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Title :

Implementation and Evaluation of the SAEM algorithm for longitudinal ordered categorical data with an illustration in pharmacokinetics-pharmacodynamics ”

Authors: Radojka M. Savic[1], France Mentré[1] and Marc Lavielle[2]

Institution:

(1) UMR 738, INSERM - Université Paris Diderot, Paris, France

(2) INRIA Saclay & Department of Mathematics, University Paris 11, Orsay , France

email: Radojka.Savic@inserm.fr

tel: +33 1 57 27 75 38

fax: +33 1 57 27 75 21

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Abstract:

Introduction: Analysis of longitudinal ordered categorical efficacy or **safety** data in clinical trials using mixed models is increasingly performed. However, algorithms available for maximum likelihood estimation using an approximation of the likelihood integral, including LAPLACE approach, may give rise to biased parameter estimates. The SAEM algorithm is an efficient and powerful tool in the analysis of continuous/count mixed models. The aim of this study is to implement and investigate the performance of the SAEM algorithm for longitudinal categorical data.

Methods: The SAEM algorithm is extended for parameter estimation in ordered categorical mixed models together with an estimation of the Fisher information matrix and the likelihood. We used Monte Carlo simulations using previously published scenarios evaluated with NONMEM. Accuracy and precision in parameter estimation and standard error estimates were assessed in terms of relative bias and root mean square error. This algorithm was illustrated on the simultaneous analysis of pharmacokinetic and discretized efficacy data obtained after single dose of warfarin in healthy volunteers.

Results: The new SAEM algorithm is implemented in MONOLIX 3.1 for discrete mixed models. The analyses show that for parameter estimation, the relative bias is low for both fixed effects and variance components in all models studied. Estimated and

empirical standard errors are similar. The warfarin example illustrates how simple and rapid it is to analyze simultaneously continuous and discrete data with MONOLIX 3.1

Conclusions: The SAEM algorithm is extended for analysis of longitudinal categorical data. It provides accurate estimates parameters and standard errors. The estimation is fast and stable.

Introduction:

Mixed effect analyses are increasingly employed for the analysis of longitudinal efficacy or **safety** categorical data measured in clinical trials (1-5). For this purpose, proportional-odds model are frequently used. Other models, such as differential-odds model has also been proposed (6). Results from these analyses, i.e. models along with parameter estimates, are often further utilized for simulation of novel scenarios with respect to new dosing schedules or new patient populations. It is also advocated that these models should be used as an essential part of drug development program**s**. Therefore it is critical that these parameter estimates are unbiased and reliable.

We focus here on maximum likelihood estimation. However, as in all nonlinear mixed models, the integral of the likelihood function cannot be explicitly solved and various approximations are employed to approximate the true likelihood (7). The most commonly used approximation is Laplace, available in the software NONMEM. Bias in parameter estimates for these models with NONMEM **VI and SAS v.8** has been studied in detail and it has been shown that the use of Laplace approximation may result **in** severely biased estimates, especially when response categories are non-evenly distributed within **the** studied population (8). This is common when analyzing clinical data and therefore the importance of using exact **evaluations** of the likelihood integral is further accentuated.

SAS implements a more exact evaluation of the likelihood using Adaptive Gaussian Quadrature . However this approach is time consuming, can be applied to models with

limited number of random effects, and is not flexible for the analysis of pharmacokinetic/pharmacodynamic data after various repeated dosage regimen (9)

In recent years, there have been several approaches/algorithms developed for the analysis of continuous data which are able to find maximum likelihood estimate**s** without a need to compute the likelihood numerically (10, 11) . A stochastic approximation version of EM algorithm linked to a Markov Chain Monte Carlo procedure has been suggested for maximum likelihood estimation within the non-linear mixed effects framework (11, 12). This procedure has been demonstrated to possess excellent statistical convergence properties as well as the ability to provide an estimator close to the maximum likelihood estimate in only **a** few iterations (12, 13). In addition to the estimation of the maximum likelihood parameters, the SAEM algorithm also provides the user with the estimate of the Fisher Information Matrix, used to assess parameter estimate uncertainty. However, there have not been studies reported with respect to application of the stochastic algorithms to the analysis of the ordered categorical data

The aims of this study were (i) to extend the SAEM algorithm for estimation of parameters in categorical data mixed models, (ii) to evaluate its performance both for parameter and standard errors estimation via Monte Carlo simulation study and, (iii) to illustrate the performance of the algorithm on a real data example where both continuous PK and discrete PD data are simultaneously analyzed.

A proportional odds model with individual-specific random effect has been employed throughout the exercise to study properties of the new SAEM algorithm. This model has been used in the area of PKPD modeling (2, 5, 14) and has been presented in detail elsewhere (2, 5, 8, 14).

Methods:

The proportional odds model with random intercept

We assume that the response is an ordered categorical variable which takes its values in (0,1,…,M). Let y_{ij} be the j^{th} observation in the i^{th} individual, i = 1, …, N. In the proportional odds model with random intercept, the cumulative probability of y_{ij} being larger or equal to *m* (*m=1, …, M*), can be defined by the following logistic regression model

$\text{logit}\left[P\left(y_{ij} \geq m\right)\right] = \alpha_1 + \ \ldots + \ \alpha_m \ + \ h(\beta, x_{ij}) + \eta_i$	Equation 1

where *logit* denotes the logit function, $\alpha_1 + \ \ldots + \ \alpha_m$ specifies the baseline for category *m* (*m=1, …, M*); *h* is the function defining predictors or covariate effect, β is a vector of fixed effects which is the same across all categories, x_{ij} *i*s the predictor vector (e.g. time, dose, concentrations) for observation *j* of individual *i* and η_i is the random effect of individual *i*. It is assumed that the random effects are normally distributed with mean 0 and variance ω^2.

Implementation of the SAEM algorithm for categorical data models

The SAEM algorithm described in [7] for continuous data models has been extended to the ordered categorical data models in a similar manner as it has been done for the count data models (13). Let $\mu = (\boldsymbol{\alpha_1}, \boldsymbol{\alpha_2}, \dots, \boldsymbol{\alpha_M}, \boldsymbol{\beta_1}, \boldsymbol{\beta_2} \dots \boldsymbol{\beta_L})$ be the vector of fixed effects of the model and Ω be the variance-covariance matrix of the random effects η_i (in our example, $\boldsymbol{\eta_i}$ **is scalar and** Ω reduces to the variance ω^2 of η_i). Then, SAEM is an iterative procedure where at iteration *k*, a new set of random effects $\eta^{(k)} = (\eta_i^{(k)})$ is drawn with the conditional distribution $p(\eta | y, \mu^{(k)}, \Omega^{(k)})$. Then, the new population parameters $\left(\mu^{(k+1)}, \Omega^{(k+1)}\right)$ are obtained by maximizing $Q_{k+1}(\mu, \Omega)$ defined as follows:

$$Q_{k+1}(\mu, \Omega) = Q_k(\mu, \Omega) + \gamma_k \left(l\left(y, \eta^{(k)}; \mu, \Omega\right) - Q_k(\mu, \Omega) \right) \qquad \text{Equation 2}$$

where $l(y, \eta; \mu, \Omega)$is the complete log-likelihood

$$l(y, \eta; \mu, \Omega) = \sum_i \log\left(p(y_i | \eta_i; \mu) \times p(\eta_i; \Omega)\right) \qquad \text{Equation 3}$$

and where (γ_k) is a decreasing sequence of step sizes. For the numerical experiments presented below, we used γ_k = 1 during the first 200 iterations of SAEM and γ_k=1/(k-200) during the next 100 iterations.

An MCMC algorithm was used for the simulation step (see [7,8] for more details).

Estimation of the Fisher information matrix

Let $\theta = (\mu, \Omega)$ be the set of population parameters to be estimated, and let $\widehat{\theta}$ be the maximum likelihood estimate of θ computed with SAEM. The Fisher Information

matrix is defined as $-\partial_\theta^2 l(y;\widehat{\theta})$ where $l(y;\widehat{\theta})$ is the log-likelihood of the observations, computed with $\theta = \widehat{\theta}$.

Several numerical experiments have shown that linearization of the model for estimating the Fisher information matrix (as implemented in MONOLIX 2.4) is satisfactory in case of continuous data (15).

In this case, the linearization of the structural model allows transformation of the non-linear model into a Gaussian model, for which one the Fisher information matrix can be computed in a closed form.

However, this approach cannot be applied for discrete data models. As alternative we propose to compute a stochastic approximation of the Fisher Information matrix using the Louis formula (see (11) for more details):

$$\partial_\theta^2 l(y;\hat{\theta}) = E\left(\partial_\theta^2 l(\gamma,\eta;\theta)|\gamma;\theta\right) + Var(\partial_\theta l(\gamma,\eta;\theta)|\gamma;\theta) \qquad \text{Equation 4}$$

The procedure consists in computing first $\hat{\theta}$ with SAEM then applying the Louis formula with $\theta = \hat{\theta}$which requires the computation of the conditional expectation and conditional variance **defined in equation** 4. These quantities are estimated by Monte-Carlo: 300 iterations of MCMC were performed for the numerical experiments. All

extensions for SAEM algorithm described here have been implemented in software MONOLIX 3.1.

Simulation settings

The performance of the SAEM algorithm was evaluated via Monte Carlo simulation-. To allow a fair comparison with other algorithms, we used identical scenarios as presented previously in the paper of Jönsson *et al* where authors explored performance of Laplace and Adaptive Gaussian quadrature algorithms (8). Overall, five different scenarios (A-E) were used. In all scenario**s** response was a four level categorical variable that takes its values in {0,1, 2,3}. Scenarios A-C describe a baseline model

$$logit\left[P(y_{ij} \geq m)\right] = a_1 + \ldots + a_m + \eta_i \ ; 1 \leq m \leq 3 \qquad \text{Equation 5}$$

with three different distributions of response categories: even (scenario A), moderately skewed (scenario B) and skewed (scenario C).

Scenario D-E included a specific baseline, placebo and drug model through two additional β parameters (Eq. 6)

$$logit\left[P(y_{ij} \geq m)\right] = a_1 + \ldots + a_m + \beta_1 c_{ij} + \beta_2 d_{ij} + \eta_1; 1 \leq m \leq 3 \qquad \text{Equation 6}$$

The placebo model was implemented as a step function ($c_{ij} = 0 \; if \; j = 1$ and $c_{ij} = 1$ if $j = 2,3,4,$), while the drug model was implemented as a linear function of the

dose ($d_{ij} = 0\ if\ j = 1$and $d_{ij} = 0,7.5,15,30\ if\ j = 1,2,3,4$ respectively. The distribution of response categories was even (scenario D) and skewed (scenario E).

Typical parameter values were chosen so as to mimic desired distribution of responses. The studied variance range was 0.5 - 40.

For each scenario, one hundred datasets each containing 1000 individuals were simulated with MATLAB. All estimation procedures were performed using MONOLIX 3.1. Overview of studied scenarios is shown in Table I. For more details on the simulation design used, reader is kindly asked to refer to the original publication of *Jönsson et al* (8).

Evaluation of the SAEM algorithm and the standard error estimates

For each scenario, the SAEM algorithm was used with the *K*=100 simulated datasets for computing the *K* parameter estimates, $\widehat{\boldsymbol{\theta}}_{\boldsymbol{k}}$, $\boldsymbol{k} = \mathbf{1}, \ldots \boldsymbol{K}$. The Fisher information matrix was also estimated for each data set, and its inverse was used to compute the *K* standard error estimates, $\widehat{\boldsymbol{se}}_{\boldsymbol{k}}, \boldsymbol{k} = \mathbf{1}, \ldots \boldsymbol{K}$. The empirical standard errors *se (*i.e.* the RMSE) were computed by equation 7:**

$$\boldsymbol{se}^{*} = \sqrt{\frac{\mathbf{1}}{\boldsymbol{K}}\sum_{\boldsymbol{k}=\mathbf{1}}^{\boldsymbol{K}}(\widehat{\boldsymbol{\theta}}_{\boldsymbol{k}} - \boldsymbol{\theta}^{*})^{\mathbf{2}}} \qquad \text{Equation 7}$$

where θ^{*} stands for the true parameter value.

To assess statistical properties of the proposed estimators, for each parameter, relative estimation errors $REE(\widehat{\theta}_k), k = 1, \dots K$ were computed as shown in equation 8a, where $x_k = \theta_k$. Similarly, for each estimated parameter standard error, relative estimation error $REE(\widehat{se}_k), k = 1, \dots K$ was computed, as shown in Equation 8a, where $x_k = se_k$. Each REE is expressed as a percentage (%). From the REEs, relative bias (RB), and relative root mean square errors (RRMSE) were computed for each parameter in each scenario as shown in Equations 8b-c.

$$REE(\widehat{x}_k) = \frac{\widehat{x}_k - x^*}{\theta^*} \times 100 \qquad \text{Equation 8a}$$

$$RB(\widehat{x}) = \frac{1}{K}\sum_{k=1}^{K} REE(\widehat{x}_k) \qquad \text{Equation 8b}$$

$$RRMSE(\widehat{x}) = \sqrt{\frac{1}{K}\sum_{k=1}^{K} REE(\widehat{x}_k)^2} \qquad \text{Equation 8c}$$

$$where\ K = 100\ and\ x = \theta\ or\ se$$

For simplicity in the notations, all these formula are vectorial formula which holds for each component of θ. Outcomes of all Monte-Carlo simulation studies exploring both, the parameter estimation procedure and estimation of Fisher information matrix, were presented as box-plots of **relative** estimation errors (REE) where bias and imprecision of the method, as defined by equation **8b** and **8c**, can easily be visualized.

CPU times needed for estimation of (i) population parameters, (ii) Empirical Bayes Estimates (EBEs) which are individual random effects and (iii) standard error estimates, were also measured to assess the efficiency of the algorithm and the runtime for the analysis.

Illustration on a real data

The well-known real PKPD dataset of warfarin was used to evaluate novel SAEM algorithm and its ability to simultaneously analyse continuous and categorical data. The data were collected in 33 patients after a single dose of warfarin for 140h post dose. In total 251 pharmacokinetic (PK) observations and 232 pharmacodynamic (PD) observations (corresponds to inhibition of prothrombin complex synthesis – PCA (%)) were available (16, 17). Original PD variable was continuous variable expressed in percentages (0 – 100 %); however for our purpose, we categorized the PCA variable into three ordered categories: 0 (if PCA is more than 50%), 1 (if PCA is between 33% and 50%) and 2 (if PCA was less than 33%). **Of note, categorization of the continuous variable is done for illustration purpose only and it is not recommended to be done in the real analysis**. The cut-offs chosen, are close to international normalized ration (INR) values commonly used in clinical practice to target optimal warfarin therapy. Low INR values (< 2) are associated with high risk of having a cloth (corresponding to category 0), high INR values (>3) with high risk of bleeding (corresponding to category 2), while

targeted value of INR, corresponding to optimal therapy is in between 2 and 3 (corresponding to category 1)**.** The raw PKPD data are shown in Figure 1. The PK model fitted was one compartment model with first order absorption and a lag time. Effect compartment model was used to mimic an effect delay. Proportional odds model with random intercept was used to fit ordered categorical response. The drug model was a linear function of warfarin concentration.

Results:

Simulation study

Overall, the estimation procedure with the SAEM algorithm for mixed categorical data models, showed satisfactory performance with low bias and high precision. Convergence was 100% for both parameter and standard error estimation. For parameter estimation, the absolute value of relative bias was less than 7.9% and 8.13% for fixed effects and the random effect variances and **RRMSE** was less than 27% and 30% for fixed effects and the random effect variances over all tested scenarios. For standard error estimation, the absolute value of relative bias was less than 3.4**%** and 5.8% for fixed effects and random effect variances and **RRMSE** was less than 2.3**%** and 5.6% for fixed effects and random effect variances. The random effect variances, shown to be severely biased when estimated with Laplace method implemented in NONMEM (8) (**8**), were precisely estimated with SAEM, exhibiting relative bias ranging from 0.03% – 8.13% across all studied scenarios. Detailed results for each scenario are listed below. The distribution of REE for all scenarios and all parameter **and standard error** estimates are shown in Figure 2A-E. The numerical results showing accuracy and precision for parameter estimation, measured as relative bias and relative root mean square error, are shown in Table II. The numerical results showing accuracy and precision for relative standard error estimation, measured as bias and root mean square error, are shown in Table III **indicating low bias (<5.78%) and high precision (RRMSE<7.42)**

The average CPU (**Central Processing Unit)** time per run over all scenarios was 29.6 s for parameter estimation, and 6.5 s for standard error estimation, with Matlab/C++ implementation of the algorithm, when ran on laptop DELL D830 2.40GHz configuration. **Median CPU times for parameter, EBEs and standard error estimation are given in Table IV, for all studied scenarios.**

Illustration of a real data

With respect to the warfarin real data example, both parameter and standard error estimation was successful. Estimation procedure was completed in less than 2 minutes, for the model containing 8 typical parameters, 6 variances and 2 residual error parameters. The example of the model implementation in MONOLIX 3.1 is shown in Figure 3. The output of MONOLIX run representing parameter estimates and respective standard errors is shown in Figure 4**. Figure 5 shows change over time of probability of each response category, based on the simulations from the final model.**

Discussion

The new SAEM algorithm has been developed, implemented and evaluated for application to categorical data models in the non-linear mixed effects framework. Five different scenarios using proportional odds model were evaluated, including those with non-even distribution of response categories. The algorithm was also implemented for computation of Fisher Information matrix in order to assess the uncertainty estimate. The SAEM algorithm performed well under all tested model scenarios resulting in accurate and precise estimation of all parameters. Variances of scenarios with non-even distribution of response categories were accurately and precisely estimated, which was not reported previously in analysis with LAPLACE method (8). **The explanation for previously observed biases with LAPLACE was related to the poor approximation of the likelihood integral. Similarly to FOCE (first order conditional estimation approximation), LAPLACE approximation likelihood estimation computes and it involves linearization of the likelihood function by means of estimating EBEs at each iteration step. Whenever the estimated EBE distribution does not reflect the true random effect distribution, the method is expected to perform poorly. Reason for deviations of EBE distribution from the true random effect distribution is due to shrinkage phenomenon. Whenever data are sparse, which may be due to design, variability or the model itself, individual random effects will shrink toward zero and empirical variance of EBE will be smaller than the corresponding estimated Ω.** Shrinkage in EBE leads to linearization around zero for the random effects, close to a FO

method, which is known to be biased (18, 19). Additionally, random effects enter models in a non-linear fashion; therefore these are most likely to suffer from the poor integral approximation, which was indeed observed in the previous work with severely biased variances (8). **Gaussian quadrature method, as implemented in SAS, performed better than LAPLACE due to better numerical approximation of the likelihood integral , therefore EBE shrinkage influence was less pronounced compared to the LAPLACE approximation (8). Similar pattern was also observed when performance of these estimation methods was evaluated for count data (20). Of note, it has been reported that this Gaussian Quadrture may become unstable and time consuming for more complex type of problems (7, 21).**

The SAEM algorithm does not involve any likelihood estimation conditioned on EBEs or any approximation of the model in computation of the likelihood integral and therefore does not suffer from any related biases. SAEM simulates large number of individual parameters using not only conditional modes, but also conditional variances at the current iteration. These conditional variances are large; therefore EBE shrinkage is not a problem under these circumstances.

Of note, small significant bias was observed in Scenario D for estimation of β_1 parameter, which is magnitude of treatment effect. This bias is most likely related to the small number of observations per subject as it disappeared when the number of observations per subject was increased.

The SAEM algorithm provides estimation of both the likelihood and Fisher information matrix, without linearization of the model. This is a favorable property of the algorithm, which leads to accurate and unbiased parameter and standard error estimates. The importance of unbiased standard error estimates has seldom been the topic of discussion. Standard errors are utilized in different aspects of pharmacometrics – they are an important aspect of prospective simulations, determination of the optimal study design, Wald test and exploration of competing study design scenarios .The SAEM algorithm appeared to satisfy requisite precision and unbiased estimates of parameter uncertainty.

In the previous analysis reported by Jönsson *et al* (8) authors concluded that CPU time was not too burdensome and estimations were generally fast for methods investigated. **This was similarly observed with the new SAEM algorithm, with the median time for parameter estimation being less than half a minute. This is somewhat slower than reported times with LAPLACE (9.87 – 17.1 s) and in the lower range of the reported times with Gaussian Quadrature (5.92 – 165 s), for different GQ methods for scenario D and E). Of note, LAPLACE and GQ runs were performed on the computer with slightly faster processor (Pentium 2.8 GHz *vs* Intel 2.40 GHz for SAEM).** All studied models converged successfully (100%), for both parameter estimation and standard error estimation with average CPU time being measured in seconds.

The SAEM algorithm is easily applied for simultaneous modeling of continuous and discrete data and the most common application of this feature is in development of the

PKPD models, with discrete PD variable. This case was also illustrated in our example with warfarin data. The advantages of simultaneous over sequential PKPD analysis has been demonstrated previously (22, 23), however to our knowledge such an analysis when PD variable is discrete has never been reported in the literature, even though simultaneous modeling of continuous and discrete data is possible with NONMEM VI. The reason for that is that LAPLACE algorithm often becomes unstable whenever the model structure is more complex. The new SAEM algorithm as implemented in MONOLIX offer simple model coding and fast and stable estimation procedure.
The SAEM algorithm, which forms the core of MONOLIX is a freeware available at http://www.monolix.org and is based on t**horoughly** evaluated and documented thorough statistical theory. Monolix is an ongoing project implementing new statistical developments in a dynamic environment. The new version of MONOLIX program includes the extension of the algorithm for the analysis ordered categorical data as well as for count data(13).

Conclusions

In conclusion, SAEM algorithm has been extended for the analysis of ordered categorical data. The parameters and standard errors are precisely and accurately estimated. The estimation procedure is stable and fast. Algorithm is easily extended for simultaneous modelling of continuous and discrete data.

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Table legend

Table I. Original study design and simulation settings. Distribution of response categories for originally simulated data sets and true parameter values used in simulations are presented.

Table II. Relative bias and relative root mean square error (**in %)** for parameter estimates for all studied scenarios**. These results correspond to the visual ones shown in the left panel of Figures 2a-e.**

Table III. **Relative bias and relative root mean square error (in %) for standard error estimates for all studied scenarios. These results correspond to the visual ones shown in the right panel of Figures 2a-e.**

Table IV. Median CPU time for parameter, EBE and standard error estimations for all studied scenarios.

Figure legend:

Figure 1. Observed pharmacokinetic (left panel) and pharmacodynamic (right panel) data of warfarin. The categorization of the continuous PD variable (PCA) is visualized with the horizontal lines representing cut-off values.

Figure 2A-E. Distribution of relative estimation error (REE) for all parameters (left panel) and standard errors (right panel) across all the models. The errors (y-axes) are given as percentages (%).

Figure 3. Implementation of the simultaneous analysis of continuous and discrete data in MONOLIX for the warfarin dataset. Pharmacokinetics is described with one compartment model with first order absorption and a lag time. Effect compartment model is used to mimic the effect delay. Proportional odds model is used to fit ordered categorical PD variable.

Figure 4. MONOLIX output for real data example. Parameter estimates are shown along with their standard error estimates.

Figure 5. **Probability change over time for each warfarin response category, based on the simulations from the final model**

Table I

Scenario	α_1	α_2	α_3	β_1	β_2	ω^2	Proportions 0/1/2/3 (%)
A (baseline)	1.85	-1.85	-1.85	-	-	4	25/25/25/25
	2.47	-2.46	-2.42	-	-	10	
	4.46	-4.44	-4.41	-	-	40	
B (baseline)	-2.45	-1.375	-1.50	-	-	4	82.5/10/5/2.5
	-3.34	-1.84	-1.99	-	-	10	
	-6.02	-3.28	-3.55	-	-	40	
C (baseline)	-2.383	-0.775	-0.965	-	-	0.5	90/5/3/2
	-2.865	-0.877	-1.05	-	-	2	
	-3.39	-1.01	-1.19	-	-	4	
	-4.59	-1.35	-1.58	-	-	10	
	-8.25	-2.43	-2.86	-	-	40	
D (baseline placebo+drug)	1.85	-1.85	-1.85	0.483	0.046	4	25/25/25/25
E (baseline placebo+drug)	-3.538	-0.447	-1.02	1.318	0.024	0.5	96.5/1.2/1.4/0.9
	-4.882	-0.548	-1.183	1.548	0.030	4	
	-11.815	-1.322	-2.962	3.851	0.072	40	

Table II

Simulation **Parameter estimates**: **Relative bias** (%)
Relative RMSE (%)

Scenario	ω^2	α_1	α_2	α_3	β_1	β_2	ω^2
A	4	-0.30	-0.09	-0.43	-	-	-0.11
		4.45	2.88	2.82	-	-	7.89
	10	-0.08	-0.23	-0.08	-	-	-0.23
		5.14	3.36	5.14	-	-	3.36
	40	0.69	-0.12	0.41	-	-	-0.03
		5.78	3.71	3.68	-	-	8.11
B	4	0.11	0.20	0.26	-	-	-0.42
		4.10	5.29	6.99	-	-	11.39
	10	0.18	0.54	-0.47	-	-	0.12
		5.53	5.22	7.01	-	-	10.82
	40	1.63	-0.03	0.49	-	-	3.01
		7.41	5.80	8.03	-	-	13.29
C	0.5	-0.21	1.15	-2.46	-	-	-8.13
		3.00	7.25	9.27	-	-	30.34
	2	-0.59	0.86	-0.49	-	-	-3.41
		3.75	7.78	8.43	-	-	16.79
	4	-0.04	1.29	-0.84	-	-	-0.44
		4.24	7.48	9.76	-	-	14.39
	10	1.28	0.43	0.49	-	-	3.18
		5.56	6.38	10.10	-	-	14.45
	40	2.04	1.54	1.11	-	-	4.94
		7.93	7.86	9.39	-	-	17.68
D	4	-0.08	0.66	0.70	7.95	-0.84	1.16
		5.41	3.23	3.34	20.83	10.46	8.13
E	0.5	-2.05	-1.31	-1.16	0.11	5.52	-7.46
		5.77	7.99	6.64	14.75	23.37	29.82
	4	-0.21	-0.94	0.79	-2.74	2.62	2.40
		5.66	9.72	6.75	14.98	24.06	14.64
	40	0.84	2.73	-0.44	-1.91	6.93	3.73
		6.90	9.27	7.77	10.86	27.45	15.95

Table III

Simulation		Standard error estimates: Relative bias (%) Relative RMSE (%)					
Scenario	ω^2	***se***(α_1)	***se***(α_2)	***se***(α_3)	***se***(β_1)	***se***(β_2)	***se***(ω^2)
A	4	0.00	0.13	0.18	-	-	-0.67
		0.14	0.15	0.20	-	-	0.87
	10	-0.23	-0.25	0.17	-	-	-1.28
		0.30	0.27	0.20	-	-	1.43
	40	-0.30	-0.10	-0.02	-	-	-0.51
		0.39	0.24	0.19	-	-	0.93
B	4	0.35	-0.36	0.01	-	-	-0.69
		0.44	0.42	0.46	-	-	1.39
	10	-0.29	-0.26	-0.10	-	-	-0.40
		0.49	0.36	0.49	-	-	1.40
	40	-0.73	-0.53	-0.61	-	-	-1.56
		0.96	0.66	1.01	-	-	2.34
C	0.5	-0.17	-0.12	-0.09	-	-	-4.19
		0.43	0.37	0.69	-	-	6.98
	2	0.02	-0.73	0.70	-	-	-2.03
		0.35	0.82	0.98	-	-	3.06
	4	0.01	-0.46	-0.77	-	-	-1.56
		0.32	0.59	1.1	-	-	2.19
	10	-0.50	0.52	-1.23	-	-	-2.01
		0.68	0.66	1.43	-	-	2.76
	40	-1.58	-0.91	-0.28	-	-	-4.27
		1.73	1.09	1.01	-	-	4.99
D	4	-0.02	0.06	-0.36	-0.08	1.27	-0.79
		0.14	0.11	0.37	0.28	1.29	0.97
E	0.5	-1.69	-0.03	0.33	-1.79	-2.48	-5.78
		1.91	0.39	0.51	2.62	2.61	7.42
	4	-0.73	-1.06	0.64	-0.11	3.37	-1.73
		0.89	1.18	0.77	0.99	3.64	2.52
	40	-1.27	-0.63	-0.36	-0.35	-0.43	-2.36
		1.43	0.84	0.66	1.09	2.35	3.39

Table IV

Scenario	ω^2	Median CPU time (s)[a] Parameters	EBE	Standard errors
A	4	29.3	12.0	5.2
	40	27.9	11.2	5.1
B	4	28.5	11.4	5.4
	40	29.0	11.0	5.1
C	0.5	28.6	11.2	5.5
	40	28.7	11.4	5.2
D	4	30.8	7.4	8.4
	0.5	33.1	7.8	8.2
E	4	30.1	9.5	8.3
	40	30.0	11.4	8.2

[a] Laptop DELL D830 2.40GHz configuration was used with Matlab/C++ implementation of SAEM

Figure 1

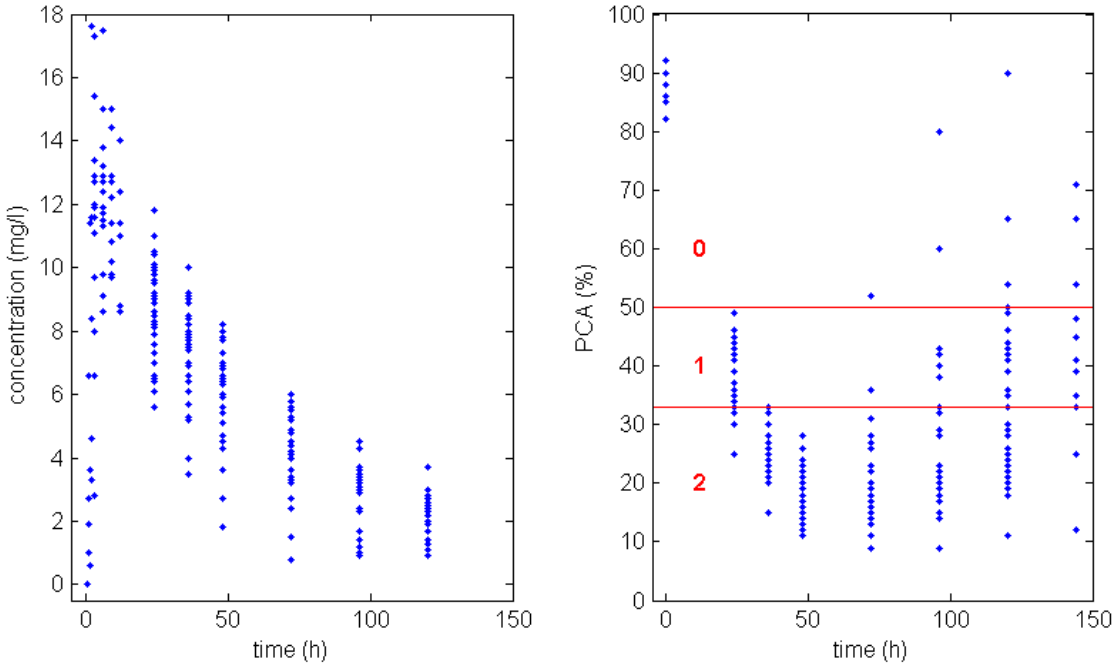


Figure 2A

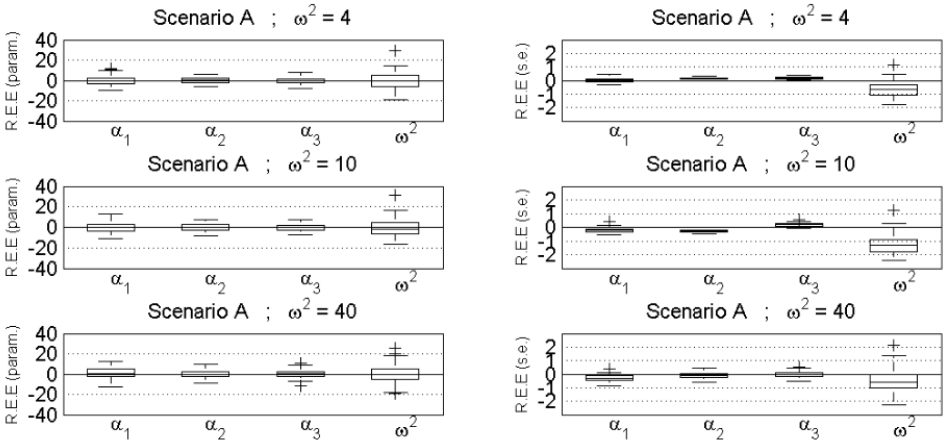

Scenario A ; ω² = 4
R.E.E (param.)
40
20
0
-20
-40
α1
α2
α3
ω²
Scenario A ; ω² = 10
Scenario A ; ω² = 40
Scenario A ; ω² = 4
R.E.E (s.e.)
2
1
0
-1
-2
Scenario A ; ω² = 10
Scenario A ; ω² = 40

Figure 2B

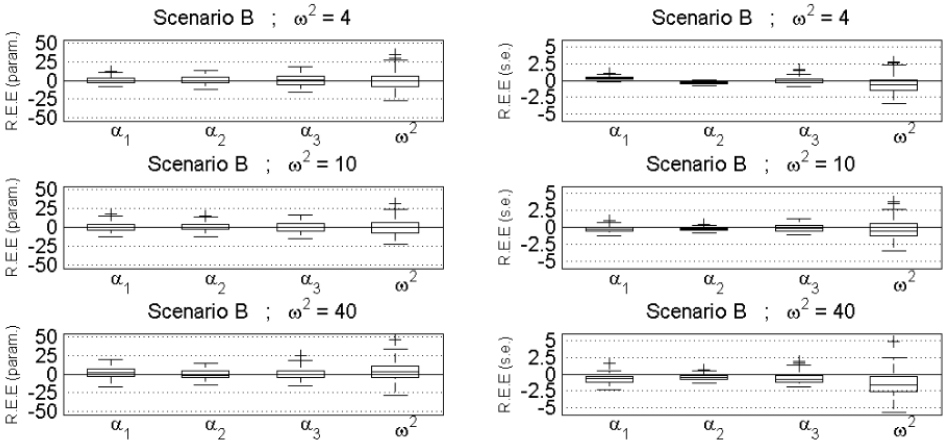

Scenario B ; ω² = 4
Scenario B ; ω² = 10
Scenario B ; ω² = 40
R.E.E (param.)
R.E.E (s.e.)
50
25
0
-25
-50
5
2.5
0
-2.5
-5
α1
α2
α3
ω²

Figure 2C

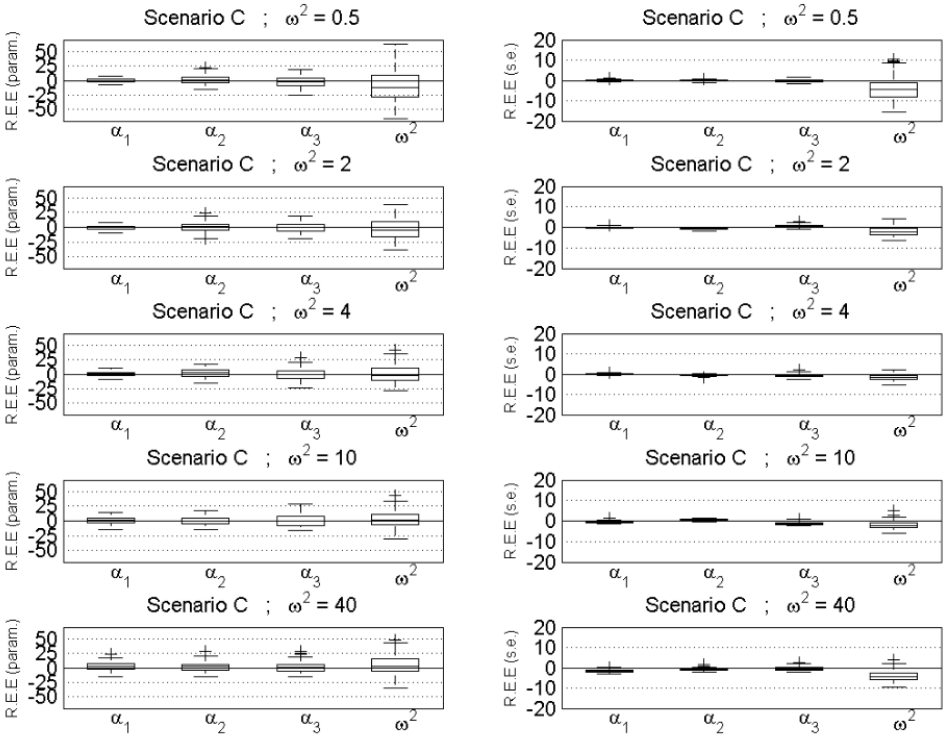

Scenario C ; ω² = 0.5
Scenario C ; ω² = 2
Scenario C ; ω² = 4
Scenario C ; ω² = 10
Scenario C ; ω² = 40
R E E (param.)
R E E (s.e.)
α1
α2
α3
ω²

Figure 2D

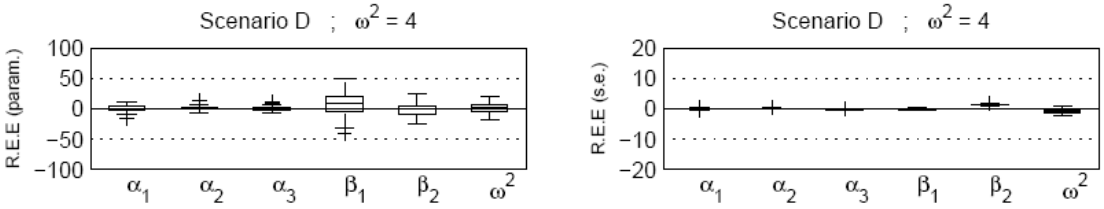

Scenario D ; $\omega^2 = 4$
R.E.E (param.)
100
50
0
−50
−100
α_1 α_2 α_3 β_1 β_2 ω^2
Scenario D ; $\omega^2 = 4$
R.E.E (s.e.)
20
10
0
−10
−20
α_1 α_2 α_3 β_1 β_2 ω^2

Figure 2E

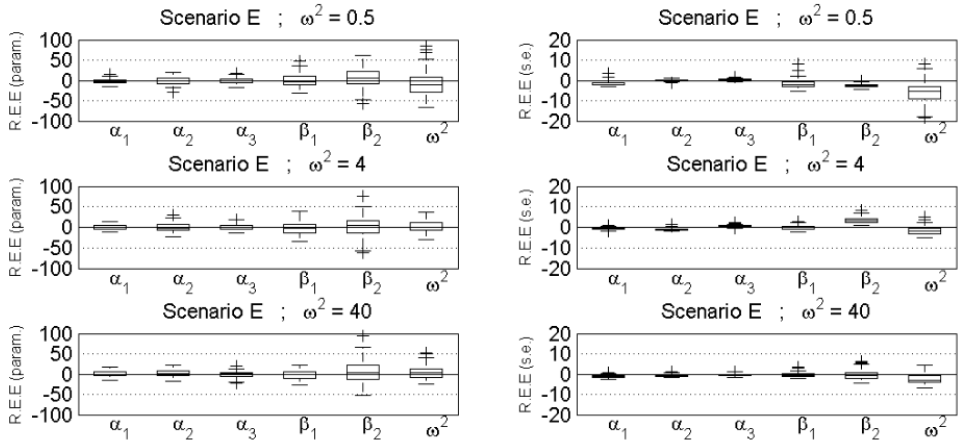

Scenario E ; $\omega^2 = 0.5$
Scenario E ; $\omega^2 = 4$
Scenario E ; $\omega^2 = 40$
R E E (param.)
R E E (s.e.)
100
50
0
-50
-100
20
10
0
-10
-20
α_1 α_2 α_3 β_1 β_2 ω^2

Figure 3

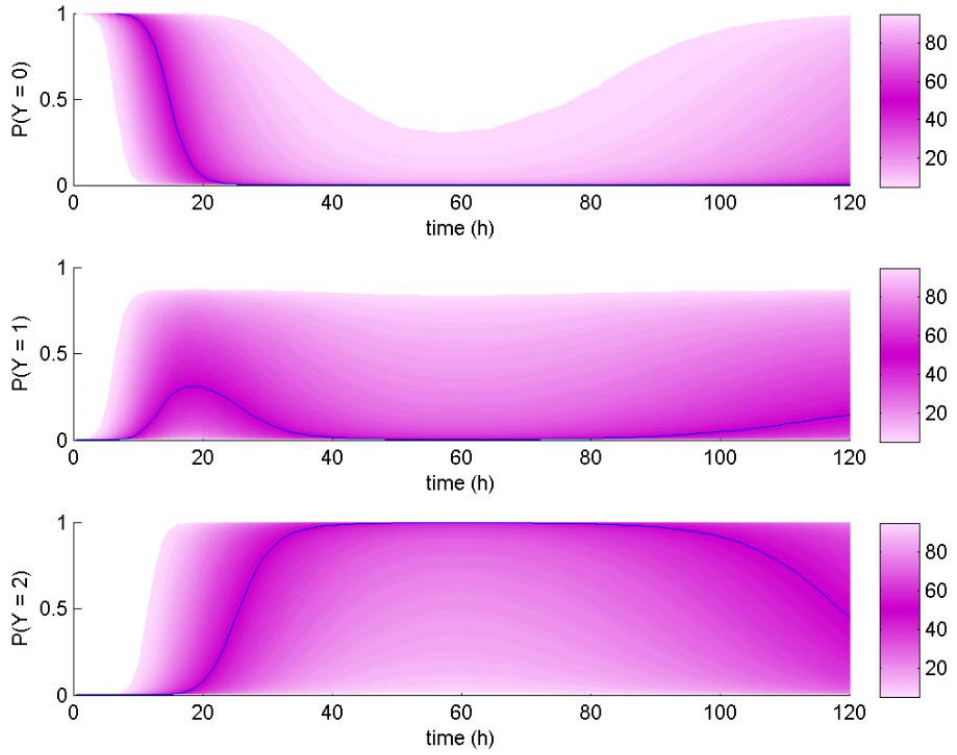
```
$PROBLEM
oral 1 with lag-time, effect compartment and ordered categorical data

$MODEL
COMP = (Qc)
COMP = (Qe)

$PSI
Tlag ka V Cl ke0 alpha1 alpha2 beta

$PK
KA1 = ka
ALAG1=Tlag
k=Cl/V

$ODE
LINEAR
DDT_Qc  = -k*Qc
DDT_Qe  = ke0*Qc-ke0*Qe

Cc=Qc/V
Ce=Qe/V

$CATEGORICAL(0,2)
LOGIT1(Y>=2)=  alpha1 + beta*Ce
LOGIT1(Y>=1)=  alpha1 + alpha2 + beta*Ce

$OUTPUT
OUTPUT1 = Cc
OUTPUT2 = LL1
```

Figure 4

Estimation of the population parameters

		parameter	s.e. (s.a.)	r.s.e.(%)
Tlag	:	0.9	0.19	21
ka	:	1.45	0.54	37
V	:	7.96	0.33	4
Cl	:	0.132	0.0067	5
ke0	:	0.0179	0.001	6
alpha1	:	-10.5	1.6	15
alpha2	:	5.41	0.92	17
beta	:	4.5	0.56	12
omega2_Tlag	:	0.252	0.15	59
omega2_ka	:	0.689	0.46	66
omega2_V	:	0.0478	0.013	28
omega2_Cl	:	0.0797	0.021	26
omega2_ke0	:	0.0229	0.02	87
omega2_alpha1	:	8.74	4.3	49
a	:	0.231	0.047	20
b	:	0.0632	0.0092	15

Figure 5.



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