On the Sensitivity of Continuous Glucose Monitoring to Insulin Infusion Faults

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Motivation

Artificial pancreas (AP)

- Continuous glucose monitoring (CGM)
- Fully automated insulin infusion
- No user input

→ Increased safety and reliability requirements

→ Need for automatic fault detection

Insulin infusion faults

- Insulin infusion sets are the «Achilles heel» of continuous insulin infusion [1]
- With in-line detection, occlusions may remain silent (for hours) [2]
- Alternative detection based on CGM, e.g. [3]
- Time delays and slow dynamics of insulin infusion and glucose sensing with the subcutaneous (SC) approach may compromise the detection based on CGM.

Variable insulin sensitivity

- Changing over time [4]
- Inter- and intrasubject variability
- Affects the glucose levels by variable insulin needs.

Aim: Distinguish insulin infusion faults from other disturbances in an artificial pancreas

Methods

Simulation model

- In absence of clinical data on infusion faults, feed-forward simulations were used.
- UVa/Padova T1DM model [5]
- 10 adult subjects
- Glucose sensing, insulin absorption and meal digestion dynamics vary with subjects.

Sensitivity analysis

- Forward sensitivity analysis using CVODES [6] in Mathworks Matlab
- Sensitivity equations solved simultaneously

$$\dot{s_i} = \frac{\partial f}{\partial G} s_i + \frac{\partial f}{\partial p_i} \qquad \mathrm{s_i}(\mathrm{t_0}) = \frac{\partial G_0(p)}{\partial p_i}$$

Local sensitivity of glucose concentration (G) to parameters (p), i.e. change of G caused by change of parameter p_i

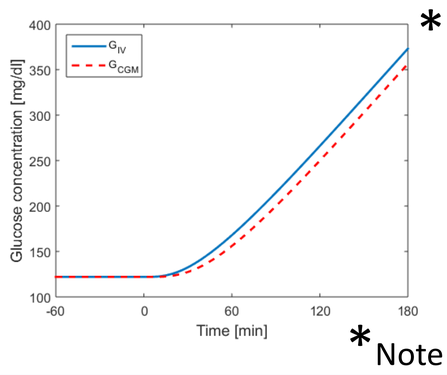
- Normalized sensitivity coefficients:

$$\widetilde{s_i}(t) = \frac{\partial G(p)}{\partial p_i} \frac{p_i}{G(t)}$$

Comparison of perturbations with glucose-increasing effect

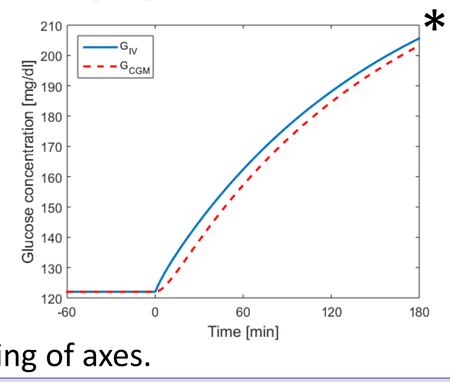
Insulin infusion fault

- Parameter R_i, rate of insulin appearance in plasma [5]
- Time course of R_i with subject's insulin needs
- Example of sudden stop:



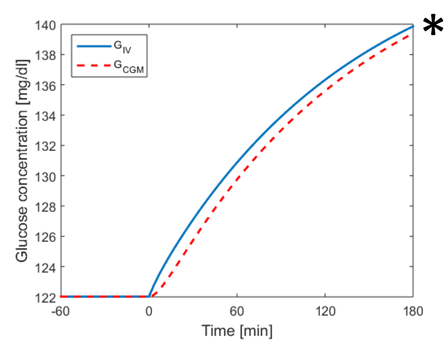
Meal disturbance

- Parameter R_a, rate of glucose appearance in plasma [5]
- Time course of R_a from meal simulation
- Example of step from 0 to 2 mg/kg/min:



Decreased insulin sensitivity

- Parameter k_{p3}, insulin action on liver [5]
- Nominal parameter value of each subject
- Example of sudden change to 50% of nominal value:

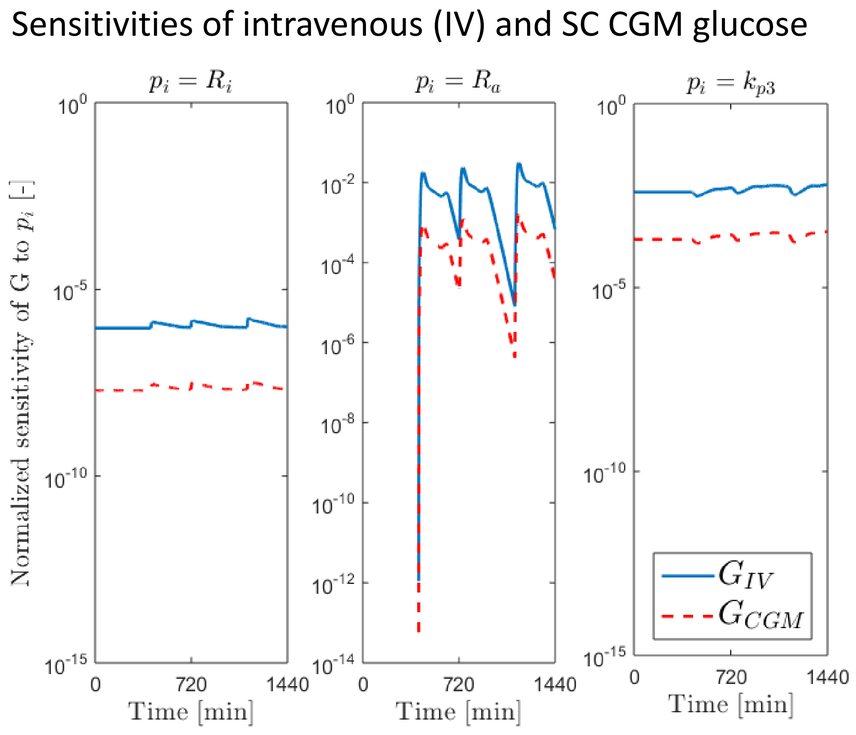


*Note scaling of axes.

Results

Sensitivity to parameter changes over time

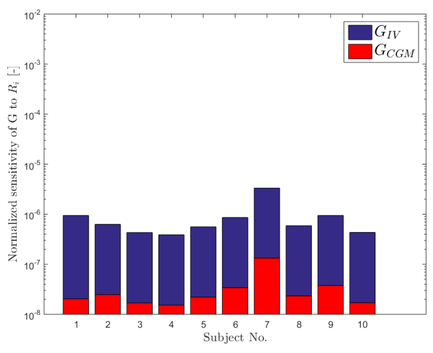
- Example of time course of a 3-meal-scenario for one subject
- Sensitivities of intravenous (IV) and SC CGM glucose



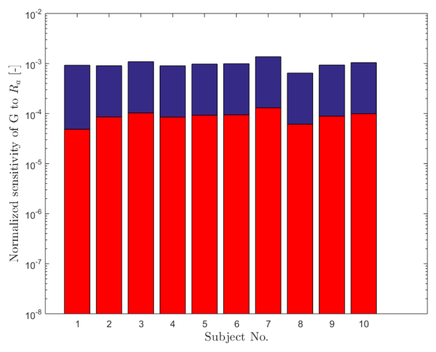
Sensitivity to parameter changes

- Mean local sensitivity after a meal of 25 g carbohydrates
- Normalized sensitivity coefficients

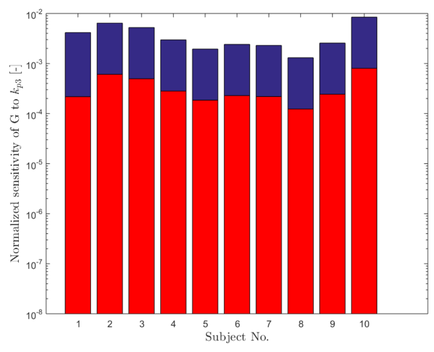
Insulin infusion fault R_i



Meal disturbance R_a



Decreased insulin sensitivity k_{p3}



Interpretation:

- Especially low sensitivity to insulin infusion faults.
- SC CGM has lower sensitivity than blood measurements.
- Significant differences between subjects.

Discussion

- Several types of perturbations can cause an increase in glucose levels.
- **Early distinction between the different perturbation types is hardly possible based exclusively on initial CGM deviations.**
- Slow glucose dynamics are part of the reason.
- Real-life dynamics are even more unpredictable.
- Sensor faults and noise are further challenges.
- Methods of pattern recognition may be investigated.

References

[1] Heinemann L, Krinelke L *Insulin infusion set: the Achilles heel of continuous glucose insulin infusion*, J Diabetes Sci Technol, 6, 2012.
[2] van Bon AC et al. *Significant time until catheter occlusion alerts in currently marketed insulin pumps at two basal rates*, Diabetes Technol Ther, 14(5) , 2012.
[3] Facchinetti A et al. *An Online Failure Detection Method of the Glucose Sensor-Insulin Pump System: Improved Overnight Safety of Type-1 Diabetic Subjects*, IEEE Trans Biomed Eng, 60(2), 2013.
[4] Visentin R et al. *Circadian Variability of Insulin Sensitivity: Physiological Input for In Silico Artificial Pancreas*, Diabetes Technol Ther, 17(1) , 2015.
[5] Dalla Man C et al. *GIM, Simulation Software of Meal Glucose-Insulin Model,* J Diabetes Sci Technol, 1(3), 2007.
[6] Hindmarsh AC and Serban R *User Documentation for CVODES v2.9.0 (SUNDIALS v2.7.0)*, 2016.