A NonLinear Mixed-Effects Approach for the Estimation of the Glucose Disposition Index

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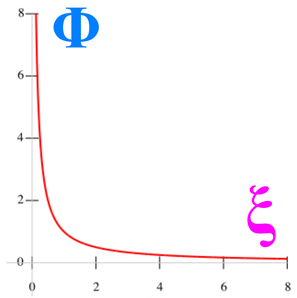
Introduction & Aim

The glucose Disposition Index (DI, Δ in the formulae) [1] is used to assess in a subject the efficiency of glucose-insulin metabolism by calculating the product of insulin sensitivity (ξ) and secretion (Φ) indices. This paradigm is called the Hyperbolic Law

$$\Delta = \xi \times \Phi$$ **Hyperbola**



More recently an alternative model has been proposed [2], with an additional parameter α as an exponent

$$\Delta = \xi^{\alpha} \times \Phi$$ **Pseudo-Hyperbola**

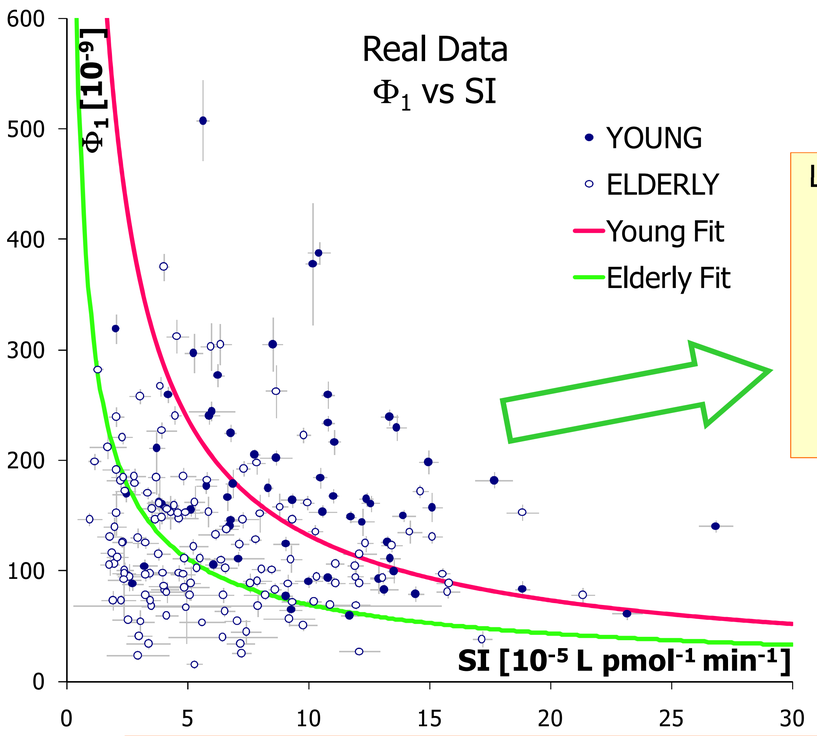
AIM: To design a new method to study the DI and probe the significance of α

Background (Geometric Fit Approach)

The traditional method to apply and investigate the validity of the DI laws is based on a geometric fit.
In a population of subjects with similar glucose disposal efficiency and supposedly sharing the same DI level,

1. First, insulin sensitivity and secretion indices are estimated in each subject together with their precision,
2. Then, a geometric fit is used to find the best curve.

In the literature, many simplifications have been proposed to deal with the difficulties of a nonlinear 2-variables fit [3-4]; some methods fit only in one variable, some log-transform the data and then fit a straight line.
As a first step, a new non-approximated Total Least Squares (TLS) method was proposed and, on simulated data, it was shown to be preferable to the previous alternative methods. However, on real data [5]…



Look at the error bars!

Even when fitting the sub-populations separately, the estimation error does NOT explain all the variability!

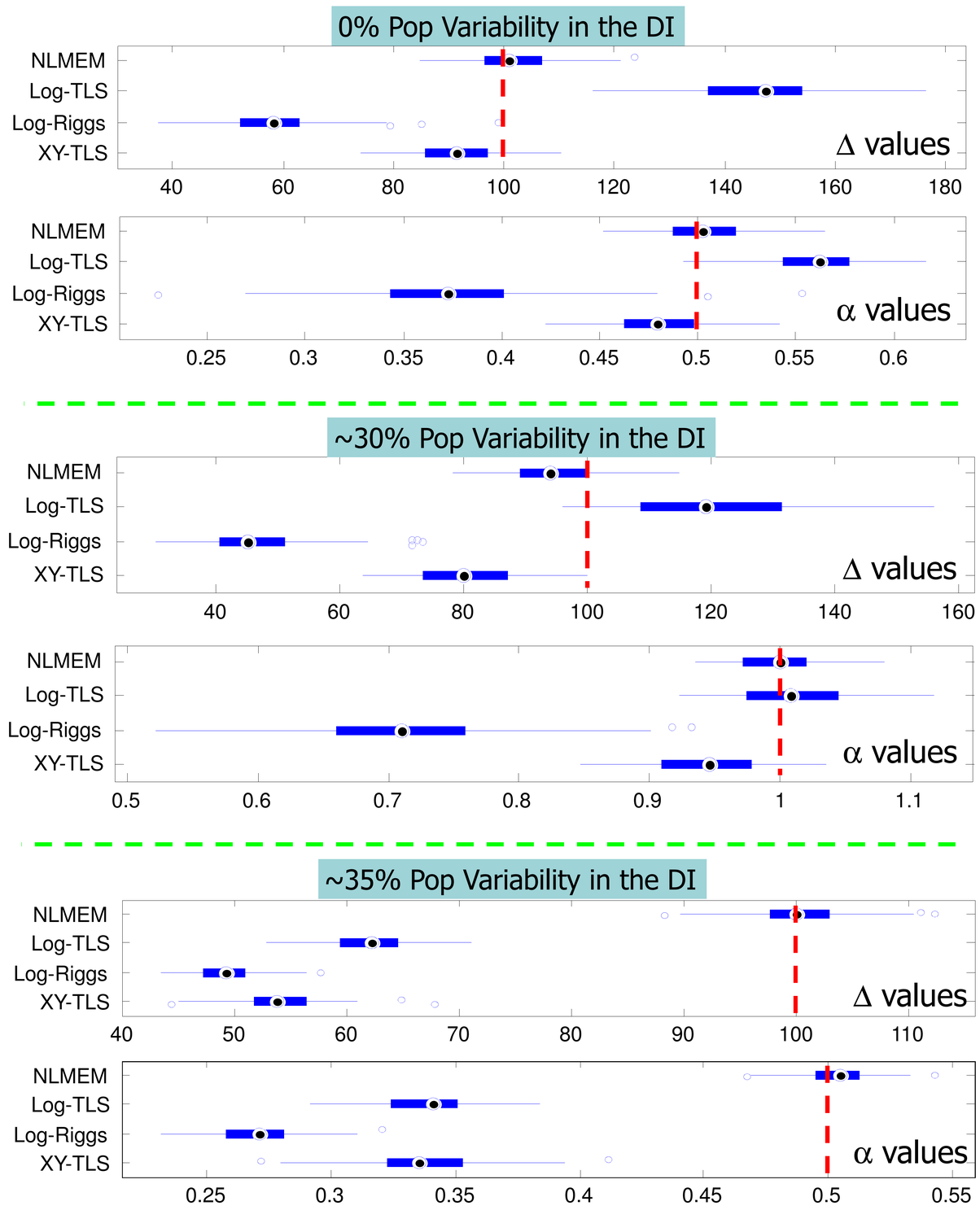
All geometric fit approaches account ONLY for the estimation error of ξ and Φ
NOT for POPULATION VARIABILITY in the DI values.

Comparison of approaches

Data were simulated with hierarchical variability:

1. Lognormal variability in the DI values,
2. Gaussian variability in the indices ξ and Φ, to mimic their estimation error.

The analysis was repeated 100 times on datasets with 1000 subjects and the results are shown in the following boxplots. Different values of α and levels of variability were used in the simulation. SPK [6] and NONMEM were used for the computation.



The NLME approach is much more reliable and works well also with no or small population variability in the DI.
Current work on real IVGTT data [5] suggests a value of α significantly smaller than 1, supporting Kahn's model.

Population approach

Assuming the population distribution of ξ and Φ as jointly lognormal (their joint covariance matrix is written in the general form)

$$\begin{bmatrix} \xi_i \\ \Phi_i \end{bmatrix} \sim LN\left(\overbrace{\begin{bmatrix} \theta_\xi \\ \theta_\Phi \end{bmatrix}}^{\theta}, \overbrace{\begin{bmatrix} \omega_\xi^2 & \rho\omega_\xi\omega_\Phi \\ \rho\omega_\xi\omega_\Phi & \omega_\Phi^2 \end{bmatrix}}^{\Omega} \right)$$

When interpreting the data with the DI pseudo-hyperbolic law, the values of DI (Δ) are also log-normally distributed

$$\xi_i^{\alpha} \cdot \Phi_i = \Delta_i \sim LN\left(\alpha\theta_\xi + \theta_\Phi,\quad \alpha^2\omega_\xi^2 + \omega_\Phi^2 + 2\alpha\rho\omega_\xi\omega_\Phi\right)$$

…and the parameter α is the ratio of the standard deviations of the parameters (ξ and Φ) ⇒ $\alpha = \frac{\omega_\Phi}{\omega_\xi}$

Therefore the Ω matrix can be rewritten as $\Omega = \omega^2 \cdot \begin{bmatrix} \frac{1}{\alpha} & \rho\alpha \\ \rho\alpha & \alpha \end{bmatrix}$

Now, using a NLME approach to estimate the population parameters, the information about the DI can be directly extracted from θ and Ω.

With ρ=-1, this paradigm accounts also for the case with no population variability in the DI values.

Conclusions

When analyzing the DI in a population, it is important to account for both estimation uncertainty and population variability. A NLME approach is much more preferable to the traditional geometric fit.

The parameters characterizing the DI (Δ and α) can be interpreted as factors shaping the population distribution and therefore as population parameters.

When building an integrated model for insulin sensitivity and secretion, it would be important to include a population correlation term to obtain information on the DI.

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