Application of Zone Model Predictive Control (Zone-MPC) Artificial Pancreas (AP) During Extended Use of Infusion-Set and Sensor: A Randomized Crossover-Controlled Home-Use Trial

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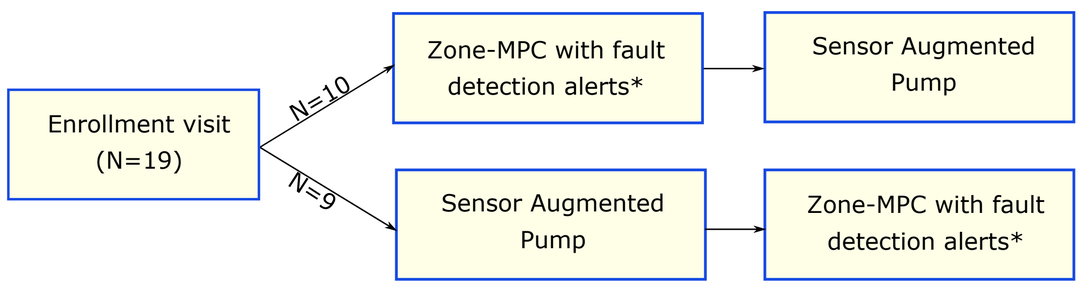
Related poster in ATTD 2017
ATTD7-0252: Real-time detection of infusion-set faults

Background

- As unsupervised home use of artificial pancreas (AP) becomes standard-of-care, real-life test of extended use of insulin infusion-set and CGM sensor is essential.
- Safety and efficacy of closed-loop AP during the extended use have not been previously evaluated in outpatient conditions.

Design

- Two-week randomized, crossover home-use study.



*See poster ATTD7-0252.

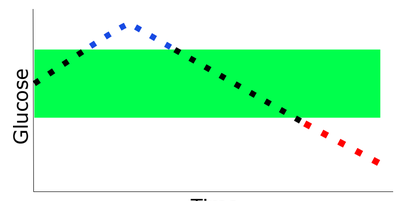
- Subjects continuously used devices to precipitate failures:
  - Extended the use of insulin infusion-set up to 7 days and extended the use of CGM sensor up to 21 days.
- Clinical protocol: Subjects followed their regular daily routines (including meal selection and pre-meal bolusing) and were monitored remotely during both arms.

Subject demographics

Cohort	19 (11F,8M)
Age [median (IQR), yrs]	23.0 (10.0)
Weight [mean (SD), kg]	86.1 (22.8)
Duration of diabetes [median (IQR), yrs]	11.0 (11.8)
Total daily insulin [mean (SD), U]	56.3 (18.4)
HbA1c [mean (SD), %]	7.99 (1.68)

Zone-Model Predictive Control

- Zone-MPC[1] uses explicit model predictions and online optimization to keep glucose values in the target zone.



Target zone (green) and glucose predictions as dots (black in the zone, blue above the zone ($\hat{z}$) and red below the zone ($\check{z}$).)

- At each step k, a state estimate is generated, optimal inputs $\{u_0, \ldots, u_{N_u-1}\}$ are calculated and *only* the first input u_0 is applied.
- Elucidation of zone-MPC optimization used in the study:

$$\min_{\{u_0,\ldots,u_{N_u-1}\}} \underbrace{\sum_{i=1}^{N_y}(\check{z}_i^2 + Q(v_i)\hat{z}_i^2 + \hat{D}\hat{v}_i^2)}_{\text{Penalize glycemic deviations } z_i \text{ from zone with assertive hyper correction and hypo prevention using glucose velocity } v_i.} + \underbrace{\sum_{i=0}^{N_u-1}(\hat{R}\hat{u}_i^2 + \check{R}\check{u}_i^2)}_{\text{Independently penalize insulin } u_i \text{ to address hyper and hypo excursions.}}$$

subject to the following constraints:

$$\left.\begin{aligned} &x_0 = x_k, x_{i+1} = Ax_i + Bu_i, \\ &y_i = Cx_i, \end{aligned}\right\} \text{Insulin-glucose dynamics}$$

$$0 \le u_i + u_{\text{basal},k+i} \le \bar{u}(t_i),\} \text{ Upper and lower bound on insulin (for safety)}$$

$$u_i \le u_{\text{IOB},k}.\} \text{ Insulin-on-Board bound on insulin (for safety)}$$

- List of variables associated with the optimization:
  - k: current sample time, i: prediction step.
  - N_y: prediction horizon, N_u: control horizon.
  - y: glucose deviation from fasting, u: insulin deviation from basal, x: state.
  - $\hat{z}$: glucose excursion above zone; $\check{z}$: glucose excursion below zone.
  - v: glucose velocity[2,3] $\approx$ rate of change of glucose, $\hat{v}$: non-negative velocity.
  - $\hat{u}, \check{u}$: positive and negative input deviation (around basal).
  - $Q(v_i), \hat{D}, \hat{R}, \check{R}$: weights used in the optimization.
  - The upper bound $\bar{u}(t_i)$ is 1U during the day and 1.8 times subject's basal during the night[1,2]. The upper bound $u_{\text{IOB},k}$ is calculated using IOB decay curves and subject's correction factor[1,2].

Glycemic metrics

- Glycemic control for AP and SAP arms evaluated on following endpoints:
  - Time in euglycemia, hypoglycemia and hyperglycemia
  - Average glucose and glucose variability
  - Fasting glucose (using CGM at 06:00)

Table 1. Glycemic metrics for full day and overnight (00:00-06:00) period.

	Day and night			Overnight		
Metric	SAP (N=19)	AP (N=19)	p-val	SAP (N=19)	AP (N=19)	p-val
%Time $<$ 50 mg/dL	0.2 (0.4)	0.1 (0.2)	0.007	0.0 (0.3)	0.0 (0.0)	0.067
%Time $<$ 70 mg/dL	2.7 (2.3)	1.3 (1.2)	0.001	1.5 (1.7)	0.7 (1.3)	0.004
%Time in [70,140] mg/dL	39.2 (13.3)	48.1 (10.5)	0.016	36.3 (16.2)	50.7 (19.0)	0.024
%Time in [70,180] mg/dL	65.2 (10.4)	71.6 (9.8)	0.008	66.1 (16.5)	73.7 (13.4)	0.020
%Time $>$ 180 mg/dL	30.9 (15.5)	24.9 (8.8)	0.030	32.7 (17.9)	25.4 (11.4)	0.030
%Time $>$ 300 mg/dL	1.8 (2.1)	0.4 (2.1)	0.025	1.0 (2.4)	0.0 (1.1)	0.277
Mean glucose†	159.0 (20.1)	148.3 (12.7)	0.059	159.4 (21.8)	150.9 (15.1)	0.126
Median glucose‡	153.2 (22.7)	140.5 (14.9)	0.036	154.6 (30.0)	138.3 (24.7)	0.064
SD glucose	55.1 (8.9)	51.9 (10.6)	0.044	53.2 (12.3)	46.4 (11.2)	0.053
Mean glu. @ 06:00	158.3 (18.6)	139.6 (19.7)	0.020	—	—	—

Data are median (IQR). Significance assessed on paired-data by Wilcoxon signed rank test[4]. †, ‡ Represents each subject's mean (median) glucose using the complete CGM signal over the study period. SD is standard deviation.

Individual glucose mean for AP and SAP arms

- 14 out of 19 subjects experienced reduction in mean sensor glucose on AP arm (see Fig.1) while 18 out of 19 subjects also spent less time below 70 mg/dL.

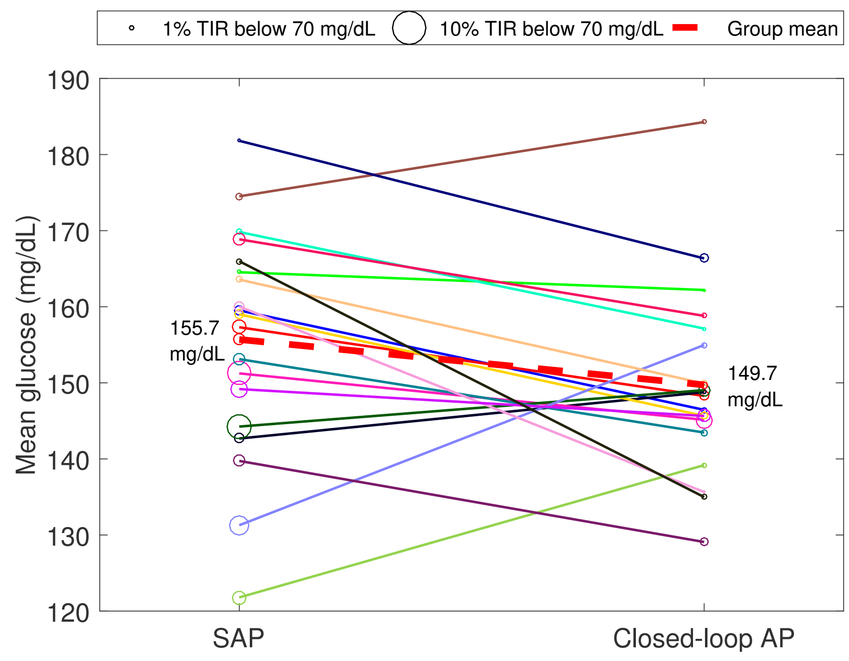


Fig 1. Paired mean blood glucose in AP and SAP arms.

Day-by-day glucose mean for AP and SAP arms

- The day-by-day mean (taken across subjects) glucose was lower during AP use on most days (11 of 13, see Fig. 2).
- The AP arm concurrently had reduced exposure to hypoglycemia over SAP arm.

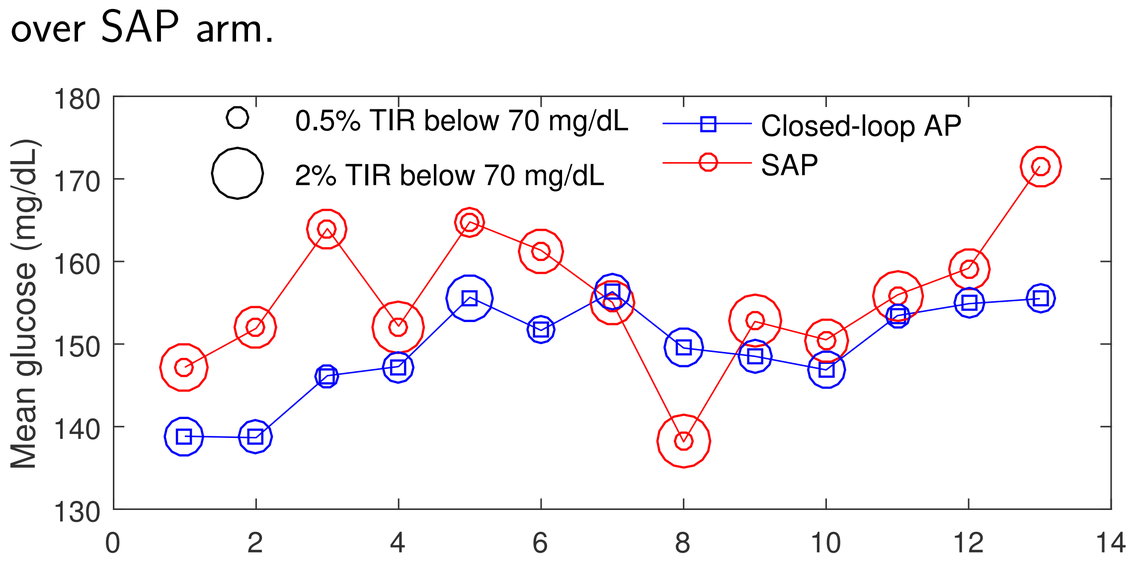


Fig 2. Day-by-day mean blood glucose in AP and SAP arms.

Discussion and Conclusions

- Under lengths of wear to induce sensor and infusion-set failure, zone-MPC based AP arm significantly outperformed SAP arm (See Table 1) with improvements in:
  - Time below 70 mg/dL: approx. 2-times reduction ($p = 0.001$)
  - Time in 70 to 180 mg/dL: 6.4% absolute increase ($p = 0.008$)
  - Time above 300 mg/dL: approx. 4.5-times reduction ($p = 0.025$)
- AP arm had lower median glucose ($p = 0.036$) with significant reduction in fasting glucose (≈ 19 mg/dL, $p = 0.02$).
- AP arm also outperformed SAP during overnight period (See Table 1) with more time in range and lower median glucose.
- A majority of subjects (14 out of 19) saw improvement in mean glucose, as well as in day-by-day mean glucose, in AP arm over SAP arm.
- A majority of subjects (18 out of 19) had reduced exposure to hypoglycemia in AP arm over SAP arm.

1) R. Gondhalekar, E. Dassau and F. J. Doyle III. Periodic zone-MPC with asymmetric costs for outpatient-ready safety of an artificial pancreas to treat type 1 diabetes. *Automatica*, 71:237-246, 2016.
2) R. Gondhalekar, E. Dassau and F. J. Doyle III. Velocity-weighting to prevent controller-induced hypoglycemia in MPC of an artificial pancreas to treat T1DM. *In Proc. of 2015 American Control Conference*, 1635-1640, 2015.
3) R. Gondhalekar, E. Dassau and F. J. Doyle III. Velocity-weighting & velocity-penalty MPC of an artificial pancreas: Improved safety & performance. *Under review*.
4) G. Forlenza, S. Deshpande *et al*. Application of zone model predictive control (Zone-MPC) artificial pancreas during extended use of infusion-set and sensor: A randomized crossover-controlled home-use trial. *In preparation*.

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