A model of insulin saturation and glucose balance for glycaemic control in ICU patients

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Abstract: Hyperglycaemia due to reduced insulin sensitivity is prevalent in critically ill patients and increases mortality and complications. However, consistent tight control has proven elusive. In particular, properly accounting for the saturation of insulin action is important in intensive insulin therapy. This paper introduces a composite metabolic model of insulin kinetics and blood glucose balance. Saturation of insulin action at high insulin concentrations is modelled as a non-linearity and reduced insulin sensitivity is modelled as either a scaling of peripheral insulin (before the non-linearity) or as a scaling of insulin effect (after the non-linearity). Retrospective clinical data from 10 intensive care patients are used to evaluate these approaches based on the resulting accuracy in predicting glycaemic response to intervention. For predictions of blood glucose longer than 1/2 hour ahead scaling of insulin effect gave a 1.6 fold smaller RMS error. Results for short-term (1-hour) and long-term (8-hour) predictions were 16% and 34% RMS error for scaling of insulin effect compared to 22% and 59% for scaling of peripheral insulin, respectively (P< 0.01). It can be concluded that scaling the insulin effect is a more suitable approach in this model structure.
1. INTRODUCTION

Since the publication of the first large, randomized, controlled study in surgical patients in 2001 [1], several groups have demonstrated the benefits and risks of tight glucose control using intensive insulin therapy [2, 3, 4, 5]. However, optimal glycaemic levels, the risk of hypoglycaemia, and which patients benefit, remain subjects of debate [6]. The cost in clinical burden and effort is also an issue in the success of practical implementations [7, 8]. In particular, tight control has been demonstrated with protocols where blood glucose is measured every one to two hours [5, 9, 10].

Model-based algorithms enable patient-specific and more optimal treatment based on their ability to successfully predict the glucose response to infusions of insulin and nutrition [11]. Success is thus a function of the model's ability to accurately capture the dynamics of insulin action over time in the highly variable critical care patient. In particular, the experimentally observed saturation of insulin effect [12, 13, 14, 15] should be taken into account by a model-based controller to limit the use of insulin. Such limitations may be critical given that insulin sensitivity tends to increase over time in critical care [16], and excessive use of insulin increases the risk of severe hypoglycaemia [17]. Lonergan et al. [18] modeled these dynamics and limited infusion rates accordingly. In contrast, glycaemic control protocols have been published that utilise maximum insulin infusion rates of 10 or 20 units per hour [2, 19] or have no limit [9].

Finally, accurate, longer-term predictions offer the opportunity to reduce the frequency of blood glucose measurements and thus reduce the clinical burden. However, very few efforts have quantified the quality of longer term (> 2 hours) predictions in critical care cohorts [20]. In specific, there is a definite trade-off between frequency of blood glucose measurements and control quality that is a function of the model and methods utilised [18].

This paper presents a composite physiological model, 'Glucosafe'. This model is used to explore two different physiological locations of insulin saturation and their ability to provide accurate long-term predictions of blood glucose. The entire analysis utilises clinical data from critical care patients.
2. MODEL STRUCTURE

2.1 Insulin kinetics

Insulin kinetics are based on a two compartment model [21] with a plasma compartment that comprises the plasma and hepatic space and a peripheral compartment that represents interstitial fluid. Insulin appears in the plasma compartment either by exogenous input (intravenous infusions and bolus injections) or by endogenous production by the pancreas. In the model only the post-hepatic insulin appearance is considered, i.e. the residual insulin that reaches the bloodstream after the first pass through the liver [22].

Insulin is irreversibly cleared by the liver and, to a lesser extent, the kidneys. Intercompartmental transport is assumed to be based on diffusion. In the peripheral compartment, insulin molecules bind to receptors at the cell surfaces, are endocytized and degraded inside the cell.

An illustration of the insulin kinetics model is shown in the left half of Figure 1. The following differential equations describe the model [21]:

\[
\frac{dI}{dt} = (-n_K - n_L) I(t) - \frac{n_I}{V_P} (I(t) - Q(t)) + \frac{P(t) + U(t)}{V_P} \\
\frac{dQ}{dt} = -n_C Q(t) + \frac{n_I}{V_Q} (I(t) - Q(t))
\]

where \(I(t)\) and \(Q(t)\) are plasma insulin and peripheral insulin concentrations [mU/l], and \(V_P\) and \(V_Q\) [l] are volumes of the plasma/hepatic and the peripheral compartment, respectively. \(n_L\), \(n_K\) and \(n_C\) are fractional rates [min\(^{-1}\)] of the insulin clearance in the liver, the kidneys and of the endocytosis.

\(I(t)\): plasma insulin concentration
\(Q(t)\): peripheral insulin concentration
\(V_P\): volume of plasma compartment
\(V_Q\): volume of peripheral compartment
\(n_L\): insulin clearance rate liver
\(n_K\): insulin clearance rate kidneys
\(n_C\): insulin clearance rate endocytosis

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**Fig. 1.** The Glucosafe model. Optionally, reduced insulin sensitivity is modeled by a factor \(s_{\text{pre}}\) that scales peripheral insulin \(Q\), or by a factor \(s_{\text{post}}\) that scales insulin effect \(i\).
$n_1$ [l/min] is the diffusion constant for insulin between the plasma and peripheral compartments. $P$ and $U$ [mU/min] are the exogenous and post-hepatic endogenous appearance rates, respectively.

Plasma and peripheral distribution volume, diffusion constant and renal clearance rate are assumed to be characteristics shared by both insulin and C-peptide. Hence, Van Cauter et al.’s [23] method to derive population values for C-peptide kinetics based on a patient’s sex, age, height, weight and diabetic diagnosis is used to calculate $V_P$ and $n_K$ (see Appendix). Provided the transport between the plasma and the peripheral compartments is passive, the peripheral volume is calculated as

$$V_Q = \frac{k_1}{k_2} V_P$$

and the diffusion constant is

$$n_1 = V_P k_1$$

where $k_1$ and $k_2$ are Van Cauter’s fractional turnover rates between compartments. Hepatic insulin clearance from plasma is calculated from an average 1.57 ml/kg/min (averaged over values in [24]). The post-hepatic appearance rate of endogenous insulin, $U(t)$, is assumed to be 35 U/d (see results) in all but type I diabetic patients, where it is set to 0. Finally, $n_C$ is calculated using steady-state assumptions in Equation 2: Setting $\frac{dQ}{dt} = 0$, $I(t) = I_{SS}$, $Q(t) = Q_{SS}$ yields

$$n_C = \frac{n_1 \left( \frac{I_{SS}}{Q_{SS}} - 1 \right)}{V_Q} = \frac{n_1 (\gamma - 1)}{V_Q}$$

where we assume the steady-state concentration ratio

$$\gamma = \frac{I_{SS}}{Q_{SS}} = \frac{5}{3}$$

of which is an estimate based on studies in which insulin concentration was directly measured in muscle interstitial fluid employing a microdialysis catheter technique and where concentration ratios of $\frac{3}{1}$ to $\frac{2}{1}$ [25], $\frac{2}{1}$ [26, 27] and $\frac{5}{3}$ [28] have been reported.

2.2 Insulin action on glucose uptake

A number of endocrine processes involve the presence of insulin; in particular, insulin mediates the uptake of glucose in insulin-sensitive tissue such as skeletal muscle and fat and increases the rate of glycogen synthesis in the liver. Earlier
studies have shown a saturating effect of insulin action on glucose uptake [12, 13, 14, 15]. Insulin effect is therefore expressed as a non-linear function of the insulin concentration in the peripheral compartment. Several physiological receptor-based models for this non-linearity have been proposed [29].

Arleth et al. [30] used the nonlinear transformation based on experimentally determined data in healthy subjects [13, 14]:

\[ i^* = \frac{u - u_0}{\sqrt{(u - u_0)^2 + k^2}} \]  

where \( i^* \) is a variable that quantifies insulin effect in response to the steady-state insulin infusion rate \( u \) [mU/kg/min] assuming normal insulin sensitivity in the investigated subjects. A least squares fit to the data points yielded the parameter values \( u_0 = 0.083 \) mU/kg/min, \( d = 1.77 \) and \( k = 0.539 \) mU/kg/min [30]. It is conceptually convenient to interpret \( i^* \) as the fraction of maximal insulin effect. \( i^* \) is therefore normalized to lie in the interval from 0 to 1,

\[ i = \frac{i^* - i^*(0)}{1 - i^*(0)} \]  

Equations 7 and 8 link steady-state infusion to fractional insulin effect. On average, steady-state plasma insulin \( I_{SS} \) and steady-state insulin infusion rate \( u \) are linked by

\[ u = \frac{I_{SS}}{C} \]  

where \( C = 98.1 \) kg min/l (see [30] for references). Combined with Equation 6 this gives the steady-state relationship

\[ u = \frac{\gamma}{C} Q_{SS} \]  

If it is assumed that the saturation of insulin effect is the same for steady-state (\( Q_{SS} \)) as for time varying (\( Q(t) \)) peripheral insulin concentrations, Equation 10 can be written as

\[ u = \frac{\gamma}{C} Q(t) \]  

In patients with reduced insulin sensitivity, this may be modeled by a factor \( s_{pre} \) that is multiplied with the peripheral insulin concentration \( Q(t) \) to give a reduced concentration \( Q_{S}(t) \) [30], thus yielding

\[ u = \frac{\gamma}{C} Q(t) s_{pre} \]  

\[ = \frac{\gamma}{C} Q_{S}(t) \]
Fig. 2. Fractional insulin effect as function of peripheral insulin. The three graphs are examples for: insulin effect in subjects with normal insulin sensitivity ($s_{\text{pre}} = s_{\text{post}} = 1$), the scaling of peripheral insulin with $s_{\text{pre}} = 0.2$ and scaling of insulin effect $i$ with $s_{\text{post}} = 0.2$.

which inserted in Equation 7 gives:

$$i^*(t) = \frac{\tilde{\gamma} Q_S(t) - u_0}{\sqrt{(Q_S(t) - u_0)^d + k^d}} = \frac{Q_S(t) - u_0 \frac{C}{\gamma}}{\sqrt{(Q_S(t) - u_0 \frac{C}{\gamma})^d + (k \frac{C}{\gamma})^d}}$$

$$= \frac{Q_S(t) - Q_0}{\sqrt{(Q_S(t) - Q_0)^d + Q_k^d}}$$

with $Q_0 = u_0 \frac{C}{\gamma} = 4.9 \text{ mU/l}$ and $Q_k = k \frac{C}{\gamma} = 31.7 \text{ mU/l}$. The middle part of Figure 1 shows the scaling of peripheral insulin with $s_{\text{pre}}$ followed by a box with the model equations of saturation of insulin effect.

A second option is to model reduced insulin sensitivity by multiplying the fractional insulin effect $i$ by a factor $s_{\text{post}}$ to give a reduced insulin effect $a$ such that:

$$a(t) = s_{\text{post}} i(t)$$

as schematically shown in Figure 1, to the right of the box with model equations. This second option implies that $s_{\text{pre}} = 1$ and therefore $Q_S(t) = Q(t)$.

$s_{\text{pre}}$ and $s_{\text{post}}$ are dimensionless factors that are assumed to be 1 for patients with normal insulin sensitivity. The scaling of peripheral insulin (Equation 12) could be interpreted as a modification in the dynamics of the binding and unbinding of insulin to its receptor, while the second option (Equation 14) could be interpreted as a downregulation of some part of the insulin signalling pathway, for example a reduction in the number of membrane-bound insulin receptors [29].
If it is assumed that insulin sensitivity scales peripheral insulin $Q$, then the peripheral concentration at which half-effect is obtained is increased. An example with $s_{\text{pre}} = 0.2$ and $s_{\text{post}} = 1$ is shown in Figure 2. If, alternatively, it is assumed that insulin sensitivity scales fractional insulin effect $i$, then the half-effect concentration is unchanged. An example with $s_{\text{pre}} = 1$ and $s_{\text{post}} = 0.2$ is shown in Figure 2.

The threshold of saturation during stress-induced hyperglycaemia has to our knowledge not been determined. Therefore, we shall consider both options.

### 2.3 Blood glucose concentration and glucose appearance

The change in blood glucose concentration $\frac{dG}{dt}$ [mmol/l/min] is a function of total glucose appearance and endogenous glucose balance and is thus modelled as:

$$\frac{dG}{dt} = \frac{(e(t) + p(t) + E(t)) W}{V_G}$$  \hspace{1cm} (15)

$E(t)$ [mmol/kg/min] is the endogenous glucose balance (see section below). $e(t)$ and $p(t)$ denote absorption rates [mmol/kg/min] from enteral and parenteral nutrition, respectively. $W$ [kg] is the body mass. $V_G$ [l] is the glucose distribution volume calculated as [30]:

$$V_G = 0.19 \times \frac{l}{kg} \times W$$  \hspace{1cm} (16)

The glucose absorption rate $e(t)$ is modelled as a nonlinear function of carbohydrate gut content $N$ as proposed by Arleth et al. [30] and shown in Figure 3. However, in critical care patients, gastric emptying is often delayed [31]. In a study of 132 critical care patients with different admission diagnoses, delayed gastric emptying was observed in 60% of patients [32]. Thus, we scaled $e(t)$ with a delay factor $m$ that was estimated from [32, 33], yielding the function graph shown in Figure 3 for the enterally fed, critically ill patient.

The model of glucose appearance from enteral and parenteral nutrition is schematically illustrated in the lower right part of Figure 1.

### 2.4 Endogenous glucose balance

The endogenous glucose balance denotes the combined turnover of hepatic glucose balance $H$ [mmol/kg/min], renal glucose excretion $R$ [mmol/kg/min], insulin-dependent peripheral absorption $P_{\text{GLUT4}}$ [mmol/kg/min] and insulin-
Fig. 3. Glucose absorption rate $e$ as function of carbohydrate gut content $N$. Dashed line: subjects with no delayed gastric emptying (taken with permission from [30]). Solid line: absorption rate in the enterally fed, critically ill patient with delayed gastric emptying, the delay factor $m$ is 0.5.

Independent peripheral absorption $P_{GLUT1+3}$ [mmol/kg/min]. Arleth et al. [30] give the following equation for the endogenous balance $E$:

$$E(t) = H(t) - R(t) - P_{GLUT4}(t) - P_{GLUT1+3}(t)$$  \hspace{1cm} (17)

Based on measured values in type one diabetic patients (see [30] for references), the hepatic glucose turnover is

$$H(t) = A_H G_1(t) + B_H a + C_H$$ \hspace{1cm} (18)

where $H(t)$ is modeled as being linearly dependent on the blood glucose concentration $G(t)$ [mmol/l] until a certain threshold $G_{thresh}$, whereafter it is independent of the blood glucose concentration. Insulin-stimulated hepatic glucose uptake is described by a linear model for the dependence on $a$, the fractional insulin effect. Values are $G_{thresh} = 11.98$ mmol/l, $A_H = -7.67 \times 10^{-4}$ l/kg/min, $B_H = -0.0247$ mmol/kg/min and $C_H = 0.0223$ mmol/kg/min [30].

Glucose is reabsorbed in the proximal tubule at normoglycaemic glucose concentrations. Reabsorption saturates at plasma concentrations exceeding 10 to 15 mmol/l and glucosuria develops. The maximal reabsorption rate $T_{max}$ is assumed to be 2 mmol/min [34, 35]. The model for the renal glucose excretion is [30]:

$$R(t) = \frac{f(\max(0, F_G G(t) - T_{max}))}{W}$$  \hspace{1cm} (19)

where f() is a function that computes a 7 mmol/l wide moving average to describe the smooth transition from total reabsorption to renal excretion [34]. $F_G$ is the glomerular filtration rate that is assumed to be [35]:

$$F_G = 0.0694 \frac{l/min}{m^2 \times BSA}$$  \hspace{1cm} (20)
Fig. 4. Endogenous glucose balance E for a 70 kg person with 1.73 m² body surface area (modified from [30]).

where BSA [m²] is the body surface area (see appendix).

Peripheral uptake $P_{\text{GLUT1+3}}$ refers to the insulin-independent GLUT1 and GLUT3 transporter mediated uptake [36] and is modeled as [30]

$$P_{\text{GLUT1+3}}(t) = \frac{J_{1+3} G(t)}{G(t) + K_{M1+3}}$$

(21)

where $J_{1+3} = 0.0093$ mmol/kg/min is the maximal uptake rate and $K_{M1+3} = 1.5$ mmol/l is the affinity of the hypothetically combined GLUT1 and GLUT3 carrier.

$P_{\text{GLUT4}}$ refers to the insulin-dependent GLUT4 transporter mediated uptake [36] and is thus modeled as being linearly dependent on the insulin effect $a$.

The model is [30]

$$P_{\text{GLUT4}}(t) = \frac{J_{4} G(t)}{G(t) + K_{M4}} a$$

(22)

with values of 0.0848 mmol/kg/min for the maximal uptake rate $J_{4}$ and 5 mmol/l for the GLUT4 carrier affinity $K_{M4}$.  

Figure 4 shows the endogenous glucose balance surface for a person with body mass 70 kg and body surface area 1.73 m², with values of $G$ ranging from 0–20 mmol/l and fractional insulin effect between 0 (no effect) and 1 (full effect).

3. PARAMETER IDENTIFICATION AND DATA ANALYSIS

Data from 10 hyperglycaemic patients, admitted to the neuro- and trauma intensive care unit (ICU) at Aalborg hospital, Denmark, between 2005 and 2007, were retrospectively gathered. Ethical approval was given by the Ethical Committee for the Region of Northern Jutland. Patients had received glycaemic control according to a local nurse-driven protocol that aims for 5 to 8 mmol/l as target blood glucose concentration. Blood samples were taken via an arterial
catheter and analysed using a blood gas analyzer (ABL™ 700, Radiometer).

All patients were given fast-acting insulin infusions and in addition to that 12 bolus injections were given to 5 patients. Height and body mass were not available. Instead, values of 170 cm and 70 kg were assumed for all patients.

Patient characteristics at admission time and glycaemic control data are listed in Table 1.

The data were used for a comparison of the two models with respect to their accuracy in predicting blood glucose over time in different patients. For each new blood glucose measurement, I(t), Q(t), N(t) and G(t) were simulated in discrete one-minute time steps over the preceding 16 hours. Simulations were run successively with both model options, i.e. first with scaling peripheral insulin and the second time with scaling of insulin effect. The first 4 of the 16 hours period were used for simulation run-in. Over the remaining 12 hours the parameters s_{pre} or s_{post} were identified by minimizing the root mean square (RMS) of the simulation errors:

\[ RMS = \sqrt{\frac{\sum_{i=1}^{n} e_i^2}{n}} \]  \hspace{1cm} (23)

where \( e_i = \ln m_i - \ln p_i \). \( m_i \) is the i'th measurement and \( p_i \) is the models simulation of the i'th measurement. A logarithmic scale is used because measurements are approximately log-normally distributed (see results).
Fig. 5. Example of model simulation and prediction with data from patient A9. At any new measurement (encircled square), a simulation is run to fit the blood glucose to the measurements in the preceding 12 hours (preceded by a 4 hour run-in, in this time measurements (light gray squares) are disregarded). The identified insulin sensitivity (0.25 for the example) is used to predict the blood glucose (3 hours shown here), starting at the last measured value.
Fig. 6. Blood glucose measurements (on log scale).

Upon each simulation followed a prediction of blood glucose measurements over the next 8 hours using either model with the identified insulin sensitivity, respectively. For each prediction $i$, the predicted blood glucose value $p_i$ and the measured value $m_i$ were recorded as well as the length of the forecast $t_i$ (i.e. the prediction time). As for the simulation errors, Equation 23 was also used to calculate the RMS of prediction errors. Figure 5 gives an example of a simulation followed by a prediction for using the model of scaling insulin effect.

The variances of predictions were compared using Levene’s test. The value for the post-hepatic endogenous insulin production rate $U$ was chosen based on the smallest RMS prediction error for different values of $U$ and was used in all calculations. SPSS software version 16.0 and MATLAB version 7.5 were used for statistical analysis and data fitting, respectively.

4. RESULTS

Figure 6 shows blood glucose measurements for all 10 patients on a logarithmic scale. The figure shows that the measurements have an approximately log-normal distribution, and hence, the model comparison is based on the analysis of logarithmic prediction errors as stated in the previous section.

Table 2 gives the means and standard deviations (SD) of the fitted values of $s_{pre}$ and $s_{post}$ that came out of the simulations. Values of $s_{pre}$ were smaller than values of $s_{post}$ and had greater variances from their means.

The logarithmic prediction errors by patient and model are displayed in the box-and-whiskers plot in Figure 7. Scaling insulin effect predicted the blood
glucose more accurately as interquartile ranges were smaller in 9 of 10 patients and there were fewer and smaller outliers in 8 patients compared to the model of scaling peripheral insulin. In both diabetic subjects A4 (type 2) and A10 (type 1) prediction errors did not differ from errors in non-diabetic patients for both model options.

Figure 7 compares the two models on the basis of prediction accuracy in different patients. Independent of the used model there was a wide spread in size of prediction errors between patients. The reason for this could be longer or shorter prediction times due to varying blood sampling intervals (the time between two consecutive measurements) in this group of patients. The histogram of the blood sampling intervals can be seen in Figure 8. It shows that in 50% of all cases intervals were shorter than 3 hours, though the range was wide between patients (min: 11 minutes in subject A10; max: 1437 minutes in subject A2) as well as within patients (all patients had min-max
Correlation testing gave inconsistent results between prediction error and prediction time in individual patients, though over all patients the correlation was significantly positive for both models (scaling insulin effect: $r=0.203$; scaling peripheral insulin: $r=0.198$; $P<0.01$).

For a comparison of the models prediction accuracy against prediction time Figure 9 shows the RMS of prediction error for 9 consecutive prediction time intervals. For both models, the RMS error increased with longer prediction times. Scaling of insulin effect yielded an about 1.6 fold smaller RMS prediction error compared to scaling of peripheral insulin in all intervals. For the shortest prediction times $t = [1–30 \text{ min}]$ the difference in RMS was insignificant (scaling insulin effect: 0.046; scaling peripheral insulin: 0.081), whereas for longer prediction times scaling of insulin effect was significantly better ($P<0.01$).

The graphs in Figure 9 are fits to the RMS data using the function $\sigma = \sqrt{\sigma_0^2 + \sigma_m^2 t}$ where $\sigma_0^2$ is an estimate of variance of two consecutive blood samples with an infinitesimal small time delay and $\sigma_m^2$ is the model prediction error variance that is assumed to increase linearly with prediction time $t$. The reported imprecision of blood gas analyzers of the ABL $^{\text{TM}}$ 700 series is 0.1 mmol/l at a 5 mmol/l level [37], or 2%. Multiplication of the RMS on the y-axis of Figure 9 with 100 gives a good approximation to absolute percent values. $\sigma_0 = 0.02\sqrt{2}$ was used for fitting the curves, with $\sqrt{2}$ being used to double the variance, because two measurements are involved. This yielded $\sigma_m = 0.01863$ (CI 0.01685; 0.02041) for scaling of insulin effect and $\sigma_m = 0.03127$ (CI 0.02828; 0.03427) for scaling of peripheral insulin.

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**Fig. 8.** Histogram over sampling intervals of all 10 patients.
Fig. 9. Root mean square of logarithmic prediction error (RMS) for short and long prediction times (first marker: all predictions up to 30 minutes ahead; second: 31–90 min; third: 91–150 min; etc.). Curves are fits to the RMS data using the function $\sigma = \sqrt{\sigma_0^2 + \sigma_m^2 t}$.

Fig. 10. RMS of prediction error at prediction times $t=\{31–90 \text{ min}\}$ for different post-hepatic endogenous insulin production rates using the model of scaling of insulin effect for patients A1 to A9. 0.03425) for scaling of peripheral insulin as identified model prediction error variances.

Figure 10 illustrates the relationship between choice of post-hepatic endogenous insulin production rate $U$ and RMS of prediction error. A constant rate of $U = 35 \text{ U/d}$, or 24.31 mU/min was found to give the smallest RMS error in non type I diabetic patients, as shown in Figure 10 for RMS of prediction error at prediction times $t=\{31–90 \text{ min}\}$ using the model of scaling of insulin effect for patients A1 to A9.

5. DISCUSSION

A composite physiology-based model of insulin kinetics and blood glucose balance has been presented and tested using retrospective ICU data. Two options for the modelling of reduced insulin sensitivity in critically ill patients were compared. The first option, proposed by Arleth et al. [30], models reduced insulin action by estimating a factor $s_{\text{pre}}$ that scales peripheral insulin concentration, as expressed in Equation 12. A second and new approach
investigated the estimation of a factor $s_{\text{post}}$ that scales fractional insulin effect, as shown in Equation 14. The identified parameters were compared and results of short- and long-term predictions were shown.

Scaling the insulin effect gave more accurate predictions of blood glucose than scaling of peripheral insulin based on a comparison of logarithmic prediction errors by patient and by length of prediction time. Short-term (1-hour) predictions yielded about 16% absolute RMS error for scaling of insulin effect and 22% for scaling of peripheral insulin, while long-term (8-hour) predictions yielded 34% and 59% error for scaling insulin effect and scaling peripheral insulin, respectively. Sampling intervals in the investigated 10 patients were highly variable and averaged around 2 to 3.5 hours. Thus the model of scaling the insulin effect is more appropriate for these patients giving better results on longer prediction times. However, mean prediction errors greater than 20 percent may be higher than desired, necessitating shorter intervals [18]. The obtained curve fits to the RMS data are model-specific and can be very practical for estimations of the model prediction error variance in clinical control applications, for example in decisions regarding the scheduling of measurements [38].

Based on the estimation of the smallest RMS error, as shown in Figure 10, a constant post-hepatic endogenous insulin production rate of 35 U/d has been used throughout the model comparison, except for type I diabetic patients, where the rate was set to 0. It has been estimated that, in any 24-hour period, 18 to 32 units per day are secreted by the pancreas under basal conditions and about the same amount is secreted in response to meals [39, 40]. This amounts to a total insulin production of 36 to 64 units per day of which 50–80% is extracted during the first liver passage [22, 24]. The post-hepatic production rate in this study lies at the high end of these values. However, this may be due to the hyperglycaemic state of the investigated patient cohort and an associated higher endogenous insulin production. Recovery from illness in these patients may downregulate the estimated value.

The results are clearly in favour of the new approach to scale insulin effect. With all input data being identical, it can be argued that this is due to a better reflection of the location of insulin action in this model than in the previously proposed model by Arleth et al., at least in hyperglycaemic ICU patients.
However, the analysis has some limitations with respect to an investigation of the impact of several model parameters. For example, if height and weight of the patients had been available, some of the parameters derived with the Van Cauter method would have differed from their values in this study. We believe that a correction of the Van Cauter parameters would be of marginal importance for this comparison, but this remains to be shown.

It was also mentioned that prediction errors for the two diabetic patients A4 (type 2) and A10 (type 1) were similar in size compared to the here investigated non-diabetics. In a previous study using retrospective ICU data, IDDM and NIDDM patients were more difficult to predict [38]. However, the available data on one of the patients (A4) were quite limited (19 measurements), whereas the other patient (A10) had short sampling intervals, half of them shorter than 2 hours. This may have contributed to a relatively greater share of small prediction errors, as prediction errors decreased with shorter prediction times.

Finally, it is noticeable that both patients received propofol over all or most of their time under glycaemic control. It has been shown that the use of propofol does not raise blood glucose levels [41, 42], however, beneficial effects on glycaemia are to the best of our knowledge not reported from clinical trials.

6. APPENDIX

The insulin model parameters $V_P$ and $n_K$ are calculated from the method proposed by Van Cauter et al. [23], in which the amplitudes and time constants of a double-exponential decay are estimated as functions of the subject’s age, sex, height, body mass and diagnosis of type-2 diabetes. Table 3 shows the equations with which the parameters are calculated. In parenthesis are given values of an example for a standard person, age $A = 40 \, yr$, height $H = 1.70 \, m$, body mass $W = 70 \, kg$ non-diabetic.

6.1 Conflict of interest statement

No conflicting financial interests exist.
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Table 1. Patient Characteristics and Blood Glucose Control

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**Patient Characteristics**

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<td>— max</td>
</tr>
<tr>
<td>— min</td>
</tr>
<tr>
<td>Time in band***</td>
</tr>
<tr>
<td>Nutrition (%)</td>
</tr>
<tr>
<td>— enteral</td>
</tr>
<tr>
<td>— intravenous</td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>— use of steroids</td>
</tr>
<tr>
<td>— propofol (% time)</td>
</tr>
</tbody>
</table>

* SAH: subarachnoid hemorrhage, SDH: subdural hematoma, card.: cardiologic, surg.: surgical, med.: other medical
** median blood glucose sampling interval in (hours:minutes)
*** percent time spent in 4–7 mmol/l band, calculated by linear interpolation between measurements
Table 2. Means and standard deviations (SD) of fitted insulin sensitivities $s_{\text{pre}}$ or $s_{\text{post}}$

<table>
<thead>
<tr>
<th>Patient</th>
<th>N</th>
<th>Mean $s_{\text{pre}}$</th>
<th>SD</th>
<th>Mean $s_{\text{post}}$</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>184</td>
<td>.169</td>
<td>.061</td>
<td>.347</td>
<td>.061</td>
</tr>
<tr>
<td>A2</td>
<td>59</td>
<td>.254</td>
<td>.057</td>
<td>.371</td>
<td>.051</td>
</tr>
<tr>
<td>A3</td>
<td>191</td>
<td>.133</td>
<td>.045</td>
<td>.280</td>
<td>.045</td>
</tr>
<tr>
<td>A4</td>
<td>48</td>
<td>.161</td>
<td>.028</td>
<td>.258</td>
<td>.039</td>
</tr>
<tr>
<td>A5</td>
<td>34</td>
<td>.226</td>
<td>.090</td>
<td>.361</td>
<td>.045</td>
</tr>
<tr>
<td>A6</td>
<td>142</td>
<td>.079</td>
<td>.039</td>
<td>.229</td>
<td>.057</td>
</tr>
<tr>
<td>A7</td>
<td>218</td>
<td>.075</td>
<td>.029</td>
<td>.224</td>
<td>.062</td>
</tr>
<tr>
<td>A8</td>
<td>161</td>
<td>.100</td>
<td>.072</td>
<td>.234</td>
<td>.124</td>
</tr>
<tr>
<td>A9</td>
<td>100</td>
<td>.070</td>
<td>.027</td>
<td>.182</td>
<td>.078</td>
</tr>
<tr>
<td>A10</td>
<td>155</td>
<td>.056</td>
<td>.024</td>
<td>.196</td>
<td>.069</td>
</tr>
<tr>
<td>total</td>
<td>1292</td>
<td>.113</td>
<td>.071</td>
<td>.257</td>
<td>.091</td>
</tr>
</tbody>
</table>
Table 3. Calculation of C-Peptide and insulin kinetics parameters using Van Cauter et al.’s method [23]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>normal</th>
<th>obese</th>
<th>NIDDM</th>
<th>example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short half life $t_{1/2}$ (min)</td>
<td>4.95</td>
<td>4.55</td>
<td>4.52</td>
<td>(4.95)</td>
</tr>
<tr>
<td>Fraction $F = \frac{A}{A+B}$</td>
<td>0.76</td>
<td>0.78</td>
<td>0.78</td>
<td>(0.76)</td>
</tr>
<tr>
<td>Long half life (min) $t_{1/2}l$</td>
<td>$0.14 \text{ min} \times A + 29.2 \text{ min}$ (34.8 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²) $A_{BSA}$</td>
<td>$\sqrt{\frac{H \times W}{36 \times kg \times m}}$ (1.82 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional turnover rates $k_2$</td>
<td>$F(b-a)+a$ (0.0487 min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n_k$</td>
<td>$\frac{ab}{k_2}$ (0.0572 min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_1$</td>
<td>$a + b - k_2 - n_k$ (0.0540 min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a = \ln 2/t_{1/2}$</td>
<td>(0.140 min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$b = \ln 2/t_{1/2}$</td>
<td>(0.0199 min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma volume, females (l) $V_p$</td>
<td>$1.11 \frac{l}{m^2} \times A_{BSA} + 2.04 l$ (4.06 l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma volume, males (l) $V_p$</td>
<td>$1.92 \frac{l}{m^2} \times A_{BSA} + 0.64 l$ (4.13 l)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>