Response to 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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We thank Eichenlaub and coworkers for their interesting letter to the editor entitled *Comment on "Minimal and Maximal Models to Quantitate Glucose Metabolism: Tools to Measure, to Simulate and to Run in Silico Clinical Trials"*. When developing the original model (1), we acknowledged that the need of fixing S_G (fractional glucose effectiveness) to a population value was an important limitation of the method. To test the implication of this assumption on the model-derived insulin sensitivity, S_I, we performed an extensive validation work against independent techniques, including glucose clamp (2) and multiple tracer experiment (3)**,** and we were able to prove that S_I is well correlated with model-independent indices. Eichenlaub and coworkers' overlook the S_I validation studies (2,3) that fully address their concerns: the correlation was 0.81 $p<0.001$ with clamp in 10 normal and 11 impaired glucose tolerant subjects (2) and 0.86, $p<0.0001$ with the multiple tracer experiment in 88 healthy individuals (3) . Therefore, their critiques cannot be sustained upfront such a large body of validation evidence (2, 3).

In addition, Eichelelaub and coworkers have only considered the *a priori (structural)* identifiability, which is a necessary but not sufficient condition of the identification problem: it is mandatory to consider also the *a posteriori (numerical)* identifiability. In fact, parameter S_G can only be estimated with poor precision during an oral challenge. To overcome this problem one has to use a priori knowledge either by fixing S_G to a population value or by using a Bayesian prior on GEZI (glucose effectiveness at zero insulin) as detailed in the Appendix of (4). Initially, the population value strategy was successfully used as documented in the validation studies (2, 3). More recently, we adopted a novel strategy, which allows to avoid to choose a population value by introducing the parameter GEZI and estimating it with a Bayesian Maximum a Posteriori estimator, which we propose as the recommended method.

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