Use of the Minimally-Invasive Oral Minimal Model to Quantify the Effect of Fat and Protein on the Postprandial Glucose Excursion in Individuals with Type 1 Diabetes under Free-living Conditions

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BACKGROUND AND AIM

Individuals with **type 1 diabetes** (T1D) have to constantly monitor and control their blood glucose (BG) levels through the administration of exogenous insulin.

Current dosing strategies requires the individual to estimate carbohydrate (C) amount in the meal to calculate the prandial insulin bolus, **without accounting for fats** (F) **and proteins** (P) that are known to affect postprandial gastric retention (GR), glucose rate of appearance (R_a) in the bloodstream, and insulin sensitivity (S_I) [1].

Such variables can be estimated, in real-life conditions, from minimally-invasive devices like continuous glucose monitor (CGM) and insulin pump (IP), using the recently-developed **Minimally-Invasive Oral Minimal Model** (MI-OMM) [2].

Aim: Applying the MI-OMM to quantify the effect of macronutrients on clinical outcomes, such as GR, R_a and S_I, in real-life scenarios.

DATASET

- **Subjects: 120 individuals with T1D** (age = 15.5±11.5 yr, BW= 51.3±28.0 kg) recruited in three different clinical centers.
- **Protocol:** Each participant underwent one admission ranging from 3 to 5 days in a supervised rental home setting under **free-living conditions**, wearing a CGM, to collect BG data, and an IP, for insulin administration. Meal timing and content (amount in grams of C, F, and P) were recorded with the assistance of the medical personnel.

METHODS

- **Meal extraction: 261 prandial CGM traces** were analyzed. These were selected with predefined criteria to avoid confounding factors in the analysis (e.g., requiring a certain distance from physical exercise and from other meals).

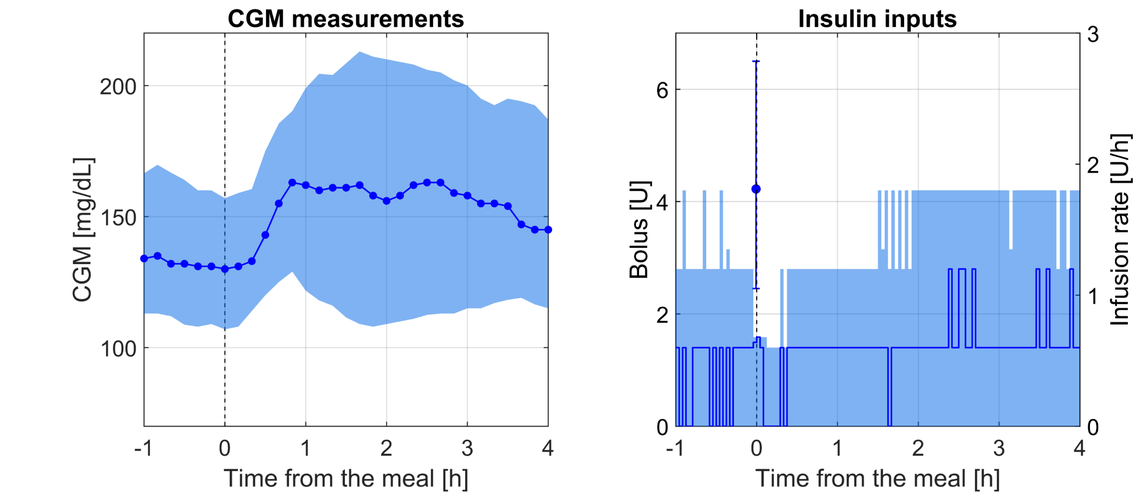

Fig. 1: Median (blue lines) and interquartile range (blue shaded areas) of the extracted data. Dashed lines represent mealtime. *Left panel:* CGM sensor measurements. *Right panel:* Insulin pump rate (right y-axis, solid line and shaded areas) and prandial insulin bolus (left y-axis, dot and bars).

- **Meal classification:** Meals were classified into low vs high F content (LF vs HF) and low vs high P content (LP vs HP), trying to keep each H- and L-class matched in terms of numerosity, BW and age of the population, as:
  - **Low-fat** (LF) meal if F<15g (n=108) or **high-fat** (HF) if F>25 g (n=101);
  - **Low-protein** (LP) meal if P<15g (n=91) or **high-protein** (HP) if P>30g (n=95).
- **Model identification:** The MI-OMM (Fig. 2) was identified on the extracted CGM traces using a **Bayesian Maximum A Posteriori estimator** implemented in Matlab [3]. To account for CGM autocorrelation, the covariance matrix of the residual error was constructed using the **Yule-Walker's equation** for an autoregressive model of order 2 [4]. Model assessment was done by checking the distribution of weighted residuals, the precision and the physiological plausibility of parameter estimates.

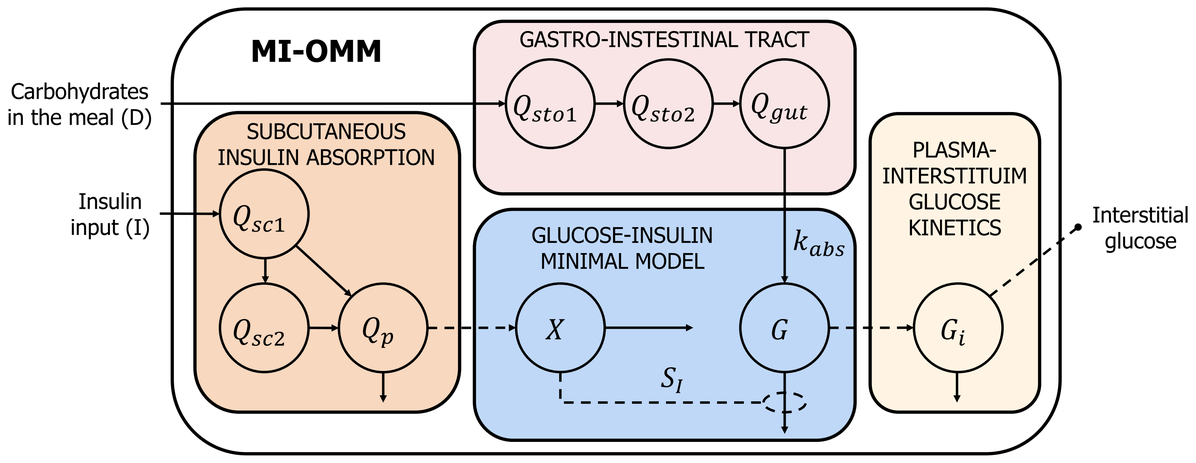

Fig. 2: Schematic representation of the MI-OMM developed in [2]. Circles represent state variables, continuous arrows represent mass transfers and inputs, dashed lines represent actions, and dashed lines with black dots represent measurement variables.

- **Meal comparison:** The MI-OMM provided estimates of $GR(t)=100\cdot(Q_{sto1}(t)+Q_{sto2}(t))/D$, $R_a(t) = f\cdot k_{abs}\cdot Q_{gut}(t)/D$, and $\mathbf{S_I}$. Then, the half-life of the GR(t) curve (**TGR50%**) and the area under the $R_a(t)$ profile in the first 2h after the meal ($\mathbf{AUR_{2h}}$) were calculated. Finally, model-derived TGR50%, AUR_{2h}, and S_I were compared in HF vs LF and HP vs LP meals with the Wilcoxon rank sum test.

RESULTS

- **Model identification:** The model was able to well describe the CGM profiles and generally provide **physiologically plausible parameter** estimates with **good precision**. Weighted residuals (Fig. 3) were well distributed and reasonably uncorrelated, passing the runs test for randomness in 186 out of 261 sessions (71%).

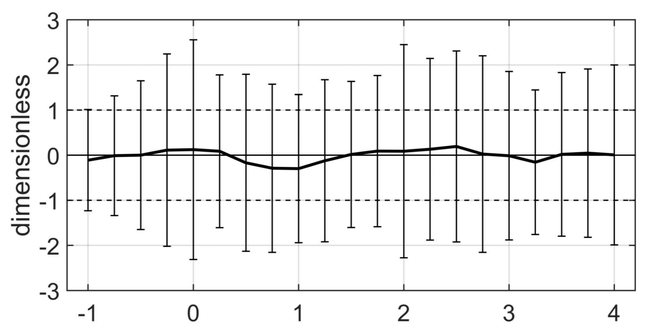

Fig. 3: Mean (black line) ± standard deviation (vertical bars) of the weighted residuals of the MI-OMM.

- **Meal comparison:** The comparison of the results obtained for different classes of meals was consistent with the literature [1], providing **slower GR and R_a for meals with HF and HP content** (Fig. 2). Table 1 provides a summary of the compared indexes. Of note, F seemed to have a slightly stronger impact on GR compared to P, whereas P showed a stronger influence on S_I.

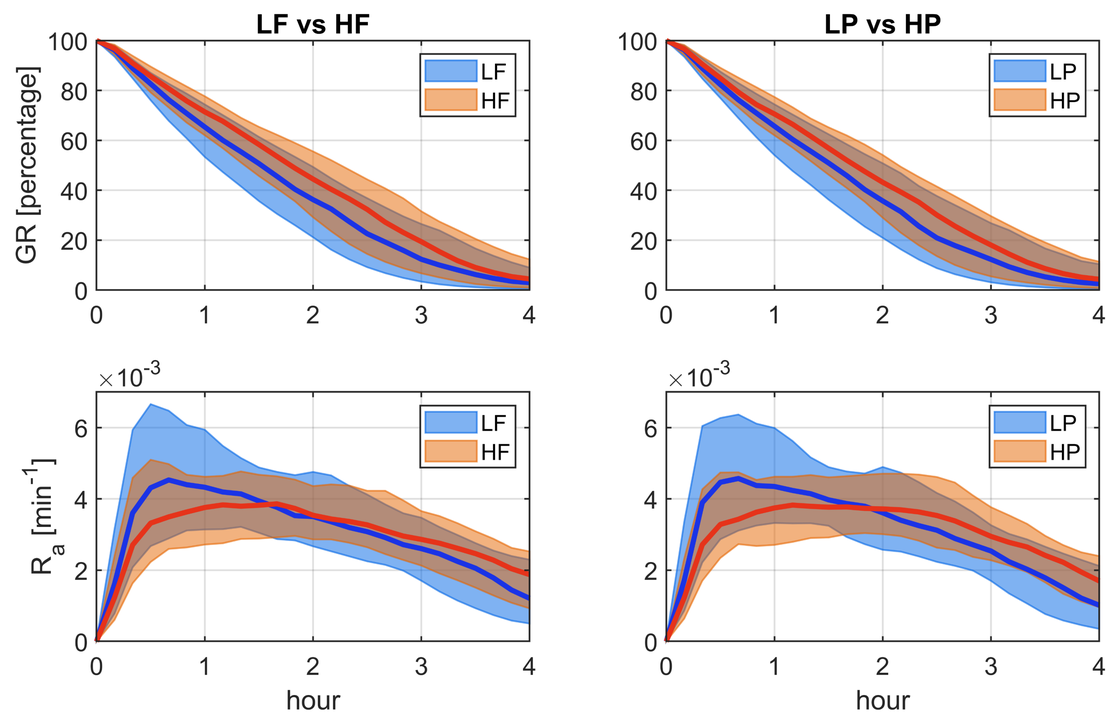

Fig. 4: Comparison of GR(t) (*top panels*) and $R_a(t)$ (*bottom panels*) predicted by the MI-OMM for different classes of meals. Thick lines represent medians, while shaded areas represent interquartile ranges. *Right panels:* LF meals, blue line and light blue area, vs HF meals, red line and orange area. *Left panels:* LP meals, blue line and light blue area, vs HP meals, red line and orange area.

Parameter [unit]	Meal Class	Median [IQR]	p-value	Meal Class	Median [IQR]	p-value
TGR50% [min]	LF	90 [65-120]	0.0053	LP	89 [67-121]	0.0233
	HF	108 [81-134]		HP	105 [82-128]	
AUR_{2h} [dimensionless]	LF	0.48 [0.38-0.62]	0.0079	LP	0.48 [0.38-0.63]	0.0050
	HF	0.41 [0.32-0.51]		HP	0.41 [0.32-0.49]	
S_I [1/(μU/mL·min)]	LF	9.6 [5.8-12] ·10^{-4}	0.0100	LP	9.4 [6.3-12] ·10^{-4}	0.0011
	HF	6.8 [4.1-11] ·10^{-4}		HP	6.3 [3.7-11] ·10^{-4}	

Table 1: Median and interquartile ranges of the TGR50%, AUR_{2h}, and S_I obtained with the MI-OMM for different classes of meals. Comparisons are done between the HF and LF meals and between the HP and LP meals. A p-value smaller than 0.05 indicates a statistically significant difference between the distribution obtained for the H- and L- class.

Main result: Higher amounts of F (25g vs. 15g) or P (30g vs. 15g) in the meal significantly slows both GR and R_a and reduces S_I.

CONCLUSIONS

- **Limitations:** Limitations of this work comes mainly from the **real-life scenario** where the data were collected, hampering model identification (e.g., **autocorrelated measurements** and **sensor calibrations**) and with difficulties in **isolating F and P** effects due to the concomitant presence of both macronutrients in the meals.
- **Significance:** To the best of our knowledge, this is the first analysis where the **effect of meal compositions** on postprandial glucose excursion **was precisely quantified** with the use of a model-based methodology in **real-life conditions**. These results can be used to **re-design current insulin therapies** accounting also for the presence of F and P in the meals. In more advanced frameworks, the model could be incorporated in algorithms for BG control or used to inform machine learning techniques for meal detection and BG prediction.

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