Report for the study "An open, single-centre, non-controlled feasibility study using a software-algorithm based insulin therapy to control blood glucose in Type 1 diabetic patients"

"REACTbyALGO"

I.1 Abstract

OBJECTIVE: We evaluated the performance of a new approach on blood glucose control in a clinical study with type 1 diabetes patients using a generic integrated physiologically-based PBPK/PD model kernel within an (adaptive) MPC scheme with PID-based offset-control.

RESEARCH DESIGN AND METHODS: Blood glucose was managed in ten subjects with type 1 diabetes without endogenous insulin secretion in a single 30-h clinical feasibility study controlling subcutaneous delivery of insulin based on plasma glucose (PG) measurements in 15 min intervals. Meal information, but no priming bolus, was given to the controller at start of each of three meals. To improve closed-loop performance of MPC, model kernels were updated with growing patient data and prediction errors were compensated with a PID-based offset-controller.

RESULTS: The overall mean (n=10) PG was 156 mg/dL, with 74% time of PG values in the target range of 70–180 mg/dL. With 2 incidents during 240 h of closed-loop control, hypoglycemia (PG < 70 mg/dL) was rare. During nighttime control, prior to model adaptation, mean PG was elevated (149 mg/dL, with 38% time in target 70–140 mg/dL). However, daytime control after kernel adaptation improved significantly (147 mg/dL, with 75% of PG in target with adaptation vs. 163 mg/dL, with 63% without). In retrospective analysis of insulin and glucagon measurements, significant glucagon surges were observed in the morning after breakfast, indicating a role of glucagon in the "dawn effect" in T1DM.

CONCLUSIONS: MPC of blood glucose for type 1 diabetes patients using a generic integrated PBPK/PD model kernel with PID-based offset-control achieved good glycemic control with significant improvements upon update of the core prediction model. Once the relevance of (postprandial) glucagon in T1DM has been analysed, fully understood and captured by PBPK/PD modeling, future trials testing the improved system (in combination with a s.c. CGM device) in controlled conditions seem very promising.

I.2 Introduction

Maintaining blood glucose levels within a normal range is crucial to reduce long-term complications in patients with diabetes mellitus (1, 2). Automation of this task would relieve patients of the burden of manual control and has been shown to lower risk of hypoglycaemia (3), increasing quality of life.

Improvements in glucose sensing and insulin analogs and their delivery devices have advanced the conditions for developing a feasible solution for a fully integrated artificial pancreas (AP) system (4, 5). The superiority of automatic glucose control (AGC) by s.c. glucose measurements and s.c. insulin infusions (s.c.-s.c. route) over manual control has already been demonstrated (6).

Although various control strategies have been designed for the AP (7-11) (12) physiologic lag times remain a core problem in reactive feedback-control solutions (12). Lag-times are best handled with feed-forward control solutions, the most widely used approach being model predictive control (MPC) (13-16)

We previously demonstrated *in silico* the feasibility of safe and effective control using, for the first time, a detailed generic whole-body physiology-based pharmacokinetic/pharmacodynamic (PBPK/PD) model (17) within a robust MPC algorithm with subcutaneous insulin infusions directed by the computer algorithm using sampled venous plasma glucose (PG) in 15-min intervals in sedentary subjects over the course of 24 h (18).

The decision to further use this control approach was based on the evaluation of accuracy and predictive reliability of the PBPK/PD modeling approach to describe glucose homeostasis (17).

Whereas most control approaches (12, 19-22), even semi-physiological MPC approaches using the UVa/Padova simulator, (23, 24), and the Cambridge Model (25) only use insulin for closed loop glucose control and also only use internal model representations of glucose and insulin dynamics in case of MPC, a new approach is bihormonal control of glucoase, including glucagon for glcaemic control (16, 26). Although El-Khatib et al. have evaluated the efficacy of exogenous glucagon in treating hypoglycaemia (27), the relevance and influence of endogenous glucagon in the control of blood glucose in T1DM is diversely discussed (28) (Short Literature Review).

It has been reported that postprandial glucagon surges may occur in individuals with T1DM (29), however, no strong evidence for postprandial glucagon was found in previous studies (16, 17, 26). Even though we did not use exogenous glucagon for control…We did measure blood glucagon levels to evaluate relevance of glucagon for glycaemic control within this control study.

We hypothesized that glycemic control could be achieved in humans with type 1 diabetes using these models as kernels for model predictive control concepts in blood glucose control by prediction of the undisturbed and sedated glucose core dynamics. In this regard, we have developed a novel control approach, which, for the first time, combines a detailed a-priori individualizable generic whole-body physiology-based pharmacokinetic/pharmacodynamic (PBPK/PD) model (17), with a robust MPC algorithm for automatic glucose control. Based on an accurate prediction (PBPK/PD) model of the individual's core dynamics of blood glucose levels (17), refined over time using continuously gathered patient data, the MPC computes an optimal feed-forward control input. To increase closed-loop stability and robustness against disturbances and model uncertainties outside the predicted core dynamics, a PID-based feedback controller is used for compensation of prediction errors (offset).

Here, we report the results of a study testing this hypothesis in a 24h feasibility study for automatic glucose control. The study was designed as a feasibility study to evaluate for the first time the in-vivo performance of the algorithm in a sedated scenario including four meal challenges.

I.3 Clinical Trials: Materials and Methods

After having evaluated the reliability of the developed PBPK/PD models of the GIM (17), and the integrated model predictive control approach (18), two mono-centric, open, non-controlled feasibility studies in subjects with type 1 diabetes were conducted in successive steps.

The glucose control algorithm (GCA) developed here has never before been used on patients in a clinical trial. The first (iteration) prototypes have been evaluated *in-silico* before tests were conducted in a first clinical feasibility (REACTbyALGO) study in Graz in Jan/Feb 2013 using, for safety reasons, accurate glucose measurements from blood.

In the second iteration, the AGC has been tailored towards blood-glucose control using subcutaneous continuous glucose monitoring (CGMs) data for the calculation of insulin dosing, which corresponds to the state of the art in (other) AGC systems currently in development (30, 31). Performance of the control system using CGM data has first been evaluated *in-silico* to assess the required sensor accuracy for save control in a clinical trial. The final system was then evaluated within the second clinical trial for AGC in Jan 2014.

In both trials, each of the 10 subjects participated in a 6h clamp and 24h-manual-closed-loop blood glucose control experiment (total 30h). The trials were performed in a controlled setting at the Clinical Research Centre (CRC) at Medical University of Graz. The patients were recruited from the diabetes outpatient clinic of the centre. The results of the 24h feasibility studies for automatic glucose control are presented in the following sections.

I.3.1Trials

I.3.1.1 REACTbyALGO (Trial #1)

We conducted two mono-centric, open, non-controlled feasibility studies in subjects with type 1 diabetes, the first in February 2013, the second in January 2014. The study protocol was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study included a total of 10 subjects and was performed in a controlled setting at the Clinical Research Centre (CRC) at Medical University of Graz. The patients were recruited from the diabetes outpatient clinic of the centre.

I.3.1.1.1 Subjects

Signed informed consent was obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during standard medical care). Subjects were 40.7 ± 12.5 (25-59) years of age and had type 1 diabetes (as defined by WHO) for at least 24 months with C-peptide levels below detection threshold. Subject's HbA1c was required to be below 10%, and the Body Mass Index (BMI) was 27 ± 3 (24-32) kg/m^2, with body weights of 87.5 ± 10.5 (67-101) kg and body heights of 179 ± 6.5 (169-191) cm. All subjects have been treated with continuous subcutaneous insulin infusion (CSII) for at least 3 months prior to start of the study. Further exclusion and withdrawal criteria, analysis methods as well as intervention and stopping rules are listed in Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**.

I.3.1.1.2 Trial Protocol

The trial protocol was adapted from the protocol of the 2PRCT. Subjects were admitted to the clinical research centre at 1:30 p.m. in the afternoon of the study day and underwent the study day examination (concomitant illness, vital signs, adverse events) and preparation (insertion of cannulas for blood sampling). Patients arrived in fasted state (last meal and above basal insulin

dose at 10:00 a.m.) and switched basal insulin delivery from their own pump to a constant basal insulin infusion rate from the study pump. Throughout the study blood glucose measurements were taken every 15 min. During clamp phase (2:00 p.m. until 5:00 p.m.), patients received additional i.v. insulin Actrapid (NovoNordisk) or i.v. glucose if required to stabilize patients at a glucose level in the range of 100 mg/dl (5.55 mmol/l) < BG < 120 mg/dl (6.67 mmol/l) at 5:00 p.m. After 5 p.m., the clamp protocol (i.v. insulin and glucose administration) was discontinued. Basal insulin (IIP) was continued. From 2:00 p.m. on blood samples for insulin and glucagon measurements are taken every 30 min postprandial and once every hour during the night.

At 6:00 p.m. the patients received standardized first dinner. The prandial insulin need is covered by a dose of short acting insulin delivered with the installed insulin pump. The basal insulin infusion rate from 1:30 p.m. until 7:30 p.m. and the insulin dose before the first standard dinner was derived from the individual insulin need and determined by the investigator. Patients received four standardized meals: Dinner (60 g CHO, 18:00 p.m. day 1), breakfast (48 g CHO, 8:00 p.m. day 2), lunch (60 g CHO, 12:00 p.m. day 2), and again dinner (60 g CHO, 18:00 p.m. day 2). From 7:30 p.m. until end of the study day all insulin doses, including the prandial insulin doses (breakfast, lunch, second dinner), have been determined by the MPC algorithm administered via the insulin infusion pump. At 7:30 p.m. the next day all patients followed their normal treatment regimen and came back 3 days later for a follow up visit.

I.3.1.2 REACTbyALGO2 (Trial #2)

I.3.1.2.1 Adapted Trial Protocol

The trial protocol was further adapted from the protocol of the first trial described above. In the first trial, initial model identification was based on the clamp data during the first 6h of the trial. At this time, insulin was infused i.v., and blood glucose levels were stabilized. The resulting smooth dynamics (containing only a reduced amount of information on dynamic model behaviour) and missing information on absorption behaviour of s.c. glucose did not suffice for good model identification. Thus, for the second trial, subjects were screened one day prior to start of the clinical trial, where they also were equipped with a CGM device. They were then admitted on the following day to the clinical research centre at the Medical University of Graz (MUG) for the clinical trial and received basal insulin from insulin pumps until initiation of closed-loop control. After start of control, the protocol and all criteria are as in the protocol for the first trial.

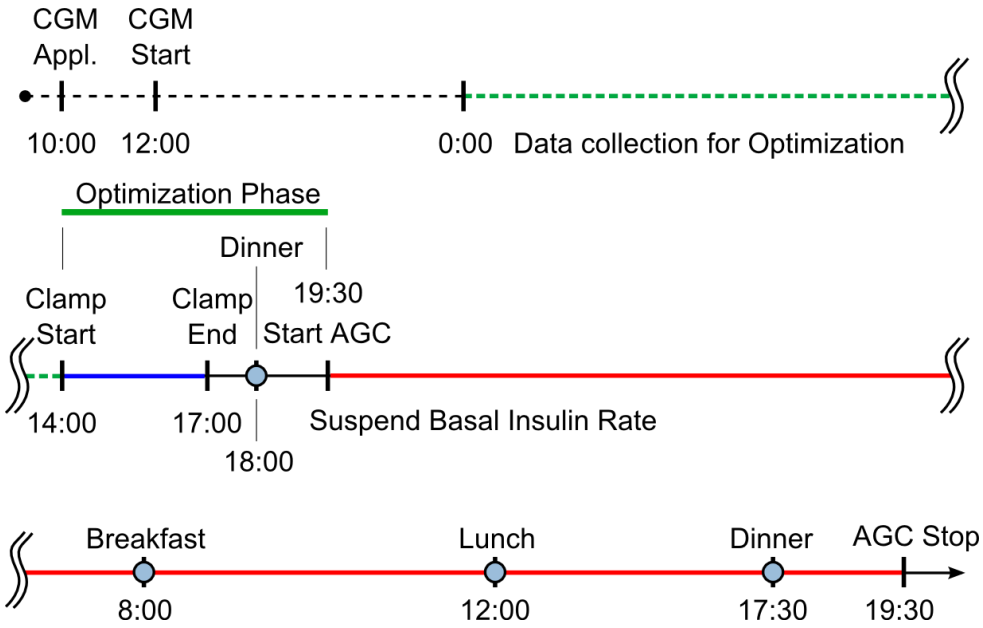

Figure 1: Trial Protocol overview from the second clinical trial (REACTbyALGO2). The first line is the day prior to the trial, when the CGM device was applied to the patient at 10:00. Day 1(starting at 14:00) and day 2 of the trial are represented by the middle and lower line, respectively. Data collected by the CGM from 0:00 to 14:00 at the day of the trial was used for model optimization (i.e. individualization).

I.3.2Outcome Measures

The specified parameters for the assessment of the effectiveness of the control system were: mean BG; Time/Percent of BG values in Target (70 - 180 mg/dl 3h postprandial and 70 - 140 mg/dl on all other times), time/percent below 70 mg/dl, and above 180 mg/dl, as well as number of hypoglycaemic events < 60 mg/dl treated with carbohydrates. Outcomes were calculated for the total of 24h of control, and separately for night-time (10:00 p.m. - 8:00 a.m.) and day-time (8:00 a.m. – 7:30 p.m.).

Two experiments from trial#1 were affected by technical failures (Subject 1 and Subject 2) in the model core (Subject 2) and associated with control algorithm parameterization (Subject 1). The results of Subject 1 were still included in the analysis as the algorithm, once corrected (there was a sign error in calculating ΔTV), quickly recovered autonomously after the second failure (Subject 1) but could not be brought back online after the first failure (Subject 2).

Outcome statistics were calculated using MATLAB®.

I.3.3Laboratory Analyses

Blood for insulin and glucagon measurements was drawn into tubes containing EDTA and put immediately on ice. Plasma was isolated by centrifugation at 4°C and frozen within 30 min from the time of sampling. Insulin and glucagon were measured by immunoassay.

I.3.4Control Algorithm

The robust MPC algorithm runs on a PC where, once every 15 min, the blood glucose data (trial#1) and CGM data (trial#2) is entered manually. After processing the data, the algorithm suggests an insulin infusion rate. This insulin infusion rate is checked for plausibility by the staff and entered manually into the insulin pump. The insulin pump is filled with short-acting insulin

(Lispro) whose PK/PD parameters are part of the kernel/algorithm. Clinical parameters and patients' clinical history data including age, sex, race, height, weight, BMI, and history of diabetes are collected prospectively.

I.4 Control Performance

The GCA has not been used on patients within a feasibility study before. Thus, within the first study glucose control was performed with intravenous glucose measurements for reasons of safety. For the second study, after adaptation of the control algorithm to cope with s.c. measurements, CGM data was used to drive the algorithm. Each of the 10 subjects in the two trials participated in a 6h clamp and 24h-manual-closed-loop blood glucose control experiment (total 30h). The aggregated results of the study are shown in Figure 2 and Table 1.

I.4.1Glycaemic Control

To demonstrate clinical performance of the AGC system, the control performance of the two trials was compared to competitor systems (for which data was available). The times in target range achieved by the different Algorithms is listed in Table 1. A visual representation of the key performance indicators is shown in Figure 2.

Table 1: Summary statistics of results of all 30-h closed-loop experiments of REACTbyALGO (RbA1 and RbA2) in comparison to trial results from studies by El-Khatib-1 et al. (with two visits for each patient, EK-11 and EK-12) (26) and the ADICOL trial (comparison of an open-loop CSII standard-of-care protocol and the Cambridge algorithm, results unpublished. Results are separated into overall, day-time-, and night-time-control. The left 3 columns correspond to the first visit/protocol/algorithm version and the right 3 columns correspond to the second visit/protocol/algorithm version of the respective clinical trial.

	EK-11	CSII	RbA1	EK-12	Cambridge	RbA2
OVERALL						
t in Target1	70 (54 to 82)	81 (56 to 97)	74 (51 to 93)	61 (50 to 70)	83 (58 to 98)	76 (60 to 93)
t in Target2	64 (50 to 81)	71 (43 to 97)	50 (32 to 80)	52 (40 to 58)	68 (42 to 92)	66 (52 to 89)
t below 50 mg/dl	3 (0 to 11)	3 (0 to 20)	0 (0 to 3)	0 (0 to 0)	0 (0 to 2)	3 (0 to 6)
t below 70 mg/dl	7 (0 to 19)	11 (0 to 44)	1 (0 to 7)	2 (0 to 8)	3 (0 to 13)	9 (0 to 17)
t above 170 mg/dl	36 (24 to 42)	26 (1 to 65)	61 (19 to 82)	51 (44 to 64)	41 (25 to 65)	32 (18 to 59)
Mean Glucose	137	117	156	161	138	128
Mean Glucose stdv	60	36	38	60	38	47
Mean Glucose Amp	215 (152 to 299)	148 (80 to 232)	157 (93 to 223)	202 (170 to 230)	154 (105 to 227)	194 (158 to 247)
OVERNIGHT						
t in Target1	91 (70 to 100)	81 (22 to 100)	79 (12 to 100)	95 (85 to 100)	95 (78 to 100)	90 (78 to 100)
t in Target2	88 (67 to 100)	71 (3 to 100)	38 (0 to 83)	81 (70 to 97)	75 (35 to 100)	78 (56 to 90)
t below 50 mg/dl	5 (0 to 18)	2 (0 to 8)	1 (0 to 7)	0 (0 to 0)	0 (0 to 3)	1 (0 to 7)
t below 70 mg/dl	9 (0 to 27)	13 (0 to 49)	2 (0 to 17)	0 (0 to 0)	2 (0 to 16)	9 (0 to 22)
t above 170 mg/dl	3 (0 to 6)	17 (0 to 100)	61 (0 to 100)	19 (3 to 30)	23 (0 to 65)	14 (0 to 34)
Mean Glucose	100	110	149	119	124	109
Mean Glucose stdv	18	17	21	24	21	27
Mean Glucose Amp	69 (37 to 107)	61 (25 to 168)	74 (49 to 133)	89 (49 to 113)	74 (39 to 151)	113 (61 to 184)
DAYTIME						
t in Target1	63 (50 to 77)	79 (37 to 100)	69 (50 to 93)	53 (23 to 61)	79 (38 to 98)	67 (54 to 85)
t in Target2	57 (45 to 70)	71 (37 to 100)	63 (43 to 93)	44 (11 to 57)	68 (28 to 87)	62 (48 to 85)
t below 50 mg/dl	2 (0 to 7)	4 (0 to 32)	0 (0 to 0)	0 (0 to 0)	0 (0 to 3)	4 (0 to 11)
t below 70 mg/dl	5 (0 to 9)	11 (0 to 63)	0 (0 to 0)	0 (0 to 0)	2 (0 to 8)	9 (0 to 17)
t above 170 mg/dl	51 (39 to 59)	32 (2 to 85)	62 (37 to 89)	65 (55 to 91)	53 (33 to 93)	43 (17 to 74)
Mean Glucose	150	123	163	175	149	140
Mean Glucose stdv	60	33	41	52	37	53
Mean Glucose Amp	189 (113 to 238)	132 (80 to 186)	142 (93 to 198)	160 (109 to 186)	135 (98 to 227)	189 (147 to 236)

As can be seen in Figure 2, the developed algorithm can compete with existing algorithms, especially in its second version in RbA2. When comparing the different trials, it has to be noted: the El-Khatib, the Cambridge, and the RbA1 trial use i.v. glucose measurements with an accuracy of approximately 2% MARE, although the Cambridge algorithm emulates the time-delay of s.c. measurements by delaying the sensor signal by 15 min. The RbA2 trial uses real s.c. measurements by CGM devices (Dexcom G4 Platinum) with an MARE of 10%. The values show that improved time-in-target is overall bought with a higher risk for hypoglycemia. When

looking only at daytime control, in both trials the controller can compete very well with other algorithms. It shows similar values for time in target an only slightly higher than average values for time in low glucose ranges (< 70 mg/dl), although still less so than the open-loop CSII standard-of-care protocol. However, the figure shows that night-time control of the system in RbA1 (trial #1) was below average (see also Figure 3). In RbA2 (trial #2), also night-time control was very good in terms of time in target.

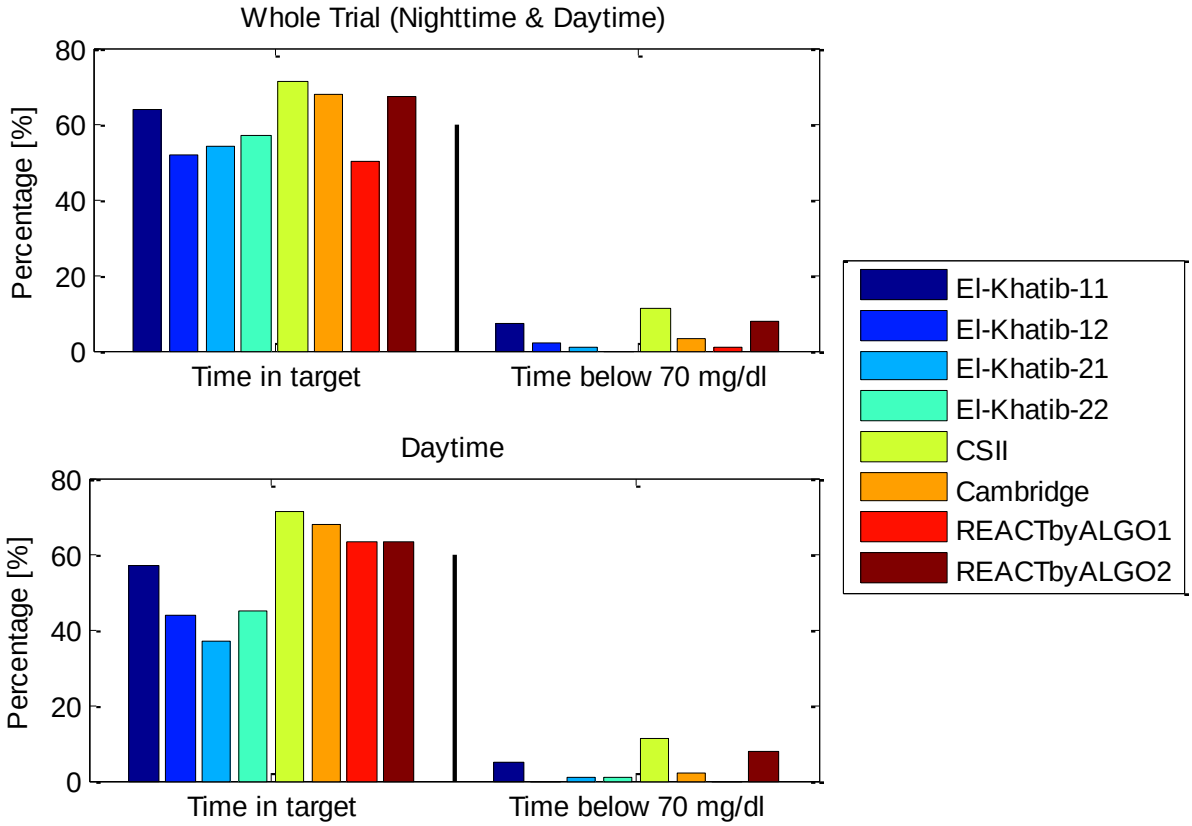

Figure 2: Graphical representation of the key performance indicators of published control trials (El-Khatib-1 (26); El-Khatib-2 (16) and unpublished Data (CSII: standard clinical (non-automated) basal-bolus therapy; Cambridge: Hovorka et al. (14)) and the REACTION control trials (REACTbyALGO1/2: the two control-trials using the control algorithm developed here). Time in Target (left) is defined as Time of measured blood glucose levels within: 70 mg/dl < BG < 140 mg/dl (in fasted state) and 70 mg/dl < BG < 180 mg/dl (for 3h postprandial). Time below 70 mg/dl (right) is defined as Time of measured blood glucose levels BG < 70 mg/dl. Displayed are percentages of measured glucose values in the respective range for overall control performance (top axis) and daytime control (bottom axis).

Even though in trial #1, the controller overall does not achieve the best scores for “Time in Target Range”, the glucose trajectories within trial #1 show the least individuals with episodes below 70 mg/dl. In general, basal insulin provision was too restrictive (especially during the night). Insulin action was overestimated and dose correction did not adapt accordingly. This was the case due to a conservative parameterization of the correction module (the FMPD controller) and due to issues in initial model identification. Initial model identification was based on the clamp data during the first 6h of the trial. At this time, insulin was infused i.v., and blood glucose levels were stabilized. The resulting smooth dynamics (containing only a reduced amount of information on dynamic model behavior) and missing information on absorption behavior of s.c. glucose did not suffice for good model identification.

In trial #2, control performance was significantly improved. Due to the change in workflow (i.e. trial protocol), initial model identification was significantly improved resulting in good glucose control right from the start and a strong improvement of night-time control. Although time in target for day-time control was very good, there were a number of incidents of hypoglycaemia after lunch/before dinner on day 2, possibly caused by overdosing of insulin during meals due to an compensation of the model deviation during meals (predictions often too low) as well as during the decrease in insulin sensitivity in the morning followed by an increase in sensitivity in the afternoon ("dawn-effect", see following Section I.4.3) by the FMPD controller.

Another reason for the suboptimal control during the night, but low amount of hypos in trial #1 compared to trial #2 were the higher rejection rates for dose recommendations (see Section I.4.4).

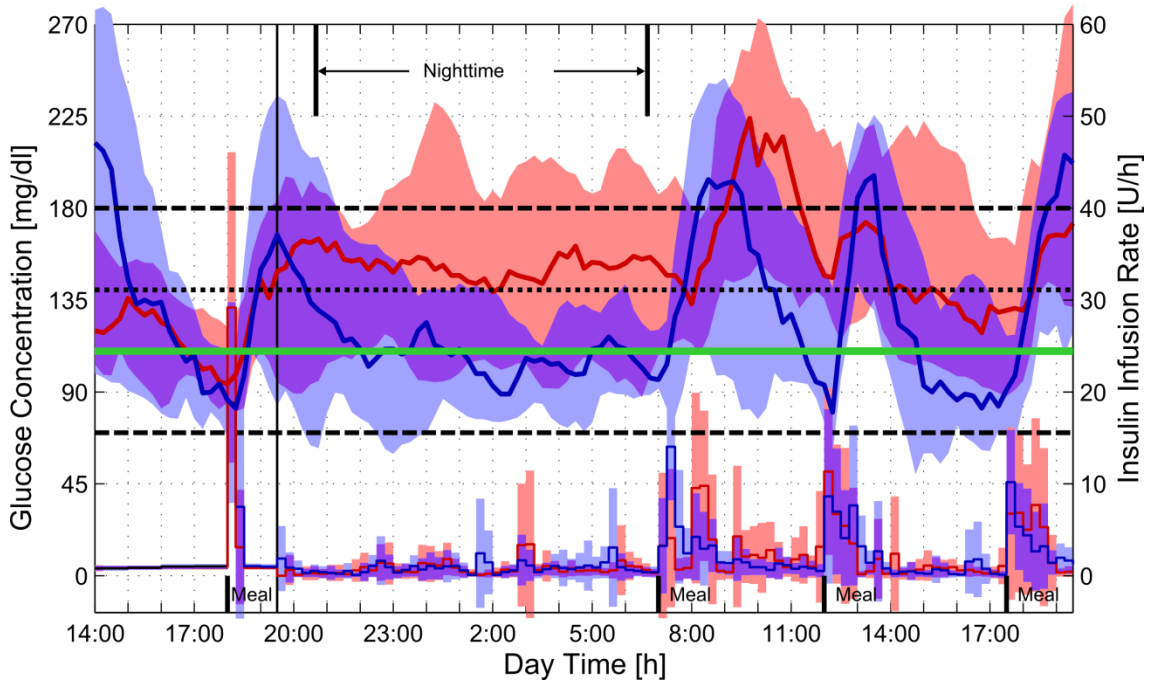

Figure 3: Mean (±SD) of venous peripheral glucose levels and insulin doses for REACTbyALGO1 (n=10, red trajectories and shaded areas) as well as REACTbyALGO2 (n=10, blue trajectories and shaded areas). The mean (SD) of venous plasma glucose (PG) levels with 15-min sampling is shown from all (N=10) 30-h experiments in ten subjects for each trial, respectively. **REACTbyALGO1**: During control (t > 330 min) the maximum in mean PG was 225 mg/dL at 10:00 A.M. after the first breakfast, and the mean nadir was 105 mg/dL at 4:45 P.M. before dinner on day 2. The overall mean of all 30-h PG results (N = 119 measurements per experiment) was 156 mg/dL. The overall mean PG during night-time (10 P.M.–8 A.M.) was 149 mg/dL (N=66 measurements per experiment). **REACTbyALGO2**: During control (t > 330 min) the maximum in mean PG was 205 mg/dL at 7:15 P.M. after the second lunch, and the mean nadir was 85 mg/dL at 12:00 P.M. before lunch on day 2. The overall mean of all 30-h PG results (N = 119 measurements per experiment) was 127 mg/dL. The overall mean PG during night-time (10 P.M.–8 A.M.) was 110 mg/dL (N = 66 measurements per experiment). The four meals are indicated by the black bar at the bottom of the plot. The mean of subcutaneous insulin infusion rates administered by the controller are plotted at lower end of plot (right axis).

I.4.2Insulin PK/PD

We have collected blood samples of insulin to evaluate if the insulin PK properties could be identified from glucose measurements. Dynamic properties of insulin were estimated from glucose response dynamics during the clamp phase and then refined during the trial by model adaptation. Parameters for insulin sensitivity (S_I), renal clearance (GFR^I_{frac}), subcutaneous

degradation (k_{SCD}^{I}), and subcutaneous unspecified binding (Q_{fac}) were identified. No a-priori assumptions on insulin PK parameters were used as compared to other algorithms (26).

In the first trial, for four out of ten subjects (Subjects 01, 03, 04 and 05), insulin PK properties were correctly identified from glucose clamp data before start of control (For all individual plots, see Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**). For all others, insulin half-life was overestimated, except for Subject 09, where it was underestimated. For Subjects 08-10, the qualitative prediction of insulin PK was significantly improved through model adaptation during control.

In the second trial, insulin PK was correctly estimated in 7 out of 10 subjects. For the remaining 3 (Subjects 7-9), the qualitative fit, with respect to t1/2, was still good. This means that insulin PK can be identified from subcutaneous glucose measurements in most cases and at least qualitatively (quantitative mismatch compensated for by insulin sensitivity S_I) in all cases.

I.4.3Endogenous Glucagon PK/PD

We have collected blood samples of glucagon to gain insight in possible dysregulation of glucagon plasma levels and to evaluate the influence of glucagon in glucose control in T1DM within a post-hoc evaluation.

The model used during the trial only assumed plasma glucose regulated endogenous secretion of glucagon resulting in basal glucagon levels throughout, with small variations during high and low glucose.

The retrieved glucagon measurements revealed, however, that for many patients, significant postprandial surges of glucagon levels were observed (Figure 4, and Appendix **Fehler! Verweisquelle konnte nicht gefunden werden.** for all individual profiles). In some patients, Subjects 3 and 4 for trial #1 (early morning until midday on the second day, see Figure 4 for Subject 03 and also Figure 5 for Subject 03 and Subject 04 from trial #1) and Subjects 1, 2, 5-9 for trial #2, glucose values remained significantly above predicted levels. This could be associated to the observed glucagon surges for all subjects except Subjects 5, 6 and 9 from trial #2, for which glucagon levels did not significantly increase.

It has been reported in literature that mixed meals may cause glucagon surges in individuals with T1DM (28, 32). This may be caused by meal composition and especially the protein content of these meals. In T1DM, influence of glucose levels on glucagon secretion subside over time probably due to a deficiency in amylin-mediated intra-islet signalling necessary for glucose sensing (33). Thus, the glucose absorbed from a meal does no longer supress glucagon secretion.

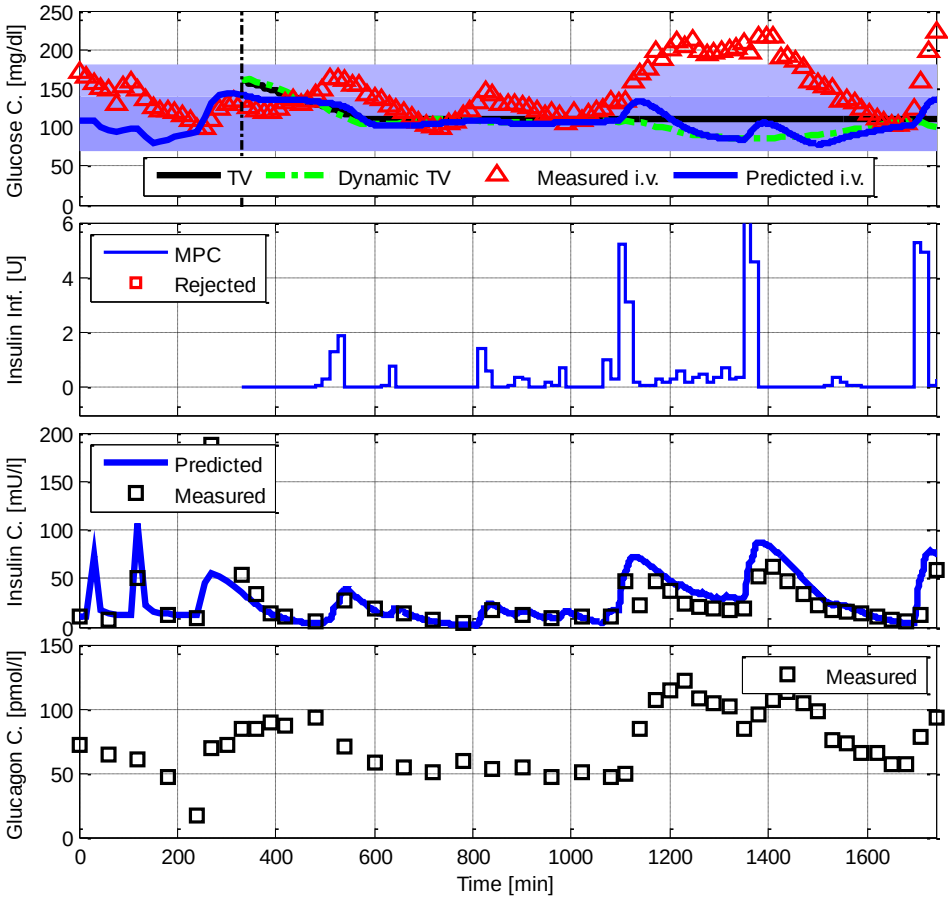

Figure 4: Glucose control experiment in Subject 03. During morning hours and early afternoon (8:00 a.m. (t = 1100 min) until 2:00 p.m. (t = 1100 min)) a systematic error of glucose predictions (underprediction) can be observed. At the same time, a distinct elevation of glucagon (postprandial glucagon surge) has been observed.

The original version of the model as it was used in the control trial was adapted to account for an alternative mode of action for glucagon on liver glucose homeostasis to better describe the observed glucagon dynamics (Figure 5). Incretin-dependent prandial glucagon secretion is modelled dependent on oral meal (glucose) absorption. In addition, a function for glucagon-dependent suppression of hepatic glucose uptake M_{NHGU},) is included which was not accounted for before but as previously hypothesized (17) could be necessary to strengthen the effect of glucagon. Two refitted simulations on Subjects 03 and 04 (From trial#1, Figure 5) are compared, once without and once with the new glucagon mechanistics to illustrate the evaluation and effect of the tested mode of action.

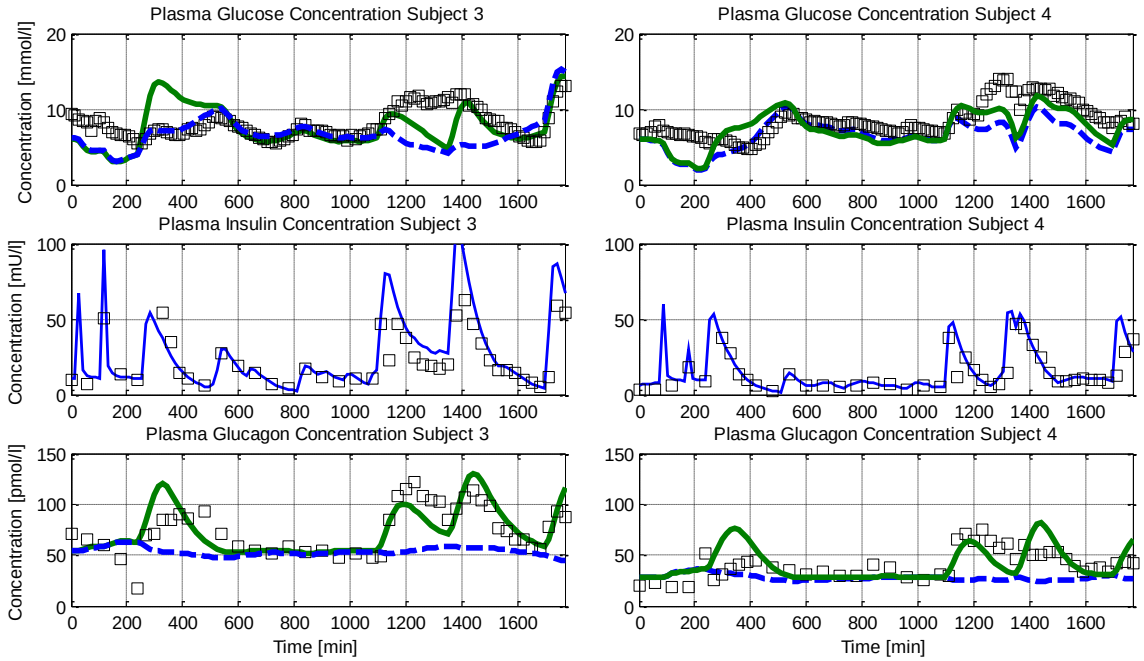

Figure 5: Post-hoc simulation: dynamics of Subject 03 and Subject 04 with the new mechanistics for prandial glucagon secretion and glucagon-dependent suppression of glucose uptake ($\boldsymbol{M_{NHGU}}$).

Although the postprandial glucagon surges are now better captured, the deviations in the morning of the second day (t = 1150 to t = 1400) remain. In return, glucose levels after dinner on day one are now overestimated, as are the underlying glucagon levels.

In the second trial, deviations of model predictions in the morning (possibly “dawn-effect”) were even more prominent, but accompanied by smaller glucagon surges. But as this effect was not associated with glucagon surges in Subjects 5, 6 and 9, and the adapted model, as shown in in Figure 5, could also not fully connect this effect to glucagon, a different explanation was sought. Thorough retrospective analysis of trial documentation of the second trial revealed that these deviations were always accompanied by consumption of coffee with breakfast. And caffeine has been associated with acute insulin resistance (34). However, morning coffee consumption was not documented consistently throughout the trial (only Subjects 1, 6, 8 & 9), limiting the impact of this observation.

I.4.4Adherence to Dose Recommendations

Adherence to dose recommendations by the medical staff during the trial was an issue. For the trial, medical doctors were present to confirm the dose recommendations given by the algorithm. Although the trial protocol provided rigorous rules for the adherence to dose recommendations within a given value range for blood glucose measurements, final decision on the given dose could still be decided on by the physician. In many cases dose recommendations were rejected although individuals were not outside (below 110 mg/dl) the specified range for glucose measurements, but rather within a range for which the recommended dose could have been feasible. An example is Subject 05 (Figure 6). Even though glucose values remain above 140 mg/dl after dinner on the first day (time > 400 min), dose recommendations were not accepted. After a further increase to 180 mg/dl (time = 800

min), a single dose recommendation was accepted but subsequent suggestions were again rejected even though glucose levels did not fall below 140 mg/dl.

This circumstance significantly reduces the impact of the aggregated statistics on the feasibility study (RbA1 in Table 1 and Figure 2). Rejection of dose recommendations in general leads to increased glucose levels and avoids low blood glucose levels. This means, that statistics of RbA1 are biased towards a higher glucose level and a lower risk for hypoglycaemia. This has to be taken into account when interpreting the results.

In the second trial, physicians were instructed to be more rigorous in adherence to the protocol. Thus, almost all, except for 3 time-periods in Subjects 1, 4 and 10, dose recommendations were adhered to. This allows interpretation of the trial results with respect to performance of the control algorithm.

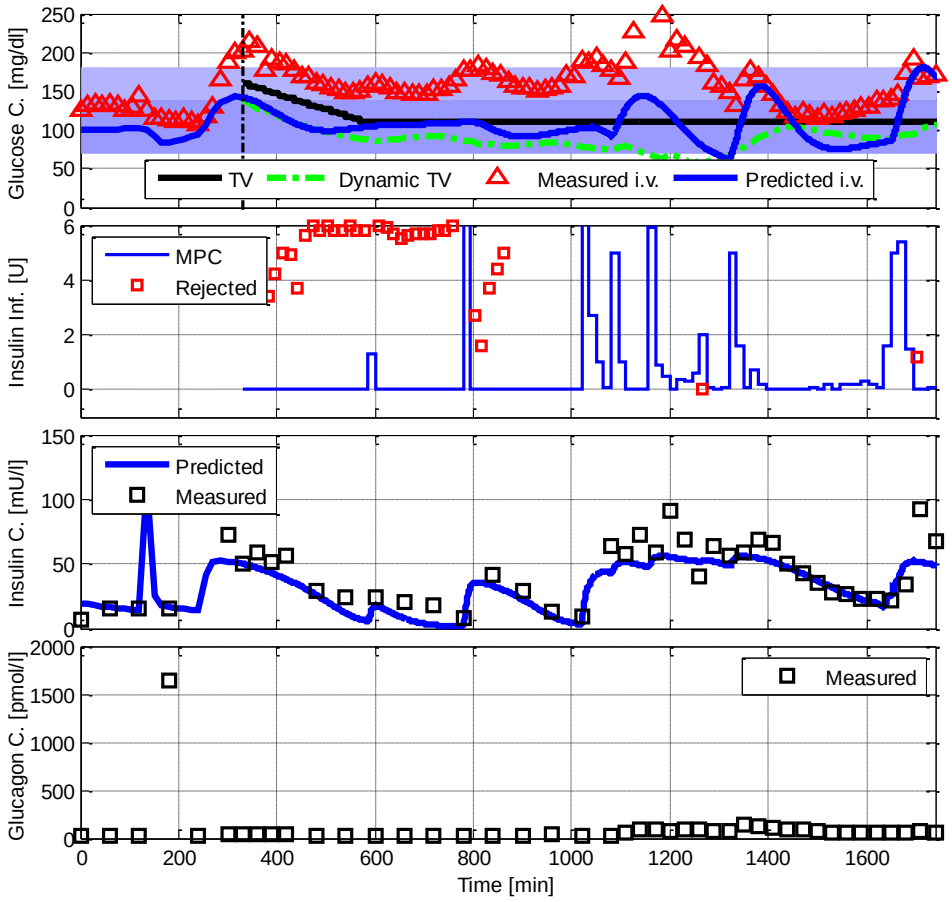

Figure 6: Glucose control experiment in Subject 05. MPC dose recommendations were rejected from the start of control (7:30 p.m., t = 330 min) until 7:00 a.m. (t = 1020 min). Following that, dose recommendations were accepted and control results were good. Two more dose rejection at 11:00 a.m. (t = 1260 min, recommendation of 0 units was raised to 2 units of insulin, unnecessarily as glucose levels were already falling steeply) and 6:15 p.m. (t = 1695 min, 1.2 U recommended, 0 U applied, medical staff was taking no risks for overdose as this was shortly before end of trial).

I.4.5Hypoglycaemia

In the first trial, there were two incidents of hypoglycemia (Glucose < 60 mg/dl, Subject 01 and Subject 02), and both were caused by technical issues.

In the second trial, there were 9 hypoglycaemia incidents caused by the algorithm, most of which occurred before dinner in between 3-5 p.m. (Subjects 2, 4-7 and 10). All of them were related to unpredicted mid-day increase in insulin sensitivity. For some (Subjects 2, 4, and 10) hypoglycaemia incidents occurred at the end of the first day (between 10 p.m. and midnight) due to sub-optimal model fits. A reason for the low number of hypoglycaemic incidents in the first trial is the fact that physicians more often rejected dose recommendations. In the second trial, almost all, except for 3 time-periods in Subjects 1, 4 and 10, dose recommendations were adhered to.

I.4.6Summary

When comparing the different trials and considering the fact that the RbA2 trial uses real s.c. measurements by CGM devices (Dexcom G4 Platinum) with an MARE of 10%, ultimately the controller can compete with current state-of-the-art algorithms and is superior to standard-of-care open-loop control.

The fact that insulin PK was correctly estimated in 7 out of 10 subjects and 10 out of 10 qualitatively shows, that the established workflow for the PBPK/PD model individualization is a feasible approach. In addition, the PBPK/PD approach also helps to reveal yet unexplained phenomena within the system and allows systematic post-hoc analysis thereof (mode-of-action analysis of “dawn-effect”).

An issue was adherence to dose recommendations, limiting the impact of the aggregated statistics on the first feasibility study (RbA1) and the outcomes are biased towards a higher glucose level and a lower risk for hypoglycaemia. This has to be taken into account when interpreting the results. This could be avoided for the second trial.

Overall, it can be said, that a tighter control of blood glucose levels (improved time-in-target) is bought with a higher risk for hypoglycaemia, even more so, if glucose measurements become less accurate and this fact poses the greatest hurdle (safety of control) for commercialization of ACG devices.

I.5 Clinical Trial

The new control approach is evaluated within two clinical feasibility studies. In the first study, as prior information, the controller only requires the individual's physiologic properties (height, weight, gender and age) and the basal rate of the insulin infusion pump prior to trial start. In the second trial, CGM data, collected 24h prior to start of the trial was required for initial model identification, i.e. model individualization. The approach combines a predictive system (MPC) with a reactive system (FMPD), increasing the controller's robustness vs. uncertainty. The controller directly calculates all insulin inputs and does not require (partial) meal-priming boluses of insulin. In the first trial, the controller shows acceptable control performance. Although the latest state-of-the-art systems are developed for s.c. glucose measurements this controller has in a first step been evaluated in a clinical setting with plasma glucose measurements for safety reasons. In the second trial, after thorough in-silico testing, the controller was applied in a control setting using s.c. glucose measurements and achieved very good control performance.

Although the controller has achieved satisfactory results in trial #1, workflow adjustments were required for the second trial. As the controller needs an initial estimate of the individualized model (18) at start of control, clamp data was used for initial model individualization. This step was required as online model adaptation within the algorithm is computationally demanding and does not deliver the required estimates in time by start of control. But data collected during the clamp phase has a high degree of uncertainty due to an unknown initial state. It was assumed that subjects arrived in a well-controlled steady state as they arrived at the clinic in a fasted state, with only the basal rate of their insulin pumps running. However, many subjects arrived in an uncontrolled state with extreme hypo/hyperglycaemia, possibly caused by distress from travelling or from anticipation of the enrolment process (preparation of catheters for clamps and sensor micro-dialysis access catheters), introducing a significant amount of disturbance/uncertainty. Partly, patients then either omitted or reduced basal insulin to correct glucose levels at time of enrolment and required either oral or i.v. glucose or insulin interventions. Also, the use of different insulin during clamp (Aspart, in contrast to the s.c. pump insulin Lispro) could have influenced model identification as insulin properties (PK and PD) of insulin Lispro and insulin Aspart were assumed as being identical, which may not be the case. In addition, conditions for model identification were suboptimal as i.v. clamping does not deliver information on absorption properties of subcutaneous insulin and the s.c. insulin infusion rate was kept constant except for the meal bolus right before start of control. Further, patients arrived in fasted state, omitting lunch. The fasted state itself may be a condition not well described by the model with processes of cellular glucose metabolism (glycogen storage and glucose production) affecting glucose homeostasis. All these criteria make initial model optimization challenging and resulted in below optimal performance of the controller.

Thus, for the second trial, an extension of the observation phase with additional time-data on the effect of s.c. insulin was decided to handle these uncertainties. This new workflow approach was successful, as the controller performance improved significantly. Although this algorithm now requires an initial model fit from a priori glucose measurements, the adapted workflow shows that this approach, by a-priori data collection or a 24h run-in phase for the algorithm, is feasible. Taking into account that long-term core dynamics (17) are stable, and the model can subsequently be adapted for long-term shifts (change in life-style etc.) as long as intra-day variability is structurally captured (glucagon dynamics) or informed (e.g. better meal characterization).

An unresolved issue in this regard is the observed deviations in model predictions on the morning of the second day ("dawn-effect"), possibly associated with meal/nutrition-dependent postprandial glucagon secretion. In most control studies, the dynamics and influence of

glucagon is omitted completely (14, 35). And in glucose control studies which explicitly use exogenous glucagon for glycemic control, these postprandial surges are not discussed as they are not observed in the studied T1DM individuals (16, 17, 26). And in trial #1 the associated model deviations are only observed in the morning, and only in the presence of glucagon surges, but this was not the case for Subjects 05, 06 and 09 from trial #2, where these deviations occurred even though no significant glucagon surges were observed. The observed peak postprandial excursion of endogenous glucagon are comparable to peak concentration levels reached in bi-hormonal control of T1DM (26) for effective treatment of hypoglycemia (27, 36). However, if at all, only in Subjects 03, 04, and 06 (trial #1) and Subjects 01, 02, 07 and 09 (trial #2), the rising glucagon may have caused these deviations, but had not effect on glucose levels in Subject 09 (trial #1) or Subject 10 (trial #2). The fact that a morning rise in glucose has been observed without a simultaneous rise in glucagon and, on the other hand, a rise in glucagon did not cause a simultaneous rise in glucose, indicates other processes involved. In T2DM, it is a well-established rule to calculate a relatively higher dose for breakfast than for later meals (37) to counteract this “dawn-effect”. But also in T2DM (38, 39) (and the elderly (40)) this does not seem to be associated with increased glucagon levels. Also, in healthy, young individuals, the “dawn-effect”, is absent, and even an inverse behavior, with increased morning glucose tolerance (37, 41), is observed, possibly by circadian insulin receptor modulation (40). In trials #1 and #2 conducted here (in T1DM), the effect seems only meal associated and unlike in T2DM (39) does not occur before onset of Breakfast. This effect could thus be a combinatory effect which occurs due to diurnal variations in regulatory hormones such as cortisol, which are known to effect glucose homeostasis and are elevated in the morning (42) and a defective regulation of postprandial intra-islet signaling, e.g. suppression of glucagon secretion by amylin (33) or glucose (29, 43-45) as well as nutrition.

As analyzed here, it is now questionable, if the rise in glucagon or change in metabolism is the main cause for the observed model deviations, as, on the one hand this effect is not observed in all patients, and not during the evening meals and on the other hand does not occur before start of a meal. Rather, nutritional effects, e.g. coffee (34) as the data from trial #2 indicates, are likely to be the cause for these episodes of insulin resistance.

In the second trial, a slight increase in the number of hypoglycaemic events was observed, especially after lunch. Data indicates that the midday increase in insulin sensitivity following the morning episode of reduced insulin sensitivity accompanied by uncertainty in meal absorption leading to a slight insulin overdose are most likely the cause for this. Nevertheless, the model developed here does not use time-variant parameters but rather builds on a mechanistic description of the systemic properties underlying these variations over time. In this regard, in combination with additional experimental studies, the “dawn-effect” in T1DM will have to be further analyzed for a better understanding of the relevant processes and effectors underlying this effect.

I.6 Conclusion

A blood glucose control system has been evaluated that combines a highly predictive whole-body physiology-based pharmacokinetic/pharmacodynamic (PBPK/PD) model (17) within a model predictive control framework and a reactive dose-correction module reacting to unpredictable individual patient behaviour.

As personalized control of blood glucose requires an understanding of the mechanistic properties within an individual subject with T1DM and PBPK/PD models deliver the ideal framework for such ambitious integration of knowledge and information. With all the remaining issues considered, the GIM model presented here shows reliable predictive capabilities, also on a long time frame, once it has been parameterized for the respective individual. The model was developed in such a way that its purpose of use is versatile. The generic modeling concept provides a rigorous framework for individualization (even across organisms), data integration, and model extension for (given the good model predictivity) e.g. mode-of-action analysis. It could thus also be used for 1) fundamental research to uncover physiological properties and the relevance of cellular processes in whole-body physiology, as well as 2) fundamental research on diabetes related drug targets and corresponding pharmaceutical intervention strategies. Last but not least, the model can be used, as it is here, for the 2) prediction and automatic control of blood glucose in T1DM.

And although the automatic control system has been developed for use in a controlled clinical environment and evaluated w.r.t. model uncertainty and carbohydrate disturbances, it would be of interest how the system would cope with sickness, medication, and stress i.e. in an intensive-care setting, or physical exercise. Although, *in-silico* evaluation and results from the feasibility study indicate that the controller can handle significant disturbances. The question for the future here is, how predictive should such a system be if it does not account for all external or internal disturbances to the patient.

Whereas the PBPK/PD model-based MPC approach is a feasible approach to AGC, the modeling framework can also help to better understand the inner working in the body's control of glucose homeostasis. Whereas existing models are built for - and continuously adapted to - an operating point, the model developed here captures glucose core dynamics in a time-invariant and global manner. Nevertheless, a better understanding of individual counter-regulatory mechanisms in extreme situations, e.g. the effect of prolonged hyperglycaemia (glucose toxicity (46)) in Subject 10 (trial #1), or hypoinsulinaemia after insulin under-dosing in Subjects 04, 06, 08, and 10 (trial #1), is required to increase efficiency (robustness and tightness) of glycemic control.

This work demonstrated, that the predictive control approach using PBPK/PD models is well suited for automated glucose control, especially to handle the long dead-time in effect of subcutaneous insulin. The trade-off for highly predictive systems is the computational power they require within a model predictive control setting and the reduced flexibility in case of short-term changes in patient behaviour. Nevertheless, the control approach showed comparable performance to competing approaches with overall promising results and significant improvement after workflow adaptation and improved online model identification.

This work brings a new approach to the AGC (or AP) community by introducing PBPK/PD models as computational kernels for the MPC algorithm. Ultimately, performance of the different systems, be it in terms of predictivity or control performance, which have been developed to date, will only be possible in a head-to-head comparison within the same clinical setting. The PBPK/PD approach has been developed with a perspective towards the increase in data availability on multiple scales and to gain a better understanding of the physiologic processes

involved in the regulation of whole-body glucose homeostasis, as e.g. the role of glucagon during the “dawn-effect”. Until this system can be brought to market it will require additional validation in a wider variation of real-life scenarios and stronger system integration, i.e. miniaturization. Similarly as for an in-silico analysis of predictivity of different model types, comparison of AGC algorithm performances from different trials is problematic and statistically questionable due to the low number of participants, and is only feasible within the same clinical field trial on a large number of individuals. Common practice is a general statistical analysis as done in Section I.4.1 giving a rough estimate of controller performance (30, 47). However it has to be noticed, that boundary conditions during clinical trials may have a strong influence on outcome measures, amongst others: the selected individuals (strong inter-individual variability, requiring a large number of subjects to achieve statistical relevant outcome measures) and trial protocol (especially initial conditions, nutrition and allowed physical activity). This should be considered when comparing different algorithms. Another difficulty for offline-AGC comparison are the additional support or add-on systems like post-sensor signal processing (48) which are not fully disseminated in the public domain.

Even within AP@Home (49), a EU research funded project currently in progress, where two different MPC AGC algorithms (50, 51) are further developed and evaluated, no head to head comparison was conducted within a single field trial. Judging from published trial summaries, a time-in-target value (70-180 mg/dl, corresponding to “target1” in Table 1, of 60 % and time in and hypoglycaemia (< 70 mg/dl) < 5 % is currently the benchmark in AGC; Values which were almost also reached within RbA2 (trial #2) here.

To this state, using predictions of the core dynamics of an individual’s blood glucose levels within the proposed control approach has proven feasible proving that once an individual’s physiologic properties have been captured with the right model parameterization, safe and good control of blood glucose levels is possible.