An integrated glucose-insulin minimal model for IVGTT

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INTRODUCTION

BACKGROUND

Glucose-Insulin kinetics during an IVGTT can be investigated to quantify insulin sensitivity and release through the so-called **minimal models (MM)** [1,2].
The MMs have been developed before the advent of non-linear mixed effects modelling (NLMEM) and thus suffer from some limitations.
In particular, the glucose-insulin system is separated into two subsystems for the MM analysis and insulin is used as known input to predict glucose, and vice versa. This procedure has been shown to have small impact on parameter estimates in a rich sampling situation [3], but it limits the simulation capabilities and may not be as robust with sparse data.

AIM

Propose an **integration of the glucose and insulin MM** by using NLMEM.

METHODS

DATABASE

An insulin modified IVGTT protocol on 204 nondiabetic subjects (118 M /86 F, age 55.53 ± 21.66, mean BMI 26.62 ± 3.39 kg/m^2) was performed. Plasma samples were taken at -120, -30, -20, -10, 0, 2, 4, 6, 8, 10, 15, 20, 22, 25, 26, 28, 31, 35, 45, 60, 75, 90, 120, 180 and 240 min.

THE GLUCOSE MINIMAL MODEL

In this implementation, the original GMM was revised with the use of a 2 compartment model as in [1] and by adding transit compartment input [4] to cater for the glucose kinetic in the first minutes of the experiment, previously customarily discarded.

THE INSULIN MINIMAL MODEL

In the insulin minimal model (IMM), a bolus of insulin (x0) is first released in response to the IV bolus of glucose, then, as the insulin reservoir is replenished, insulin is released proportionally to the glucose concentration. With respect to the original IMM, a transit model was used to to capture the delay in the first release and a second compartment for insulin kinetics was introduced.

ALLOMETRIC SCALING

Allometric scaling was introduced on each clearance and volume parameter in the following way:

$$V_i = \theta_V \cdot e^{\eta_{Vi}} \cdot \frac{predictor_i}{median_{predictor}} \qquad Cl_i = \theta_{Cl} \cdot e^{\eta_{Cli}} \cdot \left(\frac{predictor_i}{median_{predictor}} \right)^{0.75}$$

The predictors tested were body weight (BW), lean body mass (LBM), visceral abdominal fat (VAF), total body fat (TBF), total abdominal fat (TAF).

OMEGA MATRIX

The **omega matrix** was used to investigate correlations between the parameters and it was “pruned” to keep only significant terms.

ESTIMATED PARAMETERS

The final vector of **estimated parameters** is the following:
p=[CL_{SG},S_I,V_{G1}, p_2, Q_G, V_{G2}, MTT_1, G_b, Cl_n, Q_I,V_{I1}, V_{I2}, X_0, α, β, MTT_2, I_b]

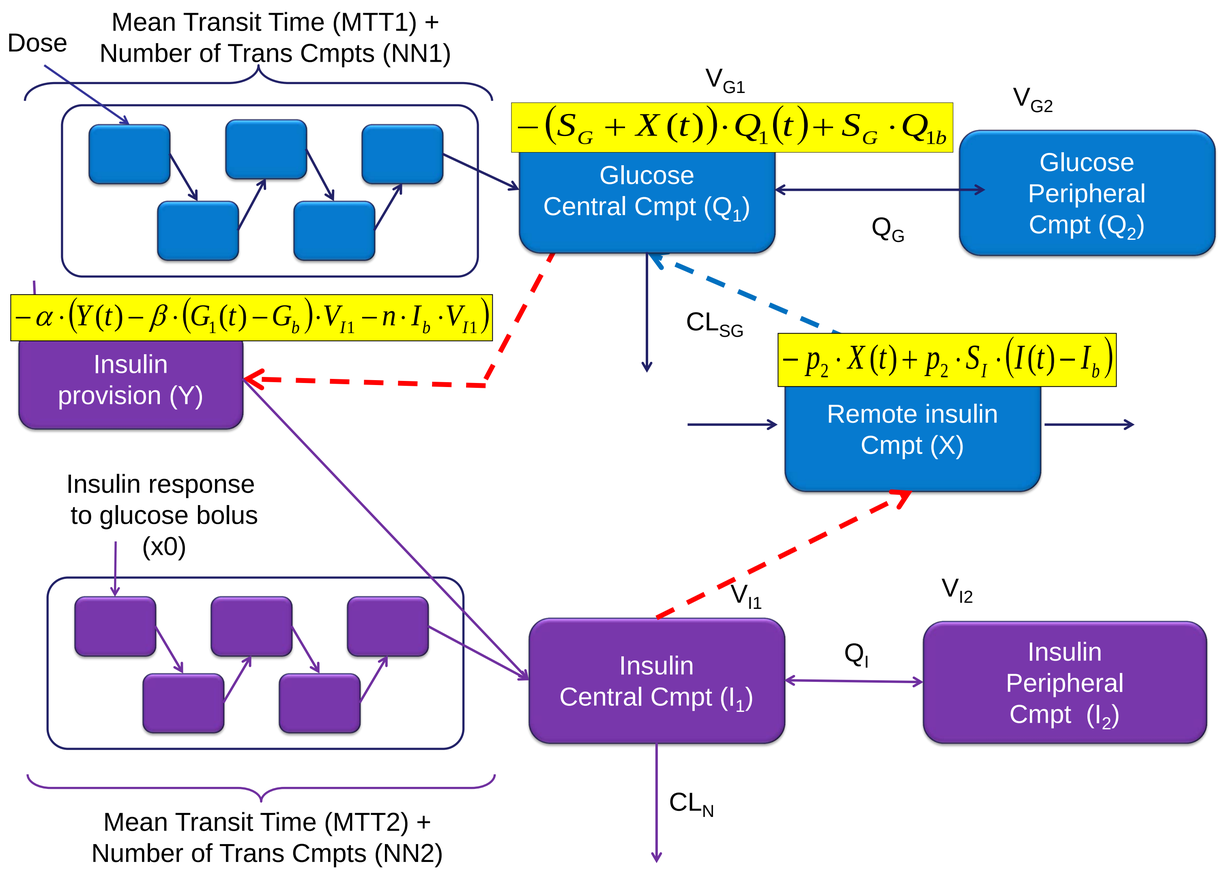

Figure1. Scheme of the integrated model

RESULTS

The model building strategy focused first on the two glucose and insulin subsystems separately, to then proceed to the integration and simultaneous fit. In figure 2 and 3 we present the comparison of the VPC of the GMM and IMM versus the corresponding VPC obtained with integrated model.

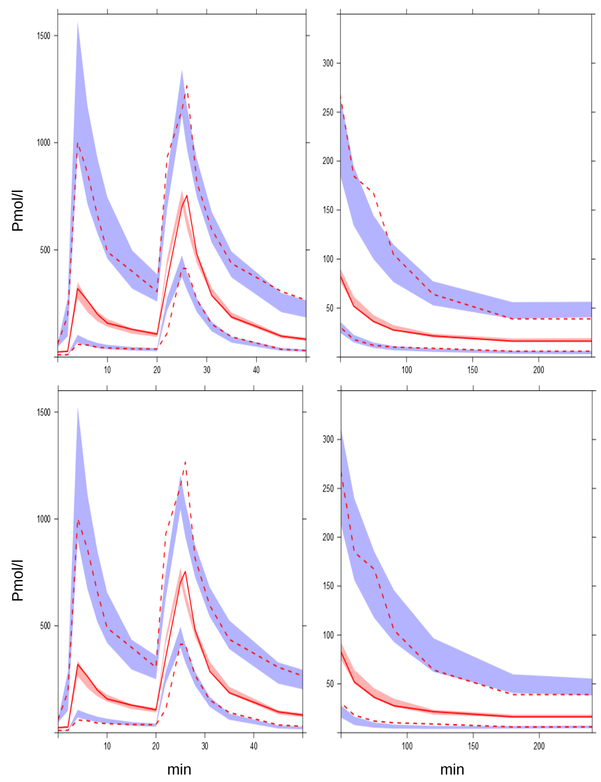

Figure2. VPC of the IMM (top) versus VPC of the insulin obtained in the integrated model (bottom)

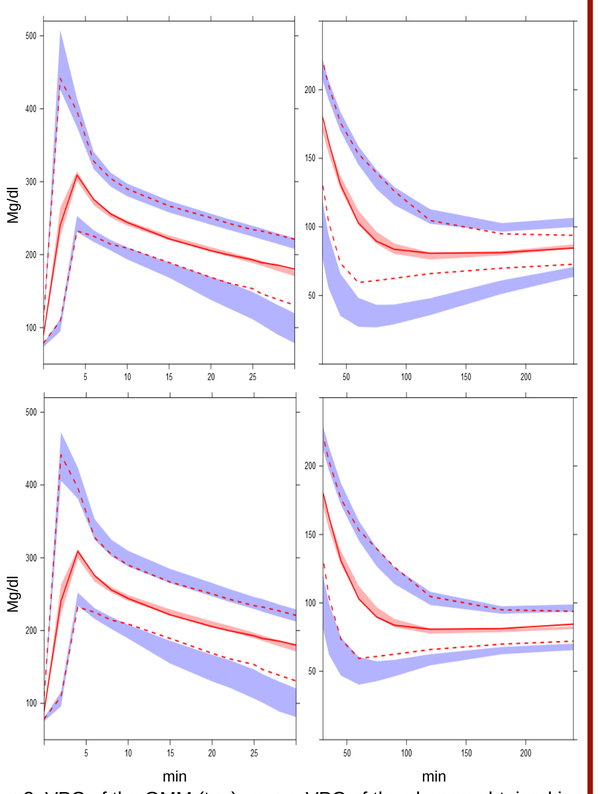

Figure3. VPC of the GMM (top) versus VPC of the glucose obtained in the integrated model (bottom)

The VPC of the integrated model shows a better description when compared to the VPCs obtained from the separated models as the simulated percentiles CIs better follow the observed data percentiles. The description of the second peak of the insulin profile can be improved by taking into account the individual deviations of the experimental protocol. The following predictors were chosen for the allometric scaling of the model: LBM for CL_{SG}, CL_{KG}, V_{G2} and BW for V_{G1}, CL_{KI}, CL_N, V_{I1} and V_{I2}. The θ estimates and the Ω obtained in the integrated model are on the whole comparable with the ones obtained on the IMM and GMM (Table 1). The most significant correlations found are between MTT_1 and MTT_2 (74.1%), S_I and p_2 (76.5%) and I_b and β (88.3%).

			θ		Ω	
	description	unit	GMM	INTEGRATED	GMM	INTEGRATED
CL_{SG}	glucose effectivness clearance	dL min^{-1}	2.43 (3%)	2.32 (3%)	20.9% (13%)	15.6% (14%)
V_{G1}	first cmpt volume	dL	84.9 (3%)	75.4 (3%)	26.3% (9%)	20.8% (5%)
S_I	insulin sensitivity	min^{-1} pmol^{-1} L	161 (5%)	127 (8%)	47.2% (8%)	61.9% (9%)
P_2	insulin action	min^{-1}	0.0179 (8%)	0.0262 (6%)	66.3% (12%)	42.9% (11%)
MTT_1	mean transit time	min	1.99 (1%)	2.03 (1%)	9.2% (8%)	8.7% (8%)
G_b	basal glucose	mg dL^{-1}	90 (1%)	92.1 (1%)	6.2% (7%)	5.6% (8%)

			θ		Ω	
	description	unit	IMM	INTEGRATED	IMM	INTEGRATED
X_0	first phase insulin secretion	pmol L^{-1}	373 (7%)	353 (9%)	70.3% (6%)	74.3% (7%)
CL_N	clearance irreversible loss	L min^{-1}	1.53 (2%)	1.54 (3%)	22.1% (8%)	20.0% (10%)
V_{I1}	first cmpt volume	L	9.42 (2%)	9.76 (2%)	19.5% (10%)	11.7% (14%)
α	constant rate	min^{-1}	0.176 (13%)	0.127 (11%)	70.1% (18%)	69.1% (16%)
β	glucose sensitivity	min^{-1} L^{-1} pmol dL mg^{-1}	0.0894 (6%)	0.0897 (7%)	49.0% (9%)	43.8% (11%)
MTT_2	mean transit time	min	2.47 (1%)	2.63 (2%)	8.7% (13%)	9.3% (14%)
I_b	basal insulin	pmol L^{-1}	22.4 (4%)	23.7 (5%)	43.7% (6%)	42.9% (7%)

Table 1. Comparison of the estimates obtained in the GMM and IMM with the estimates obtained in the integrated model. In particular are presented the fixed effects and the variances terms reported as coefficient of variation (CV) with their relative RSE% (in parenthesis).

CONCLUSIONS

This integrated model, while providing parameter estimates compatible with the traditional MM approaches, allows the simultaneous characterization of the glucose-insulin regulation system. Unlike the GMM and IMM this integrated model provides full simulation capabilities and can be used as a framework to explore disease and drug effects. The model could be further improved by integrating C-peptide kinetics, which is a better marker of pre-hepatic insulin.

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