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

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Background and Aims:
Incorporation of an insulin sensor may help to improve performance of future AP algorithms by reducing severe hypoglycemic events. Optimal insulin measurement intervals were identified for a feedback-based threshold suspend safety-layer.

Method:
Personalized Kalman filter-estimated plasma insulin concentration (EPIC) measurements were used to supplement a zone model predictive control algorithm. Insulin delivery was suspended when both CGM was <140 mg/dL and EPIC values were greater than a personalized threshold based on fasting basal insulin concentrations. EPIC measurements occurred at 5-, 30-, 60-, 120-, and 180-minute intervals. Using the UVA/Padova Simulator, the controller was evaluated across ten *in-silico* subjects for three 8-hour, 50-gram carbohydrate scenarios: 1) sixty-minute exercise, induced via increasing glucose uptake rates, one hour after an announced meal, 2) meal size overestimation by 35% with carbohydrate ratio underestimated by 25%, and 3) announced meal (baseline).

Results:
Implementing the EPIC safety-layer, the mean percent time below 70 mg/dL decreased: from 8.09±9.08% to 2.47±5.24% for 5-minute, 7.07±7.75% for 30-minute, 7.57±8.28% for 60-minute, and 7.59±8.26% for 120- through 180-minute intervals (scenario 1); from 5.07±5.33% to 0.00±0.00% for 5- through 30-minute, 0.87±2.76% for 60-minute, 2.12±4.65% for 120-minute, and 3.16±5.38% for 180-minute intervals (scenario 2); and from 0.69±2.17% to 0.00±0.00% for 30- through 120-minute, while remaining at 0.69±2.17% for 180-minute intervals (scenario 3). Infrequent measurements of 30- to 120- minutes resulted in slight performance degradation with increasing sample time.

Table 1: Glycemic control without insulin information compared with various EPIC safety-layer measurement intervals. Data are shown as mean ± standard deviation. *Indicates a p-value < 0.05.

1 Meal Scenario (8 hours)	EPIC Measurement Interval (min)	Time above 180 mg/dL (%)	p-value	Time between 70-180 mg/dL (%)	p-value	Time below 70 mg/dL (%)	p-value	Time below 63 mg/dL (%)	p-value	Time below 54 mg/dL (%)	p-value
Scenario 1: Exercise (60 minutes)	No EPIC	0.35 ± 0.92	-	91.97 ± 9.12	-	8.09 ± 9.08	-	5.65 ± 7.51	-	1.35 ± 2.63	-
	5	0.46 ± 1.13	0.177	97.21 ± 5.02	0.063	2.47 ± 5.24	0.047*	1.68 ± 3.56	0.085	0.48 ± 1.51	0.111
	30	0.39 ± 0.99	0.168	93.01 ± 7.61	0.132	7.07 ± 7.75	0.034*	2.99 ± 5.12	0.185	1.00 ± 2.46	0.175
	60	0.35 ± 0.92	NaN	92.54 ± 8.27	0.343	7.57 ± 8.28	0.112	3.82 ± 6.21	0.343	1.35 ± 2.63	NaN
	120	0.35 ± 0.92	NaN	92.54 ± 8.27	0.343	7.59 ± 8.26	0.119	3.82 ± 6.21	0.343	1.35 ± 2.63	NaN
	180	0.35 ± 0.92	NaN	92.54 ± 8.27	0.343	7.59 ± 8.26	0.119	3.82 ± 6.21	0.343	1.35 ± 2.63	NaN
Scenario 2: Overestimated Meal (35%) with Underestimated Carb Ratio (25%)	No EPIC	0.00 ± 0.00	-	95.92 ± 5.17	-	5.07 ± 5.33	-	1.08 ± 3.20	-	0.00 ± 0.00	-
	5	0.00 ± 0.00	NaN	100.00 ± 0.00	0.0344*	0.00 ± 0.00	0.015*	0.00 ± 0.00	0.314	0.00 ± 0.00	NaN
	30	0.00 ± 0.00	NaN	100.00 ± 0.00	0.0344*	0.00 ± 0.00	0.015*	0.00 ± 0.00	0.314	0.00 ± 0.00	NaN
	60	0.00 ± 0.00	NaN	99.25 ± 2.37	0.0248*	0.87 ± 2.76	0.011*	0.00 ± 0.00	0.314	0.00 ± 0.00	NaN
	120	0.00 ± 0.00	NaN	98.02 ± 4.37	0.090	2.12 ± 4.65	0.047*	0.83 ± 2.42	0.343	0.00 ± 0.00	NaN
	180	0.00 ± 0.00	NaN	97.11 ± 5.04	0.123	3.16 ± 5.38	0.066	1.08 ± 3.20	NaN	0.00 ± 0.00	NaN
Scenario 3: Announced Meal (Baseline)	No EPIC	1.72 ± 3.65	-	97.88 ± 3.52	-	0.69 ± 2.17	-	0.00 ± 0.00	-	0.00 ± 0.00	-
	5	2.18 ± 4.62	0.176	97.92 ± 4.41	0.931	0.00 ± 0.00	0.343	0.00 ± 0.00	NaN	0.00 ± 0.00	NaN
	30	1.87 ± 3.96	0.209	98.25 ± 3.70	0.521	0.00 ± 0.00	0.343	0.00 ± 0.00	NaN	0.00 ± 0.00	NaN
	60	1.72 ± 3.65	NaN	98.42 ± 3.34	0.343	0.00 ± 0.00	0.343	0.00 ± 0.00	NaN	0.00 ± 0.00	NaN
	120	1.72 ± 3.65	NaN	98.42 ± 3.34	0.343	0.00 ± 0.00	0.343	0.00 ± 0.00	NaN	0.00 ± 0.00	NaN
	180	1.72 ± 3.65	NaN	97.86± 3.52	NaN	0.69 ± 2.17	NaN	0.00 ± 0.00	NaN	0.00 ± 0.00	NaN

Conclusion:

The EPIC safety-layer *in-silico* prevented severe hypoglycemia during challenging scenarios without significant rebound hyperglycemia. Future insulin sensors could potentially be designed utilizing 30- to 120-minute measurement intervals.