. 5. The maximum difference of blood glucose concentration ΔG_{max} depending on the initial blood glucose concentration G_0. For the same animal, the measurements are marked the same.

at the beginning of each oral GTT with the same input amount. Each combination is plotted where the same mark represents the same animal. To initially approximate the observed metabolic behaviour, f was adapted for each animal individually given in the bottom line of Table 1.

4.5 Model performance

Comparisons of the measured and calculated blood glucose trajectories for minipig 5 are exemplarily shown in Fig. 6 with a test data set on the left panel and a validation data set on the right panel. The blood glucose measurements are marked by circles and the glucose trajectories generated by the model are shown by solid lines without markers. Here, an oral GTT according to Eq. (1) is followed by two subcutaneously injected insulin boli with $I_{sc} = 2\,\mathrm{IU}$ on the left graph and $I_{sc,1} = 2\,\mathrm{IU}$ and $I_{sc,2} = 1\,\mathrm{IU}$ on the right graph.

As can be seen, the model output tracks the measurement data quite well on the left graph. As the initial blood glucose concentration is lower on the right graph, the model mimics qualitatively the glucose behaviour, but shows quantitative differences which emphasizes the statement given in Section 4.4. Analyses of the model behaviour for all other minipigs produced similar results.

5. CONCLUSIONS

In conclusion, we developed a mathematical model of the diabetic glucose-insulin metabolism in Goettingen minipigs which shows satisfactory dynamics. It is valid to adapt the model to changing basal blood glucose concentrations which are defined as initial measurement values, and to body mass, as these parameters are previously known. The individual distribution volume V_I and parameter f has to be estimated by performing the test procedure once as explained in Section 2.2.

The objective of developing a model is to permit the design and performance analysis of algorithms for blood glucose control. Currently, no continuous blood glucose sensor is commercially available. Hence, control algorithms can either be based on continuous but subcutaneous and delayed glucose concentration measurements or on discrete but correct blood glucose samples. Hence, the possibility to draw blood samples each 15 min was assumed as requirement in this paper.

If a simple controller without internal model is optimally designed based on the mathematical model and subsequently applied on diabetic Goettingen minipigs *in vivo*, it should be robust enough to adequately respond to slightly different system behaviour using a sampling frequency of 1 measurement per 15 min. Even output prediction of the metabolic system is possible, if the prediction horizon remains in an adequate time window compared to metabolic time constants and the calculated control variable is adjusted in each calculation step.

To represent the glucose metabolism in greater detail, the correlation of G_0 and ΔG_{max} has to be investigated carefully and the model parameters have to be optimized. Furthermore, the renal clearance could be accounted for as the minipigs were temporarily held in a metabolism cage and existing data has to be mathematically analyzed. Finally, control algorithms have to be designed *in silico* based on the developed model and applied in animal trials to close the loop. An automated closed-loop insulin therapy will not be completed until the sensor problem is

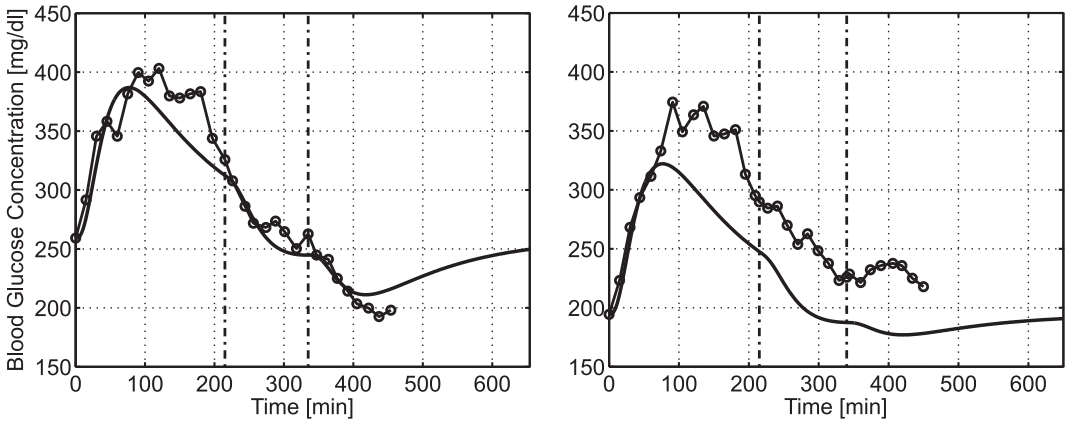

Fig. 6. Two different blood glucose trajectories of minipig 5 are shown, measurement results are marked by circles. Oral GTT according to Eq. (1) at $t = 0$ and subcutaneous insulin administration at the time points marked by vertical dash-dotted lines. The solid line marks the simulated blood glucose trajectory by the model.

solved. Until that moment, a semi-closed loop control will be the best solution which includes discrete blood glucose measurements.

6. ACKNOWLEDGEMENTS

Many thanks to Mrs. Lisa Kossmann, Mrs. Jana Schmitz and Mrs. Svenja Kügler acting as student research assistants for animal condition and supervision during the trials. Furthermore, we acknowledge the staff of the Institute for Laboratory Animal Science and Experimental Surgery, University Hospital Aachen for excellent support and numerous optimisation ideas during the animal trials. The second author acknowledges the financial support of the "von Humboldt Stiftung" which supported his stay in Aachen in the Fall of 2011.

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