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Stability analysis of insulin-glucose feedback in the Glucosafe pancreas model of endogenous insulin production

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Abstract: Hyperglycemia is common in patients hospitalized for critical illness, trauma or after surgery, and is associated with increased morbidity and mortality. The Glucosafe system was developed to provide decision support for control of stress hyperglycemia in the intensive care unit. Glucosafe uses an insulin-glucose model to predict blood glucose (BG) concentrations, based on the patients previous and current insulin infusion, nutrition, and BG measurements. As endogenous insulin production is dependent on BG in a negative feedback loop, a pancreas model of endogenous insulin production was incorporated into the Glucosafe system. We investigated the stability of the feedback loop by calculating the loop gain of the model at different steady-state BG concentrations and insulin sensitivities. We also examining the models BG oscillations, after an initial perturbation, at different insulin sensitivities. Results show that both steady-state BG and insulin sensitivity influences the size of the loop gain. The largest loop gain (6.9) occurs at an insulin sensitivity of 1.2 and a BG of 5.5 mmol/l, where the BG perturbation resulted is damped oscillations of BG and endogenous insulin production. The BG dependent endogenous insulin production did not result in an unstable Glucosafe insulin-glucose model, although it did introduce damped oscillations in BG and insulin production during rapid increases in BG. It may be prudent to investigate if these oscillations can be decreased, possibly via the construction of a pancreas model which includes both a phase-1 and phase-2 response.

1. INTRODUCTION

Hyperglycemia is common in patients hospitalized for critical illness, trauma or after surgery, and has been associated with increased morbidity and mortality (Falciglia et al., 2009; Corathers and Falciglia, 2011). Intensive insulin therapy has been tested as a means to achieve glycemic control (Van den Berghe et al., 2001; Krinsley, 2004) and the Glucosafe system was developed to provide decision support for control of stress hyperglycemia in the intensive care unit (ICU). The Glucosafe system advises on nutrition and insulin.

Glucosafe uses an insulin-glucose model to predict blood Glucose (BG) concentrations, based on the patients previous and current insulin infusion, nutrition, and BG measurements (Pielmeier et al., 2012). The Glucosafe model uses an endogenous insulin production model that produces constant rates of insulin, regardless of the patients BG concentration. However experimental studies have shown that the endogenous insulin production is not fixed but dependent on BG, with the relationship between BG concentration and endogenous insulin production being a sigmoid shape (Kronenberg et al., 2008).

A variable insulin production model (pancreas model) has previously been added to the Glucosafe model to investigate if such a model would improve Glucosafe's ability to predict BG . The shape of the sigmoid function in the pancreas model was optimized using measurements from 12 critically ill patients in a neuro-ortho-trauma intensive care unit. While the inclusion of a pancreas model did improve the predictive capability of Glucosafe the improvement was marginal and could not justify its continued inclusion, likely due to the patients having such high BG concentrations that there was little difference between the constant and variable insulin production models. (Pielmeier et al., 2012)

If Glucosafe is to be usable for less hyperglycemic patients, a pancreas model should be included. However if the insulin production becomes dependent on BG, the insulin-glucose model contains a negative feedback loop. In any system, a feedback loop with a loop gain larger than 1, has the potential to make the system unstable resulting in oscillations. The potential instability of a system can be assessed by determining the loop gain and in linear systems the stability can be determined by applying the Nyquist stability criterion. However as the Glucosafe model is non-linear, the stability cannot be assessed by use of the Nyquist stability criterion (Nyquist, 1932) but can be assessed by examining the oscillations occuring from an initial perturbation of the BG (post-perturbation oscillations).

In this paper we will evaluate the stability of the glucose-insulin model in the Glucosafe system by determining the loop gain and post-perturbation BG oscillations of the model.

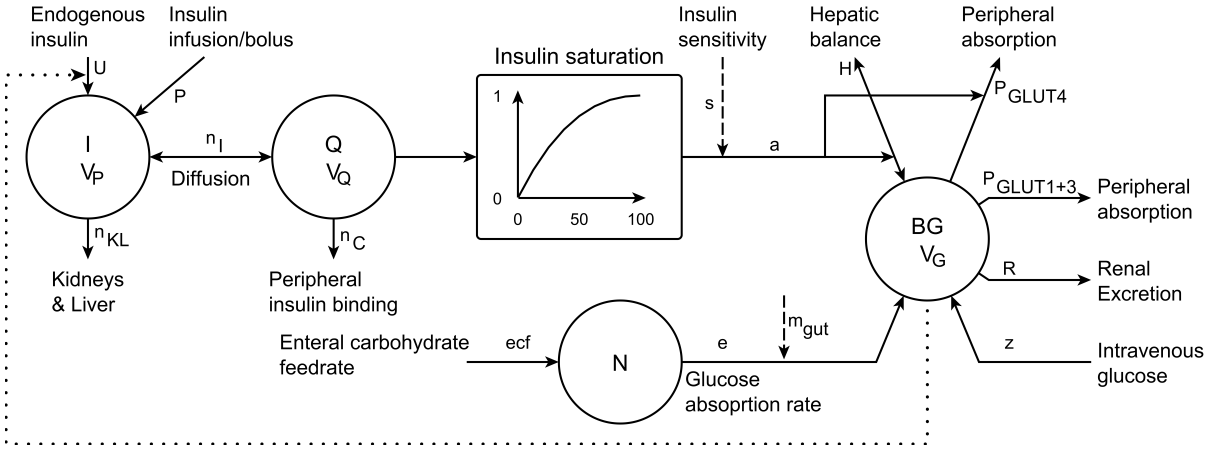

Fig. 1. A diagram of the Glucosafe glucose-insulin model for BG prediction. Solid arrows represent flow and turnover rates, dashed arrows represent effects of variables or parameters on other variables. The dotted line is the feedback loop where blood glucose concentration (BG) influences the endogenous insulin production, through the pancreas model.

2. METHODS

2.1 The Glucosafe Model

A diagram of the Glucosafe model is shown in Fig. 1. Glucosafe models plasma insulin (I) and peripheral insulin (Q) concentrations from the endogenous production (U) and exogenous infusions (P) of insulin and the removal of insulin by the kidneys and by insulin degradation in the liver and peripheral tissue. The insulin sensitivity (s) scales the effect of insulin on hepatic removal and peripheral absorption of glucose. The insulin sensitivity is a dimensionless parameter normalized to lie between zero and one, where values below one indicate insulin resistance. The blood glucose concentration (BG) is modeled from insulin-dependent and insulin-independent removal and glucose from nutrition and intravenous infusions (Pielmeier et al., 2010). Details of the model and equations can be found in appendix A.

2.2 The Pancreas Model

The pancreas model is a function with sigmoid shape that describes the rate of endogenous insulin production as a non-linear dependency of the blood glucose concentration (Kronenberg et al., 2008). The model curve is shaped by the following equation and is shown in Fig. 2:

$$U(t) = ep_{min} + (ep_{max} - ep_{min}) \cdot \left(\left(\frac{arctan((BG(t) - BG_{half} \cdot S}{\pi}\right) + 0.5\right) \quad (1)$$

where $U(t)$ is the endogenous insulin production and ep_{min} and ep_{max} are the minimum and maximum obtainable $U(t)$, respectively. $BG(t)$ is the blood glucose concentration at a given time, BG_{half} is the blood glucose at which the change in the slope of the function changes from increasing to decreasing, and S is the slope of the function at BG_{half}. The shape of the curve was previously optimized to the following values; ep_{min} = -1.9 mU/min, ep_{max} = 39 mU/min, S = 1.8, and BG_{half} = 5.6 mmol/l, using data using data from critically ill patients (Pielmeier et al., 2012). With this model the endogenous insulin production is dependent on the BG through a negative feedback loop. An increase in BG results in increasing endogenous insulin production that counteracts the rise in BG.

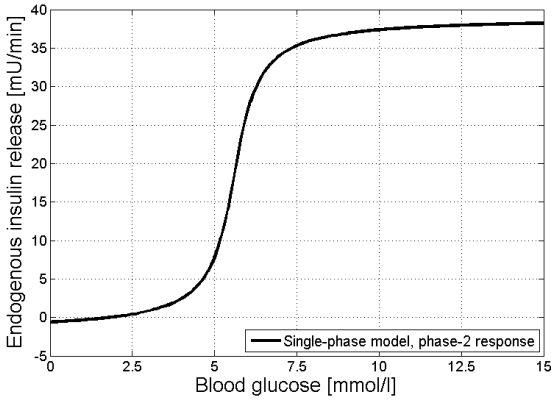

Fig. 2. The sigmoid curve representing the endogenous insulin production depending on blood glucose concentration.

2.3 Loop Gain

The stability of the pancreas model was analyzed by calculating the loop gain of the feedback loop. A loop gain larger than 1 shows that the model has the potential to become unstable and can result in oscillations in BG and endogenous insulin production.

The loop gain was calculated in the following manner:

(1) The endogenous insulin production ($U(t)$) was simulated at a specific steady state BG.
(2) A new endogenous production rate ($U(t) + \epsilon$) was calculated with $\epsilon = U(t)/10$.
(3) The new endogenous insulin production rate was fixed and a new simulation of the steady-state BG was performed.
(4) The increased insulin production ($U(t)+\epsilon$) resulted in a lower steady state BG. The endogenous production

that would have resulted from this BG if the pancreas model was used was then calculated ($U(t) + \delta$), and the value of δ was deduced.

(5) The loop gain was then calculated as:
Loop gain $= |\delta/\epsilon|$.

The loop gain was calculated for steady state BG concentrations of 3.0 mmol/l to 10 mmol/l in steps of 0.5 mmol/l, for three different levels of insulin sensitivity (s). An insulin sensitivity of 0.3 which is often seen in critically ill patients, 1.0 representing normal insulin response, and 1.2 to investigate how dependent on insulin sensitivity, the stability is. The steady state BG concentrations were obtained by using either insulin infusions or intravenous glucose infusions.

3. RESULTS

The calculated loop gains for the combinations of steady state BG and insulin sensitivity are shown in Table 1.

The results show that both steady state BG and insulin sensitivity influences the size of the loop gain. The largest loop gain (6.9) occurs at an insulin sensitivity of 1.2 and a BG of 5.5 mmol/l. Fig. 3 shows that the loop gain increases as insulin sensitivity increases and decreases as BG becomes lower or higher that 5.5-6 mmol/l.

As a loop gain larger than 1 indicates a potential for instability, the BG and endogenous insulin production was examined for oscillations. The largest loop gain occurred at a steady state BG of 5.5 - 6 mmol/l and as such this should be where the model is least stable. For each of the three insulin sensitivities the post-perturbation oscillations were examined. The impulse was a rapid 1 mmol/l increase in BG and the following changes in BG and endogenous insulin production registered. The resulting damped oscillations in BG and endogenous insulin production, for insulin sensitivities 0.3 and 1.0, are shown in Fig. 4.

Table 1. Loop gain values for combinations of steady state blood glucose concentrations (BG) and insulin sensitivities (s). Shaded values indicate that the steady state BG was obtained by using intravenous glucose, unshaded values indicate that the steady state BG was obtained by using insulin infusions.

BG	*Loop gain*		
(mmol/l)	s = 0.3	s = 1.0	s = 1.2
3.0	0,03	0,43	0,52
3.5	0,07	0,76	0,94
4.0	0,20	1,41	1,71
4.5	0,52	2,76	3,20
5.0	1,46	5,27	5,64
5.5	3,46	6,74	6,94
6.0	3,61	6,14	6,32
6.5	1,46	3,57	3,74
7.0	0,65	1,51	1,65
7.5	0,36	0,81	0,90
8.0	0,22	0,49	0,51
8.5	0,16	0,34	0,37
9.0	0,12	0,25	0,27
9.5	0,09	0,20	0,22
10.0	0,07	0,15	0,17

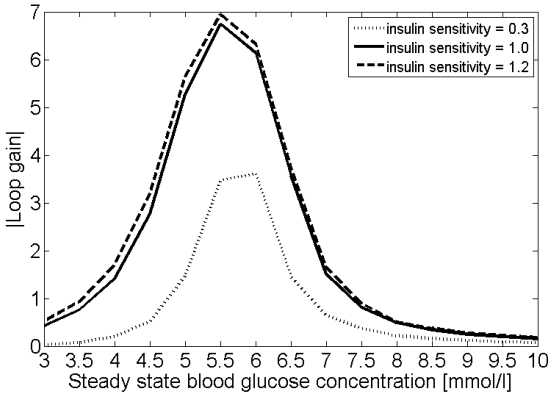

Fig. 3. A graphical representation of the calculated loop gain values at different combinations of steady state blood glucose and insulin sensitivities.

Results of the post-perturbation oscillation test show that a rapid increase in BG induces oscillations but that the oscillations die out. The BG oscillations are below 0.1 mmol/l after two hours with an insulin sensitivity of 0.3, an after four hours for an insulin sensitivity of 1.0. For an insulin sensitivity of 1.2 it took six hours before the oscillation amplitude was below 0.1 mmol/l.

4. DISCUSSION

From the results it is clear to see that the Glucosafe model has the potential to become unstable when the pancreas model feedback loop is included, as evident from the large loop gains obtained. The loop gain is clearly affected by the insulin sensitivity as the size of the loop gains decrease as insulin sensitivity decreases. This seems reasonable as the

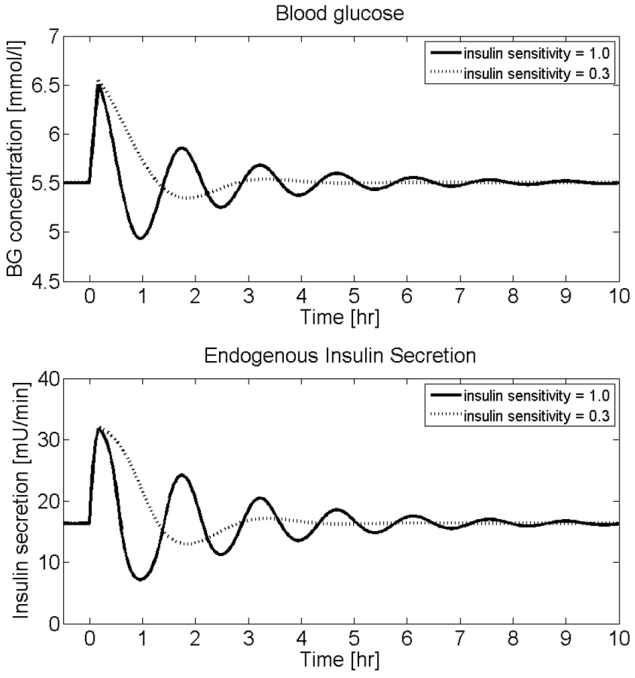

Fig. 4. post-perturbation oscillations for TOP) blood glucose and BOTTOM) endogenous insulin production. The perturbation was a rapid 1 mmol/l increase in BG, from a steady state BG of 5.5 mmol/l.

decrease in insulin sensitivity equates to less effect from the insulin and BG is thus less affected by a change in insulin production.

The loop gain also dependent on BG concentration with the biggest loop gain values observed at 5.5-6 mmol/l. This also seems reasonable as the sigmoid function of the pancreas model has the largest slope at 5.6 mmol/l and thus the largest change in insulin production relative to a change in BG. As BG increases or decreases from 5.6 mmol/l the change in insulin production relative to BG change decreases, and at high BG concentrations insulin saturation also have an effect.

Due to the non-linearity of the Glucosafe model, the stability could not be determined using the Nyquist stability criterion but was instead examined by perturbing the BG and observing the post-perturbation oscillations. The post-perturbation oscillations for BG and endogenous insulin insulin production shows that the model is not inherently unstable as the oscillations are damped. The time it takes for the oscillations to die out however may be problematic as this may affect the predictive capabilities of Glucosafe.

In conclusion the introduction of a variable endogenous insulin production model into the Glucosafe insulin-glucose model did not result in an unstable model, although it did however introduce damped oscillations in BG and endogenous insulin production during rapid increases in BG. It may be prudent to investigate if these oscillations can be decreased, possibly via the construction of a pancreas model which includes both a phase-1 and a phase-2 response.

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Appendix A. THE GLUCOSAFE MODEL

This appendix lists the equations, variable, and parameters, in the Glucosafe model. Further details on the development of the model and reasons for the equations can be found in (Pielmeier et al., 2010). An illustration of the model can be seen in Fig. 1 and the nomenclature for the variables and parameters can be found in Table A.1.

Model equations:

Changes in plasma and peripheral insulin concentrations:

$$\frac{dI(t)}{dt} = -n_{KL} \cdot I(t) - \frac{n_I}{V_P}\left(I(t) - Q(t)\right) + \frac{P(t) + U(t)}{V_P} \tag{A.1}$$

$$\frac{dQ(t)}{dt} = -n_c \cdot Q(t) + \frac{n_i}{V_Q}(I(t) - Q(t)) \tag{A.2}$$

Plasma/peripheral insulin diffusion constant:

$$n_I = V_P k_1 (^{m_C}/_{m_I}) \tag{A.3}$$

Peripheral insulin clearance rate:

$$n_C = (\gamma - 1)^{n_I}/_{V_Q} \tag{A.4}$$

Insulin removal from plasma:

$$n_{KL} = (^{BM}/_C - (1-\gamma)n_I) \cdot (^1/_{V_P}) \tag{A.5}$$

Endogenous insulin:

IF patient is type 1 diabetic THEN $U(t) = 0\ ^{mU}/_{min}$ ELSE

$$U(t) = ep_{min} + (ep_{max} - ep_{min}) \cdot \left(\left(\frac{arctan((BG(t) - BG_{half} \cdot S}{\pi}\right) + 0.5\right) \tag{A.6}$$

Insulin action on glucose uptake:

$$p(t) = (\gamma/C)Q(t) \tag{A.7}$$

$$i^*(t) = \frac{(p(t) - p_0)}{\sqrt[d]{(p(t) - p_0)^d + k^d}} \tag{A.8}$$

$$i(t) = \frac{(i^*(t) - i^*(0))}{(1 - i^*(0))} \tag{A.9}$$

$$a(t) = i(t) \cdot s \tag{A.10}$$

Glucose gut absorption:

$$\begin{aligned} &\text{IF } N(t) > 8.65\ ^{mmol}/_{kg} \\ &\text{THEN } e(t) = 0.03245\ ^{mmol}/_{kg \cdot min \cdot m_{gut}} \\ &\text{ELSE } e(t) = (-4.33 \cdot 10^{-4}\ ^{kg}/_{mmol \cdot min} \cdot N(t)^2 \\ &\qquad + 0.0075\ min^{-1} \cdot N(t)) \cdot m_{gut} \end{aligned} \tag{A.11}$$

$$\frac{dN}{dt} = -e(t) + ecf(t) \tag{A.12}$$

Hepatic balance:

$$\begin{aligned} &\text{IF } BG(t) < BG_{thresh} \\ &\text{THEN } H(t) = A_H \cdot BG(t) + B_H \cdot a(t) + C_H \\ &\text{ELSE } H(t) = A_H \cdot BG_{thresh} + B_H \cdot a(t) + C_H \end{aligned} \tag{A.13}$$

Table A.1. Nomenclature for variables and parameters in the Glucosafe model, incl. units and parameter values.

I	Plasma insulin concentration		mU/l
Q	Peripheral insulin concentration		mU/l
P	Exogenous insulin appearance rate		mU/min
U	Endogenous insulin appearance rate		mU/min
V_P	Plasma insulin distribution volume		l
V_Q	Peripheral insulin distribution volume		l
n_{KL}	Insulin clearance rate, kidneys and liver		min^{-1}
n_I	Insulin diffusion constant between plasma and peripheral compartments		l/min
n_C	Insulin clearance rate, peripheral insulin binding		min^{-1}
k_1	C-peptide diffusion constant between plasma and peripheral compartments		min^{-1}
m_C	Molecular mass of C-peptide	2.75	kDa
m_I	Molecular mass of insulin	5.8	kDa
γ	Peripheral/plasma steady state concentration ratio	5/3	
BM	Body mass		kg
C	Conversion factor between steady state plasma insulin concentration and exogenous insulin infusion	98.1	kg ·min/l
p	Steady-state insulin infusion rate per kg body mass		mU/kg/min
i^*	Insulin effect in response to p		
p_0	A parameter	0.083	mU/kg/min
d	A parameter	1.77	
k	A parameter	0.539	mU/kg/min
i	i* normalized to lie between 0 and 1		
a	Fraction of insulin effect		
s	Insulin sensitivity		
N	Carbohydrate gut content		mmol/kg
e	Glucose absorption rate for enteral nutrition		mmol/kg/min
m_{gut}	Impaired gut absorption coefficient	0.5	
ecf	Enteral carbohydrate feed rate		mmol/kgmin
BG	BG concentration		mmol/l
BG_{thresh}	BG concentration threshold	11.98	mmol/l
H	Hepatic glucose balance		mmol/l
A_H	A coefficient	$-7.67 \cdot 10^{-4}$	l/kg/min
B_H	A coefficient	-0.0247	mmol/kg/min
C_H	A coefficient	0.0223	mmol/kg/min
F_G	Glomerular filtration rate		l/min
A_{BSA}	Body surface area		m^2
R	Renal glucose balance		mmol/l
T_{max}	Maximal reabsorption rate	2	mmol/min
$P_{GLUT1+3}$	GLUT 1 and GLUT 3 mediated glucose uptake		mmol/kg/l
P_{GLUT4}	GLUT 4 mediated glucose uptake		mmol/kg/l
J_{1+3}	GLUT 1 and GLUT 3 maximal uptake rate	0.0093	mmol/kg/min
J_4	GLUT 4 maximal uptake rate	0.0848	mmol/kg/min
K_{M1+3}	Combined GLUT 1 and GLUT 3 carrier affinity	1.5	mmol/l
K_{M4}	GLUT 4 carrier affinity	5	mmol/l
V_{BG}	Glucose distribution volume		l
E	Endogenous glucose balance		mmol/kg/min
z	Glucose absorption rate for parenteral nutrition		mmol/kg/min

Renal glucose clearance:

$$F_G = A_{BSA} \cdot 0.0694 \ {}^{l}/_{min \cdot m^2} \tag{A.14}$$

$$R(t) = f(max(0, F_G G(t) - T_{max}))/BM \tag{A.15}$$

Where f(.) is a moving average function describing the transition from reabsorption to excretion (K Rave, 2006).

Peripheral glucose uptake:

$$P_{GLUT1+3}(t) = \frac{J_{1+3} BG(t)}{(BG(t) + K_{M1+3})} \tag{A.16}$$

$$P_{GLUT4}(t) = \left(\frac{J_4 BG(t)}{(BG(t) + K_{M4})} \right) a(t) \tag{A.17}$$

Endogenous glucose balance:

$$V_{BG} = BM \cdot 0.19 \ {}^{l}/_{kg} \tag{A.18}$$

$$E(t) = H(t) - R(t) - P_{GLUT4}(t) - P_{GLUT1+3}(t) \tag{A.19}$$

$$\frac{dBG}{dt} = \frac{(e(t) + z(t) + E(t))\, BM}{V_{BG}} \tag{A.20}$$

The C-peptide/insulin kinetics parameters; k_1, A_{BSA}, V_P, and V_Q are calculated using the method presented by (Cauter et al., 1992),

Initial values

- I(t) = 30 mU/l
- Q(t) = 18 mU/l
- a(t) = 0 (dimensionless)
- N(t) = 1 mmol/kg
- BG(t) = value of first measurement in mmol/l