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5 **A model of insulin saturation and glucose**
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8 **balance for glycaemic control in ICU**
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21 **Ulrike Pielmeier * Steen Andreassen * Birgitte S. Nielsen ****
22 **J. Geoffrey Chase *** Pernille Haure ****
23
24

25 ** Center for Model-based Medical Decision Support, Aalborg University,*
26 *Fredrik-Bajers-Vej 7, E4-215, 9220 Aalborg, DK (Tel: +45 9940-7458;*
27 *e-mail: upiel@hst.aau.dk)*
28
29

30 *** Neuro- and Trauma Intensive Care Unit, Aalborg Hospital, DK*
31

32 **** Dept. of Mechanical Engineering, University of Canterbury,*
33 *Christchurch, NZ*
34
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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 to 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.

Fig. 1. The Glucosafe model. Optionally, reduced insulin sensitivity is modeled by a factor s_{pre} that scales peripheral insulin Q , or by a factor s_{post} that scales insulin effect i .

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]:

$$\frac{dI}{dt} = (-n_K - n_L) I(t) - \frac{n_I}{V_P} (I(t) - Q(t)) + \frac{P(t) + U(t)}{V_P} \quad (1)$$

$$\frac{dQ}{dt} = -n_C Q(t) + \frac{n_I}{V_Q} (I(t) - Q(t)) \quad (2)$$

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

n_I [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.

n_I : diffusion constant for insulin between the plasma and peripheral compartments
 P : exogenous insulin appearance rate
 U : post-hepatic endogenous insulin appearance rate

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

$$V_Q = \frac{k_1}{k_2} V_P \quad (3)$$

and the diffusion constant is

$$n_I = V_P k_1 \quad (4)$$

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

k_1 : fractional turnover rate
 k_2 : fractional turnover rate

$$n_C = \frac{n_I \left(\frac{I_{SS}}{Q_{SS}} - 1 \right)}{V_Q} = \frac{n_I (\gamma - 1)}{V_Q} \quad (5)$$

where we assume the steady-state concentration ratio

$$\gamma = \frac{I_{SS}}{Q_{SS}} = \frac{5}{3} \quad (6)$$

I_{SS} : steady-state concentration of I
 Q_{SS} : steady-state concentration of Q
 γ : steady-state concentration ratio

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]:

$$i^* = \frac{u - u_0}{\sqrt[d]{(u - u_0)^d + k^d}} \quad (7)$$

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, yielding

$$i = \frac{i^* - i^*(0)}{1 - i^*(0)} \quad (8)$$

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

$$u = \frac{I_{SS}}{C} \quad (9)$$

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

$$u = \frac{\gamma}{C} Q_{ss} \quad (10)$$

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

$$u = \frac{\gamma}{C} Q(t) \quad (11)$$

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

$$\begin{aligned} u &= \frac{\gamma}{C} Q(t) s_{pre} \\ &= \frac{\gamma}{C} Q_S(t) \end{aligned} \quad (12)$$

i^* : insulin effect in response to u
 u : steady-state insulin infusion rate
 u_0 : a parameter value
 d : a parameter value
 k : a parameter value

i : fraction of maximal insulin effect

C : a coefficient

s_{pre} : insulin sensitivity scaling peripheral insulin concentration
 $Q_S(t)$: reduced peripheral insulin concentration

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:

$$\begin{aligned}
 i^*(t) &= \frac{\frac{\gamma}{C} Q_S(t) - u_0}{\sqrt[d]{(\frac{\gamma}{C} Q_S(t) - u_0)^d + k^d}} \\
 &= \frac{Q_S(t) - u_0 \frac{C}{\gamma}}{\sqrt[d]{(Q_S(t) - u_0 \frac{C}{\gamma})^d + (k \frac{C}{\gamma})^d}} \\
 &= \frac{Q_S(t) - Q_0}{\sqrt[d]{(Q_S(t) - Q_0)^d + Q_k^d}}
 \end{aligned} \tag{13}$$

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

Q_0 : a parameter value
 Q_k : a parameter value

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

s_{post} : insulin sensitivity scaling fractional insulin effect
 a : reduced fractional insulin effect

$$a(t) = s_{\text{post}} i(t) \tag{14}$$

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_{pre} and s_{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:

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

$E(t)$ [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]:

$$V_G = 0.19 \frac{l}{kg} \times W \quad (16)$$

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_{GLUT4} [mmol/kg/min] and insulin-

G: blood glucose concentration

E: endogenous glucose balance

e: enteral glucose absorption rate

p: parenteral infusion rate

W: body mass

V_G : glucose distribution volume

N: carbohydrate gut content

m: gut absorption delay coefficient

H: hepatic glucose balance

R: renal glucose excretion

P_{GLUT4} : GLUT 4 mediated glucose uptake

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

$$E(t) = H(t) - R(t) - P_{\text{GLUT4}}(t) - P_{\text{GLUT1+3}}(t) \quad (17)$$

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

$$H(t) = A_H G_1(t) + B_H a + C_H \quad \text{with } G_1(t) = \min(G(t), G_{\text{thresh}}) \quad (18)$$

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 $G_{\text{thresh}} = 11.98$ 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].

G_{thresh} : blood glucose concentration threshold

A_H : a coefficient

B_H : a coefficient

C_H : a coefficient

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]:

T_{max} : maximal reabsorption rate

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

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 : glomerular filtration rate

$$F_G = 0.0694 \text{ l/min/m}^2 \times BSA \quad (20)$$

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).

BSA: body surface area

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

$$P_{\text{GLUT1+3}}(t) = \frac{J_{1+3} G(t)}{G(t) + K_{M1+3}} \quad (21)$$

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.

J_{1+3} : GLUT 1 and GLUT 3 maximal uptake rate

K_{M1+3} : affinity combined GLUT1 and GLUT3 carrier

P_{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]

$$P_{\text{GLUT4}}(t) = \frac{J_4 G(t)}{G(t) + K_{M4}} a \quad (22)$$

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} .

J_4 : GLUT 4 maximal uptake rate

K_{M4} : GLUT4 carrier affinity

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 TM700, 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:

$$RMS = \sqrt{\frac{\sum_{i=1}^n e_i^2}{n}} \quad (23)$$

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).

e_i : prediction error
 m_i : i 'th measurement
 p_i : simulation of the i 'th measurement

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

Fig. 7. Log relative prediction errors e by patient and model. “Whiskers” extend to minimum and maximum values in the distribution no bigger than ± 1.5 times the interquartile range (IQR). Circles and asterisks mark outliers and extreme outliers, respectively, defined as values greater than 1.5 or 3.0 times the IQR, measured from the 25th or the 75th quartile.

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

Fig. 8. Histogram over sampling intervals of all 10 patients.

ranges > 210 min, not displayed). 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 σ_0^2 is an estimate of variance of two consecutive blood samples with an infinitesimal small time delay and σ_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 ABLTM 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;

σ : standard deviation

σ_0^2 : estimate of variance of two consecutive blood samples

σ_m^2 : model prediction error variance

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_{pre} that scales peripheral insulin concentration, as expressed in Equation 12. A second and new approach

1 investigated the estimation of a factor s_{post} that scales fractional insulin effect,
2 as shown in Equation 14. The identified parameters were compared and results
3 of short- and long-term predictions were shown.
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6 Scaling the insulin effect gave more accurate predictions of blood glucose than
7 scaling of peripheral insulin based on a comparison of logarithmic prediction
8 errors by patient and by length of prediction time. Short-term (1-hour)
9 predictions yielded about 16% absolute RMS error for scaling of insulin effect
10 and 22% for scaling of peripheral insulin, while long-term (8-hour) predictions
11 yielded 34% and 59% error for scaling insulin effect and scaling peripheral
12 insulin, respectively. Sampling intervals in the investigated 10 patients were
13 highly variable and averaged around 2 to 3.5 hours. Thus the model of
14 scaling the insulin effect is more appropriate for these patients giving better
15 results on longer prediction times. However, mean prediction errors greater
16 than 20 percent may be higher than desired, necessitating shorter intervals
17 [18]. The obtained curve fits to the RMS data are model-specific and can
18 be very practical for estimations of the model prediction error variance in
19 clinical control applications, for example in decisions regarding the scheduling
20 of measurements [38].
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23 Based on the estimation of the smallest RMS error, as shown in Figure 10, a
24 constant post-hepatic endogenous insulin production rate of 35 U/d has been
25 used throughout the model comparison, except for type I diabetic patients,
26 where the rate was set to 0. It has been estimated that, in any 24-hour period,
27 18 to 32 units per day are secreted by the pancreas under basal conditions and
28 about the same amount is secreted in response to meals [39, 40]. This amounts
29 to a total insulin production of 36 to 64 units per day of which 50–80% is
30 extracted during the first liver passage [22, 24]. The post-hepatic production
31 rate in this study lies at the high end of these values. However, this may be due
32 to the hyperglycaemic state of the investigated patient cohort and an associated
33 higher endogenous insulin production. Recovery from illness in these patients
34 may downregulate the estimated value.
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37 The results are clearly in favour of the new approach to scale insulin effect.
38 With all input data being identical, it can be argued that this is due to a better
39 reflection of the location of insulin action in this model than in the previously
40 proposed model by Arleth et al., at least in hyperglycaemic ICU patients.
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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 noticable 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 $A = 40\text{ yr}$, height $H = 1.70\text{ m}$, body mass $W = 70\text{ kg}$ non-diabetic.

A : patient age
 H : patient height

6.1 Conflict of interest statement

No conflicting financial interests exist.

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Table 1. Patient Characteristics and Blood Glucose Control

Characteristic	Patients									
	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
PATIENT CHARACTERISTICS										
Sex	F	F	F	M	M	M	M	M	M	M
Age	n.a.	58	75	60	46	63	51	65	75	41
Admission *	SAH	SAH	trauma	SDH	SAH	med.	card.	trauma	med.	med.
Diabetes type	—	—	—	2	—	—	—	—	—	1
BG at admission (mmol/l)	6.2	5.9	10.8	11.6	7.1	11.8	16.5	19.9	15.4	31.0
BLOOD GLUCOSE CONTROL										
Number of measurements	80	47	90	19	14	50	64	65	33	44
Control time (hours)	265	251	317	46	80	136	141	180	84	88
Blood glucose (mmol/l)										
— mean	7.4	7.0	7.5	6.9	7.6	7.8	8.0	8.8	8.2	9.9
— max	11.9	9.0	11.2	11.6	9.7	11.8	16.5	19.9	15.4	31.0
— min	4.5	5.4	3.5	3.9	6.3	4.2	5.0	5.0	4.7	3.2
Sampling interval **	2:53	4:16	3:03	2:30	2:06	2:38	1:57	2:37	2:21	1:52
Time in band ***	44	55	32	56	16	45	29	37	32	24
Nutrition (% time)										
— enteral	73	92	71	35	93	43	74	94	95	62
— intravenous	46	0	16	0	0	9	0	0	0	0
Medication										
— use of steroids	no	no	yes	no	no	yes	yes	yes	no	yes
— propofol (% time)	0	42	4	100	8	17	87	0	78	90

* 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_{pre} or s_{post}

Patient	N	scaling peripheral insulin		scaling insulin effect	
		Mean s_{pre}	SD	Mean s_{post}	SD
A1	184	.169	.061	.347	.061
A2	59	.254	.057	.371	.051
A3	191	.133	.045	.280	.045
A4	48	.161	.028	.258	.039
A5	34	.226	.090	.361	.045
A6	142	.079	.039	.229	.057
A7	218	.075	.029	.224	.062
A8	161	.100	.072	.234	.124
A9	100	.070	.027	.182	.078
A10	155	.056	.024	.196	.069
<i>total</i>	1292	.113	.071	.257	.091

Table 3. Calculation of C-Peptide and insulin kinetics parameters using Van Cauter et al.'s method [23]

	normal	obese	NIDDM	example
Short half life $t_{\frac{1}{2}s}$ (min)	4.95	4.55	4.52	(4.95)
Fraction $F = \frac{A}{A+B}$	0.76	0.78	0.78	(0.76)
long half life (min)	$t_{\frac{1}{2}l} = 0.14 \frac{min}{yr} \times A + 29.2 min$			(34.8 min)
body surface area (m^2)	$A_{BSA} = \sqrt{\frac{H \times W}{36 kg m^{-3}}}$			(1.82 m^2)
fractional turnover rates	$k_2 = F(b - a) + a$			(0.0487 min^{-1})
	$n_k = \frac{ab}{k_2}$			(0.0572 min^{-1})
	$k_1 = a + b - k_2 - n_k$			(0.0540 min^{-1})
	with			
	$a = \ln 2 / t_{\frac{1}{2}s}$			(0.140 min^{-1})
	$b = \ln 2 / t_{\frac{1}{2}l}$			(0.0199 min^{-1})
plasma volume, females (l)	$V_P = 1.11 \frac{l}{m^2} \times A_{BSA} + 2.04 l$			(4.06 l)
plasma volume, males (l)	$V_P = 1.92 \frac{l}{m^2} \times A_{BSA} + 0.64 l$			(4.13 l)