Minimal Model For Oral Glucose Tolerance Test

Methods and Models for Estimation Of Insulin Sensitivity

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Aims

The Minimal Model is a standard mathematical model of insulin and glucose dynamics, originally developed for the intravenous glucose tolerance test (IVGTT) and used to estimate insulin sensitivity (SI).

We modify the model for the oral glucose tolerance test (75g OGTT) by estimating rate of absorption (Ra) of glucose over a 300-min sampling period in 52 people without diabetes.

We also evaluate two numerical methodologies for the statistical estimation of model parameters including SI.

Evaluation of Numerical Methods

MAP Maximum a priori (SAAM II software)

- Pro: Faster computations
- Con: May not converge to an estimate
- Con: Statistics rely on asymptotic theory

MCMC Markov-Chain Monte Carlo (BUGS software)

- Pro: Always produces an estimate
- Pro: Handles missing/truncated data
- Pro: Detailed information on statistical correlations and uncertainty
- Con: Slower computations

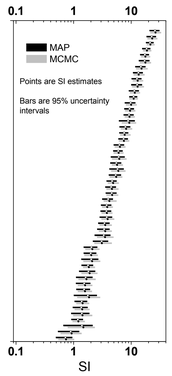


Figure 1: MAP- and MCMC-derived estimates of SI are nearly identical (r = 0.99) and the uncertainty intervals are comparable (n = 52). Estimates produced using smooth Ra model.

Not shown: SI estimates also correlate strongly (r = 0.99) under the piecewise Ra, but MCMC-derived uncertainty intervals are about 30% wider than those from MAP.

Result: MCMC is a robust platform for estimating SI following an OGTT.

Models for Rate of Absorption

We consider two forms for the rate of absorption (Ra) of glucose during an OGTT. Both Ra models have the same total absorption as quantified by AUC (area under the curve) but differ in shape and complexity.

Smooth Ra

- Three parameters: max rate, time to max rate, AUC
- Reflects assumption of physiologically "smooth" absorption

Piecewise Ra

- Seven parameters to describe AUC and sudden changes at each time point
- Allows closer fit to observed glucose concentrations, but at expense of physiological realism and overfitting model noise

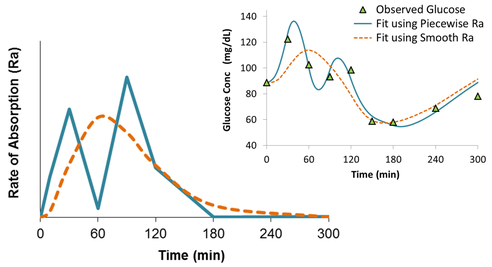


Figure 2: Smooth and piecewise Ra curves for an individual following an oral glucose dose.
Inset: Observed glucose concentrations and resulting model fits under each Ra model.

Effect of Truncated Sampling

Samples for glucose and insulin concentrations were collected over a 300-min period, however it is of interest for reasons of improved efficiencies to consider shorter sampling periods.

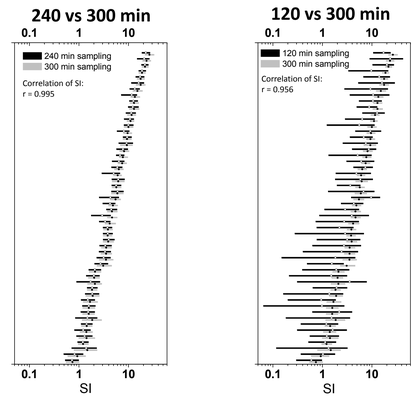
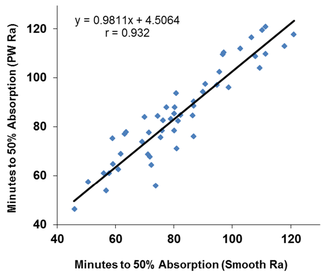


Figure 4: SI estimates and uncertainty intervals, using the smooth Ra model, for full and truncated sampling. Statistical uncertainty for individual SI values increases dramatically with truncation to 120 min. Correlation of SI is good in both cases.

Result: There is no advantage to extending the OGTT beyond 4 hours. A 2-hr study, without additional prior knowledge, appears to have too much statistical uncertainty. Choice of 150 or 180 mins could depend on projected study design.

Figure 3: The estimated time at which 50% of the glucose dose is absorbed is similar for the smooth and piecewise Ra models, despite their noticeably different Ra curves and fits to observed glucose.

Not shown: Estimated SI values obtained under the two Ra models were nearly identical (r = 0.99).



Result: The three-parameter smooth Ra model provides a more parsimonious alternative for a physiological representation of the rate of absorption of glucoses during an OGTT.

Clinical Measures

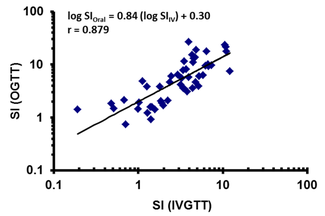


Figure 5: Correlation of estimated SI values obtained under the OGTT and IVGTT (n = 52).

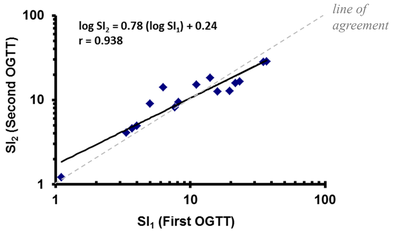


Figure 6: Within-subject correlation of OGTT SI estimates obtained in a repeat study (n = 15, median separation between studies was 6 days).

Result: SI estimations after OGTT or IVGTT correlated well (although oral SI values are systemically slightly higher). OGTT SI appears to be a reproducible estimate in repeat studies.

Summary

- A simple three-parameter model for rate of absorption (Ra) of glucose is sufficient for estimation of SI following an OGTT.
- MCMC is a flexible alternative numerical platform for statistical estimation of model parameters.
- We provide further validation of these approaches using IVGTT and repeat studies.
- Sampling periods shorter than 5 hrs are feasible