CEDA diabetes
Zentraleuropäische Diabetesgesellschaft
Central European Diabetes Association
Föderation der Internationalen Donau-Symposia über Diabetes mellitus
Federation of International Danube-Symposia on Diabetes mellitus

# Might nonlinear mixed effects modeling be a valuable tool in large epidemiological diabetes studies?

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## Summary

There is an ongoing search for less invasive, relatively inexpensive, and logistically more suitable tools designed for large clinical studies in order to estimate glucose metabolism parameters. Nonlinear mixed effects modelling provides estimates of population means, variances and co-variances of individual parameter values, as well as measures of intra-individual and inter-individual variability. This method could be a powerful tool to obtain accurate assessments of indices of insulin sensitivity and β-cell function from different tolerance tests, especially in epidemiological studies with large numbers of sparsely sampled individuals. Methodological developments and new applications in this rich class of models in the statistical and subject-matter literature could provide a tool to allow the design of less invasive and expensive clinical protocols and epidemiological studies of the glucose disposal-metabolic system.

**Key words:** diabetes, methods, epidemiology, variability, management.

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## Introduction

The prevalence of diabetes mellitus has reached pandemic levels worldwide, with a disproportionately rapid increase in developing countries [Ampofo 2020]. Intensive research on diabetes in the past few decades has enhanced our understanding and knowledge about this chronic disease, paving the way for the development of novel methods for evaluating insulin resistance and multilateral effects of drugs [Theodorakis 2017, Rizzo 2018].

CEDA Science

Unter CEDA Science veröffentlicht die Zentraleuropäische Diabetes-Gesellschaft (CEDA/FID) wissenschaftliche Artikel ihrer Mitglieder.

Several protocols and model-based approaches have been developed for direct measurement of glycemic burden, such as oral glucose tolerance testing (OGTT) and the meal tolerance test (MTT) [Breda 2001, Dalla 2002]. However, there is an ongoing search for less invasive, relatively inexpensive, and logistically more suitable tools designed for large clinical studies. In clinical practice the widely accepted method is to analyze the data from OGTT model identification in individuals using the standard two-stage (STS) approach, rather than its application at the population level. The results of such an approach very often lead to scarcely available data, particularly when performing large, epidemiological studies. It also means that less data is available for analysis, leading to imprecise or even incorrect conclusions.

Two other tests that are predominantly used in research settings to assess glucose metabolism, insulin resistance, and β-cell function, namely the clamp technique [DeFronzo 1979] and the intravenous glucose tolerance test (IVGTT) [Toffolo 1995], can frequently result in insufficient data. These two techniques are extremely useful, but of little use in population studies. In addition, the homeostatic model assessment (HOMA), a method for assessing β-cell function and insulin resistance (IR), represents a widely used tool in clinical and epidemiological studies that can result in useful data. However, robust primary input data are required, and they should be interpreted carefully, as is common with all models [Wallace 2004].

Furthermore, logarithmically transformed HOMA-IR, the Quantitative Insulin Sensitivity Check Index (QUICKI) model, carries the same limitations as the use of the HOMA equations when compared with the computer model. Therefore, population analysis methods have been proposed as a meaningful improvement over the current parameter estimation techniques and may be of particular significance when ana-

lyzing data from large clinical studies. Mathematical and statistical techniques based on "population approaches" such as population mixed effects modelling, have been widely applied in the fields of pharmacokinetic and pharmacodynamics studies in drug development [Denti 2009] and predicting insulin absorption [Faggionato 2021]. However, except for a few instances [De Gaetano 1996], their application in the context of metabolism research and investigation is largely unexploited, and the usefulness and applicability of such approaches in the study of diabetes mellitus remains to be fully evaluated.

## Nonlinear mixed effects modelling and glucose parameters

Theodorakis et al. have applied nonlinear mixed effects modelling to plasma glucose, insulin and C-peptide data obtained from a 120 minute OGTT. They confirmed that this method provides estimates of population means, variances and co-variances of model parameters and empirical Bayes estimates of individual parameter values, as well as measures of intra-individual (within-subject) and inter-individual (between-subject) variability [Theodorakis 2017]. The authors suggest that population analysis is a powerful tool to obtain accurate assessments of indices of insulin sensitivity and β-cell function from the OGTT, especially in epidemiological studies with large numbers of sparsely sampled subjects.

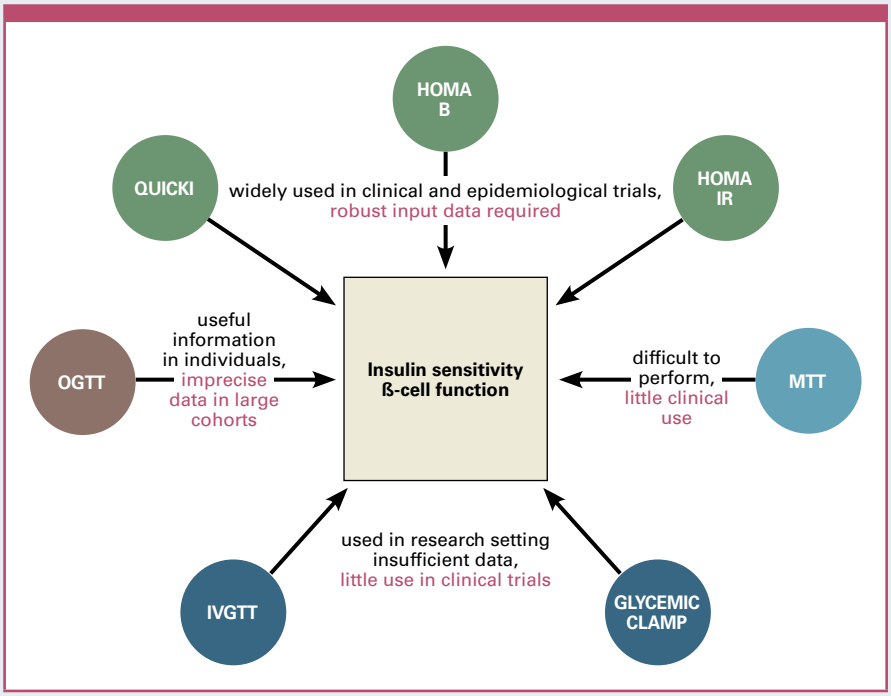


**Figure 1: Applications of nonlinear mixed effects modelling.**

The ability of the population approaches to borrow information across the population and use it to improve the individual parameter estimates has been featured as their main benefit. In addition, the use of covariates in the model further increases the power of such techniques making them very alluring methodologies to study glucose-insulin metabolism. For example, a population approach has been proposed to solve the problem of estimation of the Disposition Index (DI), which is the product of the acute insulin response and the insulin sensitivity index from IVGTT [Santos 2016]. Denti et al. further explored the

advantages of population techniques by proposing integration of covariates in the IVGTT glucose minimal model analysis [Denti 2010]. A conjectural basis would thus be established about the physiological explanation of the relationships discovered and open the door for less invasive and inexpensive methods that may be used in epidemiological studies of glucose-insulin metabolism.

Given the rapidly increasing global prevalence of diabetes, reliable tools and population-based methods to investigate qualitative patterns characterizing fasting [Aniley 2019] and/or postprandial hyperglycemia that are appropriate for use in large studies are required. Considering the high possibility of aberrant 2-hour responses regardless of fasting euglycemia, a mixed effects modelling tactic may be useful in the early identification of populations at risk for occurrence of impaired glucose tolerance and in the progression to type-2-diabetes. Some potential applications of nonlinear mixed effects modelling are shown in Figure 1.

Recent findings indicate the practicability of a population mixed effects modeling approach in analyzing the sparse data of the OGTT in a large population with varying levels of glucose tolerance. We suggest that other cardio-metabolic risk factors [Abate 2014, Bayram 2014, Rizzo 2007, Rizzo 2009, Toth 2014] could be included in future endeavours. The impact of dietary or lifestyle habits and the concentrations of various biomarkers should be taken into consideration as possible confounders which could affect the results. Although further investigation is imperative, it seems likely that the modeling of metabolic systems can notably profit from application of these techniques. Nonlinear mixed effect modeling specifically permits not only a more exact assessment of the population characteristics but also increases the individual parameter accuracy, further improving the overall estimated precision [Denti 2009].

On the contrary, Erichsen et al. reported no strong benefit with use of a population-based method in a data-rich situation, hence opposing the notion that greater number of studies provided a significant improvement for both the population and individual parameter estimates [Erichsen 2004]. However, it is possible that population methods are inherently more robust and able to compensate for the deficiency of individual data by loaning it across all subjects. The insertion into the model of other clinical covariates such as individual characteristics of each subject (e.g. age, height, weight, abdominal fat or genetic profile) may ameliorate its deficiencies and make a model more powerful. In this context, one of the main advantages of nonlinear mixed-effects models is that the regression coefficients for the physiologic variables are optimized by the algorithm together with the population parameters. Further studies will be helpful in identifying the most significant covariates and their incorporation into the model [Theodorakis 2017].

Modeling may accelerate translation from basic science to clinical medicine, streamlining experimentation, data acquisition, and technology development, overcoming translational bottlenecks, and promoting interdisciplinary research. Although the available evidence is promising, not much is known about the technique of nonlinear mixed effects population modeling as applied to different bioactive markers.

The use of simulated clinical trials and "virtual" patients can be incorporated in models that include data obtained from a clinical, as opposed to a laboratory setting. It is expected that these scales will bridge a key gap between bench biology and clinical medicine, and a growing number of translational applications of the models including patient-specific modeling for diagnosis and therapy planning. However, no one model can indicate safety and effectiveness alone [Erdemir 2020]. Close oversight from regulatory agencies to stimulate the development and validation of tools and data resources to support modeling in, for example, cardiovascular device design, will be essential.

**Abbreviations**

| | |
|---|---|
| HOMA-B: | homeostatic model assessment for assessing β-cell function |
| HOMA IR: | homeostatic model assessment for insulin resistance |
| IVGTT: | intravenous glucose tolerance test |
| MTT: | meal tolerance test |
| OGTT: | oral glucose tolerance test |
| QUICKI: | quantitative insulin sensitivity check index |

## Conclusion

Methodological developments and new applications in this rich class of models in the statistical and subject-matter literature could provide a tool to allow the designing of less invasive and expensive clinical protocols, pharmacokinetic, and epidemiological studies of the glucose disposal-metabolic system. This may have a particular relevance during this difficult and long pandemic time for patients with chronic diseases, like those with diabetes, which are now exposed to an higher risk of severe complications [Stoian 2020]; we therefore encourage more research on this topic, which may have a significant impact in clinical practice for a better management of diabetic patients.

Author Disclosure Statement:
The authors declare that this article has been written independently, without any financial or professional help, and reflects only the opinion of the authors, without any role of the industry. A.P.S. is currently Vice-President, National Diabetes Commission, Ministry of Health, Romania. M.R. is former Director, Clinical Medical and Regulatory Department, Novo Nordisk Europe East and South.

**References**

1. Abate N, Sallam HS, Rizzo M, Nikolic D, Obradovic M, Bjelogrlic P, Isenovic ER. Resistin: an inflammatory cytokine. Role in cardiovascular diseases, diabetes and the metabolic syndrome. Curr Pharm Des 2014;20:4961-9.
2. Ampofo AG, Boateng EB: Beyond 2020: Modelling obesity and diabetes prevalence. Diabetes Res Clin Pract. 2020;167:108362.
3. Aniley TT, Debusho LK, Nigusie ZM, Yimer WK, Yimer BB: A semi-parametric mixed models for longitudinally measured fasting blood sugar level of adult diabetic patients. BMC Med Res Methodol. 2019; 19(1):13.
4. Bayram F, Kocer D, Gundogan K, Kaya A, Demir O, Coskun R, Sabuncu T, Karaman A, Cesur M, Rizzo M, Toth PP, Gedik V. Prevalence of dyslipidemia and associated risk factors in Turkish adults. J Clin Lipidol 2014;8:206-16.
5. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C: Oral glucose tolerance test minimal model indexes of beta-cell func-

tion and insulin sensitivity. Diabetes. 2001; 50:150-158.
6. Dalla Man C, Caumo A, Cobelli C: The oral glucose minimal model: estimation of insulin sensitivity from a meal test. IEEE Trans Biomed Eng. 2002; 49:419-429.
7. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979; 237:E214-223.
8. De Gaetano A, Mingrone G, Castageneto M: NONMEM improves group parameter estimation for the minimal model of glucose kinetics. Am J Physiol. 1996; 271:E932-937.
9. Denti P, Bertoldo A, Vicini P, Cobelli C: Nonlinear mixed effects to improve glucose minimal model parameter estimation: a simulation study in intensive and sparse sampling. IEEE Trans Biomed Eng. 2009; 56:2156-2166.
10. Denti P, Bertoldo A, Vicini P, Cobelli C: IVGTT glucose minimal model covariate selection by nonlinear mixed-effects approach. Am J Physiol Endocrinol Metab. 2010; 298:E950-960.
11. Erdemir A, Mulugeta L, Ku JP, Drach A, Horner M, Morrison TM, Peng GCY, Vadigepalli R, Lytton WW, Myers JG Jr. Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective. J Transl Med. 2020; 18(1):369.
12. Erichsen L, Agbaje OF, Luzio SD, Owens DR, Hovorka R: Population and individual minimal modeling of the frequently sampled insulin-modified intravenous glucose tolerance test. Metabolism. 2004; 53:1349-1354.
13. Faggionato E, Schiavon M, Dalla Man C: Modeling between-subject variability in subcutaneous absorption of a fast-acting insulin analogue by a nonlinear mixed effects approach. Metabolites. 2021; 11(4):235.
14. Rizzo M, Spinas GA, Cesur M, Ozbalkan Z, Rini GB, Berneis K. Atherogenic lipoprotein phenotype and LDL size and subclasses in drug-naïve patients with early rheumatoid arthritis. Atherosclerosis 2009; 207: 502-506.
15. Rizzo M, Nikolic D, Patti AM, Mannina C, Montalto G, McAdams BS, Rizvi AA, Cosentino F. GLP-1 receptor agonists and reduction of cardiometabolic risk: Potential underlying mechanisms. Biochim Biophys Acta Mol Basis Dis 2018;1864:2814-2821.
16. Rizzo M, Berneis K. Who needs to care about small, dense low density lipoproteins? Int J Clin Pract 2007; 61:1949-56.
17. Santos JL, Yevenes I, Cataldo LR, Morales M, Galgani J, Arancibia C, Vega J, Olmos P, Flores M, Valderas JP, Pollak F: Development and assessment of the disposition index based on the oral glucose tolerance test in subjects with different glycaemic status. J Physiol Biochem. 2016; 72:121-131.
18. Stoian AP, Banerjee Y, Rizvi AA, Rizzo M. Diabetes and the COVID-19 Pandemic: How Insights from Recent Experience Might Guide Future Management. Metab Syndr Relat Disord 2020;18:173-175.
19. Theodorakis MJ, Katsiki N, Arampatzi K, Chrousos GP: Modeling the oral glucose tolerance test in normal and impaired glucose tolerant states: a population approach. Curr Med Res Opin. 2017; 33(2):305-313.
20. Toffolo G, De Grandi F, Cobelli C: Estimation of beta-cell sensitivity from intravenous glucose tolerance test C-peptide data. Knowledge of the kinetics avoids errors in modeling the secretion. Diabetes. 1995; 44:845-854.
21. Toth PP, Barylski M, Nikolic D, Rizzo M, Montalto G, Banach M. Should low high-density lipoprotein cholesterol (HDL-C) be treated? Best Pract Res Clin Endocrinol Metab 2014;28:353-68.
22. Wallace TM, Levy JC, Matthews DR: Use and abuse of HOMA modeling. Diabetes Care. 2004; 27:1487-1495.

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