A PHYSIOLOGICAL MODEL OF T2D FOR SIMULATING FASTING GLUCOSE LEVELS

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Introduction

We present a model for simulating insulin-glucose dynamics in type 2 diabetes (T2D) patients during long-acting insulin titration. The model combines a physiological model of type 1 diabetes (T1D) and an endogenous insulin production model in T2D. We use the model to simulate fasting glucose levels in T2D long-acting insulin treatment and compare the results with clinical trial results with similar study design.
The goal of this work is to create a simulation model for use in development of safe and effective titration algorithms and evaluate the contribution of adherence on fasting glucose during titration.

Methods

Simulating insulin-glucose dynamics
We use a T1D virtual patient model developed by Kanderian et al. (2009) and a meal subsystem described by Hovorka et al. (2004), and augment it with an endogenous insulin production compartment (I_{endo}) to simulate T2D (Ruan et al., 2015). The model equations are

$$\frac{dD_1(t)}{dt} = D(t) - \frac{D_1(t)}{\tau_m}, \qquad \frac{dD_2(t)}{dt} = \frac{D_1(t)}{\tau_m} - \frac{D_2(t)}{\tau_m}$$
$$\frac{dI_{sc}(t)}{dt} = \frac{U(t)}{\tau_1 C_I} - \frac{I_{sc}(t)}{\tau_1}, \qquad \frac{dI_p(t)}{dt} = \frac{I_{sc}(t)}{\tau_2} - \frac{I_{sc}(t)}{\tau_2}$$

$$\frac{dI_{eff}(t)}{dt} = p_2 S_I (I_{endo}(t) + I_p(t)) - p_2 I_{eff}(t)$$
$$\frac{dG(t)}{dt} = -\left(GEZI + I_{eff}(t)\right) G(t) + EGP + \frac{D_2(t)}{V_G \tau_m}$$
$$I_{endo}(t) = \frac{M_{I,f}(G(t) - G_b) + M_{0,f} G_b}{MCR_I W}$$

$D(t)$ is the amount of ingested carbohydrates and τ_m is the peak time of absorption. $U(t)$ is the amount of infused fast acting insulin, C_I is insulin clearance rate and τ_1 and τ_2 are time constants of insulin. p_2 is delay in insulin action after increase in plasma insulin, S_I is insulin sensitivity, $GEZI$ is effect of on glucose production at zero insulin and EGP is endogenous glucose production rate. VG is glucose distribution volume and W is the subject's body weight. The above parameters are used to simulate the first nine patients identified in Kanderian et al. (2009). The following parameters are set to median values presented in Ruan et al. (2015); the insulin metabolic clearance rate MCR_I, posthepatic glucose sensitivity $M_{I,f}$ and basal glucose sensitivity $M_{0,f}$. G_b, basal plasma glucose was set to 7.0 mmol/L.

Long acting insulin injection
The parameters of the above model are fitted to simulate fast acting insulin for pump infusion. To simulate long-acting insulin injections we used PK profiles of insulin degludec described by Heise et al. (2012) to define an infusion profile, illustrated in Figure 1.

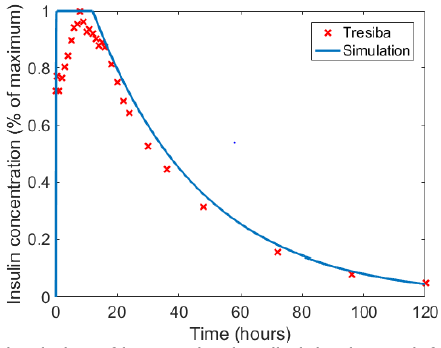

Figure 1: Simulation of long acting insulin injection as infusion.

Simulating a clinical trial
A subset of parameters were varied within a pre-defined range, defined by typical differences between T1D and T2D patients in clinical trials. These include 10%-60% increase in body weight and decrease in insulin sensitivity by 30%-70%. This resulted in 270 simulated patients (6 body weights x 5 insulin sensitivities x 9 identified patient parameters) .

Results

Simulating a clinical trial
We simulate a titration period of 26 weeks, where basal insulin dose adjustments follow a similar algorithm as a clinical trial (Zinman et al., 2012). We add variance to the simulated FG by setting

$$\widehat{FG}(t) = FG(t) + v(t), \qquad v(t) \sim N(0, (0.14 FG(t))^2)$$

where $\widehat{FG}(t)$ and $FG(t)$ are simulated fasting glucose with and without biological noise $v(t)$, respectively. In the simulations we assume a best case scenario where no insulin is omitted and biological variance is at minimum. We set the variance to 14% since In a study by Ollerton et al. (1999), day-to-day fasting glucose variability in newly diagnosed T2D patients was approximately 14%.

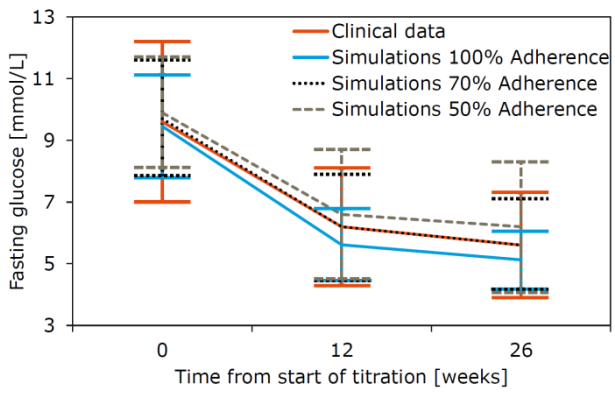

Figure 2: Results from a clinical trial (Zinman et al., 2012) and simulations of 270 T2D patients. The results represent the same drug, the same titration algorithm, and similar inclusion criteria.

Evaluating effect of adherence
To evaluate the effect of adherence on variations in fasting glucose and safety of dose guidance, we simulate a similar titration period as before but with different levels of adherence. Studies on adherence have reported adherence to insulin injections between 60% and 90% (Cramer et al., 2005; Lee et al., 2006; Peyrot et al., 2012). We choose to simulate three adherence levels, 50%, 70% and 100%.

The results from simulating a clinical trial are illustrated in Figure 2. Considering the two solid lines, the clinical trial results and simulation results assuming 100% adherence, both fall within one standard deviation of the other. Furthermore, the dynamics of average fasting glucose of the cohort are similar. The results indicate that the simulation results can be used to represent changes in fasting glucose over a titration period in a clinical trial with similar starting values, patient characteristics and dose guidance.

Conclusions

We suggest a model of glucose-insulin dynamics to generate a cohort of T2D patients initiating long-acting insulin treatment. The results indicate that the model is sufficient to simulate fasting glucose levels of T2D patients in-silico during a long-acting insulin titration period. The motivation for creating this model was to simulate fasting glucose values in T2D during a titration period. For the purpose of bolus calculations and more detailed meal simulations, the model parameters related to carbohydrate uptake should be refined. Also the choice of endogenous insulin production model should be improved to allow daily fluctuations.

References

Cramer, J.A. et al. *Diabetes Care* 2005 Jan; 28(1): 78-83.
Heise, T. et al *Diabetes Obes Metab* 2012 Sep;14(9):859-64..
Hovorka, R. et al. *Physiol Meas*. 2004 Aug;25(4):905-20.
Kanderian, S.S. et al. *J Diabetes Sci Technol.* 2009 Sep 1;3(5):1047-57.
Lee, W.C. et al. *Clin Ther* 2006 Oct;28(10):1712-25
Ollerton, R.L. et al. *Diabetes Care 1999*;22:394–398
Peyrot, M. et al. *Diabetes Metab* 2012 May;29(5):682-9.
Ruan, Y. et al. *BioMedical Engineering OnLine*2015;14:19
Zinman, B. et al. *Diabetes Care* 2012 Dec;35(12):2464-71