

Mitigation of rocuronium induced residual neuromuscular blockade risk by means of a population PK/PD model

Miriam Happa^{a,b}, Leandro F. Pippa^b, Gabriela Lauretti^c, Anthony Gebhart^b, Günther Weindl^a, Francine Azeredo^b, Valvanera Vozmediano^b, Stephan Schmidt^b, Natalia De Moraes^b

^a Pharmacology and Toxicology Section, Pharmaceutical Institute, University of Bonn, Germany.

^b Center for Pharmacometrics and System Pharmacology, Department of Pharmaceutics. College of Pharmacy. University of Florida, FL, USA

^c School of Medicine of Ribeirao Preto, University of Sao Paulo, SP, Brazil.

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Introduction

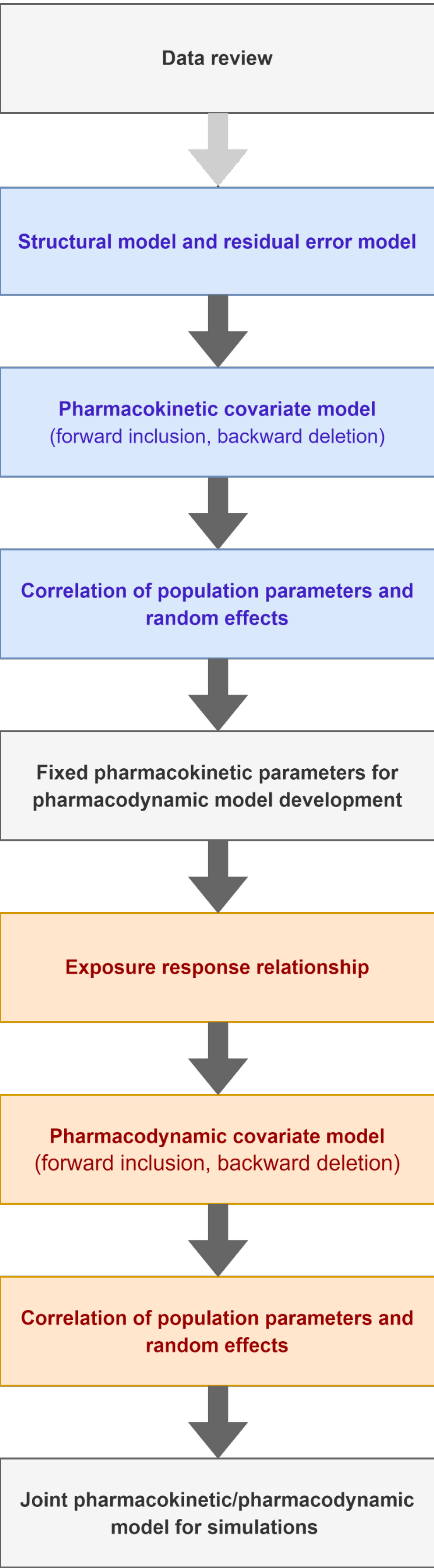
- High interindividual variability in recovery time of rocuronium¹
- frequent occurrence of residual neuromuscular blockade puts patients at higher risk for postoperative pulmonary complications²
- Identify impacting factors on variability in recovery time
- Reduce risk for residual neuromuscular block
- Inform dose adjustments and risk assessment

Methods

- 32 patients undergoing elective surgeries³
- 395 plasma concentrations
- 242 TOF ratio measurements
- Develop NLME model⁴
- Internal model validation
- Simulate covariate groups (100 patients per group)⁵
- Estimate recovery times and residual neuromuscular block risk⁵

TOF ratio: Train of Four ratio, Measurement for neuromuscular function (see Figure 2)

Modelling Workflow



Pharmacokinetic/Pharmacodynamic Model

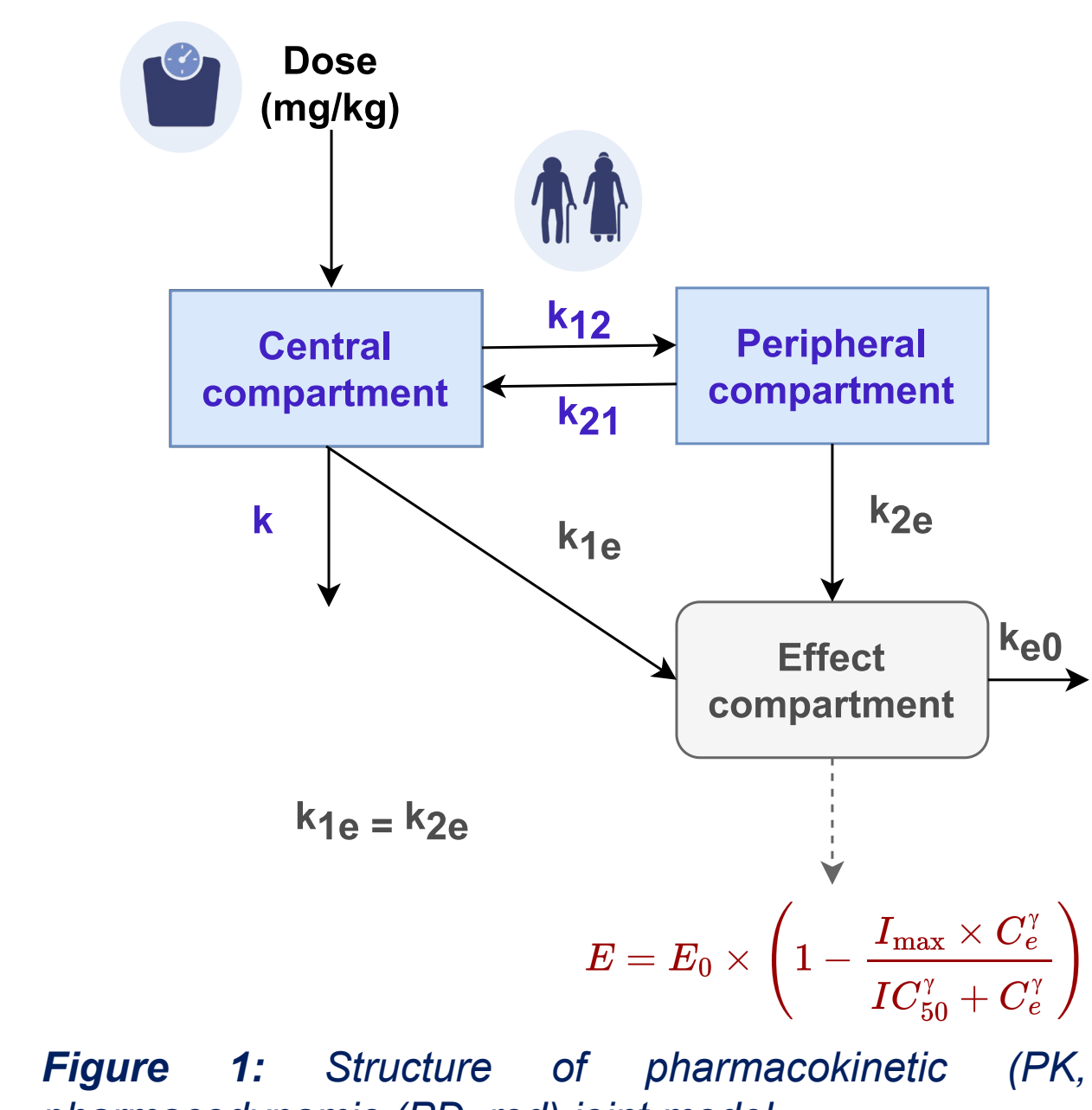


Figure 1: Structure of pharmacokinetic (PK, blue) and pharmacodynamic (PD, red) joint model.

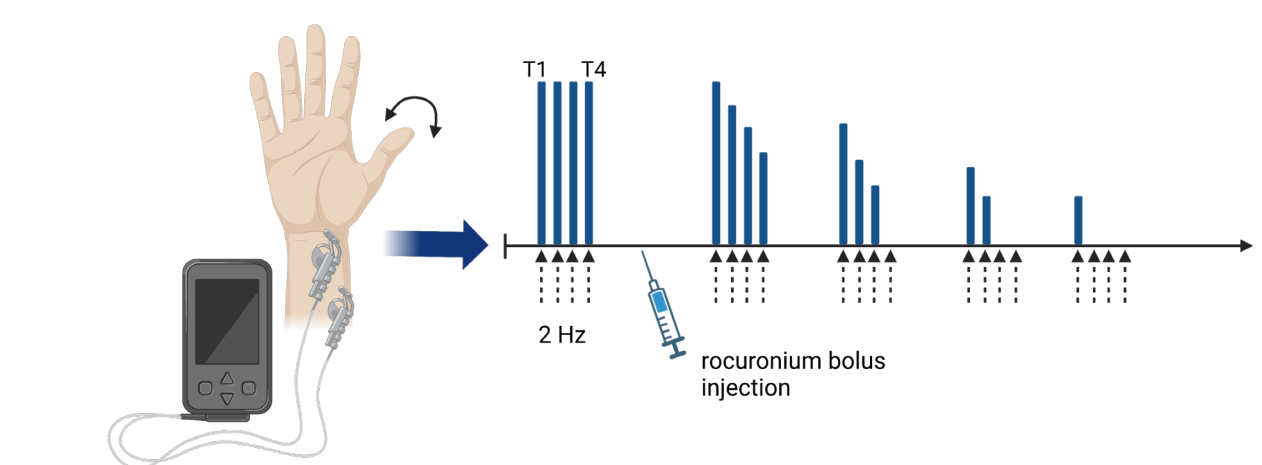


Figure 2: Measurement of Train of Four (TOF ratio = T4/T1) at the adductor pollicis muscle as quantitative measurement of neuromuscular function.⁶

Bootstrap (n = 500) median estimates for joint model		
Parameter (P5–95)	CV (P5–P95)	
V (L/kg)	0.063 (0.055–0.071)	26.4% (21.2%–32.8%)
k (h ⁻¹)	2.26 (2.06–2.50)	18.1% (12.0%–24.3%)
k ₁₂ (h ⁻¹)	2.51 (1.99–3.09)	48.5% (31.8%–60.7%)
k ₂₁ (h ⁻¹)	1.33 (1.14–1.54)	41.7% (26.4%–53.3%)
β _{k12_logtAGE}	0.68 (0.46–0.98)	
IC ₅₀ (mg/L)	0.61 (0.45–0.75)	55.7% (28.6%–76.7%)
γ	12.12 (9.01–15.96)	68.5% (37.2%–99.6%)
ke0 (h ⁻¹)	15.34 (11.71–22.06)	
E ₀	1.00 (fixed)	
Correlations		
corr_k12_k21	0.87 (0.67–0.93)	
Error Model parameters		
bCONC	0.25 (0.23–0.27)	
aTOF	2.42 (1.94–2.79)	

CV: Coefficient of Variation, V: central volume of distribution, k: elimination rate, k₁₂, k₂₁: transfer rates between compartments, β_{k12_logtAGE}: age covariate parameter on k₁₂, IC₅₀: half maximum inhibitory concentration, γ: shape factor, ke0: elimination rate from effect compartment, E₀: baseline effect, aTOF: additive residual error, bCONC: proportional residual error.

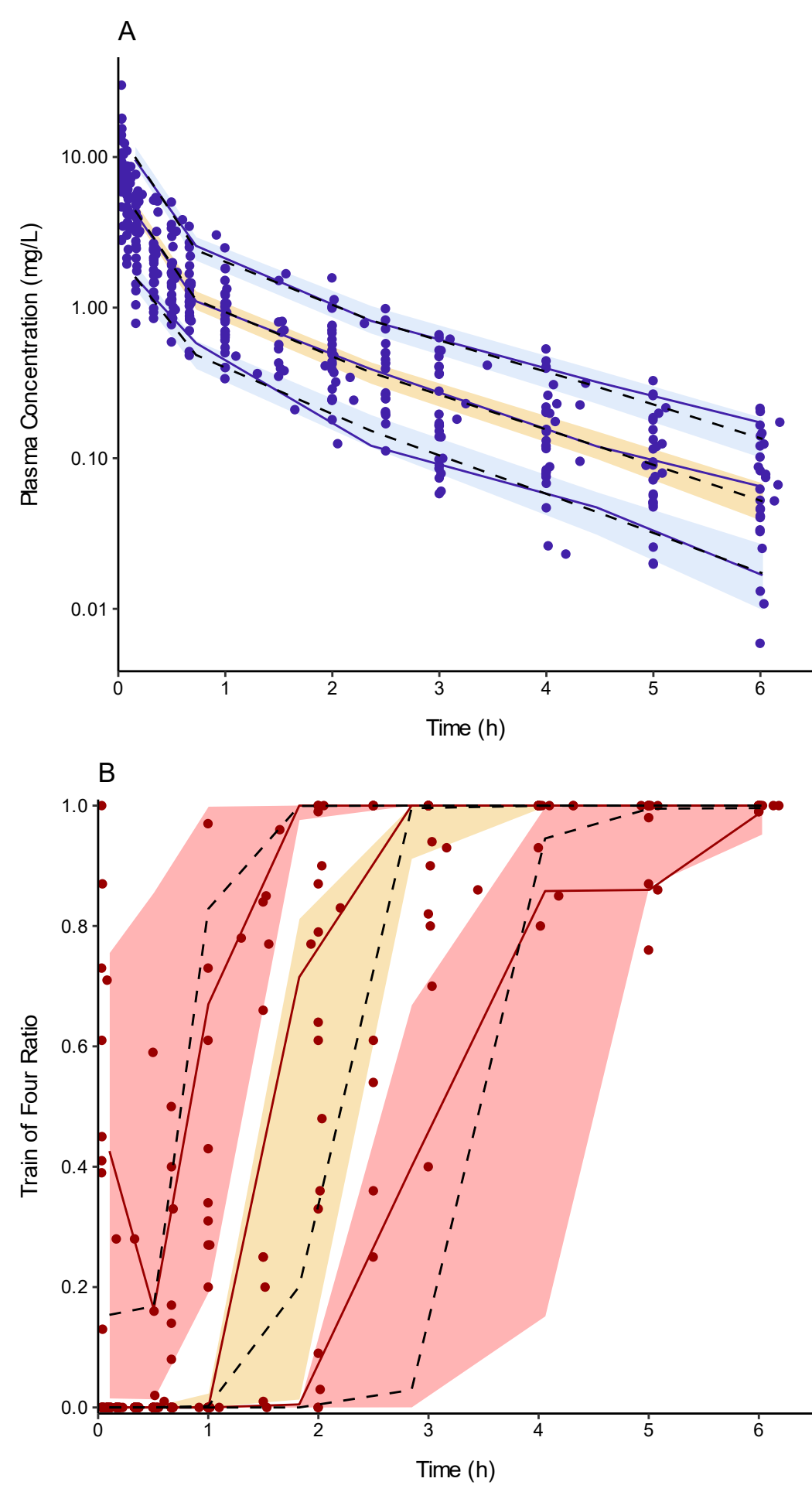


Figure 3: Visual predictive checks of PK (A, blue) and PD (B, red) of the joint model, with observed data (●), empirical 10th, 50th, and 90th percentiles (---), model-predicted 10th, 50th, and 90th percentiles (—) and prediction intervals.

Clinical Implications

Pre-Surgery:

Dose individualization based on patient age, body weight and anticipated surgery length

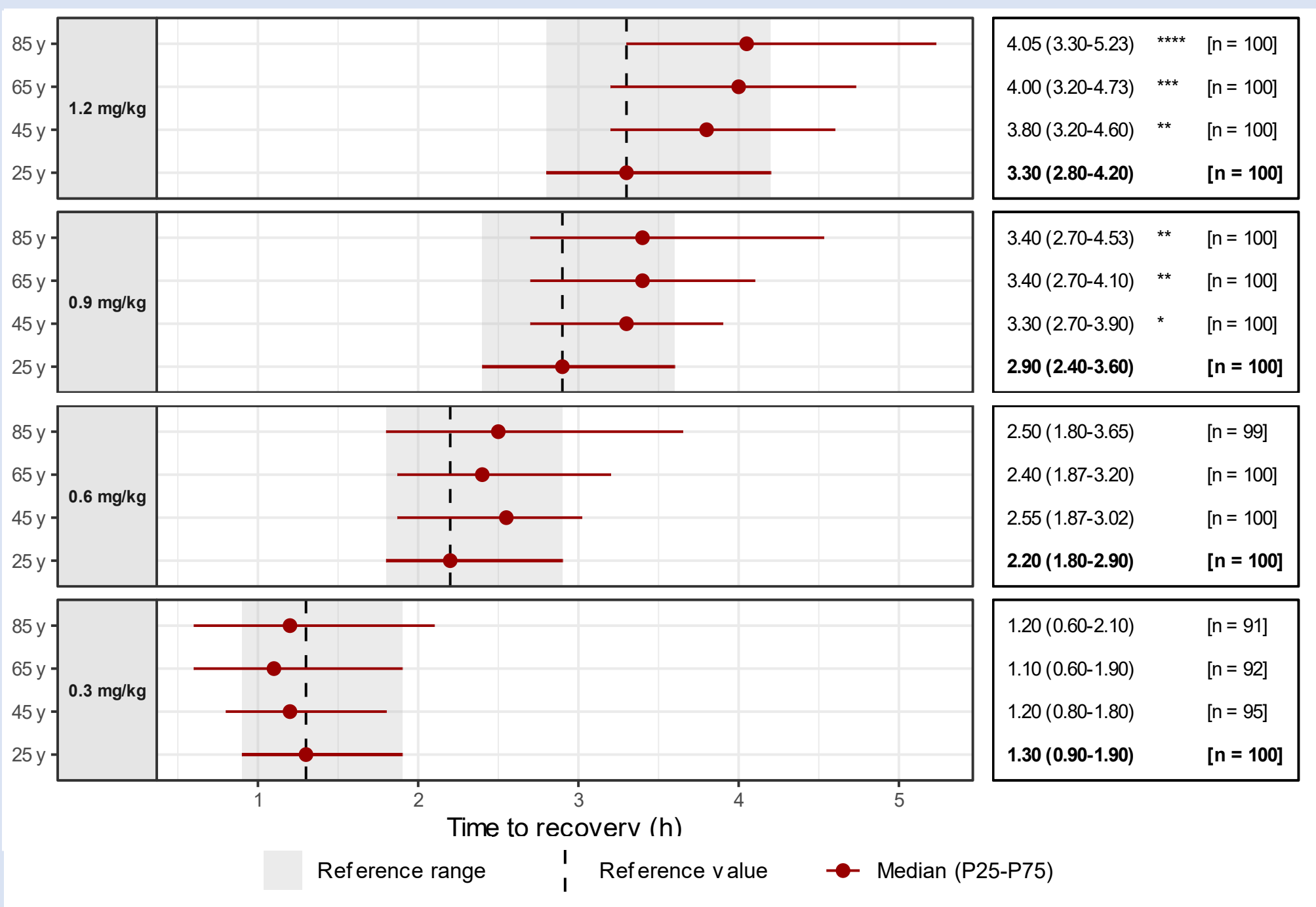
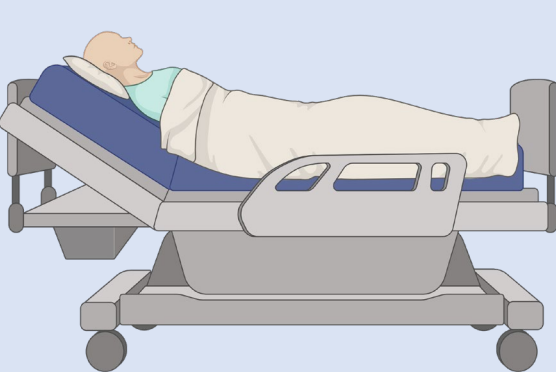


Figure 4: Simulated recovery time (time to TOF ≥ 0.9), groups defined as average age ± 0.1 SD, same individuals across doses. 45, 65, and 85-year-old groups compared to 25-year-old group (—) by Mann-Whitney U test.⁷ p < 0.05; (*) p < 0.05; (**) p < 0.01; (***) p < 0.001; (****) p < 0.0001.

During Surgery:

Continuous monitoring and risk assessment before extubation to assess need for reversal agents and state of recovery

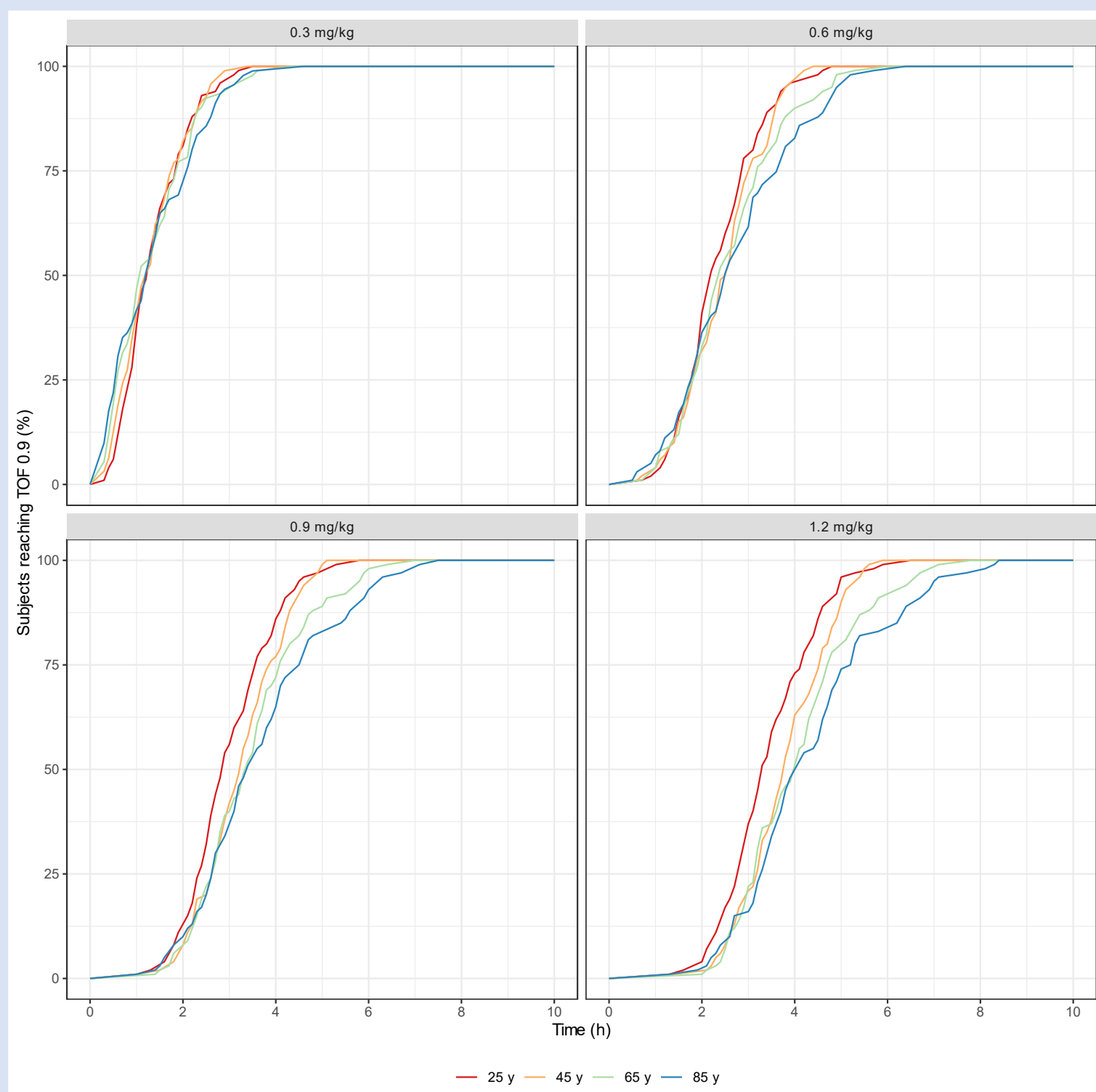
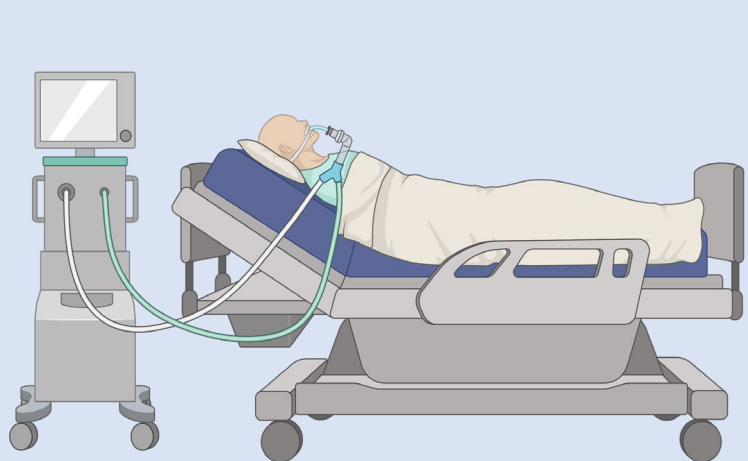
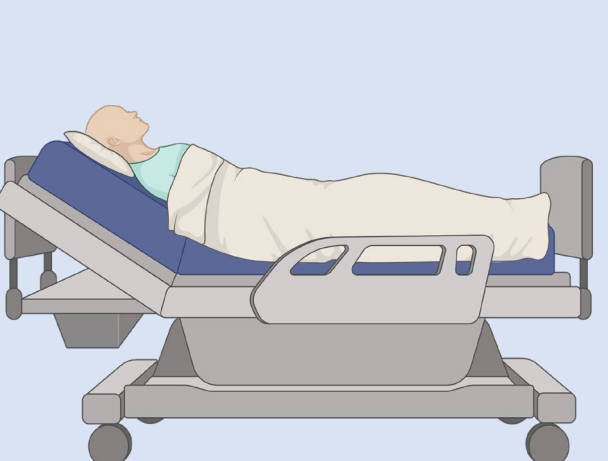


Figure 5: Percentage of recovered simulated patients over time (recovered: TOF ≥ 0.9), groups defined as average age ± 0.1 SD, same individuals across doses. Subjects not achieving TOF < 0.9 were excluded.

Post-Surgery:

Safe extubation after full recovery is achieved at TOF ratio ≥ 0.9



Conclusions

- Geriatric patients are at higher risk for residual neuromuscular blockade
- Model shows promising opportunities for application to
 - Reduce risk of residual neuromuscular block
 - Reduce need for expensive reversal drugs
 - Model informed precision dosing

Future Directions

- External validation and extension to other patient populations
- Bayesian Estimation tool to support multiple dosing
 - Incorporating real-time TOF measurements
 - Developing easy to use bedside tool for clinicians



References

- (1) Maybauer et al. Anesthesia 62: 12-17 (2007)
 - (2) Murphy et al. Anesth Analg 107: 130-137 (2008)
 - (3) Varriquer et al. J Pharm Pharmacol 68: 1351-1358 (2016)
 - (4) Monolix 2021R1, Lixoft SAS, a Simulation Plus company
 - (5) Simulx 2023R1, Lixoft SAS, a Simulation Plus company
 - (6) Figure was modified from Boon et al. F1000Research 167 (2018)
 - (7) R Statistical Software (4.2.2; R Core Team 2022)
- Elements of Figure 1, Figure 2 and Icons in this poster were created with Biorender.com