University of Cape Town

Longitudinal Data Analysis

Nonlinear Mixed-Effects Modeling of Pyrimethamine Concentration–Time Profiles in a 42-Day Malaria Trial

Author:
Andomei Smit

Student Number:
SMTAND051

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Contents

1 Introduction

This report uses non-linear mixed-effects (NLME) modelling to analyse Pyrimethamine concentration–time profiles from a repeated-measures antimalarial trial with follow-up on days 0, 1, 2, 3, 7, 14, 21, 28, and 42. The design is hierarchical (repeated measurements within subjects, within sites) with additional information on treatment arm (SP vs SP/ACT) and demographics. The objective is to characterise the Pyrimethamine concentration curve and evaluate between-arm differences while adjusting for relevant covariates, and to give due consideration to random-effects, variance, and within-subject correlation structures.

We model the concentration trajectory using a one-compartment oral, first-order absorption model with log-parametrization (lKe, lKa, lCl) and estimate parameters via nlme in R. Fixed effects allow for key demographics (e.g., centred weight and its square) and treatment arm on selected PK parameters; subject-level heterogeneity is captured through random effects (primarily on lKe). We assess alternative residual variance specifications and serial correlation structures (e.g., CAR(1), ARMA), compare candidates with likelihood-based criteria (Maximum Likelihood AIC/Likelihood Ratio Tests), and judge adequacy using standard diagnostics (residuals vs fitted, Q–Q plots, and residual Autocorrelation Functions).

2 Data and Methods

2.1 Data Description

The given malaria dataset consists of the following variables:

- Pyrconcentration: Pyrimethamine drug concentration measurement taken on each for the measurement days, namely days 0, 1, 2, 3, 7, 14, 21, 28 and 42.
- arm: the treatment arm that a subject was assigned to, namely SP (Sulfadoxine and Pyrimethamine) or SP/ART which adds Artemisinin to SP.
- site: four sites where subjects were treated, namely Boane, Catuane, Magude, and Namaacha.
- pid: the unique subject ID used to identify different subjects.
- pday: the day on which the measurement of drug concentrations was taken, made up of days 0, 1, 2, 3, 7, 14, 21, 28 and 42.
- gender: classification of each subject as Male or Female.
- weight: the weight of each subject at the start of the treatment.

- age: the age of each subject at the start of the treatment.

One important aspect that was not stated explicitly at the outset of the study was the clinical protocol across the different sites and if that was homogenous. This project will assume that the protocols were homogenous and that differences in subject weights and ages would trigger the same dose adjustments of the drug concentration across different sites.

2.2 Data Cleaning and Preparation

During the data preparation stage, the following changes were made to the data.

- All rows that had missing values for Pyrimethamine were removed.
- Some of the subjects exhibited an increase in Pyrimethamine drug concentration after day 3. This was assumed to be an error as the drug would be absorbed into the person's system and would not show an increase after day 3. Thus, all subjects where the drug concentration increased after day 3 were removed.
- Two new variables were created that centred age and weight.
- The original dataset had a Year and Country variable that was the same for all subjects, thus was removed. Other variables available in the original dataset such as the Haemoglobin readings or parasite densities were ignored as the focus of this project is to only take into account demographic variables.
- 6 subjects had missing values for weight. These subjects were removed from the study.

2.3 Exploratory Data Analysis

Various checks were done to ensure that the data could be used to make inference on the differences in drug concentration curves between the two treatment arms. Some initial checks were done at a high-level to get an understanding of the distribution of treatment arm, subjects and gender between the different sites and to spot any anomalies or issues.

2.3.1 Initial Investigations

Preliminary exploratory checks were performed to evaluate whether the data exhibited substantial skewness or structural complexities. The findings were as follows:

- There was 245 unique subjects after all rows with missing values for Pyrimethamine were removed.

- Age and weight were found to be constant within subject for the entire treatment duration, thus these were assumed to be the age and weight at day 0.
- 64% of all subjects were female, meaning that overall the study was not dominated by one gender.
- The treatment arms were equally split among subjects.
- An imbalance was noticed between the number of subjects within each site. The smallest site was Catuane with only 37 subjects, compared to the largest site, Magude with 124 subjects. Namaacha and Boane had 48 and 77 subjects, respectively. Figure 1 shows that Magude is to the North of Maputo, whereas Namaacha, Boane and Catuane are to the South. Due to the imbalance of the number of subjects within the sites, it was decided to combine the three sites to the south and compare the overall difference in treatment between the Northern and Southern sites. In total, the Northern sites had 124 subjects and the Southern sites 162.
- The treatment arms were roughly equally split among subjects within each region, meaning that there wasn't a region that predominantly administered one treatment arm.
- Within each region, both treatment arms included adequate numbers of male and female subjects. This indicates that there was no systematic bias toward assigning a particular treatment to one gender. Although the proportion of female participants varied across regions from 50% to 65%, these figures are broadly consistent with the overall sample, in which females represented 64% of participants.

2.3.2 Correlation between age and weight

It was noted that age and weight had a correlation of 0.85. This does make sense biologically. In order to avoid multicollinearity, only one of these will be used in the final model. Two models will be compared, one with weight and one with age, to determine which is the superior model.

2.3.3 Distribution of age and weight

The distribution of age and weight across treatment arm and region is plotted in Figure 2. This plot shows that the age and weight distributions between the two regions are very similar, with the South having slightly older and heavier subjects. The subjects in the north are mostly younger than 20, whereas the south sees a higher number of older subjects. Overall, these distributions between regions does

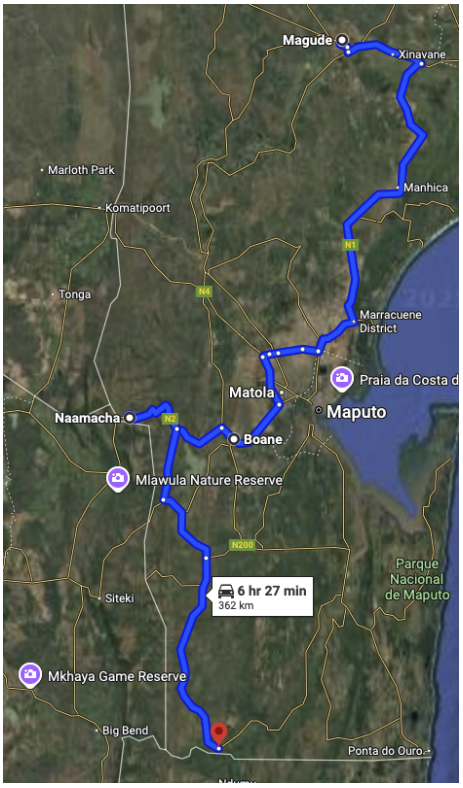
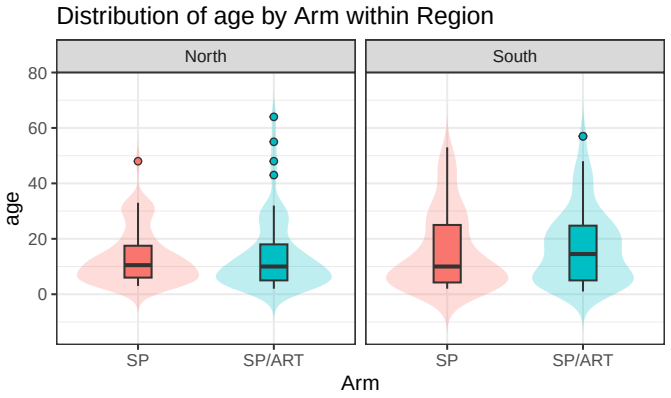


Figure 1: Locations of Boane, Catuane, Magude, and Namaacha in Maputo Province, Mozambique. Catuane can be seen as the location at the bottom of the map with the red location pointer. The regions to the South will be grouped together, whereas Magude in the North is the only site making up the Northern region.

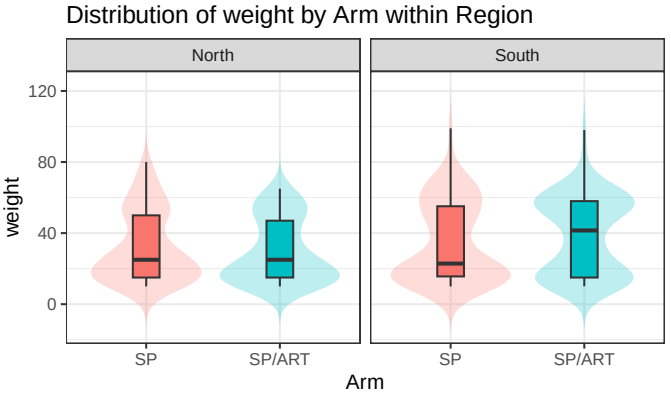
not identify clear differences in treatment protocol triggered by different subject ages or weights.

2.3.4 Interactions within the data

Because interaction terms substantially increase the number of parameters to be estimated, they can cause overfitting and convergence difficulties. For this reason, we restricted attention to the most biologically plausible interaction, namely between treatment arm and weight. Weight is known to influence drug pharmacokinetics, particularly the rate at which a drug is distributed and cleared from the body[1]. This interaction will formally be tested for in the modelling section.



(a) The distribution of age within region for the two different treatment arms.



(b) The distribution of weight within region for the two different treatment arms.

Figure 2: The distribution of age and weight by region and treatment arm. It can be seen that the ages and weights do not differ significantly between the regions. It can also be noted that the distributions of age look similar to those of weight.

2.3.5 Subject Profiles

The subject profiles are plotted in Figure 3. The observed pattern is very common in oral drug concentrations. There is an initial increase the concentration as the drug is administered (absorption), then a sharp decline (elimination), followed by a steady decrease (clearance) for the remainder of the treatment time.

This plot also show differences in intercept and slopes between arms for both drugs, and indicated variability in decay rates across subjects. It can also be seen that some subjects have much longer absorption times (i.e. the time in which the drug

concentration increases), while others have a rapid increase in drug concentration in days 0 and 1 followed by an immediate and sharp decline from day 2 onwards. Thus, both a random intercept and slope will be tested in the modelling section.

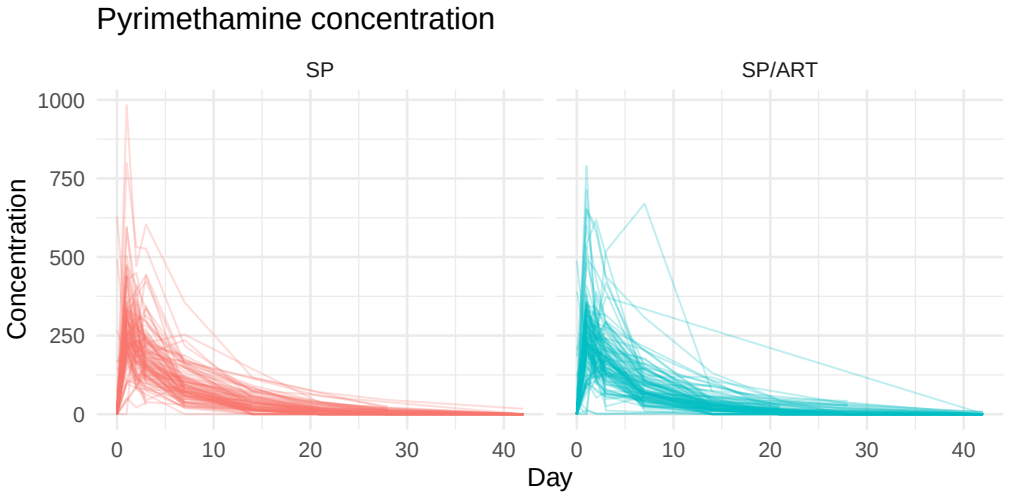


Figure 3: Subject profiles (repeated measures of Pyrimethamine) for each treatment arm. There appears to be some difference in intercept and slope between subject, but this will still formally be tested in the modelling section.

2.3.6 Dropout Rates of Subjects

Finally, the dropout rates of subjects was compared between Regions (Northern and Southern) and between treatment arms to see if there are any clear issues within a region or treatment arm. Figure 4 shows the dropout rate between the two treatments arms (left) and the different Regions (right). These show that the dropout rates between treatment arms are almost identical. The dropout rates between Regions seem comparable, with the only noticeable difference being a vertical shift in the number of participants, but the difference in the lines stays relatively constant over the treatment course, i.e. the dropout rates are relatively constant between the two Regions.

2.4 Model Specification

The shape of the curves observed in Figure 3 and the nature of response that we want to model is well suited to a first-order open-compartment model. In this model, the Pyrimethamine concentration at time t can be expressed as:

$$c_t = \frac{Dk_e k_a}{Cl(k_a - k_e)}[\exp(-k_e t) - \exp(-k_a t)], \tag{1}$$

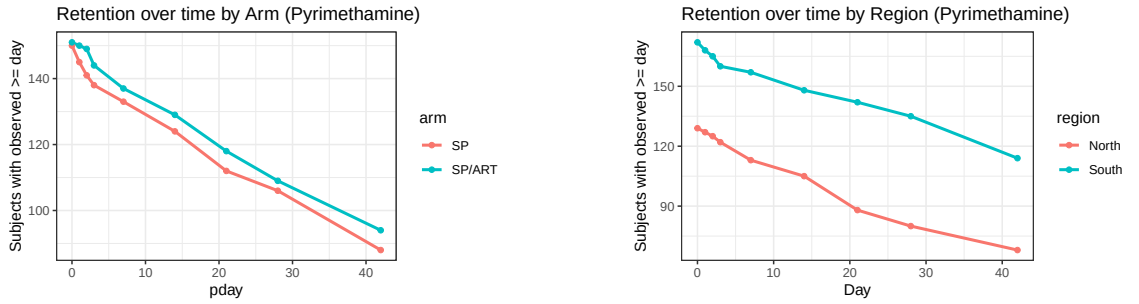


Figure 4: A plot to show the difference in dropout rates for different treatment arms and Regions.

where k_e is the elimination rate constant, k_a is the absorption rate constant, Cl is the clearance and D is the dose of the drug given at the start of the experiment. But, since the only meaningful values of these parameters are those greater than zero, the model can be parametrised as

$$c_t = \frac{D\ \exp(lK_e + lK_a - lCl)}{\exp(lKa) - \exp(lK_e)}\{\exp[-\exp(lK_e)t] - \exp[-\exp(lK_a)t]\}, \qquad (2)$$

where $lK_e = \log(k_e)$, $lK_a = \log(k_a)$ and $lCl = \log(Cl)$.

The above three parameters was modelled using various fixed and random effects in the Model Building Section. This model formulation forms part of the Non-Linear Mixed effects models framework. Note, however, that in the current Malaria dataset we do not have the Dose that was given to each subject. In order to overcome this, a constant Dose of 1 was assigned to each subject.

3 Model Fitting Results

3.1 Individual models for each subject

To start off with, an individual model for each subject was fit using the nlsList function that is part of the nlme package in R. This function allows us to fit a curve to each subject's drug concentration curve, thus estimating lK_e, lK_a and lCl for each subject individually. Further, the SSfol function that is a self-starting function for the first-order open-compartment model, was used that fits the equation that is in Equation 2 to model the drug concentration.

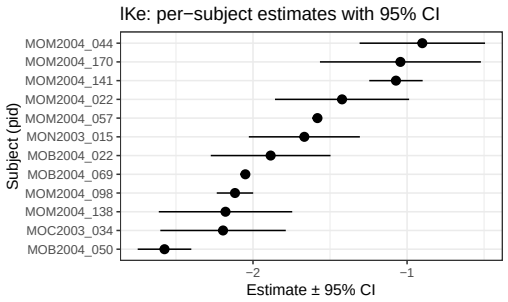
From this formulation, theoretically, confidence intervals for each parameter estimate can be calculated for each subject. However, since the data is very sparse for some subjects (i.e. they do not have an observation at each day), the parameters were not able to be estimated and the function did not converge. Thus, the confidence intervals for the parameters of those subject's whose estimation did converge are plotted in 5. The individual estimates suggests that there is a lot of variation on a subject-to-subject level between each estimate, the largest being for clearance and the elimination rate constant. However, this was deemed to show enough evidence that all three parameters should be included in the random effects.

Formally, this model can be expressed as in Equation 3.

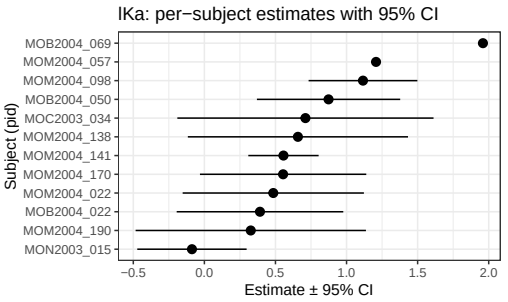
$$
\begin{aligned}
c_{ij} &= \frac{D_i \exp(lKe_i + lKa_i - lCl_i)}{\exp(lKa_i) - \exp(lKe_i)} \\
&\quad \times \Big\{ \exp[-\exp(lKe_i)\, t_{ij}] - \exp[-\exp(lKa_i)\, t_{ij}] \Big\} + \epsilon_{ij}, \\
\boldsymbol{\phi}_i &= \begin{bmatrix} lKe_i \\ lKa_i \\ lCl_i \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix} + \begin{bmatrix} b_{1,i} \\ b_{2,i} \\ b_{3,i} \end{bmatrix} = \boldsymbol{\beta} + \mathbf{b}_i, \\
\mathbf{b}_i &\sim \mathcal{N}(\mathbf{0},\, \Psi), \\
\epsilon_{ij} &\sim \mathcal{N}(0, \sigma^2).
\end{aligned}
\tag{3}
$$

3.2 Fitting the base model

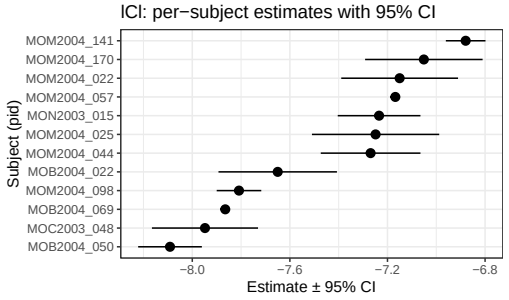
The previous section informed the decision of what the base model should include. This is a model with random effects (and by default fixed effects too) for all three parameters, lK_e, lK_a and lCl. However, for the given dataset, convergence with all



(a) Confidence Intervals for each subjects for lK_e.



(b) Confidence Intervals for each subjects for lK_a.



(c) Confidence Intervals for each subjects for lCl.

Figure 5: Confidence intervals of the three parameters when an individual model was fitted for each subject.

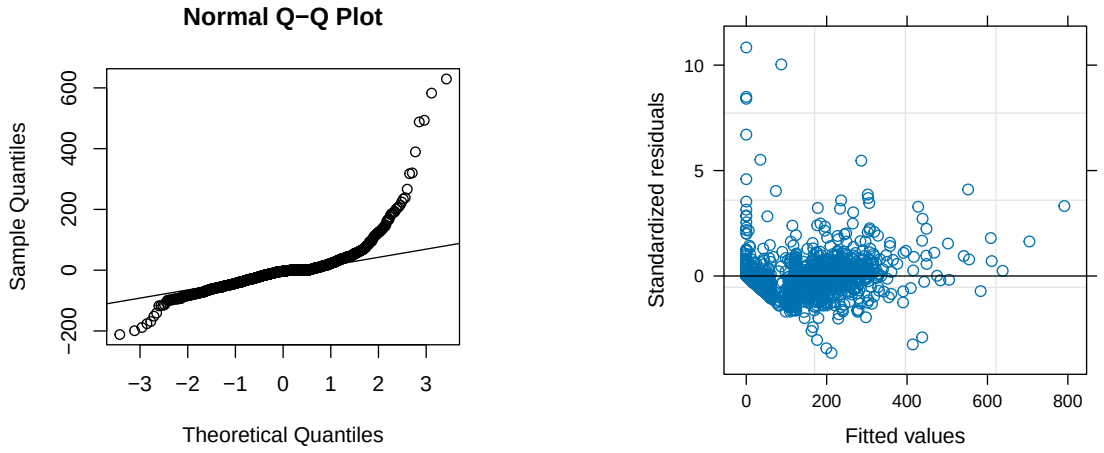
three of these parameters as random effects proved impossible. Numerous attempts were tried with various different control levels, but none worked.

Thus, it was decided to remove some random effects with the suspicion that the model may be overparameterized and thus lead to singularities or convergence issues. The following was found (note that in all the cases below the fixed effects remained the same in that it included all three parameters and Restricted Maximum Likelihood (REML) was used to fit the Non-linear Mixed-effects model (NLME):

1. Fitting a model with only lK_e and lK_a as random effects led to immediate convergence without having to change the control parameters of the estimation method.
2. Fitting a model with only lK_e and lCl as random effects did not converge even after extensive tries at altering the control parameters.
3. Fitting a model with only lK_a and lCl as random effects did not converge even after extensive tries at altering the control parameters.

Thus, it was decided to use the model that only used lK_e and lK_a as random effects. Investigating the output of this model revealed that lK_a had a near zero standard deviation estimate, indicating that it could be removed as a random effect. lK_e had a standard deviation estimate of 0.45.

The residual versus fitted plot and Q-Q-plot of this base model are in Figure 6. It is very clear from both of these plots that the model is not performing well and that there are structural issues with the current formulation. The Q-Q-plot shows that the residuals greatly deviate from the 45 degree normal line at the tails. The plot of the residuals against the fitted values also do not show a random scatter, but rather a clustering of points on the bottom-left corner. Thus, further modelling and investigation was needed.



(a) Q-Q-plot of the residuals of the base model.

(b) A plot of the residuals against the fitted values of the base model.

Figure 6: Q-Q-plot of the residuals and a plot of the residuals against the fitted values of the base model.

In order to proceed, the estimation method was changed from REML to Maximum Likelihood (ML). This is because nested NLME models with different random or fixed effects cannot be compared using REML. Since the next step was to consider adding covariates to either the fixed or random effects, it was necessary to switch to ML in order to compare likelihood ratio test results. When switching estimation methods and holding all other things constant, the estimates of the fixed effects and random effects were nearly identical. Further, the Q-Q-plot of the random effect lKe in Figure 7 shows that the distributional assumption that the random effects follow a Normal Distribution was not violated. Thus, our attention was turned to

adding covariates.

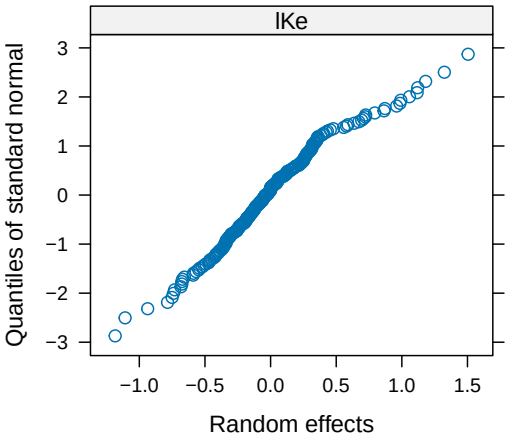


Figure 7: A Q-Q-plot of the random effects for lKe of the base model in Equation 3.

3.3 Adding covariates

The purpose of including covariates in this framework is to explain systematic between-subject differences in parameters such as lKe. By doing so, the model attributes less unexplained variation to the random effects, which can reduce their estimated variance and improve interpretability and predictive performance. In order to determine which covariates to add, the random effects of lKe was plotted against each covariate to determine which showed patterns that could be included in our model.

The continuous covariates, weight and age that were centred are plotted in Figure 8, while the categorical covariates are plotted in Figure 9. It is clear from Figure 8 that there is a structural relationship between age and weight with the random effects estimates of lKe as seen by the curve in the blue line that is a least squares line that was added to the plot. Both of these variables and their squared version were added and testing in the model in the following section. The squared version was added to account for the curvature that can be seen in the fitted line. However, since these two variables are highly correlated, only one of them was included in the final model.

None of the categorical variables were considered as covariates to be added to the model. This decision was based on Figure 9 where the box plots show that there is no significant difference in the random effects estimates of lKe and the different levels of

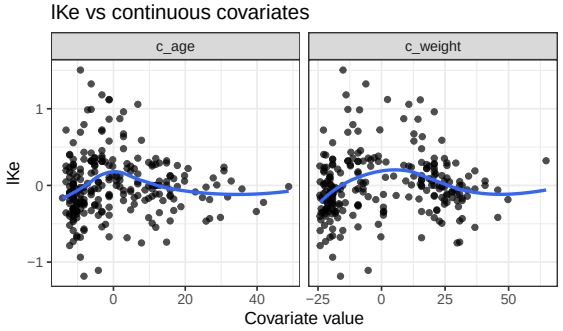
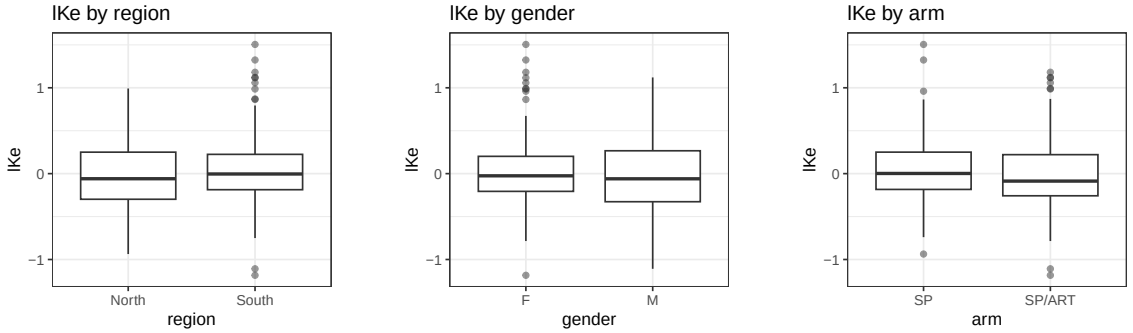


Figure 8: A plot of the random effects estimates for lKe for each subject plotted against (centred) age (left) and (centred) weight (right).



(a) A boxplot of the random effects estimates for lKe for each subject within each region.

(b) A boxplot of the random effects estimates for lKe for each subject for each gender.

(c) A boxplot of the random effects estimates for lKe for each subject within each treatment arm.

Figure 9: Box plots of the random effects estimates for lKe against different levels of the three categorical variables, region, gender and arm.

region, gender and arm. Thus, there is strong enough evidence to suggest that adding any of these as covariates would not aid in modelling a structural aspect of the data currently included in the random effects estimates. Further, reducing the number of likelihood ratio test to be carried out reduces curbs the issue of unknowingly increasing the Type-I error rate from repeated hypothesis testing. Thus, only age and weight and their squares were tested formally.

To test if age and weight significantly improved the model, they were added as fixed effects to model lKe. In other words, lKe is modelled to have a population mean and a random slope determined by age and weight. Beginning with weight, a model was built that added weight and weight^2 to the lKe fixed effects. Both of these

terms were highly significant with p-values of < 0.01 each. The anova likelihood ratio test between the base model and this model had a p-value of 0.0004, proving that the addition of both of these terms significantly improved the model fit.

Next, the same was repeated for age, where age and age^2 was added to the base model. In this case age had a p-value of 0.07, whereas age^2 had a p-value of 0.01. Thus only age^2 was significant at the 5% level. However, in order to be able to model the curve seen in Figure 8, the linear term was left in and the anova test was carried out. The addition of the two age covariates significantly improved the model fit with a p-value of 0.05.

Finally, since age and weight are highly correlated, the AIC and BIC of the model that added weight and its square and the model that added age and its square were compared. The model that added weight had an AIC and BIC of 18257 and 18294, respectively, while the model that added age had an AIC and BIC of 18264 and 18302, respectively. Since the model that added weight and its square had the lower AIC and BIC, it was determined to be the superior model.

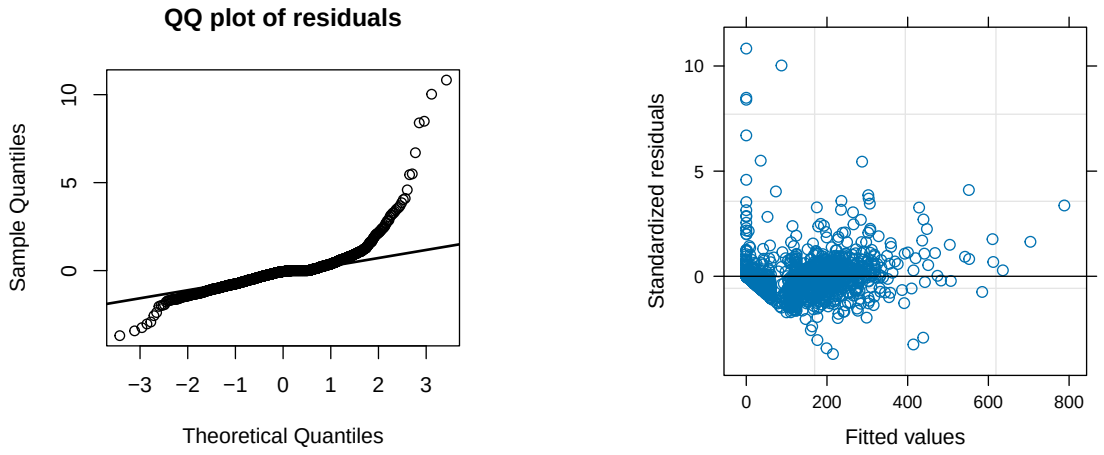
The base model had a variance estimate of lKe of 0.20, while this new model had an estimate of 0.19. Thus a small amount of the random effects were accounted by the structural element of a subject's weight. Call this new model base-plus-weight. Since the random and fixed effects parts of the model were finalized, the base-plus-weight model was updated using REML estimation.

This Q-Q plot of the residuals and the residuals against the fitted values of the base-plus-weight model is again plotted in Figure 10. From these two figures it is clear that the model fit is not improved and that the model assumptions (of the normality and homoscedasticity of the errors) are clearly being violated. Unfortunately the addition of the covariates did not improve this aspect and further attention needed to be paid to the variance and correlation structures of the model. This was done in the sections below.

3.4 Assessing the Need for a Variance Structure

One of the assumptions of this model is that the residual variance is homogeneous across levels of grouping factors such as treatment arm, gender, or region. If this assumption is violated, a variance–covariate structure (e.g., different residual variances per subgroup) may be required to obtain valid standard errors and improve model fit.

To evaluate this assumption, the normalized residuals from the fitted model against key categorical covariates (arm, gender, and region) was plotted. Box plots were used to visualise whether the spread of residuals differed systematically across the



(a) Q-Q-plot of the residuals of the base-plus-weight model.

(b) A plot of the residuals against the fitted values of the base-plus-weight model.

Figure 10: Q-Q-plot of the residuals and a plot of the residuals against the fitted values of the base-plus-weight model.

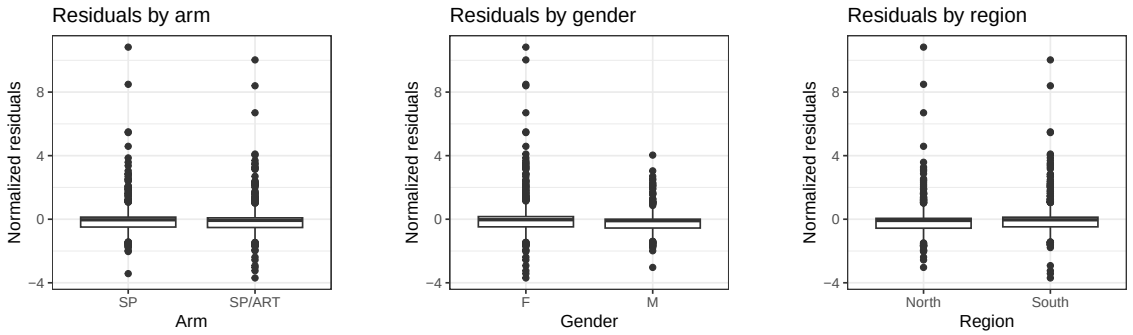
subgroups. The rationale was straightforward:

- If residual variance is consistent across groups, the box plots should show similar spread and symmetry across arms, genders, and regions.
- If residual variance differs (e.g., much wider spread for one arm than another), this would indicate heteroscedasticity, suggesting the need to specify a variance structure such as varIdent in the model.

The plots in Figure 11 showed no meaningful differences in residual spread across arm, gender, or region. Therefore, introducing an additional variance structure to account for different variances for each level of a factor was not deemed necessary.

Another potential variance structure would model the variance as a function of the fitted values to account for an increase in variance as the fitted values increase. However, the plot of residuals against the fitted values of the base-plus-weight model did not show a fanning effect where residuals increase with fitted values systematically. Thus this variance structure was also not deemed as necessary.

Finally, the consideration was made if the variance of residuals increased with weight. Figure 12 plots the normalised residuals of the base-plus-weight model against the centred weight of subjects. This plot clearly shows no substantial increase in variance as the weight of the subjects increase, thus this variance structure was also not



(a) A boxplot of the residuals of the base-plus-weight model for each treatment arm.

(b) A boxplot of the residuals of the base-plus-weight model for each gender.

(c) A boxplot of the residuals of the base-plus-weight model for each region.

Figure 11: Box plots of the residuals of the base-plus-weight model against different levels of the three categorical variables, region, gender and arm.

deemed appropriate for the given model.

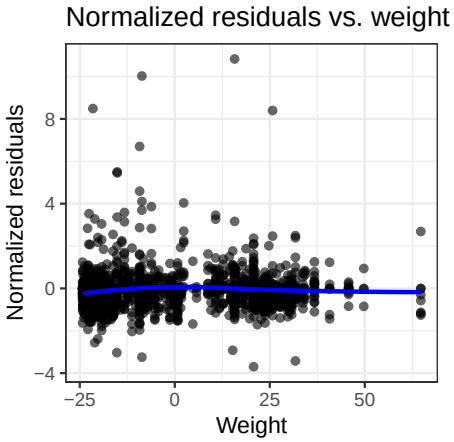


Figure 12: A plot of the normalised residuals of the base-plus-weight model against the centred weight of subjects.

Since none of the variance structured seemed well suited for the problem at hand, attention was given to investigate the need for a change in the correlation structure.

3.5 Assessing the Need for a Correlation Structure

Another assumption of non-linear mixed-effects models is that residuals are independent within subjects. In longitudinal pharmacokinetic data, however, measurements

close in time are often correlated. If this correlation is ignored, standard errors can be biased and the model may not fit well.

To investigate this, the autocorrelation function (ACF) of the normalized residuals from the base model without any correlation structure was examined, as shown in Figure 13. The ACF plot showed evidence of residual autocorrelation at low lags, specifically at day 1, 2 and 3, suggesting that an additional correlation structure might be warranted.

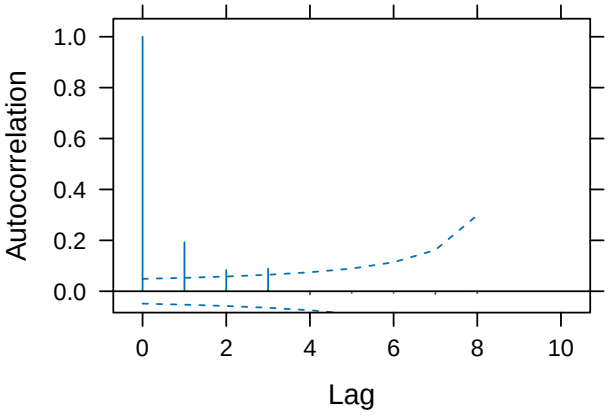


Figure 13: An autocorrelation function (ACF) of the normalized residuals from the base model without any correlation structure.

The model was therefore refit with a series of candidate correlation structures:

1. Continuous-time AR(1): which models correlation decaying with time lag when observations are unequally spaced.
2. Discrete-time ARMA structures using including:
    - AR(1): autoregressive of order 1
    - MA(1): moving average of order 1
    - ARMA(1,1): autoregressive–moving average with one parameter of each type
    - AR(2): autoregressive of order 2
    - MA(2): moving average of order 2
    - ARMA(2,1): autoregressive of order 2 with moving average of order 1

- ARMA(1,2): autoregressive of order 1 with moving average of order 2

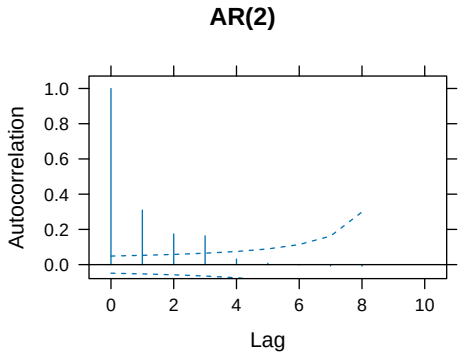
Note that the ARMA(1,1) and MA(1) models did not converge, even after increasing the number of allowed iterations to 2000. The remaining models were compared to the base-plus-weight model using AIC, and where possible, nested comparisons were formally tested using likelihood ratio tests. The likelihood ratio test was only possible in the Continuous-time AR(1) model case. All of the candidate correlation structures improved model fit slightly relative to the base model except for the Continuous-time AR(1) that had a p-value of 0.9992 in the anova test. This can be seen by the lower AIC values in Table 1.

Model	df	AIC
base-plus-weight	7	18296.25
Continuous-time AR(1)	8	18298.25
AR(1)	8	18167.44
AR(2)	9	18167.41
MA(2)	9	18174.49
ARMA(1,2)	10	18176.01
ARMA(2,1)	10	18169.37

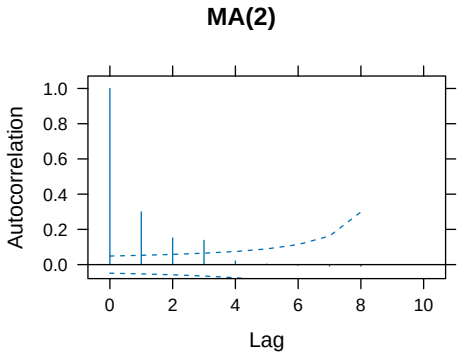
Table 1: Model comparison by AIC.

However, when re-examining the residual ACF plots for the better-fitting alternatives (AR(1), AR(2), MA(2), ARMA(1,2) and ARMA(2,1)), in all cases, serial correlation in the residuals persisted, indicating that the correlation misspecification was not adequately resolved by these structures. Figure 14 shows three of these ACF functions for the AR(2), MA(2) and ARMA(1,2) models as an example. From these plots it is clear the the correlations for day 1, 2 and 3 remain significant.

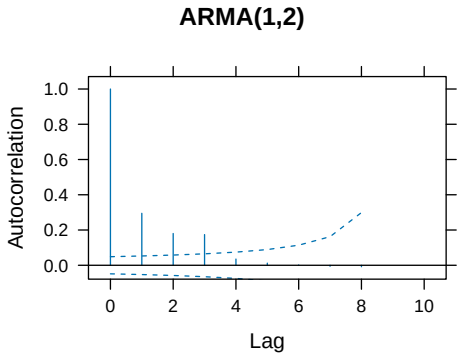
Although residuals displayed some autocorrelation, adding conventional correlation structures — including CAR(1), AR(1), MA(2), AR(2), ARMA(1,2) and ARMA(2,1)— did not meaningfully improve model fit or eliminate the residual dependence. This suggests that the remaining correlation reflects other forms of model misspecification (e.g., missing covariates or non-linear dynamics) rather than a simple ARMA process. As a result, the simpler model without an additional correlation structure was retained.



(a) An autocorrelation function (ACF) of the normalized residuals from the base model with a AR(2) correlation structure.



(b) An autocorrelation function (ACF) of the normalized residuals from the base model with a MA(2) correlation structure.



(c) An autocorrelation function (ACF) of the normalized residuals from the base model with a ARMA(1,2) correlation structure.

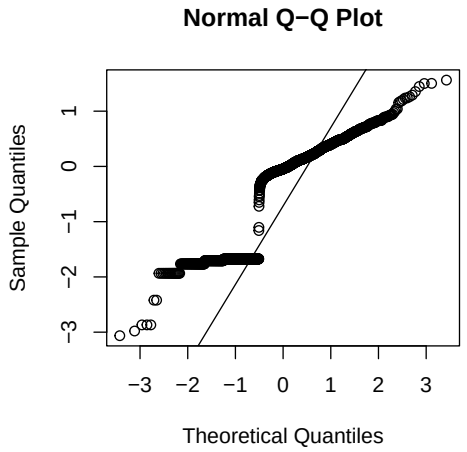
Figure 14: Autocorrelation functions for three of the correlation structures that were examined.

3.6 Final Consideration: Log-Transforming the Response

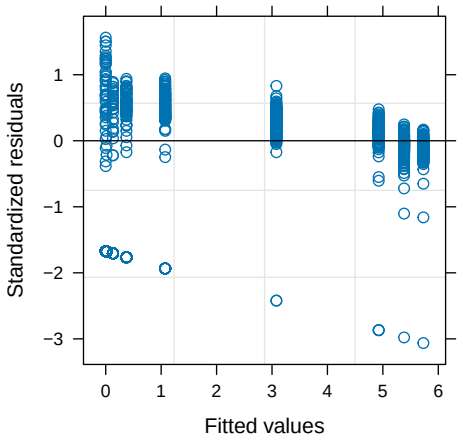
As a final considering in an attempt to improve the model fit, a log transformation of the response was attempted. The whole modelling procedure above was repeated where individual models were fit using nlsList and the self-start function SSfol. Thereafter, it was attempted to fit a NLME with all three parameters as random effects, but this did not converge. Reducing to a single random effect on lKe converged, but the estimated standard deviation of the random effect was near

zero, indicating minimal between-subject heterogeneity on the log scale.

The same covariates used on the raw scale were then added to lKe, namely weight and its square. None were significant; a likelihood ratio test comparing the covariate model to the intercept-only log model gave a p-value of 0.96, so covariates were not retained. A REML refit of the basic log model confirmed the near-zero lKe random effect standard deviation.



(a) Q-Q-plot of the residuals of the log-transformed response model.



(b) A plot of the residuals against the fitted values of the log-transformed response model.

Figure 15: Q-Q-plot of the residuals and a plot of the residuals against the fitted values of the log-transformed response model.

However, residual diagnostics on the log-scale model were problematic. Figure 15 indicates the following:

- Residuals vs fitted: vertical banding/striping (many repeated fitted values), suggesting the model is not capturing subject-level variability or dynamics.
- Q–Q plot: piecewise/stepped pattern with horizontal runs which is inconsistent with normality.

The log-scale model had a lower AIC of 9240 compared to the base-plus-weight model's AIC of 18296. However, these criteria are computed on different response scales (log-normal vs normal error models), so AIC are not strictly comparable across transformations. Even setting that caveat aside, the substantive residual abnormalities on the log scale outweigh the numeric AIC advantage.

In conclusion, although logging the response yielded lower information criteria, the log-scale model exhibited clear misspecification and effectively eliminated between-subject variability (near-zero lKe random effect standard deviation). The raw-scale model, while having higher AIC, provides a more realistic description of individual-level heterogeneity and cleaner diagnostics. Therefore the raw-scale specification was retained.

4 Conclusion and Discussion

The final model in this report, i.e. the base-plus-weight model, can be formulated as below.

$$
\begin{aligned}
c_{ij} &= \frac{D_i \, \exp(lKe_i + lKa_i - lCl_i)}{\exp(lKa_i) - \exp(lKe_i)} \left\{ \exp\left[-\exp(lKe_i)\, t_{ij} \right] - \exp\left[-\exp(lKa_i)\, t_{ij} \right] \right\} + \epsilon_{ij}, \\
lKe_i &= \beta_{1,0} + \beta_{1,1}\, c_{w,i} + \beta_{1,2}\, c_{w,i}^2 \; + \; b_{1,i}, \\
lKa_i &= \beta_{2,0}, \\
lCl_i &= \beta_{3,0}, \\
b_{1,i} &\sim \mathcal{N}(0, \omega_1^2), \qquad \epsilon_{ij} \sim \mathcal{N}(0, \sigma^2),
\end{aligned}
\tag{4}
$$

Between-arm differences was explored by trying to adding arm as a fixed effect on lKe. Exploratory diagnostics (random effects estimates and residuals by arm) showed no clear signal of arm-related differences. When arm was included, the model failed to converge or produced a "Singularity in backsolve at level 0" error. Given the absence of a visual signal and the numerical instability upon inclusion, the final model omits arm and results are interpreted as pooled across arms; this is noted as a limitation.

Residual diagnostics (Q-Q plots and residuals versus fitted in Figure 10) indicated systematic departures from model assumptions, suggesting misspecification of the mean and/or error structure. As such, close attention was not paid to exact covariate parameter estimates, but fitted curves for a random sample of 9 subjects are presented for illustration purposes in Figure 16. From these curves it is clear that the model can detect the general shape of the curves as well as some differences between the curves of different subjects, but does worse for some of the subjects. For example, MOC2003_024, where the fitted line misses most of the observations in the middle section.

Another thing to note is that the first subject in this figure shows that some subjects

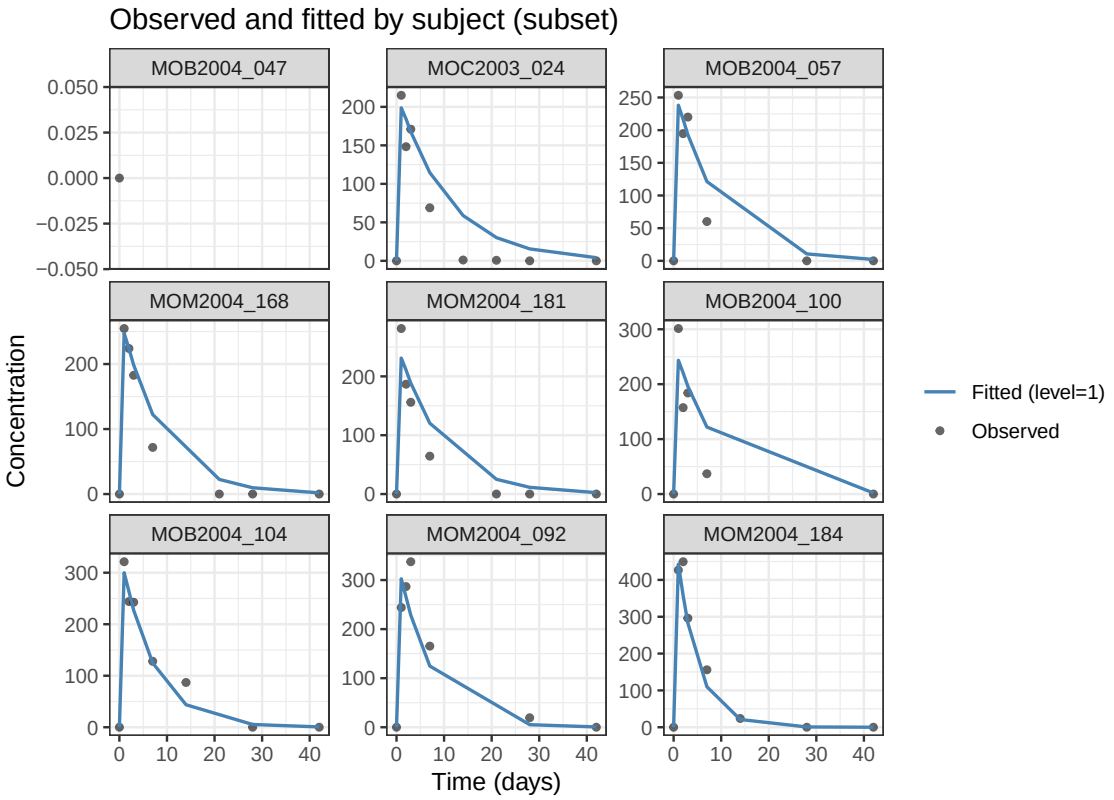


Figure 16: Fitted prediction curves for a random sample of 9 subjects using the base-plus-weight model.

had very sparse data. A possible future extension could be to impute the missing values and to refit the models.

5 Appendix

Appendix: R Code Repository

The full R code used in this analysis is available at:

`github.com/Annie0619/LDA-Assignment-2-2025`

References

[1] William C. Zamboni, Rosane Charlab, Gilbert J. Burckart, and Clinton F. Stewart. Effect of obesity on the pharmacokinetics and pharmacodynamics of anticancer agents. *The Journal of Clinical Pharmacology*, 63(S2):S85–S102, 2023.