Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Identification of IVGTT minimal glucose model by nonlinear mixed-effects approaches

Paolo Denti, Alessandra Bertoldo, Paolo Vicini, Claudio Cobelli, *Fellow, IEEE*

Abstract — **Glucose minimal model parameters are commonly estimated by applying weighted nonlinear least squares to each individual subject's data. Sometimes, parameter precision is not satisfactory, especially in "data poor" conditions. In this work, the use of population analysis through nonlinear-mixed effects models is evaluated and its performance tested against the parameter estimates obtained by the standard individual approach through weighted nonlinear least squares. In particular, we compared the performance of two likelihood approximation methods to estimate nonlinear mixed-effects model parameters, i.e. the First-Order Conditional Estimation (FOCE) and the Laplace approximation (Laplace) methods. The results show that nonlinear mixed-effects population modeling using the FOCE approximation can be successfully used in order to accurately estimate individual minimal model parameters**

I. INTRODUCTION

Glucose effectiveness (S_G) and insulin sensitivity (S_I) are two important metabolic indexes used in clinical and epidemiological studies of diabetes and hyperglycaemia. Estimates of S_G and S_I from an intravenous glucose tolerance test (IVGTT) are normally obtained by using the single-compartment minimal model method [1]. Usually, the minimal model parameters are numerically identified by resorting to Fisherian parameter estimation techniques, such as maximum likelihood (ML), applied separately in each subject. After having obtained individual estimates for each subject, the sample mean and the variance of all the model parameter estimates are calculated and can be assumed to approximate the first- and the second-order moment (expected value and variance) of the subject population distribution. However, unsatisfactory individual parameter estimates are sometimes obtained, e.g. S_I estimates virtually zero or unrealistically high and affected by very large uncertainty, making the practical use of the minimal model method difficult, especially in presence of a reduced sampling schedule ("data poor" situation). Of note is that a reduced sampling scheme is highly desirable, both for ethical and practical reasons, above all when clinical trials are performed in a large number of subjects: a reduced sampling scheme allows in principle to minimize experimental invasiveness and trial costs. Bayesian parameter estimation techniques have been shown to be less sensitive, in terms of both accuracy and precision, with respect to these estimation difficulties [2]. The drawback of this estimation method is that it requires some independent *a priori* statistical (i.e., mean, variance, covariance) knowledge on the model parameters. This drawback can potentially heavily compromise the parameter estimation process, when *a priori* information is unavailable or its quality is poor. However, Bayesian parameter estimation techniques are not the only alternative to the standard Fisherian individual estimation of minimal models parameters.

The present work was performed in order to understand if the use of techniques of population analysis could bring a significant contribution to the minimal model method. Population analysis aims at quantitative assessment of model parameters, taking advantage of the entire collection of measures obtained from a population of individuals, and finds its natural application in quantification of data poor studies, e.g. when the number of samples available for each individual subject is rather small in comparison with model complexity, but the number of subjects is comparatively large. Among all available kinetic data analysis methods, population approaches using nonlinear mixed-effects models have become an increasingly important tool, since they not only allow one to quantify both population and individual parameters, but also to identify the biological sources of between- and within-subject variability.

In this work, we will evaluate the use of population analysis through nonlinear mixed-effects models [3] to identify single-compartment minimal model parameters in a population of subjects composed of healthy and young adults. In particular, we will compare the performance of two of the three most commonly used approximate methods to estimate maximum likelihood nonlinear mixed-effects model parameters, i.e. the First-Order Conditional Estimation (FOCE) and the Laplace approximation (Laplace) methods [3]. The third method, i.e. the First-Order method (FO), was not considered on the basis of the results shown in [4] where use of FO resulted to be detrimental to minimal model parameter estimation.

The performance of FOCE and Laplace will be tested against the parameter estimates obtained by the standard individual Fisherian. By selecting the method performing best, we will have developed an important estimation tool for handling of sparse sampling protocols used in physiological and metabolic modeling and for ultimately studying the biological sources of between- and within-subject variability.

Of note is that, while a few studies have been published on the use of population modeling approach to estimate minimal models parameters [5]-[6], this work is the first one that systematically evaluates and compares FOCE and Laplace methods by assuming different characteristics of the population inter-individual probability distribution.

This study was partially supported by NIH grant P41 EB-001975.

P. Denti, A. Bertoldo and Claudio Cobelli* are with the Department of Information Engineering, University of Padova, Via Gradenigo 6/B, 35131 Padova, Italy (*corresponding author, phone: +39 049 827 7616; fax: +39 049 827 7699; e-mail: cobelli@dei.unipd.it).

P. Vicini is with the Department of Bioengineering, University of Washington, Seattle, WA, USA.

I. MATERIALS AND METHODS

A. Subjects

Standard IVGTT [dose 330 mg/kg] studies were performed on 58 nondiabetic young subjects (mean age 23±3 and mean BMI 24.5±2.9 kg/m^2) in the Clinical Research Center at the Mayo Clinic, Rochester, MN, USA. Subjects received the glucose bolus at time 0 and blood samples were collected 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 for measurement of glucose and insulin concentrations.

B. The Minimal Model

The classic one-compartment minimal model [1] can be described by:

$$\begin{aligned} \dot{Q}(t) &= -[S_G + X(t)]Q(t) + S_G Q_b \quad Q(0) = D + G_b V \\ \dot{X}(t) &= -p_2 X(t) + p_2 S_I [I(t) - I_b] \quad X(0) = 0 \\ G(t) &= Q(t)/V \end{aligned} \tag{1}$$

where D is the glucose dose, Q(t) (mg/kg) is glucose mass in plasma with Q_b denoting its basal value, G(t) (mg/dl) is plasma glucose concentration, I(t) (pmol/l) is insulin concentration, G_b and I_b are their basal values, and X(t) is insulin action (min-1). The model has four uniquely identifiable parameters: S_G (min^{-1}), glucose effectiveness, S_I (min^{-1} pmol^{-1} l), insulin sensitivity, P_2 (min^{-1}), the insulin action parameter, and V (dl/kg), the glucose distribution volume per unit of body mass. The model parameters are estimated by assuming I(t) as a known, error-free input (forcing) function.

C. Individual Estimation Approach

We used weighted nonlinear least squares as implemented in SAAM II [7]. Assuming that the observed data are statistically related to the individual true parameters $\mathbf{p}_j$ through the measurement equation: $G_j(t_i) = G(\mathbf{p}_j, t_i) + \varepsilon_j(t_i)$, the cost function to be minimized is:

$$\mathrm{WRSS}(\mathbf{p}_j) = \sum_{i=1}^{N} \frac{[G_j(t_i) - G(\mathbf{p}_j, t_i)]^2}{\sigma_{i,j}^2} \tag{2}$$

where N is the number of glucose samples, $G_j(t_i)$ is the ith time point for the jth of M subjects, $\sigma_{i,j}$ is the standard deviation of the measurement error of the ith data point, and $G(\mathbf{p}_i,t_i)$ is the minimal model prediction of glucose concentration. Measurement error was assumed additive, uncorrelated, Gaussian, zero mean, and with a standard deviation given by:

$$\sigma_{i,j} = 0.02 \cdot G_j(t_i) \tag{3}$$

The estimates yielded by this individual analysis were considered as the "gold-standard", which we used to assess the quality of the estimates eventually obtained by using the population approach methods.

D. Population Analysis: Nonlinear Mixed-Effects Model Approach

The nonlinear mixed-effects modeling approach assumes that the individual parameters $\mathbf{p}_j$ are characterized by some physiologically meaningful attributes that do not vary across the population of M subjects (fixed effects, i.e. values that are common to all subjects) and some others that do (random effects, i.e. values typical of a specific subject). Mathematically, this can be written as:

$$\mathbf{p}_j = d(\boldsymbol{\theta}, \boldsymbol{\eta}_j) \tag{4}$$

where d is a known (possibly nonlinear) function that describes the expected value of $\mathbf{p}_j$ as a function of the fixed effects, $\boldsymbol{\theta}$, and the random effects, $\boldsymbol{\eta}_i$. More specifically, the individual parameter can be written as:

$$\mathbf{p}_j = d(\boldsymbol{\theta}, \mathbf{a}_j, \boldsymbol{\eta}_j) \tag{5}$$

with $\mathbf{a}_j$ being known individual specific covariates such as weight, age, body mass index, etc. Thus, considering the jth individual, the model takes the general form:

$$\mathbf{G}_j = \mathbf{f}_j(d(\boldsymbol{\theta}, \mathbf{a}_j, \boldsymbol{\eta}_j) + \mathbf{v}_j \tag{6}$$

where $\mathbf{v}_j$ is the measurement error assumed to be Gaussian distributed with zero mean and standard deviation described, in accordance with the standard minimal model identification approach, as $\sigma_{i,j} = \xi \cdot G_j(t_i)$ with ξ being an additional parameter to estimate. Parametric mixed-effects modeling requires to postulate at least some characteristics of the population probability distribution for the random effects (e.g. whether it is Gaussian or lognormal). We assume the random effects to be independent, with:

$$\boldsymbol{\eta}_j \in N(0, \boldsymbol{\Omega}) \tag{7}$$

with $\boldsymbol{\Omega}$ being either a diagonal variance matrix or a full positive definite covariance matrix. In order to ensure positive parameter estimates, the parameter are described by:

$$\mathbf{p}_j = \boldsymbol{\theta} e^{\boldsymbol{\eta}_j} \tag{8}$$

which implies a lognormal distribution for the minimal model parameters.

The last step required to perform nonlinear mixed-effects modeling is to select an appropriate method to obtain estimates of both fixed and random effects. Most of the available nonlinear mixed-effects model methods estimate the parameters by the maximum likelihood approach. Due to the parametric nonlinear dependencies, it is computationally taxing or impossible to calculate the appropriate likelihood function, and thus several approximate methods have been proposed in the pioneering work of Sheiner and Beal [3]. The most frequently used are the First-Order (FO), the First-Order Conditional Estimation (FOCE) and the Laplace approximation methods [8]. Of these three methods, we used the two expected to provide more accurate estimates, i.e. FOCE and Laplace.

In order to obtain plausible values as initial estimates for the algorithms, we first used the Standard Two-Stage algorithm (STS) [10]. This algorithm consists of two steps: in the first the individual parameter values are separately calculated by fitting the experimental data with weighted least squares, while in the second, population information is inferred as the sample mean and sample variance of the individual estimates previously determined. This analysis provided suitable initial values for all the necessary input parameters of the tested methods: $\boldsymbol{\theta}$ (the vector of fixed effects), $\boldsymbol{\Omega}$ (the – possibly full – covariance matrix characterizing the probability distribution of the random effects $\boldsymbol{\eta}_j$) and ξ (which determines the size of the measurement error).

The version of FOCE and Laplace we used was as described in [9]. We used the implementation of FOCE (Expected Hessian), Laplace and STS available in the SPK software, the System for Population Kinetics, which is being developed at the Resource Facility for Population Kinetics [10], a NIH / NIBIB research resource in the Department of Bioengineering at the University of Washington.

E. Comparison

The agreement between the parameter estimates yielded by the population approach and the individual ones obtained by the standard Fisherian approach, was performed by linear regression analysis and the results graphically displayed using scatter plots.

In addition, in order to evaluate the goodness of the fit, we also calculated, for each of the methods we applied, the overall sum of the squared residuals:

$$SSR = \sum_{j=1}^{M}\sum_{i=1}^{N}\left[G_j(t_i) - G(p_j, t_i)\right]^2 \qquad (9)$$

where M is the number of subjects and N is the number of glucose samples.

Finally, in order to test whether the initial assumptions on the random effects were satisfied *a posteriori*, the Kolmogorov-Smirnov test was used to check the normality of the resulting estimated random effects $\boldsymbol{\eta}_j$.

II. Results

The population description obtained from FOCE and Laplace in terms of fixed effects and inter-subject variability is shown in Table 1 together with the first- and the second-order moment of the standard individual subject estimates (IND).

Both FOCE and Laplace methods show to be able to accurately describe the population in terms of fixed effects in comparison with IND results. A difference on inter-subject variability is shown with both FOCE and Laplace for S_G and P_2 in comparison with that obtainable by using the IND approach. On the contrary, S_I and V inter-subject variability is very similar to the IND results. Different assumptions on the structure of $\boldsymbol{\Omega}$ do not seem to have any relevant impact on FOCE and Laplace performance at population level.

TABLE I

	S_G (min^{-1})	S_I x 10^5 (min^{-1} $pmol^{-1}$ l)	P_2 (min^{-1})	V (dl/kg)
IND	0.019 (0.112)	8.818 (0.277)	0.041 (0.247)	1.633 (0.017)
FOCE $\boldsymbol{\Omega}$ *diag*	0.020 (0.021)	8.758 (0.301)	0.044 (0.108)	1.640 (0.011)
Laplace $\boldsymbol{\Omega}$ *diag*	0.019 (0.015)	8.671 (0.303)	0.045 (0.094)	1.642 (0.011)
FOCE $\boldsymbol{\Omega}$ *full*	0.020 (0.042)	8.846 (0.273)	0.042 (0.152)	1.639 (0.014)
Laplace $\boldsymbol{\Omega}$ *full*	0.019 (0.018)	8.846 (0.271)	0.043 (0.107)	1.642 (0.014)

FOCE and Laplace fixed effects and inter-individual variability, (between brackets), together with the first- and second-order moments (between brackets) for IND approach, assuming a log-normal probability distribution for the parameters. Fixed effects' units of measurement are indicated above, whereas the units of the inter-individual variability are CV squared.

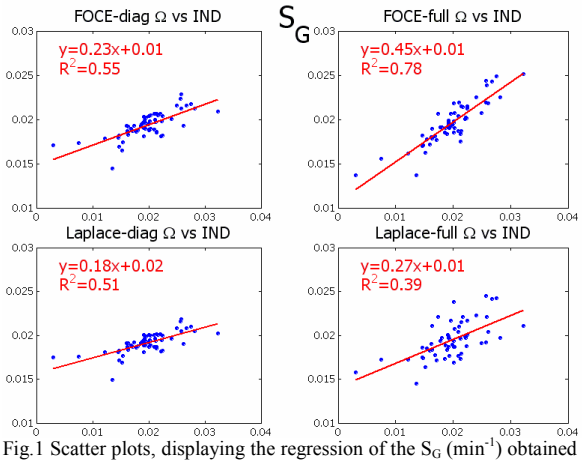

Fig.1 Scatter plots, displaying the regression of the S_G (min^{-1}) obtained by population vs individual "gold-standard" approach.

Figures 1 to 4 contain the scatter plots of the parameter estimates provided by the nonlinear mixed-effects modeling approaches regressed against the "gold-standard" individual approach.

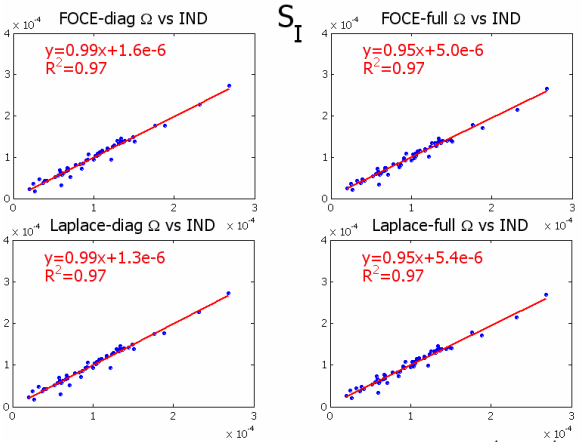

Fig.2 Scatter plots, displaying the regression of the S_I (min^{-1} $pmol^{-1}$ l) obtained by population vs individual "gold-standard" approach.

In comparison with IND, FOCE with $\boldsymbol{\Omega}$ taken as a full covariance shows the best results (figs. 1-4). In particular, looking at the scatter plots and the regression results, FOCE with full $\boldsymbol{\Omega}$ provides the best results for S_G (fig. 1), P_2 (fig. 3), and V (fig. 4) while only for S_I (fig. 2) there is not any

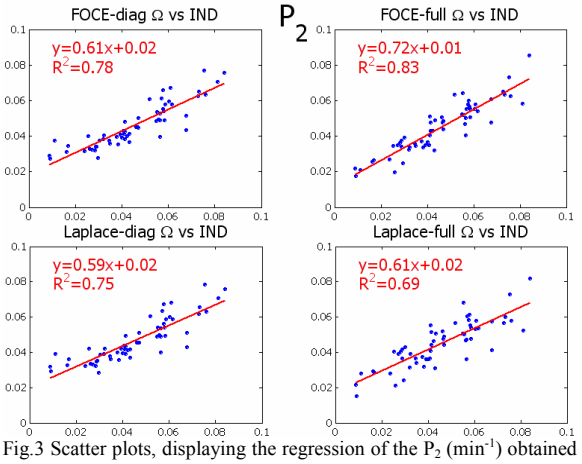

Fig.3 Scatter plots, displaying the regression of the P_2 (min^{-1}) obtained by population vs individual "gold-standard" approach.

substantial difference between FOCE and Laplace. By analyzing more in detail the performance of FOCE with full Ω throughout the model parameters, S_I FOCE estimates are in good agreement with S_I IND, V and P_2 FOCE are reasonably close to the IND ones, while S_G FOCE individual estimates exhibit a less strong correlation with IND S_G results.

The SSR values are virtually identical for both FOCE and Laplace (results not shown).

Finally, the normality test on the random effects, gave positive results in most of the cases. The only estimated random effects which occasionally resulted not normally distributed were the ones corresponding to P_2 and S_I, the former with FOCE with full **Ω** and the latter with both versions of Laplace.

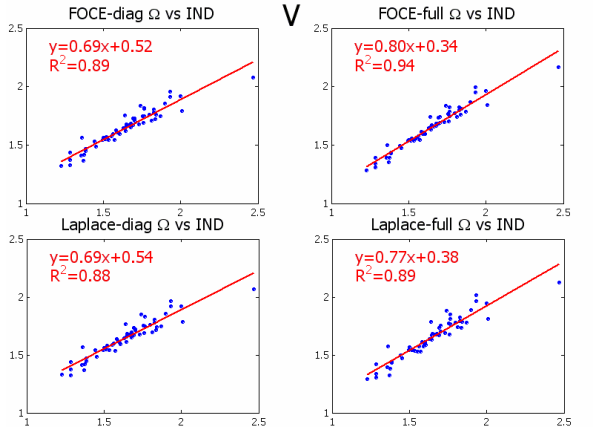

Fig.4 Scatter plots, displaying the regression of the V (dl/kg) obtained by population vs individual "gold-standard" approach.

III. Discussion

Our results show that nonlinear mixed-effects population modeling can be successfully used in order to estimate the minimal model parameters. In particular, both FOCE and Laplace, both with **Ω** being a diagonal or a full covariance matrix, return a population description virtually identical to that obtainable considering the first- and the second-order moment of the standard individual subject estimates. At the individual level, however, FOCE with **Ω** being a full covariance matrix shows a superior performance providing S_I, P_2 and V estimates very close to the "gold standard" IND results, while S_G FOCE estimates are less strongly correlated to the IND ones.

Of note is that a great drawback for the use the Laplace method may lie in the extreme sensitivity to the initial choices for the parameter values. The initial values provided by STS were always suitable for FOCE, whereas they required some retuning in order to obtain a successful run with Laplace. Moreover, with the ultimate purpose of performing an objective comparison with the same starting conditions, these retuned values were then used again for FOCE, but they did not affect its result.

In conclusion, our results show that nonlinear mixed-effects are promising in the context of minimal model IVGTT analysis. FOCE with full **Ω** proves best in describing both population and individual results in comparison with the "gold standard" ones. Further work will be required in order to evaluate FOCE performance with a different data set and in presence of "data poor" situation (i.e. reduce sampling).

References

[1] Bergman R.N., Y.Z. Ider, C.R. Bowden, and C Cobelli (1979). Quantitative estimation of insulin sensitivity. Am J Physiol. 236: E667-E677.

[2] Sparacino G, C Tombolato, and C Cobelli (2000). Maximum-likelihood versus maximum a posteriori parameter estimation of physiological system models: the C-peptide impulse response case study. IEEE Trans Biomed Eng. 47: 801-11.

[3] Beal SL, and LB Sheiner (1982). Estimating population kinetics. Crit Rev Biomed Eng. 8: 195-222.

[4] Bertoldo A., Vicini P., Cobelli C. The glucose minimal model: population vs individual parameter estimation, accepted for 6th IFAC Symposium on Modelling and Control in Biomedical Systems (Including Biological Systems), 2006.

[5] De Gaetano A., G. Mingrone, M. Castagneto (1996). NONMEM improves group parameter estimation for the minimal model of glucose kinetics. Am J Physiol 271(5 Pt 1): E932-937.

[6] Erichsen L, O.F. Agbaje, S.D. Luzio, D.R. Owens, and R. Hovorka (2004). Population and individual minimal modeling of the frequently sampled insulin-modified intravenous glucose tolerance test. Metabolism.53: 1349-54.

[7] Barrett PH, BM Bell, C Cobelli, H Golde, A Schumitzky, P Vicini, and DM Foster (1998). SAAM II: Simulation, Analysis, and Modeling Software for tracer and pharmacokinetic studies. Metabolism.47: 484-92.

[8] Beal SL, and LB Sheiner (1992). NONMEM Users Guide. NONMEM Project Group, UCSF, San Francisco, CA.

[9] Bell B.M. (2001). Approximating the marginal likelihood estimate for models with random parameters. Appl. Mathem. Comput., 119: 57-75.

[10] RFPK, http://www.rfpk.washington.edu