Assessment of bias in model parameter estimates of continuous time Markov models for categorical data

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Background and Objectives

•Models with Markovian elements where the estimated parameters are rate constants describing the flow of probability over time [1,2,3] are a fairly new way of modeling categorical data with high correlation between consecutive observations.

•These models generally require fewer parameters than ordinary Markov models and do not assume equally spaced observations; there is also less need to know the exact time of transition, i.e. to have observations on all time points.

•When modeling ordered categorical or repeated time to event data and the number of observations is low in one category or only a few individuals have multiple events the LAPLACE method in NONMEM has been prone to bias [4].

•The objective was therefore to assess bias for continuous time Markov models and assess the type I error rate.

Methods and Materials

Two models of the continuous time type Markov model for categorical data formed the basis for the evaluation. The first model, which described EPS events of antipsychotic drugs, had only one parameter for inter-individual variability (IIV) [3] while six IIV parameters were included in the second model characterizing ACR response [1].

a

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EFF=THETA(6)*AUC
K21=THETA(1)*EXP(-THETA(4)*TIME)*EXP(ETA(1))*(1+EFF)
K12=THETA(2)*EXP(-THETA(5)*TIME)*EXP(ETA(1))
K32=THETA(2)*EXP(-THETA(4)*TIME)*EXP(ETA(1))*(1+EFF)
K23=THETA(3)*EXP(-THETA(5)*TIME)*EXP(ETA(1))
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b

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TVK10=THETA(1)*(1+THETA(8)*TIME)
EMX10=THETA(11)*CP/(THETA(12)+ CP)
K10=TVK10*(1+EMX10))*EXP(ETA(1)

TVK01=THETA(2)*(1+THETA(9)*TIME)
EMX01=THETA(15)* CP /(THETA(12)+ CP)
K01=TVK01*(1+EMX01))*EXP(ETA(2)

TVK21=THETA(3)*(1+THETA(9)*TIME)
K21=TVK21*(1+THETA(13)* CP))*EXP(ETA(3)

TVK12=THETA(4)*(1+THETA(9)*TIME)
EMX12=THETA(15)* CP /(THETA(12)+ CP)
K12=TVK12*(1+EMX12))*EXP(ETA(4)

TVK32=THETA(5)*(1+THETA(9)*TIME)
K32=TVK32*(1+THETA(13)*CP))*EXP(ETA(5)

TVK23=THETA(6)*(1+THETA(9)*TIME)
EMX23=THETA(15)* CP /(THETA(12)+ CP)
K23=TVK23*(1+EMX23))*EXP(ETA(6)
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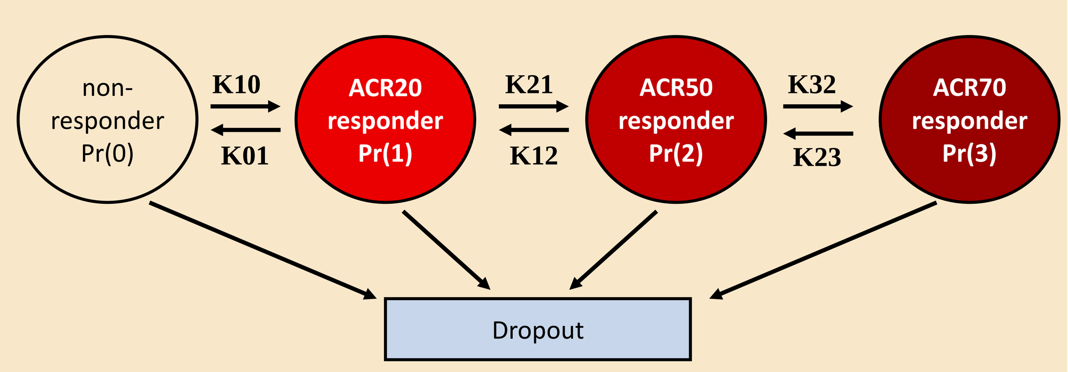

Figure I. Model structure and code excerpt for EPS model (a) and the ACR model (b)

The smaller EPS model (Fig1a) was used to assess the influence of sparse data in 2 scenarios. The typical parameters were changed from estimated values to simulate the two main scenarios 1&2, then the impact of variability was tested by varying inter-individual variability. (Table I) The setups were :

1) Simulate a skewed distribution of occurrences of events; down to ~1-2 % individuals having an event of the least occurring category; (Moderate /Severe EPS).
2) Simulate different number of individuals with any transitions and individuals with more than one transition. In the most sparse simulations not more than ~10 individuals were having more than one transition

Table I. EPS data [3] Number of individuals in the most sparse category, number of individuals that have at least one transition and number of individuals with more than one transition. Observed is from the real data as reference values. N_{tot} =1187

			OMEGA				
	Observed	Scenario	0	0.25	1	4	16
N_{sparse}(%)	46	1	19 (1.6)	21 (1.7)	29 (2.4)	50 (4.2)	80 (6.7)
		2	27 (2.2)	32 (2.6)	87 (7.2)	117 (9.8)	270 (22.7)
$N_{transition}$(%)	180	1	219 (18.5)	238 (20.0)	298 (25.1)	473 (39.9)	738 (62.2)
		2	72 (6.0)	84 (7.1)	121 (10.2)	312 (26.3)	786 (66.2)
$N_{1+ transitions}$ (%)	17	1	10 (0.8)	13 (1.0)	24 (2.0)	67 (5.6)	145 (12.2)
		2	11 (1.0)	16 (1.3)	30 (2.5)	94 (7.9)	229 (19.3)

For the bigger ACR model (N_{ind} = 938)(Fig 1b), the impact of data density on parameter bias was evaluated with parameters obtained from real data. The least supported parameter (K23) had 0.6 % of the data being informative on that parameter.

One-hundred simulations and re-estimations were performed to assess the bias using PsN and the LAPLACIAN estimation method in NONMEM 7. Type I error were assessed by simulation and re-estimation including a false covariate. One-thousand samples were used for this purpose.

Results

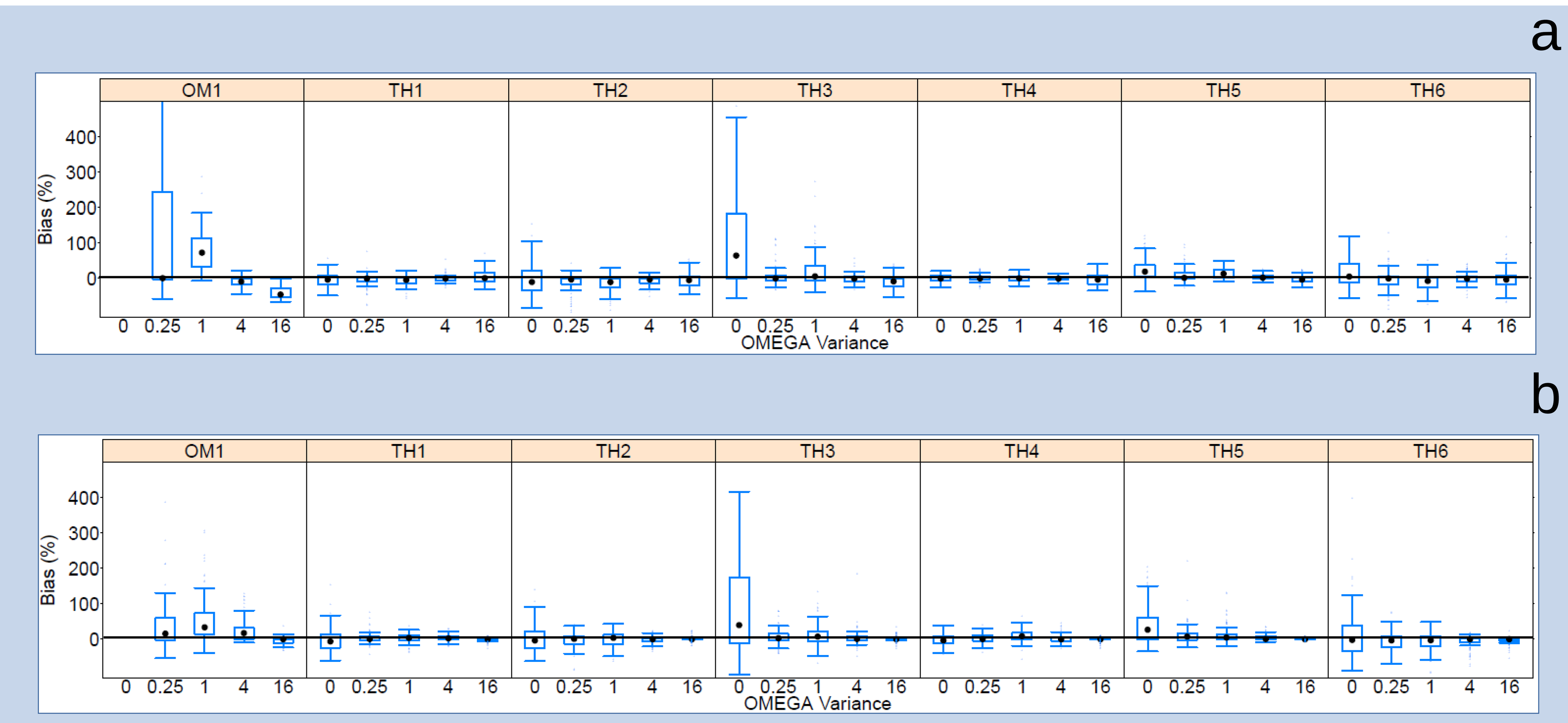

Figure 2. Bias of parameters in EPS model; a: scenario 1, b: scenario 2.

For the EPS model, the highest absolute bias (mean 40%) was seen when the number of individuals in category 3 was low. The mean bias was up to 20% when the number of transitions was low. Bias was highest in IIV estimates and rate constants associated with the most sparse observation type (K23). Bias decreased with increased IIV (Fig. 2) Low IIV or omission of IIV in the model would occasionally yield datasets with very few or no observations in the most sparse category, as a result one or more population parameters were then not estimable.

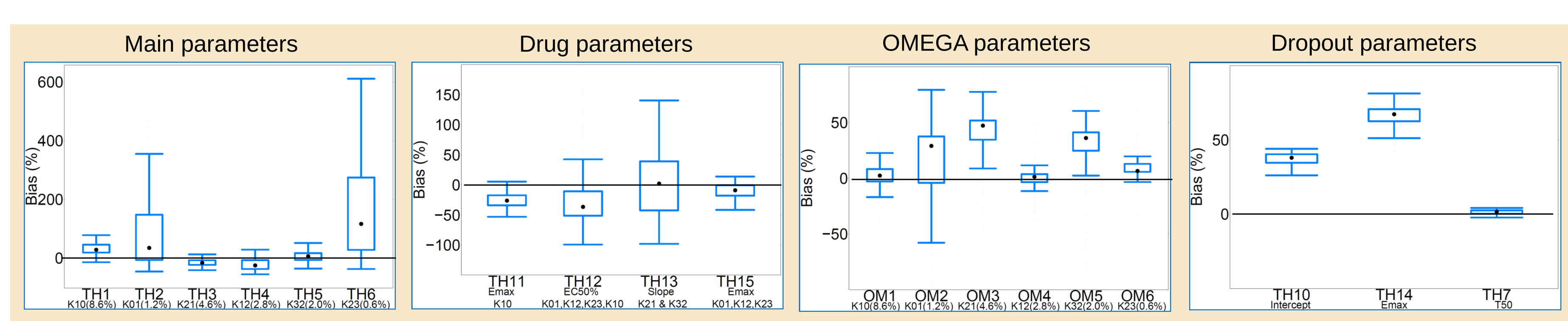

Figure 3. Bias of parameters in ACR model; separated for parameter type. For main parameters (rate constants) and OMEGAs the observed proportion of the individuals having a transition of this type is shown.

The ACR model parameter showed similar relationship between data sparseness and bias. The most biased parameters, K01 and K23, had a bias of 85 and 170 % and were the least supported (1.2 and 0.6 % of individuals having this transition). This finding was also true for IIV estimates (Fig. 3).

Type I error rates were slightly elevated, ΔOFV was 6.7 for 5% error rate and appoximately 10 for 1% error rate.

Conclusions

Bias was seen for continuous type Markov models and seems to be more sensitive to skewed data distributions than low number of transitions. Increasing the variability and thus the number of individuals in the most sparse category and overall number of transitions decreased bias as more information was available with more transitions.

The knowledge of slightly elevated Type I error rates will be used in further model development

References

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Acknowledgements

The computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project p2011064.

Klas Peterssons doctoral studies are sponsored by Janssen Pharmaceutical Companies.