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Technology Report

Automated Oral Minimal Models for Rapid Estimation of Insulin Sensitivity and Beta-Cell Responsivity in Large Scale Data Sets: A Validation Study

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Abbreviations: (OMM) Oral Minimal Model, (AOMM), Automated Oral Minimal Model, (OGTT) Oral Glucose Tolerance Test, (IVGTT) Intravenous Glucose Tolerance Test, (Si) Insulin Sensitivity, (Φ) Beta-cells Responsivity, (DI) Disposition Index.

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Abstract

The Oral Minimal Model (OMM) is an insightful method for assessing glucose–insulin regulation during glucose challenges. However, its manual, test-by-test implementation limits scalability in large studies. We introduce the Automated Oral Minimal Model (AOMM), a tool that streamlines and automates the entire OMM workflow while preserving analytical fidelity, enabling efficient batch processing of large datasets.

Built using SAAM II software, AOMM was validated against manually extracted results from *Sunehag* et al. (*Obesity*, 2008), accurately reproducing key parameters such as insulin sensitivity (*Si*) and beta-cell responsivities (*Φ*) with high precision and substantial time savings.

AOMM, with its user-friendly interface, empowers broader application of minimal modeling in research and clinical studies.

Introduction

An individual's metabolic health is determined by how effectively their body regulates blood glucose; a process primarily managed by insulin. Key metrics such as insulin sensitivity (*Si*) and beta-cell responsivity (Φ) are derived from oral glucose tolerance tests (OGTT) or meal tolerance tests using oral minimal model (OMM) analysis. These metrics provide deeper insights into how well insulin is functioning and its overall effectiveness in maintaining blood glucose levels [1].

OMMs are mechanistic (first-principles) mathematical models designed to analyze the glucose-insulin-C-peptide system [1]. The glucose OMM estimates insulin sensitivity (*Si*), which reflects how efficiently the body manages external glucose. The C-peptide OMM provides beta-cell metrics (Φ), quantifying the efficiency of insulin secretion in response to external glucose [1]. OMMs have proven to be reliable predictors compared to the more labor-intensive Intravenous Glucose Tolerance Test (IVGTT) [2], and potentially, more informative than other oral glucose tolerance indices [3].

The minimal model analysis has been in use for over 40 years, with more than 500 publications [4]. Initially focused on pathophysiological studies in clamps, it later expanded to oral tests (Oral Minimal Model, OMM), with or without tracers (e.g., [5]). Its applications now encompass nutrition research (e.g., [6]), clinical trial evaluations and staging (e.g., [7–9]), and diabetes progression studies (e.g., [10]). In essence, in any metabolic status assessment via a meal or OGTT is needed, OMM metrics can be applied [11]. As tolerance tests data collection becomes more widespread, the demand from stakeholders for efficient software to support OMM analysis has grown substantially.

Unlike other indices that can be calculated using simple spreadsheet computations, OMM analysis requires specialized software. Only a few software tools have been validated by the community for minimal model analysis [12,13]. Among these, SAAM II gained popularity for its proven reliability in analyzing minimal models, including the oral minimal model analysis and the user-friendly graphical interface. All users can perform OMM analyses eliminating the need for coding [12,14,15].

Despite its intuitive interface, lack of coding requirements, and established role in OMM, previous versions of SAAM II still required users to manually create two separate files per tolerance test—one for glucose and one for C-peptide and run model identification on a one-by-one basis. This involved entering various parameters, including glucose dose, sampling times, plasma concentrations, and patient characteristics such as body weight and age as well as tuning modelling variables on an individual basis to optimize the accuracy of the parameters estimates. While manageable in small studies, this “manual” setup can become tedious, slow, and error-prone in larger cohorts, significantly limiting the scalability and usability of OMM, for example, in clinical trials, diabetes progression studies, or prevention research. As a result, groups using minimal model analysis stand to benefit significantly from the adoption of an automated tool, the Automated Oral Minimal Model (AOMM).

To support AOMM, we expand on the original manual OMM setup in SAAM II and upgrade the software to allow high-throughput parameter extraction. First, a new preprocessing tool is introduced to automatically convert spreadsheet data into SAAM II format, eliminating the time-consuming steps of manual copying, pasting, and formatting. A key addition in preprocessing is the automatic calculation of the glucose first derivative, which is required for the OMM analysis. Previously, this step was left to the users who relied on

external, non-standard scripts and using various methods—leading to numerical errors when computing secretion Φ parameters. Now, the derivative is computed within the preprocessing stage using the regularized deconvolution method [16], ensuring consistency and good practice with OMM theory [1].

Second, the built-in batch processor is made more flexible for AOMM. Earlier versions of the SAAM II's batch processor were designed for strict pharmacokinetic models, where the process would stop if any warning or error occurred [14]. For instance, in OMM analysis, estimation issues arose when insulin sensitivity (Si) approached zero in subjects with severely impaired glucose utilization. Previously, SAAM II would flag Si as unprecise and therefore the tests was skipped or halted; now, AOMM handles this as physiologically valid and either accepts the result or reassigns it using the GEZI method [17]. Finally, postprocessing is now streamlined: AOMM generates a single spreadsheet with results from all subjects, avoiding the need to open and extract each file manually.

In this paper, we show that AOMM gives the same results as the manual method, with the same level of accuracy, but much faster, effectively leading to a validation for usage at larger scale.

Methods

The streamlined workflow for automated minimal model (AOMM) analysis is illustrated in Figure 1. Assuming *N* tolerance tests (assuming OGTT here) are recorded in a spreadsheet (e.g., in *.csv* or *.xls* format), the process involves the following steps:

1. **Files Creation (preprocessing)**: Generate 2x*N* SAAM II files from the *N* OGTT records. Specifically, *N* files are used for the glucose AOMM to compute insulin sensitivity values (*Si*), and the other *N* files are used for the C-peptide AOMM to derive beta-cell responsivity values (*Φ*).
2. **Parameter Extraction (new batch function)**: Use the SAAM II engine's "batch" function to extract OMM parameters (described in detail in [11]).
3. **Result Export (postprocessing)**: Export the results in a spreadsheet format (e.g., *.csv* or *.xls*) for further analysis. OMM parameters are automatically tabulated.

To validate the AOMM implementation, we compared its outcomes with data from reference data from Sunehag *et al.* [5], who conducted OGTT studies on 11 healthy participants (Table A1 in Supplementary), collecting 25 samples in the -30–420 minutes range, per test (Supplementary S1). These data had been validated using triple-tracer studies and anchored on IVGTT, ensuring approximation to “true” insulin sensitivity and insulin secretion . Mathematical derivation of insulin sensitivity *Si* and insulin responsivity (*Φ*) indices are reported in the Supplementary S2. Insulin responsivities include the response to a change in glucose concentration *Φd* (dynamic), the response to a given glucose concentration *Φs* (static), and the total response to the glucose stimulus *Φtot*, as defined in Equations in Supplementary S2 and illustrated in Figure S1. AOMM’s estimate precision, calculated using

SAAM II's asymptotic parameter precisions based on the Fisher Information Matrix method [14], was expressed as coefficient of variation (CV) and evaluated against the 25% threshold defined by the reference work [5]. To assess agreement between two methods, manual OMM vs AOMM, we performed Bland–Altman analyses for each index. For each participant, the average and difference between methods were calculated and plotted. Bias (mean difference) and 95% limits of agreement (mean ± 1.96 SD) were derived to evaluate systematic and random discrepancies.

Both automated and manual methods used the same modeling conditions, where sometimes not fully stated in [5], we tracked down other assumptions, or initial and boundary conditions from references listed in [5], i.e., [18,19]. Briefly, basal values were averaged from -30, -20, -10 and 0 min samples; Population parameters such as glucose effectiveness was set to 0.035 min^{-1}, and glucose volume to 2.40 dl/kg [5]; The dynamic rate of insulin action *p2* was set to Bayesian conditions (prior mean 0.002 with CV=20%); Measurement errors were assumed independent, zero-mean normal: 2% for glucose, and $2000 + 0.001 \times [\text{C-peptide}]^2$ for C-peptide. AOMM was run and validated using SAAM II v2.4 (Nanomath LLC, Spokane, WA, www.nanomath.us/saam2) on a Windows 11 laptop (Alienware M15 R7, Intel i9 14-core CPU, 32 GB RAM).

Results

AOMM ran successfully on the entire cohort, with no fitting issues and good parameter precision. AOMM indices were compared to the manual reference OMM and are summarized in Table 1. Insulin sensitivity (*Si*) and beta-cell responsivity parameters (*Φ*) showed identical estimates, supporting AOMM's validity. The Bland–Altman analysis across all parameters — insulin sensitivity (*Si*), dynamic response (*Φd*), static response (*Φs*), and total response (*Φtot*) — showed zero bias and no dispersion, with all differences as zero. This indicates agreement between OMM and AOMM methods in this dataset (Bland–Altman plots in Supplementary Figure S2). No fitting errors or warnings were returned.

In terms of precision, AOMM consistently achieved coefficients of variation (CV) below the reference threshold of 25%, for all the parameters (Figure 2). On average, CV was 7.5, 7.5, 3.8, and 3.3% for *Si*, *Φd*, *Φs*, *Φtot*, respectively.

In terms of computational performance, AOMM extracted *Si* and *Φ* parameters in a fraction of a second on the test machine—approximately 5 *Si* and 3 *Φ* estimates per second—compared to days usually required with manual OMM analysis (personal communication from original paper [5]).

In summary, AOMM produced results identical to the manual method with good precision, confirming that automation introduced no errors. All components of the AOMM workflow—preprocessing (including automatic derivative computation), upgraded batch processing, and postprocessing tabulation—were thus successfully validated.

Discussion

Despite the use of tools like SAAM II, minimal model analysis has remained time-consuming due to manual processing such as data cleaning, derivative calculation, and parameter extraction. As a result, OMM studies are typically limited to small cohorts (10–30 participants), creating a major barrier for large-scale or longitudinal studies. In settings like Phase 2 trials with 100–300 subjects, manual analysis becomes impractical and could take months. The need for automation was clear and driven by stakeholders' demand.

In this study, we propose AOMM, the first automated tool that could be used at scale. The users will only have to prepare the spreadsheets with their tolerance tests and feed them into the AOMM (see in Figure 1) where a table with parameters is returned for analysis. Based on the results here, computational time could potentially extract parameters in 100 tests under few minutes with good precision.

SAAM II was chosen for developing AOMM – not only for continuity with its established use in manual OMM analysis – but also for its unique advantages: the Bayesian Maximum A Posteriori (MAP) estimator, the forcing function method, and a modified extended least squares algorithm, all of which support fast and reliable parameter identifiability in OMM [14,15,20].

However, automation introduces challenges that must be continuously addressed to sustain the performance reported here. It can amplify minor issues typically corrected manually, such as unit mismatches, outliers, missing data, tolerance tests with fewer timepoints, misreported demographics (e.g., implausible BMI), and variability in baseline values. A fully automated AOMM system must be capable of handling edge cases, such as $Si \sim 0$, which might occur in large tolerance test datasets. Consequently, future updates may be necessary to address additional automation issues that did not emerge during this validation.

Moreover, since the reference data used for validation involved young adults without diabetes, further optimization might be required when applying AOMM to other populations, such as individuals at different stages of diabetes.

Conclusion

The first fully Automated Oral Minimal Model (AOMM) was successfully developed, delivering accurate and precise results compared to reference data. AOMM allows minimal model parameters to be extracted at scale, in a fraction of the time required by manual methods. This advancement could enhance the wider use of OMM in larger studies, where its physiological insights can be especially valuable.

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Figures and Tables

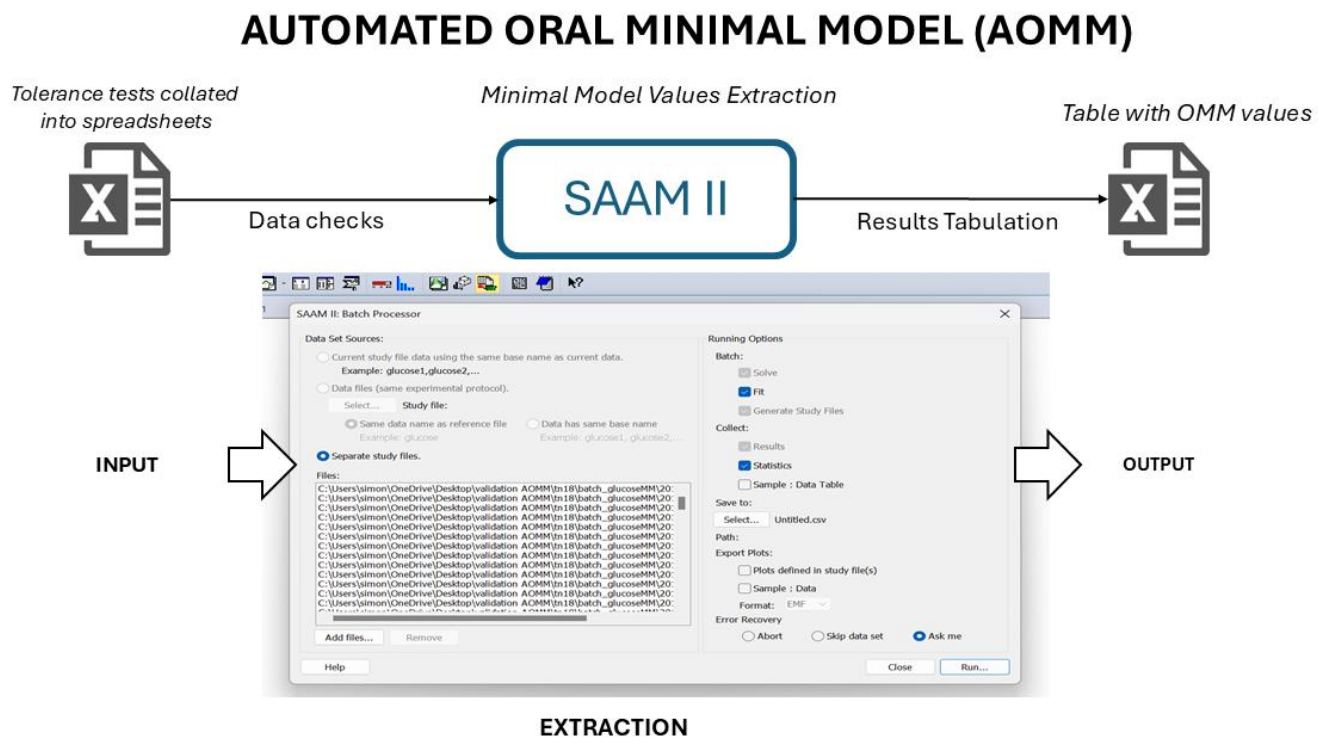

Figure 1. The Automated Oral Minimal Model (AOMM) framework enables fast and automated extraction of Oral Minimal Model parameters. By organizing tolerance tests (e.g., OGTT) datasets into spreadsheets, SAAM II processes the entire cohort in batch mode, automatically extracting parameters and compiling them into spreadsheets for further analysis.

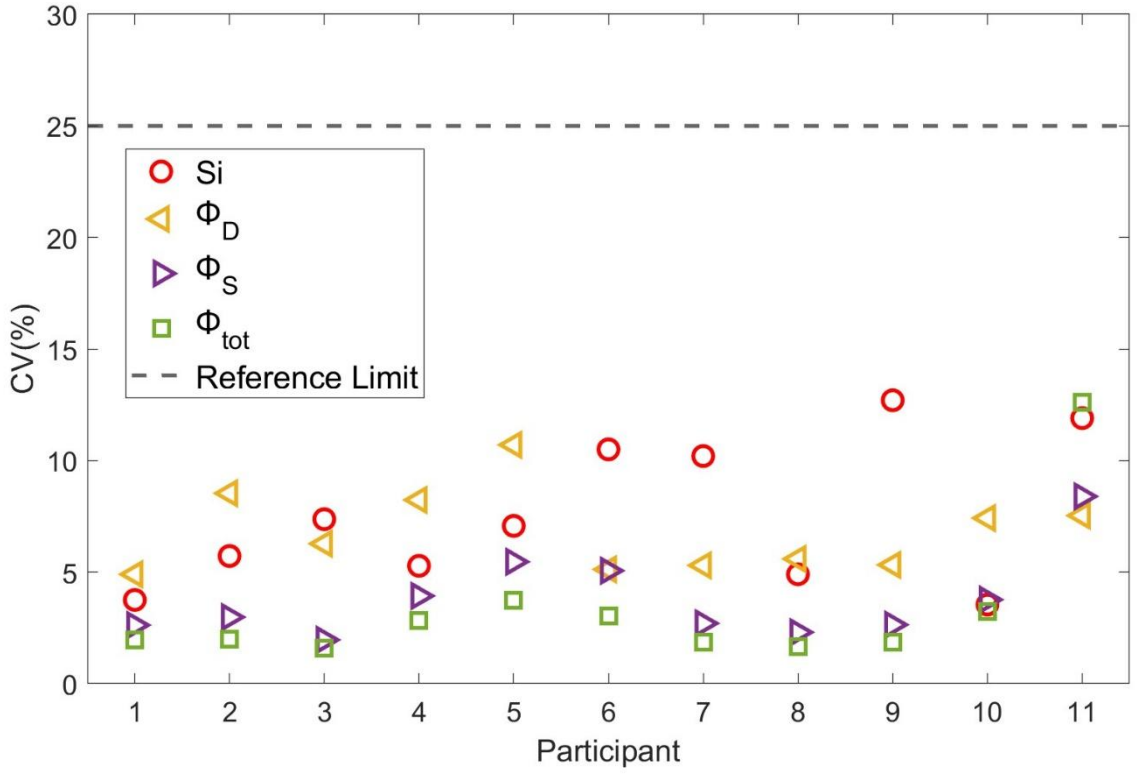

Figure 2. AOMM estimate precision expressed as coefficient of variation (CV%), compared to the 25% threshold defined by the reference OMM study. Symbols indicate CVs for different parameters: circles for ***Si***; left-pointing triangles for $\boldsymbol{\Phi_d}$, right-pointing triangles for $\boldsymbol{\Phi_s}$, and squares for $\boldsymbol{\Phi_{tot}}$.

Table 1. Comparison of parameter estimates between the manual reference OMM and the automated AOMM.

Participant	Insulin Sensitivity ***Si*** (10^{-4} *dl/kg/min per pmol/l*)		Dynamic Response Φ_d, (10^{-9})		Static Response Φ_s, (10^{-9} *min*$^{-1}$)		Total Response Φ_{tot} (10^{-9} *min*$^{-1}$)	
	OMM	**AOMM**	OMM	**AOMM**	OMM	**AOMM**	OMM	**AOMM**
1	19	**19**	210	**210**	44	**44**	44	**44**
2	14	**14**	550	**550**	20	**20**	25	**25**
3	4.5	**4.5**	870	**870**	48	**48**	64	**64**
4	14	**14**	2300	**2300**	81	**81**	140	**140**
5	30	**30**	660	**660**	16	**16**	17	**17**
6	31	**31**	2500	**2500**	29	**29**	95	**95**
7	4.6	**4.6**	2100	**2100**	59	**59**	80	**80**
8	7.3	**7.3**	890	**890**	38	**38**	48	**48**
9	9.2	**9.2**	900	**900**	37	**37**	51	**51**
10	14	**14**	2500	**2500**	100	**100**	220	**220**
11	9.3	**9.3**	2000	**2000**	100	**100**	120	**120**
Mean	14	14	1400	**1400**	52	**52**	82	**82**