Investigating Effects of Insulin Estimation on Future Insulin Sensors' Design and Implication for AP Diabetes Management

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MOTIVATION & OBJECTIVE

- Incorporation of an insulin sensor may help to improve the performance of future artificial pancreas (AP) algorithms.
- Proof-of-concept evaluation can help to determine the potential benefit of using insulin level in a safety framework for hypoglycemia prevention for those with type 1 diabetes mellitus (T1DM).
- Identifying optimal insulin measurement intervals is needed for a feedback-based threshold suspend safety-layer.
- **Developing future insulin sensors could improve the safety of AP systems.**

METHODS

Kalman Filter EPIC Measurements

- A Kalman filter (KF) was designed as a state observer to estimate insulin concentration. Personalized KF-estimated plasma insulin concentration (EPIC) measurements aided a validated zone model predictive control (Zone-MPC) algorithm through a feedback-based threshold suspend safety layer [1].
- **Insulin delivery was suspended when:**
  - **CGM < 140 mg/dL AND**
  - **EPIC values > [fasting basal + 0.02 IU]**
- **EPIC measurements occurred at 5-, 30-, 60-, 120-, and 180-min intervals.**

Kalman Filter Sequence:

1. Prediction

Based on approximate insulin profile model

State Estimate $\hat{x}$:

$$\hat{\boldsymbol{x}}_{k-1|k-1} = \boldsymbol{A}_d \hat{\boldsymbol{x}}_{k|k} + \boldsymbol{B}_d \boldsymbol{u}_k$$

($\boldsymbol{u}_k$: Insulin delivery input)

Uncertainty $\boldsymbol{P}$:

$$\boldsymbol{P}_{k-1|k-1} = \boldsymbol{A}_d \boldsymbol{P}_{k|k} \boldsymbol{A}_d^T + \boldsymbol{Q}$$

($\boldsymbol{Q}$: Model uncertainty)

Model matrix: $\boldsymbol{A}_d$
Input matrix: $\boldsymbol{B}_d$
Measurement matrix: $\boldsymbol{C}_d$

2. Measurement/Update

Compare prediction to measurements

Kalman Gain $\boldsymbol{K}$:

$$\boldsymbol{K}_{k+1} = \boldsymbol{P}_{k+1|k} \boldsymbol{C}^T \left[\boldsymbol{C}\, \boldsymbol{P}_{k+1|k} \boldsymbol{C}^T + \boldsymbol{R}\right]^{-1}$$

($\boldsymbol{R}$: Measurement uncertainty)

State Update $\hat{x}$:

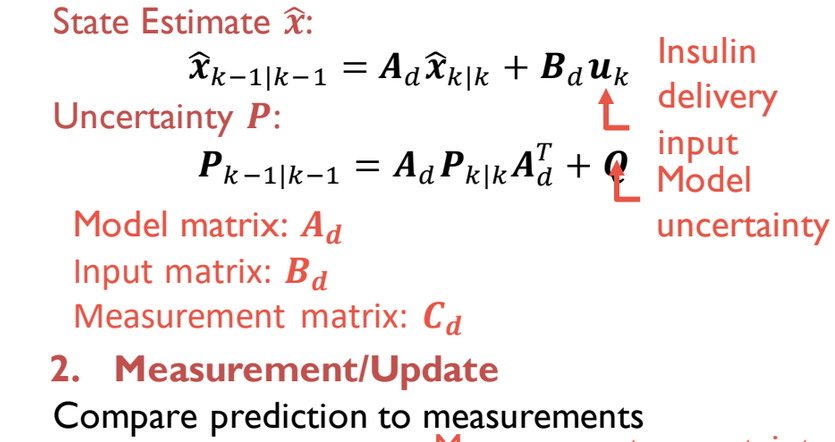
$$\hat{\boldsymbol{x}}_{k+1|k+1} = \hat{\boldsymbol{x}}_{k+1|k} + \boldsymbol{K}_{k+1}\left[\boldsymbol{y}_{k+1} - \boldsymbol{C}\, \hat{\boldsymbol{x}}_{k+1|k}\right]$$

($\boldsymbol{y}_{k+1}$: Measured state)

Uncertainty $\boldsymbol{P}$:

$$\boldsymbol{P}_{k+1|k+1} = [\boldsymbol{I} - \boldsymbol{K}_k \boldsymbol{C}]\boldsymbol{P}_{k+1|k}$$

Insulin Suspend Safety-Layer Feedback



METHODS CONTINUED

UVA/Padova T1DM Metabolic Simulator *In-silico* Protocol

The safety-layer was evaluated across **10 *in-silico* subjects** for a closed-loop **8-hour simulation** with a **single 50g-carbohydrate (CHO) announced meal** [2]. Three experiments were performed to introduce **challenging scenarios that might induce severe hypoglycemia:**

Scenario 1: Exercise
60-min exercise, induced via increased glucose uptake rates, 1-hr after an announced meal.

Scenario 2: Meal size & carbohydrate ratio (CR)
Meal size overestimation by 35% (e.g. 37 g-CHO with 50 g-CHO coverage) and CR underestimated by 25% (e.g. if CR was 1:10, the CR used in simulation would be 1:7.5, thus, more insulin is delivered).

Scenario 3: Baseline
Announced meal (baseline)

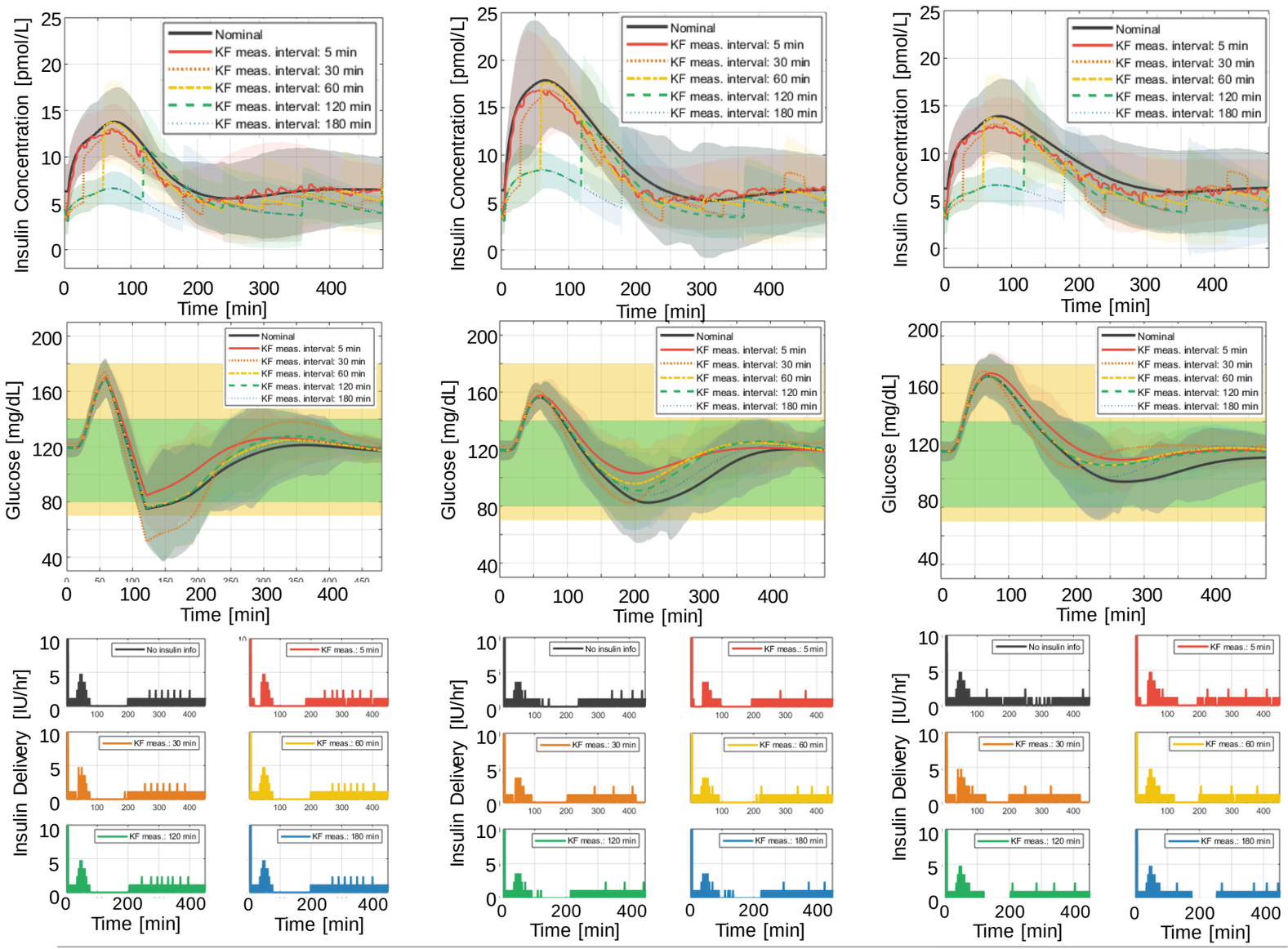
RESULTS

- **Percent time below 70 mg/dL** (mean ± standard deviation, *indicates *p*-value < 0.05)

	No EPIC	5-min	30-min	60-min	120-min	180-min
Scenario 1	8.1±9.1%	2.5±5.2%*	7.1±7.7%*	7.6±8.3%	7.6±8.3%	7.6±8.3%
Scenario 2	5.1±5.3%	0.0±0.0%*	0.0±0.0%*	0.9±2.8%*	2.1±4.6%*	3.2±5.4%
Scenario 3	0.7±2.2%	0.0±0.0%	0.0±0.0%	0.0±0.0%	0.0±0.0%	0.7±2.2%

- The plots below compare scenario results without insulin information to EPIC safety-layer KF measurement intervals for **insulin concentration**, **glucose level**, and **insulin delivery**.

EPIC safety-layer measurement intervals (mean ± standard deviation plotted)**:**
No insulin info (nominal) | 5 min | 30 min | 60 min | 120 min | 180 min



CONCLUSION

- Incorporating insulin measurements reduced hypoglycemia during *in-silico* metabolic experiments
- Insulin measurements every 30 to 120 min yielded benefits similar to more frequent measurements, **supporting feasibility of intermittent determination of insulin levels**
- Incorporating insulin estimates may help to **improve performance of future AP algorithms by reducing severe hypoglycemia events during challenging scenarios** without significant rebound hyperglycemia.

[1] Gondhalekar, *et al.*, *Automatica* 91, 2018
[2] Dalla Man, *et al. J Diabetes Sci Technol* 8(1), 2014

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