Assessing insulin sensitivity, glucose effectiveness, and β-cell responsivity using an integrated glucose, insulin, and C-peptide minimal model

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BACKGROUND AND AIM

Intravenous glucose tolerance tests (IVGTT) are widely used to investigate the glucose-insulin interaction using the **glucose** (GMM) [1], and the **insulin** and **C-peptide minimal models** (IMM, CMM) [2].

The identification of these models is usually performed at individual level, and separately for each analyte. However, this approach may lead to incorrect propagation of the measurement error and to **biased parameter estimates**.

Using **nonlinear mixed-effects** (NLME) **modelling**, one can overcome these limitations, as in [3], where GMM and IMM were integrated.

This work aims to extend the model in [3] by **incorporating the CMM**, since C-peptide and insulin are secreted in a 1:1 ratio, but, unlike insulin, C-peptide is not extracted by the liver and is a better marker of insulin secretion.

DATASET

❍ Subjects:

204 non-diabetic subjects: 118 M and 86 F, age = 65 [27,71] years, body weight, BW = 79 [69,87] kg, fat-free mass, FFM = 58 [43,63] kg.

❍ Protocol:

Insulin-Modified IVGTT (IM-IVGTT) consisting of an intravenous injection of glucose (0.330g/kg) for 2 min from time 0, followed by a constant insulin infusion (0.02U/kg) for 5 min from time 20 min. **Frequent blood sampling** was performed for 4h and glucose, insulin, and C-peptide concentrations were determined.

METHODS

❍ Structural model:

The model structure is represented in Fig. 1. It assumes **two-compartment kinetics** for each of the three substances (parameters V_{G1}, V_{G2}, Q_G, CL_I, V_{I1}, V_{I2}, Q_I, CL_C, V_{C1}, V_{C2}, and Q_C). The model includes a description of how glucose itself (GE) and insulin control **glucose regulation** (p_2, and S_I), and how the variation in glucose concentration stimulates **insulin and C-peptide secretion** (m_I, α_I, β_I, $X_{I,0}$, m_C, α_C, β_C, $X_{C,0}$, and τ_X). Basal levels were also estimated (G_b, I_b, and C_b). With respect to the original models in [1] and [2], peripheral compartments of glucose and insulin were added and the two input infusions were modeled with a zero-order lag time (τ_G and τ_I).

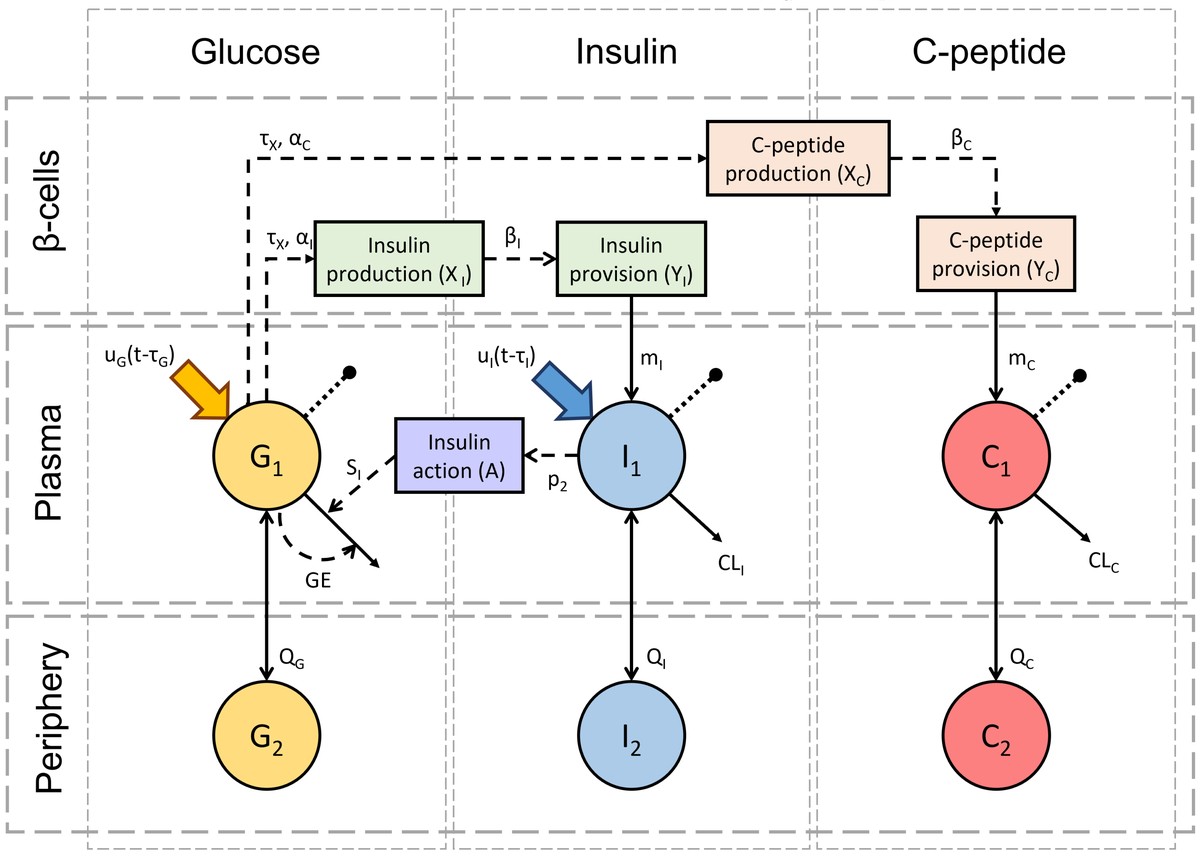

Fig. 1: Schematic representation of the model. Circles represents kinetic compartments of the model, while boxes represent effect compartments. Continuous arrows are fluxes of substances, while dashed arrows are dynamical effects. Dashed lines ending with a dot identify measured quantities. The big yellow arrow represents the first infusion of glucose, while the big blue arrow represents the subsequent infusion of insulin.

❍ Stochastic model:

The between-subject variability of model parameters was assumed log-normal with a **full covariance matrix** (Ω), except for those related to infusion delays.

❍ Allometric scaling:

Allometric scaling with fixed coefficients was used to describe volumes and clearances employing either BW or FFM of the subjects.

❍ Error model:

Standard deviation of the residual unexplained variability of the three substances was assumed the sum of a constant (a) and a proportional (b) component.

❍ Identification strategy:

Model identification was performed in NONMEM (version 7.5.1, ICON plc.) using the **stochastic approximation of expectation maximization** for parameter estimation and an **importance sampling** algorithm to compute the likelihood of the model.

RESULTS

Results of model identification are reported in Tab. 1. Parameter estimates were **physiologically plausible** and estimated with **good precision** (max RSE=38%).

GMM		IMM		CMM	
Model parameter	**Value (CV) [RSE]**	**Model parameter**	**Value (CV) [RSE]**	**Model parameter**	**Value (CV) [RSE]**
GE	2.28 dL/min (17%) [1.6%]	CL_I	1.62 L/min (23%) [3.9%]	CL_C	0.221 L/min (16%) [0.9%]
V_{G1}	81.5 dL (25%) [0.4%]	V_{I1}	7.03 L (21%) [0.8%]	V_{C1}	3.63 L (21%) [1.3%]
V_{G2}	59.7 dL (24%) [0.5%]	V_{I2}	4.95 L (25%) [1.3%]	V_{C2}	5.05 L (24%) [1.1%]
Q_G	18.4 dL/min (30%) [0.8%]	Q_I	0.5 L/min (82%) [8.1%]	Q_C	0.452 L/min (56%) [5.3%]
G_b	90 mg/dL (5.3%) [0.1%]	I_b	23.8 pmol/L (42%) [1%]	C_b	428 pmol/L (30%) [0.4%]
p_2	0.0191 min^{-1} (74%) [1.4%]	m_I	0.9 min^{-1} (38%) [27.2%]	m_C	1.33 min^{-1} (56%) [14.1%]
S_I	$1.76 \cdot 10^{-4} \frac{L}{pmol} min^{-1}$ (50%) [0.8%]	α_I	0.16 min^{-1} (80%) [3.1%]	α_C	0.133 min^{-1} (75%) [2.7%]
-	-	β_I	$0.126 \frac{dL/mg}{pmol/L} min^{-1}$ (46%) [1.7%]	β_C	$0.525 \frac{dL/mg}{pmol/L} min^{-1}$ (27%) [3.2%]
-	-	$X_{I,0}$	523 pmol/L (70%) [0.8%]	$X_{C,0}$	1495 pmol/L (46%) [0.5%]
τ_G	0.90 min (45%) [38%]	τ_I	0.80 min (61%) [24%]	τ_X	1.38 min (16%) [4.3%]
Error parameter	**Value [RSE]**	**Error parameter**	**Value [RSE]**	**Error parameter**	**Value [RSE]**
a_G	4.42 mg/dL [1.6%]	a_I	3.79 pmol/L [2.3%]	a_C	36.8 pmol/L [3.9%]
b_G	0.016 [3.5%]	b_I	0.109 [1.3%]	b_C	0.078 [1.3%]

Tab. 1: Parameter estimates. CV = Coefficient of variation. RSE = Relative Standard Error.

Relative standard error for all the elements of Ω (not reported) was <8% for each element. Strong **correlations** were found between IMM parameters and their CMM counterparts. Significant **correlations** were found between β_C and S_I (ρ=-0.48), and β_C and I_b (ρ=0.71) as previously found in the literature.

The **visual predictive check** in Fig. 2 showed satisfactory fit for all analytes.

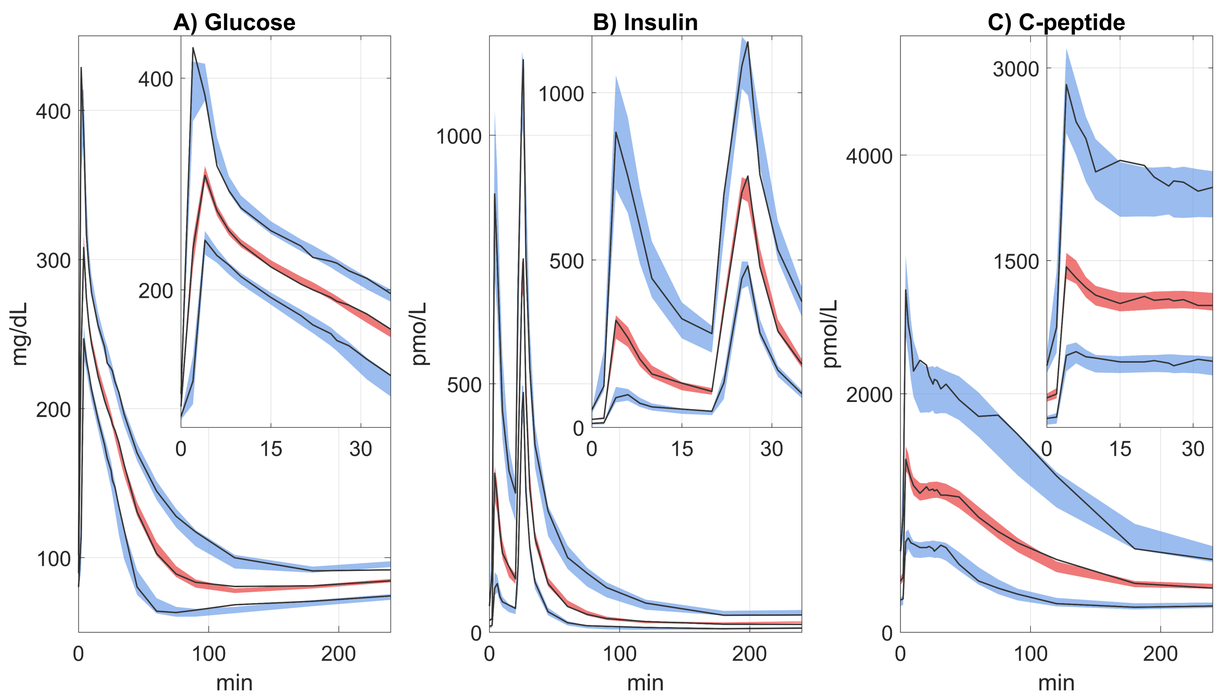

Fig. 2: Visual predictive check of the model. Ninety-five percent prediction intervals of 5th (blue lower areas), 50th (red central areas), and 95th (blue upper areas) percentiles are compared with 5th, 50th, and 95th observed percentiles (continuous black lines). A magnification of the first 30min is present in the insets. *Panel A*: plasma glucose concentration. *Panel B:* plasma insulin concentration. *Panel C:* plasma C-peptide concentration.

Integrating the three models, we could assess **insulin sensitivity** (S_I) and **glucose effectiveness** (GE) as in [3], plus the **first** (Φ_1) and **second phase** (Φ_2) **β-cell responsivity** to glucose, calculated as: $\Phi_1 = X_{C,0}/\max[\Delta G(t)] = 116\ min^{-1}$, and $\Phi_2 = \beta_C = 9.4\ min^{-1}$.

CONCLUSIONS

We successfully **integrated the widely used GMM, IMM, and CMM** in an NLME model that can simultaneously provide estimates of S_I, GE, and β-cell function (Φ_1 and Φ_2) during an IM-IVGTT. The model provided a complete characterization of the joint parameter distribution of a healthy population.

Further work will focus on exploring the **covariate** in the model, integrating the **secretion of IMM and CMM** to assess also the hepatic extraction, and extending the model to **diabetic populations**.

REFERENCES

[1] R. N. Bergman et al., "Quantitative estimation of insulin sensitivity," *Am J Physiol*, 236(6): E667–77, 1979.
[2] G. Toffolo et al., "A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction," *Am J Physiol Endocrinol Metab*, 290(1): E169–76, 2006.
[3] A. Largajolli et al., "An integrated glucose-insulin minimal model for IVGTT," *22nd PAGE meeting*, Abstr 2762, http://www.page-meeting.org/?abstract=2762, 2013.

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