

Covariate model selection in an Alzheimer disease progression model

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Background

Although in the past two decades hundreds of molecules were tested against Alzheimer disease (AD) only five were approved for symptomatic treatment.. Regulatory agencies have recently recognised the importance of modelling & simulation tools to better design clinical studies and consequently decrease the high drug development attrition rate for this indication. Population characteristics are an important determinant in AD studies and therefore, an exhaustive assessment of the relationships between parameters and population covariates would be highly valuable. In this work we compare different stepwise-covariate model building (SCM) approaches to evaluate the impact of population characteristics on treatment response.

Methods

Data: The studies included in the covariate analysis were placebo/background therapy arms from several aggregated AD studies (patient characteristics in table 1, left).

Model: An already existing indirect response model¹ was used as structural model for the covariate analysis (figure 1) where k_{in} is time-dependent and k_{out} a constant term.

Covariate model: Parameter-covariate relationships were assessed using bootstrap SCM and cross-validated SCM routines (figure 2). Tested covariates included age, baseline MMSE (bMMSE) and gender. In addition, different parameter-covariate relationships were considered, including linear, exponential and power functions (table 1). With the exception of the standard SCM, all methods used a linearization procedure and allowed parallel evaluation of the parameter-covariate states. The standard SCM as well as the bootstrap SCM involved forward and backward selection routines, whereas forward selection was used for the cross-validated SCM.

Validation: The final model including all significant covariates was validated with a bootstrap (1000 samples).

Modelling analyses were executed using NONMEM 7.2 and PsN 3.4.2. Data manipulation, as well as graphical and statistical summaries were done in R 3.0.2.

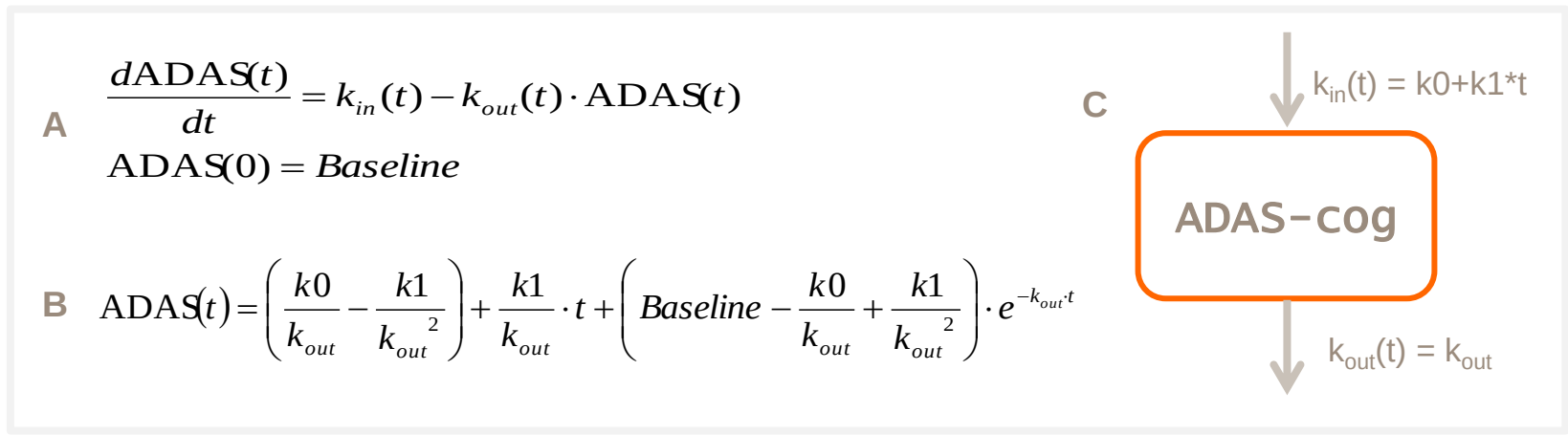


Figure 1: Indirect response model used for the fitting of ADAS-cog scored in mild to moderate AD patients. A) Differential equation describing the ADAS-cog score in the compartment where *Baseline* is the initial condition 2) Analytical solution of equation 1, used in the covariate analysis C) Schematic view of the model, where k_{in} is time-dependent and k_{out} is constant

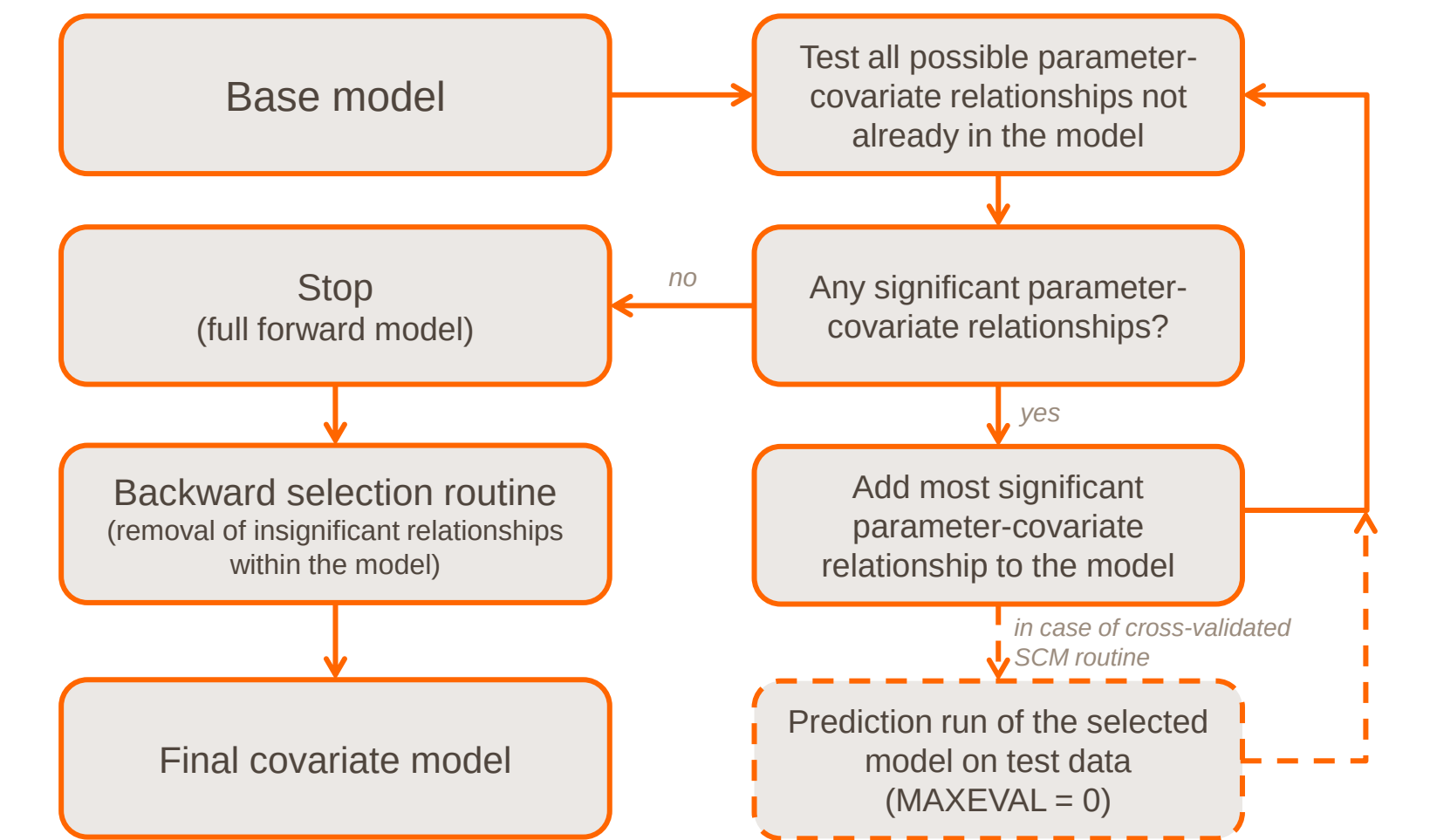


Figure 2: Stepwise covariate model routine used for the analysis of the covariates. Both the standard SCM and the bootstrap SCM were performed with forward and backwards steps. Cross-validated SCM was based on forward inclusion steps only.

Table 1: Left table shows the different parameters along with the covariates and tested states.				
Patient characteristics (10 studies, n=3343)	Mean (sd)	Parameters	Covariates	States
Age (y)	74 (8.2)	k1	Age	Linear
Gender (% female)	55	k0	Gender	Exponential
Baseline MMSE (points)	21 (3.7)	kout	Baseline MMSE	Power
ADAS-cog (points)	24 (11)	Baseline		

Results

Standard SCM: Eight different parameter-covariate relationships were chosen by this method (not shown here) consisting of both age and bMMSE for each of the parameters.

Bootstrap SCM: This method showed a distribution of the parameters included in the final model centred around 7 (Figure 3, top left), similarly to the standard SCM. Of all final model relationships, only 5 relationships were included in the final model for 80+% of the time: Baseline-bMMSE, k0-bMMSE, k1-bMMSE, kout-bMMSE, k1-AGE (Figure 3, top right).

Cross-validated SCM: The optimal number of steps was found to be 4, after which the decrease in objective function was not significant ($P > 0.05$), or highly variable (figure 4, top). During the first 4 steps, 4 different parameter-covariate relationships were selected: Baseline-bMMSE, k0-bMMSE, k1-bMMSE, kout-bMMSE (figure 4, bottom).

In either method, both age and gender did not seem to have a significant effect on model performance, the only exception being the effect of age on k1 as seen in the bootstrap SCM results.

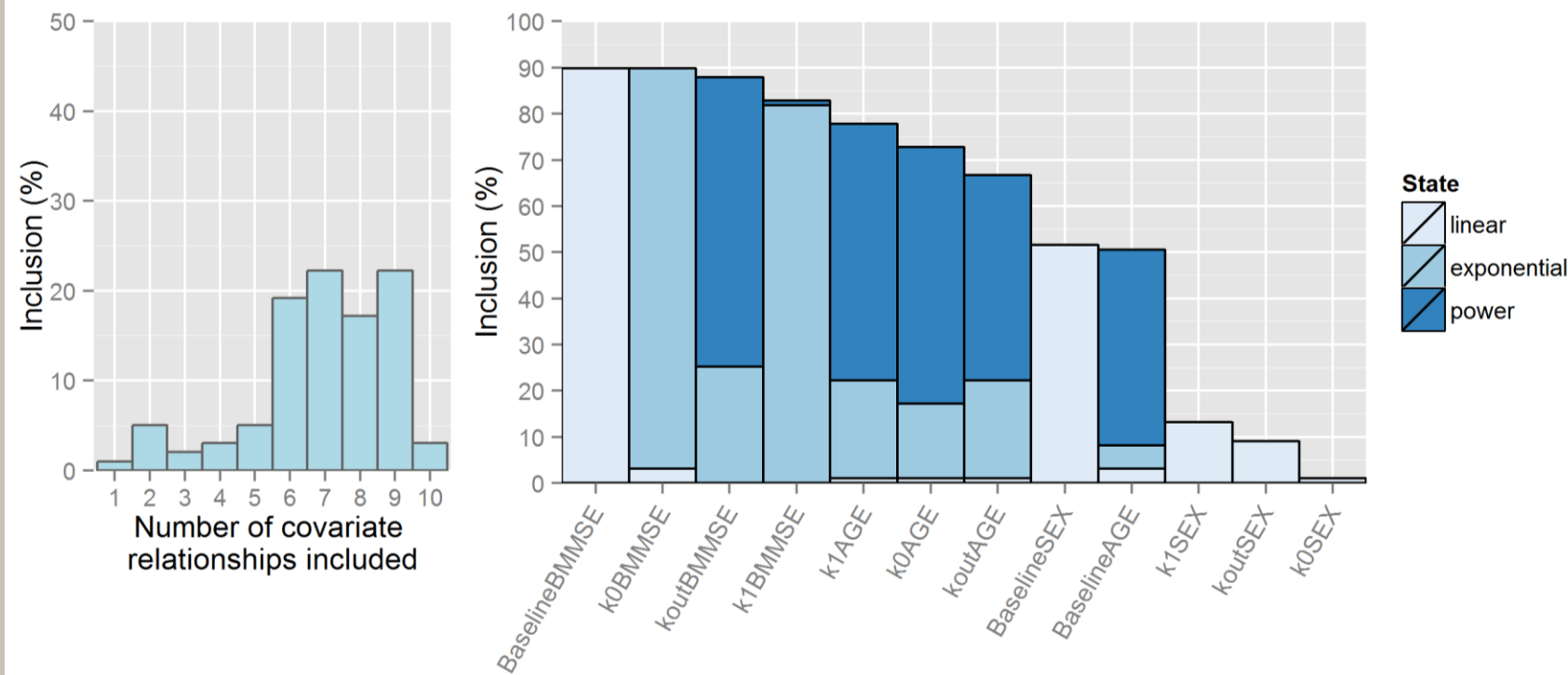


Figure 3: Bootstrap SCM results (100 samples). Left: distribution of the number of parameter-covariate relationships included into each of the final SCM models. Right: inclusion percentage of the various relationships grouped by parameter-covariate combinations.

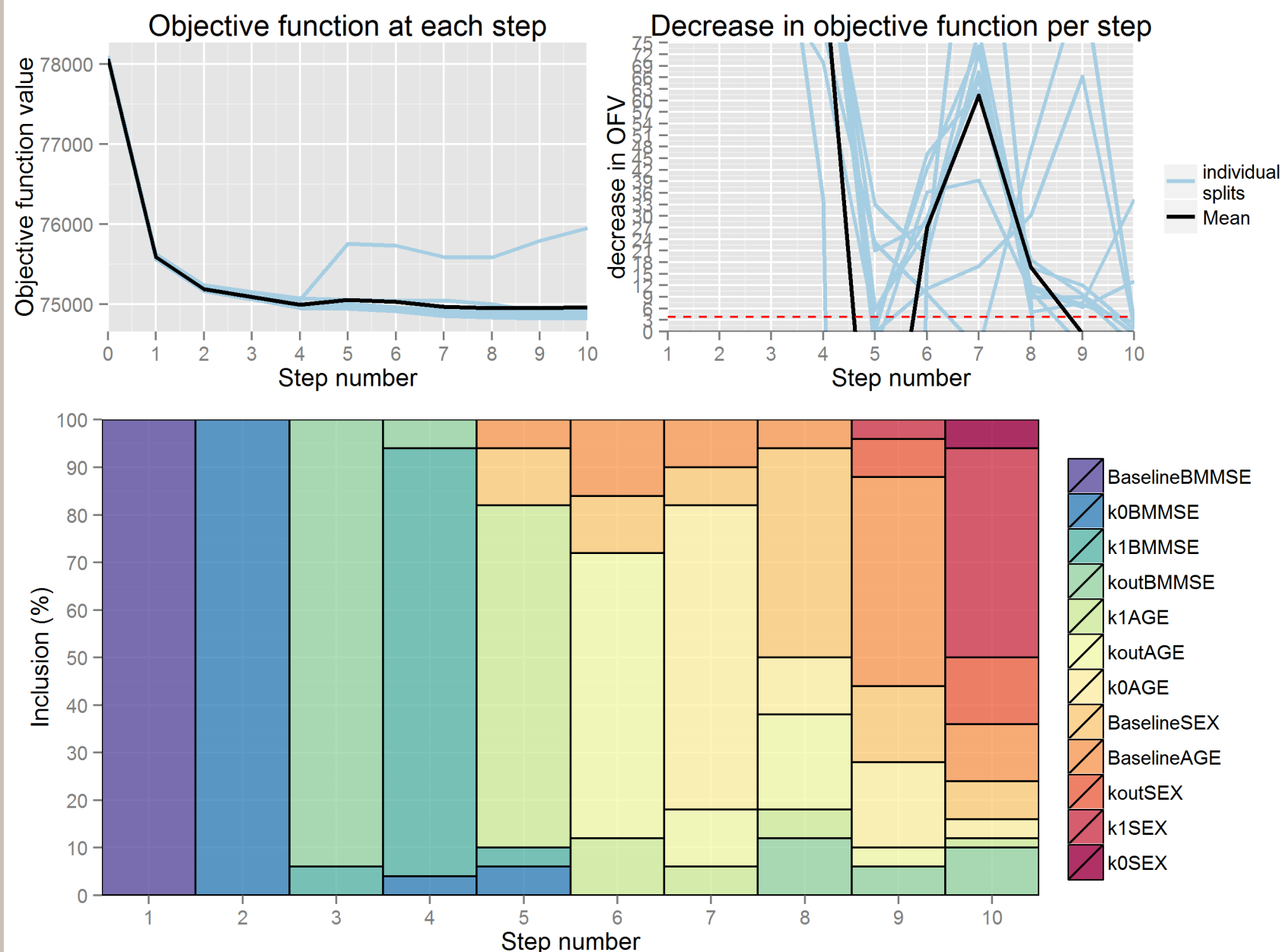


Figure 4: Cross-validated SCM results (10 splits, 5 groups). Top left: objective function value of the model on the test dataset for each of the steps. Top right: decrease in the objective function after each step. Each blue line represents one split, the black line shows the mean OFV, whereas the red dashed line represents $P < 0.05$. Bottom: parameter-covariate relationship inclusion percentage at each step, different states for the same parameter-covariate pair are grouped together.

Table 2: Final model including the identified parameter-covariate relationships. Bootstrap was performed using 1000 samples. bMMSE_i represents individual bMMSE values.

	Parameter	Final model estimate	Bootstrap Mean (90% CI)	Relation
Population parameters	Baseline	21.20	21.17 (20.99 - 21.37)	
	k0	0.080	0.081 (0.073 - 0.089)	
	k1	0.001	0.001 (0.001 - 0.001)	
	kout	0.003	0.003 (0.002 - 0.003)	
Covariate effects	bMMSE - Baseline	-0.079	-0.079 (-0.081 - -0.077)	$1 + \theta_{BaselinebMMSE} \cdot (bMMSB_i - 21)$
	bMMSE - k0	-0.072	-0.074 (-0.088 - -0.059)	$\exp(\theta_{k0bMMSE} \cdot (bMMSB_i - 21))$
	bMMSE - k1	-0.152	-0.146 (-0.181 - -0.117)	$\exp(\theta_{k1bMMSE} \cdot (bMMSB_i - 21))$
	bMMSE - kout	1.770	1.750 (1.203 - 2.350)	$(bMMSB_i/21)^{\theta_{koutbMMSE}}$
Variability	IIV Baseline	0.076	0.076 (0.072 - 0.080)	exponential
	IIV k0	0.866	0.860 (0.753 - 0.960)	exponential
	IIV k1	1.680	1.717 (1.411 - 2.022)	exponential
	IIV kout	0.525	0.514 (0.381 - 0.651)	exponential
	Residual error	3.300	3.294 (3.247 - 3.346)	proportional

Conclusion

Both the bootstrap SCM and the cross-validated SCM indicate that **bMMSE** affects all model parameters. In addition the bootstrap SCM points to a covariate effect of **age**, most frequently on k1. In fact, age is chosen 95% of the time as a covariate on at least 1 parameter during the bootstrap. However, when this relationship is added, the cross-validated SCM shows no actual improvement of the model's predictive capabilities in the test datasets. Therefore, age has not been included as a covariate in the final model.

In contrast to epidemiological evidence of incidence difference in the male and female population², **gender** showed no significant effect on model performance when either fitting or predicting, and was therefore not included either. Final model is shown in table 2.

Overall the different methods have decreased the number of parameter-covariates relationships in the final model compared to the standard SCM in a time efficient manner, this will allow a wider range of covariates to be tested.

References

- Gomeni, R. et al. Modeling Alzheimer's disease progression using the disease system analysis approach. *Alzheimer's & Dementia* 8, 39–50 (2012).
- Carter, C. L. et al. Sex and Gender Differences in Alzheimer's Disease: Recommendations for Future Research. *Journal of Women's Health* 21, 1018–1023 (2012).