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The development of a glucose prediction model in critically ill patients

M. van den Boorn^{a,*,#}, V. Lagerburg^{b,#}, S.C.J. van Steen^{a,c}, R. Wedzinga^{a,b}, R.J. Bosman^a, P.H.J. van der Voort^d



^a OLVG, Department of Intensive Care, Oosterpark 9, 1091 AC Amsterdam, The Netherlands

^b OLVG, Medical Physics, Oosterpark 9, 1091 AC Amsterdam, The Netherlands

^c Amsterdam UMC, University of Amsterdam, Department of Endocrinology, Meibergdreef 9, Amsterdam, Netherlands

^d University of Groningen, University Medical Center Groningen, Department of Intensive Care, Hanzeplein 2, 9713GZ Groningen, The Netherlands

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ABSTRACT

Purpose: The aim of the current study is to develop a prediction model for glucose levels applicable for all patients admitted to the ICU with an expected ICU stay of at least 24 h. This model will be incorporated in a closed-loop glucose system to continuously and automatically control glucose values.

Methods: Data from a previous single-center randomized controlled study was used. All patients received a FreeStyle Navigator II subcutaneous CGM system from Abbott during their ICU stay.

The total dataset was randomly divided into a training set and a validation set. A glucose prediction model was developed based on historical glucose data. Accuracy of the prediction model was determined using the Mean Squared Difference (MSD), the Mean Absolute Difference (MAD) and a Clarke Error Grid (CEG).

Results: The dataset included 94 ICU patients with a total of 134,673 glucose measurements points that were used for modelling. MSD was 0.410 ± 0.495 for the model, the MAD was 5.19 ± 2.63 and in the CEG 99.8% of the data points were in the clinically acceptable regions.

Conclusion: In this study a glucose prediction model for ICU patients is developed. This study shows that it is possible to accurately predict a patient's glucose 30 min ahead based on historical glucose data. This is the first step in the development of a closed-loop glucose system.

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1. Introduction

Acute hyperglycemia is a common finding in patients at the Intensive Care Unit (ICU) as a response to severe illness [1,2]. This stress-induced hyperglycemia may occur independently of pre-existing diabetes mellitus and is associated with poor outcome and mortality [3–5]. Also, both hypoglycemia and glucose variability are associated with poor outcome [6–8]. Tight glucose regulation may reduce glucose variability [9,10], however the optimal blood glucose level in ICU patients is still debated [11]. Intervention studies show conflicting results on effect and safety of tight glucose control (i.e. risk for hypoglycemia). However, it may result in better outcomes if safely implemented [2,9,10,12,13].

The safe implementation of tight glucose control is difficult in clinical practice. Current protocols require frequent human interventions. In most ICUs, nurses perform glucose measurements by protocol at specified discrete time intervals with Point of Care (PoC) equipment. Then, insulin dose is manually adapted based on the results of these measurements and is administered via a syringe pump. Boluses are given when necessary [14]. It has been demonstrated that this approach is labour-intensive [15,16]. The protocol is not always followed properly in daily practice, especially in times with an increased workload for the nurses.

Closed-loop systems are a promising tool for tight glucose regulation and reducing workload [16–19]. For example, Leelarathna et al. showed that patients spent significantly more time in the target glucose range using a closed-loop glucose control system compared to local protocol [20]. In general, in a closed-loop system, blood glucose is continuously measured with a Continuous Glucose Monitor (CGM), which detects the glucose levels (near-)continuously in the interstitial space. These measurements are used to predict future blood glucose levels or insulin sensitivity.

* Corresponding author: OLVG, Department of Intensive Care, Oosterpark 9, 1091 AC Amsterdam, The Netherlands.

E-mail address: M.vandenBoorn@olvg.nl (M. van den Boorn).

These two authors contributed equally.

Based on these predictions the appropriate amount of insulin is automatically administered to keep blood glucose level in the target range.

The use of CGMs is already common in diabetes patients [21], however not in ICU setting. The accuracy of subcutaneous CGMs is satisfactory and they are most likely able to detect important glucose fluctuations and hypoglycemic events quicker than the traditional PoC glucose measurement [22,23], while reducing nursing workload [15]. The majority of available glucose prediction algorithms are targeted on an outpatient diabetic population [24–27]. These algorithms use a wide variety of parameters, such as physical activity, insulin administration and carbohydrates intake. In ICU patients the main factors influencing glucose regulation and the occurrence of insulin resistance are the severity of illness, (physical) stress and medication [28–30]. Therefore these factors should be taken into account when developing a glucose prediction algorithm for the ICU. Two main categories of prediction algorithms in ICU patients are available: algorithms that predict insulin sensitivity or insulin admittance and algorithms that predict glucose levels.

Most available algorithms calculate or predict changes in insulin sensitivity or directly predict the insulin admittance, such as the different versions of the STAR algorithm [39–41], the Model Predictive Control algorithm [42–49], proportional integral derivative algorithms [50], Bayesian network models [51] or AI models [52]. In some of the versions of the MPC algorithms and the STAR model, e.g. Wang et al [43] and Penning et al [41] the predicted insulin sensitivity is used to calculate a range of possible future glucose values, but none of them calculates an exact value. Furthermore, most of these algorithms are based on PoC measurements and not on CGM measurements.

Algorithms that predict glucose levels are scarce [31–37]. All of these algorithms have their limitations, some are based on PoC measurements instead of CGM, others are only tested in specific patients groups and only a few of them are used in clinical practice nowadays. The algorithms use extended and different techniques with a number of input values. E.g. Pappada et al. [38] developed a neural network to predict glucose, but they only included patients with either a diagnosis of type 1 diabetes mellitus (DM1) or type 2 diabetes mellitus (DM2) or no pre-existing DM diagnosis but an initial glucose of ≥ 150 mg/dl upon ICU admission. Zhang et al [36] developed a prediction model, but they only predict acute hypoglycemic events and not the glucose values itself.

In our research we focus on the development of a glucose prediction model, which we think is the first step in a closed-loop model. The prediction of glucose is preferred for the tight glucose regulation and management, because it is possible to validate the glucose prediction. This makes it possible to validate and optimize every single step of the closed-loop model.

We believe that a simple algorithm is necessary to make it broadly applicable and accepted in the ICU population. Therefore, a new ICU prediction algorithm has to be developed. The aim of the current study is to develop a glucose prediction model applicable for all patients admitted to the ICU with an expected ICU stay of at least 24 h. The intention is to incorporate the model in a closed-loop glucose system to continuously and automatically control glucose values.

2. Methods

2.1. Data collection

Data of a previous single-center randomized controlled study was used [53]. The patients in this research were recruited between September 2015 and June 2016. The patients recruited in this study were all mixed ICU patients, both surgical and non-

surgical admitted to ICU of the OLVG hospital in the Netherlands. Patients were recruited if they were older than 18 years and if the patients had an expected length of stay in the ICU of at least 48 h. Continuous glucose measurements of at least 4 h. had to be available. Patients were excluded when they were admitted for a ketoacidosis or after a pancreatectomy.

Patients received standard care during the study. Glucose of the patients was regulated with intravenous insulin guided by a computerized guideline [14], PoC tests and manual adjustments of the insulin pump. The glucose target range was 6.0–9.0 mmol/L. All patients received a FreeStyle Navigator II subcutaneous CGM system from Abbott (Abbott Park, Illinois, United States) during their ICU stay. The CGM system needed calibration 1, 2, 10, 24 and 72 h after application of the sensor. Calibrations were performed manually. The CGM device has a 1-h stabilization period, during which glucose measurements were not performed. The sensor was connected through wireless communication to a receiver, which displayed the real-time glucose values every minute and saved glucose values every 10th minute. For ten patients the data was exported every 1 min, because the default settings were changed. The study was approved by the local medical ethics committee based on Dutch and European legislation.

2.2. Data preparation

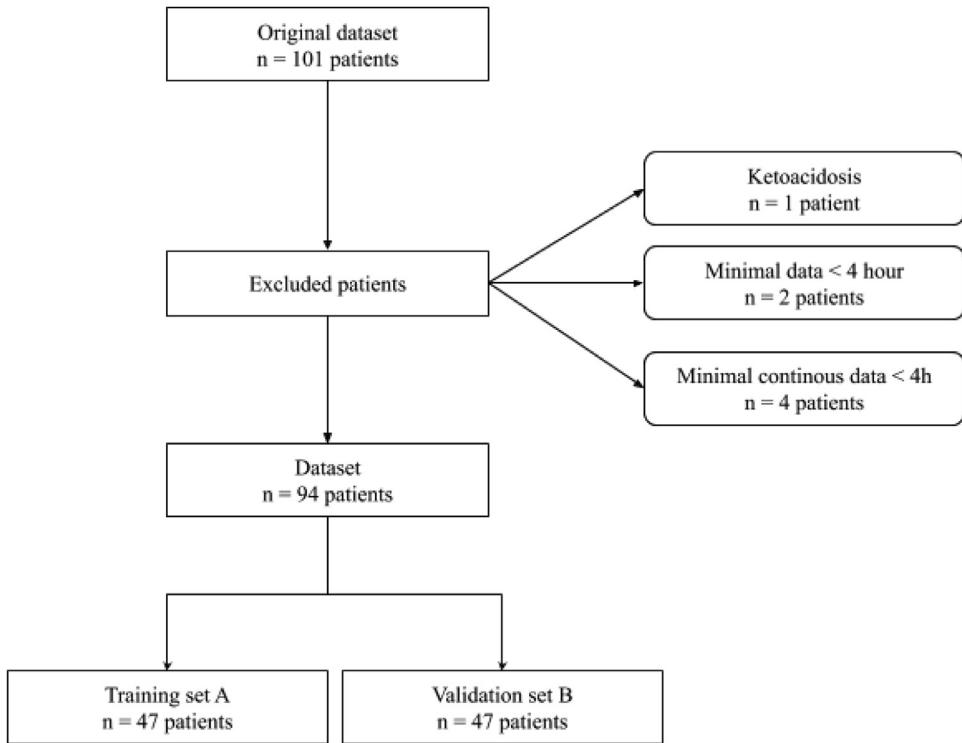
The CGM data was checked for data gaps. We defined a data gap as missing glucose measurements for more than 15 min. If a data gap existed, the data set was separated and the largest part without missing data per patient was used. If the data gap was smaller than 15 min, the data was interpolated. If the total amount of data left was less than 4 h, patients were excluded from the study. Finally, the total dataset was randomly divided into two groups: a training set A and validation set B. It was ensured that both sample sets had comparable patient characteristics with respect to gender, age, Body Mass Index (BMI) and severity of illness measured by Acute Physiology And Chronic Health Evaluation IV (APACHE IV) [54].

2.3. Mathematical model

A mathematical glucose prediction model was developed. In this model, individual characteristics involved in the insulin-glucose interaction were indirectly estimated using historical glucose data. The first and second derivative of previous data points of glucose data were calculated in this model to predict the glucose value over 30 min. The first derivative was used to predict the change of glucose (dG in mmol/L) over time (dT in minutes) and the second derivative was used to predict the speed of the change. Using Eq. 1 the blood glucose (mmol/L) of the patient is predicted 30 min ahead.

$$\begin{aligned} BG_{\text{mat}}(T_{x+30}) = & G_x + 30 * \left[\text{mean} \left(\frac{dG}{dT} \right)_{x-t_h}^x \right] \\ & + 30 * \left[\text{mean} \left(\frac{d^2G}{dT^2} \right)_{x-t_h}^x \right] \end{aligned} \quad (1)$$

where BG_{mat} is the predicted glucose in (mmol/L) at time T plus 30 min, G is the glucose of the current observation x in mmol/L, 30(min) is the interval over which the glucose is predicted, $\frac{dG}{dT}$ and $\frac{d^2G}{dT^2}$, are the first and second derivative and t_h is the time over which the first and second derivative are averaged. The derivative is calculated by taking the difference between two consecutive data points.

**Fig. 1.** Overview of the inclusion of patients.

2.4. Parameter optimization

Parameter t_h was optimized based on the data in group A. For this, the outcome parameters Mean Squared Difference (MSD) and Clark Error Grid (CEG) were used [55].

In order to optimize the averaging time t_h (used to calculate the difference between first and second glucose measurement) of the mathematical model the values of t_h of 30, 60, 90, 120, 150 and 180 min were used. Parameter t_h was determined based on test dataset A and the optimal value was used in the validation data set B.

2.5. Analysis/statistics

To analyse the accuracy of the prediction model, different approaches were used. First, the MSD was used to calculate the accuracy of the prediction model in comparison to the golden standard (see Eq. 2).

$$MSD = \frac{1}{n} \sum_{n=1}^n (glucose_n - model_n)^2 \quad (2)$$

Secondly, the Mean Absolute Difference (MAD) in percentages was calculated, see Eq. 3. The MAD demonstrates the prediction error of the mean absolute difference between the prediction model and the golden standard.

$$MAD = \frac{1}{n} \sum_{n=1}^n \frac{|model_n - glucose_n|}{glucose_n} * 100\% \quad (3)$$

A CEG was used to analyse the accuracy of the model. A CEG consists of five different regions [55]. Region A represents glucose values that deviate from the reference by no more than 20%, or are in the hypoglycemic range (<3.9 mmol/L) when the reference is also <3.9 mmol/L. Values within this range are considered clinically accurate, because they would lead to clinically correct treatment decisions. Upper and lower region B represents values

that deviate from the reference by $>20\%$ but would lead to benign or no treatment based on the predicted value. Region C values would result in overcorrecting acceptable blood glucose levels; such treatment might cause the actual blood glucose to fall below 3.9 mmol/L or rise above 10 mmol/L. Region D represents "dangerous failure to detect and treat" errors. Actual glucose values are outside of the target range. Region E represents an opposite therapy treatment, in which a hyperglycemia is treated as hypoglycemia or vice versa.

The model and statistics were implemented in Python 3.0 and SPSS 22.0 respectively. Mean and Standard Deviation (SD) were given when data was normally distributed and median and Interquartile Range (IQR) when not.

3. Results

The dataset contained data of 101 general ICU patients, of which one patient was diagnosed with ketoacidosis, and no patients had a pancreatectomy. Two patients were excluded because they had continuous glucose measurements for less than 4 h. Another four patients were excluded because they had no continuous data set of at least 4 h due to datagaps. Fig. 1 gives an overview of the included and excluded patients. The definitive dataset of 94 ICU patients contained a total of 134,673 glucose measurements that were used for modelling. The data was divided into a training set (A) and a validation set (B) of equal size. Patient characteristics were comparable between these data sets. In Table 1 patient characteristics of both groups are shown. In Table 2 data characteristics of the patients, such as number of datapoints and information about hyper- and hypoglycaemic events is shown.

3.1. Parameter optimization

The MSD for different t_h is shown in Table 3. The lowest MSD was found for a t_h of 180 min. At a t_h of 180 the highest percent-

Table 1
Patient characteristics for training set A and validation set B.

Variable	Training set A (n = 47)	Validation set B (n = 47)	Total Cohort
Age (years) ± SD	69.4 ± 10.8	68.7 ± 12.3	69.1 ± 11.5
Sex, male	22 (46.8%)	31 (66.0%)	53 (56.4%)
History of diabetes	10 (21.3%)	9 (19.2%)	19 (20.2%)
Admission	18 (38.3%)	12 (25.5%)	30 (31.9%)
– Medical	26 (55.3%)	33 (70.2%)	59 (62.8%)
– Surgical	3 (6.4%)	2 (4.3%)	5 (5.3%)
– Unknown			
BMI (kg/m ²) ± SD	27.5 ± 5.4	27.5 ± 4.3	27.5 ± 4.9
APACHE IV pm* (%) ± SD	41.0 ± 30.6	38.5 ± 29.8	39.8 ± 30.1
Died in the ICU	10 (21.3%)	8 (17.0%)	18 (19.2%)

*predicted mortality

Table 2
Data characteristics of group A and B.

Variable	Training set (n = 47)	Validation set (n = 47)	Total Cohort
Data points*	65,724	68,949	134,673
# patients with hypo	2	10	41
# patients with hyper	31	36	38
duration of hypo in minutes (median ± IQR)	17**	31 ± 85.5	
duration of hyper in minutes (median ± IQR)	41.5 ± 157.59	36 ± 129.5	
# boluses	27	35	62

*total amount of data points used for modelling

** indefinite IQR

Table 3
Accuracy of the model with different t_h.

t _h (minutes)	MSD (median ± IQR)	Clark error (region A,B,C,D,E)	Percentage of datapoints in region A (%)
30	0.42 ± 0.81	(59860, 4193, 55, 51, 3)	93.3
60	0.31 ± 0.49	(60168, 3167, 33, 32, 1)	94.9
90	0.27 ± 0.50	(59766, 2819, 22, 32, 0)	95.4
120	0.25 ± 0.50	(59175, 2678, 0, 33, 0)	95.6
150	0.25 ± 0.49	(58658, 2434, 0, 33, 0)	96.0
180	0.23 ± 0.49	(58082, 2249, 2, 29, 0)	96.2

Table 4

Accuracy values of the model in the test (A) and validation group (B).

Variable	MSD (median ± IQR)	MAD(median ± IQR)	Clark error (region A,B,C,D,E)	Percentage of datapoints in region A (%)
Model group A	0.27 ± 0.50	5.03 ± 3.12	(59766, 2819, 22, 32, 0)	95.4
Model group B	0.40 ± 0.45	5.19 ± 2.63	(62541, 3300, 14, 115, 3)	94.8

age (96.2%) of data points where in region A. We continued with a t_h of 90 min in the validation data set.

3.2. Model validation

Fig. 2 shows the measured glucose values and the predicted values of a typical patient.

The model is validated in validation data set B. During this validation, a t_h of 90 min was used. In table 4 the results of the validation are shown.

In Fig. 3 the Clarke Error Grid of all patients of group B is shown.

In group A of the mathematical model 62,575 data points (99.9%) were in the clinical acceptable regions (i.e. in regions A or B); 95.4% in region A and no values were found in region E. In group B 65,841 data points (99.8%) were in the clinical acceptable regions; 94.8% in region A and 3 points were in region E (0.004%).

The data points in region E for validation set B were caused by measurements in two patients. The result of one of these patients is visualized in Fig. 4. 98 of the 115 data points in region D were also caused by this patient. Please observe the level of fluctuating glucose values in this patient.

4. Discussion

In this study, a glucose prediction model for ICU patients was developed. It was hypothesized that historical glucose data could be a predictor for future glucose values. This study shows that our model was able to accurately predict a patient's glucose level 30 min ahead, based on historical glucose data.

Previous studies that developed a glucose prediction model for ICU patients used different model approaches like a neural network model [25,34], a linear model with several input variables [24] or a mathematical model with constant endogenous glu-

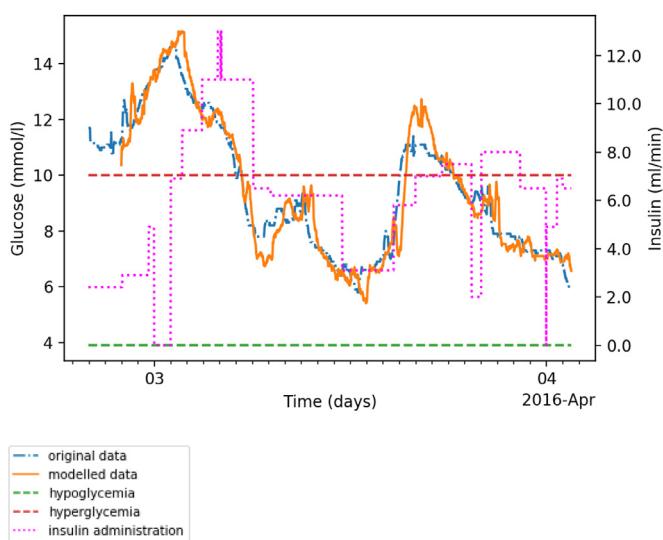


Fig. 2. Results of the model for a typical patient.

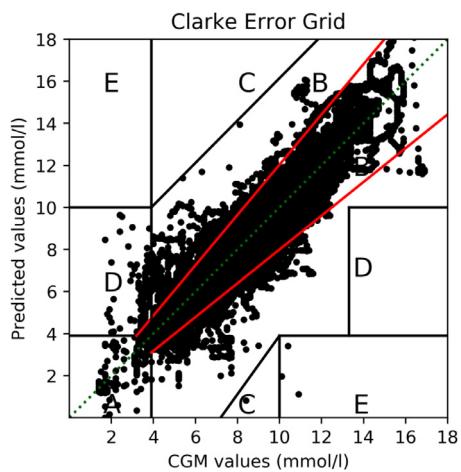


Fig. 3. Clarke Error Grid of all patients in group B.

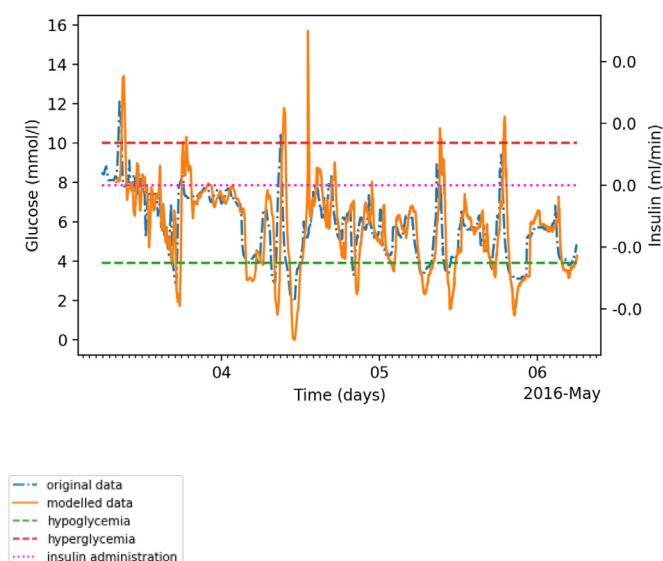


Fig. 4. Results of the model for a patient with 2 data points in region E.

cose production and other physiological parameters for a real time model [26]. Different techniques were used to quantify and validate these models. A mean absolute difference percentage of 9% and a CEG with 100% of the data points in region A and B were measured in the first model of Pappada et al. [25]. This model was based on data from 14 patients and tested on only 5 patients. No hypoglycaemic events occurred in the data from these 5 test patients, but the authors hypothesize that the model may overestimate hypoglycaemic extremes. The model also had a reduced ability to predict hyperglycaemia, with a successful prediction value of 53.6% in elevated glucose values. In the updated model of Pappada et al. [34] an average mean absolute difference percentage of 10% was reported, which ranged from 1.0% for a prediction horizon of 5 min to 10.6% for the maximum prediction horizon of 135 min. The model demonstrated accuracy in prediction of hyperglycemic glucose values (>86% of values predicted for a prediction horizon of 135 min), but the predictive accuracy for hypoglycemic values was significantly less: 53.6%, 34.4%, and 0.0% of hypoglycemic values (< 70 mg/dL) reported in CGM data for prediction horizons of 30, 60, and 135 min respectively. The model of Zhang [31] had an adjusted R-squared value of 0.83. Zhang developed a multivariable linear regression model based on discontinuous glucose measurements from finger pricks and is therefore not suitable for a closed-loop glucose system, in which continuous adaptation of the insulin delivery should be possible. The model of Lin et al. [33] is based on physiological parameters, such as insulin kinetics and gastric glucose absorption. This model requires many population assumptions, which is difficult to assess in a diverse patient population at a general ICU. It described a 75th percentile prediction error within the lower bound of typical glucometer measurement errors of 7–12% [26]. Unfortunately the authors did not present a CEG, thus eliminating the possibility to describe whether the model performs consistently well in all glucose ranges. Zhang et al [36] developed a model to predict hypoglycemic events. Their classification tree models accurately predicted 82.12% of acute hypoglycemic events and 76.99% of severe acute hypoglycemic events. It is difficult to compare these results with our results, but our CEG shows that almost all data point are in the clinical acceptable range. Van Herpe et al. [37] developed an adaptive input-output model and predicted the glucose value 1 and 4 h ahead. This model results in a mean MSE of 171 (mg/dL²) with a standard deviation of 90 (mg/dL²) for the prediction one hour ahead. When converted to mmol/L this results in a MSE of 0.73. They used a dataset of only 15 patients.

The resulting model of our study performed with a MSD of 0.4, a MAD of 5.2% and more than 99% of the data points in the clinical acceptable region. Compared to the results of the models described above, this is better than most models and comparable with the model of Van Herpe et al [37]. The mean time of a hypoglycaemic event was 62 min and the mean time of a hyperglycaemic event was 110 min. In total, 16.2% of the data points were in the hypo- or hyperglycaemic region. The different insulin sensitivity prediction studies used the time in target range as a model result, which is not comparable with our outcome parameters.

Currently there is no standard for the accuracy of continuous glucose sensors in ICU patients, although this would be of value in the comparison of the different sensors [56]. We therefore used the standard for glucose sensors for self-testing. According to ISO 15197:2013 criteria, regarding glucose sensor for self-testing, at least 95% of the values should be in region A and no more than 5% of the values in region B [28]. Our model predicts with an accuracy of 95.4% in region A and 4.5% in region B, surpassing the ISO norm. Predicting the correct glucose value in ICU patients is more difficult than in patients with diabetes mellitus, because the insulin sensitivity may vary during their ICU stay due to changes in severity of the patients' condition. Because the predicted glucose values will be used in a closed-loop system, the accuracy of

the prediction is very important for further research. The key to acceptance of a closed-loop glucose system on an ICU is a system that prevents the occurrence of hypo- and hyperglycemic events. Therefore, it is necessary that the prediction model predicts these events correctly. A Clark Error Grid is a good method to show how well the model performs in those clinical relevant regions [55]. In the test data set there were no data point in regions D and E where the treatment for hypoglycemia and hyperglycemia are exchanged. In the validation group 3 data points are in region E. These data points are caused by measurements from two patients, which contributed respectively 2 and 1 data points in region E. This is caused by an over- and undershoot in the prediction model because of fast changing glucose values in these patients. Although, in a previous study [53] the reliability of the CGM was satisfactory, we expect these values were caused by wrong measurements of the sensor. However, due to a limited amount of Accucheck measurements and intermittent glucose level measurements of these patients, we cannot determine this with certainty.

During the preparation of the dataset, several gaps in the data set were found. Most of these gaps were found in the middle of the study period, making it unlikely that insertion mistakes or expiration of the sensor were responsible for these gaps [53]. The sensor requires calibration after certain time slots. In some patients, the calibration was not performed on time, which led to data gaps. This led to less data to include in our study, but still over 130,000 data points were available. The required calibration was performed during the measurements. In some patients the calibration resulted in an adaptation of the glucose value. We did not include the calibration value into the model, because the model itself will adapt after a couple of data points. In further studies a sensor with an increased accuracy and a decreased calibration error is preferred.

In our model we used a maximum averaging time of 180 min. This maximum was chosen, because of practical reasons; averaging over more than 180 min, needs at least $180 + 30 = 210$ min to start the first prediction while it was preferred to start the prediction model as soon as possible. However, the model needs some time to have enough data points to be able to calculate the forthcoming glucose value. The results show that increasing the averaging time results in a lower MSD (0.23 at $x = 180$ and 0.27 at $x = 90$ min) and a higher percentage of measurements in region A of the CEG (96.2% compared to 95.4%). The time of 90 min was chosen to use as averaging time, after a consideration between performance and practical use. CGM data contains noise, therefore an average time of 90 min is necessary to optimize data with at least 9 data points.

The model we developed does not include any physiological parameters. In case of insulin rate changes or variations in glucose intake (IV or enteral), this could result in a delayed response of the model. To investigate if this impacts the accuracy of the model, we calculated the correlation of the deviations between the predicted and the observed CGM values and the insulin administration and glucose intake. We did not find such a correlation. Therefore addition of a physiological component to the model would not improve the outcome.

The training set and validation set showed different numbers of patients with hypoglycaemic and/or hyperglycaemic events. The patients were divided in two groups based on their patient characteristics and not on the amount of hypo- and hyperglycaemic events. Despite these differences the model performed well on dataset B, with less than 1% of the data points in region D and E of the Clark Error Grid.

5. Conclusion

The prediction of glucose value of ICU patients is the first step in the development of a closed-loop system to regulate glucose of

critically ill patients. In this study a prediction model was developed and tested in a critically ill patient population. The model predicted glucose values within the clinically relevant range for 99.8% of the cases in the validation dataset, which was within the ISO 15197:2013 criteria.

Declaration of Competing Interest

None declared.

References

- [1] K.M. Dungan, S.S. Braithwaite, J.C. Preiser, Stress hyperglycaemia, *Lancet* 373 (9677) (2009) 1798–1807.
- [2] G. van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninxckx, M. Schetz, D. Vlaeselaers, P. Ferdinand, P. Lauwers, R. Bouillon, Intensive insulin therapy in critically ill patients, *N. Engl. J. Med.* 345 (19) (2001) 1359–1367.
- [3] S.E. Capes, D. Hunt, K. Malmberg, H.C. Gerstein, Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview, *Lancet* 355 (9206) (2000) 773–778.
- [4] S. Yendamuri, G.J. Fulda, G.H. Tinkoff, Admission hyperglycemia as a prognostic indicator in trauma, *J. Trauma* 55 (1) (2003) 33–38.
- [5] L.S. Williams, J. Rotich, R. Qi, N. Fineberg, A. Espay, A. Bruno, S.E. Fineberg, W.R. Tierney, Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke, *Neurology* 59 (1) (2002) 67–71.
- [6] J.S. Krinsley, A. Grover, Severe hypoglycemia in critically ill patients: risk factors and outcomes, *Crit. Care Med.* 35 (10) (2007) 2262–2267.
- [7] J.S. Krinsley, Glycemic variability: a strong independent predictor of mortality in critically ill patients, *Crit. Care Med.* 36 (11) (2008) 3008–3013.
- [8] J. Hermannides, T.M. Vriesendorp, R.J. Bosman, D.F. Zandstra, J.B. Hoekstra, J.H. Devries, Glucose variability is associated with intensive care unit mortality, *Crit. Care Med.* 38 (3) (2010) 838–842.
- [9] G. Van den Berghe, A. Wilmer, G. Hermans, W. Meersseman, P.J. Wouters, I. Milants, E. Van Wijngaerden, H. Bobbaers, R. Bouillon, Intensive insulin therapy in the medical ICU, *N. Engl. J. Med.* 354 (5) (2006) 449–461.
- [10] M. Vogelzang, F. Zijlstra, M.W. Nijsten, Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit, *BMC Med. Inform. Decis. Mak.* 5 (2005) 38.
- [11] S. Lv, P. Ross, K. Torii, The optimal blood glucose level for critically ill adult patients, *Nurs. Crit. Care* 22 (5) (2017) 312–319.
- [12] N.-S.S. Investigators, S. Finfer, D.R. Chittock, S.Y. Su, D. Blair, D. Foster, V. Dhingra, R. Bellomo, D. Cook, P. Dodek, et al., Intensive versus conventional glucose control in critically ill patients, *N. Engl. J. Med.* 360 (13) (2009) 1283–1297.
- [13] P.E. Marik, J.C. Preiser, Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis, *Chest* 137 (3) (2010) 544–551.
- [14] E. Rood, R.J. Bosman, J.I. van der Spoel, P. Taylor, D.F. Zandstra, Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation, *J. Am. Med. Inform. Assoc.* 12 (2) (2005) 172–180.
- [15] D.T. Boom, M.K. Sechterberger, S. Rijkenberg, S. Kreder, R.J. Bosman, J.P. Wester, I. van Stijn, J.H. DeVries, P.H. van der Voort, Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial, *Crit. Care* 18 (4) (2014) 453.
- [16] M. Hoekstra, M. Vogelzang, E. Verbitskiy, M.W. Nijsten, Health technology assessment review: Computerized glucose regulation in the intensive care unit—how to create artificial control, *Crit. Care* 13 (5) (2009) 223.
- [17] P.D. Salinas, C.E. Mendez, Glucose management technologies for the critically ill, *J. Diabetes Sci. Technol.* 13 (4) (2019) 682–690.
- [18] T. Tamura, T. Yatabe, T. Namikawa, K. Hanazaki, M. Yokoyama, Glucose control using a closed-loop device decreases inflammation after cardiovascular surgery without increasing hypoglycemia risk, *J. Artif. Organs* 22 (2) (2019) 154–159.
- [19] F. Chee, T. Fernando, P.V. van Heerden, Closed-loop control of blood glucose levels in critically ill patients, *Anaesthet. Intensive Care* 30 (3) (2002) 295–307.
- [20] L. Leelarathna, S.W. English, H. Thabit, K. Caldwell, J.M. Allen, K. Kumareswaran, M.E. Wilinska, M. Nodale, J. Mangat, M.L. Evans, et al., Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial, *Crit. Care* 17 (4) (2013) R159.
- [21] W. Majeed, H. Thabit, Closed-loop insulin delivery: current status of diabetes technologies and future prospects, *Expert Rev. Med. Devices* 15 (8) (2018) 579–590.
- [22] S.C. van Steen, S. Rijkenberg, J. Limpens, P.H. van der Voort, J. Hermannides, J.H. DeVries, The clinical benefits and accuracy of continuous glucose monitoring systems in critically ill patients—a systematic scoping review, *Sensors (Basel)* (1) (2017) 17.
- [23] P. Kopecky, M. Mraz, J. Blaha, J. Lindner, S. Svacina, R. Hovorka, M. Haluzik, The use of continuous glucose monitoring combined with computer-based eMPG algorithm for tight glucose control in cardiosurgical ICU, *Biomed. Res. Int.* 2013 (2013) 186439.
- [24] C. Zecchin, A. Facchinetto, G. Sparacino, C. Cobelli, How much is short-term glucose prediction in Type 1 Diabetes improved by adding insulin delivery and

- meal content information to CGM Data? A proof-of-concept study, *J. Diabetes Sci. Technol.* 10 (5) (2016) 1149–1160.
- [25] H.C. Schaller, L. Schaupp, M. Bodenlenz, M.E. Wilinska, L.J. Chassin, P. Wach, T. Vering, R. Hovorka, T.R. Pieber, On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: evaluation under fasting conditions in patients with Type 1 diabetes, *Diabet. Med.* 23 (1) (2006) 90–93.
- [26] R. Hovorka, L.J. Chassin, M.E. Wilinska, V. Canonico, J.A. Akwi, M.O. Federici, M. Massi-Benedetti, I. Hutzli, C. Zaugg, H. Kaufmann, et al., Closing the loop: the adiclo experience, *Diabetes Technol. Ther.* 6 (3) (2004) 307–318.
- [27] S. Oviedo, J. Vehi, R. Calm, J. Armengol, A review of personalized blood glucose prediction strategies for T1DM patients, *Int. J. Numer. Method Biomed. Eng.* 6 (2017) 33.
- [28] C. Pretty, J.G. Chase, J. Lin, G.M. Shaw, A. Le Compte, N. Razak, J.D. Parente, Impact of glucocorticoids on insulin resistance in the critically ill, *Comput. Methods Programs Biomed.* 102 (2) (2011) 172–180.
- [29] C.G. Pretty, A.J. Le Compte, J.G. Chase, G.M. Shaw, J.C. Preiser, S. Penning, T. Desaive, Variability of insulin sensitivity during the first 4 days of critical illness: implications for tight glycemic control, *Ann. Intensive Care* 2 (1) (2012) 17.
- [30] L. Langouche, S. Vander Perre, P.J. Wouters, A. D'Hoore, T.K. Hansen, Van den Berghe G: Effect of intensive insulin therapy on insulin sensitivity in the critically ill, *J. Clin. Endocrinol. Metab.* 92 (10) (2007) 3890–3897.
- [31] Z. Zhang, A mathematical model for predicting glucose levels in critically-ill patients: the PIgnOLI model, *Peer J.* 3 (2015) e1005.
- [32] S.M. Pappada, B.D. Cameron, D.B. Tulman, R.E. Bourey, M.J. Borst, W. Olorunto, S.D. Bergeese, D.C. Evans, S.P. Stawicki, T.J. Papadimos, Evaluation of a model for glycemic prediction in critically ill surgical patients, *PLoS One* 8 (7) (2013) e69475.
- [33] J. Lin, N.N. Razak, C.G. Pretty, A. Le Compte, P. Docherty, J.D. Parente, G.M. Shaw, C.E. Hann, J. Geoffrey Chase, A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients, *Comput. Methods Programs Biomed.* 102 (2) (2011) 192–205.
- [34] S.M. Pappada, M.H. Owais, B.D. Cameron, J.C. Jaume, A. Mavarez-Martinez, R.S. Tripathi, T.J. Papadimos, An artificial neural network-based predictive model to support optimization of inpatient glycemic control, *Diabetes Technol. Ther.* 22 (5) (2020) 383–394.
- [35] A. Le Compte, J.G. Chase, A. Lynn, C. Hann, G. Shaw, X.W. Wong, J. Lin, Blood glucose controller for neonatal intensive care: virtual trials development and first clinical trials, *J. Diabetes Sci. Technol.* 3 (5) (2009) 1066–1081.
- [36] Y. Zhang, Predicting occurrences of acute hypoglycemia during insulin therapy in the intensive care unit, *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* 2008 (2008) 3297–3300.
- [37] T. Van Herpe, M. Espinoza, B. Pluymers, I. Goethals, P. Wouters, G. Van den Berghe, B. De Moor, An adaptive input-output modeling approach for predicting the glycemia of critically ill patients, *Physiol. Meas.* 27 (11) (2006) 1057–1069.
- [38] S.M. PappadaT.J. Papadimos., An Artificial Neural Network-based Predictive Model to Support Optimization of Inpatient, *Diabetes Technol and Therapeutics*, Mary Ann Liebert, Inc, 2020.
- [39] J.L. Dickson, J.G. Chase, A. Lynn, G.M. Shaw, Model-based glycaemic control: methodology and initial results from neonatal intensive care, *Biomed. Tech. (Berl.)* 62 (2) (2017) 225–233.
- [40] S. Penning, A.J. Le Compte, P. Massion, K.T. Moorhead, C.G. Pretty, J.C. Preiser, G.M. Shaw, F. Suhami, T. Desaive, J.G. Chase, Second pilot trials of the STAR-Liege protocol for tight glycemic control in critically ill patients, *Biomed. Eng. Online* 11 (2012) 58.
- [41] S. Penning, A.J. Le Compte, K.T. Moorhead, T. Desaive, P. Massion, J.C. Preiser, G.M. Shaw, J.G. Chase, First pilot trial of the STAR-Liege protocol for tight glycemic control in critically ill patients, *Comput. Methods Programs Biomed.* 108 (2) (2012) 844–859.
- [42] J.J. Cordingley, D. Vlasselaers, N.C. Dormand, P.J. Wouters, S.D. Squire, L.J. Chassin, M.E. Wilinska, C.J. Morgan, R. Hovorka, G. Van den Berghe, Intensive insulin therapy: enhanced Model Predictive Control algorithm versus standard care, *Intensive Care Med.* 35 (1) (2009) 123–128.
- [43] Y. Wang, H. Xie, X. Jiang, B. Liu, Intelligent closed-loop insulin delivery systems for ICU patients, *IEEE J. Biomed. Health Inform.* 18 (1) (2014) 290–299.
- [44] M.E. Wilinska, J. Blaha, L.J. Chassin, J.J. Cordingley, N.C. Dormand, M. Ellmerer, M. Haluzik, J. Plank, D. Vlasselaers, P.J. Wouters, et al., Evaluating glycemic control algorithms by computer simulations, *Diabetes Technol. Ther.* 13 (7) (2011) 713–722.
- [45] K. Amrein, M. Ellmerer, R. Hovorka, N. Kachel, H. Fries, D. von Lewinski, K. Smolle, T.R. Pieber, J. Plank, Efficacy and safety of glucose control with Space GlucoseControl in the medical intensive care unit—an open clinical investigation, *Diabetes Technol. Ther.* 14 (8) (2012) 690–695.
- [46] X.W. Wong, J.G. Chase, G.M. Shaw, C.E. Hann, T. Lotz, J. Lin, I. Singh-Levett, L.J. Hollingsworth, O.S. Wong, S. Andreassen, Model predictive glycaemic regulation in critical illness using insulin and nutrition input: a pilot study, *Med. Eng. Phys.* 28 (7) (2006) 665–681.
- [47] B. Xu, W. Jiang, C.Y. Wang, L. Weng, X.Y. Hu, J.M. Peng, B. Du, Comparison of space glucose control and routine glucose management protocol for glycemic control in critically ill patients: a prospective, randomized clinical study, *Chin. Med. J. (Engl.)* 130 (17) (2017) 2041–2049.
- [48] J. Blaha, B. Barteczko-Grajek, P. Berezowicz, J. Charvat, J. Chvojka, T. Grau, J. Holmgren, U. Jaschinski, P. Kopecky, J. Manak, et al., Space GlucoseControl system for blood glucose control in intensive care patients—a European multi-centre observational study, *BMC Anesthesiol.* 16 (2016) 8.
- [49] R. Kulnik, J. Plank, C. Pachler, M.E. Wilinska, A. Groselj-Strele, D. Rothlein, M. Wufka, N. Kachel, K.H. Smolle, S. Perl, et al., Evaluation of implementation of a fully automated algorithm (enhanced model predictive control) in an interacting infusion pump system for establishment of tight glycemic control in medical intensive care unit patients, *J. Diabetes Sci. Technol.* 2 (6) (2008) 963–970.
- [50] X.W. Wong, I. Singh-Levett, L.J. Hollingsworth, G.M. Shaw, C.E. Hann, T. Lotz, J. Lin, O.S. Wong, J.G. Chase, A novel, model-based insulin and nutrition delivery controller for glycemic regulation in critically ill patients, *Diabetes Technol. Ther.* 8 (2) (2006) 174–190.
- [51] S.K. Nachimuthu, A. Wong, P.J. Haug, Modeling glucose homeostasis and insulin dosing in an intensive care unit using dynamic Bayesian networks, *AMIA Annu. Symp. Proc.* 2010 (2010) 532–536.
- [52] L. DeJournett, J. DeJournett, In silico testing of an artificial-intelligence-based artificial pancreas designed for use in the intensive care unit setting, *J. Diabetes Sci. Technol.* 10 (6) (2016) 1360–1371.
- [53] S. Rijkenberg, S.C. van Steen, J.H. DeVries, P.H.J. van der Voort, Accuracy and reliability of a subcutaneous continuous glucose monitoring device in critically ill patients, *J. Clin. Monit. Comput.* 32 (5) (2018) 953–964.
- [54] J.E. Zimmerman, A.A. Kramer, D.S. McNair, F.M. Malila, Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients, *Crit. Care Med.* 34 (5) (2006) 1297–1310.
- [55] W.L. Clarke, D. Cox, L.A. Gonder-Frederick, W. Carter, S.L. Pohl, Evaluating clinical accuracy of systems for self-monitoring of blood glucose, *Diabetes Care* 10 (5) (1987) 622–628.
- [56] D.C. Klonoff, The need for clinical accuracy guidelines for blood glucose monitors, *J. Diabetes Sci. Technol.* 6 (1) (2012) 1–4.