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PROPOFOL BREATH MONITORING AS A POTENTIAL TOOL TO IMPROVE THE PREDICTION OF INTRAOPERATIVE PLASMA CONCENTRATIONS.

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1. Introduction & Objectives

Monitoring of drug concentrations in **breathing gas** is routinely being used to individualize drug dosing for the inhalation anesthetics. For **intravenous anesthetics** however, no decisive evidence in favor of breath concentration monitoring has been presented up until now. At the same time, questions remain with respect to the performance of currently used plasma PK models, implemented in **target-controlled-infusion (TCI) systems**. In this study we set out to investigate whether breath monitoring of propofol could improve the **predictive performance** of currently applied TCI models and to compare the feasibility of using $IPRED_{breath}$ and $IPRED_{plasma}$ as driving force in a model to predict propofol induced changes in BIS.

2. Patients & Methods

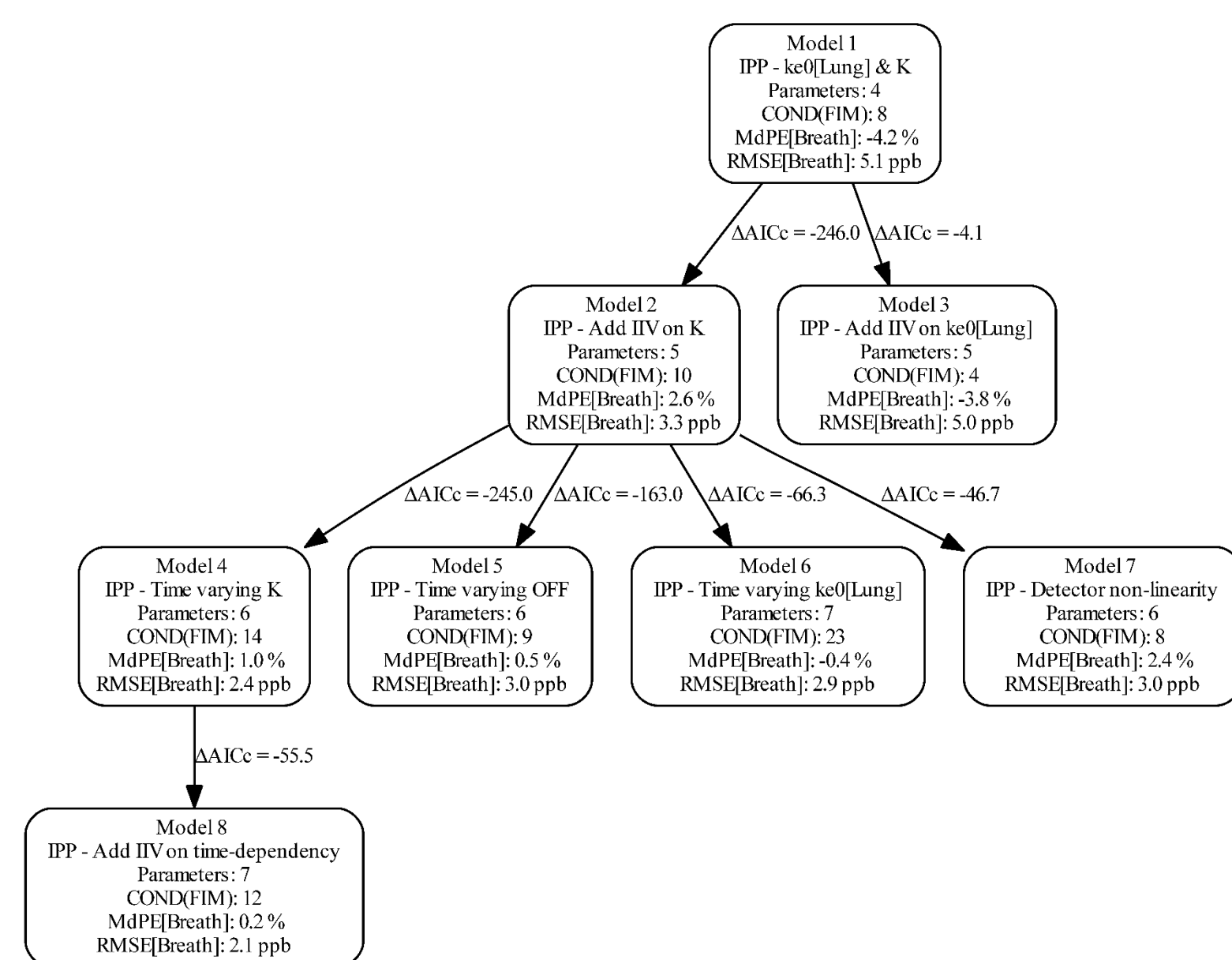
20 healthy volunteers received 0.4 mg.kg⁻¹.min⁻¹ i.v. propofol for ten minutes followed by a 20 min recovery period. Afterwards, TCI based on Schnider et al.^a was used to achieve target plasma concentrations of 2, 3, 4, and 5 µg.ml⁻¹.

After data reduction and median filtering the dataset included a median of 22 arterial plasma propofol concentrations, 22 propofol breath concentrations and 30 BIS measurements per subject.

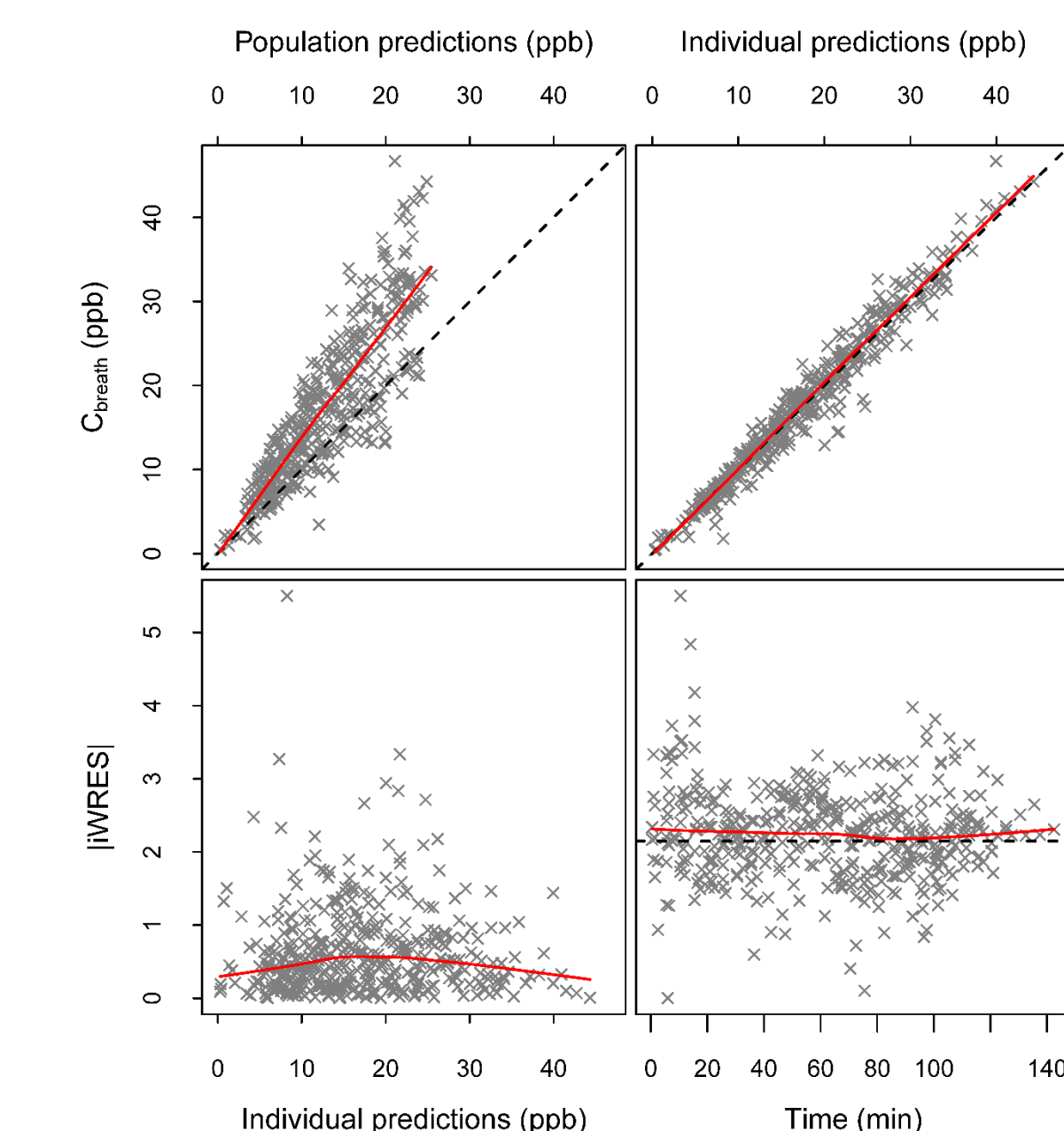
NONMEM® (version 7.3) was used to fit different PKPD models to the dataset using, as a starting point, the individual post-hoc PK parameters from the Eleveld PK model^b.

3. Results & Discussion

1. Model development for C_{breath}



- Final model: $IPRED_{breath} = C_e \times K_i \times e^{Slope_i \times t}$
- An exponential time correction was introduced to correct for a time-dependent bias in the CWRES versus time. Physiological phenomena, such as venous-arterial mixing and/or detector-related issues might cause this time dependency and should be further investigated.



- GOF plot for the final model (model 8). Parameter estimates were obtained using the IPP approach. The top-left panel shows the apparent bias in the *a priori* PK model which is passed on to the population predictions for the breath concentrations (C_{Breath}) of the final breath model.

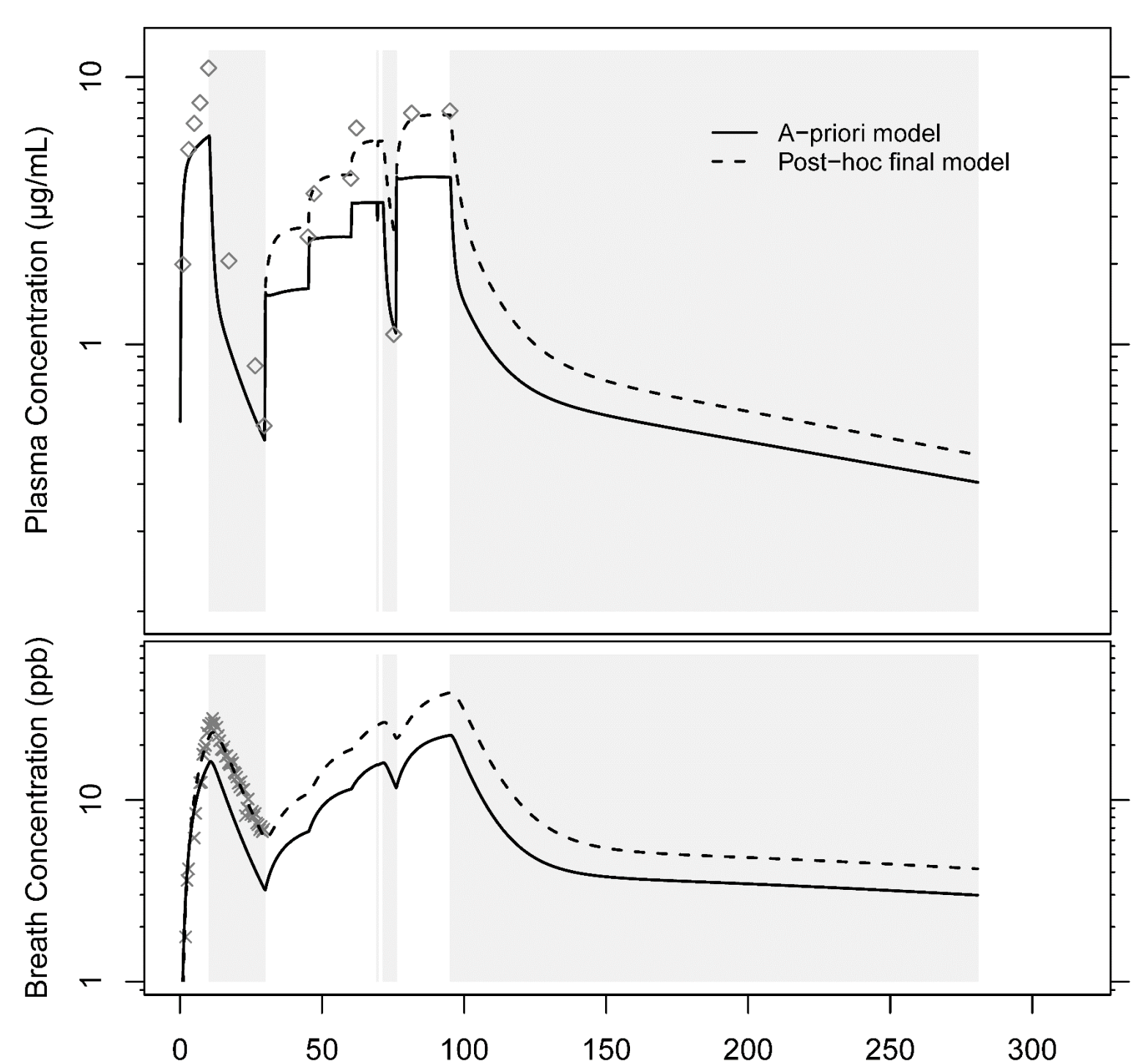
2. Final models for C_{breath} & BIS

Parameter	Model 8		BIS-f(C_e)		BIS-f($IPRED_{breath}$)	
	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	RSE (%)
$Ke_{0, lung}$ (min ⁻¹)	0.152	5.7	0.152	5.7	0.146	9.0
$Ke_{0, BIS}$ (min ⁻¹)			0.107	12.3		
K (ppb mL µg ⁻¹)	3.56	6.7	3.56	6.7	3.81	9.0
$Slope$ [ppb mL (µg min ⁻¹) ⁻¹]	0.022	8.8	0.022	8.8	0.017	20.7
BL_{BIS}			94.3	1.0	95.0	1.0
E_{max}			80.9	7.3	77.6	5.6
EC_{50}			2.71 µg/mL	11.0	12.4 ppb	8.2
γ			2.43	20.0	2.49	18.6
IV_K (%) ^a	23.7	37.6	23.7	37.6	25.8	37.4
IV_Slope (%) ^a	40.9	38.2	40.9	38.2	30.8	50.0
IV_E_0 (%) ^a			0.716	30.0	0.656	29.1
IV_EC_{50} (%) ^a			28.7	25.9	25.9	42.5
$\sigma_{BIS, proportional}$ (%) ^b	21.6		21.6		21.6	
$\sigma_{BIS, additive}$ (%) ^b	11.7		11.7		10.3	
$\sigma_{BIS, additive}$ (ppb) ^b	0.982		0.982		1.40	
$\sigma_{BIS, additive}$ (%) ^b			0.47		0.45	

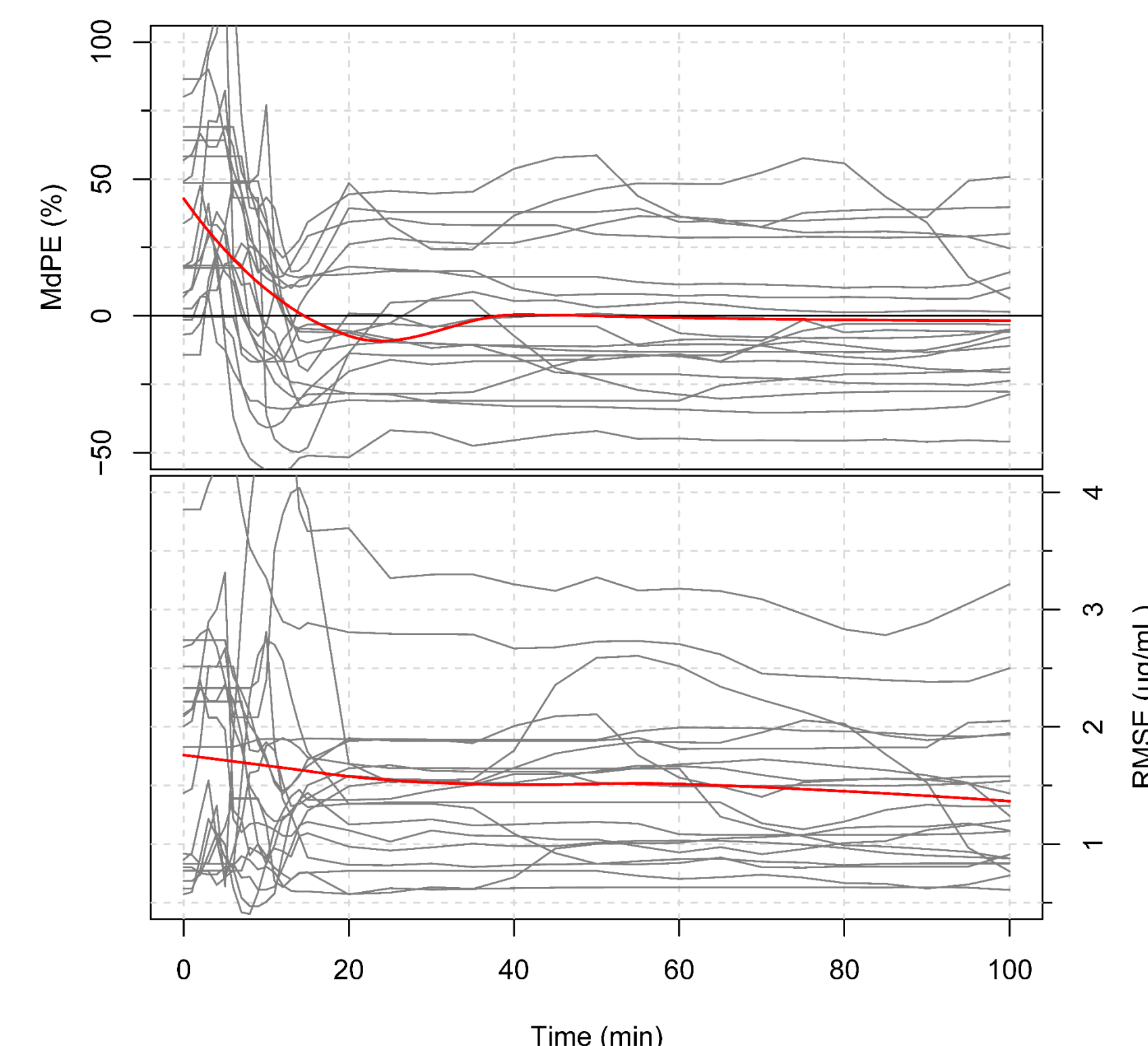
^a CV(%) is calculated according to: $\sqrt{CV^2 - 1} \times 100\%$
^b Residual unexplained variability expressed as a standard deviation
^c Residual unexplained variability expressed as a relative standard deviation
^d IV expressed as a variance in logit domain

- Final parameter estimates and SEs for the final model (model 8) and for 2 models evaluating BIS as a function of the modelled plasma effect-side concentrations (C_e) and predicted breath concentrations ($IPRED_{breath}$), respectively.
- C_{breath} could serve as a surrogate to the predicted effect site concentrations which are frequently used in the clinic to predict BIS. In this respect, the EC_{50} of 12.4 ppb might provide an alternative measurable target to the established hypothetical effect compartment EC_{50} of 2.71 µg.mL⁻¹.

3. Bayesian forecasting to predict intraoperative propofol plasma concentrations



- A representative individual showing the C_{plasma} (grey diamonds) and model predictions for the a-priori model (solid line) and the *post hoc* prediction of our final model (dashed line).
- The Bayesian adaptation of the *a priori* model was implemented 30 min into the treatment, using the first 30 min of breath concentration measurements only. During this process the model was blinded for the C_{plasma} . Grey shaded areas show periods when no drug was infused.



- Change in predictive performance (estimated using 4-fold X-validation) as a function of the time-frame in which C_{breath} are monitored.
- The MdPE and RMSE for the different individuals in our study are shown with a grey solid line. The solid red lines depict the overall change in predictive performance in our study population.
- MdPE decreased from 42.8% to -1.05% and RMSE decreased from 1.63 to 1.39 µg.mL⁻¹ (i.e. 15% reduction)

4. Conclusions

- On-line measurements of exhaled propofol concentrations improve the predictive performance of the current state-of-the-art pharmacokinetic model and allow a more stringent control on the targeted plasma concentrations during TCI guided general anesthesia.
- Individually measured exhaled propofol concentrations provide an easily measurable target which is closely correlated to the drug's cerebral effects.