New Technologies in the Treatment of Type 1 Diabetes

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The following four papers form the basis of the thesis:

I.
Use of an Automated Bolus Calculator in MDI-Treated Type 1 Diabetes: The BolusCal Study, a randomized controlled pilot study
Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B, Nørgaard K
Diabetes Care. 35: 984-990. 2012.

II.
Sensor-Augmented Pump Therapy at 36 Months
Schmidt S, Nørgaard K
Diabetes Technology & Therapeutics. 14: 1174-1177. 2012.

III.
Effects of Everyday Life Events on Glucose, Insulin, and Glucagon Dynamics in Continuous Subcutaneous Insulin Infusion-Treated Type 1 Diabetes: Collection of Clinical Data for Glucose Modeling
Schmidt S, Finan DA, Duun-Henriksen AK, Jørgensen JB, Madsen H, Bengtsson H, Holst JJ, Madsbad S, Nørgaard K.
Diabetes Technology & Therapeutics. 14: 210-217. 2012.

IV.
Model-Based Closed-Loop Glucose Control in Type 1 Diabetes – The DiaCon Experience
Schmidt S, Boiroux D, Duun-Henriksen AK, Frøssing L, Skyggebjerg O, Jørgensen JB, Poulsen NK, Madsen H, Madsbad S, Nørgaard K
Journal of Diabetes Science and Technology. 7: 1255-1264. 2013.

1. INTRODUCTION

In the past decade, interest in the use of technologies in the treatment of diabetes has grown. Two journals focusing solely on research in diabetes technologies have emerged (Journal of Diabetes Science and Technology and Diabetes Technology & Therapeutics) and annual scientific meetings with the same focus have become increasingly popular (Advanced Technologies & Treatment for Diabetes, Diabetes Technology Meeting and Clinical Diabetes Technology Meeting). Furthermore, diabetes technology has also made its entry into the established scientific diabetes meetings (ADA and EASD) in recent years. The expansion in this area of diabetes research and clinical practice is clearly driven by advances in technologies but also patients associations. The Juvenile Diabetes Research Foundation (www.jdrf.org), the leading global type 1 diabetes (T1D) advocacy group, funds the development of diabetes technologies, and one of the group's priority areas is to influence regulatory authorities and insurance companies to give people with T1D access to the latest diabetes management technologies. The selection of treatment tools available to the patients is large and diverse including insulin delivery and glucose sensing devices, various applications for phones and computers, insulin dose calculators and telemedicine-based tools. The launch of these products has long since surpassed the realization of studies testing their clinical efficacy and this leaves the health care provider (HCP) without the evidence base needed to offer proper guidance and perform cost-benefit analyses when met with patient queries and demands.
This thesis gives an introduction to diabetes technologies available to patients in 2012. Special attention is given to devices accessible to Danish patients and devices tested in the studies that form the basis of this thesis.

2. BACKGROUND

2.1 TYPE 1 DIABETES

T1D was already recognized and described 2000 years ago [1]. It was, however, not until the discovery of insulin in the early 1920s that T1D was transformed from a fatal condition into a treatable chronic disease [2]. In T1D the insulin-producing cells of the pancreas are destroyed and therefore patients are dependent on lifelong exogenous insulin administration to maintain metabolic homeostasis. Insulin is essential in blood glucose regulation, but insulin dosing is a fine balance: overinsulinization resulting in

hypoglycemia may cause severe discomfort, seizures, coma, and in worst case death; on the other hand, the acute adverse effect of underinsulinization is diabetic ketoacidosis and prolonged periods of hyperglycemia are associated with diabetic micro- and macrovascular complications. In 1993 the landmark Diabetes Control and Complications Trial (DCCT) demonstrated that intensive treatment of T1D could delay the onset and slow the progression of diabetic retinopathy, neuropathy and nephropathy [3]. In addition, it was established twelve years later that the treatment regimen could also reduce the risk of cardiovascular disease [4]. Intensive treatment included administration of insulin three or more times daily with dosage adjustments according to the result of self-monitoring of blood glucose (SMBG), food intake and activity level. Today, intensive insulin treatment is the recommended therapy for T1D with near-normalization of blood glucose levels and an HbA1c < 7.0% as the treatment goals [5,6]. The benefits of intensive treatment observed in the DCCT, however, came with a three times higher risk of severe hypoglycemia compared with conventional therapy with one or two daily insulin injections. Fear of hypoglycemia keeps many patients from intensive treatment and achievement of recommended glycemic goals and to some it is the main limiting factor in the treatment of diabetes [7]. In addition to hypoglycemia fear, the constant efforts required to manage T1D have major impact on the patients' everyday life. Developments in diabetes technology focus on easing the patient burden of constant diabetes management and on helping patients and HCPs achieve glycemic goals.

2.2 INSULIN ADMINISTRATION

Intensive treatment of T1D is usually administered by multiple daily injections (MDI) of insulin or as a continuous subcutaneous insulin infusion (CSII), i.e. by insulin pump.

2.2.1 Multiple Daily Injections

In MDI therapy, long-acting insulin is injected one or two times daily into the subcutaneous tissue. This insulin covers the body's basal insulin needs. Additionally, rapid-acting insulin is injected several times per day with snacks and meals. Human or analog insulin or a combination of the two can be used in MDI therapy. Insulin analogs are in most cases preferable because of the flatter pharmacokinetic/dynamic profile of the long-acting insulin analogs and the steeper profile of the rapid-acting analogs compared with human insulin. The benefits of analog insulin with regards to HbA1c reduction are minimal; however, they have been demonstrated to reduce the number of hypoglycemic episodes, especially during night time [8].

2.2.2 Continuous Subcutaneous Insulin Infusion

CSII treatment is based on rapid-acting insulin only. A continuous infusion of insulin administered via an insulin pump covers the basal insulin needs and at mealtimes additional insulin boluses are infused via the pump. The delivery of basal insulin is preprogrammed into the pump and basal rates may vary during the course of 24 hours. Most often analog insulin is used in pumps as it has been shown to provide better glycemic control than human insulin based CSII-treatment [9].
In Denmark, 50% of children and 9% of adults with type 1 diabetes are currently using insulin pumps and the numbers are increasing [10]. Reasons for increased insulin pump use include improvements in metabolic control (mean improvement in HbA1c 0.3% – 0.5%; larger effects in patients with high baseline HbA1c), reduction of hypoglycemic episodes compared with MDI, and patient preference [11–13]. Moreover, it has been demonstrated that in the long term the socioeconomic costs of CSII does not exceed the costs of MDI treatment [14].

2.3 GLUCOSE MONITORING

Glucose monitoring is an integral part of intensive treatment of T1D. It is impossible for both patients and HCPs to make rational insulin dose adjustments and evaluate treatment decisions without blood glucose measurements.

2.3.1 Self-Monitoring of Blood Glucose

Patients treated with MDI or CSII should self-monitor their blood glucose at least prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic and prior to critical tasks such as driving [5]. For some patients more frequent glucose monitoring may be needed to achieve glycemic goals safely. Capillary blood is obtained by a finger stick and applied to one of the many different meters (reporting plasma glucose values) available to patients [15]. Large database studies have demonstrated that frequency of SMBG is associated with lower HbA1c-levels [16–18]. Performing SMBG is however not sufficient in itself – patients should of course be trained in interpreting and acting upon measured blood glucose values.

2.3.2 Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) is a supplemental tool to SMBG and can be used in both MDI and CSII therapy. A disposable glucose sensor inserted in the subcutaneous tissue, typically in the abdominal area, measures interstitial glucose values. Every one to five minutes, a glucose value is wirelessly transmitted from the glucose sensor to a receiver device that displays the value on a screen along with graphic presentations of previous values and arrows indicating the direction and rate of change of glucose level. Additionally, the system can be set to alarm when high and low glucose levels are detected [19]. Calibration of a CGM system using a capillary blood glucose value is required, typically twice daily but depending on manufacturer. One of the strengths of CGM is the information richness it provides compared with the point-in-time measurements obtained by SMBG. A limitation however is sensor inaccuracy and despite continued improvements in sensor accuracy, CGM is still limited by a mean absolute relative difference between CGM and YSI glucose values in the range 11.8-20.2% [20]. This is partly caused by the 4- to 10-minute lag time between capillary glucose values and the glucose value in the subcutaneous tissue where the sensor is inserted making sensor inaccuracy particularly pronounced at times of rapid glucose fluctuations [21]. Other factors affecting sensor performance include tissue damage and regeneration following both sensor insertion and minor movements of the sensor during everyday use [22,23]. For treatment guidance in everyday life, CGM systems providing real-time glucose values are used. CGM systems that record glucose values for later download, also

known as blinded CGMs, can be applied for shorter time periods for retrospective identification of glucose patterns [24].
Intensive treatment of T1D combined with CGM can lower HbA1c in adults and reduce time spent in hypoglycaemia [25–28]. A comprehensive meta-analysis suggested that CGM can reduce HbA1c by 0.9 %-point when the baseline HbA1c is 10% and by 0.56 %-point when baseline HbA1c is 7%, provided that CGM is used continuously [29]. For every one day of the week CGM is not in use, the effect on HbA1c is reduced by 0.15 %-point.
Despite the documented effectiveness of CGM, some patients still choose to use CGM less than recommended or discontinue use. Although mechanisms underlying patient adherence to CGM are still not fully understood, CGM adherence has been associated with body image, patient motivation and coping skills [30–32]. Additionally, CGM is a costly therapy and reimbursement policies are still not fully clarified, which may also keep patients from endorsing the technology.

2.4 FLEXIBLE INTENSIVE INSULIN THERAPY

Flexible intensive insulin therapy (FIIT) is a systematic method for insulin dosing. In FIIT, patients adjust insulin dosage according to blood glucose level, food and alcohol intake, exercise level, and health status on a day-to-day basis. This approach contrasts with more traditional practice in which patients are encouraged to adapt their behavior to a fixed insulin regime prescribed by the HCP. Both MDI and CSII users can benefit from FIIT. In DCCT, strict glycemic control was achieved by FIIT in the intensively treated study group [3].
FIIT has been shown to improve metabolic control, quality of life, treatment satisfaction and psychological wellbeing in adults with T1D who participated in the 5-day UK DAFNE training course [33,34]. Furthermore, participants experienced increased dietary freedom from FIIT and this was not associated with deteriorations in cardiovascular risk factors (weight, total cholesterol, HDL cholesterol, triglycerides) [33]. Put informally, FIIT allows patients to eat whatever and whenever they want, nevertheless, they should still comply with general dietary guidelines that also apply to healthy people to get essential nutrients and avoid weight gain. Programs similar to DAFNE are practiced in other countries [35–40], however, in Denmark the use of FIIT has not been widespread and only recently have recommendations on FIIT in the treatment of T1D been included in the national treatment guidelines [6].
Food intake has major impact on blood glucose. Different strategies are used to determine the insulin dose needed to match the effect of a meal. These include carbohydrate counting (CC), exchange systems, Healthy Food Choices and Total Available Glucose. DCCT results documented a 0.5% lower HbA1c in patients who almost always adjusted their insulin dose to food intake using one of these strategies compared with patients who never made adjustments [41]. As the Danish national treatment guidelines recommend CC in meal bolus calculation, focus will be put on CC-based FIIT in the remainder of this thesis [6].
CC is based on the assumption that carbohydrate is the nutrition component with the greatest impact on postprandial blood glucose level and that the effect of protein and fat is negligible. Users of CC must be trained in estimating the amount of carbohydrate (in grams) in a meal [42]. In addition, patients use individualized “rules of calculation” when determining the size of an insulin bolus: the insulin sensitivity factor (ISF) and the insulin to carbohydrate ratio (ICR) [43,44]. ISF is the reduction in blood glucose level induced by one unit of rapid-acting insulin. ICR is the amount of carbohydrate needed to match the blood glucose lowering effect of one unit of insulin. In the situation where the patient measures a blood glucose that is above the target range but does not intend to eat anything the ISF can still be used to estimate the size of a correction bolus that will bring the blood glucose back into target. It may be relevant to adjust a meal or correction bolus further by taking into account factors such as activity level, alcohol consumption, stress and illness. As a starting point, a patient’s personal ISF can be determined by the 100 rule, i.e. by dividing 100 by the total number of insulin units (basal + bolus) injected per day and the ICR can be determined by the 500 rule, i.e. by dividing 500 by the total number of insulin units injected per day [43,44]. Further individualization and diurnal variation of the ISF and ICR may be needed and adjustments can subsequently be made based on work sheets that the patient brings to the clinic. Figure 1 gives an example of insulin dosage estimation using the principles of CC-based FIIT.

$$\frac{9.6\ \frac{\text{mmol}}{\text{l}} - 5.2\ \frac{\text{mmol}}{\text{l}}}{2.2\ \frac{\text{mmol}}{\text{l}}/\text{U}} + \frac{65\ \text{g CHO}}{12\ \frac{\text{g CHO}}{\text{U}}} \times 110\% = 8.2\ \text{U}$$

Figure 1 Example of insulin dosage estimation using the principles of CC-based FIIT. The premeal blood glucose value is 9.6 mmol/l. The target blood glucose is 5.2 mmol/l. The insulin sensitivity factor is 2.2.mmol/l/U. The meal contains 65 grams of carbohydrate (CHO). The insulin to carbohydrate ratio is 12 g CHO/U. The patient has a mild cold and therefor the insulin need is increased by 10%.

2.5 BOLUS CALCULATORS

A bolus calculator is a device that facilitates insulin dosage estimation. A wide variety of bolus calculators is available to patients ranging from simple cardboard wheels to electronic pocket calculators, bolus calculators with integrated blood glucose meters, apps for smart phones and telemedicine products [45–51]. All insulin pumps of today have advanced built-in bolus calculators. Bolus calculations are based on current blood glucose, target blood glucose, ISF, ICR and total grams of carbohydrate in the meal as described in section 2.4. However, only insulin pump bolus calculators and two recently introduced automated bolus calculators (ABCs) for MDI-treated patients include insulin on board (IOB) in the calculations, i.e. the amount of active insulin that remains in the body from previous boluses [45,51]. Without an IOB function the patient may end up “stacking” insulin, potentially leading to hypoglycemia [52]. Another advantage of these new and advanced ABCs is the memory function. Blood glucose values, insulin doses and other input are stored in the device memory and can be reviewed by both patient and health care professional. In popular terms, the ABC is a logbook that automatically fills.
Although, FIIT is a systematic method for insulin dosage adjustment based on simple math as demonstrated above, to many patients the resulting equations may still be too complicated to manage in everyday life. Poor numeracy skills are common also in patients with T1D and associated with worse glycemic control than that of patients with higher levels of numeracy [53,54]. Even when the exact amount of carbohydrate in a meal was given to

201 patients, 114 (57%) came to a false result by manual insulin dose calculation [45]. However, when provided with a bolus calculator the proportion of false results was reduced to 7%. Use of a bolus calculator reduces the number of correction boluses and the amount of carbohydrate required to compensate for post-prandial glycemic excursions and equally important, it reduces fear of hypoglycemia [55,56].
Only few studies of bolus calculator use have been published and the results are diverging. Some of the publications reported improvements in HbA1c of up to 0.9% whereas others found no effect of bolus calculators on metabolic control [46,47,49–51,57]. An increase in frequency of hypoglycemic episodes has been demonstrated in only one study of a device that was never launched in the market [48]. The authors concluded that the underlying cause of this was the lack of an IOB function in that particular device.
A bolus calculator is no panacea. The effects of bolus calculators are limited by user skills, which is a factor that also affects bolus calculator study outcomes. Even with the most advanced devices valid information must be given to the bolus calculator to get valid insulin dosage advice. Prerequisites for success are that correct carbohydrate information is given to the calculator, that SMBG is performed correctly and that the patient has insight into and takes appropriate precautions regarding other factors affecting blood glucose, e.g. physical activity. Furthermore, the competences of the diabetes HCP team in providing patient education and adjusting ISF, ICR and basal insulin may also affect the outcomes of bolus calculator use.

2.6 SENSOR-AUGMENTED PUMP THERAPY

Sensor-augmented pump (SAP) therapy is the combined use of the most advanced insulin administration method, i.e. CSII, and the most advanced glucose monitoring system, i.e. CGM. In a SAP, the insulin pump doubles as receiver for the CGM and glucose values and curves are displayed on the pump screen. SAP therapy has the potential to improve glycemic control and treatment satisfaction in adults with sub-optimally controlled T1D as well as reduce fear of hypoglycemia and magnitude of diabetes-related problems [27,28,58–67]. The largest randomized study to date comparing SAP with MDI therapy documented an improvement in HbA1c of 0.6% in SAP patients compared with MDI-treated patients and the study further suggested that the effects of the combined use of CSII and CGM were greater than that of CSII or CGM alone [63].
The SAP insulin infusion set and the glucose sensor are two separate components and patients are recommended to insert the two at least five centimeters apart. However, a new product combining the insulin infusion and the glucose sensing function in one component is currently being developed and tested in patients [68]. In this product the overall size of devices and adhesive attached the patients' body is reduced, which is a matter of great importance to user satisfaction and treatment adherence [30–32].
Only one SAP system, Paradigm Veo (Medtronic, Northridge, CA), has functionally integrated the CGM and the pump, such that the pump automatically suspends the basal insulin delivery for up to two hours if hypoglycemia is detected by CGM and the patient does not respond to the hypoglycemia alarm. Automatic basal insulin suspension has been demonstrated to be safe and reduce hypoglycemia exposure [69–73]. The next step towards an artificial pancreas is a SAP that automatically suspends the basal rate already when hypoglycemia is predicted based on the glucose value and the trend of the glucose curve [74].

2.7 CLOSED-LOOP GLUCOSE CONTROL

The SAP automatic basal rate suspension is a step forward in the development of a fully closed-loop (C-L) glucose control system, also known as an artificial pancreas. For more than 50 years a C-L system has been the ultimate goal in T1D technology research since such system is expected to revolutionize treatment by optimizing glycemic control and freeing the patient from the burden of constant treatment decision making [75]. A C-L system consists of a glucose sensor, a mathematical control algorithm and an insulin delivery device. In brief, the glucose sensor transmits glucose values to the control algorithm and based on the continuous stream of glucose values, the algorithm regulates insulin dosing via the insulin delivery device (Figure 2).
At present, no off-the-shelf C-L system exists. With currently available glucose sensors and insulin delivery devices, the subcutaneous-subcutaneous approach to C-L glucose control, i.e. use of CGM and CSII, has the greatest potential for commercialization and is also the approach applied by most C-L study groups [76–82]. Still, each C-L group has a unique approach with differences in choice of CGMs and insulin pumps, computers running the control algorithm, mathematical methodologies implemented in the control algorithm and different platforms communicating data between system components. Some groups have added further components to their systems including patches heating the insulin delivery site for faster insulin absorption and supplemental drugs such as glucagon, amylin and GLP-1 [83–85].

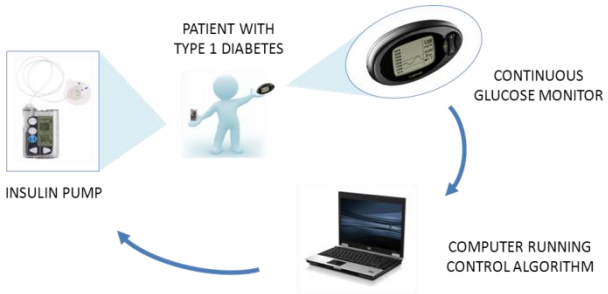

Figure 2 Closed-loop glucose control system.

2.7.1 Closed-Loop Control Algorithms

Various mathematical methodologies have been explored in the construction of glucose control algorithms [86], however, two methodologies are mainly used: proportional-integral-derivative (PID) control and model predictive control (MPC). In PID control, insulin dosing is regulated based on deviations from the target blood glucose level (proportional component), area under the curve between the measured and the target blood glucose level (integral component) and blood glucose level rate of change (derivative component) [87]. PID algorithms can be categorized as reactive as they respond to changes in glucose levels over time. MPC, on the other hand, can be categorized as proactive because insulin dosing is regulated based on predictions of future glucose levels. MPC algorithms include a model of human glucose meta-

bolism and they compensate well for the delays associated with subcutaneous glucose sensing and insulin delivery [75,88].

2.7.2 Virtual Closed-Loop Studies

Clinical testing of C-L systems is resource-demanding. Computer-based simulations in a virtual environment – also known as in silico testing – are an alternative to time-consuming, costly clinical C-L studies and they are not restrained by ethical patient considerations [89,90]. C-L simulation studies can be used to evaluate and optimize mathematical control algorithms, and run-to-run specifications of study protocol, study population, method of glucose measurement and insulin delivery as well as outcome measures can be made. Even hazardous scenarios can be tested in the virtual T1D population. In 2008 the American Food and Drug Administration approved a T1D simulator as an alternative to animal trials for pre-clinical C-L studies [91]. Despite proven efficacy of in silico testing, good insilico performance does not guarantee good in vivo performance. The virtual patients are developed based on models of glucose-insulin dynamics; however, they do not fully reflect the complexity of human metabolism and do not include complex mechanisms such as hypoglycemia counterregulation [90]. Furthermore, often the models of glucose-insulin dynamics are derived from data collected during studies of non-diabetic subjects [92]. Improvements of current simulation environments have been proposed and a simulation environment based on T1D data including several of the hormones involved in glucose metabolism is under construction [89,93].

2.7.3 Clinical Closed-Loop Studies

The first clinical study of a C-L system based on subcutaneous glucose sensing and subcutaneous insulin delivery was published in 2006 [76]. Since then, several study groups have entered the field of C-L research and increasingly more complex study protocols are performed. Studies of up to 36-hours have investigated C-L glucose control in different situation including food and alcohol intake, exercise and corticosteroid administration and study subjects were both children, adults and pregnant women [77,78,80,82,84,85,94–102]. Until now, all studies have been carried out under close surveillance but out-patient C-L studies are under preparation [103–105].
Despite the increasing number of C-L studies performed and despite initial positive results that have encouraged further research in the field there are still major obstacles to overcome before a fully C-L system becomes a reality: 1) As recognized by all study groups, CGM accuracy and reliability needs to be improved. The control algorithm doses insulin based on input from the CGM and if the input is false and blindly trusted there is a high risk that the system will induce hypo- or hyperglycemia. Various strategies for coping with this challenge have been suggested, e.g. the use of multiple CGMs or alternative sensing technologies. 2) The time from insulin administration to insulin action and – not least – the intra-individual variation in this delay is a challenge to most controllers. Different attempts to reduce the time delay and the variation have been proposed such as insertion site heating and addition of hyaluronidase, but faster acting insulin is desirable and new insulin formulations are being developed [106,107]. 3) Control algorithms need to be further developed. To date only small meals can be handled by controllers without running the risk of postprandial hypo- and hyperglycemia and most controllers need meal announcement. A C-L system that requires meal announcement may perform well in the lab when the exact carbohydrate content of the meal is known and given to the system at an appropriate time, but if the same system is to be used in everyday life, performance would rely on the patient's ability to count carbohydrates and on the patient giving this information to the system timely. Such system is referred to as semi-automatic C-L control because it cannot function without patient interaction. In addition, control algorithms that can capture and handle the increased insulin sensitivity induced by physical activity are also needed. To meet the reduction in insulin demand the C-L system should reduce insulin supply at the beginning of or perhaps even prior to the exercise session. The latter would again rely on the patient announcing planned activity, i.e. semi-automatic C-L control, but the former may be achieved by connecting an accelerometer to the C-L-system. 4) Still more C-L study groups have developed dual-hormone systems [78,85,97,108]. These systems have a second pump for glucagon infusion in case of imminent hypoglycemia. Encouraging study results have been obtained by this approach mimicking the hormonal interplay of non-diabetic people; however, currently available glucagon formulations are only approved for use immediately after reconstitution as they form fibrils over time which until further limits dual-hormone systems to in-clinic study use only.

3. STUDIES

3.1 USE OF AN AUTOMATED BOLUS CALCULATOR IN MDI-TREATED TYPE 1 DIABETES: THE BOLUSCAL STUDY, A RANDOMIZED CONTROLLED PILOT STUDY

3.1.1 Background and Aim

The benefits of FIIT have long been established, nevertheless only few Danish T1D patients practice the method except those treated with CSII. It may be that the relative complexity of FIIT equations is a barrier to MDI-treated patients whereas CSII-treated patients enjoy the benefits of the bolus calculator integrated in the insulin pump. A recently launched ABC (Accu-Chek Aviva Expert; Roche Diagnostics, Mannheim, Germany) targeted MDI-treated patients provides bolus advice based on the current blood glucose (it has an integrated blood glucose meter), target blood glucose, ICR, ISF, IOB, time of day, carbohydrates to be consumed, exercise level and health status (Figure 3). We hypothesized that non-optimally MDI-treated patients with T1D could achieve better metabolic control, quality of life and treatment satisfaction by CC-based FIIT and that metabolic control could be further improved by concurrent use of the ABC. Additionally, we wanted to test the feasibility of teaching CC-based FIIT in only four hours (3-hour group teaching + 1-hour individual follow-up session).

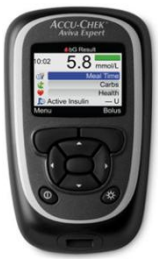

Figure 3
Automated Bolus Calculator. Accu-Chek Aviva Expert is a trademark of Roche. © Roche 2012.

3.1.2 Methods

We designed at 16-week randomized controlled study with three parallel study arms: a control arm (Control) that continued MDI-treatment with empirical insulin dose estimation; an intervention arm (CarbCount) that continued MDI-treatment but were trained in FIIT; and a second intervention arm (CarbCountABC) continuing MDI-treatment but with the use of FIIT and the ABC. The primary study outcome was change in HbA1c from baseline to 16 weeks. Secondary study outcomes included change in distribution of glucose values assessed by one week of blinded CGM (iPro2; Medtronic, Northridge, CA) at baseline and end of study as well as psychosocial measures assessed by diabetes-specific questionnaires: the Diabetes Treatments Satisfaction Questionnaire [109], the Audit of Diabetes Dependent Quality of Life [110], the Problem Areas in Diabetes Questionnaire [111], and the Hypoglycemia Fear Survery [112].
The power calculation was based on the assumption that HbA1c would not change in Control but that there would be a marked decrease in HbA1c in CarbCount of 0.8% and an even greater decrease in CarbCountABC of 1.2%. We wanted to compare changes in outcomes between all three study arms (ANOVA) as well as between the two intervention arms (Student t-test). Consequently, we allocated patients to the three study arms in a 1:3:3 ratio.
Irrespective of group allocation, patients received the same amount of attention from the diabetes team. After screening they all participated in a 3-hour group teaching session held by a diabetes nurse and a dietician. Control received general diabetes training, CarbCount received the same general diabetes training plus training in CC-based FIIT, and CarbCountABC received the same general diabetes training, training in CC-based FIIT and were provided with the ABC.
The general diabetes training included guidelines for a healthful diet as recommended by the Danish Ministry of Food, Agriculture and Fisheries, information about appropriate SMBG and insulin injection techniques, insulin profiles and the effects of exercise, illnesses, menstrual periods, alcohol intake and stress. Patients in Control were encouraged to make day-to-day insulin adjustments, but they were not provided with 'rules of calculations', i.e. ISF and ICR. In practice, this meant that they would use the meal dose recommendations provided by their physician as a starting point and then add or subtract insulin if the premeal blood glucose was out of target range or if the meal differed in size from their average meal. The contents of the general diabetes training were similar to the one-on-one training that we normally provide to T1D patients attending our clinic and it was primarily intended as a brush-up.
The CC training included both theory and hands-on sessions, and ISF and ICR were calculated for each patient.
Two weeks after the group teaching participants attended a 1-hour follow-up session with a diabetes nurse and a dietician. At four weeks and ten weeks participants received a phone call from a diabetes specialist and finally at 16 weeks they attended an end-of-study visit. During all contacts basal and bolus insulin as well as ISFs and ICRs were adjusted if needed based on 3-day work sheets filled out by the patients in advance.

3.1.3 Results

We included 63 FIIT-naïve patients with long-standing, poorly controlled T1D in the study. Twelve patients (19%) dropped-out before 16 weeks. The 51 patients who completed the study had the following characteristics at baseline: female sex, 49%; age, 42 ± 10 years; BMI 26.5 ± 4.2 kg/m2; diabetes duration 19 ± 10 years; HbA1c 9.0 ± 0.7%. All were treated with analog insulin and following a basal-bolus regime. There was no significant between-group difference in patient characteristics at baseline, however, despite randomization there was a clinically important difference in HbA1c (Control 9.1%; CarbCount 9.2%; CarbCountABC 8.8%). As a consequence of the between-group difference in HbA1c, we adjusted for baseline HbA1c and found a borderline significant (P = 0.056) difference in change in HbA1c between all three study arms, however there was no difference between the two intervention arms. Within CarbCount and CarbCountABC there were significant changes in HbA1c of -0.8% (P = 0.001) and -0.7% (P < 0.001), respectively, but there was no change in HbA1c in Control (-0.1%, P = 0.795).
By comparing CGM recordings obtained at baseline and 16 weeks, we found no significant between-group changes in distribution of glucose values. Nonetheless, all changes within CarbCountABC were in favor of better glycemic control. Time spent in hyperglycemia (>7.8 mmol/l) was also reduced in CarbCount at 16 weeks; however, this was at the cost of more time spent in hypoglycemia (< 3.9 mmol/l). The number of self-reported episodes of mild and severe hypoglycemia did not differ between study arms.
At the end-of-study consultation we asked patients to report their use of the principles of FIIT by marking a scale from 0 to 100%. Average use was 70% of time in CarbCount and 89% in CarbCountABC (P = 0.010).
Diabetes Treatment Satisfaction Questionnaire scores exhibited an interesting pattern. From baseline to two weeks, questionnaire scores improved significantly in both CarbCount and CarbCountABC. However, from two weeks to 16 weeks, further significant improvements were seen in CarbCountABC whereas questionnaire scores deteriorated significantly in CarbCount, although they did remain significantly improved compared with baseline scores. Treatment satisfaction scores improved slightly but not significantly during the study in Control. The changes described resulted in overall significant differences in change in diabetes treatment satisfaction scores between all three study arms as well as between the two intervention arms.
Questionnaires did not demonstrate any changes in fear of hypoglycemia, problem areas in diabetes or diabetes dependent quality of life.

3.1.4 Discussion and Conclusions

The BolusCal Study documents clinically important effects of FIIT in poorly controlled MDI-treated T1D patients; however, we could not demonstrate an additional metabolic effect of ABC use as initially hypothesized. Nevertheless, treatment satisfaction was greater in CarbCountABC than in CarbCount at 16 weeks.
Our results are similar to the outcomes of a 6-month study of a telemedicine system, the Diabetes Interactive Diary, which included a bolus calculator [46]. One-hundred-thirty patients (81% MDI-treated; 19% CSII-treated) who had no previous education on FIIT were randomized to two groups: FIIT with and without the Diabetes Interactive Diary. The average change in HbA1c was -0.5% with no difference between the two groups. However, change in Diabetes Treatment Satisfaction Questionnaire score was significantly greater in the Diabetes Interactive Diary group than in the non-user group.
BolusCal was a small pilot study of only 16 weeks. Retrospectively, the pre-study power calculation was overoptimistic and larger studies are needed to ultimately determine the effect of

the ABC. Long-term studies of ABC use are also needed to determine whether the beneficial effects obtained during BolusCal are persistent or if they will diminish as the patients return to routine clinical practice. We tried to assess and account for the Hawthorne effect by including a control group that received the same amount of attention from the study team as the intervention groups, however, as the study was un-blinded patient behavior may still have been influenced by group allocation. Large and long-term studies could also determine whether the improved treatment satisfaction in patients practicing technology-assisted FIIT mediates increased long-term treatment adherence compared with patients using standard methods for FIIT such as mental calculations or pen and paper. The significant difference in use of the principles of FIIT found in BolusCal indicates that this may be the case.

Although the inclusion criteria were wide, the patients studied still represent a selected group. Additionally, 61 eligible patients declined to participate and 12 included patients dropped-out or were excluded before 16 weeks. This means that the BolusCal Study outcomes may not be transferable to the T1D population in general, but only to those who are willing to change their current treatment regimen and for a period invest a little extra time in their diabetes care. In the evaluation of the BolusCal Study results, the limitations of bolus calculators discussed in section 2.5 should also be kept in mind, i.e. that patients' CC skills and general T1D self-care may have affected study outcome.

We chose to test the feasibility of teaching FIIT in a 3-hour training course for two reasons: Firstly, we wanted other clinics to be able to adopt our FIIT teaching approach and only few clinics can allocate resources for patient courses of several days' duration. Secondly, we assumed that the target population, i.e. patients who had long been in poor metabolic control, would not prioritize to spend long time on diabetes training.

It would have been interesting to investigate the association between numeracy and change in HbA1c in CarbCount and CarbCountABC and assessment of numeracy should be performed in future studies.

In conclusion, in a 16-week pilot study of use of CC-based FIIT and an ABC in poorly controlled MDI-treated T1D, we found beneficial metabolic effects of FIIT but no additional metabolic effect of concurrent ABC use. However, ABC use improved treatment satisfaction significantly. In addition, we demonstrated that the principles of FIIT can be effectively communicated during a 3-hour group teaching session combined with a 1-hour individual follow-up session.

3.2 SENSOR-AUGMENTED PUMP THERAPY AT 36 MONTHS

3.2.1 Background and Aim

From 2007 to 2009, 24 adults with poorly controlled T1D were recruited from the diabetes clinic at Copenhagen University Hospital, Hvidovre into the 26-week European multicenter Eurythmics Trial investigating the effects of SAP (Paradigm® REAL-Time System; Medtronic, Northridge, CA. Figure 4) compared with MDI therapy [62]. Of the 24 patients, 13 were randomized to the intervention group and started SAP therapy while 11 were randomized to the control group continuing MDI therapy. After completion of the Eurythmics Trial, the 13 Danish patients from the intervention group were offered to continue SAP therapy and the 11 Danish patients from the control group were offered to start SAP therapy; all 24 patients accepted the offers. The cost of SAP devices and consumables was covered by public health services. To study the long-term effects of SAP therapy we assessed SAP use, metabolic control and psychosocial factors 36 months after SAP initiation in the 24 Danish patients who had previously participated in the Eurythmics Trial.

Figure 4
Sensor-augmented pump. Paradigm REAL-Time System is a trademark of Medtronic.

3.2.2 Methods

All 24 patients were invited to participate in this 36-month follow-up study. Invitations were sent out approximately 27 months after SAP initiation. One patient did not respond; 23 patients gave informed consent to participation, however, one person died before completion of the follow-up period from a condition unrelated to his diabetes113. Of the remaining 22 patients, 16 were still using SAP at 36 months whereas six had ceased SAP use. Five of the six non-users were using the insulin pump only and one patient had returned to MDI therapy. We collected HbA1c values from medical records from three years prior to SAP initiation, from SAP initiation to follow-up study entry and prospectively until 36 months. We downloaded the patients' insulin pumps at 33 and 36 months thus obtaining data from a total of 6 months and additionally at 36 months we distributed diabetes questionnaires that had also been distributed in the Eurythmics Trial (the Diabetes Treatment Satisfaction Questionnaire109, the Hypoglycemia Fear Survey112, and the Problem Areas in Diabetes questionnaire114).

3.2.3 Results

In the 16 patients still using SAP therapy at 36 months, HbA1c decreased from 8.8% to 7.0% in the first six months of SAP use ($P < 0.0001$). From six months to 36 months an insignificant increase in HbA1c of 0.3% was observed ($P = 0.067$) but the 36-month HbA1c value remained significantly different from the baseline value ($P < 0.0001$) (Figure 5).

Surprisingly, HbA1c-levels at 36 months did not differ between patients still using SAP (7.3%) and the four patients (pregnant woman excluded) using the insulin pump only (7.1%). The self-reported duration of SAP use in the former SAP users varied greatly (mean 13.0 ± 9.3 months).

Diabetes Treatment Satisfaction Questionnaire scores improved significantly from SAP initiation to 36 months in the 16 SAP-users (from 23.1 to 32.1; $P < 0.0001$) and significant improvements in Problem Areas In Diabetes questionnaire scores were also observed (from 27.0 to 16.2; $P = 0.013$). Hypoglycemia Fear Survey scores improved (from 25.8 to 20.3; $P = 0.152$), however, changes were neither statistically significant nor clinically important, i.e. changes were less than half the baseline standard deviation.

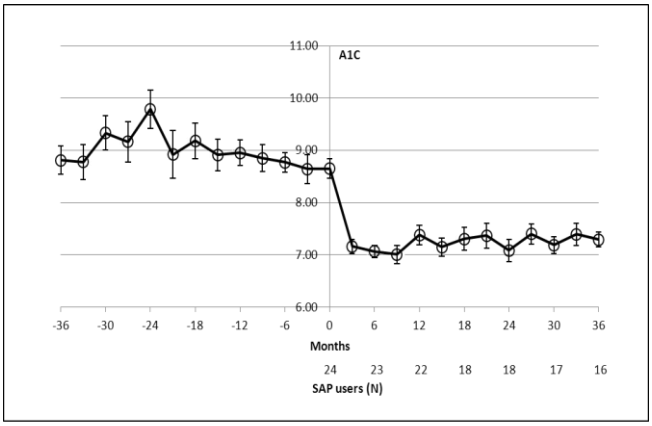

Figure 5 Glycated hemoglobin (HbA1c) 36 months before and after sensor-augmented pump (SAP) therapy start (0 month). Data are mean ± SEM (bars) values.

3.2.4 Discussion and Conclusions

This study demonstrates that significant and clinically relevant improvements in glycemic control, treatment satisfaction and perceived magnitude of diabetes related problems are present 36 months after SAP initiation. Though small, this study presents novel information as it has the longest follow-up of all SAP studies published to date. After completion of the Eurythmics Trial the 24 Danish patients attended quarterly visits at our diabetes clinic and the results largely reflect the effects of SAP therapy in routine clinical practice.

It was an unexpected finding that the four patients who had ceased SAP use and were using the insulin pump only had HbA1c-levels comparable to the 16 current SAP users. It is however impossible to draw any conclusions based on this sample of non-users because of sample size and the variation in duration of SAP use. One could claim that the effect of SAP is no different from the effect of insulin pump use without CGM but this would be in contrast with the results of large randomized studies [61,66,115]. An alternative hypothesis could be that during SAP use, patients gained important insights into their diabetes disease and that they were able to use this information and therefore maintain good metabolic control even after terminating SAP use. Still this is also in contrast with published studies demonstrating that CGM termination and intermittent CGM use are associated with loss of glycemic control [29,115]. What we can conclude from this follow-up study is that a group of T1D patients who had long been in poor metabolic control achieved significant and clinically important metabolic and psychosocial benefits from SAP initiation and that these benefits are maintained at 36 months.

3.3 EFFECTS OF EVERYDAY LIFE EVENTS ON GLUCOSE, INSULIN, AND GLUCAGON DYNAMICS IN CONTINUOUS SUBCUTANEOUS INSULIN INFUSION-TREATED TYPE 1 DIABETES: COLLECTION OF CLINICAL DATA FOR GLUCOSE MODELING

3.3.1 Background and Aim

Models of glucose metabolism are used in the development of simulation environments and control algorithms for C-L glucose control. Although blood glucose regulation is complex and affected by multiple factors such as meals, physical exercise and health status, most models are simple and include only few of these factors [89,91]. Some models are even developed by extending data from healthy persons or persons with type 2 diabetes [116]. The aim of this study was to collect data for the development of improved and more advanced models of T1D glucose metabolism using a novel study design. Models should of course be able to reflect everyday life of T1D patients but because ambulatory data are unsuitable for modeling purposes – they are noise corrupted and events of interest are often introduced in an inappropriate order – we designed an in-clinic study mimicking everyday life events and collected high quality data under controlled conditions.

3.3.2 Methods

The clinical study consisted of 24 unique study days with three everyday life events influencing blood glucose. There were no repeat events on the same day. The modified factorial study design is depicted in figure 6 and the events are described in table 1.

The first event of a study day was always a un-bolused or under-bolused meal. The following event was introduced 2.5 hours later and was either a bolus or a 20-min bout of exercise. The last event of the day introduced after another 2.5 hours was an insulin bolus, an exercise bout or a snack. The meal, bolus and the exercise events had two levels (Figure 6 and Table 1). We included 12 T1D patients and each patient participated on two days separated by at least three weeks performing two randomly assigned event sequences.

We took 10-min plasma glucose measurements throughout the study. Blood samples for insulin, glucagon, growth hormone, cortisol and catecholamine analysis were drawn every 10 minutes for the first 30 minutes after an event, then every 30 minutes. In addition, interstitial glucose measurements were obtained every 5 minutes by CGM. Insulin was administered via the patients' insulin pumps and basal insulin was dosed according the patients' usual basal rate pattern. To measure energy expenditure, patients wore a small device on their chest recording heart rate and acceleration (Actiheart; CamNtech Ltd., Cambridge, UK). Exercise was performed on a treadmill.

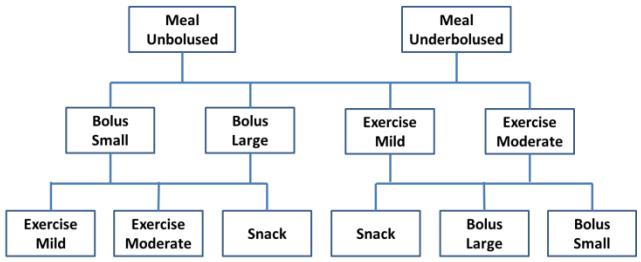

Figure 6 Study design

Event type	Level	Description	No of sequences in which event appears
Meal	Un-bolused	Solid meal w. drink. 1g CHO per kg body weight. No meal bolus.	12
	Under-bolused	Solid meal with drink. 1g CHO per kg body weight. 50% reduction of meal bolus.	12
Exercise	Mild	0.5 x (max HR - resting HR) + resting HR	10
	Moderate	0.7 x (max HR - resting HR) + resting HR	10
Bolus	Small	Bolus estimated to lower PG by 3 mmol/l	10
	Large	Bolus estimated to lower PG by 6 mmol/l	10
Snack	N/A	Liquid meal. 0.4g CHO per kg body weight	8

Table 1 Description of study events and event levels. CHO, carbohydrates. HR, heart rate. PG, plasma glucose.

3.3.3 Results

The characteristics of the 12 patients (75% female sex) included were the following (mean ± SD): age 34.3 ± 9.1 years; BMI 25.1 ± 4.3 kg/m2; diabetes duration 16.5 ± 10.2 years; HbA1c 6.7 ± 0.4%; total daily insulin dose 0.63 ± 0.11 U/kg.
Plots of plasma glucose, CGM and hormone values as well as energy expenditure for each individual study day can be found in appendix B.

3.3.4 Discussion and Conclusions

We set up this study to gather information-rich data for the development of advanced models of the glucoregulatory system to be used in model based control algorithms and simulation environments. The modified factorial study design used in this study has not been widely applied in medical clinical research. Our choice of study design was driven by the aim of the study, i.e. to collect information-rich data, as well as resource and ethical concerns, i.e., we wanted to obtain as much data as possible from each patient within one study day.
It has been pointed out that the highly controlled conditions in the lab where events are introduced one at a time do not reflect the unevenly and sometimes unpredicted introduction of events in real life [117]. However, models cannot be developed from chaos. First the individual contribution of each event must be identified, but later, when the model is finished, chaos can be simulated.
From a clinical perspective one could argue that the different events on the study days were overlapping, i.e. the effect of one event was still influencing glucose homeostasis when the next event in a sequence was introduced. For instance, the effect of an insulin bolus is approximately four hours, yet there were only 2.5 hours between each event. Looking back it might have been worthwhile separating the three events on each study day more; still with advanced statistics it is possible to identify the effects of one event even though a subsequent event is introduced.
In addition to gathering data for modeling purposes, this study provided new insights into the glucose dynamics of CSII-treated patients. We obtained detailed profiles for each patient of hormones involved in the regulation of plasma glucose (appendix B). Reactions to food intake and insulin bolus administration were as expected, however it was a somewhat surprising finding that plasma insulin concentration increased during exercise. This finding – if replicable – may impact future models for glucose control and simulation. Exercise-induced increases in plasma insulin concentration have previously been observed [118–123]. The mechanisms responsible for the mobilization of subcutaneously administered insulin have been heavily debated nevertheless consensus has not been reached. One prevailing theory is that a pumping effect of contracting muscles – on surrounding tissue or on depots of intramuscularly injected insulin – plays a central role. The contracting muscle hypothesis, however, is not supported by our results as the patients in our study infused insulin into abdominal or lumbar subcutaneous tissue and not into an exercising limb.
In summary, this study was successfully executed with no deviations from protocol and the data obtained are of high quality. Currently ongoing modeling work will determine whether this novel study design is the most suitable means for collecting data for T1D glucose modeling [124].

3.4 MODEL-BASED CLOSED-LOOP GLUCOSE CONTROL IN TYPE 1 DIABETES – THE DIACON EXPERIENCE

3.4.1 Background and Aim

In 2009 the DiaCon collaboration was established with participating scientific partners from Copenhagen University Hospital, Hvidovre and Technical University of Denmark and with Novo Nordisk A/S as commercial partner. A main focus area of the DiaCon collaboration was to develop a system for C-L glucose control. In less than three years, we built an MPC algorithm and conducted extensive performance testing in a virtual environment; we constructed a set-up for clinical testing of the algorithm including a user interface for algorithm-physician communication; and we developed a protocol for our first in-clinic C-L study. The aim of this first study was simply to prove feasibility and safety of the system. Therefore we conducted the study in the overnight time period as this is the time with fewest system challenges such as meals and exercise but also the period during which patients normally run the greatest risk of developing hypoglycemia [125].

3.4.2 Methods

The study comprised two randomized cross-over substudies (Figure 7): Study I was a controlled study comparing C-L with O-L glucose control; Study II compared control algorithm performance following start of C-L glucose control during euglycemia (C-L-Eu) and hyperglycemia (C-L-Hyper), respectively.

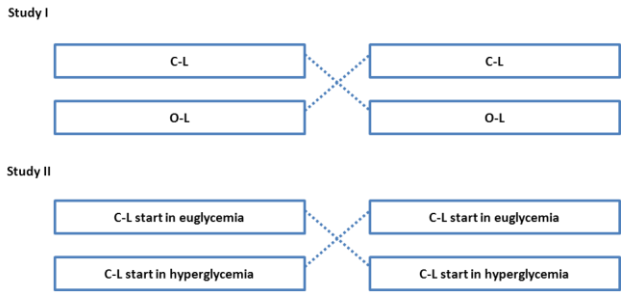

Figure 7 Study design

The patient arrived at the hospital in the late afternoon and was served a standardized meal at 18:00. In study I, meal insulin was dosed according to bolus advice given by the bolus calculator in the patient's insulin pump. In study II, meal insulin was reduced on C-L-Hyper to achieve a hyperglycemic blood glucose value at the time of C-L initiation. On all study nights, glucose was controlled by O-L, i.e. insulin was administered according to the patient's usual basal rate settings, from study start to 22:00. On C-L study nights, the algorithm took over insulin administration at 22:00 and continued until end of study at 07:00 the next morning. On O-L study nights, the insulin pump infused the patient's usual basal rates throughout the study.
Interstitial glucose values were continuously measured by a CGM inserted in the abdominal subcutaneous tissue and wirelessly transmitted to a receiver. Every 5 min the CGM receiver reported a new glucose value, which was transmitted to a laptop computer via a USB cable. The laptop was running the control algorithm and based on the incoming glucose values, the algorithm calculated an insulin doses to be administered. A new insulin dose calculation was presented every 15 min and each time the attending

physician should read the suggested dose and subsequently manually enter the dose into the insulin pump. If needed the physician could overrule and modify the insulin dose. Insulin was not administered as a continuous infusion but as microboluses.
For safety reasons and to assess CGM accuracy, venous samples for plasma glucose determination (YSI) were drawn every 30 min when plasma glucose was > 4.4 mmol/l and every 15 min when plasma glucose was 3.0–4.4 mmol/l. If plasma glucose was < 3.0 mmol/l or if the patient experienced uncomfortable symptoms of hypoglycemia intravenous glucose was infused to raise plasma glucose to 4.5 mmol/l. YSI values were not given to the control algorithm, which controlled glucose based on input from the CGM solely.

3.4.3 Results

Six CSII-treated T1D patients were recruited for each substudy; however, one withdrew from study I after the first study night for reasons of discomfort. Characteristics of the 11 patients were: 45% female sex; age 41 ± 9 years; BMI 24.9 ± 3.5 kg/m2; HbA1c 7.2 ± 0.4%; c-peptide 49.0 ± 18.0 pmol/l; and total daily insulin dose 0.6 ± 0.1 U/kg/day.
In study I, the CGM glucose values were identical at 22:00 on O-L and C-L study nights. The overnight (22:00-07:00) mean glucose values were also similar; however, the distribution of glucose values favored C-L control: On C-L study nights more time was spent in normoglycemia and less time was spent in hypo- and hyperglycemia compared with O-L study nights (Figure 8).
In study II, glucose values were significantly higher at 22:00 on C-L-Hyper study nights compared with C-L-Eu night as intended; 11.3 and 6.3 mmol/l, respectively. Nevertheless, the overnight (00:00-07:00) distributions of glucose values were similar with regards to time spent in the range 3.9-10.0 mmol/l (80.4% in C-L-Eu and 82.1% in C-L-Hyper) (Figure 9).
On three of the 11 C-L study nights, intravenous glucose was administered because of a plasma glucose value <3.0 mmol/l. Two of the three patients experienced only a single episode of hypoglycemia, whereas the third patient needed five administrations of intravenous glucose; however, on this patient's O-L study night glucose was given six times.
The mean absolute relative difference between CGM and YSI in the overnight period (22:00-07:00) was 19.8%. Out of 3.564 possible CGM values, 196 were not reported by the CGM and therefore not transferred to the control algorithm. Only on one occasion did we overrule an insulin dose suggestion from the control algorithm. This was for safety reasons, as the CGM value was 7 mmol/l higher than the YSI value.
Please refer to appendix C for a complete collection of study plots.

3.4.4 Discussion and Conclusions

In this first DiaCon C-L study, we demonstrated that a functional C-L study set-up and an effective and safe model based control algorithm for the overnight period have been developed. Although this was a feasibility study that was not designed to prove C-L superiority, it was encouraging that time spent in the range 3.9-8.0 mmol/l as measured by CGM increased from 43.7% during O-L to 78.5% during C-L control. CGM inaccuracy was greater than expected and was actually the cause of one hypoglycemic episode.

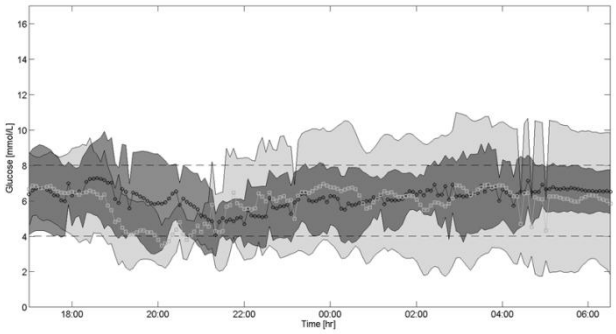

Figure 8 Summary of glucose control measured by CGM during study I. Data are mean CGM-value ± SD. Light grey curve and area represent O-L study nights. Dark grey curve and area represent C-L study nights. C-L control was started at 22:00.

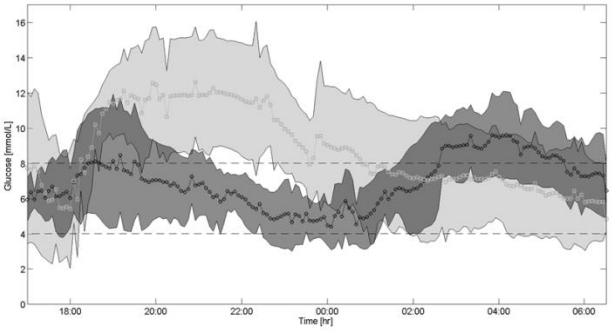

Figure 9 Summary of glucose control measured by CGM during study II. Data are mean CGM-value ± SD. Light grey curve and area represent C-L-Eu study nights. Dark grey curve and area represent C-L-Hyper study nights. C-L control was started at 22:00.

Direct comparisons of the results of different C-L studies are practically impossible because of dissimilarities in study protocols, system specifications and not least in the reporting of study results. Most of these differences, although highly influential, are only briefly described in study publications. One example is choice of study population: The better pre-study metabolic control the harder it is to prove that C-L is superior to O-L glucose control. However, improving metabolic control is not the only focus of C-L research. Of equal importance is the possibility of improving quality of life in patients and relatives by easing the burden of constant disease management.
Still, one study – a multinational study conducted at universities in Virginia, Padova and Montpellier – has a patient population and a study set-up similar to ours and a comparison between the two studies is sensible [81]. With regards to time spent in the range 3.9-10.0 mmol/l during C-L, the outcome of the multinational study is comparable with the outcome of study I (90.7% vs. 89.0% of time). In study II, on the other hand, time spent in 3.9-10.0 mmol/l was only 82.1% and accordingly time spent > 10.0 mmol/l was markedly longer on the six equivalent study days, i.e. the study days on which C-L was initiated during euglycemia. The reason for this may be that in study II the glucose values were higher at study start, but most likely the reason is inter-individual differences between patients in study I and II affecting study outcomes due to the small sample size. Frequencies of hypoglycemic events were also equivalent in the two studies, 0.3 and 0.4 per patient in the multinational and in our own study, respectively.
Currently, various aspects of C-L glucose control are being explored which justifies the multiform study protocols. At some point, however, an international testing guideline is needed to allow

direct comparisons of performance between the different systems.

In conclusion, this first clinical test of the DiaCon C-L system documented that the system is effective and safe and that we have a solid base to build future C-L developments on. Only few patients experienced hypoglycemia and these episodes were mainly attributable to the CGM. Sensor inaccuracy and instability were identified as the main Achilles heel of the C-L system and improving robustness of glucose input to the controller will be addressed in future work along with strategies for controlling glucose in everyday life situations including food intake and exercise.

4. CONCLUDING REMARKS AND PERSPECTIVES

The studies included in this PhD thesis covers three different areas within technologies and T1D treatment: Firstly, bolus calculators for MDI-treated adults; Secondly – a step up the technology ladder – SAP therapy; Thirdly and technologically most advanced, virtual simulation and C-L glucose control system development.

In the BolusCal Study we investigated the effects of an ABC that was about to be launched on the Danish market. Now that the device is commercially available, we can easily apply experience and results from the study into routine clinical practice. So far more than 110 out of 700 MDI-treated T1D patients from the diabetes clinic at Copenhagen University Hospital, Hvidovre have attended a BolusCal patient training course and are now using the ABC. Additionally, approximately 250 HCPs from other diabetes clinics in Denmark have attended BolusCal HCP training courses qualifying them to provide and teach their own patients CC and how to use the ABC.

The 36-month observational study of patients using SAP therapy in routine clinical practice is an important contribution to SAP research. It has by far the longest follow-up of SAP studies published to date and it documents sustained beneficial effects of SAP even after long-term use in routine clinical practice. Unfortunately, long-term SAP studies and long-term use in general have been limited by the cost of glucose sensors. The issue of glucose sensor reimbursement is an on-going debate internationally.

The concept of C-L glucose control has fascinated patients, clinicians and theoreticians for generations. In the past five years there has been an almost exponential increase in the numbers of C-L study groups and publications addressing the concept and now the DiaCon group has also made its contribution. The growth owes much recent technological developments, in particular within glucose sensing. Nonetheless, glucose sensors remain one of the main weaknesses of C-L systems which we also experienced in our C-L studies. In addition, the most suitable mathematical approach for C-L glucose control including effective control of glucose fluctuations related to food and alcohol intake, exercise, illnesses and other aspects of everyday life remains to be identified. Until now, several solutions – each with its strengths and weaknesses – have been proposed, and it may be that a final C-L system will combine several of these. A fully automated C-L glucose control system working 24-7 is unlikely to become a reality with the glucose sensors and insulin and glucagon formulations currently available. On the other hand, a staged introduction of C-L glucose control in step with the technological development starting with the overnight period could prove a rational strategy. Of the treatment modalities mentioned in this thesis, fully automated C-L glucose control is the only one completely independent of human interaction. The efficacy of all other diabetes technologies relies to a certain extent on the user. For instance, even the most accurate glucose sensor is useless if the patient does not use it, or wears it but does not reflect upon the results. In some cases, training and information about technology use and advantages are sufficient to change behavior; in other cases it is an informed choice made by the patients not to make use of the technology, even though it may be beneficial. This means that the results of our studies of ABC and SAP use as well as other technology studies can be transferred only to the selected proportion of T1D patients who are able and ready to change behavior and adopt the new technologies. Not all patients prioritize good metabolic control. The reasons for this may be lack of the time or energy required to practice intensive insulin therapy or it may that the patients are not willing to run the associated risk of hypoglycemia. Factors affecting health behavior and treatment adherence are still poorly understood and further exploration of underlying psychological mechanisms and possibilities of modifying these should be pursued.

Undoubtedly more technologies will enter the T1D market in coming years. Perhaps the future will bring sensor-augmented bolus calculators or accelerometer-guided insulin dosing? The HCP is likely to face an abundance of devices, most of them with only sparse or no prelaunch studies of effects and adverse events associated with use making it difficult to evaluate the full potential of each device. In addition patients will seek advice on and present new devices to the diabetes team and they may even initiate use themselves as some devices e.g. applications for smartphones, are available without prescription. This requires the HCPs to be willing to continuously investigate new technologies. In each case the HCP should consider the risks associated with introducing a device that later proves to be ineffective, i.e. the risks associated with making a statistical type 1 error. Potential side effects, hypoglycemia in particular, must be taken into consideration in the evaluation and selection of new technologies to implement in the treatment of T1D. Increased risk of hypoglycemia is unacceptable if a treatment is otherwise ineffective. If a device turns out to be ineffective there is also a risk that the patient will be skeptic or dismissive the next time a new device is presented. One should also consider socio-economic aspects of treatments that have not been proven to be effective. Some technologies are inexpensive and one-time investments; however, for others start-up and consumable prices are considerable.

As with current T1D treatments, one technology will hardly fit all. While waiting for documentation of treatment efficacy, identification of target population and not least clarification of human factors affecting treatment adherence of each new technology, HCPs and patients are left to a trial and error approach. In this process it is important continuously to involve patients in their diabetes management, inform the patient about potential effects and adverse events associated with technology use, and provide diabetes training empowering the patient to make rational treatment decisions.

5. SUMMARY

Type 1 diabetes is a chronic condition characterized by insufficient production of insulin, a hormone needed for proper control of blood glucose levels. People with type 1 diabetes must monitor their blood glucose throughout the day using a glucose meter or a continuous glucose monitor, calculate how much insulin is needed to maintain normal blood glucose levels, and administer the

insulin dose by pen injection or insulin pump infusion into the subcutaneous tissue. In recent years, several new technologies for the treatment of type 1 diabetes have been developed. This PhD thesis covers two studies of the effects of commercially available technologies - sensor-augmented pump therapy and automated insulin bolus calculators - when used in clinical practice. Both studies demonstrated that these technologies have the potential to improve diabetes care. In addition, two in-clinic studies related to emerging technologies - closed-loop glucose control and virtual simulation environments - are included in the thesis. The results of these experiments provided proof of concept and will serve as a basis for further research in these fields.

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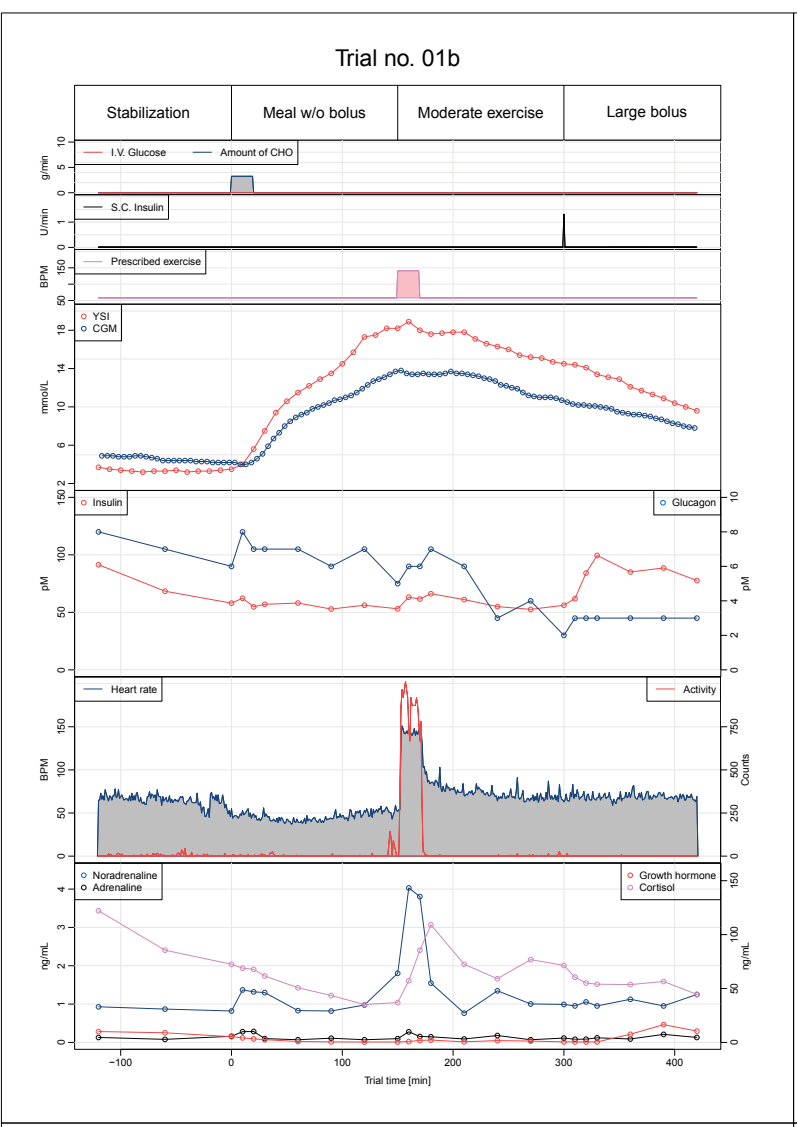
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Moderate exercise
Large bolus
I.V. Glucose
Amount of CHO
S.C. Insulin
Prescribed exercise
YSI
CGM
Insulin
Glucagon
Heart rate
Activity
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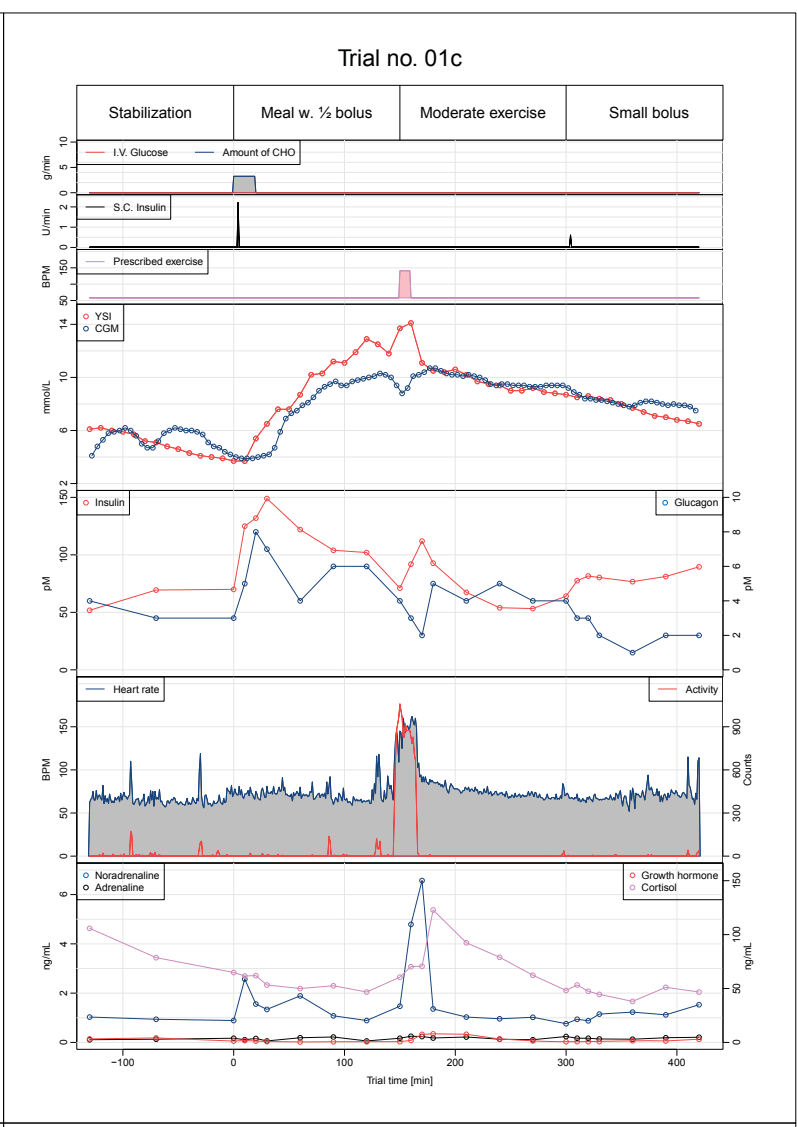
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Small bolus
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Amount of CHO
S.C. Insulin
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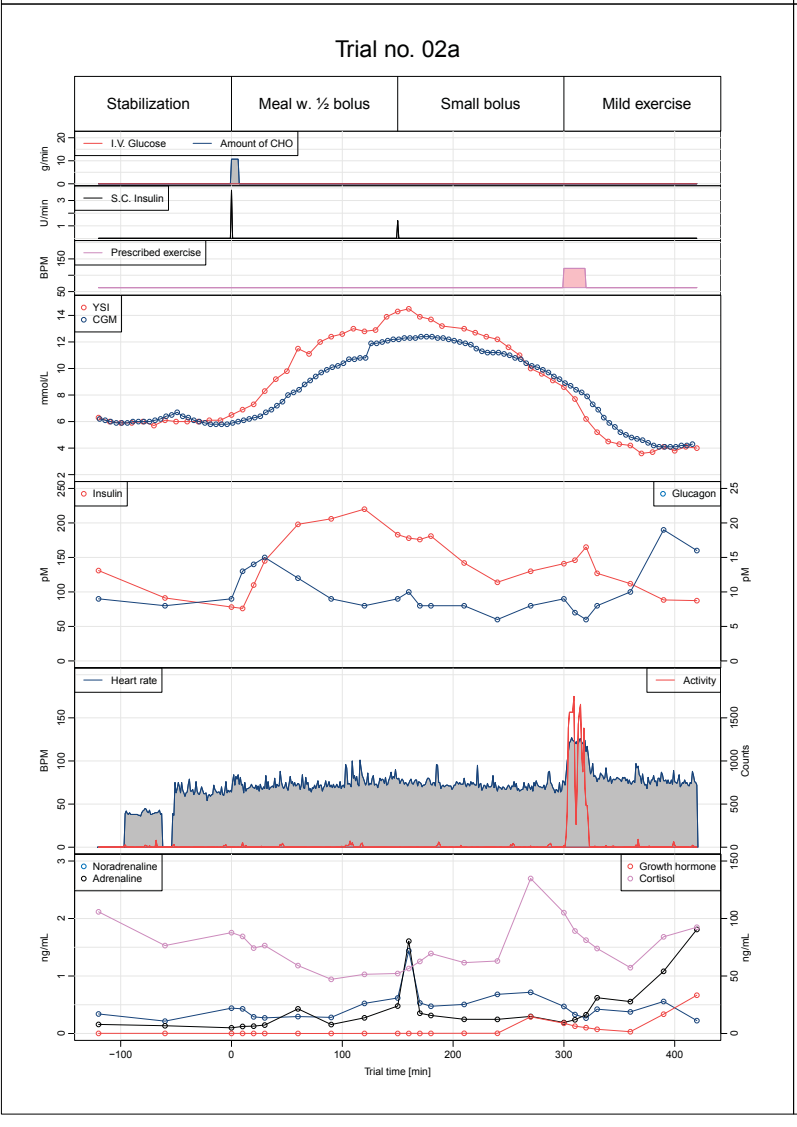
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Small bolus
Mild exercise
I.V. Glucose
Amount of CHO
S.C. Insulin
Prescribed exercise
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CGM
Insulin
Glucagon
Heart rate
Activity
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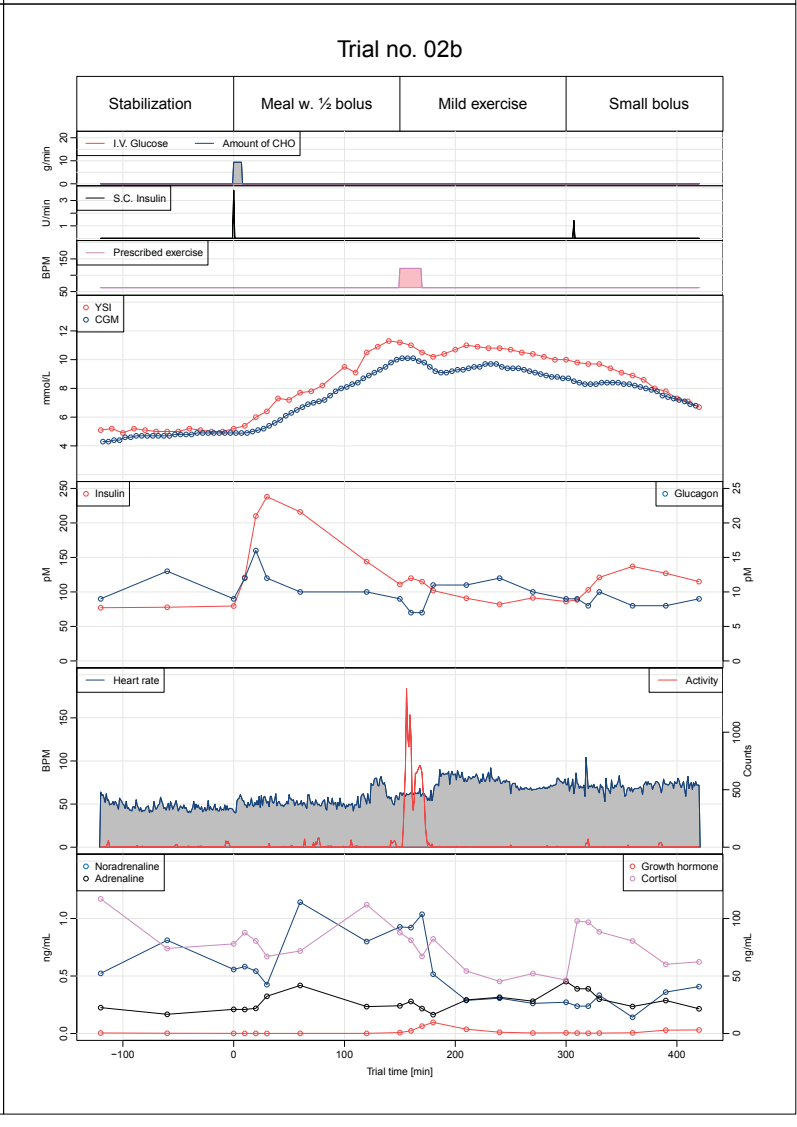
Trial time [min]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Stabilization
Meal w. ½ bolus
Mild exercise
Small bolus
I.V. Glucose
Amount of CHO
S.C. Insulin
Prescribed exercise
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Insulin
Glucagon
Heart rate
Activity
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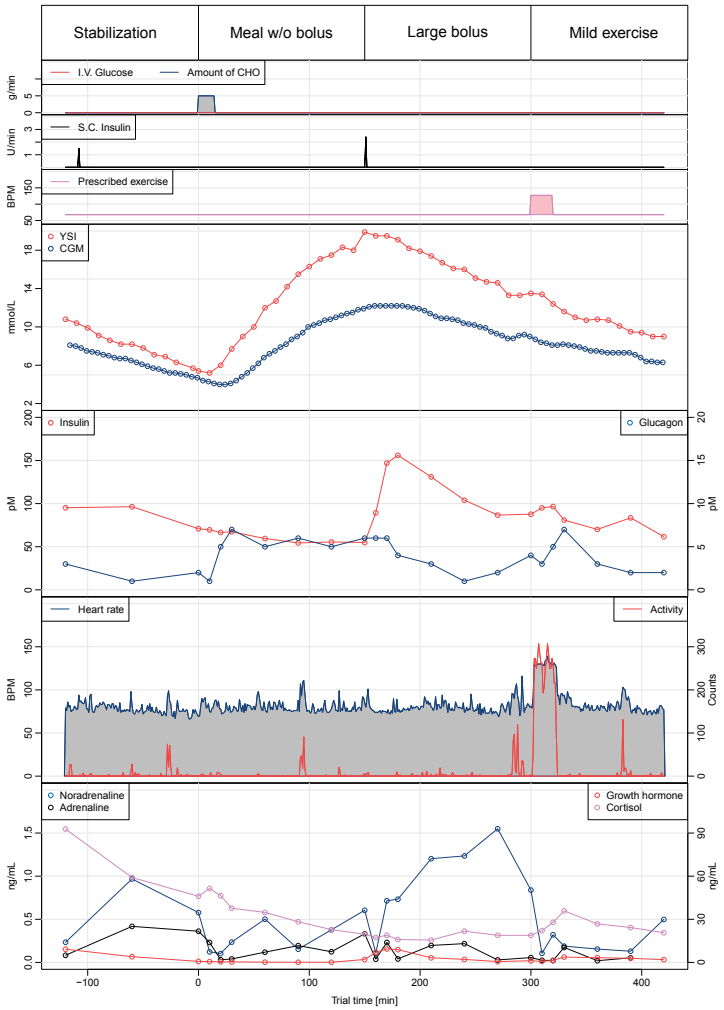
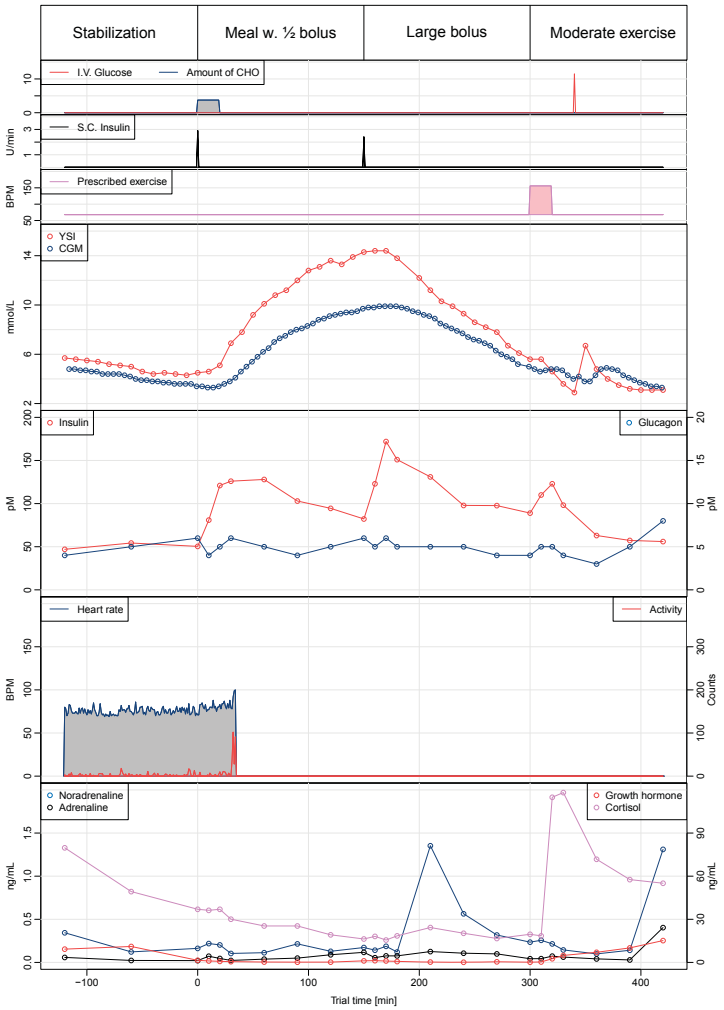
Adrenaline
Growth hormone
Cortisol
g/min
U/min
BPM
mmol/L
pM
Counts
ng/mL
Trial time [min]

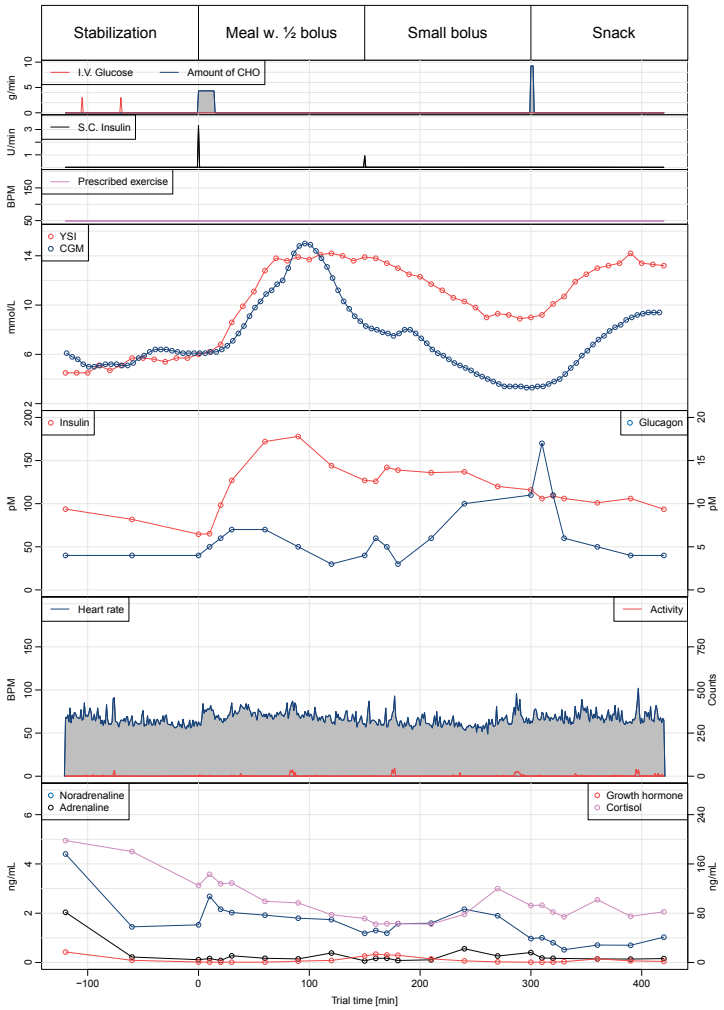
Trial no. 03a



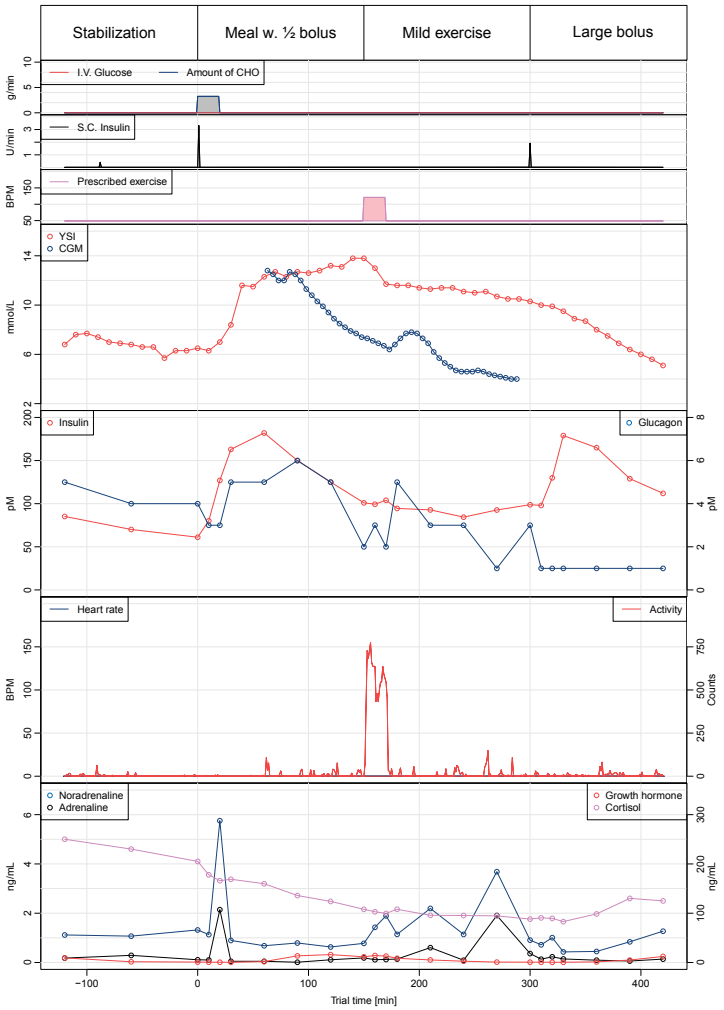
Trial no. 03b



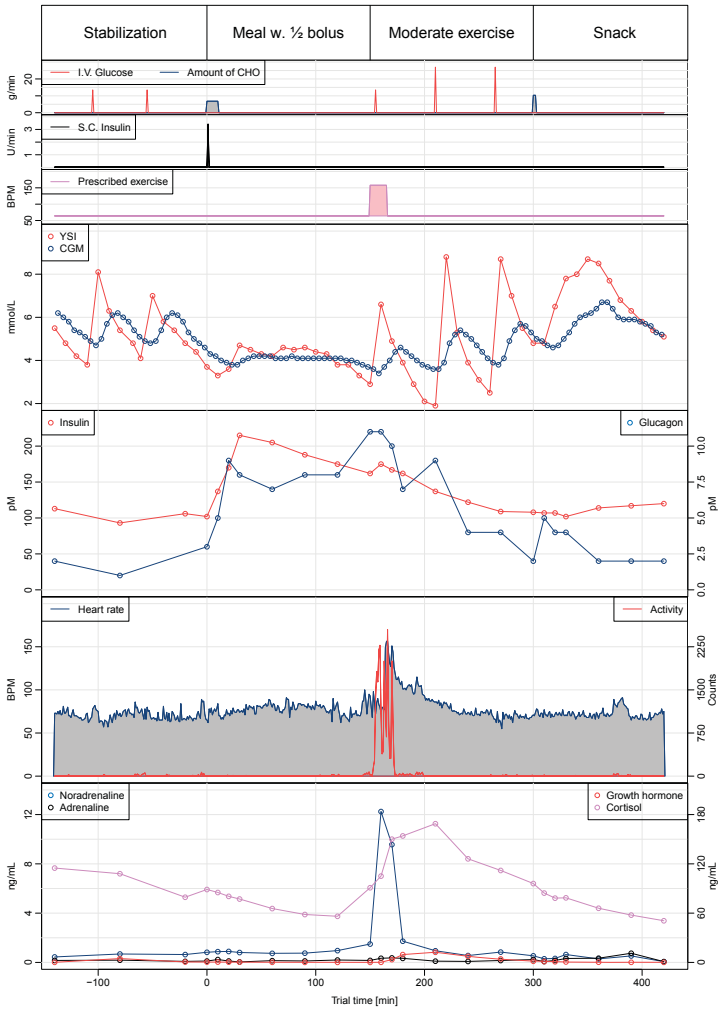
Trial no. 04a



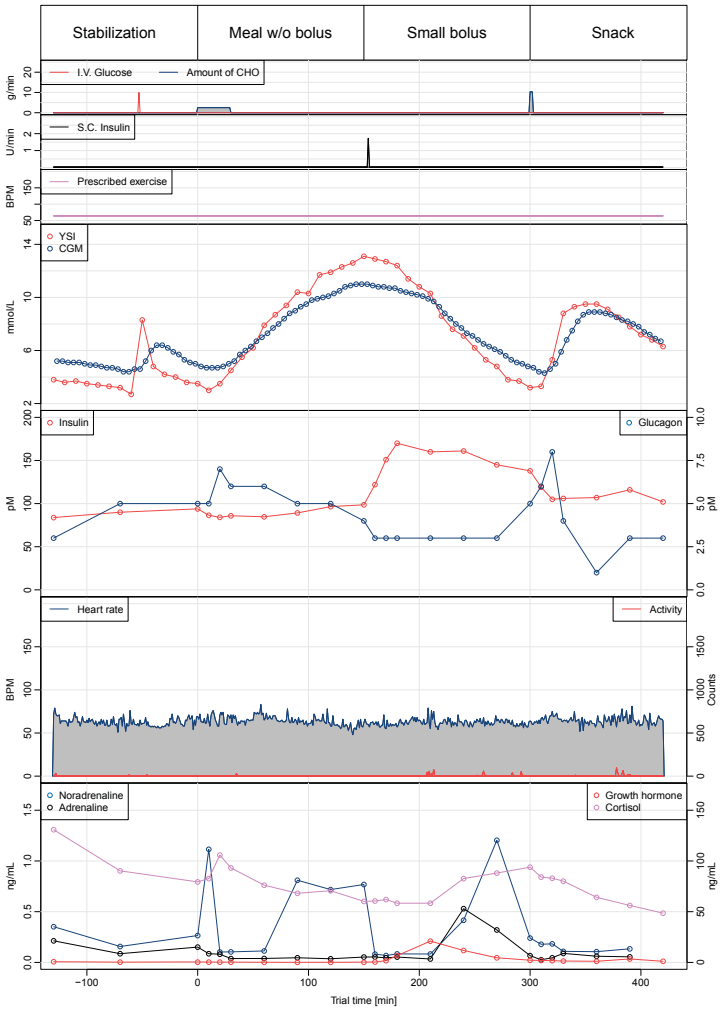
Trial no. 04b



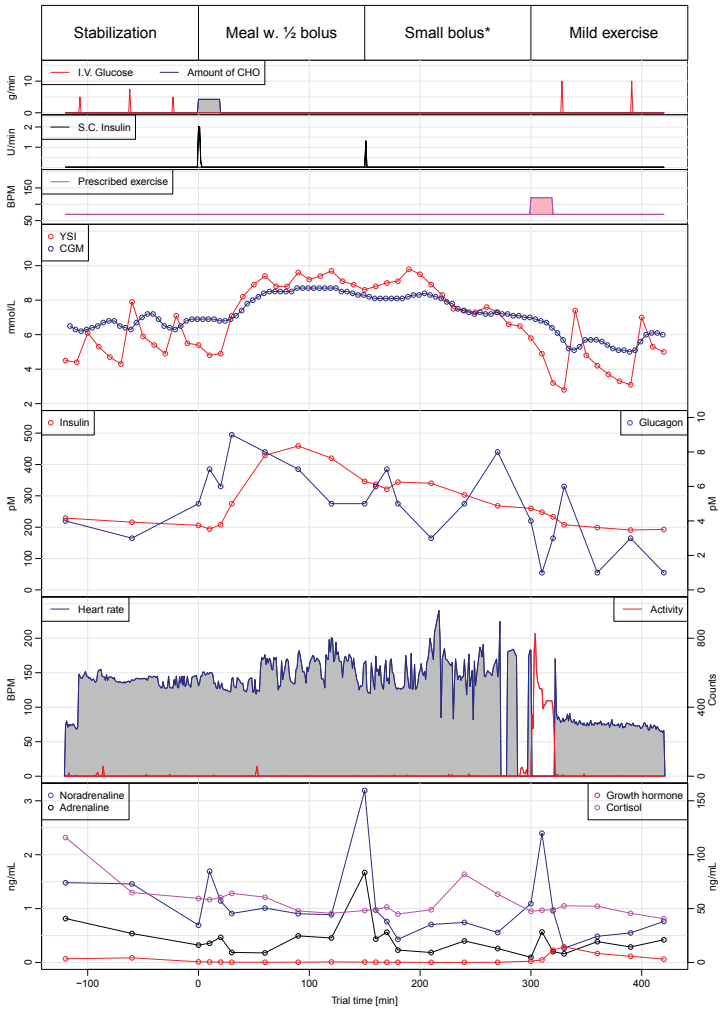
Trial no. 05a



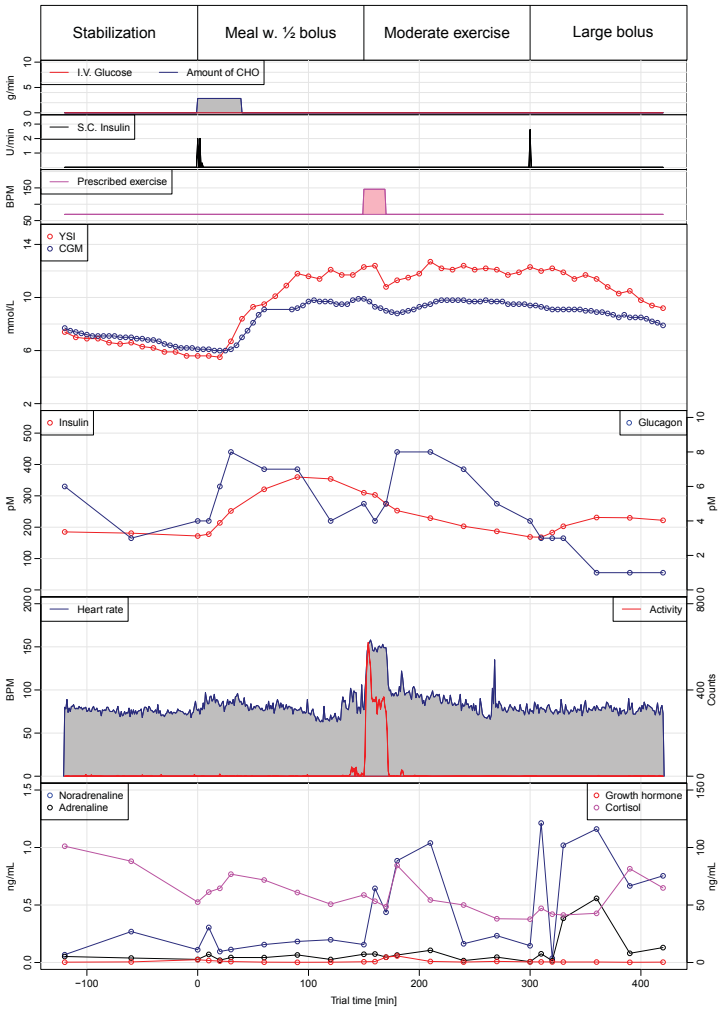
Trial no. 05b



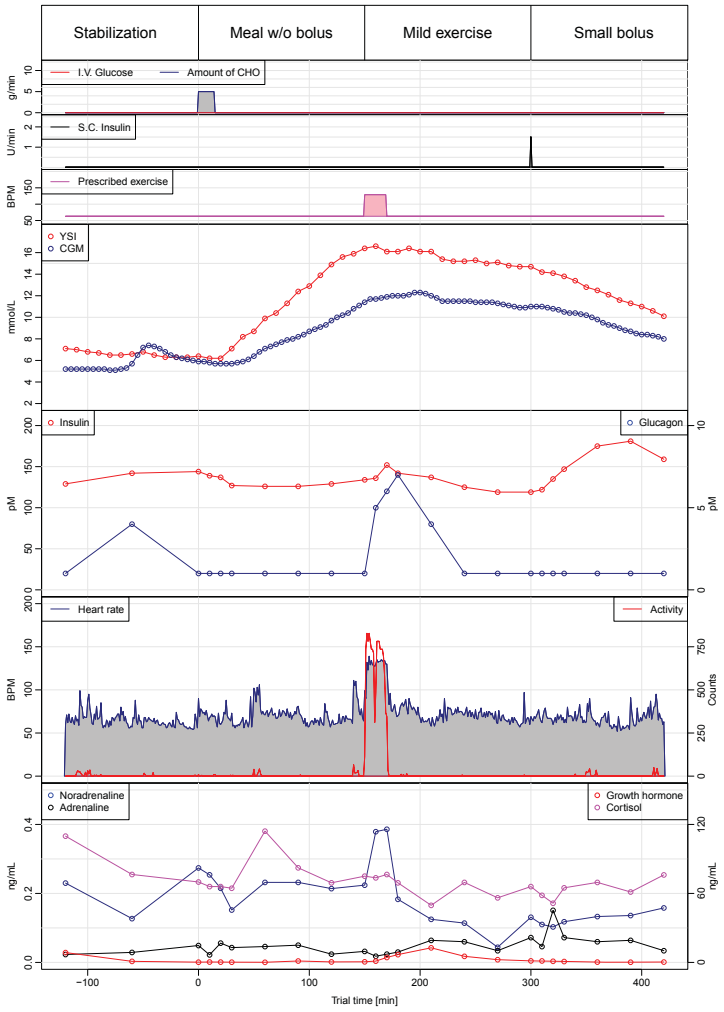
Trial no. 06a



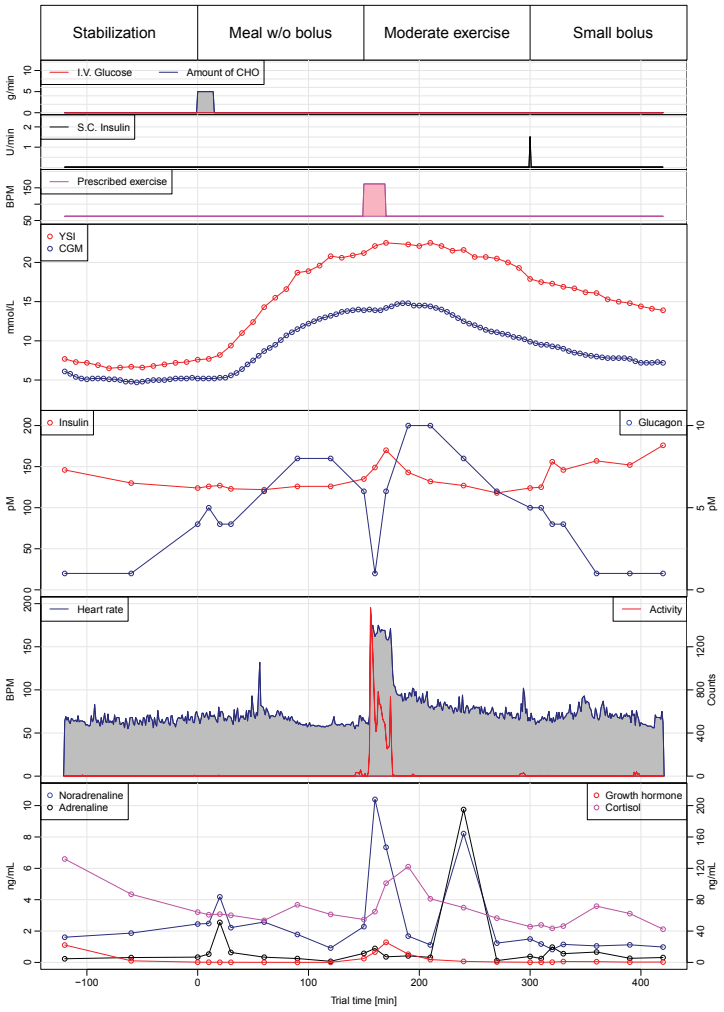
Trial no. 06b



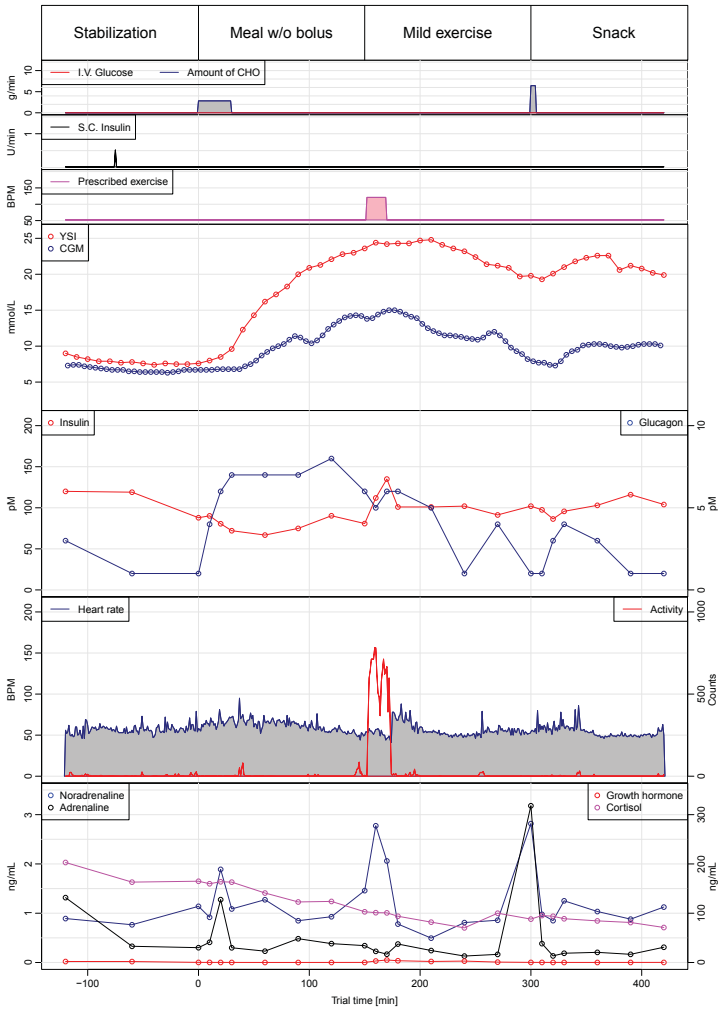
Trial no. 07a



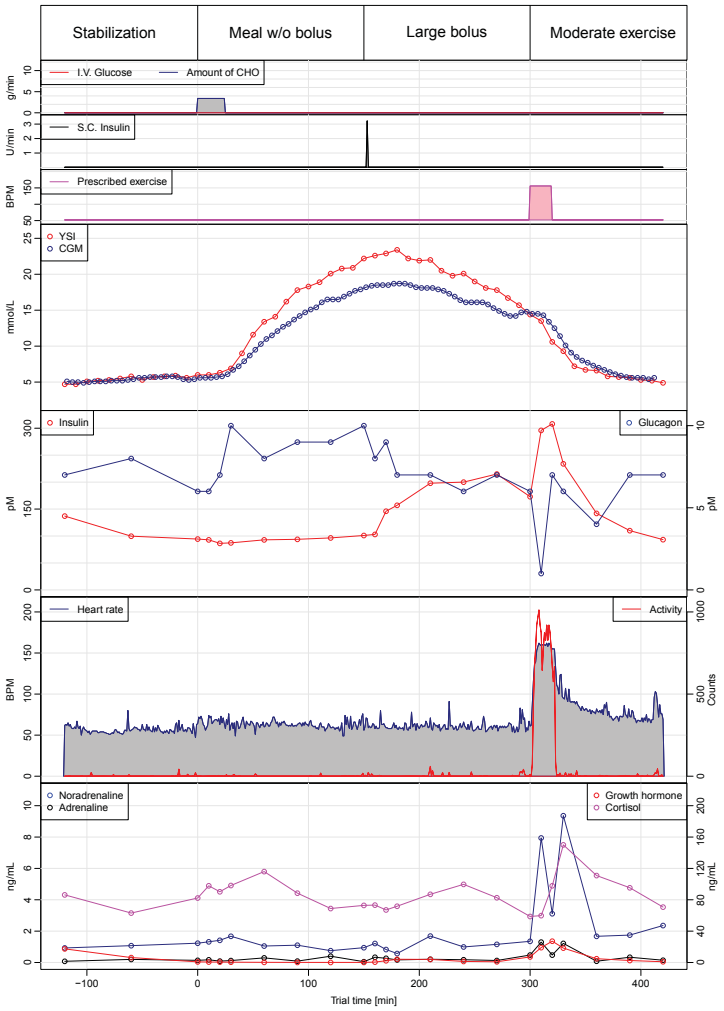
Trial no. 07b



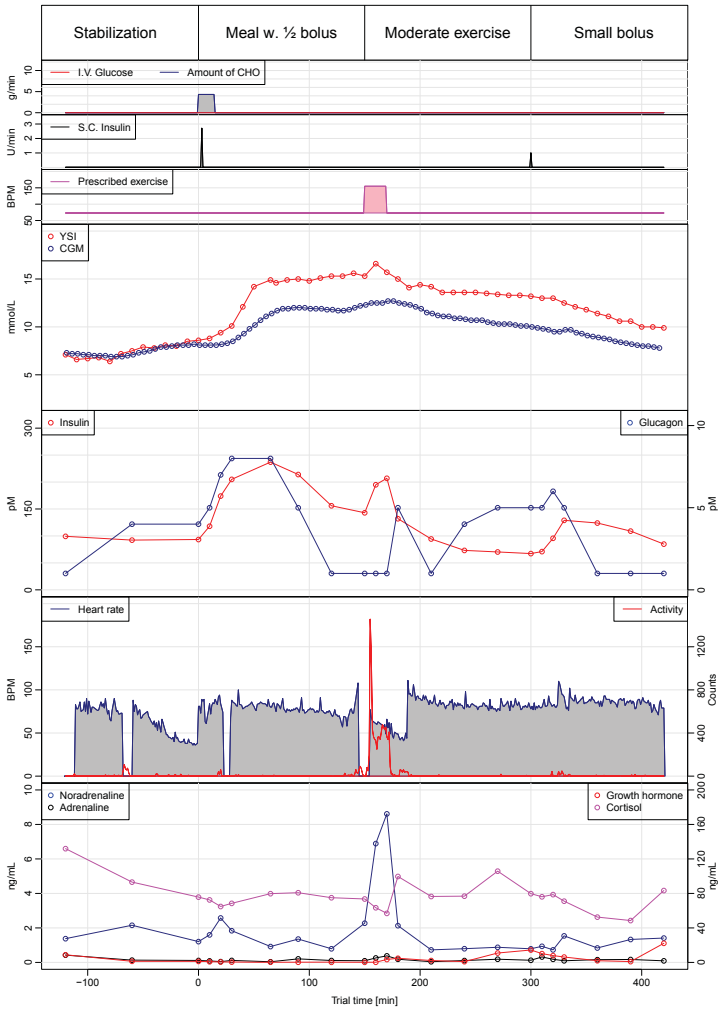
Trial no. 08a



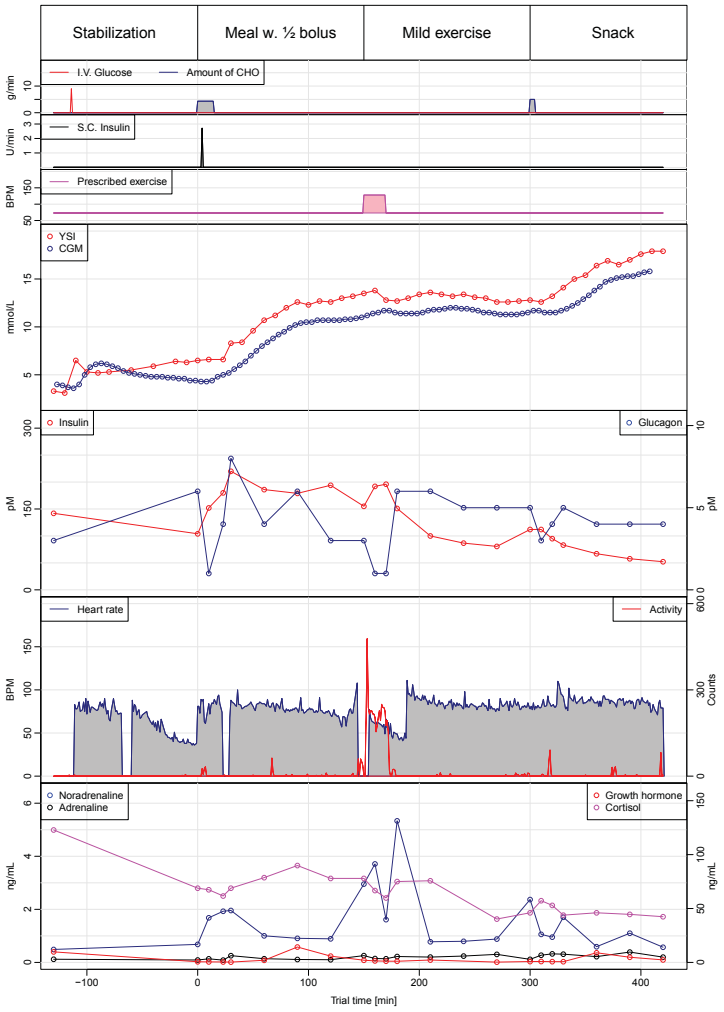
Trial no. 08b



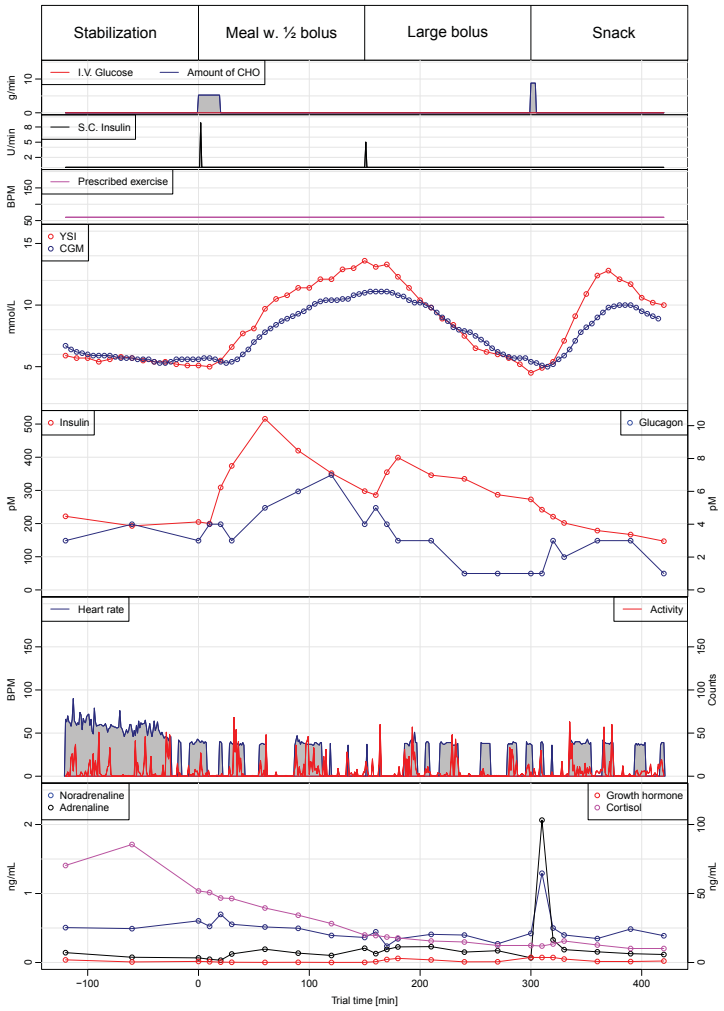
Trial no. 10a



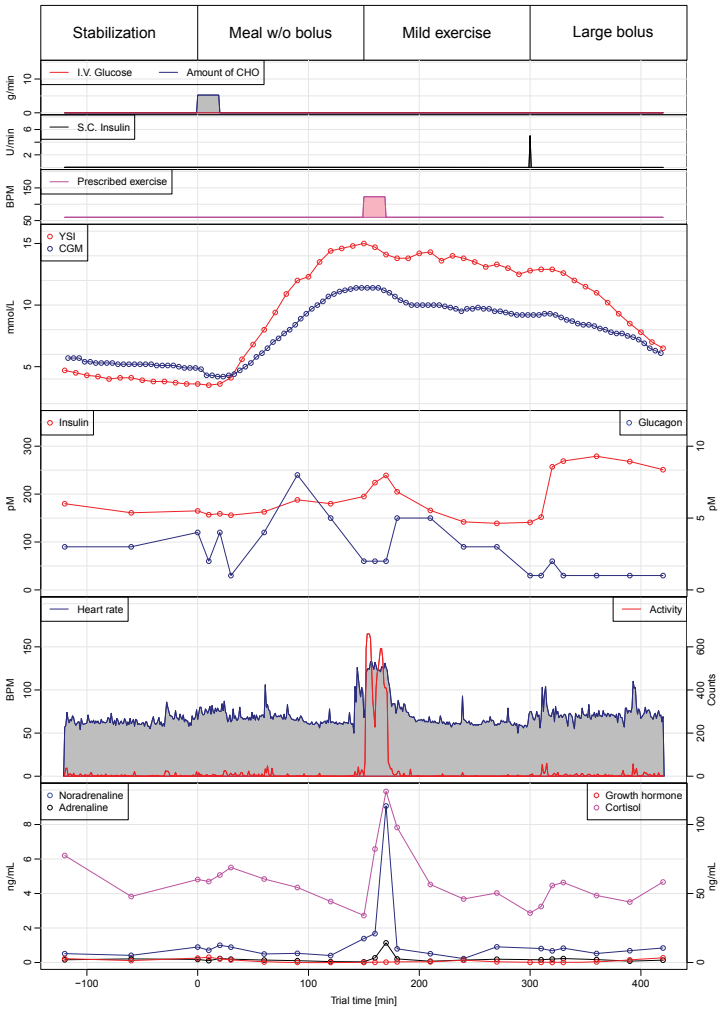
Trial no. 10b



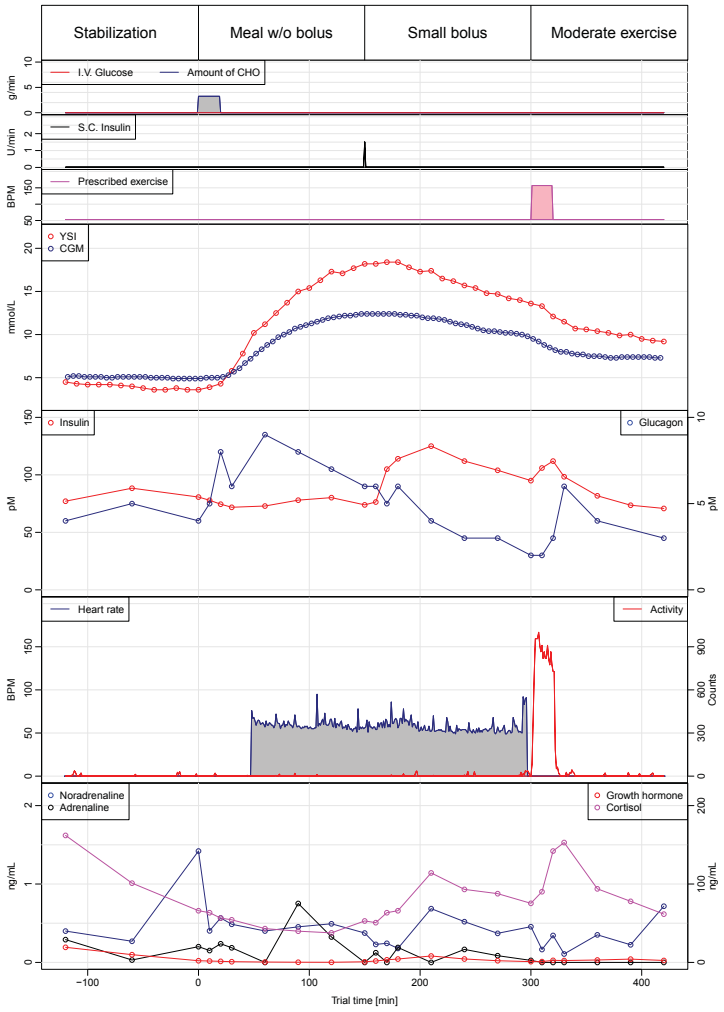
Trial no. 11a



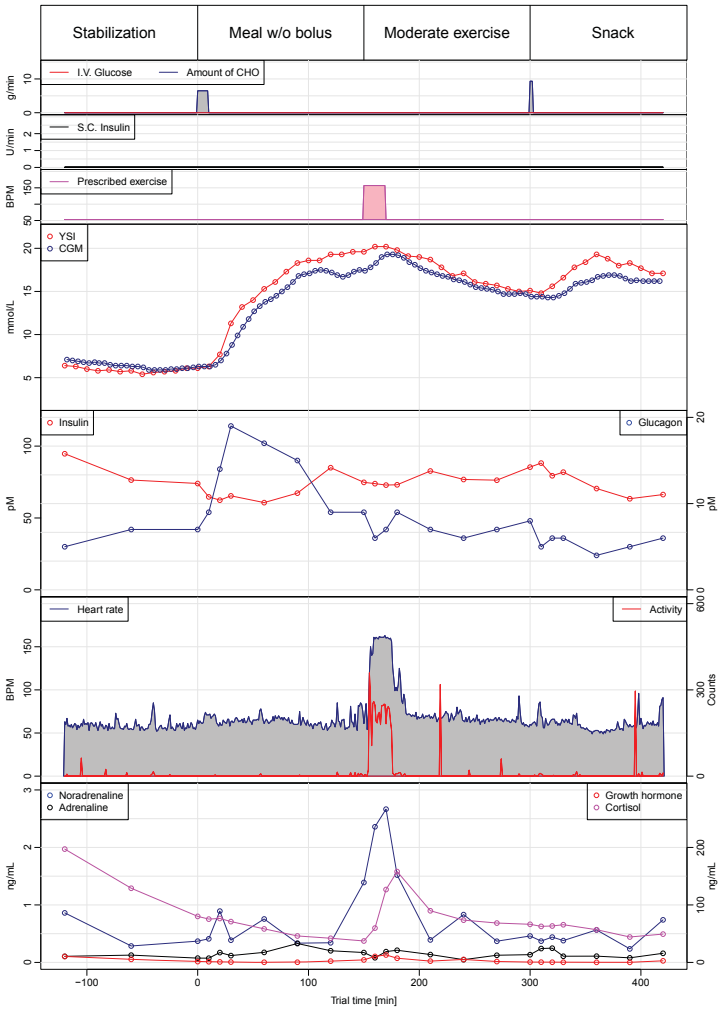
Trial no. 11b



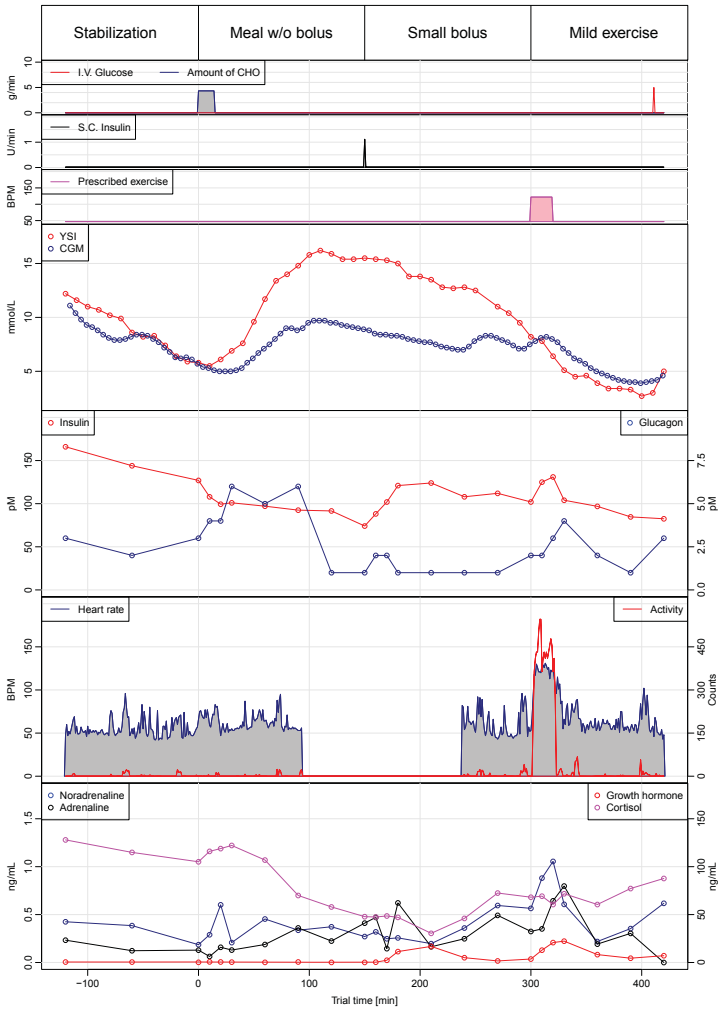
Trial no. 12a



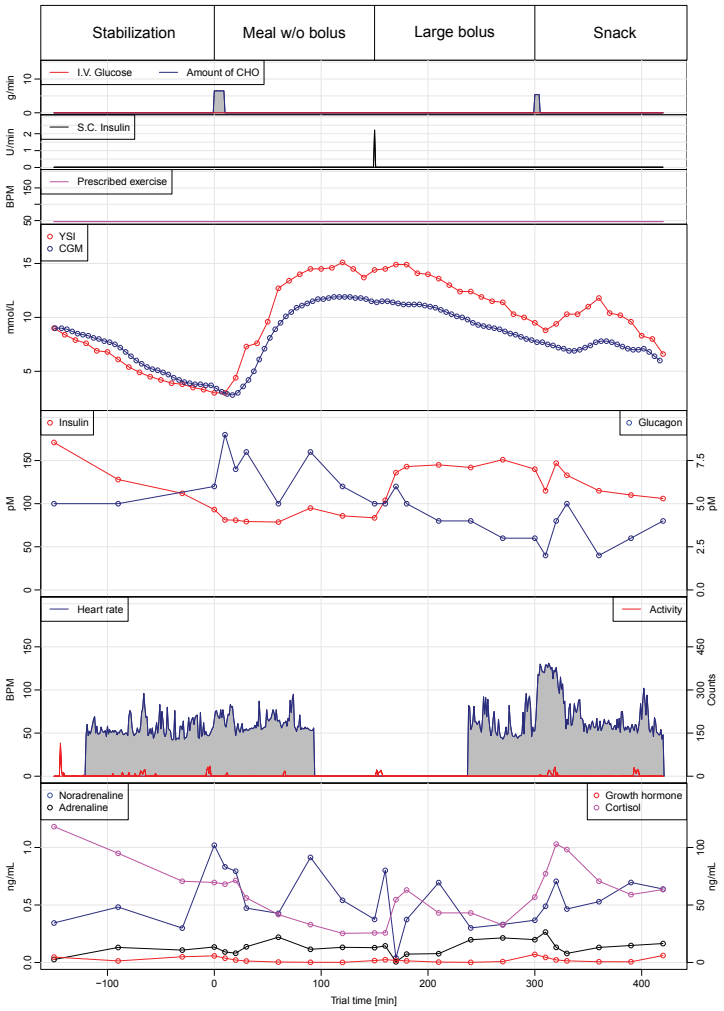
Trial no. 12b



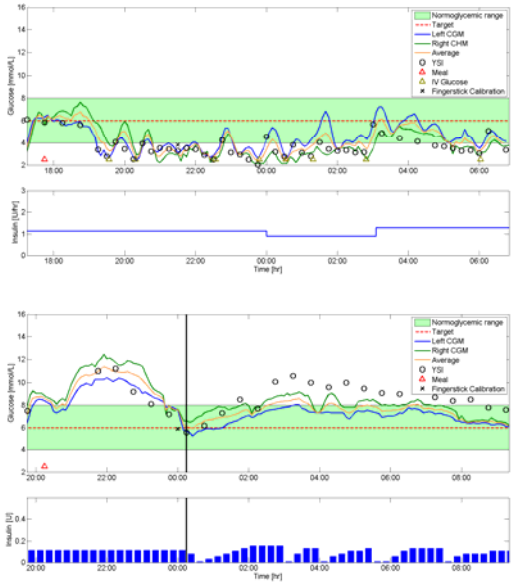
Trial no. 13a



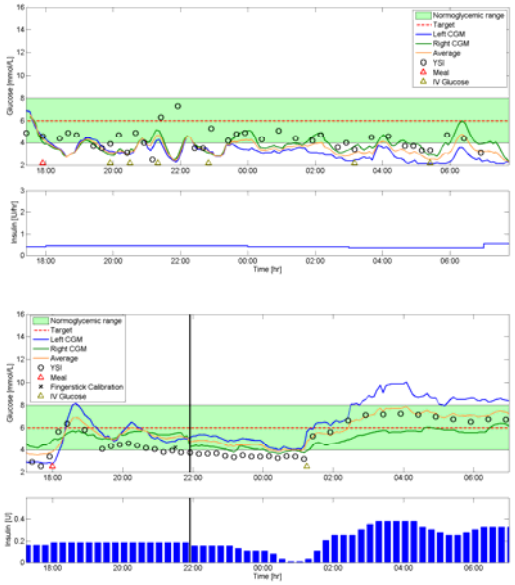
Trial no. 13b



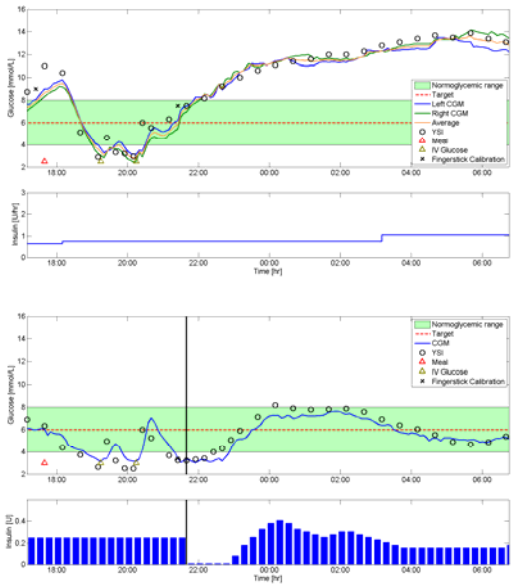
Subject 1. Study I. Open-Loop (upper panel) and Closed-Loop (lower panel)



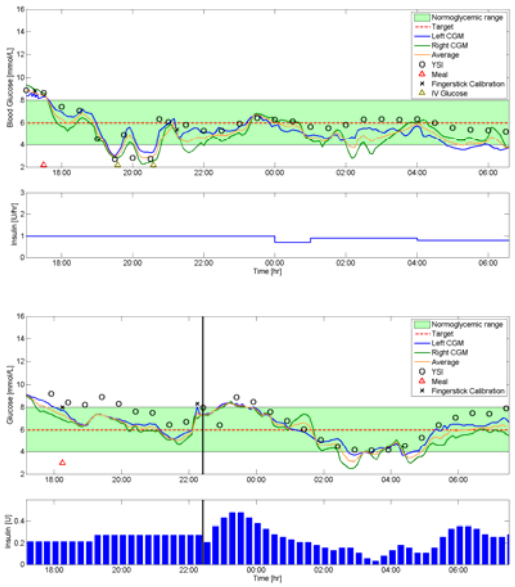
Subject 2. Study I. Open-Loop (upper panel) and Closed-Loop (lower panel)



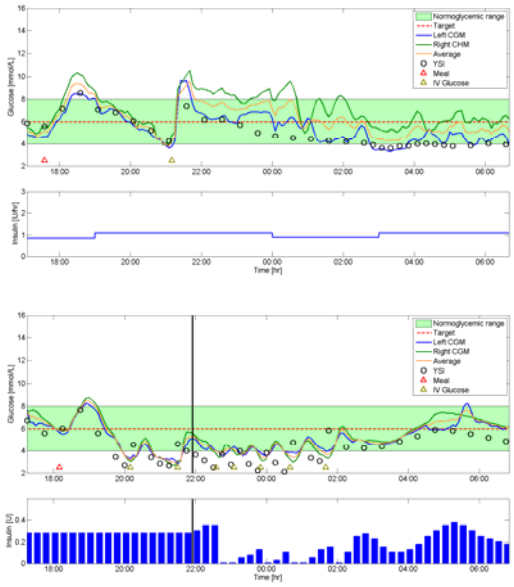
Subject 3. Study I. Open-Loop (upper panel) and Closed-Loop (lower panel)



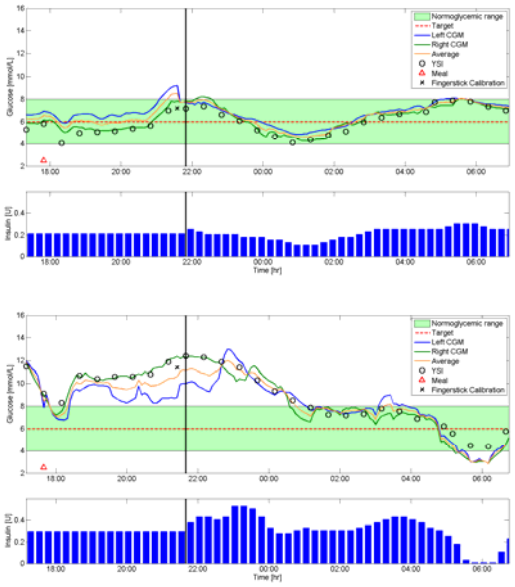
Subject 4. Study I. Open-Loop (upper panel) and Closed-Loop (lower panel)



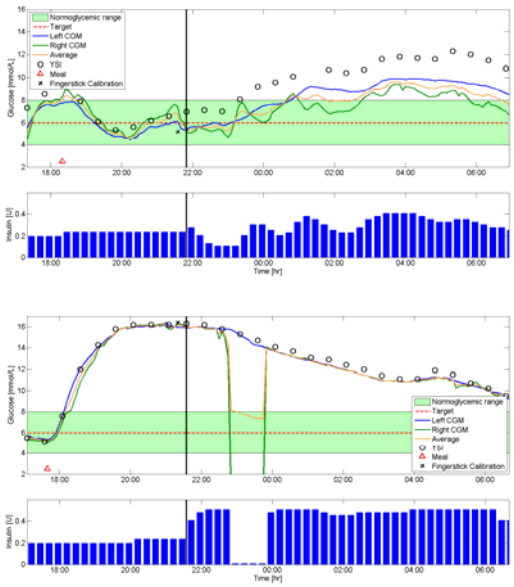
Subject 5. Study I. Open-Loop (upper panel) and Closed-Loop (lower panel)



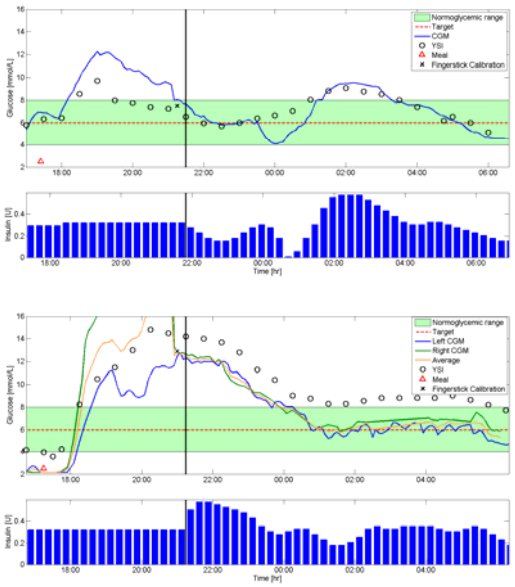
Subject 7. Study II. Closed-Loop-Eu (upper panel) and Closed-Loop-Hyper (lower panel)



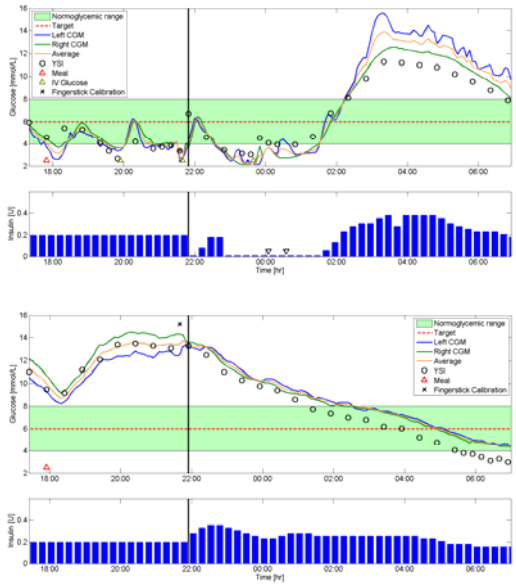
Subject 8. Study II. Closed-Loop-Eu (upper panel) and Closed-Loop-Hyper (lower panel)



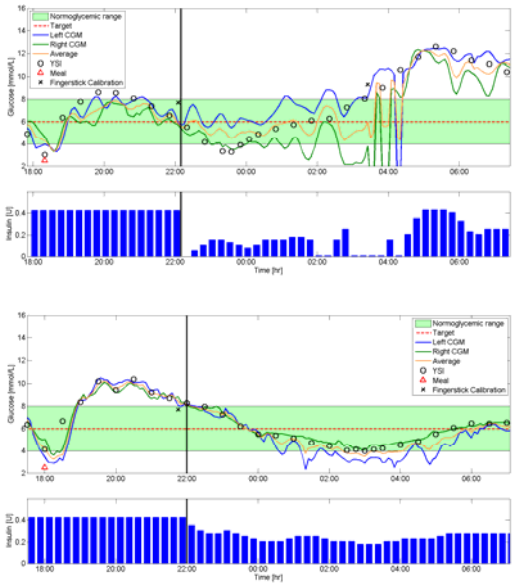
Subject 9. Study II. Closed-Loop-Eu (upper panel) and Closed-Loop-Hyper (lower panel)



Subject 10. Study II. Closed-Loop-Eu (upper panel) and Closed-Loop-Hyper (lower panel)



Subject 11. Study II. Closed-Loop-Eu (upper panel) and Closed-Loop-Hyper (lower panel)



Subject 12. Study II. Closed-Loop-Eu (upper panel) and Closed-Loop-Hyper (lower panel)