ASSESSMENT OF THE ORAL GLUCOSE MINIMAL MODEL BY NONLINEAR MIXED-EFFECTS APPROACHES

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INTRODUCTION

The **oral minimal model (OMM)** has been proposed and validated at individual level [1] to estimate after an oral glucose perturbation the **rate of appearance of glucose (Ra)** and the **insulin sensitivity (SI).**
As commonly done in metabolic modeling, the OMM parameters are estimated by weighted nonlinear least square (WNLS) separately in each subject. Due to the complexity of the model, parameter precision is sometimes not satisfactory, especially in a "data poor" situation.

AIM

In this work, the performance of the nonlinear-mixed effects modeling, applied to the OMM, is tested.

MATERIAL AND METHODS

DATA BASE

A triple tracer mixed meal (10 Kcal/Kg, 45% carbohydrate, 15% protein and 40% fat) containing 1± 0.02 g/Kg glucose was administered to 50 normal subjects (20 males and 30 females, age 47.42±24.7, body weight 69.72±10.6 Kg). The plasma samples were collected at -120, -30, -20, -10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360 and 420 minutes.

ORAL MINIMAL MODEL

The **OMM** combined with a parametric model of the **Ra**, the piecewise linear model (PML), is used in this study to estimate the Ra (α_1, α_3, α_4, α_5, α_6, α_7, α_8 – mg $Kg^{-1}\,min^{-1}$) and the SI ($\underline{S}_i$ – ml $uU^{-1}\,min^{-1}$) from plasma glucose (mg/dl) and insulin (uU/ml) concentrations measured after an oral glucose perturbation. To obtain a uniquely identifiable model the glucose effectiveness (S_G - min^{-1}) and the glucose apparent distribution volume per unit of body mass (Vol – dl/Kg) are fixed to population values from literature whereas the square root of the insulin action parameter (p_2 - min^{-1}) is supposed to have a normal distribution N(0.11,0.011)[1].

$$\dot{Q}(t) = -[S_G + X(t)]\cdot Q(t) + S_G \cdot G_{SS} \cdot Vol + Ra(t) \qquad Q(0) = G_b \cdot Vol$$

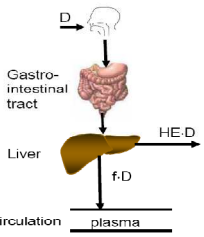
$$\dot{X}(t) = -p_2 \cdot X(t) + p_2 \cdot SI \cdot [I(t) - I_b] \qquad X(0) = 0$$

$$G(t) = \frac{Q(t)}{Vol}$$

$$Ra(t) = \begin{cases} \alpha_{i-1} + \dfrac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}} \cdot (t - t_{i-1}) & t_{i-1} \le t \le t_i \qquad i = 1 \ldots 8 \\ 0 \qquad otherwise \end{cases}$$

The fraction (f) of the ingested glucose that appears in plasma due to hepatic extraction (HE) is fixed to population value 0.9. Moreover the constrain of α_i can be obtained from:

$$\int_0^\infty Ra_{meal}(t) = \frac{D \cdot f}{BW} \quad \rightarrow \quad \sum_{i=1}^{8} \frac{(\alpha_i + \alpha_{i+1}) \cdot (t_i - t_{i-1})}{2} = \frac{D \cdot f}{BW}$$



THE INDIVIDUAL APPROACH

Model parameters were estimated in [1] using weighted nonlinear least square (WNLS) as implemented in SAAM II [2]. In this study we use STS implemented in NOMEM VI whose results were in agreement with those obtained in SAAM.

THE POPULATION APPROACH

The nonlinear mixed effects modeling approach describes the variability in the data using two steps:

1. **The between subject variability (BSV) :** a lognormal distribution was assumed for all parameters except for $\sqrt{p_2}$ that was assumed to have a Gaussian distribution. Population typical vaues were estimated for SI and the Ra parameters α_1, α_3, α_4, α_5, α_6, α_7 and α_8.
2. **The residual unexplained variability (RUV) :** in this study the measurement error is assumed to be proportional to the measured data.

ESTIMATION METHODS

To estimate the individual and population parameters the following two methods were used in NOMEM VI:

1. The **standard two-stage method (STS)** whose results where used as **reference** for further comparisons
2. The **FOCE INTERACTION** that has been proved suitable for a similar model [3]

The FOCE estimates were then compared to the reference values to assess the consistence with the already validated individual approach. The structure of the omega matrix was also investigated: we tried a full matrix (FULL), a diagonal matrix (DIAG) and a matrix with nonzero terms on the diagonal and on the adjacent correlation terms of the Ra parameter (DIAG1).

RESULTS

Population parameters The estimates of the fixed effects are very close to reference (fig.1). However the BSV obtain with FOCE is smaller than the one obtained with STS method as previously reported in literature [4]. Since all the Ra parameters behave the same we report just one of them.

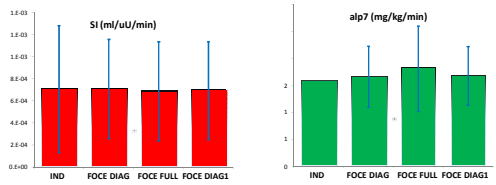


Fig.1 Plots of the fixed effects of a subset of the parameters using the two methods and three formulations of the omega matrix.

At individual level (fig.2-fig.3), we show some boxplots and correlations of the selected parameters. A very high correlation was detected between the FOCE individual estimation of SI, with each of three covariance matrix structure, and the reference. We also detect a good agreement among the reference and the PML parameters. The same can be said for p2. Moreover, it is possible to observe shrinkage on p2 with the two omega diagonal matrix formulations.

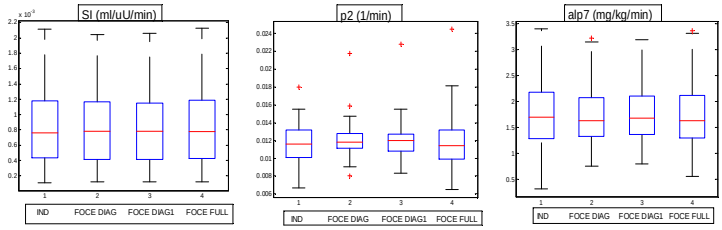


Fig.2 Boxplots of a subset of the parameters using the two methods and three formulations of the omega matrix.

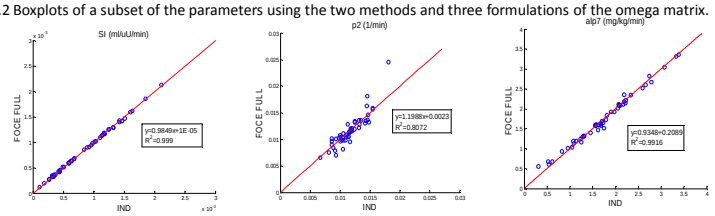


Fig.3 Correlation of the individual estimates of a subset of the parameters obtained with FOCE full and the individul approach.

We also compared the individual goodness of fit (the **sum of squared residual - RSS**) for the two methods. As can be seen from the high correlation the two methods provide comparable goodness of fit at individual level(fig. 4).

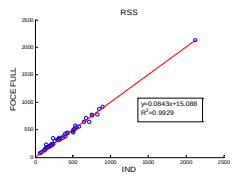


Fig.4 Correlation of the RSS of the individual prediction obtained with the FOCE full and the individual approach.

CONCLUSIONS

These results show that the population approach to the OMM parameter estimation is in agreement with the already validated individual approach, especially for the estimation of SI which is the most clinically useful parameter. For the sake of comparison, the same modeling assumptions that were made at the individual level were used. This study paves the way to further exploration of the application of population analysis methods in the context of an information-rich protocol like the meal glucose tolerance test.

RERFERENCES

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