# Comparison between NONMEM and the Monte-Carlo Expectation Maximization (MC-PEM) Method Using a Physiologically-Based Glucose-Insulin Model

Robert Bauer[1], Serge Guzy[1], Hanna E Silber[2], Petra M Jauslin[2,3], Nicolas Frey[3], Mats O Karlsson[2]

(1)Pop-Pharm Inc.,Berkeley,CA (2)Uppsala University, Uppsala, Sweden and (3)Hoffmann-La Roche Inc., Basel, Switzerland

## Objective

To compare the methodologies of NONMEM and MC-PEM (Monte Carlo Parametric Expectation Maximization, as applied in the software package S-ADAPT) using an advanced model for regulation of glucose and insulin kinetics.

## Introduction

In NONMEM, a linearized form of the likelihood function is maximized. The MC-PEM method, by using Monte-Carlo simulations during the expectation step, allows one to maximize the exact likelihood while avoiding complicated integration algorithms. The MC-PEM algorithm consists of two main consecutive steps: the first one is the expectation step (E-Step) in which Monte-Carlo sampled model parameters contribute to the assessment of the conditional means and variances for each subject, at the current values of the population parameters and inter-subject variances. The second one is the maximization step which updates the population parameter characteristics. As the MC-PEM algorithm is particularly suited for complex models with highly dimensioned inter-subject variances, the comparison between the MC-PEM algorithm and the NONMEM algorithm has been conducted by using the physiologically based glucose-insulin model previously developed by HE Silber and PM Jauslin [1, 2].

## Methods

***Test Model***

An integrated model (Fig 1) for the regulation of glucose and insulin concentrations and of control mechanisms involved in this regulation following both intravenous and oral provocation experiments in 42 type 2 diabetic patients (Fig 2: glucose and insulin profiles of patient 28 displayed as example) was used as a test case to compare the performance of NONMEM and S-ADAPT [3].

- The glucose sub-model was a two-compartment model with elimination from the central compartment, which was composed of an insulin-dependent and an insulin-independent part. The insulin-dependent elimination of glucose was controlled by plasma insulin concentrations. The addition of labeled (hot) glucose allowed for the characterization of endogenous glucose production.
- Insulin disposition was described by a one-compartment model, and its secretion was controlled by plasma glucose concentrations. The oral absorption of glucose was modeled using a chain of transit compartments. The enhanced insulin response to an oral glucose provocation due to the incretin effect was described as a direct effect using an Emax model. For the purpose of the comparison between NONMEM and S-ADAPT, all the parameters that were fixed in the published glucose-insulin model [2] were unfixed and re-estimated in NONMEM. Forty-four parameters were estimated in total: 23 fixed effects, 17 variances and 4 covariances. The same model was then implemented in S-ADAPT.

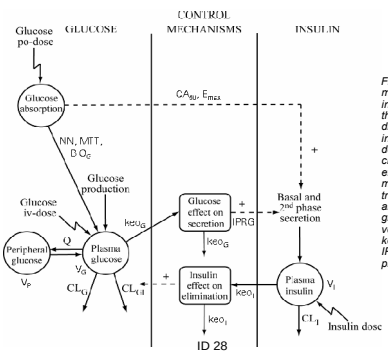


*Figure 1. Schematic representation of the glucose-insulin model. Full arrows indicate flows and broken arrows indicate control mechanisms. VG, volume of distribution of the central glucose compartment; VP, volume of distribution of the peripheral glucose compartment; CLG, insulin-independent glucose clearance; CLGI, insulin-dependent glucose clearance; Q, inter-compartmental clearance of glucose; keoG, rate constant for the glucose effect compartment; BIOG, bioavailability of glucose; MTT, mean transit time of glucose absorption; NN, number of transit compartments; Emax, maximal effect of the absorption rate of glucose on insulin secretion; CA50, glucose absorption rate producing 50 % of Emax; VI, volume of distribution of insulin; CLI, insulin clearance; keoI, rate constant for the insulin effect compartment; IPRG, control parameter for the glucose effect on insulin production.*

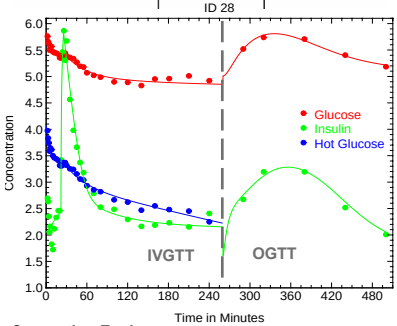


*Figure 2. Observed concentration-time profiles of glucose [log(mg/dL)], hot glucose [log(mg/dL)] and insulin [log(mU/L)] in individual 28. IVGTT (0-240min) and OGTT (260-500 min) are displayed on the same time scale following each other. In reality, the two experiments were performed on two subsequent days. The full lines represents post-hoc fits from the S-ADAPT full analysis.*

***Computing Environment***

All analyses were performed on a Dell Pentium 4 3.20 Ghz computer, with 1 gigabyte non-ECC 400 MHz DDR2 memory, and an 80 GB SATA 7200 rpm hard drive with Data Burst Cache. The operating system was Windows XP. Both S-ADAPT and NONMEM were compiled using Intel Fortran 9.1.

***Modeling software***

The S-ADAPT analysis was performed using importance sampling MC-PEM. Post-hoc fits and standard errors were assessed evaluating the Fisher information 2nd derivative matrix from Monte Carlo constructs derived during the MC-PEM analysis. Non-linear mixed effects modeling in NONMEM was performed using the first order conditional estimation (FOCE) method of NONMEM version VI and the differential equation solver ADVAN6. In analogy to S-ADAPT, the R matrix (second derivatives) was used for calculation of standard errors.

***Performance comparison***

Criteria for performance comparison between NONMEM and S-ADAPT were parameter estimates and precision, the objective function value, the predictive performance, individual predictions and run times. The predictive performances of sets of parameters obtained by NONMEM and S-ADAPT, respectively, were assessed by performing a visual predictive check (VPC).

***Full S-ADAPT analysis***

A full S-ADAPT analysis was performed, allowing all parameters, variances and covariances to vary (164 parameters in total: 23 fixed effects, 21 variances and 120 covariances). A comparative NONMEM analysis was precluded due to the restricted number of estimable parameters. This limitation could be overcome by re-installation and modification of the SIZES settings, thus leading to even longer and eventually unmanageable run times.

## Results

***Comparison of NONMEM and S-ADAPT***

- Similar objective function values were obtained in NONMEM (-14749) and S-ADAPT (-14760).
- Both algorithms provided similar parameter estimates and standard errors. The ratios of S-ADAPT and NONMEM parameter estimates were close to 1 for most parameters, as displayed in figure 3 (left panel). The few deviating variances and covariances did not have a major impact on model predictions, as could be verified by comparison of the predictive performance of both sets of parameters (see next point). Most of the standard error estimate ratios were also close to 1 (Fig. 3, right panel), and most of the deviating ones were standard error ratios of parameters that are not well estimated in NONMEM (CV>30%).
- Similar predictive performance was achieved with both methods. The results of the visual predictive checks are displayed graphically in figure 4. No major differences in model predictions were observed.
- Close to identical populations and individual predictions were generated by the two software packages.
- CPU times in S-ADAPT (6 hrs) were considerably shorter than in NONMEM (33 hrs).

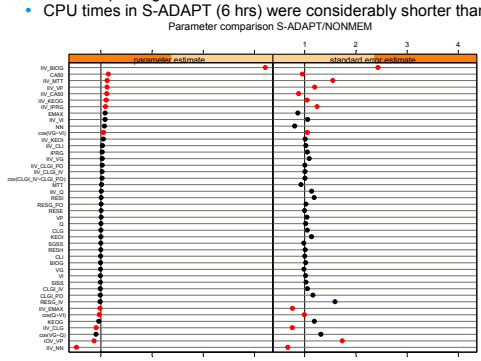


*Figure 3. Ratios of S-ADAPT parameter estimates/ NONMEM parameter estimates (left) and ratios of the standard errors obtained in both analyses (right).Red dots indicate parameters that were not well estimated in NONMEM (CV> 30%). IIV, inter-individual variability; IOV, inter-occasion variability; cov, covariance; IV, specific parameter for the intravenous glucose tolerance test; PO, specific parameter for the oral glucose tolerance test; SGSS, scaling parameter for the glucose baseline; SISS, scaling parameter for the insulin baseline; RESG, residual error for total glucose; RESI, residual error for insulin; RESH, residual error for hot glucose; RESE, multiplying error factor for early time points (<2 minutes); for all other parameters see legend of figure 1*

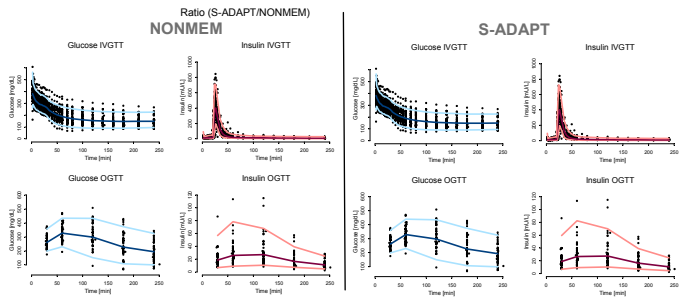


*Figure 4. Visual predictive check (VPC) using NONMEM (left panel) and S-ADAPT (right panel) parameters. 100 IVGTT and OGTT data sets were simulated. Above, IVGTT profiles (left: glucose and right: insulin) and below, OGTT profiles (left: glucose and right: insulin) are displayed. Observations from the original data set are plotted as points. The dark lines show the medians of the individual predictions of the 100 simulations, the light lines indicate the 5th and 95th percentiles*

***S-ADAPT Full Analysis***

The full covariance model MCPEM analysis in S-ADAPT required 7 hrs running time, including standard error assessment. The final objective function value was -15018, i.e. a drop in the objective function value of 269 points as compared to test case 1 could be achieved by the full analysis, adding 120 parameters. This represents a significant model improvement (P<0.001). The comparison of the predictive performance between the full covariance model and the test model is displayed in figure 5. An example post-hoc fit shows that the model represented all components of the concentration-time profiles very well (Fig 2).

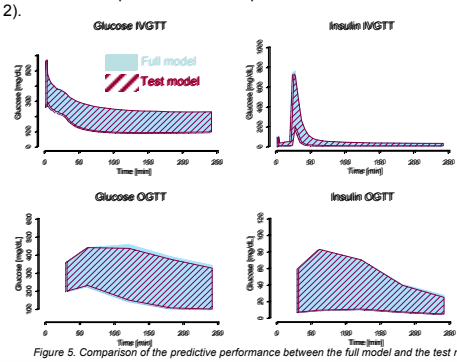


*Figure 5. Comparison of the predictive performance between the full model and the test model*

## Discussions and Conclusions

- In a test setting estimating a limited number of covariances, NONMEM and S-ADAPT provided very similar results. However, S-ADAPT's run times were approximately 5 times shorter.
- The full model implementation in S-ADAPT allowed us to obtain an analysis of data with a complex model such as the glucose-insulin model presented here, without having to resort to selective constraints on the inter-subject variance-covariance matrix. The MC-PEM process was very stable and executed to completion without requiring intervention during its analysis. Based on the full analysis results, one may optionally apply reasonable constraints on the inter-subject variance-covariance matrix. However, in the case of the current test model, estimating a full variance-covariance matrix did not lead to an improvement of model performance.

## References

[1] Silber H, Jauslin PM, Frey N, Gieschke R, Simonsson USH, Karlsson MO. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. J Clin Pharmacol, (in press).

[2] Jauslin PM, Silber HE, Frey N, Gieschke R, Simonsson USH, Jorga K, Karlsson MO. An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics. J Clin Pharmacol, (in press).

[3] Bauer RJ, S-ADAPT/MCPEM User's Guide. Version 1.54. Berkeley, CA.; 2007. http://bmsr.usc.edu/Software/Adapt/sadapt.html