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Comment on “Minimal and Maximal Models to Quantitate Glucose Metabolism: Tools to Measure, to Simulate and to Run in Silico Clinical Trials”

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In their recent article entitled “Minimal and Maximal Models to Quantitate Glucose Metabolism: Tools to Measure, to Simulate and to Run in Silico Clinical Trials” Cobelli and Dalla Man¹ presented an overview of their work on the mathematical modeling of glucose metabolism. The article is interesting and showcases the influential work of the authors over the past decades; however, there is an inaccurate statement in regards to the parameter identifiability of one of the presented models, the oral minimal model (OMM) of glucose dynamics.

The OMM was first proposed in 2002² and allows the estimation of a non-accessible key parameter representing insulin sensitivity based on postprandial glucose and insulin measurements after an oral glucose tolerance test or a meal with mixed macronutrient content. Model equations¹ (1) to (3) contain unknown parameters to be estimated, in particular fractional glucose effectiveness S_G , rate constants p_2 and p_3 related to insulin sensitivity, glucose distribution volume V and amplitudes, denoted by vector α , of the piecewise-linear function describing glucose appearance rate in plasma from the oral input. Before describing the numerical parameter estimation procedure, the authors report their structural identifiability results, likely based on an analysis presented earlier², by stating: “Parameters α render the model not a priori uniquely identifiable because V is non-identifiable and S_G is non-uniquely identifiable. Thus, V and S_G are usually fixed to population values”¹. While the parameter V is truly non-identifiable, in 2008 Saccomani et al.³ demonstrated that S_G is uniquely identifiable by using a differential algebra method. Eichenlaub et al.⁴ then recently confirmed these results by combining the Taylor series method with symbolic computation, showing that conclusions drawn on the sole basis of a truncated expansion may be incorrect. Details regarding the underlying mathematical analysis can be found in the respective publications.^{3,4}

The OMM is part of the “oral minimal model method” which has been used in a large number of clinical studies to investigate the regulation of the postprandial metabolism dependent on various factors such as age, sex, ethnicity and glucose tolerance as well as the effect of different drugs used for diabetes treatment.^{5,6} To assess the impact of the here discussed error in the modeling procedure, it is important to note that ignoring or not recognizing the structural identifiability of parameters can result in unreliable model estimates. This in turn could have led to wrong model interpretations affecting the results of the large number of

clinical studies mentioned previously. In particular, fixing parameter S_G to population values may, in principle, introduce errors in the insulin sensitivity estimate, which is used to characterize the glucose metabolism.

Declaration of conflicting interests

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