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Validation of a Simulation Model Describing the Glucose-Insulin-Glucagon Pharmacodynamics in Patients with Type 1 Diabetes

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Introduction

Currently, no consensus exists on a model describing endogenous glucose production (EGP) as a function of glucagon concentrations. Reliable simulations to determine the glucagon dose preventing or treating hypoglycemia or to tune a dual-hormone artificial pancreas control algorithm need a validated glucoregulatory model including the effect of glucagon.

This poster presents the results from the leave-one-out cross-validation of a glucoregulatory model with interacting effects of insulin and glucagon [1]. We present model fits to data, and simulations with the model showing the glucagon dose-response relationship at varying insulin levels [2].

Materials and Methods

Eight type 1 diabetes patients received a subcutaneous (SC) bolus of insulin (NovoRapid®) on four study days to induce mild hypoglycemia followed by a SC bolus of saline (A) or 100 (B), 200 (C) or 300 (D) µg glucagon (GlucaGen®). Samples were analyzed for concentrations of glucagon, insulin, and glucose.

The PD model is mainly inspired by Hovorka *et al.* [3].

$$\begin{aligned} \frac{dQ_1(t)}{dt} &= -F_{01} - F_R - S_T x_1(t) Q_1(t) + k_{12} Q_2(t) + G_{GG}(t) + G_{GNG} \\ \frac{dQ_2(t)}{dt} &= S_T x_1(t) Q_1(t) - (k_{12} + S_D x_2(t)) Q_2(t) \\ \frac{dx_i(t)}{dt} &= k_i (I(t) - x_i(t)) \quad i = 1, 2, 3 \end{aligned}$$

$Q_1(t)$ and $Q_2(t)$ are the masses of glucose per BW (µmol/kg) in the accessible and non-accessible compartments. Glucose concentration (mmol/L) in the accessible compartment is Q_1/V with V fixed at 160 mL/kg. $I(t)$ is the insulin concentration (mIU/L) in the accessible compartment. $x_i(t)$ are remote effects of insulin (mIU/L). F_{01} is the non-insulin-dependent glucose flux. F_R is the renal glucose clearance. k_{12} and k_i are transfer rate constants. S_D , S_E , and S_T are insulin sensitivities. The model is modified so $G_{GG}(t)$ is the insulin and glucagon dependent EGP corresponding to glycogenolysis and G_{GNG} is the constant EGP contribution from gluconeogenesis [1].

$$G_{GG}(t) = \frac{1 - S_E x_3(t)}{1 - S_E I_b} \left((E_{max} - G_{GNG}) \frac{C(t)}{C_{E50} + C(t)} \right)$$

$C(t)$ is the glucagon concentration (pg/mL) in the accessible compartment. $I_{b,y}$ is the fixed basal insulin concentration (mIU/L) for subject y , and E_0 is the minimum EGP fixed at 8 µmol/(kg·min). E_{max} is the maximum EGP at $I_{b,y}$. C_{E50} is the glucagon concentration at half maximum EGP.

The PD model validation was carried out as a 4-fold leave-one-out cross-validation leaving all data from one visit out per fold. To quantify the simulation accuracy of the model on datasets not used for parameter optimization, the bias was calculated by the mean prediction error (MPE) and the precision calculated by the mean absolute prediction error (MAPE). Test-visit fits were accepted if $MPE < \pm 15\%$ and $MAPE < 20\%$.

$$\begin{aligned} MPE &= \frac{1}{N} \sum_{j=1}^N \left[\left(\frac{pred_j - obs_j}{obs_j} \right) \cdot 100 \right] \\ MAPE &= \frac{1}{N} \sum_{j=1}^N \left[\left(\frac{|pred_j - obs_j|}{obs_j} \right) \times 100 \right] \end{aligned}$$

All non-outlier visits were used to estimate the final model parameters for each patient using maximum a posteriori with the CTSM-R package in R (<http://ctsm.info/>).

The seven virtual patients each underwent an *in silico* euglycemic (5 mmol/L) clamp study where the insulin infusion rate (IIR) was constant at 1-5 times the basal IIR. Meanwhile, the responses to glucagon boluses ranging 1 µg-10 mg were assessed by 60-minutes area under the curve (AUC_{60min}).

Results

Table 1: Result of leave-one-out cross-validation.

Patient	Accepted Test-visit fits (Training-visits)
1	A (BD), B (AD)
2	C (ABD), D (ABC)
3	A (BCD), B (ACD)
4	B (ACD)
5	A (BC), B (AC), C (AB)
6	A (BD), D (AB)
7	C (ABD), D (ABC)
8	None

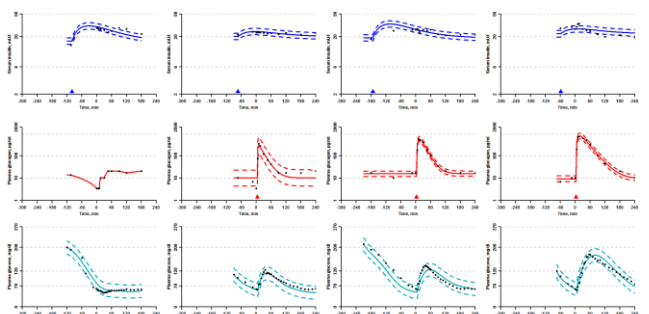


Figure 1: Data and model fits of patient 7. Insulin PK (top), glucagon PK (middle), glucose PD (bottom) during visits A-D (left to right).

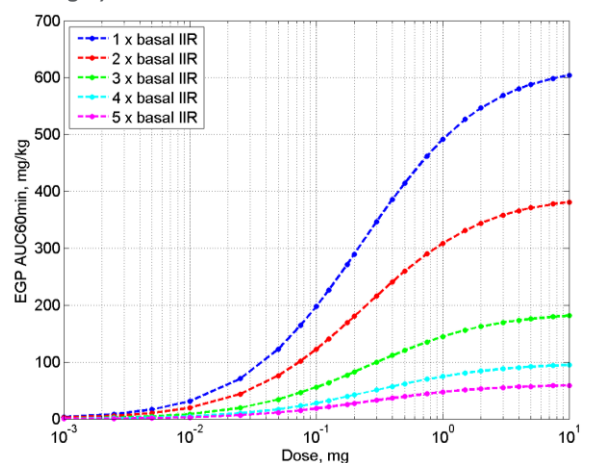


Figure 2: Simulation of glucagon dose-response relationship at varying insulin levels.

Conclusions

We successfully validated a model describing the glucose-insulin-glucagon dynamics by leave-one-out cross-validation in seven type 1 diabetes patients. We used patient specific parameter sets to establish a virtual population. Simulations with the virtual patients showed that the ambient insulin level affects the maximum EGP response to glucagon, but has little influence on the dose yielding half maximum response.

References

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