

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

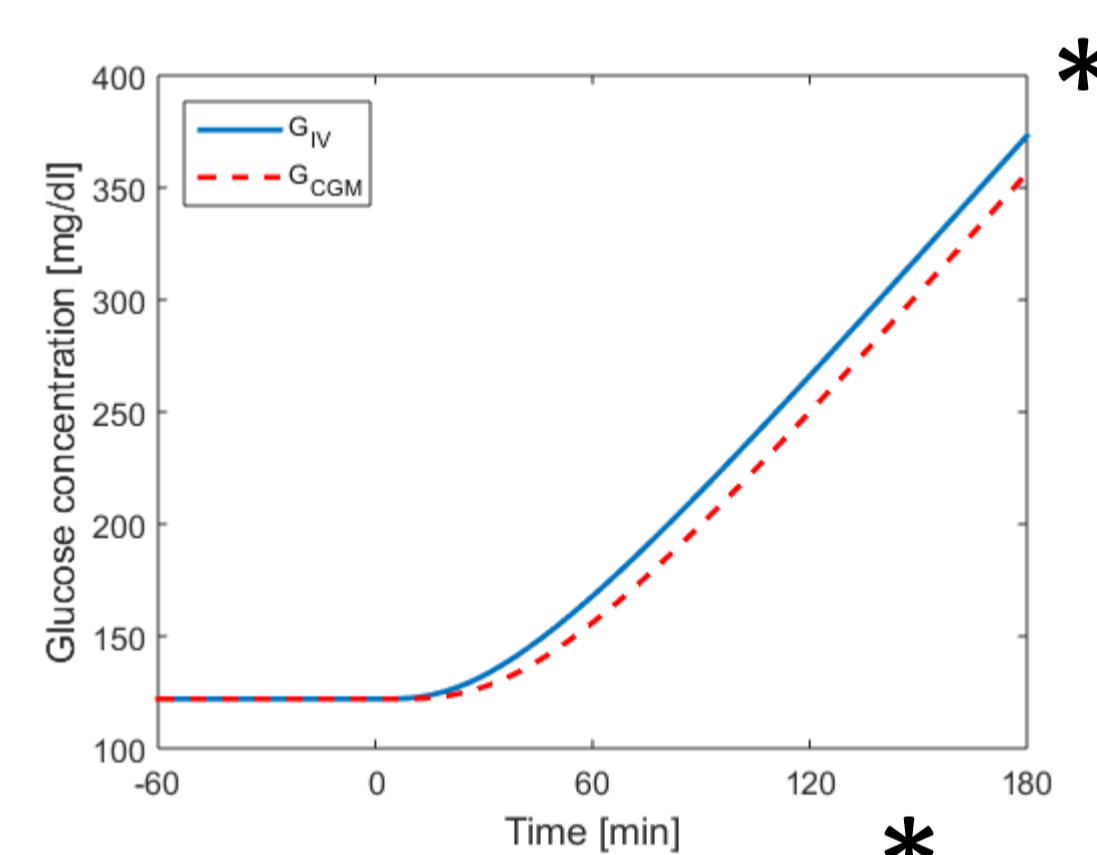
Simulation model

- 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.

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:



Sensitivity analysis

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

$$\dot{s}_i = \frac{\partial f}{\partial G} s_i + \frac{\partial f}{\partial p_i} \quad s_i(t_0) = \frac{\partial G_0(p)}{\partial p_i}$$

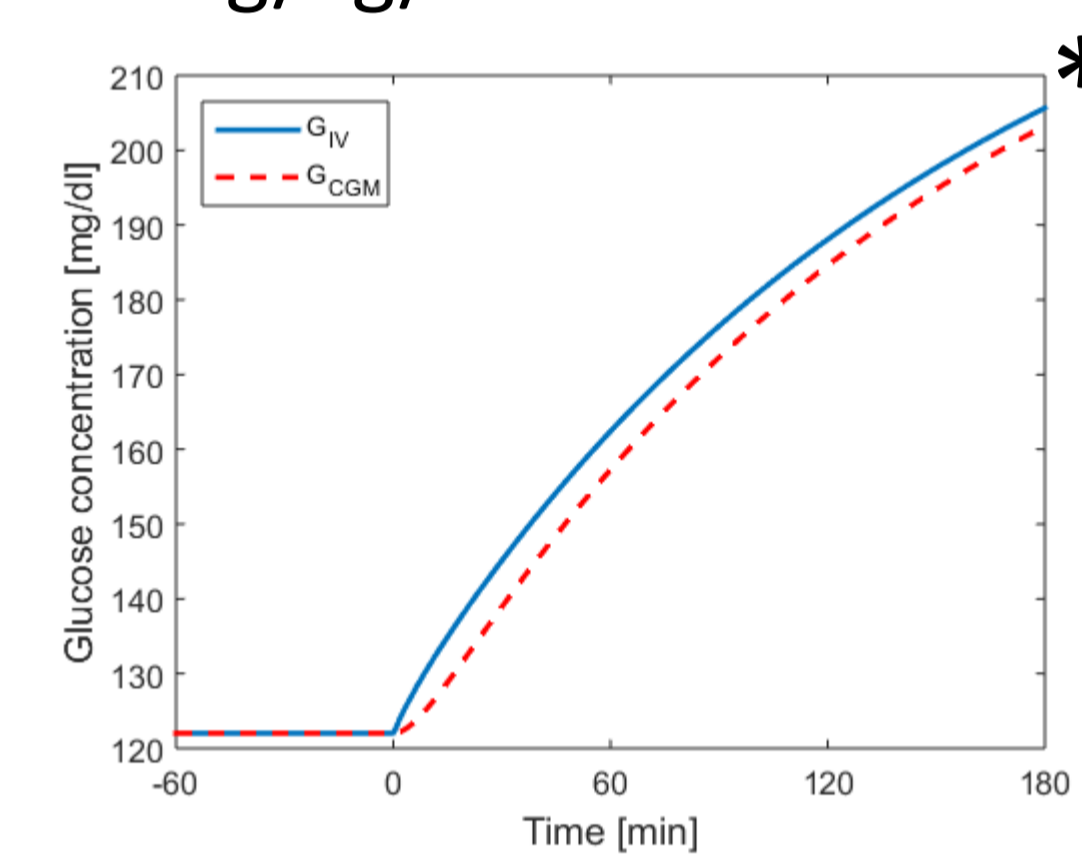
Local sensitivity of glucose concentration (G) to parameters (p), i.e. change of G caused by change of parameter p_i

- Normalized sensitivity coefficients:

$$\tilde{s}_i(t) = \frac{\partial G(p)}{\partial p_i} \frac{p_i}{G(t)}$$

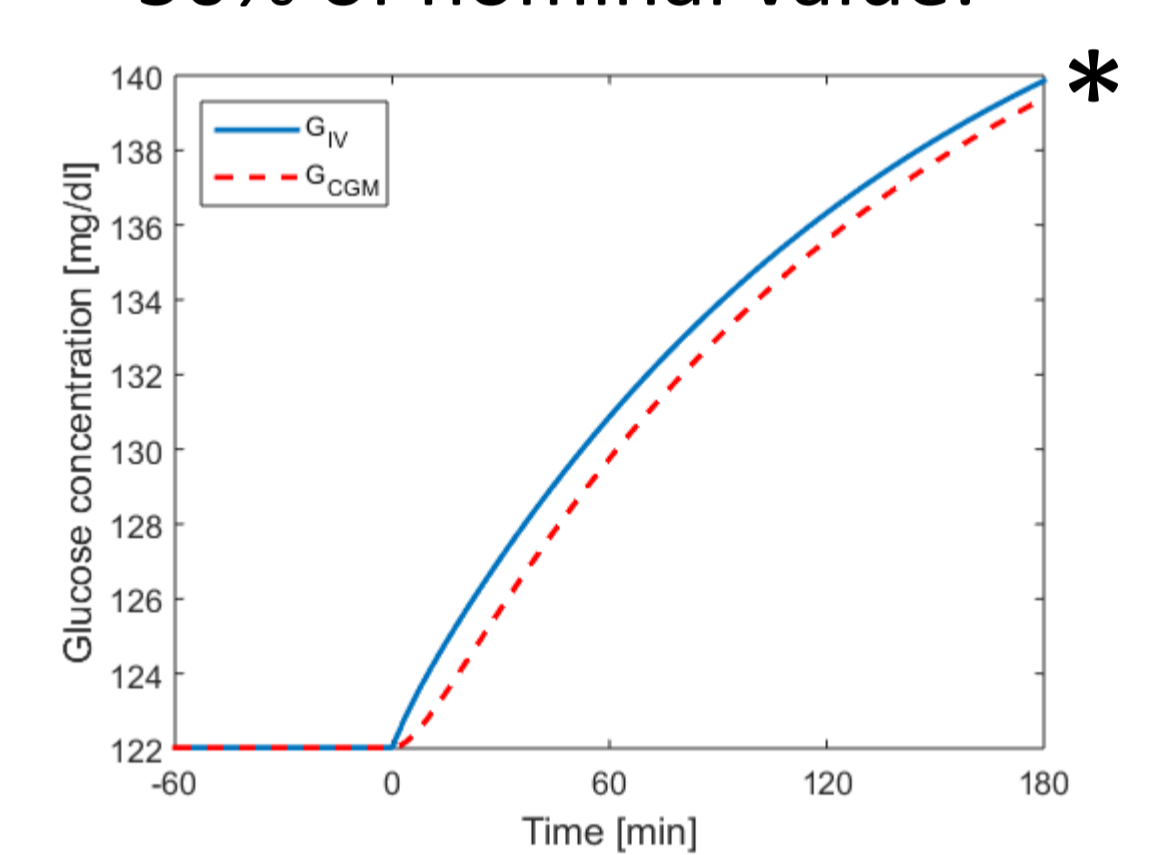
Meal disturbance

- 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:

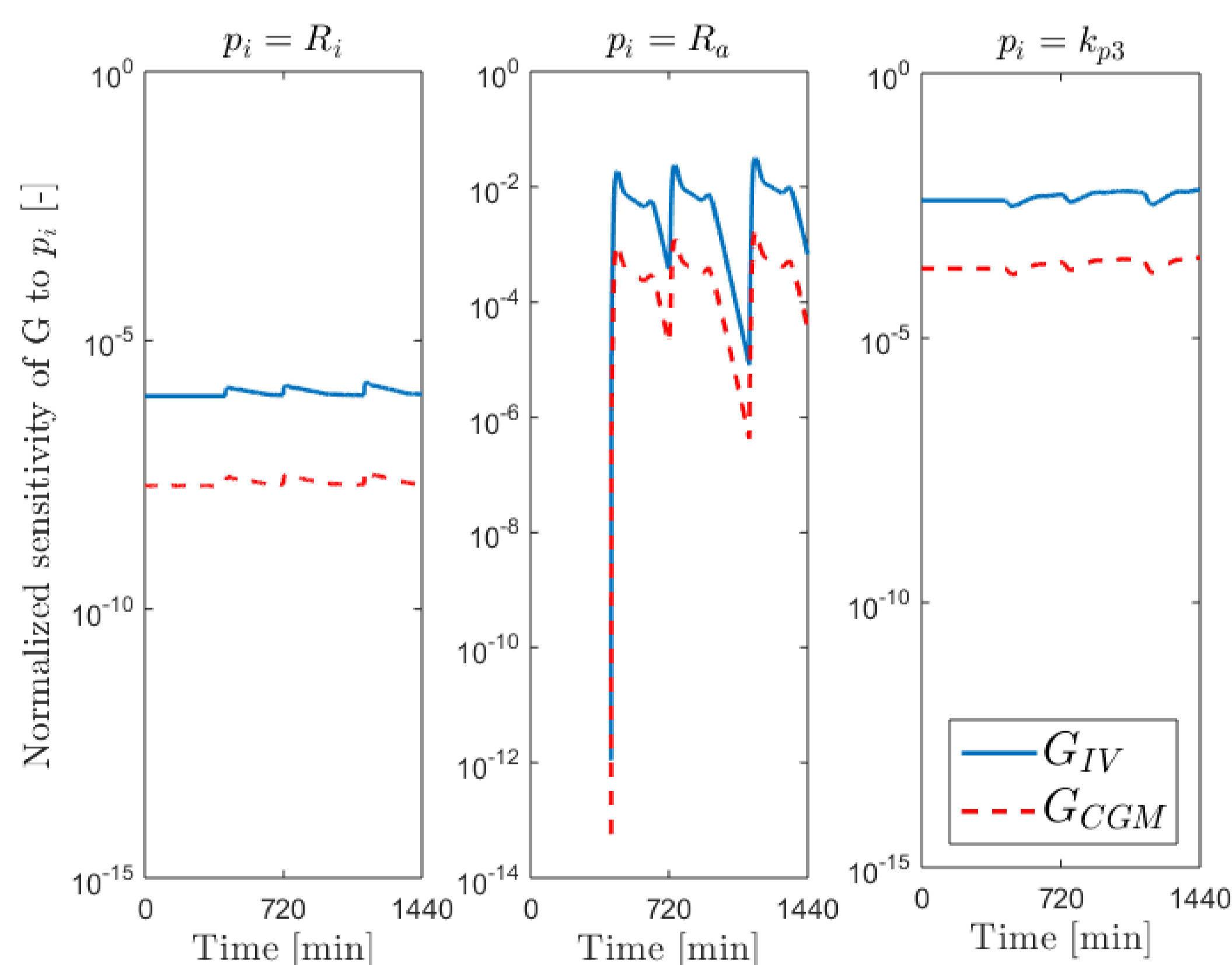


* Note scaling of axes.

RESULTS

Sensitivity to parameter changes over time

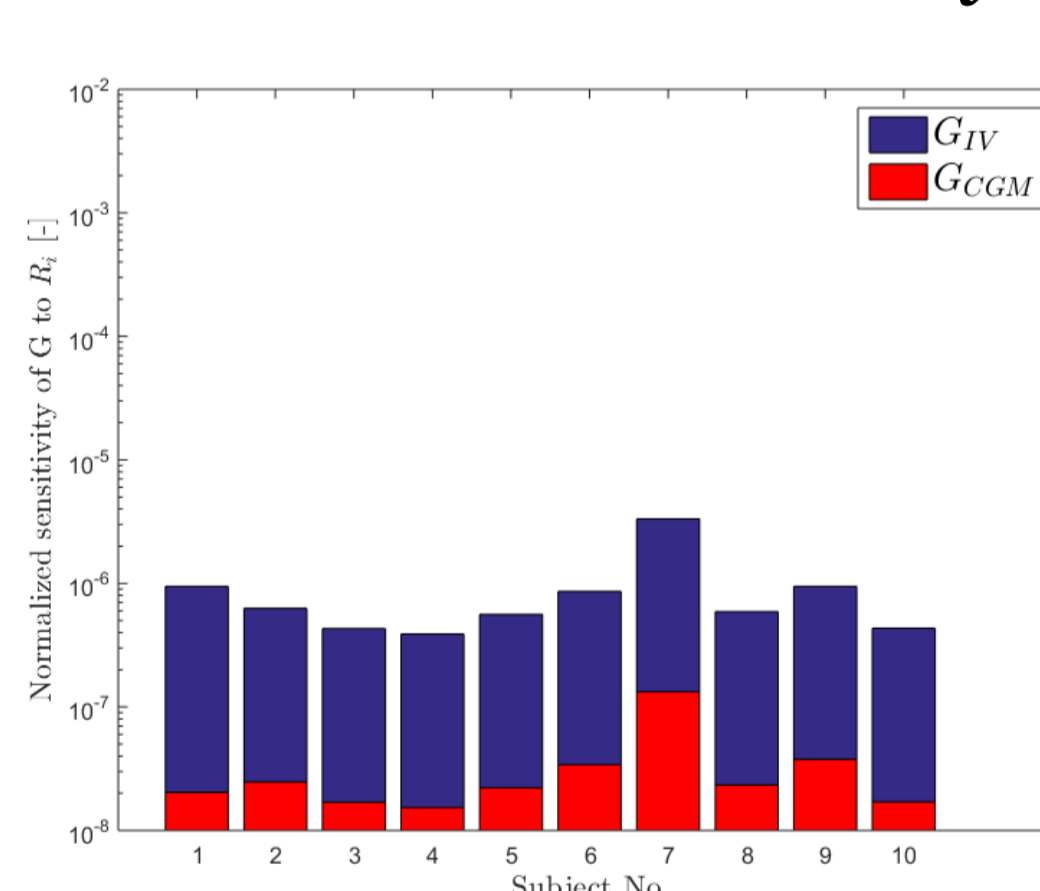
- Example of time course of a 3-meal-scenario for one subject
- Sensitivities of intravenous (IV) and SC CGM glucose



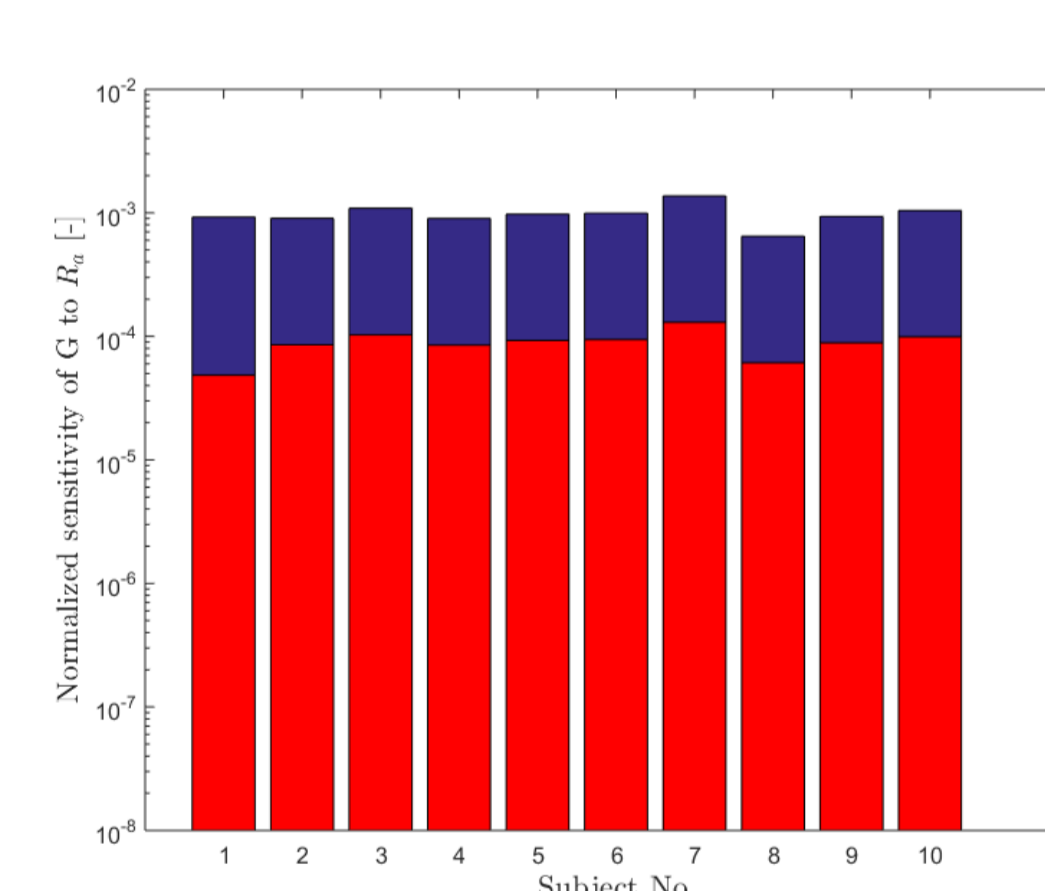
Sensitivity to parameter changes

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

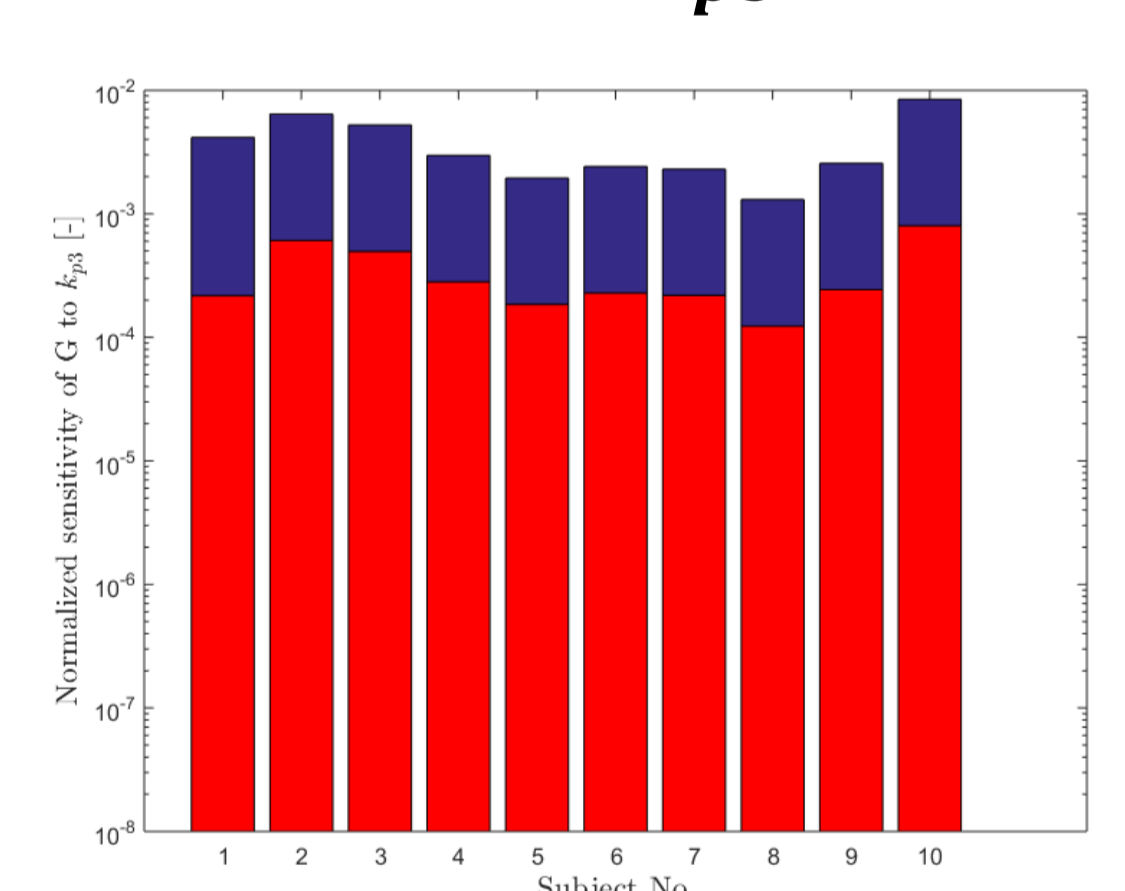
Insulin infusion fault R_i



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, Krinkel 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.