

Appendices

Appendix A – The RLME model specification

The RLME model with decomposition for each level:

Level 1: Within-patient (sample level)

The modelling the outcome variable y for each measurement occasion j (time points: 1h, 6h, 12h, 24h) within each patient i . In the equation (1) the model includes fixed effects for time, group, and their interaction, plus patient-specific adjustments (random intercepts).

$$y_{ij} = \pi_{0i} + \pi_{1i}(time_{ij}) + \epsilon_{ij} \quad (1)$$

where π_{0i} is the overall effect for patient i (including the base level of the outcome and the patient-specific deviation captured by the random intercept); $\pi_{1i}(time_{ij})$ represents the time-specific effects, adjusted for interactions with groups and confounders; ϵ_{ij} is the residual error for patient i at time j , assumed iid $N(0, \sigma^2)$.

Level 2: Between-Patient

At this level, by the equation (2) we model the random effects and the influence of patient-level predictors (e.g., treatment group, confounders). The intercepts are considered as outcomes influenced by these higher-level predictors.

$$\pi_{0i} = \beta_0 + \beta_4 group_i + X_i^T \beta_X + b_{0i}, \quad (2)$$

$$\begin{aligned} \pi_{1i}(time_{ij}) = & \beta_1 \cdot \delta(time_{ij}, 6h) + \beta_2 \cdot \delta(time_{ij}, 12h) + \beta_3 \cdot \delta(time_{ij}, 24h) + \\ & + \beta_5 \cdot \delta(time_{ij}, 6h) \times group_i + \beta_6 \cdot \delta(time_{ij}, 12h) \times group_i + \beta_7 \cdot \delta(time_{ij}, 24h) \times group_i, \quad (3), \end{aligned}$$

where $\beta_0, \beta_1, \beta_2, \beta_3$ are the fixed effects coefficients for the baseline and time points; $\beta_4, \beta_5, \beta_6, \beta_7$ are the coefficients for group effects and interaction terms between group and time; δ is the indicator function, 1 if the condition is true and 0 otherwise (a mathematical way to handle categorical variables in equations); X_i – is the vector of confounders for patient i ; b_{0i} – is the random intercept for each patient i , assumed $N(0, \sigma^2_{b0})$.