Covariate Selection for the IVGTT Minimal Model of Glucose Disappearance

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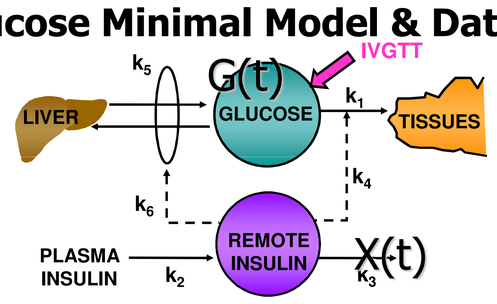
Introduction & Aims

The minimal model of glucose disappearance [1] is widely employed in epidemiologic studies of glucose-insulin metabolism, but traditionally, parameter estimation is performed via Weighted Least Squares (WLS) on single subject data. This requires intensive sampling, which is both costly and inconvenient. More recently, nonlinear mixed-effects modelling and its advantages with regard to sparse sampling have been discussed in the context of glucose-insulin metabolism [2-3-4].

Here we further employ these techniques by introducing covariates in the analysis of an Intra-Venous Glucose Tolerance Test (IVGTT) with the minimal model.

Glucose Minimal Model & Datasets



SG – Glucose Effectiveness (min^{-1})

SI – Insulin Sensitivity (min^{-1} $pmol^{-1}$ L)

P2 – Insulin Kinetics (min^{-1})

VOL – Apparent Volume (L/kg)

Insulin (assumed as error-free) acts on glucose disappearance from a remote compartment, influencing both tissue uptake and liver production.

204 healthy subjects (118 M, 86 F) were tested with an Insulin-Modified (at 20 min) IVGTT, and covariate data were collected [5]

Code	Covariate Name	Min	1stQ	Median	Mean	3rdQ	Max
AGE	Age (years)	18	27	65	55.53	71	87
BH	Body height (cm)	145	163	171	170.9	178	194
BW	Body weight (kg)	53	68.9	79	77.94	87	127
BMI	Body mass index (kg/m^2)	19.6	24.23	26.76	26.61	29.06	34.85
BSA	Body surface area (m^2)	1.505	1.771	1.937	1.917	2.047	2.596
LBM	Lean body mass (kg)	30.1	38.5	51.84	49.53	58.68	74.58
VAF	Visceral abdominal fat (cm^2/CT slice)	11.86	62.62	127.5	141.8	204.7	478.2
TAF	Total abdominal fat (cm^2/CT slice)	43.94	195.1	294.5	301.8	404.4	837.5
TBF	Total body fat (grams)	4884	17370	22570	23410	28420	46990
%TBF	Percent total body fat (%)	7.3	25.85	31.55	32.39	39.68	56.7
GBSL	Fasting glucose (mg/dL)	72.96	86.74	90.31	91.34	94.72	123.8
IBSL	Fasting insulin (mg/dL)	5.4	18.71	23.85	27.25	32.29	80.25

Population Model Building

The model parameters were assumed to be log-normally distributed and the error structure included both an additive and a proportional term.

The significant terms of the Ω matrix are shown on the right.

$$\Omega = \begin{bmatrix} \omega_{SG}^2 & \omega_{SG-VOL} & 0 & 0 \\ \omega_{SG-VOL} & \omega_{VOL}^2 & \omega_{VOL-SI} & 0 \\ 0 & \omega_{VOL-SI} & \omega_{SI}^2 & \omega_{SI-P2} \\ 0 & 0 & \omega_{SI-P2} & \omega_{P2}^2 \end{bmatrix}$$

The parameter values from the base model were regressed on the covariates using a script in R to identify the best candidate sets of covariates.

These were then implemented as NLMEMs in SPK [6], and the chi-square test was used on the OFV as a criterion for covariate inclusion. After the inclusion, covariate significance was retested for potential elimination.

Results

The best model incorporated the covariates according to the equations below (barred values denote averages). VOL was estimated separately for males and females.

$$\mathbf{SG}=\theta_{SG}\cdot\exp(\eta_{SG})$$

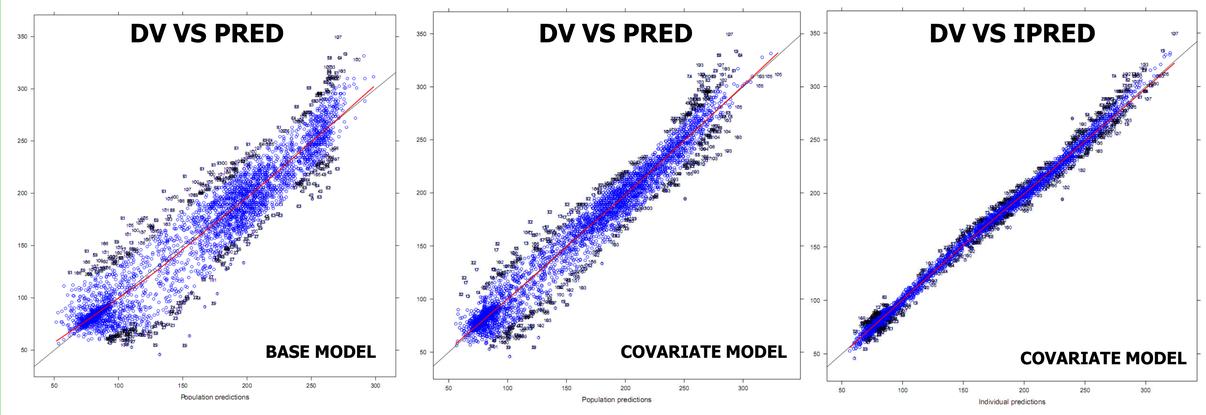
$$\mathbf{VOL}=\theta_{VOL\_Male/Female}\cdot\exp\left(\theta_{AGE\_VOL}\cdot\left(\mathbf{AGE}\text{-}\overline{\mathbf{AGE}}\right)+\theta_{\%TBF\_VOL}\cdot\left(\mathbf{\%TBF}\text{-}\overline{\mathbf{\%TBF}}\right)+\theta_{GBSL\_VOL}\cdot\left(\mathbf{GBSL}\text{-}\overline{\mathbf{GBSL}}\right)+\eta_{VOL}\right)$$

$$\mathbf{SI}=\theta_{SI}\cdot\exp\left(\theta_{AGE\_SI}\cdot\left(\mathbf{AGE}\text{-}\overline{\mathbf{AGE}}\right)+\theta_{VAF\_SI}\cdot\left(\mathbf{VAF}\text{-}\overline{\mathbf{VAF}}\right)+\theta_{IBSL\_SI}\cdot\left(\mathbf{IBSL}\text{-}\overline{\mathbf{IBSL}}\right)+\eta_{SI}\right)$$

$$\mathbf{P2}=\theta_{P2}\cdot\exp\left(\theta_{AGE\_P2}\cdot\left(\mathbf{AGE}\text{-}\overline{\mathbf{AGE}}\right)+\theta_{TAF\_P2}\cdot\left(\mathbf{TAF}\text{-}\overline{\mathbf{TAF}}\right)+\theta_{IBSL\_P2}\cdot\left(\mathbf{IBSL}\text{-}\overline{\mathbf{IBSL}}\right)+\eta_{P2}\right)$$

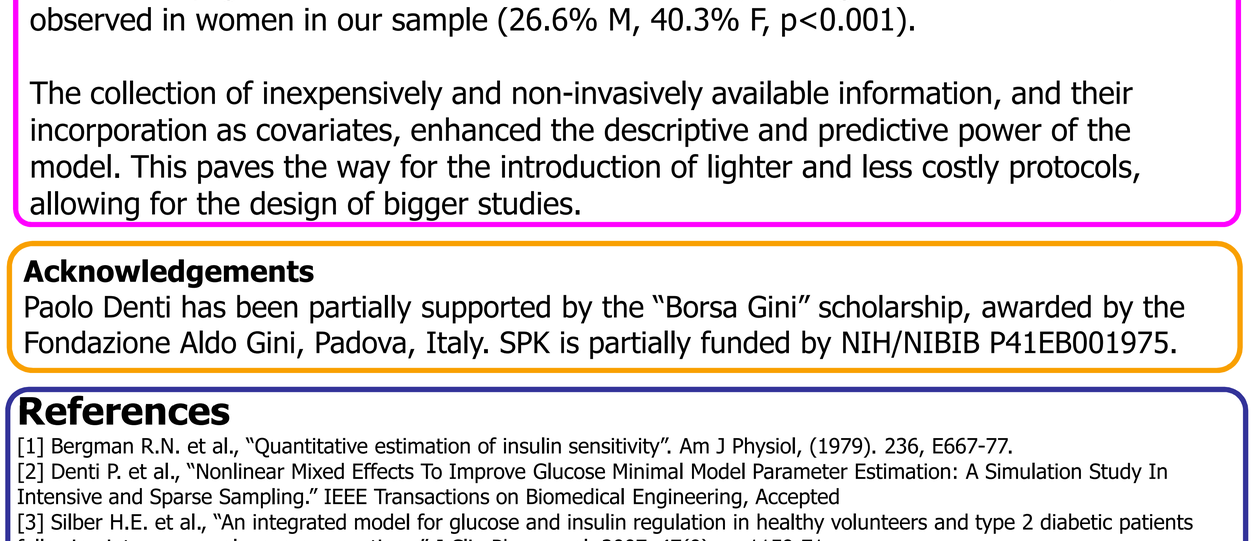
The optimal values are shown in the following table. Since the covariates were included in the exponent, they can be approximated as percentage changes in the parameter values per unit of covariate.

SG		VOL		SI		P2	
THETA	CV %	THETA	CV %	THETA	CV %	THETA	CV %
0.193	21.2	1.68	12.1	5.74×10^{-5}	72.1	0.253	50.5
0.0191	20.9	1.65 (F) 2.28 (M) AGE 0.00181 %TBF -0.0101 GBSL -0.00311	10.5	5.83×10^{-5} AGE -0.00733 VAF -0.00243 IBSL -0.0275	46.9	0.0254 AGE -0.00892 TAF -0.00063 IBSL -0.0117	37.1



Apparent from the goodness-of-fit plots above, the amount of unexplained BSV decreases substantially for SI and P2, but only modestly for VOL. The log-likelihood ratio test pointed to BH, BW, BSA as predictors for SG, but strong collinearity among these variables and their opposing effects on SG led us to withdraw them from the model.

A VPC showed good predictive properties of the model, although a slight underprediction can be detected in the latter stages of the IVGTT, when the glucose and insulin concentrations return to baseline values.



Discussion and conclusions

Physiologically meaningful covariate relationships were detected in our analysis.

SI was negatively correlated with AGE, VAF and IBSL, as previously reported [7]. Similar trends were observed for P2.

VOL/kg was negatively correlated with %TBF. Consistently, females were found to have a lower VOL/kg than males. This can be explained by the higher amount of body fat observed in women in our sample (26.6% M, 40.3% F, $p<0.001$).

The collection of inexpensively and non-invasively available information, and their incorporation as covariates, enhanced the descriptive and predictive power of the model. This paves the way for the introduction of lighter and less costly protocols, allowing for the design of bigger studies.

Acknowledgements

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References

[1] Bergman R.N. et al., "Quantitative estimation of insulin sensitivity". Am J Physiol, (1979). 236, E667-77.

[2] Denti P. et al., "Nonlinear Mixed Effects To Improve Glucose Minimal Model Parameter Estimation: A Simulation Study In Intensive and Sparse Sampling." IEEE Transactions on Biomedical Engineering, Accepted

[3] Silber H.E. et al., "An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations." J Clin Pharmacol, 2007. 47(9): p. 1159-71.

[4] Krudys K.M. at al., "Population approaches to estimate minimal model indexes of insulin sensitivity and glucose effectiveness using full and reduced sampling schedules." Am J Physiol Endocrinol Metab, 2006. 291(4): p. E716-23.

[5] Basu R. at al., "Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction." Diabetes, 2006. 55(7): p. 2001-14.

[6] System for Population Kinetics (SPK). Available from: http://spk.rfpk.washington.edu.

[7] Gastaldelli A. at al., "Metabolic effects of visceral fat accumulation in type 2 diabetes." J Clin Endocrinol Metab 87: 5098-5103, 2002.