The Type 1 Diabetes Patient Decision Model Reproduces the Glycemic Outcomes of the REPLACE-BG Trial

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1. INTRODUCTION

The type 1 diabetes (T1D) patient decision model - recently developed by our group [1] - models the physiology of T1D subjects and their behavior in making treatment decisions based on self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM).

The T1D patient decision model allows generating reliable multiple-day in silico trials and, thus, it could be a very useful tool for the design and preclinical test of new therapies and technologies for diabetes management. However, the T1D patient decision model has been validated only vs. adjunctive-CGM treatment data.

2. AIM

To validate the T1D patient decision model also in the nonadjunctive-CGM configuration, by comparing simulated data vs. the REPLACE-BG 26-week trial outcomes [2].

3. DATABASE

Data of the REPLACE-BG trial [2] includes the CGM traces recorded in:

- 76 T1D subjects using CGM adjunctively for 26 weeks
- 148 T1D subjects using CGM nonadjunctively for 26 weeks

Patients on adjunctive CGM use were instructed to collect SMBG i) 12 h after sensor insertion, ii) on a sick day, iii) for 4 h after taking acetaminophen, iv) for symptoms suggestive of hypoglycemia discordant with CGM readings, v) for 20 min after treating a low CGM value if CGM had not begun to rise, vi) before insulin dosing if CGM is >250 mg/dl, vii) when fasting CGM >300 mg/dl or during the day if CGM > 300 mg/dl for at least 1 h.

4. THE T1D PATIENT DECISION MODEL

The T1D patient decision model [1] includes four components:

A. the UVA/Padova model of T1D patient physiology [3];
B. models of glucose monitoring devices:
   - SMBG: model of Bayer Contour Next USB [4];
   - CGM: model of Dexcom G5 Mobile [1] with variability over one week of sensor wear;
C. a model of the patient's behavior in making treatment decisions;
D. a model of insulin infusion pump.

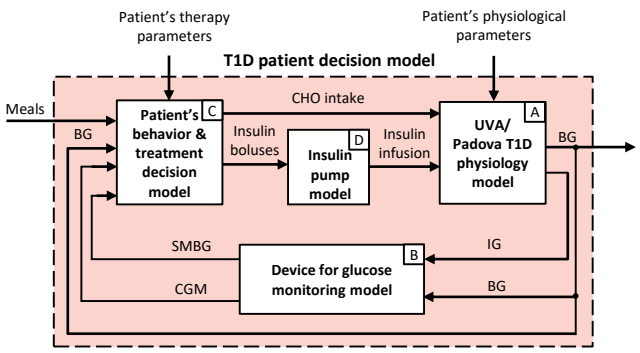

Fig. 1. Schematic representation of the T1D patient decision model.

The patient's behavior and treatment decision model was designed to reproduce treatments based on adjunctive CGM use (Fig. 2) and nonadjunctive CGM use (Fig. 3) as in the protocol of the REPLACE-BG trial.

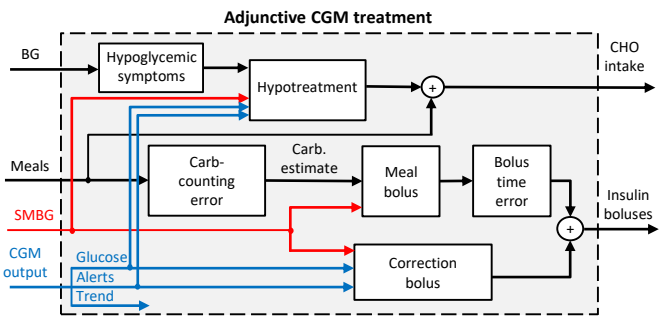

Fig. 2. Schematic representation of the patient's behavior and treatment decision model with adjunctive CGM use.

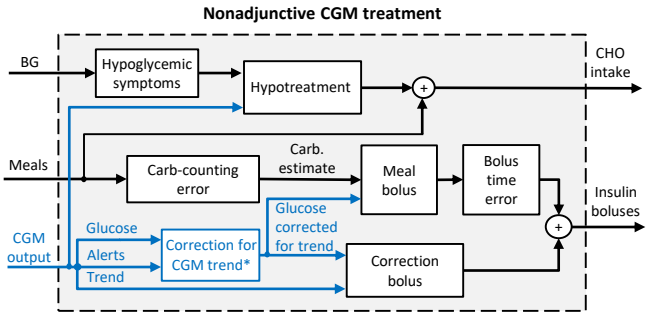

Fig. 3. Schematic representation of the patient's behavior and treatment decision model with nonadjunctive CGM use.

Remarks:

In the model of adjunctive CGM treatment, it was not possible to implement conditions ii) and iii) for SMBG collection in REPLACE-BG trial, since there is no model of sickness and acetaminophen in the model.

In the model of nonadjunctive CGM treatment, corrections for CGM trend are in accordance to guidelines proposed by Scheiner [5].

4. IN SILICO TRIAL AND ASSESSMENT CRITERIA

In silico trial

- 100 virtual T1D adults
- One week, 3 meals per day
- Two treatment scenarios: adjunctive and nonadjunctive CGM use.

Metrics

Percentage of time spent in 70-180 mg/dl, below 70 mg/dl, below 50 mg/dl, above 180 mg/dl, above 250 mg/dl.

Assessment

Metrics were calculated for both simulated data and a subset of real data obtained randomly extracting one week per subject. This comparison was repeated for 100 different random selections of study weeks.

5. RESULTS

Table 1: Metrics calculated on simulated data and REPLACE-BG data for adjunctive and nonadjunctive CGM use

Metric	Simulation		REPLACE-BG	
	Adj. CGM	Nonadj. CGM	Adj.CGM	Nonadj. CGM
Time in 70-180 mg/dl [%]	63.93 [13.48]	64.43 [13.80]	63.87 [13.85]	61.81 [15.59]
Time below 70 mg/dl [%]	3.03 [0.79 – 4.89]	1.63 [0.61 - 2.97]	3.38 [1.55 - 5.86]	2.91 [1.15 - 5.73]
Time below 50 mg/dl [%]	0.38 [0.00 - 1.29]	0.08 [0.00 – 0.50]	0.35 [0.01 – 0.94]	0.26 [0.00- 0.88]
Time above 180 mg/dl [%]	32.36 [13.16]	33.35 [13.55]	31.97 [15.23]	34.28 [16.65]
Time above 250 mg/dl [%]	7.32 [3.64 – 11.54]	7.53 [3.55 – 12.14]	6.34 [2.76 – 12.36]	7.98 [3.20 – 14.38]

Mean [SD] are reported for time in 70-180 mg/dl and time above 180 mg/dl, median [25th -75th percentile] are reported for the other metrics.
For REPLACE-BG, in particular, we report the mean of metric values obtained in the 100 random selections of study weeks.

- Adjunctive CGM use: metrics obtained in silico well match those derived from the REPLACE-BG trial (confirming the results of the validation of [1])
- Nonadjunctive CGM use: in silico results follow the REPLACE-BG trial indications, by increasing the time in hyperglycemia and decreasing the time in hypoglycemia

6. CONCLUSION

The T1D patient decision simulator is able to realistically reproduce the outcome of trials also based on nonadjunctive CGM use - some work to better match hypoglycemia outcomes is still needed - and can be used to test in silico new therapies for T1D management.

REFERENCES:
[1] M. Vettoretti et al., *IEEE Trans Biomed Eng*, 2017.
[2] Aleppo et al., *Diabetes Care*, 2017.
[3] Dalla Man et al., *J Diabetes Sci Technol,* 2014.
[4] Vettoretti et al., *J Diabetes Sci Technol*, 2017.
[5] Scheiner, Practical CGM, 2015.

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