SUPPLEMENTARY MATERIAL TO

Automated Oral Minimal Models (AOMM) for Rapid Estimation of Insulin Sensitivity and Beta-Cell Responsivity in Large Scale Data Sets: A Validation Study

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JDST online material.

OULTINE

S1. DATASET DESCRIPTION

PARTICIPANTS

The dataset consists of 11 non-diabetic adolescents (4 males, 7 females; mean age 15 ± 1 years) spanning a broad BMI range (13.4–34.4 kg/m^2), including 7 lean, 2 overweight, and 2 obese individuals based on age-specific percentiles. All participants had reached Tanner stage IV–V of puberty and were in good health, with no history of diabetes, medication use, or metabolic disorders. Ethnic diversity was represented, including African American, Hispanic, European American, and mixed heritage individuals. In Table S1, the characteristic of each participant is reported in detail. Further details in [1], [2].

Table S1. Dataset Demographics

Subject	Ethnicity	Gender		Age (yr)	Weight (kg)	BMI (kg/m²)
1	AA	F		14.4	48.3	17.7
2	AA	M		14.5	60.5	20.9
3	H	F		13.8	56.1	22.2
4	AA	M		16.9	69.3	22.1
5	M	M		16.0	42.9	16.6
6	AA	F		16.4	76.5	26.3
7	AA	F		13.9	91.0	31.0
8	AA	F		16.2	63.9	22.7
9	AA	M		16.1	64.0	23.7
10	Mixed	F		14.5	88.8	34.4
11	C	F		14.5	78.5	26.5

Mean ± SEM: Age = 15.3 ± 0.3 yr, Weight = 67.3 ± 4.7 kg, BMI = 24.0 ± 1.6 kg/m^2

Note: AA = African-American; H = Hispanic; C = Caucasian; M = Male; F = Female.

PROTOCOL

As a part of separate study aimed at estimating glucose fluxes, meal, endogenous production and utilization (aka triple-tracer method) for estimation of “true” insulin sensitivity and secretion, the 11 healthy adolescents underwent a 7-hour oral glucose tolerance test (OGTT) and received an oral glucose bolus corresponding to 1 g/kg lean body weight (not exceeding a total of 75 g). A total of 21 blood samples were collected: Plasma samples were collected at times –30, –20, –10, 0 min, before the time when the bolus was administered and then at time 10, 20, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210,

240, 270, 300, 330, 360, 390, 420 min for determination of glucose, insulin and C-peptide plasma concentrations using established methods. Further details in [1], [2].

S2. MATHEMATICAL DESCITPION of AOMM

ORAL GLUCOSE MINIMAL MODEL

The oral glucose minimal model couples the classic single-compartment description of glucose kinetics of the IVGTT minimal model together with a parametric description of the oral glucose rate of appearance (*Ra*) into plasma (Figure S1-left):

$$\begin{cases} \dot{G}(t) = -[S_G + X(t)] \cdot G(t) + S_G \cdot G_b + \frac{Ra(\alpha,t)}{V} & G(0) = G_b \\ \dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] & X(0) = 0 \end{cases} \quad \text{(S1)}$$

and,

$$Ra(\alpha,t) = \begin{cases} \alpha_{i-1} + \frac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}} \cdot (t - t_{i-1}) & for\ t_i - t_{i-1} \le t \le t_i, i = 1, \dots, \\ 0 & otherwise \end{cases} \quad \text{(S2)}$$

Where **G** and **I** represent plasma glucose and insulin concentrations, respectively, and **X** denotes the insulin action on both glucose production and disposal. **V** is the glucose distribution volume. S_G is the fractional glucose effectiveness, quantifying glucose's intrinsic ability—independent of insulin—to enhance glucose disposal and suppress hepatic glucose production. The parameter p_2 defines the rate at which insulin action decays, while p_3 determines the strength or magnitude of the insulin effect. The rate of appearance of ingested glucose (***Ra***) is modeled as a piecewise-linear function, with fixed time breakpoints (t_i= 20, 45, 60, 90, 150, 210, 300, and 420 minutes) and unknown amplitudes (α_i) that are estimated from the data. So, the insulin sensitivity is given by:

$$S_i = \frac{p_3}{p_2} V. \quad \text{(S3)}$$

ORAL C-PEPTIDE MINIMAL MODEL

The oral C-peptide minimal model (Figure S1-right) describes the plasma C-peptide concentration in relation to the observed changes in glucose concentration. Model equations are:

$$\begin{cases} \dot{CP}_1(t) = -(k_{01} + k_{21}) \cdot CP_1(t) + k_{21} \cdot CP_2(t) + SR(t), & CP_1(0) = 0 \\ \dot{CP}_2(t) = -k_{21} \cdot CP_2(t) + k_{12} \cdot CP_1(t) & CP_2(0) = 0 \end{cases} \quad \text{(S4)}$$

where CP1 and CP2 denote C-peptide concentration (above basal) in the accessible and peripheral compartment respectively, k01, k21, k12 are transfer rate parameters, SR is the secretion above basal entering the accessible compartment, normalized by the volume of distribution of compartment 1.

SR is described as the sum of two components controlled by glucose concentration (static glucose control, SRs) and by its rate of increase (dynamic glucose control, SRd), respectively:

$$SR(t) = SR_s(t) + SR_d(t). \quad \text{(S5)}$$

SRs represents the provision of new insulin to the β-cells and is controlled by glucose concentration *G* above a threshold level *h* in a linear dynamic fashion, i.e., after a stepwise increase of glucose SRs approaches a steady state value linearly related to it through a parameter β, with a rate constant α and, thus, a delay *T = 1/α*:

$$SR_s(t) = -\alpha \left\{ SR_s(t) - \beta [G(t) - h] \right\} \quad \text{(S6)}$$

SRd represents the secretion of promptly releasable insulin stored in the β cells, and is proportional to the rate of increase of glucose through a parameter k_d:

$$SR_d(t) = \begin{cases} k_d \, \dot{G}(t), & \dot{G}(t) > 0 \\ 0 & \dot{G}(t) \leq 0 \end{cases} \quad \text{(S7)}$$

So, beta-cell responsivity indices Φ are calculated as follows:

$\Phi_d = k_G$ *(DYNAMIC)* (S8)

$\Phi_s = \beta$ (STATIC) (S9)

$\Phi_b = \frac{k_{01} \cdot c_{1b}}{G_b}$ *(BASAL)* (S10)

$\Phi_{tot} = \Phi_s + \Phi_d \cdot \frac{(G_{max} - G_b)}{AUC_G - h \cdot t_{end}}$ *(TOTAL)* (S11)

With t_{end} = 420 min and AUC_G calculated by considering the extrapolation to 120 min.

PARAMETER ESTIMATION

[Automatic] identification of AOMM required several assumptions, like in the manual OMM case, with more details in [3]. First, to ensure identifiability, fixed values for glucose effectiveness (S_G) and glucose distribution volume (V) were assumed. Second, a Gaussian Bayesian prior on the insulin action decay rate (p_2) was introduced to improve the numerical identifiability of the remaining parameters (p_2, p_3, and αi, for i = 1…8). Third, a constraint was imposed on the area under the curve (AUC) of the rate of appearance of oral glucose (*Ra*) align with the known ingested glucose dose. The error on glucose was assumed gaussian, independent with zero mean and CV=2%. The forcing function insulin was assumed without error [1].

The C-peptide minimal model was numerically identified on C-peptide and glucose data by fixing C-peptide kinetic parameters to standard population values, following the method proposed by *Van Cauter* et al. [4]. C-peptide measurement error was assumed to be uncorrelated, Gaussian, with zero mean and a variance linked to C-peptide measurements (CP1) according to the model: Var =2,000 + 0.001× $CP1^2$ while glucose

concentration, now playing the role of the model forcing function, was assumed to be known without error [5].

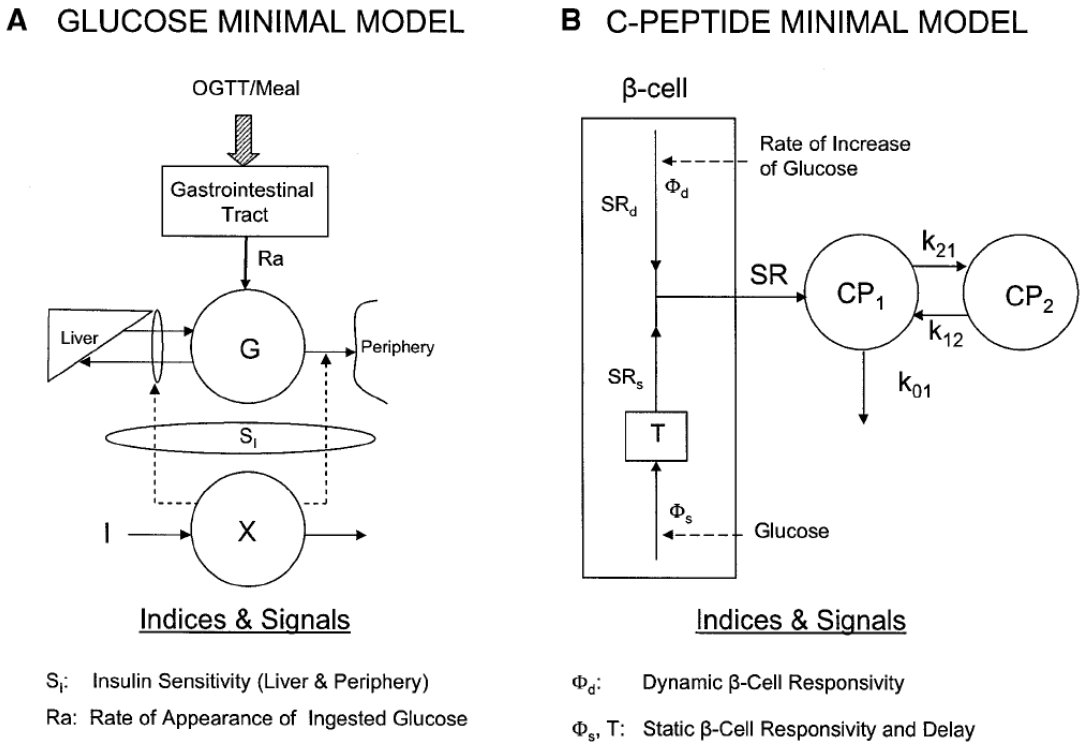

Figure S1. Conceptual OMM scheme with indexes – left glucose OMM; right C-peptide OMM – Figure with permission from [6].

S3. STATISTICAL ANALYSIS RESULTS FOR EACH SUBJECT

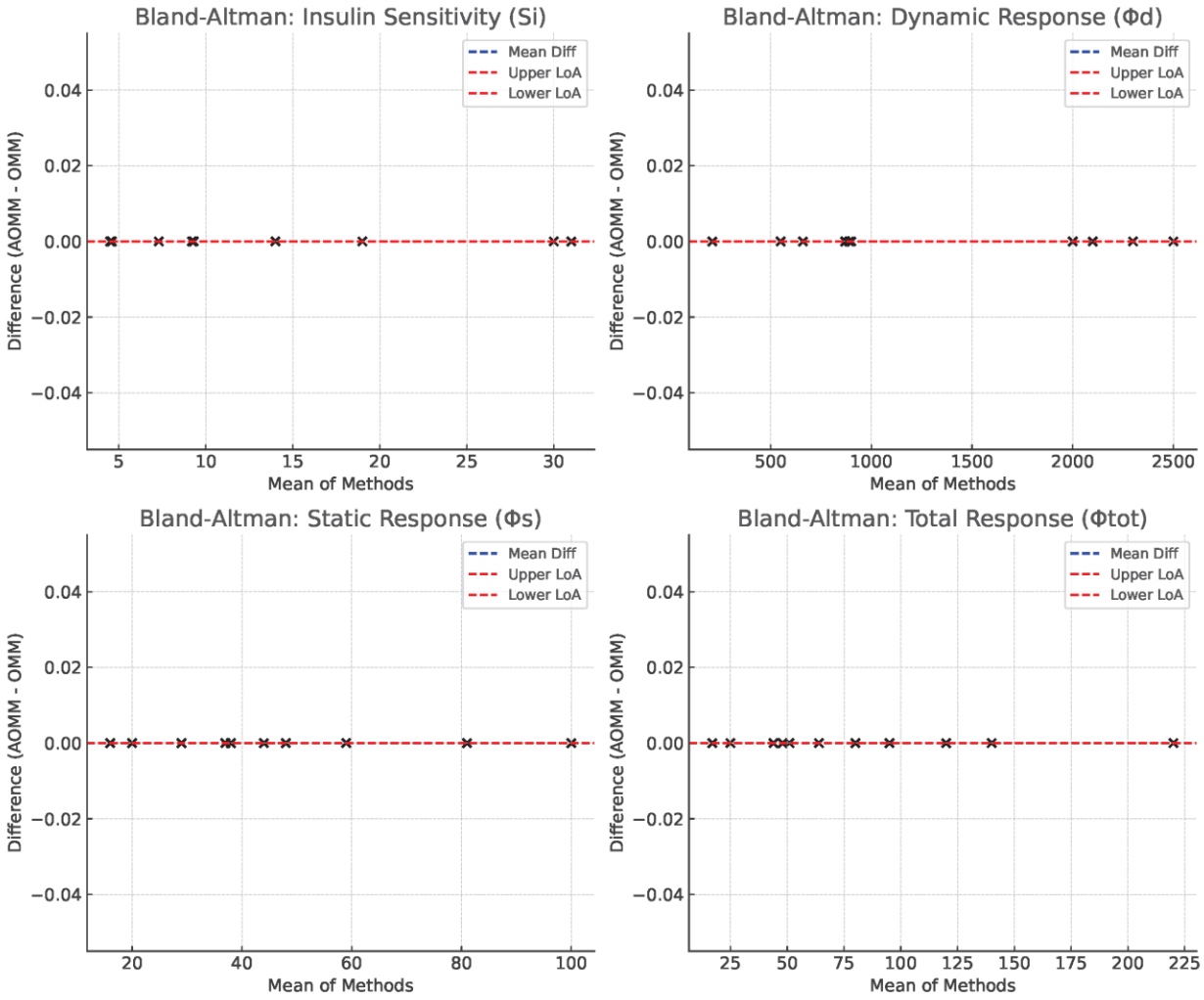

Figure S2. Results of the Bland–Altman analysis across all parameters and participants to compare OMM vs AOMM methods of extraction of minimal model parameters.

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