Comparison of Different Population Analysis Approaches to the IVGTT Glucose Minimal Model

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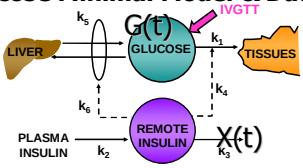
Introduction & Aims

The Glucose Minimal Model is widely employed in epidemiologic studies to estimate Insulin Sensitivity and Glucose effectiveness.
With the traditional WLS estimation approach, unsatisfactory individual parameter estimates are sometimes obtained: SI estimates virtually zero or unrealistically high and affected by very large uncertainty. We test some population approaches on both real and simulated data to assess the advantages of these approaches.

Glucose Minimal Model & Datasets



SG – Glucose Effectiveness (min^{-1})
SI – Insulin Sensitivity (min^{-1} $pmol^{-1}$ L)
P2 – Insulin Kinetics (min^{-1})
VOL – Apparent Distr. Volume (L/Kg)

204 healthy subjects - AGE ~56 yrs (18-87) - BMI ~27 kg/m^2 (20-35)
Mean Insulin-modified IVGTT - Full Schedule (FSS), Reduced Schedule (RSS):
0, 2, 4, 6, 8, 10, 15, 20, 22, 25, 26, 28, 31, 35, 45, 60, 75, 90, 120, 180, 240
First real data, then simulated (4% CV) profiles from the same subjects

Population Analysis setup

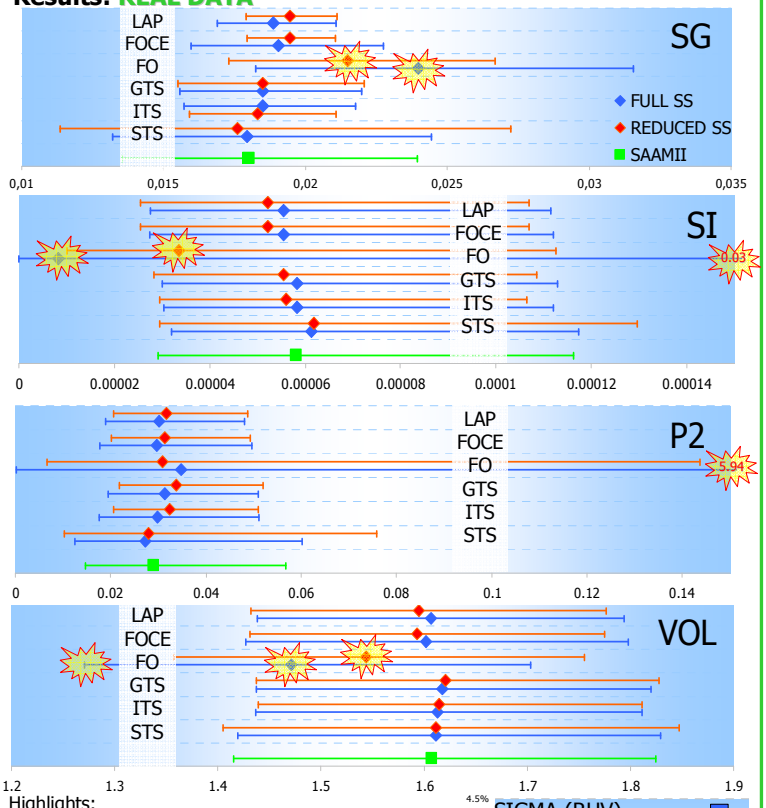
Parameters were assumed LOG-NORMAL, PROPORTIONAL error model

$$P = \exp(\theta + \eta) \qquad \eta \sim N(0, \Omega)$$ → Between-Subject Variability (BSV)

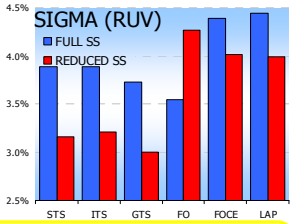
$$y(t) = F(P,t)\cdot(1+\varepsilon) \qquad \varepsilon \sim N(0, \Sigma)$$ → Residual Unknown Variability (RUV)

Methods employed:
- SAAMII + Statistical Analysis (Only for real data)
- SPK:
  - Standard Two-Stage (STS)
  - Iterative Two-Stage (ITS)
  - Global Two-Stage (GTS)
  - First-Order (FO)
  - First-Order Conditional Estimation (FOCE)
  - Laplace Approximation (LAP)

Results: REAL DATA

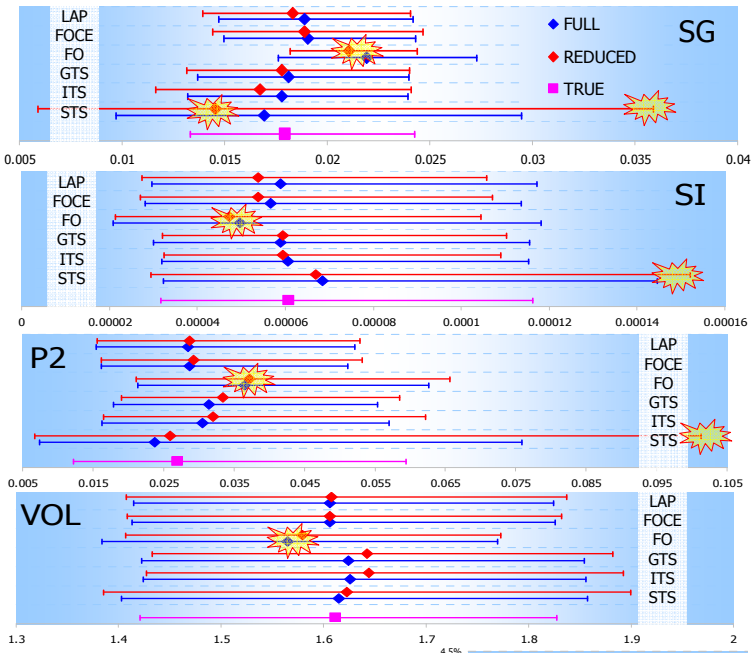


Highlights:
- FO fails in estimating some key population features, especially SI and P2
- FOCE and LAP provide in general very similar results
- SG suffers the most appreciable shrinking of the variance (shrinkage towards the mean)
- Two-Stage methods provide lower estimates of SIGMA and are negatively affected by RSS

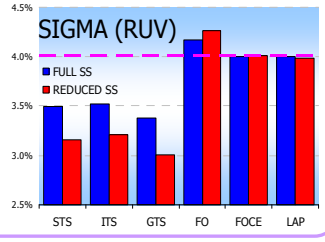


To perform an objective comparison, we used the SAAMII individual values to generate a SIMULATED DATASET.
We used the same Insulin Profiles, assumed error-free, and generated with Matlab new Glucose time profiles, adding proportional noise (4% CV)

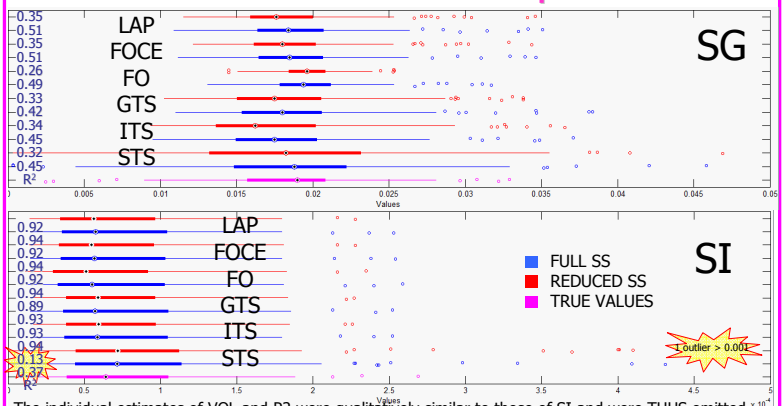
Results: SIMULATED DATASET – Population parameters



Highlights:
- FO's performance is still poor, but not as much as in the real data case
- STS overestimates the population variance for all parameters and is heavily affected by the use of the RSS
- FOCE and LAP correctly estimate the %CV, regardless of the schedule
- Two-Stage methods underestimate the %CV and deteriorate with the RSS



Results: SIMULATED DATASET – Individual parameters



The individual estimates of VOL and P2 were qualitatively similar to those of SI and were THUS omitted

Highlights:
- STS provides poor SI individual estimates, and proves not robust when the RSS is used, some spurious values very far from the population are detected
- The other population methods prove more reliable and robust to the use of the RSS

Conclusions

- In presence of high noise levels in the data, the traditional WLS Minimal Model estimation paradigm (STS) performs poorly, generally over- or underestimation of pop mean and overestimation of pop variance, even more if RSS is employed
- FO's approximation proves unsatisfactory, seemingly for parameters with very high population variability
- The other population approaches prove reliable and more robust with RSS, but only the NLMEMs (FOCE and LAP) seem to correctly estimate RUV
- As far as individual results are concerned, all the population methods (except FO) provide estimates more reliable (especially with RSS) than the traditional WLS approaches (STS)
- To optimize the model, further research might aim at investigating the optimal shape of the OMEGA matrix, in order to neglect the least significant off-diagonal terms

References

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