Masterarbeit

Investigation of Glucagon Administration Methods in a Bihormonal Artificial Pancreas

Author: Matthias Reiter

Supervisor: Prof. Luigi del Re
Florian Reiterer, MSc

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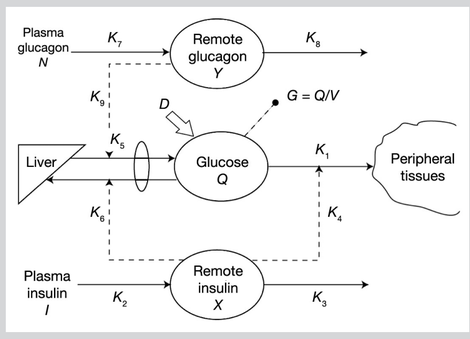
Abstract

Since diabetes is a disease of huge global impact, many therapies have been developed to allow an unburdened life for diabetics. One of them is the artificial pancreas, which is a closed loop control system consisting of an insulin pump, a continuously measuring glucose sensor and a control algorithm. Recent studies have also tried to introduce a second hormone, glucagon, to further increase the flexibility in blood glucose (BG) regulation.
In this thesis an existing model of the human glucoregulatory system was combined with a model for the CGM to yield a simulation environment for the evaluation of different control strategies. At first an insulin-only MPC was tuned and then different methods for glucagon administration were investigated.
The results show that the "always active mode" leads to an increased overall performance but needs more of both hormones. The "safety mode" only reduces the time below a certain threshold but generates more careful input actions. It also has been shown that it is possible to calculate single input spikes, which mimic the usage of a glucagon pen.

Simulation Model

An existing model for the human glucoregulatory system was used[a]. It consists of several compartments and rate equations. As can be seen from the equations below the model is nonlinear and the parameters are time-varying in the original publication.

$$\dot{G}(t) = -(S_G + X(t) - Y(t))G(t) + S_G G_b + \frac{Ra(t)}{V}$$
$$\dot{X}(t) = -p_2 X(t) + p_2 S_I (I(t) - I_b)$$
$$\dot{Y}(t) = -p_3 Y(t) + p_3 S_N (N(t) - N_b)$$



Additionally, diffusion models for the glucose rate of appearance Ra and the subcutaneous hormone absorption had to be implemented. A model for the continuously measuring CGM made the simulation more realistic by introducing a further lag and sensor noise.

[a] P. Herrero et al. A composite model of glucagon-glucose dynamics for in silico testing of bihormonal glucose controllers. Journal of Diabetes Science and Technology, 7(4):941–951, July 2013

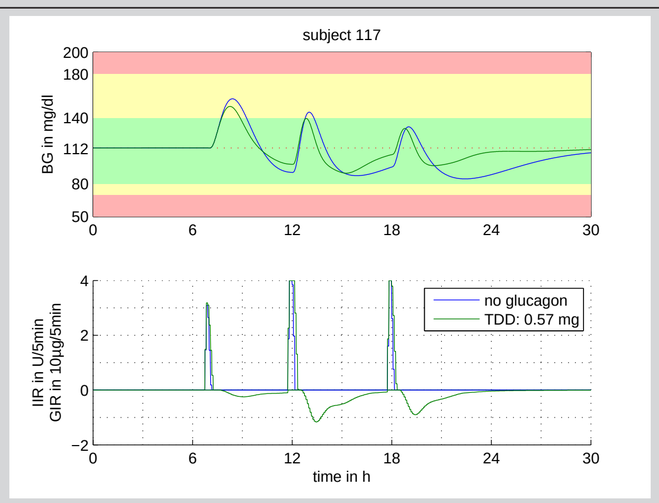
MPC Implementation

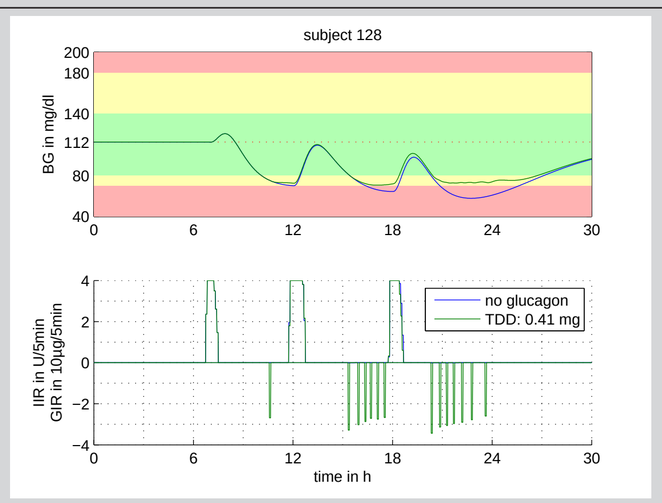
A linear model predictive controller was implemented and extended by several extensions that are useful for BG regulation. These include asymmetric cost function, zone objective and measured disturbance. The absolute input weight was used to vary the amount of infused hormones or to totally switch it off in the case of glucagon. A special choice of $\mathcal{R}$ was used to obtain doses for pen injections. The prediction equation was used to look ahead about three hours and it also recognized impending hypoglycemic events, which was necessary to enable glucagon in the "safety mode".

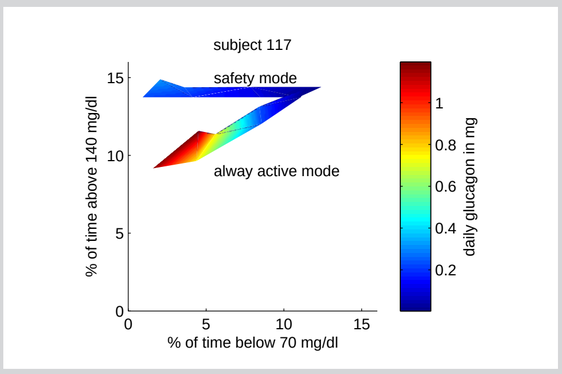
$$J_k = [\mathbf{Y}_k - \mathbf{T}_k]^\top \mathcal{Q} [\mathbf{Y}_k - \mathbf{T}_k] + \Delta \mathbf{U}_k^\top \mathcal{R} \Delta \mathbf{U}_k + \mathbf{U}_k^\top \mathcal{S} \mathbf{U}_k$$

$$\mathcal{S} = \begin{bmatrix} \mathbf{S}_0 & 0 & \cdots & 0 \\ 0 & \mathbf{S}_1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \mathbf{S}_{n_{CH}-1} \end{bmatrix} \qquad \mathbf{S}_i = \begin{bmatrix} S_{i,insulin} & 0 \\ 0 & S_{i,glucagon} \end{bmatrix}$$

Results





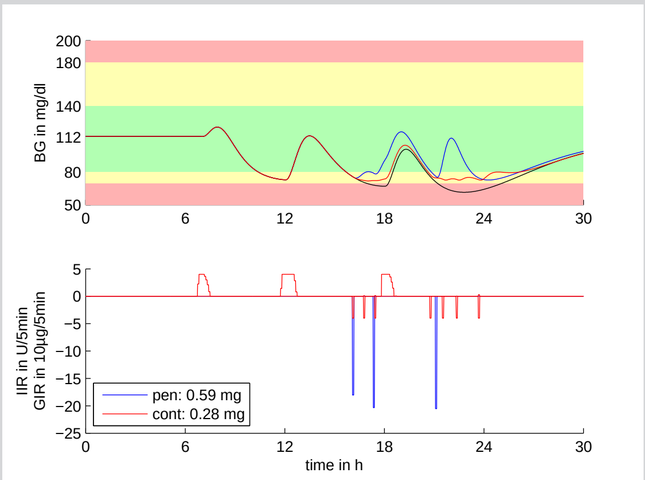


In the "always active mode" the controller can optimize doses for both hormones at any time. Therefore more insulin is infused because its effect can be compensated by the glucagon afterwards. The result is a tight BG control but also an increased need of both hormones.

In the "safety mode" the glucagon input is disabled during normal operation, but when hypoglycemia is impending the secondary hormone is activated. The result is a more economic usage of both hormones but still the hazardous events of low BG can be avoided.

A comparison of the two methods shows that the "always active mode" can reduce the time in low and high BG ranges whereas the "safety mode" only reduces the risk of hypoglycemic events. A drawback of the "always active mode" is the increased amount of glucagon and insulin.

Pen Administration



The figure on the left shows the BG profile for three ingested meals when the meal announcements are wrong. In particular 90 % too much carbohydrates were estimated. Without glucagon intervention (black line) the BG concentration falls below the threshold of 70 mg/dl, which is already a dangerous region.
In this case also the continuous administration of glucagon (red line) leads to short infusion spikes, but only the control algorithm optimized for pen usage (blue line) ensures a minimal number of injections.
From the legend it can be seen that the continuous administration needs less glucagon than the pen injections. This might be due to technical reasons (e.g. inaccurate state estimation) but also due to physiological ones (e.g. quicker action of glucagon).

Conclusion and Outlook

Although the "always active mode" seems to have benefits in terms of performance it has to be enjoyed with caution because it induces potentially dangerous situations. Contrarily, the "safety mode" is capable of avoiding hypoglycemic events and needs less insulin and glucagon.
When glucagon is needed seldom the opportunity of administering it by a pen can be an interesting option because no second infusion pump is needed. But before the technical investigation can go on, some issues about glucagon like the price and the patients' needs should be clarified first.