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Glucose regulation in the intensive care: an algorithmic approach

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Contents

1 Introduction

It is common for critically ill patients to experience increased levels of blood glucose [1]. This is especially true in medical and surgical patients both with and without diabetes [2], [3]. Glucose levels of 4.4 to 6.1 mmol/L are considered normal [6], but in critically ill patients transient increases up to 11 mmol/L was not considered to be harmful to health [4], [5]. Rather, it was seen as an adaptive response to stress.

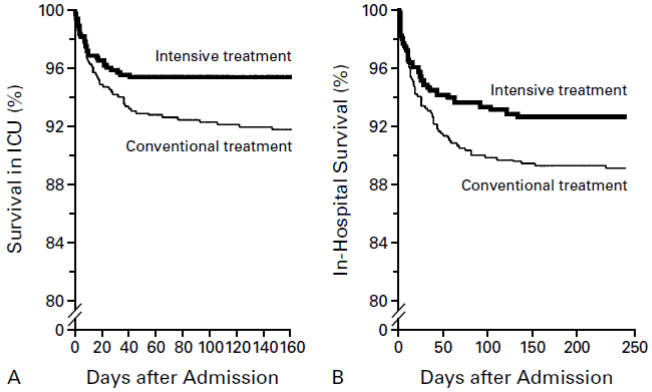

Figure 1: Results of first Leuven study [6]. Mortality is much lower among patients undergoing intensive insulin therapy.

The Leuven Intensive Insulin Therapy Trial [6] changed the perspective radically. Surgical Intensive Care Unit (ICU) patients were treated with insulin in order to maintain blood glucose levels between 4 and 6 mmol/L. A 30 percent decrease in mortality and 40 to 50 percent decrease in morbidity compared to conventionally treated patients was observed, see figure 1. This spectacular result led to a wide adoption of intensive insulin therapy (IIT), not just in surgical ICU patients, but also in general ICU patients.
However, the years following the first Leuven Study saw several disapointing results concerning the benefits of intensive insulin therapy. Subsequent randomized controlled trials held in different hospitals and in a larger, more general groups of critically ill patients reported mixed results [7], [8], [9], [10]. More often than not, patients treated with insulin did not have a significantly lower mortality.

There are several explanations for these contradicting results. First and foremost, IIT increases the risk of hypoglycemia: glucose values below the normal range. Two randomized controlled trials had even been stopped prematurely because of the high incidence of hypoglycemia in the experimental arm [8], [9]. Since hypoglycemia is associated with worse outcomes, occurence of hypoglycemia might balance possibly positive effects of IIT. Indeed, even a single episode of severe hypoglycemia is associated with an increased risk of mortality [11],[12], independently of other cofounders. This has been demonstrated even for normal glucose levels [13], [14], [15]. See figure 2.

A second explanation for the mixed results of IIT is that the quality of glucose control is not just determined by the incidence of hyper- and hypo-

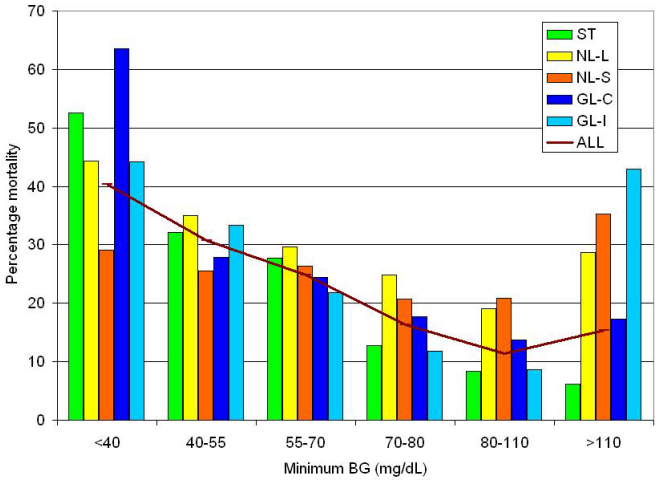

Figure 2: Hypoglycemia as marker of increased mortality. Mortality is lowest among patients with a minimum glucose in the normoglycemic range [13].

glycemia. Glycemic variability is considered to be the last of the three 'domains of glycemic control' [19], [20], [21], [22]. Just like hypoglycemia, glycemic variability is independently associated with an increased risk of mortality. Figure 3 shows mortality rates of patients with different mean glucose during stay. For all ranges of mean glucose, mortality is lowest in the lowest quartile of variability. Interestingly, this relationship is particularly strong for patients with mean glucose in the normoglycemic range, see Figure 3.

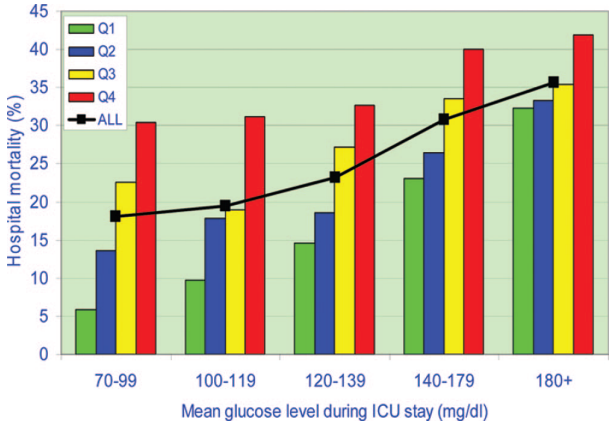

Figure 3: Glycemic variability as marker of increased mortality. Figure shows mortality per quartile of glycemic variability for different ranges of mean glucose.

To complicate things even further, the optimum within the three domains is dependent on patient background: diabetic status greatly influences the optimum glucose range. Relatively high glucose values may be optimal for diabetic patients [36], [24]. A final explanation for the mixed results is the difference in research design between the randomized controlled trials [16]. Staff experience, glucose target range and protocols used for achieving this target range

vary greatly. Methodological issues even led to doubts about the validity of the original results from the Leuven trial, see [17].
Even today, 13 years after the first Leuven Study, there is no absolute consensus concerning the optimal goals of glycemic control and the best way to achieve this goal. The dangers of both hyper- and hypoglycemia do suggest that extreme glucose values lead to suboptimal patient outcome. More recent results show the existence of an u-shaped relationship between mean blood glucose and patient outcome [25]. See Figure 4.

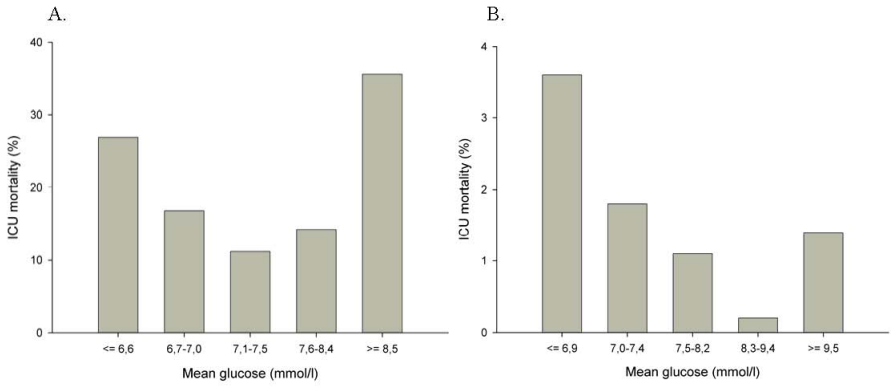

Figure 4: The u-shaped relationship between mean blood glucose and hospital mortality [25]. Medical population left, surgical population right.

Given the complex nature of glucose control, standarized protocols governing insuline infusion according to a patients' need are of potentially great value by improving patient safety and efficiency while minimizing workload. This is especially true for computerized clinical decision support systems (CDSS) [26], [27], [28]. In order to minimize the risk of both hyper- and hypoglycemia, frequent measurements of blood glucose are necessary. This, however, And poses an additional burden on patients either in the form of discomfort or blood loss or both. It also increases the workload of the nurses. Measurement frequency should therefore be dependent on the risk of dysglycemia by striking a balance between being as frequent as needed for adequate control and being as infrequent as possible to minimize workload.

Glucose control algorithms can roughly be divided in 3 categories [29]. Perhaps the most elementary form is that of a flow chart. Simple if-then rules lead to an advise on the optimal insulin pump rate as well as the next time for measurement. This advice is typically based on the current glucose and glucose trend. A protocol of this type was used in the first Leuven Study [6]. A more advanced class is that of the Proportional-Integral-Derivative (PID) algorithms. These algorithms attempt to correct blood glucose values 'on the go'. This is typically done by changing the control parameter, insulin value, proportional to a linear combination of the deviation from target glucose, glucose trend and the sum of historical deviations. The final and most complicated class is that of

the predictive controllers. Algorithms of this type seek to model the dynamics of blood glucose and administered insulin in the human body and are therefore bound to be complex.
In this project, we will discuss two algorithms. The first is GRIP, a PD-type algorithm (lacking the integral part) developed at the university Universitair Medisch Centrum Groningen (UMCG), and is now in use in several ICU in the Netherlands. The second is a flow chart algorithm originating from the Onze Lieve Vrouwe Gasthuis (OLVG) hospital.

1.1 GRIP algorithm

The first subject of our studies is an algorithm called Glucose Regulation in Intensive care Patiens (GRIP) [32]. Designed by Vogelzang, Nijsten and Zijlstra approximately a decade ago, the algorithm takes a patient's blood glucose, glucose trend and previous insulin doses as input. Glucose measurements are performed with a point-of-care blood gas analyser (BGA), while the insulin is administered by a continuous pump. Measured glucose values and insulin rate are used to compute a recommendation both for the new optimal insulin pump rate as well as the time at with the next glucose measurement should be taken. At the heart of the insulin recommender lies the following equation. On time t, the proposed change in insulin pomp is determined by [31]:

$$\Delta I = (1 + 0.25 \cdot \overline{I_{4h}}) \cdot \big(0.3(G(t) - G_{\text{target}}) + 0.2\Delta_{4h}G\big),$$

where $\overline{I}_{4h}$ is the average insulin pump rate during the last 4 hours, $G(t)$ is the current blood glucose value, and $\Delta_{4h}G$ is the change in blood glucose value between now and 4 hours ago. We note the following things. First of all, the proposed change ΔI increases with increasing average insulin over the past 4 hours. The latter is denoted by $\overline{I_{4h}}$. Furthermore, blood glucose above the target value also leads to a higher pump rates, whereas too low levels naturally lead to a lower ΔI. Finally, an upwards (downwards) glucose trend represented by a positive difference with the (interpolated) glucose 4 hours ago leads to a higher (lower) insulin advice. The through (1) calculated insulin advice is then proportionally decreased in case of a recently lowered glucose intake. In case the insulin advice is given within 4 hours of a patients' admission to the ICU, GRIP wil increase the insulin advice in precence of insulin resistance causing patient characteristics.
Directly after calculating the pump update, GRIP recommands the time to the next measurement. First, three provisional advices are calculated. These are based on the estimated risk of hypoglycemia, current and extrapolated glucose levels and the new insulin advice, respectively. The actual time advise is than taken to be the minimum of the three provisional advises.

We will look at the quality of glucose control achieved by GRIP by calculating typical metrics of glucose control. Furthermore, we will perform a sensitivity analysis of GRIP's performance based on various inputs used. Finally, we will compare GRIP with the algorithm used by OLVG. We will do this based on historical data.

1.2 OLVG algorithm

The other algorithm we will investigate is a paper-based flow chart type used by the Onze Lieve Vrouwengasthuis (OLVG) hospital. Rood et al. previously reported on the implementation and performance of the algorithm [27]. The first part of the flow chart as published in the aforesaid paper can be seen in Figure 5. Based on glucose as well as relative glucose change since the previous measurement and current pump rate, the algorithm advises on the new optimal pump rate as well as on the next time a glucose measurement should be taken. In contrast with GRIP as well as the Leuven protocol, the algorithm does advise a bolus of insulin in case of hyperglycemia.
We will analyse the algorithm based on the data from a randomized controlled trial in 178 ICU patients made available to us. The purpose of this trial was to compare glucose control using (1) measurements by a point-of-care (POC) fingerprints with (2) measurements made by a continuous monitoring (CGM) device. This comparison is motivated as follows. For optimal control over the three domains of glycemic control, a clear picture of a patient's blood glucose is essential. This makes the recent development of (semi-) continuous measurement devices very promising. Both the achievement of glucose control and the assesment of its quality are potentially greatly improved by a very frequent measurements. However, the accuracy of measurements is also important. This poses a challenge for continous monitoring systems. We will investigate the accuracy of the system used during this trial. We will also look at compliance with the OLVG-algorithm, and simulate its behaviour in a CGM-context. This can be seen as a first step towards the revision of the algorithm for usage in combination with CGM.

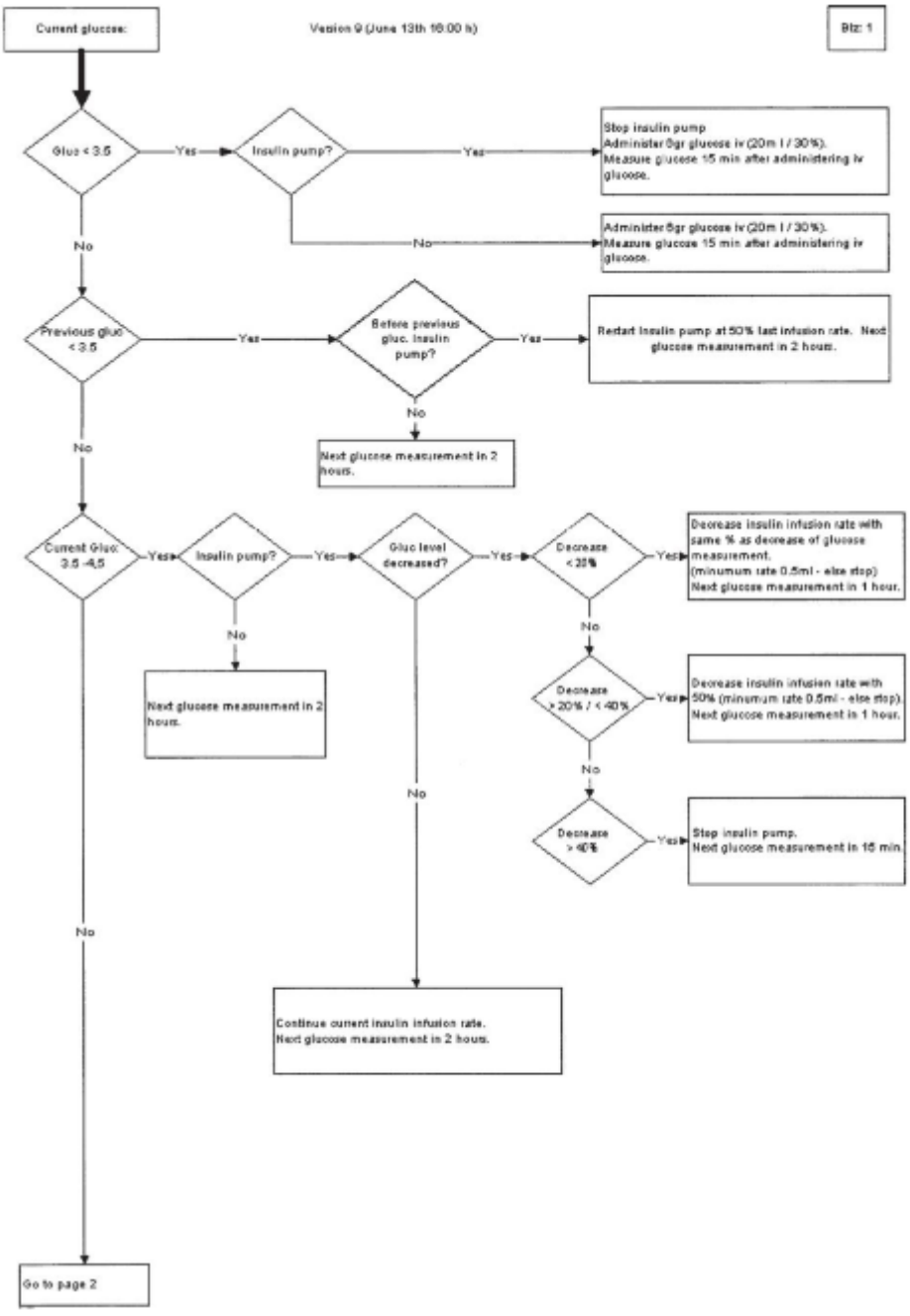

Figure 5: First part of the OLVG algorithm.

2 Data analysis

This chapter is devoted to the process of exploring, cleaning and analyzing the two datasets used. We will start by exploring the GRIP and the OLVG dataset. Then, a comparison is made of the glycemic control achieved by the algorithms. In section 2.4, the accuracy of the continuous glucose measurement (CGM) device used in the OLVG trial is assesed. Finallly, we perform a senstivity analysis of both algorithms by analyzing the influence of the current blood glucose values and insulin pump rates on future glucose levels.

2.1 GRIP data

The analysis of GRIP is done based on a dataset of over 8 million 'events'. Each event consists of the encrypted patient ID, type of record (e.g. glucose measurement), value (e.g. 7 mmol/L), and the event time. The data was collected in 13441 patients admitted to the ICU. Not all records are relevant to our analysis. Of first interest is the glucose and insulin data. GRIP also uses data on patient background (BMI, diabetic status, reason of admission) and on the administered enteral and parenteral feeding. Together with the glucose and insulin data, these comprise approximately 67 % of the dataset. As an example, all glucose measurements made within a particular patient can be seen in Figure 6.

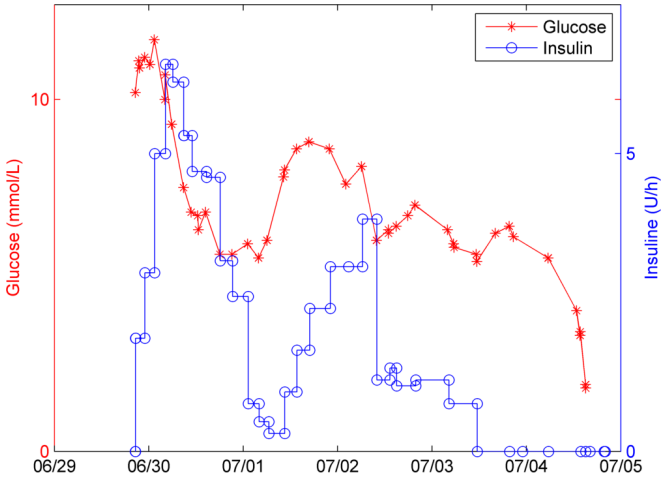

Figure 6: Glucose and insulin data for a single patient.

We will first have to preprocess the data before starting with the actual analysis. The first issue we encounter is the occurence of 307 pairs of glucose records made within the same patient and with the same time stamp but with a different glucose value. These records were indeed different samples. The recorded times coincide because one of these records was made in a sample sent to the central laboratory. This changes the recorded time of the measurement. There is no way to determine which one of the two was actually made at the particular time and which one was made earlier. Fortunately, the difference between the pairs was typically at most 0.5 mmol/L. We therefore decided to

replace each pair by the mean of the two.
The second issue is the occurence of outliers. Extreme glucose values are to be expected considering the nature of the patient population. A number of records however, appears to be clinically impossible. See Figure 7 for an example. We first select all glucose records which are potentially incorrectly filed by looking at the difference between values made within 24 hours of each other, as well as the absolute deviation from normoglycemia. Visual inspection of the resulting 46 glucose values leads to the elimination of 15 ($<$0.01%) definitely clinically impossible values. Note that this is a very small number compared to the size of the whole dataset.

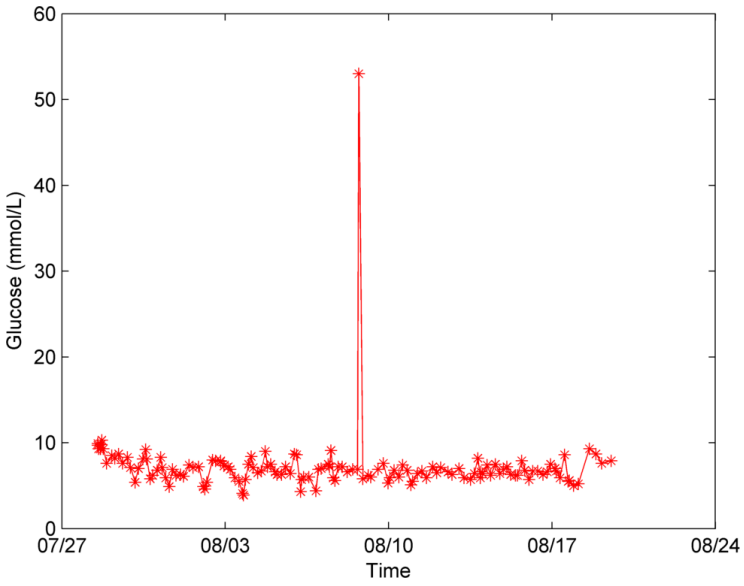

Figure 7: All glucose and insulin data for a single patient.

The decisions on how to counter the first two issues are not of vital importance for the analysis because of the small size of the involved data. This is different for the third issue: data recorded in readmitted patients. We are facing two choices: using these corresponding data for analysis, or excluding them. Including the data leads to an overrepresentation of the patients who were readmitted. Excluding the data, on the other hand, introduces a bias towards survivors. It also means loss of valuable data. The database contains 188127 (37%) of all glucose data recorded in readmitted patients.We decided to adhere to convention and exclude all data collected during readmissions.
As the fourth step in data preprocessing, we looked at missing values. There are sample numbers missing, but this will not hinder our study. We did have to deal with lacking IDs in 46 ($<$0.01%) glucose and 11681 (2.7%) insulin records. Because we have no reason to suspect a bias in the data with missing IDś and there is no feasonable way to recover the IDś, we omit these records.

2.2 OLVG data

We will perform a retrospective analysis of the data collected during a randomized controlled trial previously described by Boom et al. [33]. The goal of the study was to compare the quality of Intensive Insulin Therapy (IIT) guided by subcutaneous continuous glucose measurements on one hand, with IIT guided by frequent point of care measurements on the other. Primary endpoints were incidence of severe hypoglycemia (glucose below 2.2 mmol/L) and percentage of time in target range (5 to 9 mmol/L).

Patients included in the intervention group were monitored by a subcutaneous continuous glucose monitor [CGM] (FreeStyle Navigator®, Abbott Diabetes Care, Alameda, CA, USA). Every 10 minutes, a glucose reading is saved. During the trial a glucose reading was used only when the algorithm required a new input. Also, the CGM generated an alarm in case of dysglycemia, and the reading at that time was also entered in the algorithm, resulting in a new advice. The control group was monitored using an Ppoint-Of-Care [POC] device (the Accu-Chek ®Roche/Hitachi, Basel, Switzerland) monitor. Additionally, in all patients glucose was measured six times a day using a blood gas analyser [BGA] (Radiometer, Copenhagen, Denmark). Whereas the accuracy of both the CGM and POC devices is not perfect, a BGA measurement is considered to be the 'gold standard' of glucose monitors in terms of accuracy.

The study by Boom et al. was the second randomized controlled trial in which CGM-measurements were used for glycemic control in critically ill patients. The first study reported less severe hypoglycemia in the CMG group [34], whereas Boom et al. did not. A possible explanation is the use of a higher target range by Boom and collegues [33]. We will analyse the quality of glycemic control during the study and make a comparison with the data from UMCG. Also, we will look at the accuracy of the CGM. Finally, we will perform an dynamic analysis of the OLVG-algorithm.

The data for our analysis was collected in 178 patients. Of those, 87 (49%) were included in the intervention (CGM) group, 90 (51%) belonged to the control (POC) group, see Table 1. One patient was not included in any group because of a randomization error. For these patients, the following data is available: glucose measurements (either CMG or POC) used as input for the algorithm, CMG readings every 10 minutes, BGA-measurements made 6 times per day and the insulin pump rates and boluses administered. The dataset also includes categorical data on the use of steroids, diabetical status, and BMI. Figure 8 shows all data for a particular patient included in the CGM-group.

2.3 Glycemic control

Our first goal is to assess the quality of glycemic control achieved by both algorithms. For GRIP, this was done before in a smaller patient population [32] [35]. We will also compare the results obtained by both algorithms.

Adequate glycemic control comes down to controlling the three domains: hyperglycemia, hypoglycemia and glycemic variability [36]. There is an abundance

	Total	CGM-group	POC-group
Patients	178 (100%)	87 (49%)	90 (51%)
CGM-measurements	70531	37572	32959
glucose input	14461	8346	6055
insulin			
pump	14461	8346	6055
bolus	648	354	292

Table 1: Main contents of the OLVG-dataset.

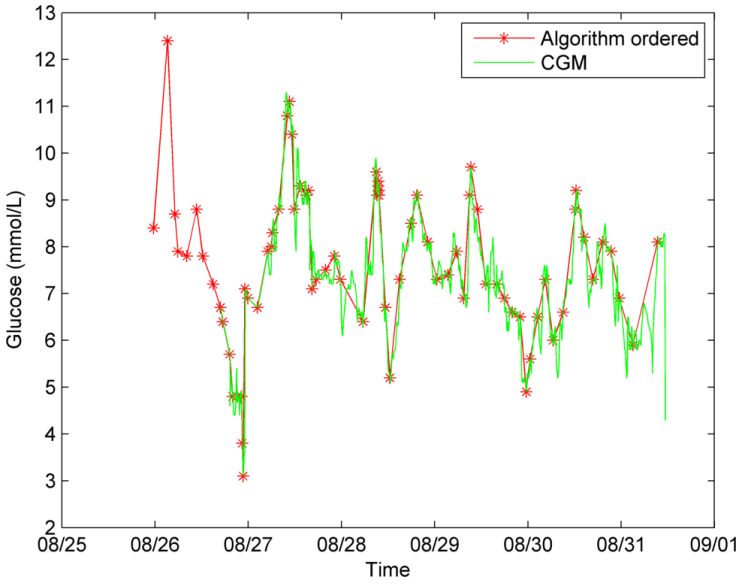

Figure 8: Data for a single patient included in the CGM-group.

of metrics available to test each of these three domains [37]. Unfortunately, a lack of consensus on the 'best' metrics is hampering the comparison of research results [38], [39]. We decided to use the metrics used in the original GRIP paper [32]. The result can be seen in Table 2. All glucose statistics are based on BGA-measurements. Two points should be taken into account when comparing the data from Table 2. First, the density of GRIP measurements is dependent on the (estimated) risk of dysglycemia, whereas the OLVG measurements are taken on fixed times with the sole purpose of calibrating the CGM. Secondly, the two algorithms use different target ranges. GRIP originally aimed to keep glucose between 4.5 and 7.5 mmol/L. In 2009, the upper limit to 8 mmol/L. OLVG aims higher: at the 5 to 9 mmol/L range.
GRIP achieves a higher time in range (Table 1) and less moderate hypoglycemia as well as less hyperglycemia (Table 2). In constrast to the GRIP patients, no severe hypoglycemia was recorded among OLVG patients. This could be explained by the smaller size of the OLVG dataset and the higher range. Table 3 shows that OLVG patients receive more insulin than GRIP patients.

Indicator	OLVG (AC)	OLVG FS	GRIP
First glucose measurement	8.8 [7.9, 10.4]	8.1 [6.7, 9.7]	7.2 [5.9, 9.5]
Glucose change in first 24 hours	0.6 [0, 1]	0.9 [0, 1]	0 [−1.4, 2.1]
Glucose after 24 hours	9.7 [8.5, 10.9]	8.7 [7.5, 10.2]	7.2 [6.4, 8.2]
% of time in range [5, 9]	69%[49%, 88%]	74% [52%,92%]	89% [71%,100%]
Hyperglycemic index (mmol/L)	0.24 [0.07,0.69]	0.17 [0.01,0.65]	0.04 [0.0,0.28]
Number of algorithm measurements per day	7.1 [5.9,8.7]	7.2 [6.5,8.0]	6.6 [5.0, 8.6]
Number of BGA-measurements per day	7.0 [5.9, 8.4]	7.1 [6.4, 7.8]	6.6 [5.0, 8.6]
Time weighted glucose	8.1 [7.6,9.1]	7.9 [7.2,8.8]	7.3 [6.7, 8.1]

Table 2: All glucose statistics are median [IQR] and in mmol/L.

Glucose at least one in range:	OLVG (AC)	OLVG (FS)	GRIP
$[0, 2.5)$ mmol/L	0 (0%)	0 (0%)	158 (1%)
$[0, 5)$ mmol/L	20 (27%)	29 (38%)	3510 (24%)
$(9, \infty)$ mmol/L	59 (81%)	59 (77%)	7477 (52%)
Total: $[0, \infty)$ mmol/L	73 (100%)	77 (100%)	14394 (100%)

Table 3: Percentages of patients experiencing at least one episode of dysglycemia. Any dysglycemia within 6 hours of admission was specifically not taken into account.

2.4 Accuracy

We will analyse the accuracy of the Freestyle continuous glucose by comparing the continuous data with the measurements made by a blood gas analyser (BGA). We used the following approach. First we collected all 2934 BGA-measurements. Subsequently, we find for every BGA-measurements the the closest CGM measurement. Following [40], we select all pairs for which the time difference between the BGA and the CGM measurement was at most 10 minutes and for which the BGA measurements are at least 15 minutes apart. This results in 2769 BGA-measurements and the corresponding 2769 closest CGM-measurements available. The median absolute time difference between the BGA and FreeStyle pairs is small: 2 minutes with an IQR of 1 to 4 minutes. All BGA and FreeStyle measurements for a patient from the CGM group can be seen in Figure 9.

Naturally, the absolute difference between the measured (here CGM) and the actual (BGA) glucose should be small. But what matters in the end is whether the clinical decision based on the glucose measured glucose is close to what would have been done based on the actual glucose. The relative difference is much more important in this respect. The Clarke Error Grid (CEG) was developed to quantify the clinically relevant difference between a set of 'true' reference glucose values and the corresponding measured values. The CEG is made by splitting the x-y (reference value - estimated value) plane in 5 regions: A to E. Measurement pairs consisting of a reference and measured value contained in region A are marked as good. Region B contains estimations in which the error made would not lead to inappropriate treatment. The next regions each correspond to a worse estimation, leading to an unacceptable difference in treatment.
We perform a Clarke Error Grid analysis to asses the accuracy of the FreeStyle

Indicator	OLVG	GRIP
Time weighted insulin pump	2.1	1.5
Time weighted bolus	0.2	0.0
Time weighted total insulin	2.3	1.5
Average number of pump changes per day	7 [4, 8]	5 [2, 8]

Table 4: All insulin statistics are in inuline units per hour, rounded to 1 decimal place.

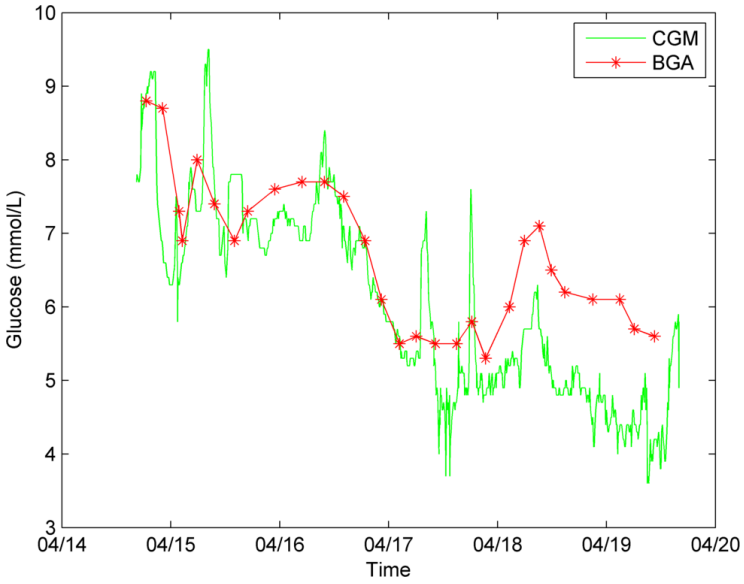

Figure 9: Data showing a suboptimal agreement between FreeStyle measurements BGA measurements.

device. The results are shown in Table 5 and Figure 10. Overall, most measurement pairs fall into the 'A' region. Still, almost 30 percent of all measurements is contained in regions B to E. The FreeStyle device seems to underestimate glucose, especially in the hyperglycemic range. The resulting errors are contained in the D-region (on the middle-right). There are also quite some errors made when the FreeStyle device overestimated very low glucose values. These cases are contained in the left D-region. C-errors are rare, because they correspond to underestimation (lowest C-region) or overestimation (highest C-region) of normoglycemic values. Table 5 shows that accuracy is worse when actual glucose is dysglycemic.
We also analysed the accuracy of Accu-Chek measurements and the agreement between Accu-Chek and FreeStyle measurements. The latter is comparable to the agreement between BGA and FreeStyle, the former is quite good. See Figures 11 and 12.

BGA-measurement	Number (%)	A	B	C	D	E
$[0, \infty)$	2769 (100 %)	70.3	28.5	0.0	1.1	0.1
$[0, 4.5)$	65 (2.3%)	56.9	23.1	0.0	20.0	0.0
$[4.5, 6)$	320 (11.6%)	78.1	21.6	0.3	0.0	0.0
$[6, 9)$	1622 (58.6 %)	74.4	25.6	0.0	0.0	0.0
$[9, 12)$	645 (23.3%)	63.4	36.3	0.0	0.0	0.3
$[12, 14)$	75 (2.7%)	38.7	50.7	0.0	10.7	0.0
$[14, \infty)$	42 (1.5 %)	38.1	40.5	0.0	21.4	0.0

Table 5: Results of the Clarke Error Grid analysis: BGA versus Freestyle.

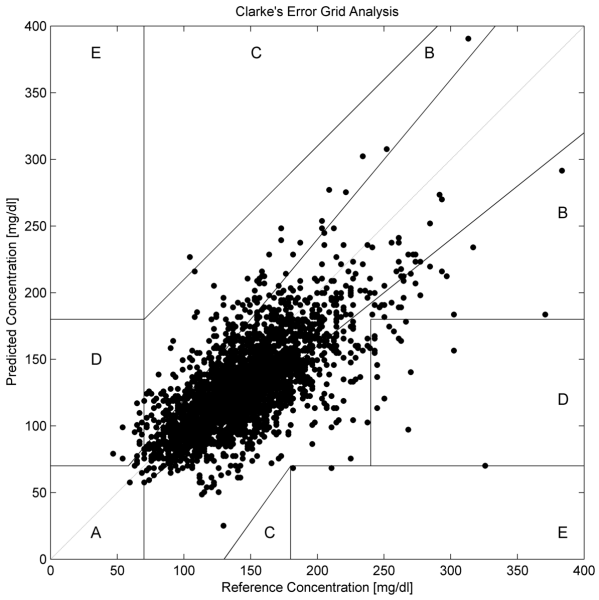

Figure 10: The Clarke Error Grid containing all 2769 pairs of BGA and FreeStyle measurements.

3 Sensitivity analysis

Recall the main equation of the new advice calculated by GRIP, see page 6. We will perform a senstitivity analysis by studying the influence of the three inputs on future glucose levels. That is, given the data used by the algorithms on time $t = 0$, what are the chances of a the next glucose measurement being in the dysglycemic range?

3.1 GRIP

We start by looking at the average insulin preceding the advice (Table 6). The risk of hyperglycemia seems to be an asymmetric u-shaped function of previous insulin rate. The highest percentage of hyperglycemic measurements are seen after high insulin infusions. This is not too surprising, since such high doses are naturally the result of earlier hyperglycemia. However, this does indicate that a more aggressive approach may be benificial. Especially since the very

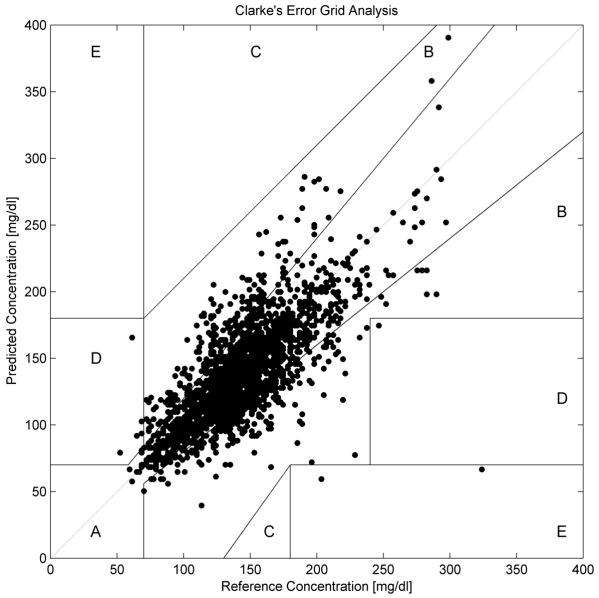

Figure 11: The Clarke Error Grid containing all measurement pairs of Accucheck and FreeStyle with time difference at most 10 minutes.

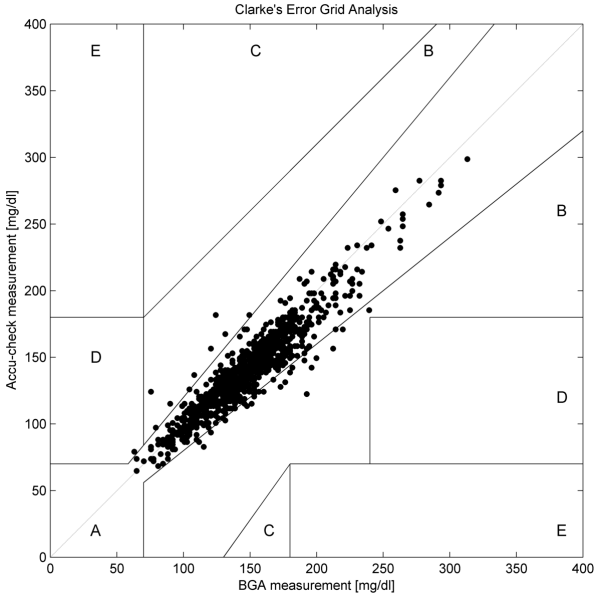

Figure 12: The Clarke Error Grid containing all 889 pairs.

high insulin doses do not seem to be followed by an sharply increased risk of hypoglycemia. In contrast, the risk of hypoglycemia is the biggest in patients who previously recieved either no insulin, or 4 to 6 insulin units per hour. Hyperglycemia is also relatively common in patients who recieved no insulin.

The second input parameter of GRIP is the difference between the last glu-

$\overline{I_{4h}}$	Total	$G > 8$	$G > 15$	$G < 4$	$G < 2.5$
0	35.61	38.6	4.9	1.5	0.11
$(0, 2]$	30.4	32.9	0.8	0.6	0.05
$(2 - 4]$	18.8	27.2	0.7	0.8	0.04
$(4, 6]$	8.1	26.8	1.0	1.2	0.06
$(6, 8]$	3.5	27.8	1.4	0.8	0.04
$(8, 10]$	2.9	42.8	1.7	0.3	0.04
$(10, 12]$	0.4	67.1	3.53	0.2	0.09
$(12, \infty)$	0.3	75.8	9.4	0.1	0
Total	100	33.7	2.3	1.0	0.07

Table 6: Discretized average insulin versus risk of hyper- and hypoglycemia. The 'Total' column gives the percentage of glucose records with previous $\overline{I_{-4h}}$ in the corresponding interval. The 'Total' row shows the percentages of glucose records within the corresponding range.

cose measurement and the target value. We will simply look at the last glucose in order to make the relationship with future glucose values easier to appreciate. As expected, lower (higher) previous glucose values correspond to lower (higher) new glucose values. The only interesting observation here is that very low glucose values (below 2.5 mmol/L) are occasionally followed by a high glucose value. This is probably due to an acutely increased glucose intake.

G_0	Total	$G > 8$	$G > 15$	$G < 4$	$G < 2.5$
$[0, 4.5]$	1.2	15.3	1.4	26.7	2.33
$(4.5, 5.5]$	8.2	13.2	0.4	2.8	0.11
$(5.5, 6.5]$	19.3	13.9	0.2	0.5	0.03
$(6.5, 7.5]$	26.8	16.9	0.2	0.5	0.03
$(7.5, 8.6]$	18.2	31.8	0.3	0.6	0.03
$(8.5, 10.5]$	15.3	63.1	1.1	0.6	0.05
$(10.5, 14.5]$	8.1	87.4	5.9	0.4	0.04
$(14.5, 21.5)$	2.5	94.5	46.1	0.5	0.04
$[21.5, \infty)$	0.4	96.8	86.5	0.4	0.09

Table 7: Discretized target difference versus risk of hyper- and hypoglycemia.

Finally, we look at the glucose trend over the last 4 hours represented by $\Delta_{-4h}G = G_0 - G_{-4h}$. Table 8 shows that an upward trend corresponds to an increased risk of hyperglycemia, while an downward trend corresponds to an increased risk of hypoglycemia. The converse is not necessarily true: a strong downward (upward) trend also increases the risk of hypoglycemia (hypoglycemia). However, this relationship is not as clear as its more obvious counterpart. We conclude that in general, very strong trends in glucose values lead to an increase in risk of both hyper- and hypoglycemia.

$G_0 - G_{-4h}$	Total	$G > 8$	$G > 15$	$G < 4$	$G < 2.5$
$(-\infty, -3)$	6.4	36.6	4.4	3.3	0.22
$[-3, -1)$	17.1	29.1	1.6	1.5	0.09
$[-1, 0)$	26.4	24.5	1.4	0.1	0.07
$[0, 1)$	29.5	27.7	1.0	0.5	0.03
$[1, 3)$	15.2	50.7	2.6	0.7	0.03
$[3, \infty)$	5.5	77.8	13.2	0.8	0.09

Table 8: Discretized glucose trend over the last 4 hours versus risk of hyper- and hypoglycemia.

3.2 OLVG

The sensitivity analysis of the OLVG algorithm is based on the average insulin over the previous 4 hours and current glucose. Table 9 shows that higher pump rates are followed by higher incidence of hyperglycemia. This is to be expected because the algorithm advises more insulin exactly when glucose is higher. Note that the incidence of hypoglycemia is slightly higher than average in case of a high insulin pump. This suggests that a lower pump might have been optimal.

$\overline{I}_{4h} \setminus G_1$	all: $[0, \infty)$	$[0, 4.5)$	$[4.5, 6)$	$[6, 9)$	$[9, 12)$	$[12, 14)$	$[14, \infty)$
all: $[0, \infty)$	100	3.9	16.5	53.7	21.9	2.8	1.3
0	17.3	5.1	21.1	55.4	15.5	1.9	1.1
$(0, 3]$	53.5	3.7	17	54	21.4	2.7	1.1
$(3, 6]$	20.6	4.4	14.9	50.8	25.2	3.1	1.6
$(6, 9]$	6	6.2	11.8	58.8	19.7	2.2	1.3
$(9, 12]$	1.8	4.2	15.9	61.4	14.8	2.7	1.1
$(12, \infty)$	0.8	6	21.6	49.1	19	0.9	3.4

Table 9: Influence of average insulin pump rate during the hours preceding G_0 on the value of G_1.

Table 5 shows that a measurement in a given glucose range is most likely followed by yet another measurement in that particular range. We also looked at the influence of BMI, diabetic status on the incidence of dysglycemia. This did not result in any significant results. We also did not find a statistically significant relationship between prednisone administration and dysglycemia. However, we only had binary data, indicating whether a patient was treated with prednisone. This made it impossible to establish a possibly dose-response relationship.

$G_0 \setminus G_1$	$[0, \infty)$	$[0, 4.5)$	$[4.5, 6)$	$[6, 9)$	$[9, 12)$	$[12, 14)$	$[14, \infty)$
all: $[0, \infty)$	100	3.9	16.5	53.7	21.9	2.8	1.3
$[0, 4.5)$	3.9	53.5	32.6	12.7	1.1	0	0.2
$[4.5, 6)$	16.3	8	55.1	34.3	2.2	0.3	0.1
$[6, 9)$	53.4	0.7	10.5	74.2	13.5	0.8	0.3
$[9, 12)$	22	0.4	2.5	34.2	56.7	4.8	1.3
$[12, 14)$	2.9	0.2	1.4	10.2	48.7	30.2	9.3
$[14, \infty)$	1.4	0	1	9	22.6	28.6	38.7

Table 10: Influence of glucose at the time of advice G_0 on next glucose G_1.

4 Dynamic Analysis

In this chapter we look at how compliant the actual insulin therapy is with the regime prescribed by the protocol. First we study the compliance to the insulin advice, then compliance to time advice. This is done by running the OLVG algorithm on the data of all 178 patients. We implemented the algorithm in Matlab, and this way calculated the advice at each time the insulin pump was adjusted during the study. Finally, we compared this advice with what actually happened. After looking at compliance, we try to simulate the algorithms behaviour in a near-continuous setting (section 4.3).

4.1 Insulin compliance

Nurses followed advised pump rates by the algorithm 53.6% of all cases. Adherence to the protocol is better in some patients than in others: mean (SD) compliance time per patient was 46.8 (20.5 %), see Figure 13. Compliance in the CGM-group is 56.6% versus 49.9 % in the POC-group. Overall, the time averaged total insulin (pump and bolus) as dictated by the algorithm does not differ much from the time weighted actual insulin, see Table 11. The amount of insulin per individual patient is also similar (Table 12).
Clear differences do occur when distinguishing between different glycemic ranges used by the algorithm, see Figure 14. Compliance is relatively high for glucose values within the target range, but low outside the target range. Figure 15 shows the direction of deviation. Given a hypoglycemic measurement, the actual insulin dose is on average higher than advised. Given a hyperglycemic measurement, the actual insulin is typically lower. Non-compliance might in principle be advantageous. In that case the algorithm should be changed. It can also be suboptimal when the advise would have led to better glucose control. Table 13 suggest that more often than not, the latter is the case. Giving a higher dose than advised increases the chance of hypoglycemia. Giving a lower than advised doses increases the chance of hyperglycemia. For the available trial data, we have for example:

$$\frac{P(\text{ Severe hyper } |I < I_{advies})}{P(\text{Hyper})} \approx \frac{7}{4} = 1.75,$$

and

$$\frac{P(\text{Severe hypo}|I > I_{advies})}{P(\text{Severe hypo})} \approx \frac{8}{4} = 2.00.$$

This result should be carefully examined. From Figure 15, we know that the administered insulin, on average, exceeds the advised insulin. From our sensitivity analysis, we know that a hypoglycemic measurement is often preceded by another hypoglycemic measurement. Therefore, drawing conclusions from the statistics in Table 13 is not as simple as it may seem. Nevertheless, giving a lower insulin dose increases, *ceteris paribus*, future glucose values. If the future glucose turns out to be too low, a lower dose would have been better. We therefore conclude that better compliance to insulin advice in the dysglycemic ranges would lead to a possible improvement in the quality of glycemic control.

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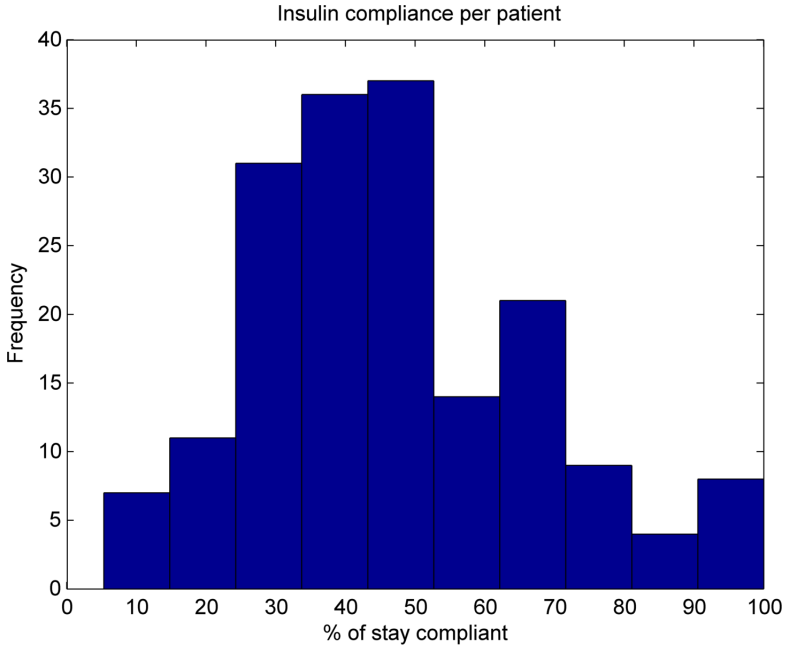

Figure 13: Distribution of compliance time per patient.

	Actual	Advised
$\overline{I}_{pump}$	2.12	2.11
$\overline{I}_{bolus}$	0.16	0.13
Total insulin	2.28	2.24

Table 11: Time averaged insulin (IU/h).

4.2 Time compliance

On average, one measurement is made every 127 minutes. The average advised time to the next measurement was 83 minutes. This corresponds to an average of 11.3 and 17.3 measurements per day, respectively. Hence, glucose is measured less often than advised. In general, time compliance is low. In only 17 percent of all advices, the next measurement time falls within 10 minutes of the adviced time. Compliance to the time advice is higher given a dysglycemic last measurement, see Figure 16. According to this retrospective analysis, glycemic range is related to time compliance by a U-shaped curve. Figure 17 shows just how much the mean deviation of the time advice is. In the hypoglycemic range, measurements are later than advised. In the normoglycemic range and higher, the measurement times are on average closer to the adviced times.

4.3 Input frequency

For the experimental group, insulin advice was based on the FreeStyle measurements on times, adviced by the algorithm as well. However, these measurements were made much more frequently, namely every 10 minutes. We can use these measurements to calculate the hypothetical insulin advice for time intervals

	Actual	Advised
$\overline{I}_{pump}$	2.22 (1.85)	2.23 (1.80)
$\overline{I}_{bolus}$	0.26 (0.39)	0.21 (0.35)
Total insulin	2.48 (2.03)	2.44 (2.00)

Table 12: Mean (SD) per patient Time averaged insulin (IU/h).

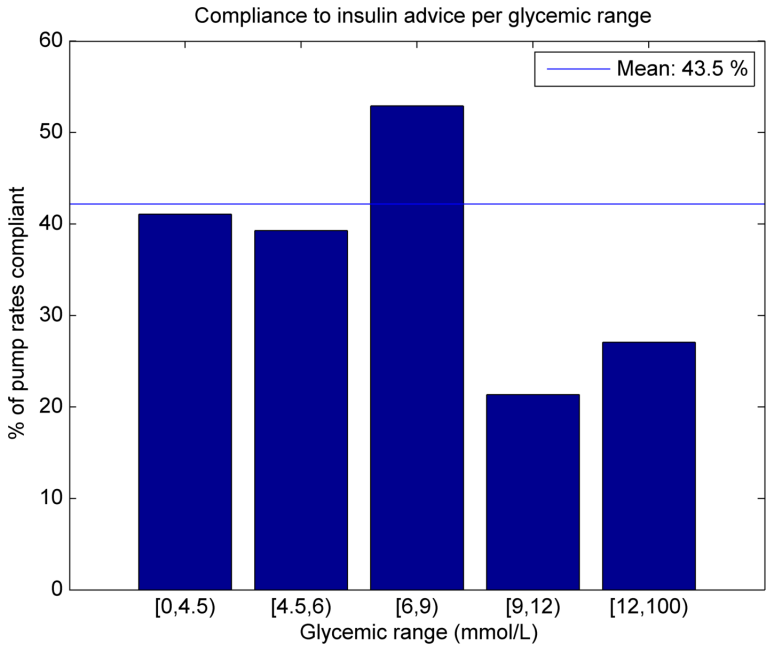

Figure 14: Compliance to insulin advice per glycemic range.

	All	$I_{t_0} < I_0^{advice}$	$I_0 = I_0^{advice}$	$I_0 > I_0^{advice}$
Total	100.0	29	43	28
% of $G_1 \in [0, 4)$	4	1	4	8
% of $G_1 \in [4, 6)$	17	10	18	22
% of $G_1 \in [6, 9)$	54	50	60	49
% of $G_1 \in [9, 12)$	21	32	15	19
% of $G_1 \in [12, \infty)$	4	7	3	2

Table 13: Compliance: insulin. We divide glucose measurement values G_1 in 5 different subintervals, $[0, 4)$ to $[12, \infty)$. For every range, we list the number of cases contained in this subinterval. Also, we list the percentage of times the preceding insulin rate was lower than, equal to, or higher than the adviced rate. For example, 4% of the glucose measurements was below 4 mmol/L. Of these measurements, in 29%, the preceding insulin rate was lower than the adviced insulin rate.

shorter than the advised time. This simulates the behaviour of the algorithm when used in combination with a CGM. In this section we will analyze the behaviour of the algorithm when a new glucose value is given every 30 minutes.

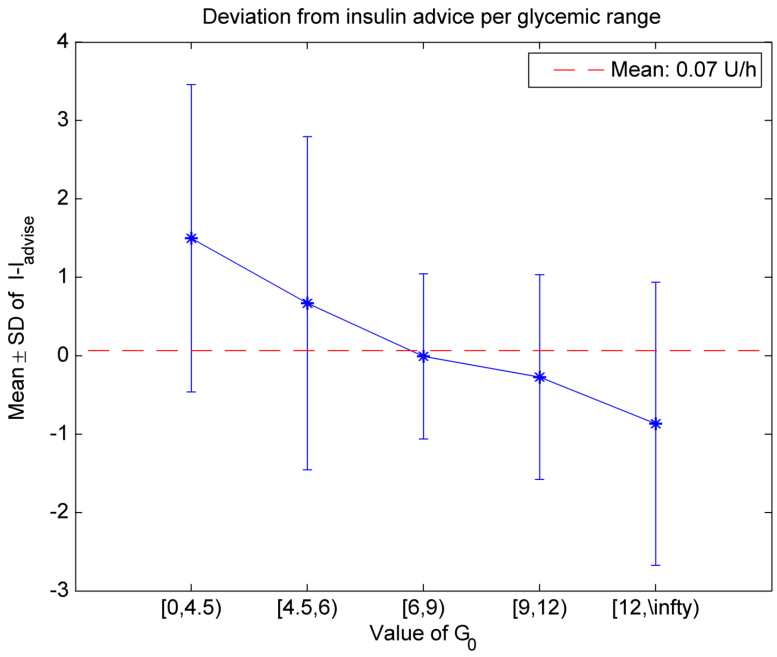

Figure 15: Deviation $I - I_{\text{advice}}$ per glycemic range.

	All	Early	On time	Late
Total	100.0	37	17	46
$[0, 4.5)$	4	4	32	63
$[4.5, 6)$	16	22	15	63
$[6, 9)$	53	39	15	47
$[9, 12)$	22	52	18	31
$[12, \infty)$	4	32	28	40

Table 14: Compliance: time. Early: at least 10 minutes early, on time: within 10 minutes (before or after) advice time, late: at least 10 minutes later than advice.

Table 15 shows that, on average, the algorithm advises higher pump rates when feeded 30 minutes. Table 16 shows that there are sharp differences in mean pump rate per patient. Visual inspection of individual patients shows why. The algorithm's advice is, besides glycemic range, based on the relative change in glucose compared to the previous measurement. A simple example is the advice when the current glucose is higher than 14 mmol/L. If this value is lower than the previous measurement, but the decrease is at most 40%, the pump should be increased with 2 U/h. If the decrease is more than 40%, the current pump rate should not be changed. This treshold of 40% is based upon an time interval of at least an hour. Naturally, the treshold will be passed less frequently when reducing the interval to half an hour. This is true in general: the relative changes used by the algorithm should be decreased in order to make the algorithm sensitive enough to detect changes within 30 minutes. Perhaps the most evident change would be to convert the percentages to the change in 30

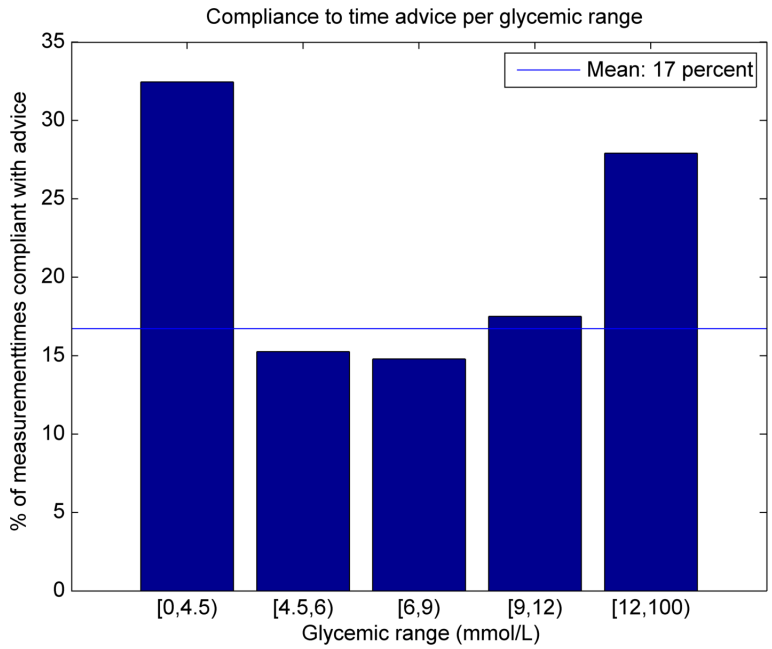

Figure 16: Percentage of measurements compliant (within 10 minutes) of advised measurement time. Glycemic range indicates glucose value at the moment the time advice was given.

minutes which would, when extrapolated to the original time interval, amount to the original change. For example, a decline of 40 % over an hour corresponds to an approximate decline of 22.5% over half an hour.
Another possible update of the algorithm would be to smooth the CGM trace. This can be done by using the moving average of, or linear regression on the last couple of measurements in stead of the last measurement. This method also has the advantage of incorporating all data available from the CGM-device.

	Actual	Advised	Every 30 m.
$\overline{I}_{pump}$	2.11	2.05	2.94
$\overline{I}_{bolus}$	0.17	0.11	0.11
Total insulin	2.27	2.16	3.05

Table 15: Time averaged insulin (IU/h) *during study*.

4.4 Comparison: actual GRIP and simulated OLVG advice

The comparison between GRIP and OLVG made in chapter 2 was made by comparing the same metrics calculated for two different data sets. Hence, this approach assesses the performance of both algorithms in different patients. The comparison is therefore only valid in case of comparible datasets. Unfortunately, the datasets are quite different in terms of characteristics of included patients

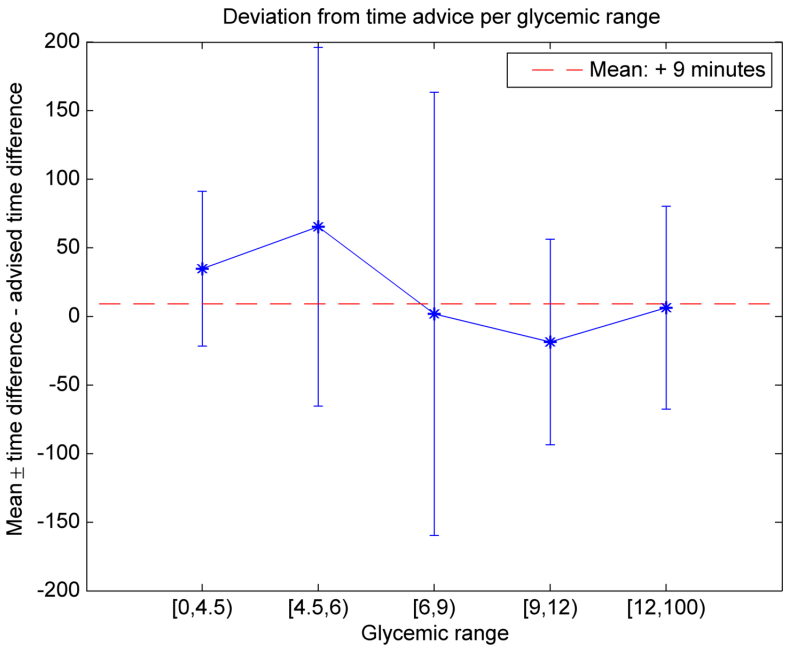

Figure 17: Deviation of time advice. Glycemic range indicates glucose value at the moment the time advice was given.

	Actual	Advised	Every 30 m.
$\overline{I}_{pump}$	2.23 (1.79)	2.17 (1.74)	3.44 (7.25)
$\overline{I}_{bolus}$	0.23 (0.42)	0.18 (0.44)	0.21 (0.75)
Total insulin	2.46 (1.98)	2.35 (1.98)	3.66 (7.54)

Table 16: Mean (SD) time averaged insulin (IU/h) *during study* per patient.

and recorded parameters. Concerning the latter: the GRIP dataset is a lot 'richer' than the OLVG dataset.
In this section we present a comparison of the algorithms based on an alternative approach. We will simulate the behaviour of the OLVG algorithm on the GRIP dataset in the following manner. For every insulin advice given by GRIP, we calculate the advice that would have been given by OLVG based on the available data. After doing this, we can compare the actual GRIP and simulated OLVG advice. It should be noted that the adherence to the GRIP insulin advice is very high. Our calculations show that almost 95 % of the actual pump rates are equal to the adviced pump rates. Using the actual GRIP pump rates is hence close to using the GRIP advised pump rates.
Since we do not know what would have happend when the OLVG advice was followed, it is impossible to determine which of the two advices is better. However, it does make sense to compare recent advices followed by an dysglycemic measurement. In case of hypoglycemia, it is reasonable to consider the the lowest of the two (GRIP and OLVG) as the best advice. In case of hyperglycemia, the highest of the two is the best.
For different glycemic ranges, Figure 18 shows the time weighted average in-

sulin of both the actual GRIP advice and the OLVG advice. The GRIP and OLVG pump rates look similar. Hypoglycemic measurements are preceded by a slightly lower OLVG pump rate. Hyperglycemic measurements are preceded by a higher OLVG pump rate. A different picture emerges when taking the advised boluses into account. These strongly increase the total OLVG insulin, especially in the hyperglycemic range. Consequently, the total OLVG advised insulin is higher for all glycemic ranges (Figure 19). It's notable that the mean recent bolus is not zero for hypoglycemic measurements. This indicates that administering boluses sometimes lowers a patients' glucose levels too much.

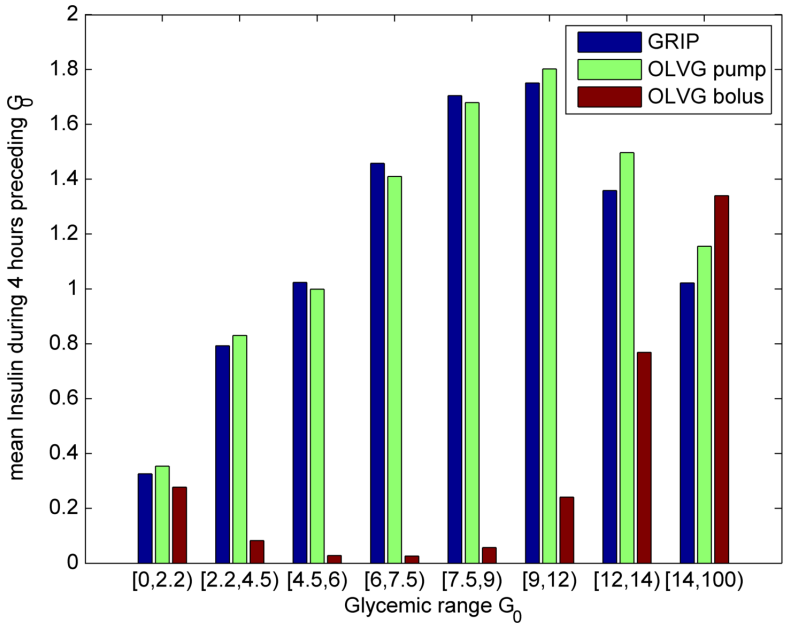

Figure 18: Time weighted recent insulin pump (actual GRIP and advised OLVG) per glycemic range.

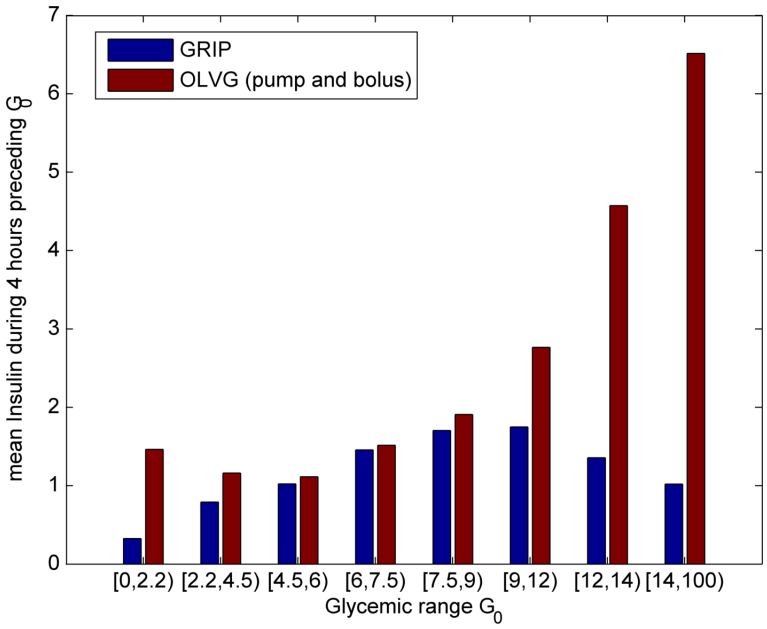

Figure 19: Time weighted recent insulin pump (actual GRIP and advised total OLVG) per glycemic range.

5 Conclusion

Critically ill patients commonly suffer from dysglycemia, i.e. blood glucose values outside the normal range. Since dysglycemia is associated with a worse outcome, this poses a challenge in critical care. Several algorithms have been developed during the last decade for performing this difficult task. These algorithms use intermittent glucose measurements to compute the insulin administration and the time of the next glucose measurement. In this bachelor's thesis, we compared two of such algorithms.
More recently, continuous glucose monitors (CGMs) have been developed. When sufficiently accurate, CGM has the potential to revolutionize glycemic control by using a patient's actual blood glucose values. It could furthermore reduce workload by relieving nurses of the obligation to frequently check glucose. Eventually, a closed loop system could be the new optimal way of glycemic control. New algorithms should be developed that fully exploit the potential of CGM. As a start, we simulated the behaviour of the traditional OLVG algorithm in a near continuous context.

We have analysed two of these algorithms. The first one is GRIP, developed at the academic hospital Universitair Medisch Centrum Groningen (UMCG). GRIP tries to control blood glucose values by proportionally correcting the insulin pump rate based on the deviation from the target range and the glucose trend. This puts GRIP in the class of proportional-derivative algorithms. The second algorithm is a computerized flow chart used by the Onze Lieve Vrouwe Gasthuis hospital. By nature, this algorithm is less complicated than GRIP. Based on current glucose and the relative change since the previous measurement, the algorithm calculates the optimal change in insulin pump rate, possibly accompanied by the administration of an insulin bolus. In contrast with GRIP, the adviced change is not proportional to the input.

The analysis of both algorithms was done based on historical data. The GRIP dataset consists of data recorded in 13441 ICU patients admitted the ICU of the UMCG between 2006 and 2014. The OLVG data was collected in 178 ICU patients enrolled in a randomized controlled trial previously described by Boom et al [33]. Blood glucose of patients in the conventional group was controlled by measuring glucose values with a Point-of-Care (POC) device. For patients in the experimental group, continous glucose monitoring (CGM) was used to measure glucose. For both groups, a glucose value was entered in the OLVG algorithm only then when it was required. However, the CGM-device measured glucose every 10 minutes.
In Chapter 2, we compared the performance of GRIP and OLVG by looking at typical metrics of glycemic control. Both algorithms perform satisfactory. By comparing the continous with the intermittent glucose records from the OLVG dataset, we analysed the accuracy of the used CGM-device. The CGM typically underestimates blood glucose. We concluded chapter 2 with a sensitivity analysis based on the data used by both algorithms.

Chapter 3 concentrated on the dynamic analysis of the OLVG-algorithm. We first looked at compliance, how well the staff adheres to the advice given by the algorithm. This was done by running the algorithm every time an actual

pump update was made. In general, compliance to insulin advice is not very high. Patients are on adviced insulin pump rates only 55% of the time. Insulin compliance is higher following a normoglycemic measurement, but lower following a dysglycemic measurement. Interestingly, average insulin pump rates are higher in the hypoglycemic range, but lower in the hyperglycemic range. Giving a higher (lower) insulin dose than advised increases the change of hypoglycemia (hyperglycemia). This suggests that better compliance to the insulin advice would potentially improve glycemic control. Compliance with the time advice is even lower. On average, measurements are 9 minutes later than advised. This is mainly caused by poor compliance in the hypoglycemic range. The next measurement following a hyperglycemic measurement is, on the other hand, is generally on time or even earlier than advised.

As third part of our dynamic analysis, we used the CGM-traces of the OLVG dataset to run the algorithm every 30 minutes. The result shows that the current algorithm probably needs to be revised before it can be used in combination with CGM. Mainly, this is because the algorithm uses the relative change between the current and previous glucose measurement without explicitly accounting for the elapsed time. A second way in which the algorithm could be updated is the following. Instead of using the most recent glucose measurement every 30 minutes, a moving average of or regression on the previous measurements could be used. This smoothens the variable CGM traces and uses all measurements in stead of only every fourth measurement.

Finally, we compared the two algorithms by running the OLVG algorithm on the GRIP dataset. The results shows that OLVG pump rates are lower just before hypoglycemic measurements and higher just before hyperglycemic measurements. The boluses advised by the OLVG algorithm increase the total insulin in such a way that the total insulin (pump and bolus) is higher than the GRIP insulin for all glycemic ranges.

The possibility of CGM leads to new challenges and questions. We would like to direct future reseach to this area, building upon some of the results presented in this thesis. In general, it is important to think about what an algorithm guided by CGM should look like. An analysis of the performance of GRIP when combined with CGM would be a next step. Especially because GRIP handles glucose trend in a way different (proportional) from the OLVG algorithm. We would also like to dive deeper into the comparison of GRIP and OLVG by using the approach from chapter 4. Furthermore, a thorough analysis of the compliance with GRIP might indicate ways to improve glucose control by either improving the algorithm or improving compliance. Finally, the most exciting direction of further research might be the development of an learning control algorithm. An adaptation of GRIP which improves its performance over time by learning from past experiences seems like a potentially valuable idea.

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