Biomedical Signal Processing and Control 22 (2015) 155–160

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Stability of the insulin–glucose feedback loop in Glucosafe: A comparison of pancreas models

Mark Lillelund Rousing*, Ulrike Pielmeier, Steen Andreassen

Center for Model-Based Medical Decision Support (MMDS), Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7E, DK-9220 Aalborg East, Denmark

ARTICLE INFO

Article history:
Received 11 August 2014
Received in revised form 30 June 2015
Accepted 30 June 2015
Available online 1 August 2015

Keywords:
Medical decision support
Tight glycaemic control
Physiological modelling
Endogenous insulin release
Pancreas models
Stability analysis
Biomedical modelling

ABSTRACT

Glucosafe is a medical decision support system developed for glycaemic control in critically ill patients. The system recommends nutrition and insulin doses based on a physiological insulin–glucose model. This model assumes constant endogenous insulin release, in contrast to experimental data from healthy humans where a dual-phase insulin release (i.e. a phase-1 and phase-2 response) has been found along with evidence of a 2-pool insulin system. We included two different pancreas models in Glucosafe, one with a phase-2 response (Phase 2 model) and one with a phase-1 and phase-2 response (Phase 1 + 2 model) and studied the stability of Glucosafe with each applied model.

The pancreas models were fitted to plasma glucose and insulin data from 14 healthy subjects receiving meals, and compared by calculating the respective loop gains (LG) for each model. The models were also compared by short perturbations of the simulated blood glucose with 1 mmol/l increases over 10 min and measuring the predicted subsequent oscillations of blood glucose and endogenous insulin production. In this second comparison, the time constant (τ) for the decay of the oscillations was used as stability marker of the models.

When fitting the models to the pooled data, a better fit ($p < 10^{-7}$) was achieved with the Phase 1 + 2 model with an RMS error of 3.7 mU/l compared to the Phase 2 model with an RMS error of 5.2 mU/l. Blood glucose perturbations resulted in damped oscillations in both models. The Phase 1 + 2 model proved more stable ($\tau = 40$ min) than the Phase 2 model ($\tau = 92$ min) despite a slightly larger LG (6.6) compared to the Phase 2 model (6.1). The greater stability of the Phase 1 + 2 model is most likely due to the phase-lead nature of the phase-1 response, which in a linear system can improve stability.

In conclusion, a pancreas model with both a phase-1 and phase-2 insulin response results in a Glucosafe model which is more stable than Glucosafe with a Phase 2 pancreas model. What remains to be investigated is to which extent the damped oscillations simulated by Glucosafe match the physiological response to a BG perturbation in normal subjects and in patients, and to investigate if a Phase-1 + 2 model improves accuracy of Glucosafe's BG predictions.

1. Introduction

Stress-induced hyperglycaemia is a common response to altered metabolism induced by critical illness and has been associated with increased morbidity and mortality [1,2]. Intensive insulin therapy has been used as a means to achieve glycaemic control [3,4]. Glucosafe is a decision support system developed for control of stress hyperglycaemia in the intensive care unit (ICU). The system is based on an insulin–glucose model and recommends nutrition and insulin dosing using insulin sensitivity estimates and predicted blood glucose (BG) concentrations [5]. The Glucosafe model assumes constant endogenous insulin release, regardless of the patient's BG concentration. The purpose of this paper is to provide Glucosafe with a pancreas model, which is in better agreement with experimental data on endogenous insulin release. It will be tested if the model will oscillate due to the negative feedback loop created.

Early work by Cerasi and Luft [6] found a dual-phase nature of insulin release (i.e. a phase-1 and phase-2 response) in healthy humans, during glucose infusion tests. Around the same time Porte and Pupo [7] found evidence of a 2-pool insulin system. They tested the relationship between BG and insulin in a clinical trial using intravenous injections of glucose and measurements of BG and insulin responses.

* Corresponding author. Tel.: +45 99409787.
E-mail addresses: mlr@hst.aau.dk (M.L. Rousing), upiel@hst.aau.dk (U. Pielmeier), sa@hst.aau.dk (S. Andreassen).

http://dx.doi.org/10.1016/j.bspc.2015.06.013
1746-8094/

The work by Cerasi and Luft, and Porte and Pupo suggests that the nature of pancreatic insulin release is a dual-compartment, dual-phase process, with the phase-1 insulin response being dependent on the rate of rise of BG (dBG/dt) and the phase-2 response being dependent on the BG concentration.

Grodsky [8] built a model of pancreatic insulin secretion with two insulin compartments. The compartments were modelled with a larger stable compartment containing 98% of the stored insulin and a smaller labile compartment containing 2% of the stored insulin. Transport between the compartments was governed by the BG with insulin secretion occurring from the labile compartment only. Hovorka et al. [9] also constructed (as part of a model of glucose regulation) a model of insulin secretion. Like the Grodsky model, the model by Hovorka et al. only modelled the phase-2 response, using a linear relationship between BG and endogenous insulin release. While neither the Grodsky nor the Hovorka model was tested for stability, Steil et al. [10] performed stability tests with models of insulin secretion by combining them with a one-compartment insulin kinetics model and a minimal model of glucose kinetics [11].

A BG dependent model of the phase-2 endogenous insulin response has previously been added to the Glucosafe model to investigate if such a model would improve the prediction accuracy [5]. In this Phase 2 model, a sigmoidal relationship between BG and endogenous insulin release was assumed [12] and the shape of the sigmoid function was fitted to measurements from 12 critically ill patients in a neuro-ortho-trauma intensive care unit. The inclusion of the Phase 2 model did not significantly improve the predictive accuracy of Glucosafe. The lack of significant improvement was most likely due to the patients' high BG levels, at which the insulin release from the sigmoid function differed very little from the constant release rate [5].

Inclusion of the Phase 2 model created a negative feedback loop with a loop gain (LG) larger than 1. In any system, a feedback loop with an absolute value of the loop gain (|LG|) larger than 1 has the potential to make the system unstable, resulting in oscillations or damped oscillations. Simulations with the Phase 2 model showed that if the BG of a person with normal insulin sensitivity was perturbed by a glucose injection over a 10 min period, then BG and insulin release responded by a damped oscillation [13].

In this paper we compare the stability of Glucosafe with the Phase-2 model [5] to Glucosafe with a new dual-phase, dual compartment, pancreas model including both a phase-1 and phase-2 response (the Phase 1+2 model). In a linear system a phase-1 response with a dependence on dBG/dt is a phase lead response. A phase lead response often makes it easier to comply with the Nyquist stability criterion [14] and may increase the stability of the model. The Phase 1+2 model will be fitted to published BG and plasma insulin data [15]. Stability will be assessed by determining the loop gain at different insulin sensitivities and by using Glucosafe to simulate responses to a perturbation of BG around the BG where the loop gain is maximal.

2. Methods

2.1. The Glucosafe model

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 (Ex) of insulin and the removal of insulin by the kidneys and by insulin degradation in the liver and peripheral tissue.

The insulin sensitivity scales the effect of insulin (a) on hepatic removal and peripheral absorption of glucose. The insulin sensitivity is a dimensionless normalized parameter so a value of one indicates normal insulin sensitivity and values below one indicate insulin resistance. The blood glucose concentration (BG) is a model variable that depends on insulin-mediated and insulin-independent glucose clearance from plasma and glucose uptake from intravenous infusions and nutrition. The insulin-mediated glucose clearance is affected by the non-linear insulin saturation function [16]. A further description of the Glucosafe model, including equations, can be found in [13].

2.2. The pancreas model

The new pancreas Phase 1+2 model, incorporated into the Glucosafe model, is shown in Fig. 1. The Phase 2 model includes only the sigmoid curve (Eq. (3)).

The total endogenous insulin release is both the phase-1 (P_1) and phase-2 (P_2) response

$$U(t) = \mathrm{Max}(0, (P_1(t) + P_2(t))) \tag{1}$$

with the exception of type 1 diabetes patients, where endogenous insulin production is assumed to be zero.

The phase-1 response is proportional to the rate of change of BG, and to the amount of insulin in insulin reservoir 2 as shown in Eq. (2)

$$P_1(t) = \mathrm{Max}\left(0, R_2 \cdot \frac{\mathrm{dBG}}{dt} \cdot K_2\right) \tag{2}$$

where R_2 is the current content of the insulin reservoir (mU) and K_2 is a constant.

The phase-2 response is a sigmoid curve that describes the rate of endogenous insulin release as a non-linear dependency on the blood glucose concentration. The sigmoid relationship between BG and insulin secretion has been shown experimentally by Henquin et al. [12]. The model curve is shaped by the following equation

$$P_2(t) = \mathrm{ep}_{\min} + (\mathrm{ep}_{\max} - \mathrm{ep}_{\min}) \cdot \left(\left(\frac{\arctan((\mathrm{BG}(t) - \mathrm{BG}_{\mathrm{half}}) \cdot S)}{\pi}\right) + 0.5\right) \tag{3}$$

where $\mathrm{ep}_{\min}$ and $\mathrm{ep}_{\max}$ are the minimum and maximum obtainable $P_2(t)$, respectively. BG(t) is the blood glucose concentration at a given time, $\mathrm{BG}_{\mathrm{half}}$ is the blood glucose at which the slope of the function is steepest, and S is the slope of the function at $\mathrm{BG}_{\mathrm{half}}$.

The contents of the two insulin reservoirs (R_1 and R_2) are governed by the following equations.

$$\frac{dR_2(t)}{dt} = F_3(t) - F_4(t) - U(t) \tag{4}$$

$$\frac{dR_1(t)}{dt} = F_1(t) - F_2(t) - F_3(t) + F_4(t) \tag{5}$$

where

$$F_1 = \mathrm{ep}_{\max} \tag{6}$$

$$F_2 = F_1 \cdot \frac{R_1(t)}{R_{1\,\max}} \tag{7}$$

$$F_3 = \mathrm{Min}((\mathrm{BG}(t) \cdot R_1(t) \cdot K_1), (R_{2\,\max} - R_2(t))) \tag{8}$$

$$F_4 = F_3 \cdot \frac{R_2(t)}{R_{2\,\max}} \tag{9}$$

$$R_{1\,\max} = R_{\mathrm{total}} \cdot 0.98 \tag{10}$$

$$R_{2\,\max} = R_{\mathrm{total}} \cdot 0.02 \tag{11}$$

where $R_{1\max}$ and $R_{2\max}$ are the maximum contents of the respective reservoirs and R_{total} being the maximum amount of stored insulin.

With this model the endogenous insulin production is dependent on the BG through a negative feedback loop. An increase in BG