Statistical Methods for Hierarchical Crossover Data With Pain Related PRO's

2025 GRBIO Retreat

Pau Esteve Bricullé

Director: Nuria Perez Alvarez
Co-director: Guadalupe Melis Gómez
Tutor: Jimena Fernández Carnaedo

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Outline

1. Introduction
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3. Methodology
4. Results (WIP)
5. Conclusions
6. References

How I Got Here

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Treball Final Master

Models lineals d'efectes mixtes:
Aplicació i avaluació en estudis clínics

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BCNpeptides

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MOB-02
Clinical Trial

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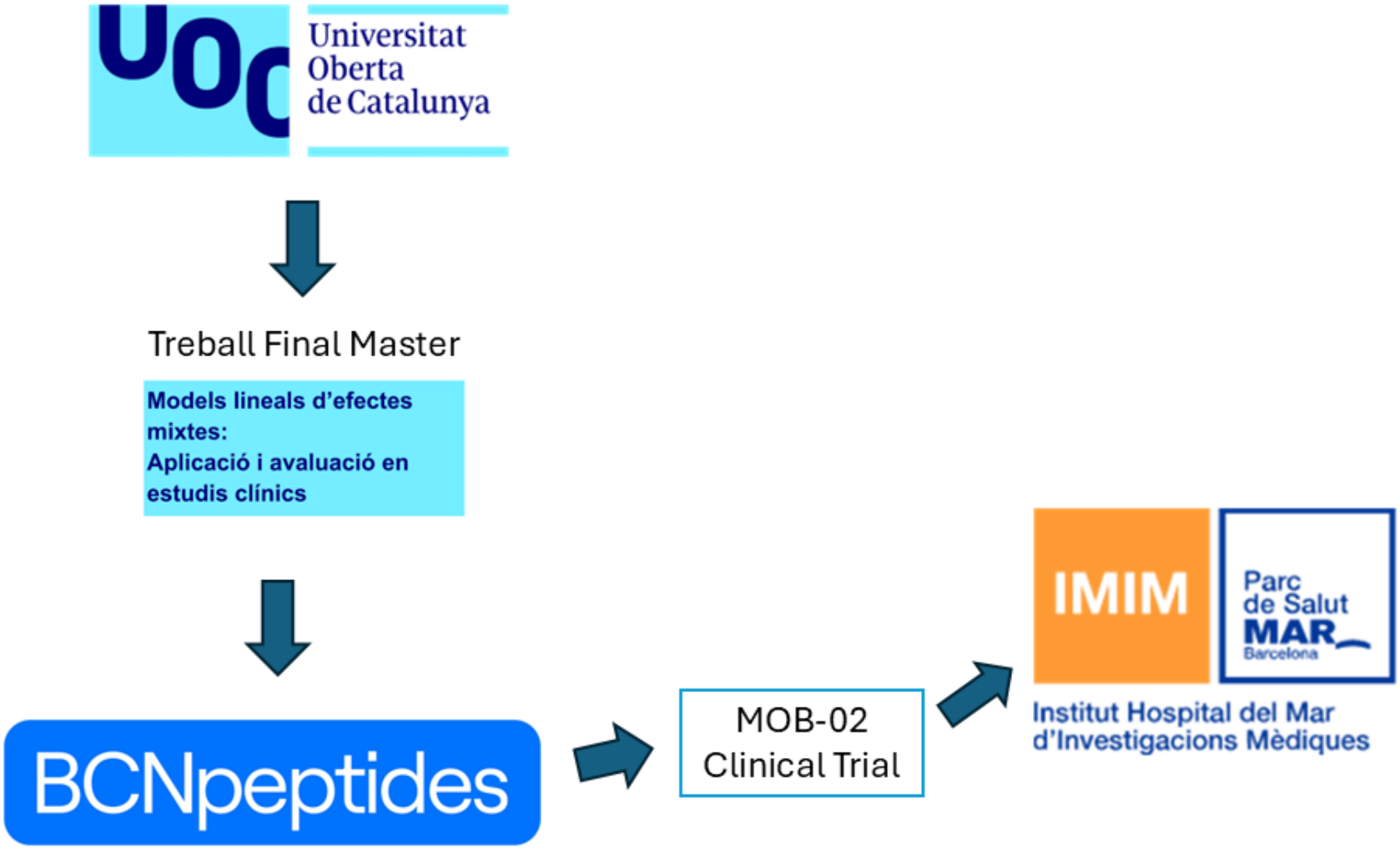

How I Got Here

Universitat Oberta de Catalunya

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Models lineals d'efectes mixtes: Aplicació i avaluació en estudis clínics

Klaus Langohr

UPC

IMIM

Parc de Salut MAR Barcelona

Institut Hospital del Mar d'Investigacions Mèdiques

MOB-02 Clinical Trial

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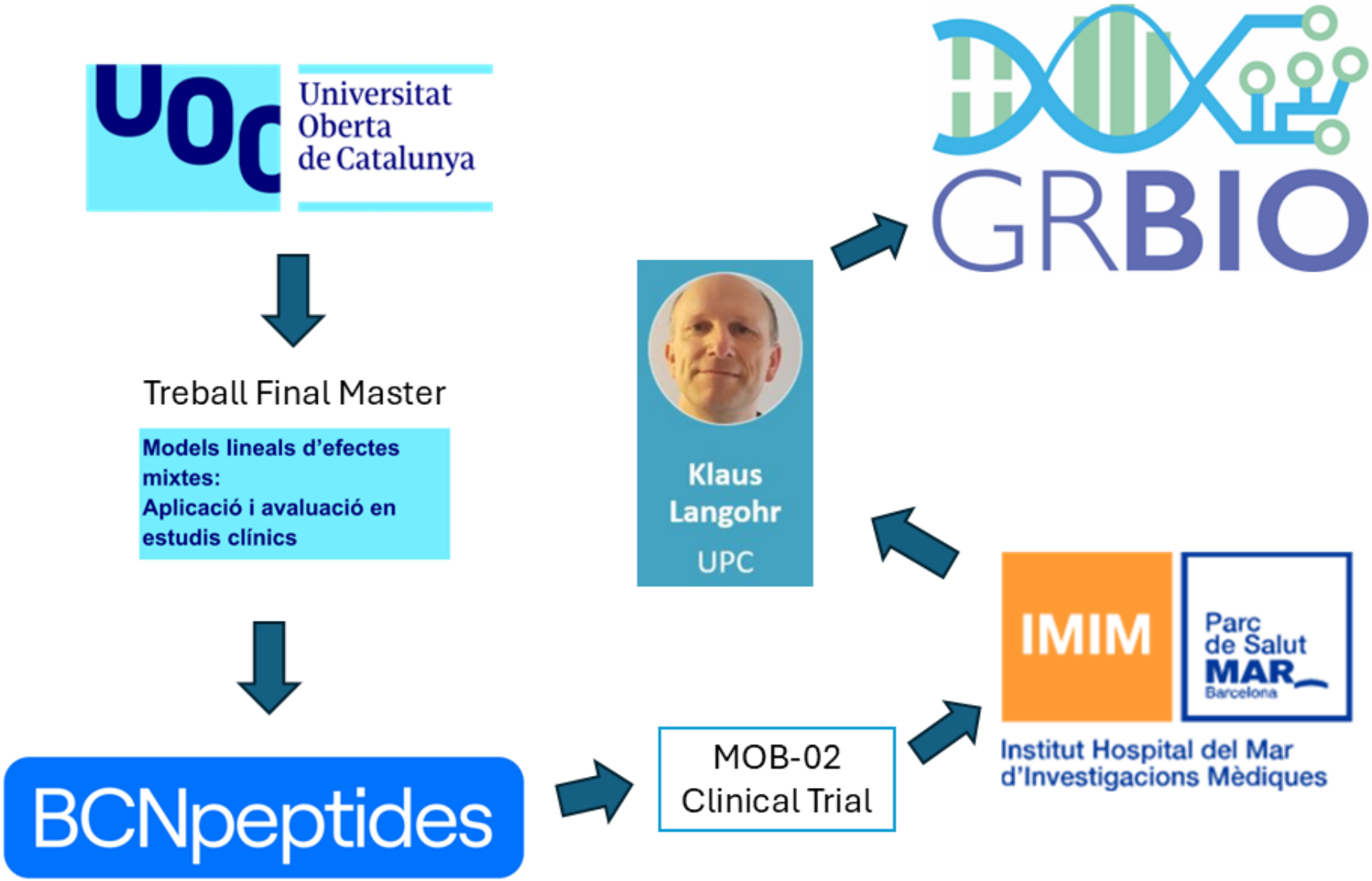

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MOB-02 Design: Transient Pain Clinical Trial

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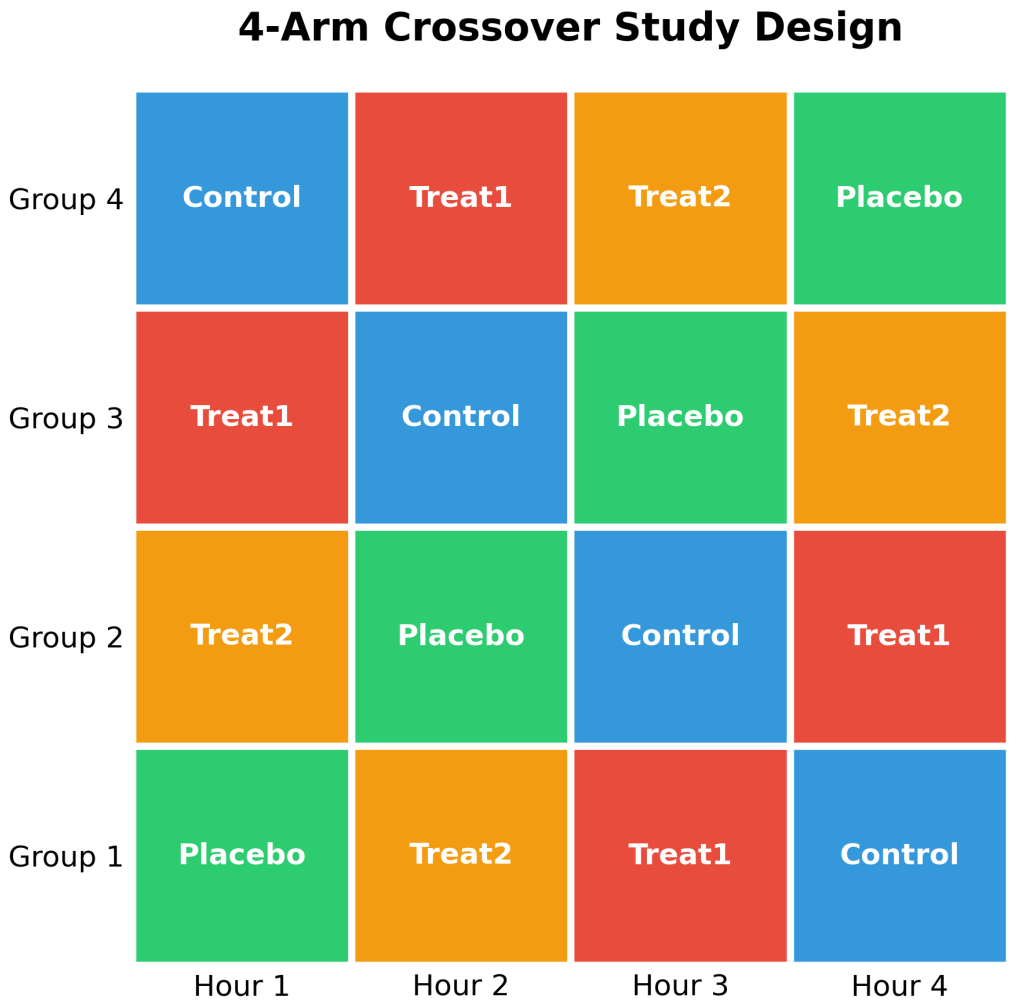

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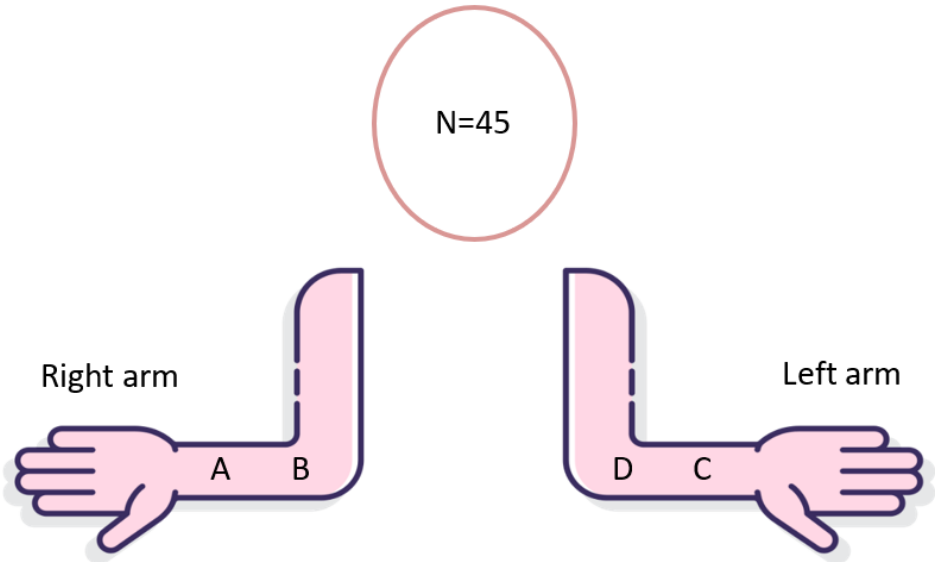

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- **Primary Outcome:** Patient-Reported Outcomes (PROs) capturing subjective itch intensity through the Visual Analogue Scale (VAS) scores from 0 to 10, collected at multiple time points over 1 hour.

Statistical Methods for crossover studies

Method	Estimates	Key Features
LMM (Linear Mixed Models)	Subject-specific	Handles missing data, models random effects
GEE (Generalized Estimating Equations)	Population-averaged	Robust to misspecification, marginal inference
RM-ANOVA (Repeated-Measures ANOVA)	Group-level means	Simpler framework, assumes sphericity

- All methods account for repeated measures and time effects.
- LMM and GEE are more flexible for skewed or non-linear data trajectories.

Objectives

1. **Simulate crossover trial data** that mimic longitudinal, correlated patient-reported outcomes with time-varying responses.
2. **Evaluate model performance** (LMM, GEE, RM-ANOVA) in estimating treatment effects under multilevel (patients within treatments over time) structures.
3. **Assess the impact of missing data** (MCAR, MAR) on estimation robustness in hierarchical repeated-measures data.

Methodology

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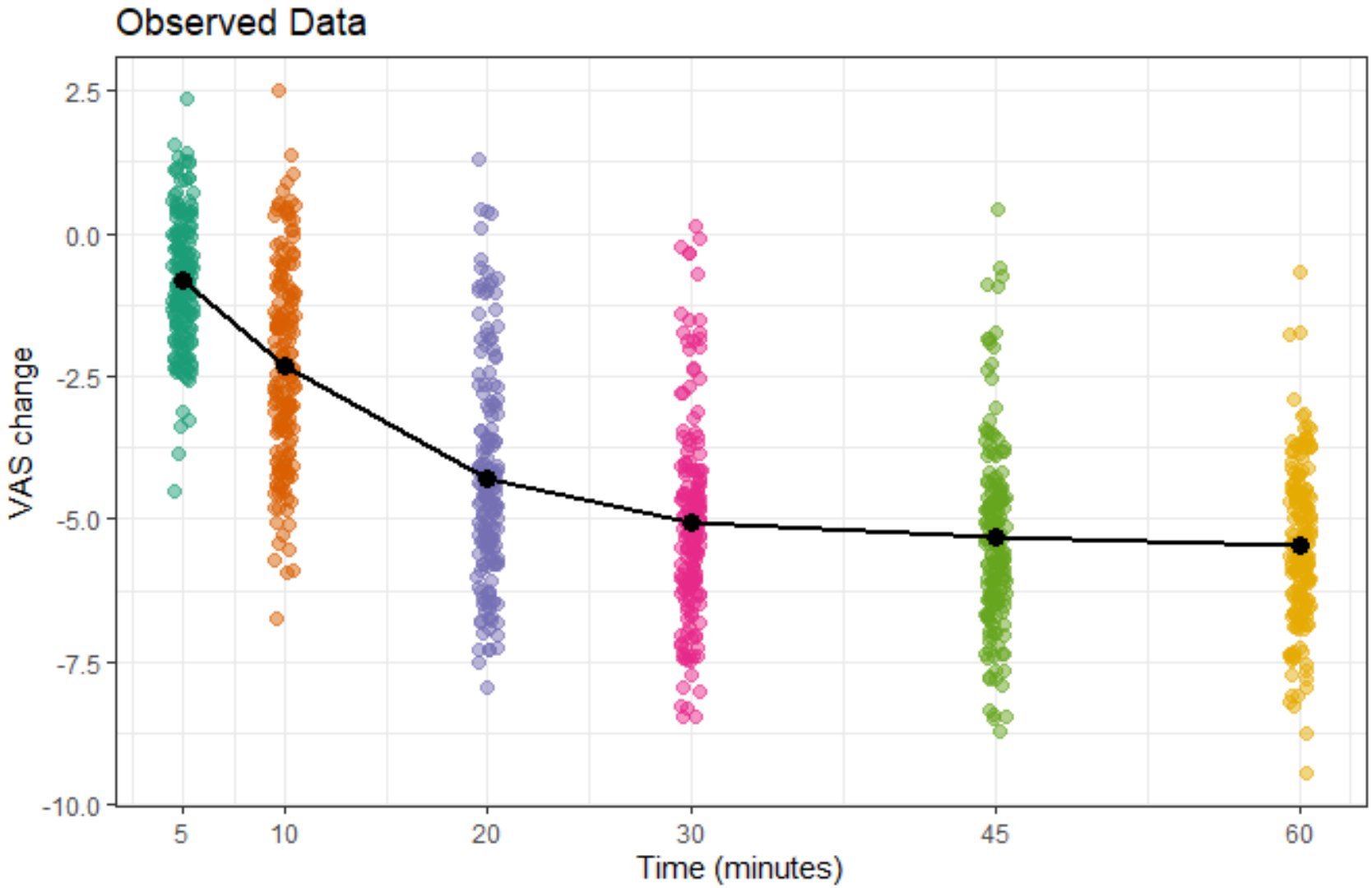
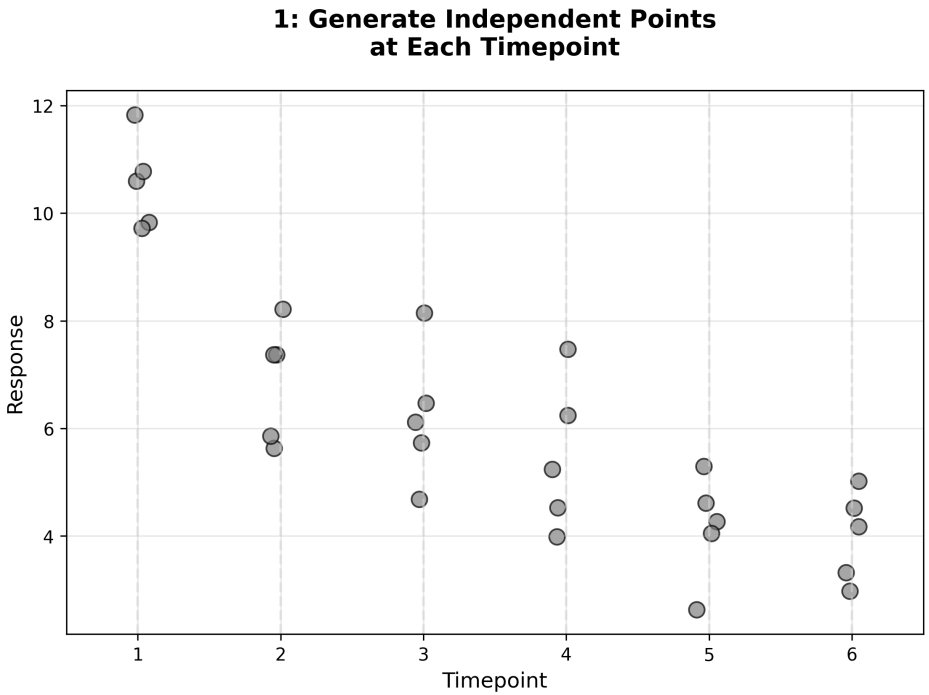
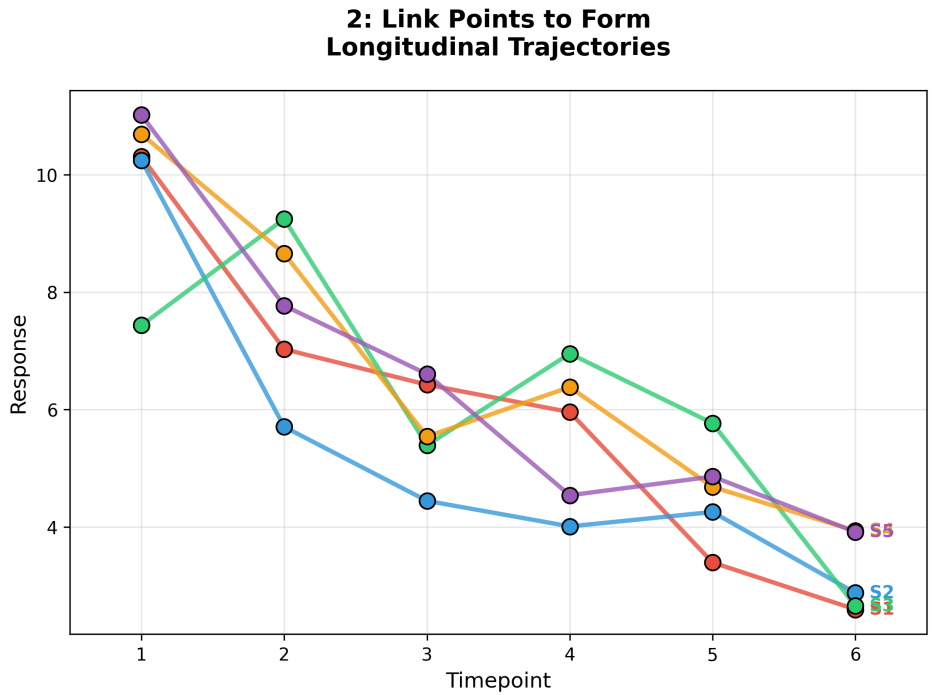
Data Simulation



Data Simulation

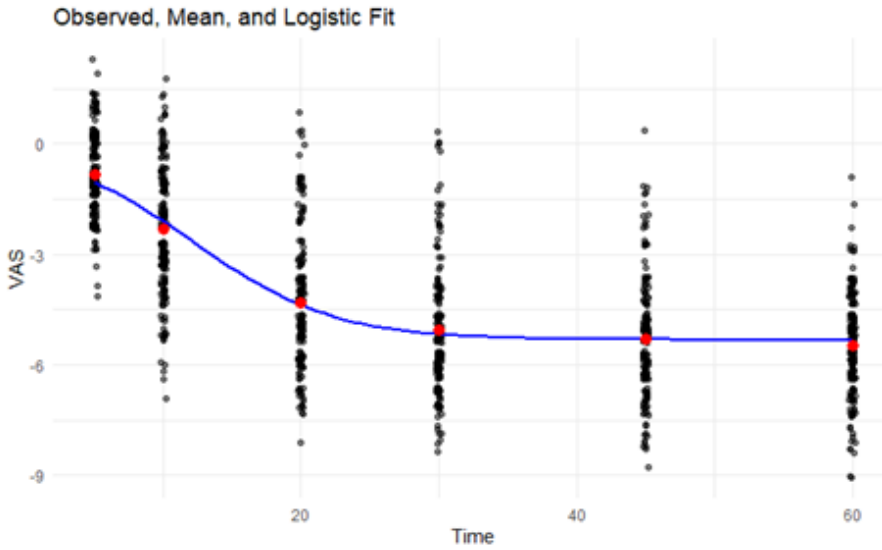
- **Approach 1**

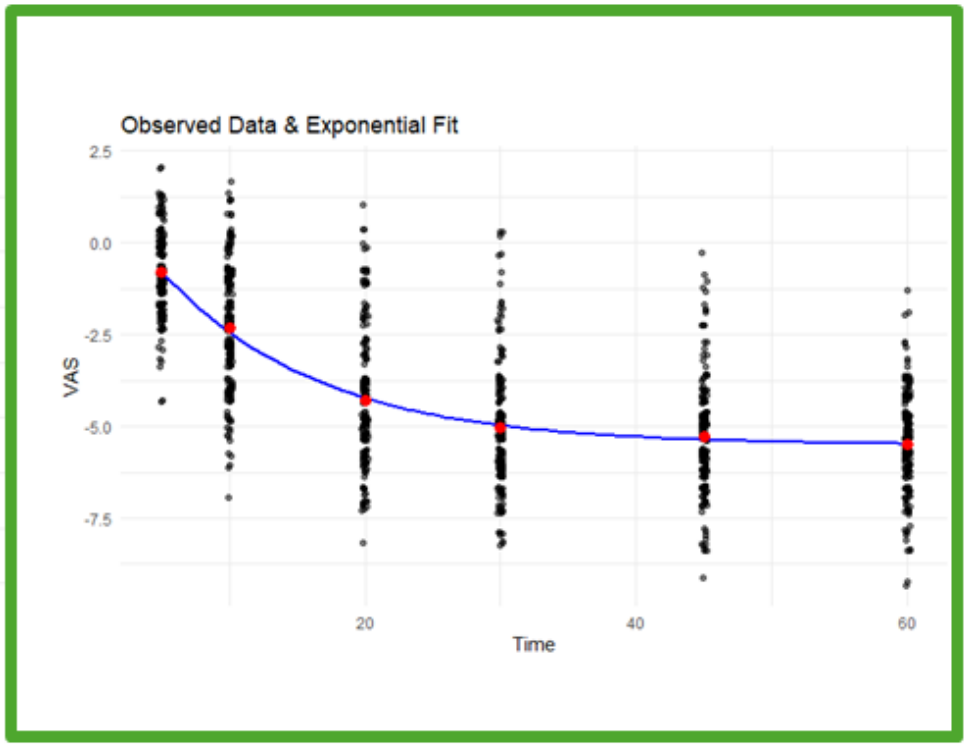




Data Simulation

- **Approach 2**





$$VAS(t) = a \cdot e^{b \cdot t} + c$$

How ICC Target is Achieved in Simulation

ICC Definition

$$\text{ICC} = \frac{\sigma^2_{\text{between}}}{\sigma^2_{\text{between}} + \sigma^2_{\text{within}}}$$

Step 1: Decompose Total Variance

- Target ICC $= \rho$ (e.g., 0.3, 0.5, 0.7)
- Total variance $= \sigma^2_{\text{total}}$
- Between-patient variance: $\sigma^2_b = \rho \cdot \sigma^2_{\text{total}}$
- Within-patient variance: $\sigma^2_w = (1 - \rho) \cdot \sigma^2_{\text{total}}$

Step 2: Generate Variance Components

- Patient effects: $u_i \sim N(0, \sqrt{\rho} \cdot \bar{\sigma})$
- Residual errors: $\epsilon_{ij} \sim N(0, \sqrt{1 - \rho} \cdot \sigma_j)$
- Where $\bar{\sigma} = \frac{1}{T} \sum_{j=1}^{T} \sigma_j$ (mean SD across timepoints)

How ICC Target is Achieved in Simulation

Step 3: Combine Components

$$Y_{ij} = \mu_{ij} + u_i \cdot \frac{\sigma_j}{\bar{\sigma}} + \epsilon_{ij}$$

Where:

- Y_{ij} = VAS for patient i at time j
- μ_{ij} = Fixed effects (treatment, time trend)
- u_i = Patient-specific random effect
- ϵ_{ij} = Residual error at time j
- σ_j = Time-specific standard deviation
- $\bar{\sigma}$ = Mean standard deviation across times

Patient effects are scaled by $\frac{\sigma_j}{\bar{\sigma}}$ to maintain target ICC across timepoints with different variances (heteroscedasticity).

Models Used for Simulation

Linear Mixed Model (LMM):

$$Y_{ij} = \beta_0 + \beta_1 \text{Treatment}_{ij} + \beta_2 \text{Time}_{ij} + \beta_3 (\text{Treatment} \times \text{Time})_{ij} + u_i + \varepsilon_{ij}$$

- $u_i \sim \mathcal{N}(0, \sigma_u^2)$: random intercept per patient
- $\varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$: residual error

Generalized Estimating Equation (GEE):

$$E[Y_{ij}] = \beta_0 + \beta_1 \text{Treatment}_{ij} + \beta_2 \text{Time}_{ij} + \beta_3 (\text{Treatment} \times \text{Time})_{ij}$$

- Correlation structures: AR(1) across time within patient

Repeated Measures ANOVA (RM-ANOVA):

$$Y_{ij} = \mu + \alpha_{\text{Treatment}} + \beta_{\text{Time}} + (\alpha\beta)_{\text{Treatment} \times \text{Time}} + \text{Subject}_i + \varepsilon_{ij}$$

Performance Measures Summary

1. Mean Squared Error (MSE)

$$\text{MSE}_x = \frac{1}{n_{\text{sim}}} \sum_{i=1}^{n_{\text{sim}}} (\hat{x}_i - x_i)^2$$

2. Type I Error Rate

- Probability of rejecting the true null hypothesis (false positive).

$$\text{Type I Error}_x = \frac{1}{n_{\text{sim}}} \sum_{i=1}^{n_{\text{sim}}} 1(p_i \leq \alpha \mid H_0 \text{ true})$$

3. Statistical Power

- Probability of correctly rejecting a false null hypothesis.

$$\text{Power}_x = \frac{1}{n_{\text{sim}}} \sum_{i=1}^{n_{\text{sim}}} 1(p_i \leq \alpha \mid H_1 \text{ true})$$

Results (WIP)

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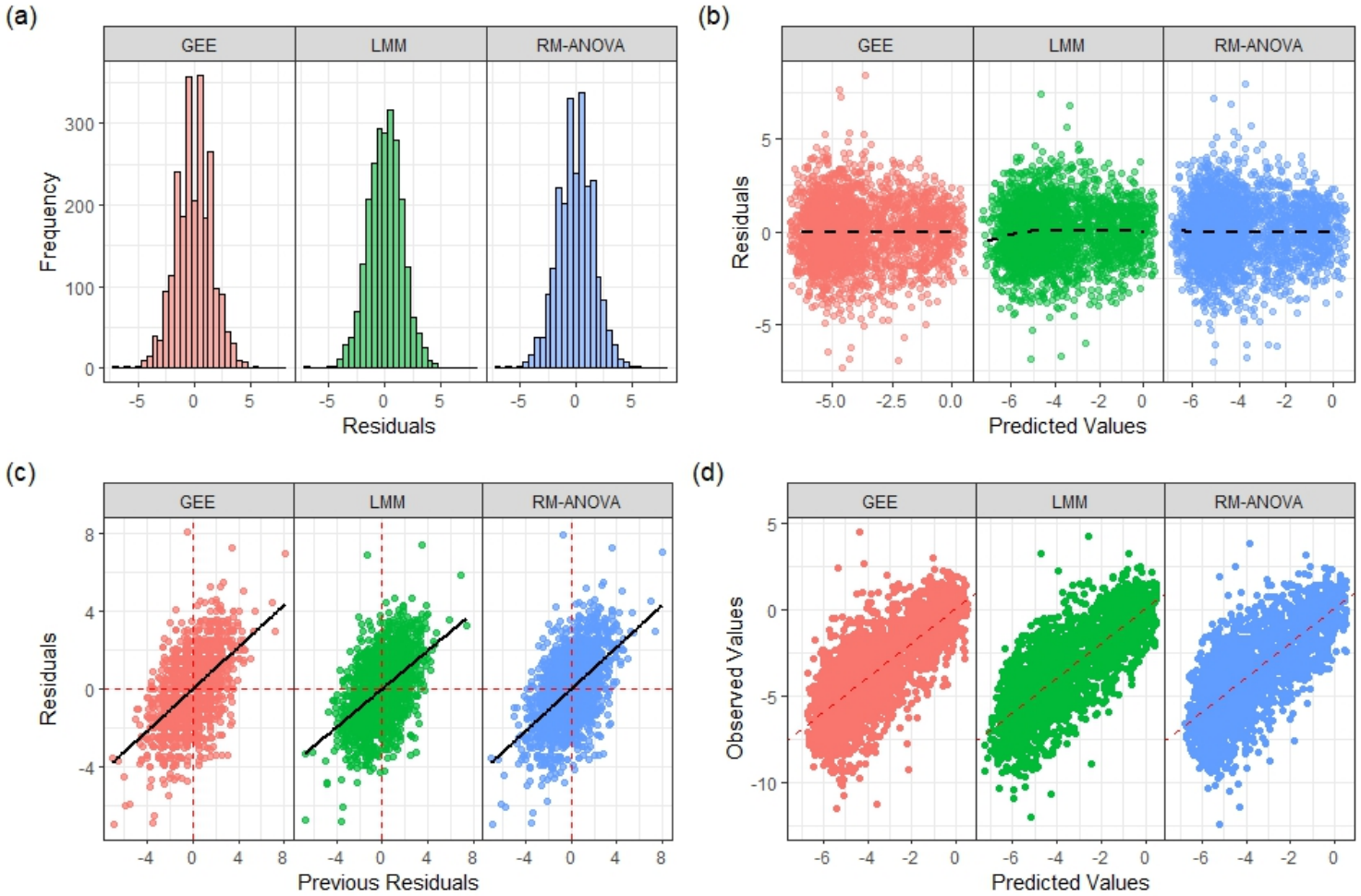
Model Fits: Residuals Analysis

- Residual distribution of all 3 models (a), Model predicted values vs residuals (b) and observed values (d), and observed Residuals vs previous residual (c).



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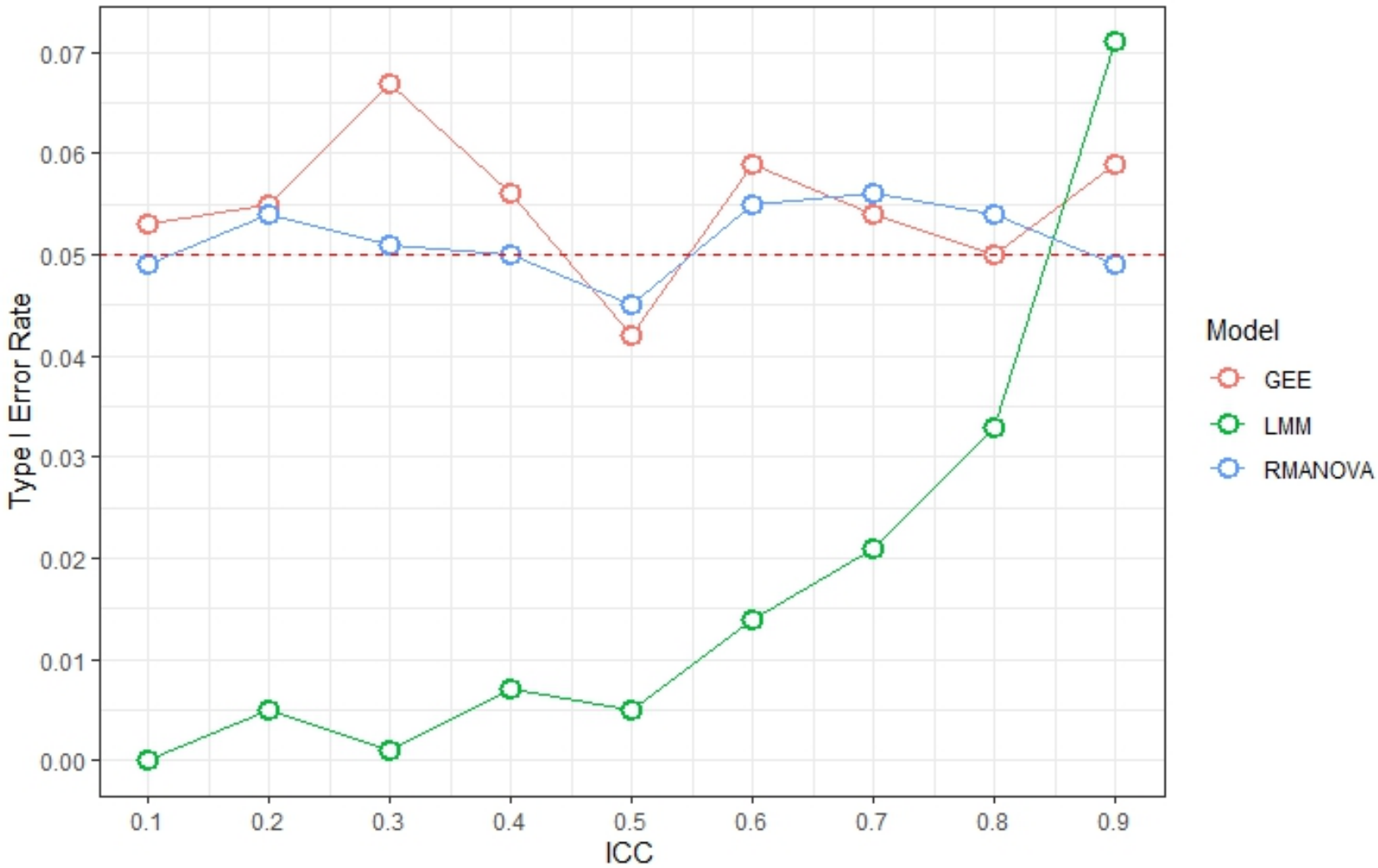
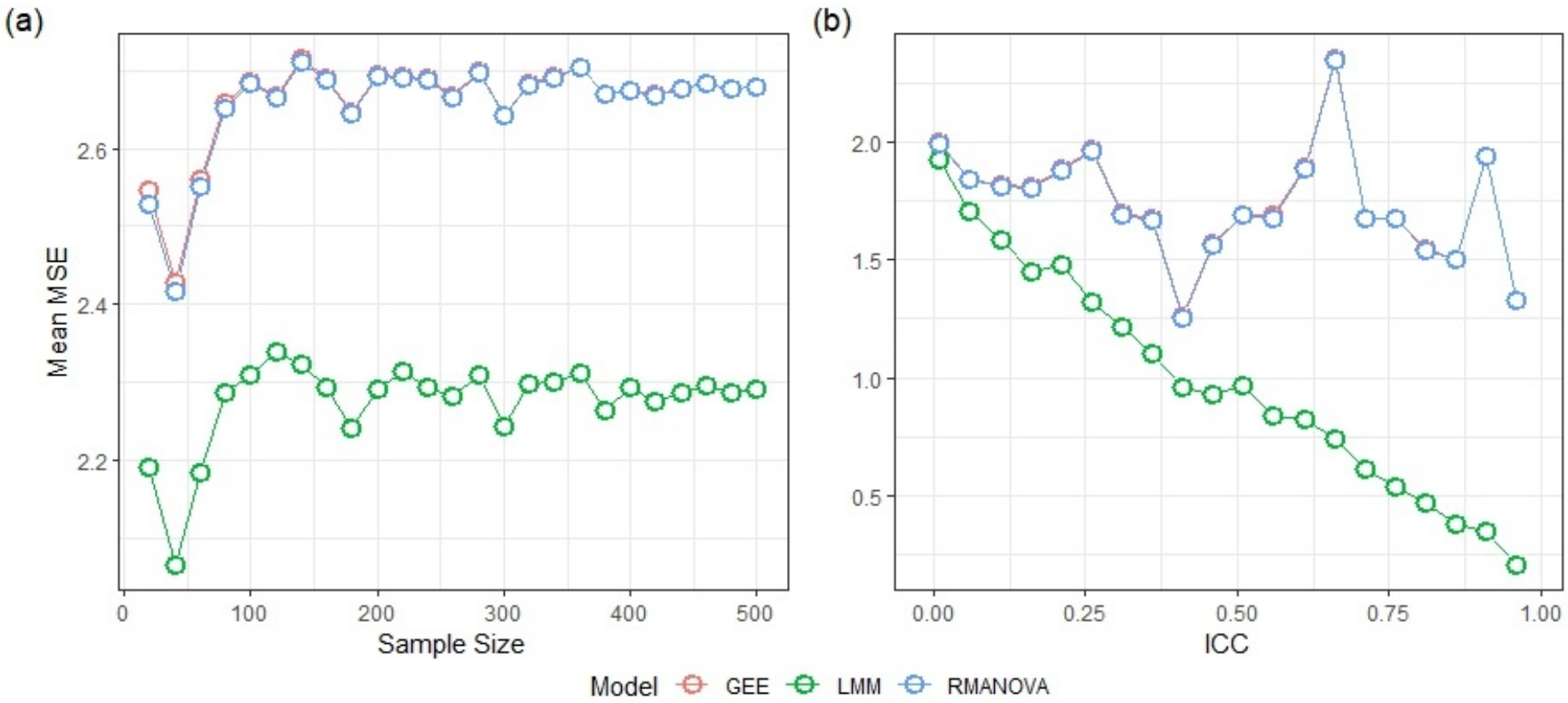
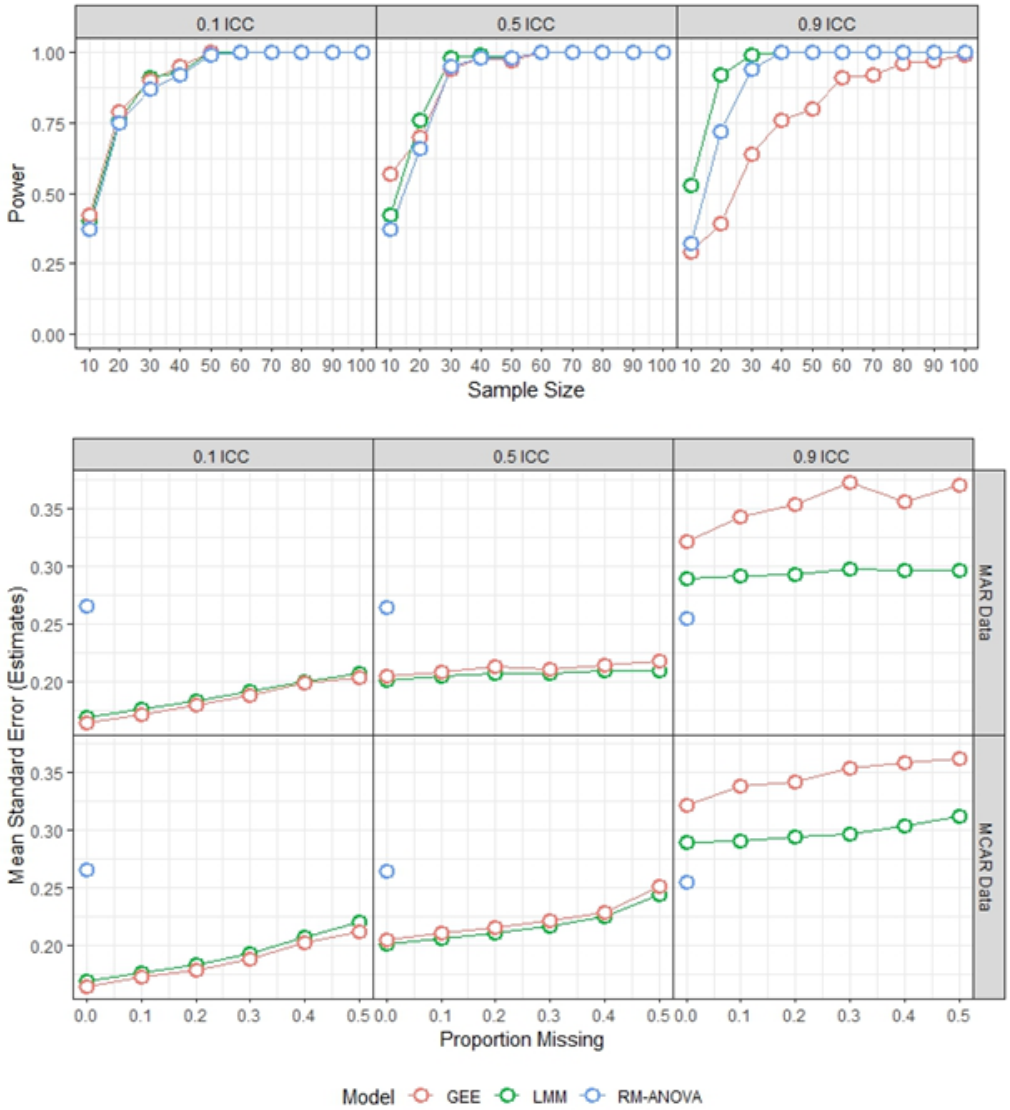


Mean Squared Error

- **Performance of different models in terms of MSE across varying sample sizes (a) and ICC values (b)**



ICC Effect on Power and Missing Data



Conclusions

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Conclusions and Future Work

Conclusions

- Marginal models are largely unaffected by ICC in terms of estimates.
- LMM's are more efficient at higher ICC levels due to their hierarchical structure.
- No substantial differences were found between MCAR and MAR missingness in terms of bias.

Future Work

- Run additional simulations
- Investigate unexplained behaviors

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Thank you for your attention.

Questions?

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