



Comparison of seven NLMEM approaches to test for drug effect using real placebo data

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Objectives

Assess **7 NLMEM approaches** in the same framework using real ADAS-cog placebo data, in the context of drug effect assessment using balanced 2 arms design: standard selection (**STDs**), relative STDs (**RSTDs**), corrected likelihood ratio test¹ (**cLRT**), randomized cLRT (**rcLRT**), model averaging across drug models² (**MAD**) or across placebo and drug models (**MAPD**), and individual model averaging³ (**IMA**).

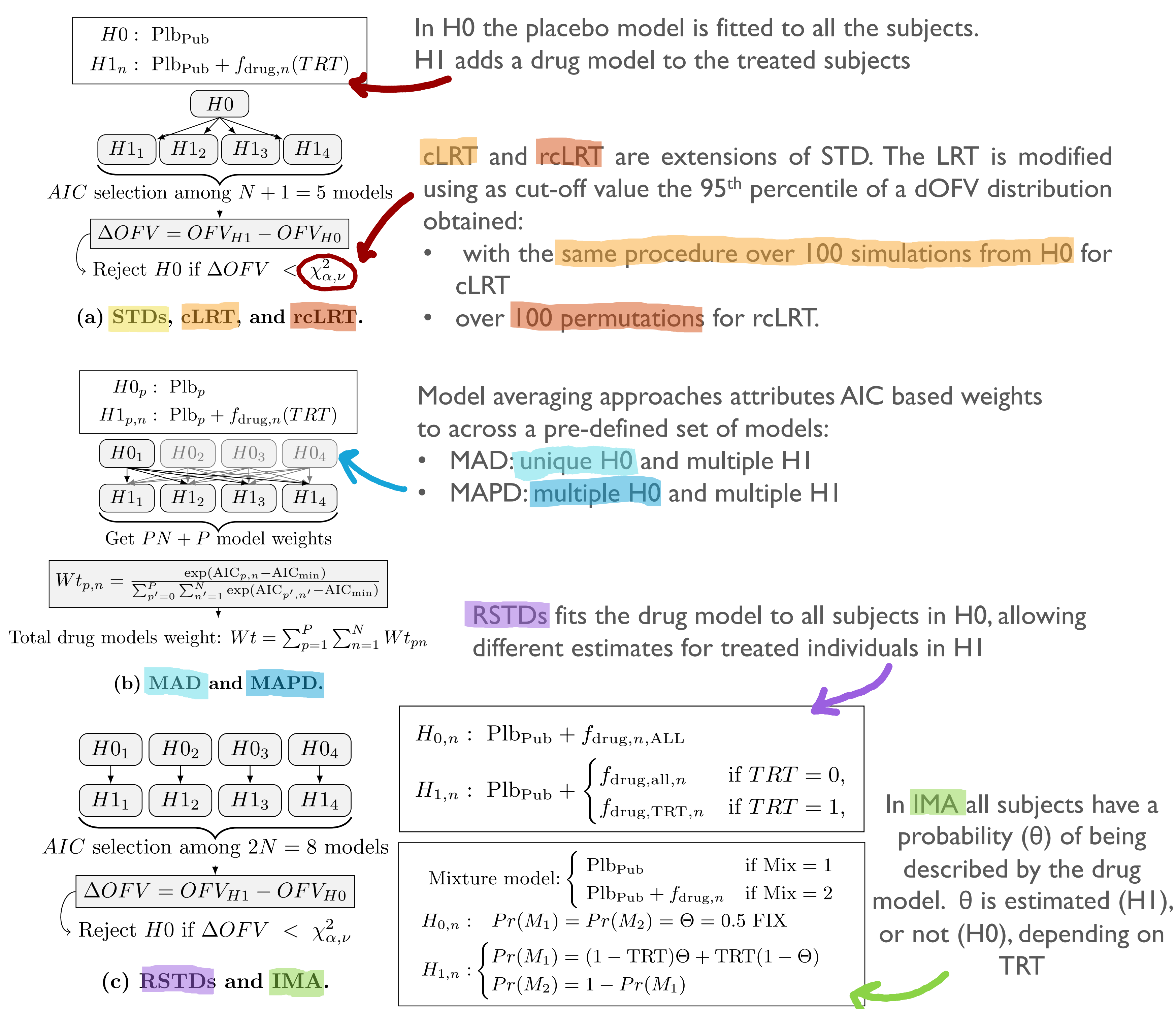


Figure 1: Description of the 7 NLMEM approaches

Methods

Methods assessment

The **type I error** was assessed randomizing artificially ($n=100$, 1:1) patients to the placebo ($\text{TRT}=0$) or the treatment ($\text{TRT}=1$) arm. It was computed as the frequency with which the best alternative hypothesis (H_1), according to the AIC, was significant ($\alpha=0.05$) relative to the null hypothesis (H_0) using the LRT. 4 drug effect models were used: offset with and without IIV, disease modifying with and without IIV (see QR code for equations). For the model averaging approaches it was reported as average of the total weight of the drug models.

Power and **accuracy** in drug estimates computed via RMSE were assessed for the methods with controlled type I error, after addition of a simulated ($n=100$) drug effect to the individuals randomized to $\text{TRT}=1$. 8 cases were simulated using an offset or a disease modifying drug model, with or without 30% IIV, for a low (2) and a high (8) typical effect.

Data and published model⁴

ADAS-cog scores from 817 untreated patients modelled as continuous data⁴.

$$\begin{aligned} \text{ADAS}_{\text{cog},i}(t) &= \text{ADAS}_{\text{cog},i}(0) + \alpha_i t + \varepsilon \\ \text{ADAS}_{\text{cog},i}(0) &= a_i + b_i \cdot \text{MMSE}_i(0) \\ \alpha_i &= f(\text{Cov}_i, \Theta, \eta_i) \end{aligned}$$

Equation

Placebo models The published model⁴ (Plb_{pub}) was used for all approaches but MAPD for which 4 pre-defined placebo models were also considered (see QR code for equations).

Results

Table 3: Type I error per approach ($n=100$)

Approach	Placebo model	Type I error (%)
STDs	Published	100
RSTDs	Published	17
cLRT	Published	100
rcLRT	Published	6
MAD	Published	100
MAPD	Pre-defined set	100
IMA	Published	6

2.5-97.5th percentiles (1.6-11.3) of a binomial distribution for a probability of success of 5% on 100 replicates

Controlled type I error

Table 4: Power and RMSE for rcLRT and IMA, for the eight drug effect scenario ($n=100$)

Simulation model	Typical effect	rcLRT		IMA	
		Power (%)	RMSE	Power (%)	RMSE
Offset	2	100	0.26	99	0.84
Offset IIV	2	100	0.42	99	0.84
DM	2	6	0.32	63	1.23
DM IIV	2	6	0.32	67	1.29
Offset	8	100	0.26	100	0.48
Offset IIV	8	100	0.29	100	0.41
DM	8	100	0.55	100	0.57
DM IIV	8	100	0.57	100	0.61

Discussion and conclusion

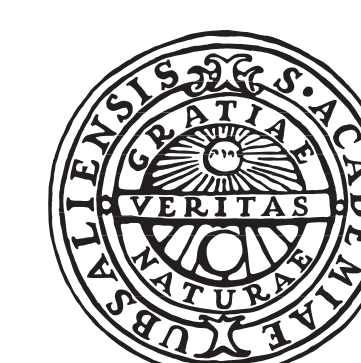
- Only rcLRT and IMA showed good control type I error
- All other methods were sensitive to placebo model misspecification and/or multiple testing
- rcLRT had superiority in accuracy, but IMA was superior for power.

Table 5: Robustness of each approaches towards type I inflation factors.

Approaches	Placebo model misspecification	Multiple testing
STDs	-	-
RSTDs	(+)	-
cLRT	-	+
rcLRT	+	+
MAD	-	+
MAPD	-	+
IMA	+	-

¹Buatois S, Ueckert S, Frey N, Retout S, Mentré F. cLRT-Mod: An efficient methodology for pharmacometric model-based analysis of longitudinal phase II dose finding studies under model uncertainty. Stat Med. 2021 May 10;40(10):2435-2451. doi: 10.1002/sim.8913. Epub 2021 Mar 2. PMID: 33650148. ²Aoki Y, Røshammar D, Hamrén B, et al. Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection. J Pharmacokinet Pharmacodyn. 2017; 44:581-597. https://doi.org/10.1007/s10928-017-9550-0 ³Chasseloup E, Tessier A, Karlsson MO. Assessing Treatment Effects with Pharmacometric Models: A New Method that Addresses Problems with Standard Assessments. AAPS J. 2021 May 3;23(3):63. doi: 10.1208/s12248-021-00596-8. PMID: 33942179; PMCID: PMC8093168. ⁴Ito K, et al. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. Alzheimers Dement. J. Alzheimers Assoc. 7, 151-160 (2011).

More equations



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Table 1: Drug effect models and equations.

Drug effect model (abbreviation)	Equation
Offset model (with/without IIV)	$\theta + \eta_i$
Disease modifying (with/without IIV)*	$\alpha_i(1 - (\theta + \eta_i))$

*For the power simulations and fit, the disease modifying model was the following: $\frac{\theta + \eta_i}{36} t$ to avoid any placebo model assumptions in the simulation step.

Table 2: Alternative placebo models for MAPD, derived from the published model

Modified component	Modification	dOFV
Statistical model	Boxcox transformation*	-60
	t-distribution*	-57
	IIV on RUV	-60
Structural model	Time exponential	-23

*The change in the IIV distribution was applied to the baseline IIV

Link to the model publication:

<https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1016/j.jalz.2010.03.018>