



Emerging Methods in Progression Modelling of Alzheimer's Disease

A Comparative Analysis

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1 Simulation Study

An important aspect of the application of this thesis is to fit non-linear mixed models to different data sets and use these models to determine a treatments effect. Therefore, this simulation study will investigate how well models based on the Lindstrom and Bates algorithm, and Laplace approximation extrapolate. For this the packages `nlme` and `lme4` will be used. The `nlme` package uses the Lindstrom and Bates algorithm, while the `lme4` package uses the Laplace approximation. Both assume that the random effects and errors are normally distributed, however, the assumption of normality can not be ensured in practice. Hence, this simulation study will also examine how the parameter estimates and the predictions will be affected if the assumption of normally distributed random effects and errors does not hold. Lastly, it will shortly be investigated how the models are affected by the size of the data set.

Based on this simulation study, we hope to gain insight into which estimation is best to use for our application, based on the characteristics of our data.

1.1 Gaussian Random Effects and Errors

In the first part of the simulation study, data will be simulated based on a non-linear mixed model for repeated measures with random effects and errors that are normally distributed. The model that will be used for simulating the data is based on a data set presented in [Halimi, 2005], which regards a study on how breast tumors evolve in rats. This model is used since the trial, that it is based upon, somewhat resembles the data from CPAD. That is, it has repeated measures, the model is time-dependent, and is related to a medical study with multiple subjects, in different treatment.

The study involves 60 22-day-old rats which were examined once a week for breast tumors over a period of 25 weeks. These rats were split into three different arms where they received three different diets during the trial period. [Halimi, 2005] suggests a model to describe the volume of the breast tumor which depends on time, which for the i th rat at the j th measurement is given as

$$y_{i,j} = \frac{\nu_{1,i} \cdot \exp(t_{i,j} - \nu_{2,i})}{1 + \exp\left(\frac{t_{i,j} - \nu_{2,i}}{\nu_{3,i}}\right)} + \varepsilon_{i,j} \quad (1.1)$$
$$\nu_{1,i} = \beta_1 + U_{1,i}, \quad \nu_{2,i} = \beta_2 + U_{2,i}, \quad \text{and} \quad \nu_{3,i} = \beta_3 + U_{3,i},$$

for $i = 1, 2, \dots, 60$ and $j = 1, 2, \dots, 25$. Here $\beta^\top = (\beta_1, \beta_2, \beta_3)$ represents the fixed effects, whilst $U_i^\top = (U_{1,i}, U_{2,i}, U_{3,i})$ represents the subject-specific random effects. Specifically, the fixed effects in the trial represent the mean of maximal tumor volume, time until 50% of maximal volume, and growth rate. Lastly, $\varepsilon_{i,j}$ represents the error for subject i at time $t_{i,j}$. This model is chosen because it effectively captures the significant variability seen in tumor growth dynamics, accommodating various patterns such as logistic growth, exponential expansion, and even periods of stagnation followed by decline. For further description of the choice of model for the specific trial see [Halimi, 2005, p. 76-89]. Hence, we have a non-linear

mixed model with ten parameters. These parameters include the three fixed effects, the covariance structure of the random effects (six parameters), and the within-group variance (one parameter).

Furthermore, [Halimi, 2005] presents some empirical estimates for both the fixed effects and the covariance matrices for both the random effects and the errors, which we wished to use for simulating the data, such that the simulations are thus expected to mimic real life data. This, however, is not possible. The values of the fixed effects and the covariance matrices, Ψ and $\Sigma_i = \sigma^2 I$, for the random effects and errors estimated by [Halimi, 2005] using experimental data are

$$\beta = \begin{bmatrix} 5.0512 \\ 13.8670 \\ 0.8487 \end{bmatrix}, \quad \Psi = \begin{bmatrix} 51.8863 & -1.0499 & -0.0546 \\ & 15.8465 & -0.0459 \\ & & 0.0136 \end{bmatrix} \quad \text{and} \quad \Sigma_i = 0.9399^2 I. \quad (1.2)$$

Furthermore, the random effects and errors are chosen to have mean 0.

We want to simulate 600 subjects instead of the 60 subjects in the original trial, presented in [Halimi, 2005], to make it more coherent with the analysis of the data from the CPAD database, as well as easing the interpretation of the distributions. Data generated using the model in (1.1) and the above-mentioned structure for the fixed effects, random effects, and errors, can be seen in Figure 1.1, where the trajectories of five subjects are highlighted. More precisely, the volume of the breast tumor, measured in mm^3 , is plotted for each subject against time measured in weeks.

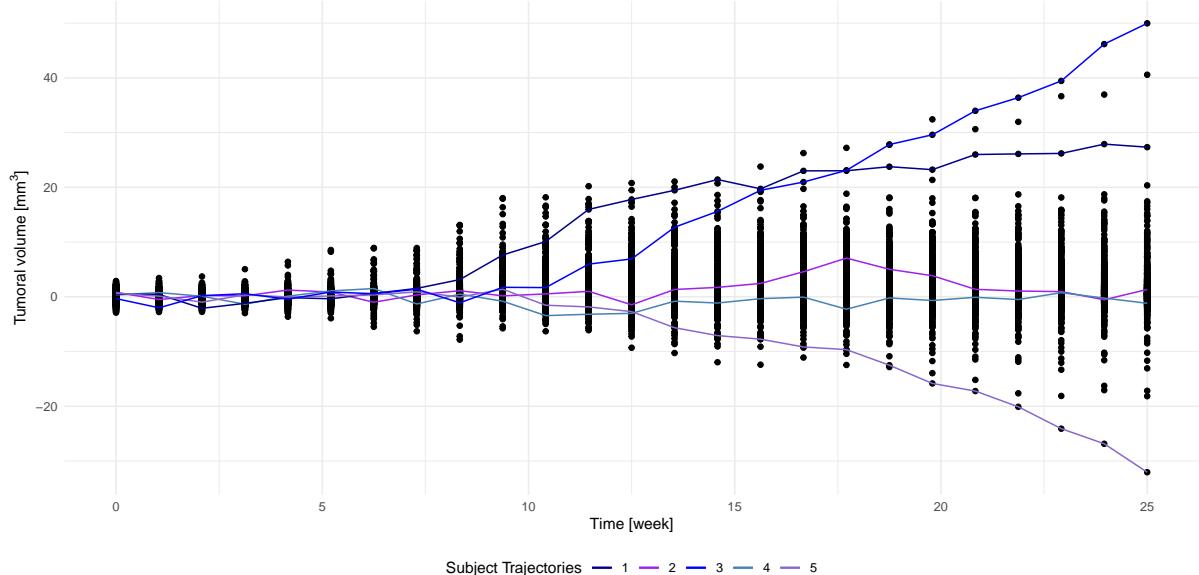


FIGURE 1.1: Simulated data for tumoral volume for 600 subjects over 25 weeks, including the trajectories of five of the subjects.

As illustrated in Figure 1.1, the initial tumoral volumes for each subject are approximately zero, and over the course of the trial, these volumes progressively diverge, exhibiting increasing variability. For example, we see that the tumoral volumes of subject one and three pass 20 mm^3 at the 16th measurement and subject three progresses to 50 at the end of the trial. At the other end of the spectrum there is subject five whose tumoral volume is just below -30 mm^3 .

mm^3 at the end of the trial. However, most of the subjects' tumoral volumes keep within an interval of -20 mm^3 and 20 mm^3 .

We then need to fit a non-linear mixed model to each of these simulations using the `nlme` function from the `nlme` package and `nlmer` function from the `lme4` package. When using `nlme` we opt to use "ML" (maximum likelihood) as the estimation method, a maximum of 1000 iterations in the Lindstrom and Bates algorithm, and a maximum of 1000 iterations within each of the PNLS and LME steps. Furthermore, using the `nlmer` function 10000 iterations in the optimisation procedure was opted for. The number of iterations are based upon an investigation wherein 50, 100, 1000, and 10000 iterations were tested, to determine which one performed best. Evaluating the results, it was evident that there was no significant improvement when transitioning from 100 to 1000 iterations using the `nlme` function. As a result, the decision was made to opt for 1000 iterations to ensure more robust results. Furthermore, 10000 iterations in the `nlmer` function was chosen for the same reasons. The ML method is to be used in the `nlme` function since this is the only choice in the `nlmer` function. Hence to make a comparison of the two function, also by comparing the AIC and BIC, the ML method should be used in both function. Additionally, a time constraint of five minutes for the optimisation procedure during model fitting was chosen for both the `nlme` and `nlmer` function. These time limit was implemented to control the duration of the model fitting process, which is particularly crucial when dealing with scenarios where multiple data sets need to be simulated, and a model fitted for each one. More precisely, this choice was made because during our testing, we observed instances where the estimation method failed to converge at all. In contrast, estimation methods that did converge generally did so within the designated time limits. However, a few times the model fitting process seems to take up till 20 minutes and hence to control the time we use for fitting each model we make this time constraint. This constraint becomes especially relevant when conducting many simulations of data where a model should be fitted to each of them.

After simulating the 1000 different data sets we tried to fit a model using both the `nlme` and `nlmer` function. Here we saw that there where no problems fitting a model using the `nlme` function, that is no errors and an output of parameter estimates. However, none of the models using the `nlmer` function converged, which is to say that the optimisation procedure in the Laplace approximation did not converge. We attempted to adjust several different arguments within the function itself, including the maximum number of iterations in the optimisation procedure and initial values, but this did not help. Subsequently, we tried altering various parameters in the model when simulating the data to which the models were to be fitted. We found that the function using Laplace approximation to fit a model is not as stable when the variance and correlation in the random effects are large. Therefore, we chose to scale the covariance matrix by a factor of 1/100, such that the two estimation methods could be compared. However, based on this, we acknowledge that the function using Laplace approximation may not be suitable for the application if the variance and correlation between the random effects are large. Hence, the parameters that will be used are

$$\boldsymbol{\beta} = \begin{bmatrix} 5.0512 \\ 13.8670 \\ 0.8487 \end{bmatrix}, \quad \boldsymbol{\Psi} = \begin{bmatrix} 0.518863 & -0.010499 & -0.000546 \\ & 0.158465 & -0.000459 \\ & & 0.000136 \end{bmatrix} \quad \text{and} \quad \boldsymbol{\Sigma}_i = 0.9399^2 \mathbf{I}. \quad (1.3)$$

Furthermore, throughout the simulation study, the random effects and errors are chosen to have mean 0. Data generated using the model in (1.1) and the new above-mentioned structure for the fixed effects, random effects, and errors, can be seen in Figure 1.2, where

the trajectories of five subjects are highlighted. Again, it is the volume of the breast tumor, measured in mm³, plotted for each subject against time measured in weeks.

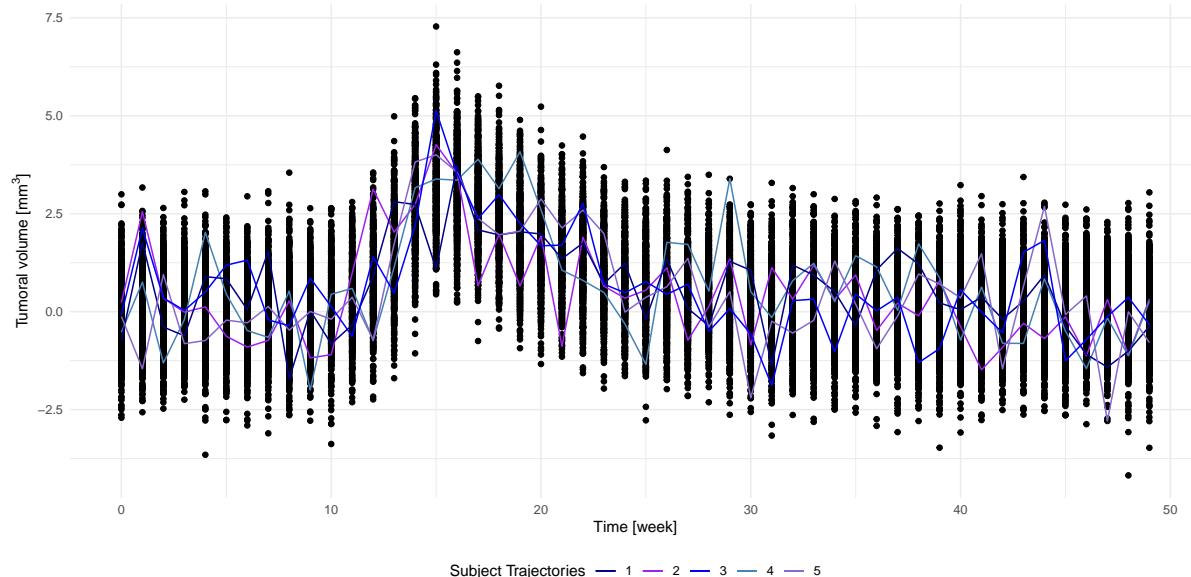


FIGURE 1.2: Simulated data for tumoral volume for 600 subjects over 50 weeks, including the trajectories of five of the subjects.

It can be seen in Figure 1.2 that the difference between the trajectories and hereby subjects are not as large as before. Moreover, it is evident that all subjects follow the same trend, namely, a rise from approximately week 12 to around week 16, followed by a subsequent decline. Again, both negative and positive values are seen, and, obviously, a negative volume does not make any sense and one should maybe have a lower limit of zero in the real study. Negative values may be caused by multiple factors in the model, such as a negative errors or the nominator being negative. Given that the primary objective of this simulation study is to assess the performance of non-linear mixed models rather than examining how well the model fits the particular trial data, we do not intend to conduct a more detailed investigation of this problem. Furthermore, here there has been generated data for 50 weeks instead of 25 weeks, which is due to the fact that we not only want to see how close the parameter estimates from the models are to the true values, but also how well the models predict. Hence the models are based on the first 25 weeks and the prediction can then be made for the next 25 weeks.

1.1.1 Model

After generating the data seen in Figure 1.2 models are fitted using both the `nlme` and `nlmer` function, after which there should be checked whether or not the model assumptions, normally distributed random effect and errors, and for this model, independent and homoscedastic errors, are fulfilled. In Figure 1.3 the standardized residuals are plotted against an index, where the indices correspond to the magnitude of the fitted values. Index 1 corresponds to the smallest fitted value, and the last index corresponds to the largest fitted value. This approach provides a visual representation of how the residuals vary across the spectrum of fitted values. Examining this plot helps identify patterns and/or trends in the residuals. In

Figure 1.3 it can be seen that standardized residuals are symmetrically centered around zero, exhibiting a consistent variance. Hence the homoscedastic assumption seems to be fulfilled.

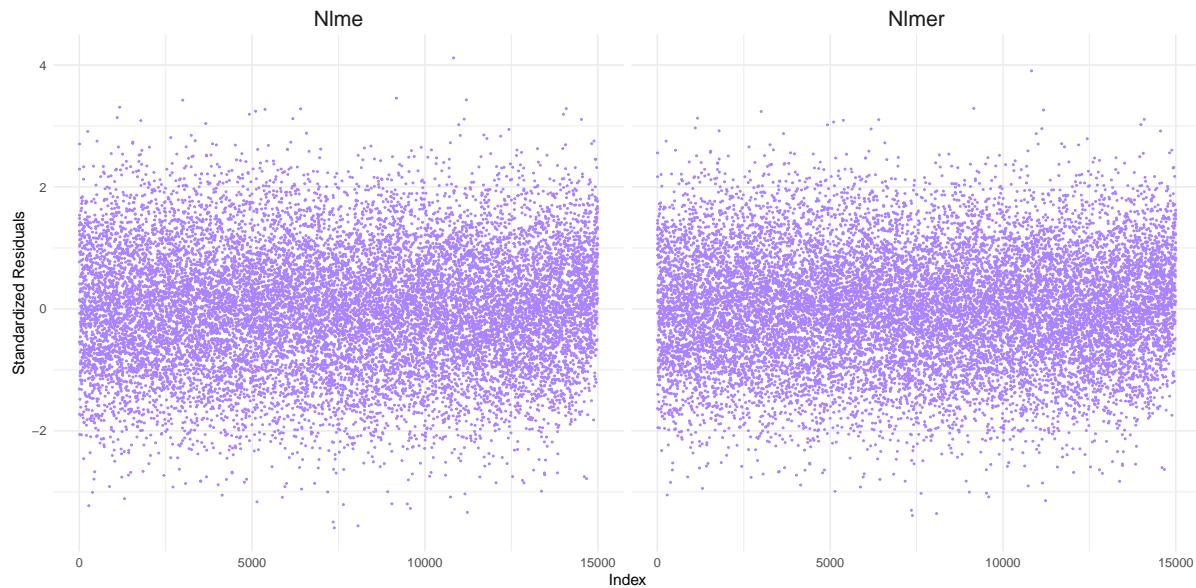


FIGURE 1.3: The standardized residuals for the nlme and nlmer model.

To determine if the assumption of normally distributed random effects and errors are satisfied we investigate their histograms and QQ-plots. In Figure 1.4 and Figure 1.5 the histograms of the three random effects and the errors estimated by the two models are illustrated. Additionally, the distribution of these values, the distribution which they were simulated from and the sampled random effects used for generating the data are illustrated by a purple-, blue-, and light blue curve, respectively.

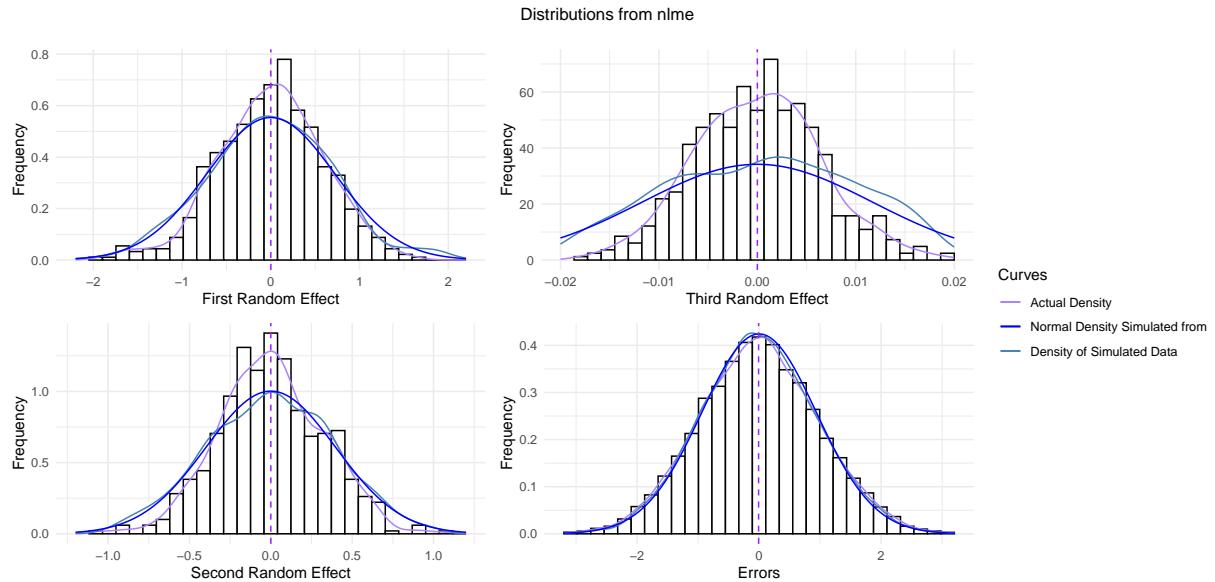


FIGURE 1.4: Histograms of the three random effects and the errors from the *nlme* model, including their densities (purple curve), the normal density (blue curve) used to simulate the data and the sampled random effects from the data. The dashed line represents the mean of the model values.

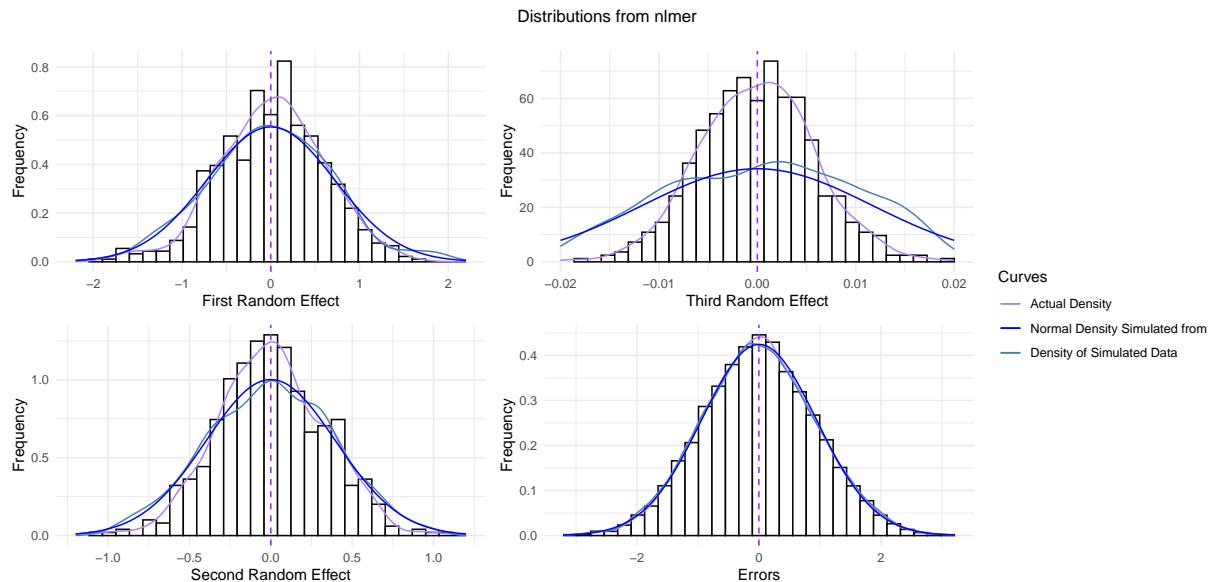


FIGURE 1.5: Histograms of the three random effects and the errors from the *nlmer* model, including their densities (purple curve), the normal density (blue curve) used to simulate the data and the sampled random effects from the data. The dashed line represents the mean of the model values.

Figure 1.4 and Figure 1.5 show that the second and third random effects are more leptokurtic than the densities they were simulated from, as opposed to the first random effect, which seems to fit the density it was simulated from closely. Moreover, the errors seem to follow the correct normal distribution more closely than the random effects do. However, the QQ-plots,

Figure A.1 and Figure A.2 in Appendix A, show that the random effects and the errors follow normal distributions. The histograms show that even though the random effects follow normal distributions, these are not the ones they were simulated from. Furthermore, by conducting a Ljung-Box test and looking at the ACE, Figure A.3 and Figure A.4 in Appendix A, of the residuals for each of the model, there are no indication of auto-correlation in the residuals. Hence, this indicates that the residuals are independent. Overall it seems like the model assumptions are somewhat fulfilled for both the nlme and nlmer model, which coincides with how the data set is generated.

After a model has been fitted to the data set and we have looked at how the random effects and errors in the model behave, we can start comparing how well the two models fit the data, estimates the parameters and predicts. At first we look at the AIC- and BIC values for each of the models to see how they compare. The nlmer model has an AIC value of 41782.38 and a BIC value of 41858.54, whereas the nlme model has an AIC value of 41783.11 and a BIC value of 41859.27. The AIC- and BIC values indicate that the nlmer model is the best, however, the AIC- and BIC values for the two models are very close. Hence, we should investigate further into the models to determine which model is best. We can further see how well the two models fit the data by for example plotting the mean trajectory of the data and those predicted by the two models. Looking at this could give an indication of which model fit is the best.

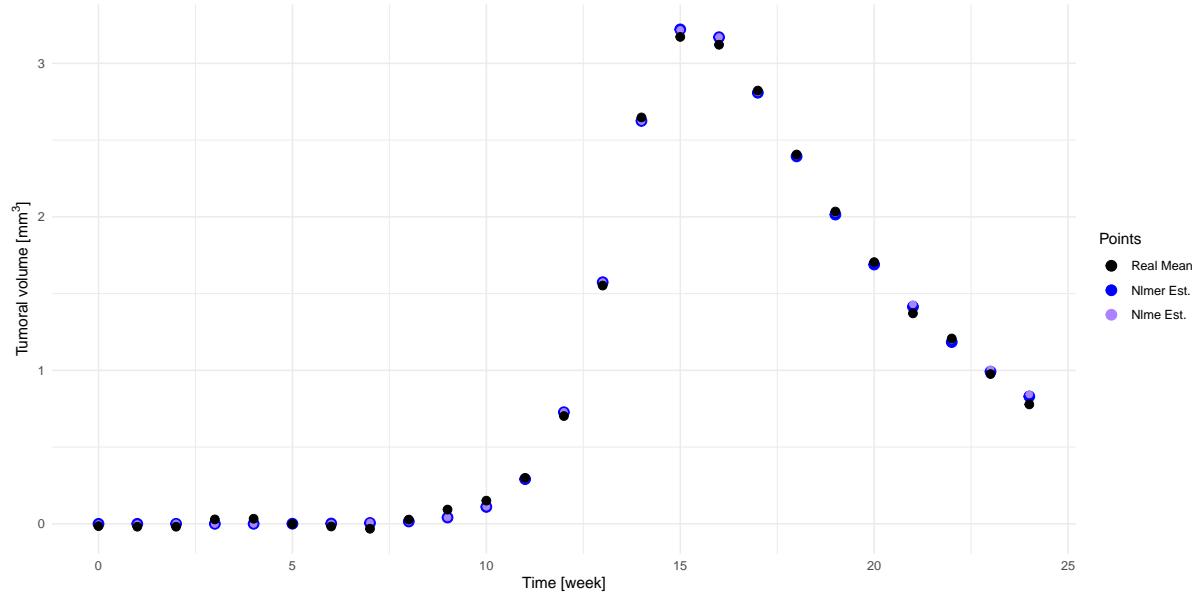


FIGURE 1.6: The mean of the simulated data, including the mean trajectory predicted by the two models.

Furthermore we can also look at the fit for one subject for the two models, which is presented in Figure 1.7.

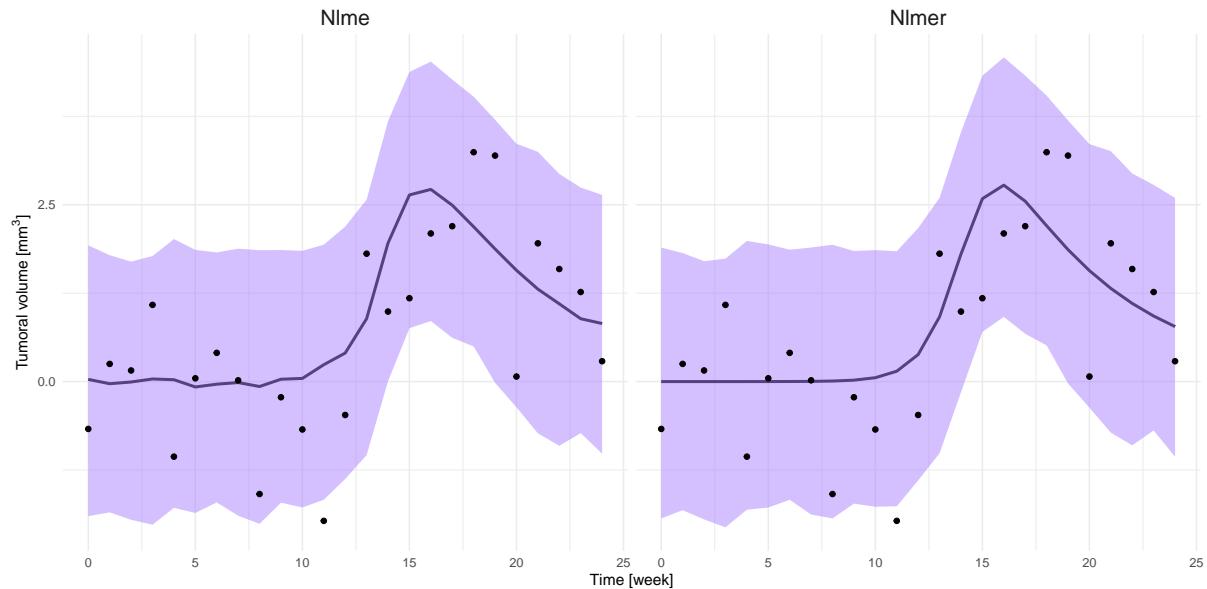


FIGURE 1.7: Simulated data for one subjects, including model estimated trajectory together with 95% prediction bands.

In both Figure 1.6 and Figure 1.7 it can be seen that the two models perform very similar. In Figure 1.7 there is also only seen very small differences in the prediction bands, where only one of the 25 points in both plots are outside the prediction bands. The mean absolute error (MAE) over the first 25 weeks for the nlme and nlmer model estimates of the mean are 0.007 and 0.003, respectively. This difference in MAE could be explained by the parameters being slightly worse estimated in the nlme model than in the nlmer model. Figure 1.8 illustrates the bias for the ten parameter estimates for both the nlme- and nlmer model.

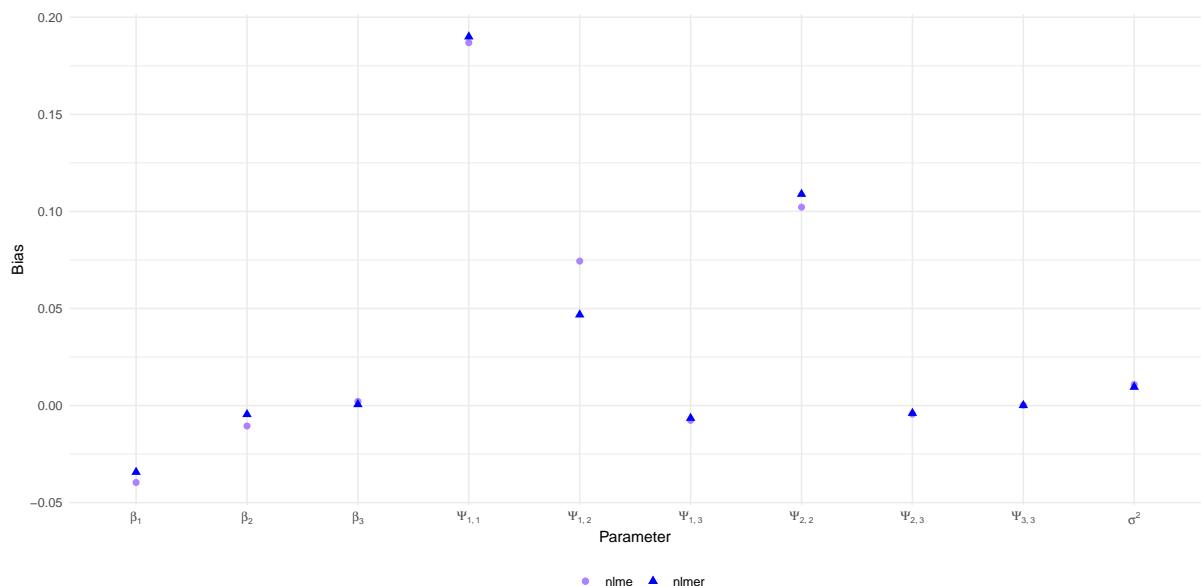


FIGURE 1.8: Bias for the ten parameters for the two models.

Here it can also be seen that the two models estimate the ten parameters quite well, with a maximal deviation from the true value at 0.187 and 0.190 for respectively the nlme and nlmer

model, for which the true value is 0.519. Figure 1.8 also shows that the `nlmer` model estimates the parameters at the same level or better than the `nlme` model except for the variance of the first- and second random effect. This could explain why the estimated trajectories of the `nlmer` model are slightly better than those of the `nlme` model.

This indicates a slightly better fit for the `nlmer` model, however, this analysis is on the data for which the model has been trained upon. It is even more interesting to look at how this affects future predictions. The figure below shows the data and the predictions along with the prediction bands of the mean trajectory of the data. Here the pink points are the real mean of the data set.

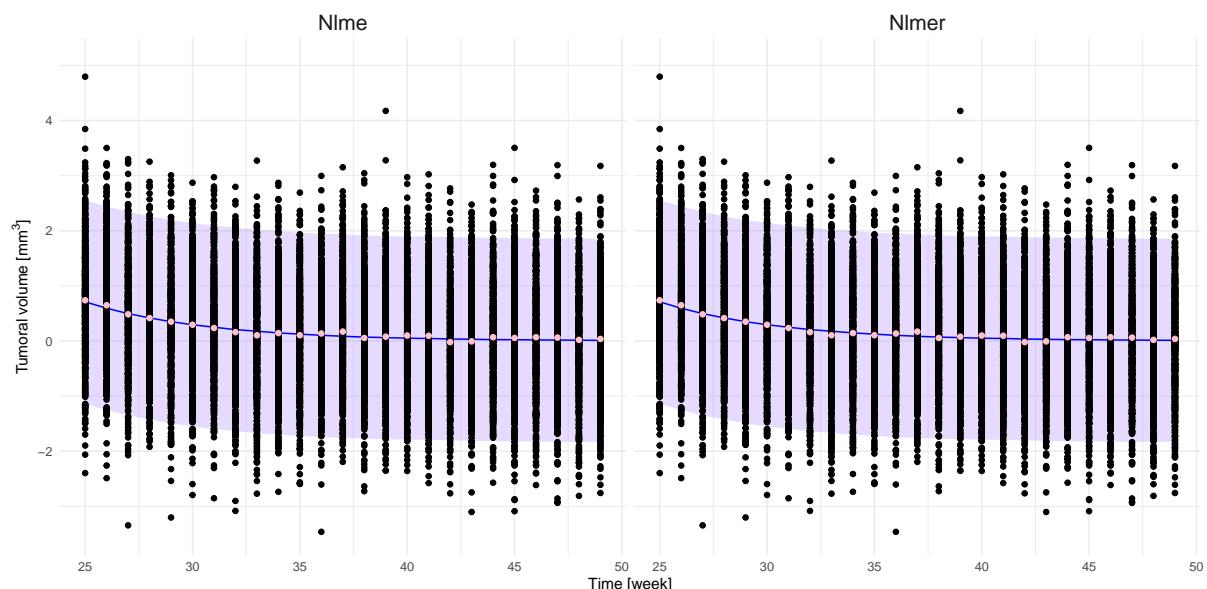


FIGURE 1.9: Simulated data for week 25 to 49, including mean and model predicted trajectories alongside 95% prediction bands.

Figure 1.9 also show that both models predict the mean trajectory of the data fairly well with prediction bands that are approximately as wide as those seen in Figure 1.7. Again, the `nlmer` model is slightly better than the `nlme` model.

However, as described above, we only observed a small difference between the models when looking at the AIC values, BIC values, parameter estimates, and predictions. These small deviations could be caused by the starting values in each of the optimisation procedures in the two different models and further small sampling differences in the data set could make a difference. To make a more robust conclusion of whether the `nlmer` function outperforms the `nlme` function in general, we repeat this process as just described multiple times. This should give a greater insight into the uncertainty and variability of the estimation method for slight sampling deviations. Specifically, we opted to conduct 100 simulations, where each simulation included both simulating the random effects, the errors, and the corresponding response variables, as well as fitting a non-linear mixed model to this data with both the `nlmer`- and `nlme` function. We opted to conduct 100 simulations as we thought this would be sufficient to take the uncertainty and variability of the estimation method into account.

1.1.2 Multiple simulations

As mentioned, we opted to conduct 100 simulations wherein the data used for both the `nlmer` and `nlme` models were the same. Additionally, as we just saw for one simulation, we will present some of the results that we will use to determine which of the methods that should be used for the progression models for repeated measures.

First we look at the AIC- and BIC values of the models, followed by the estimates of the parameters for each of the two models. Figure 1.10 illustrates the AIC- and BIC values of the 100 `nlme` and `nlmer` models.

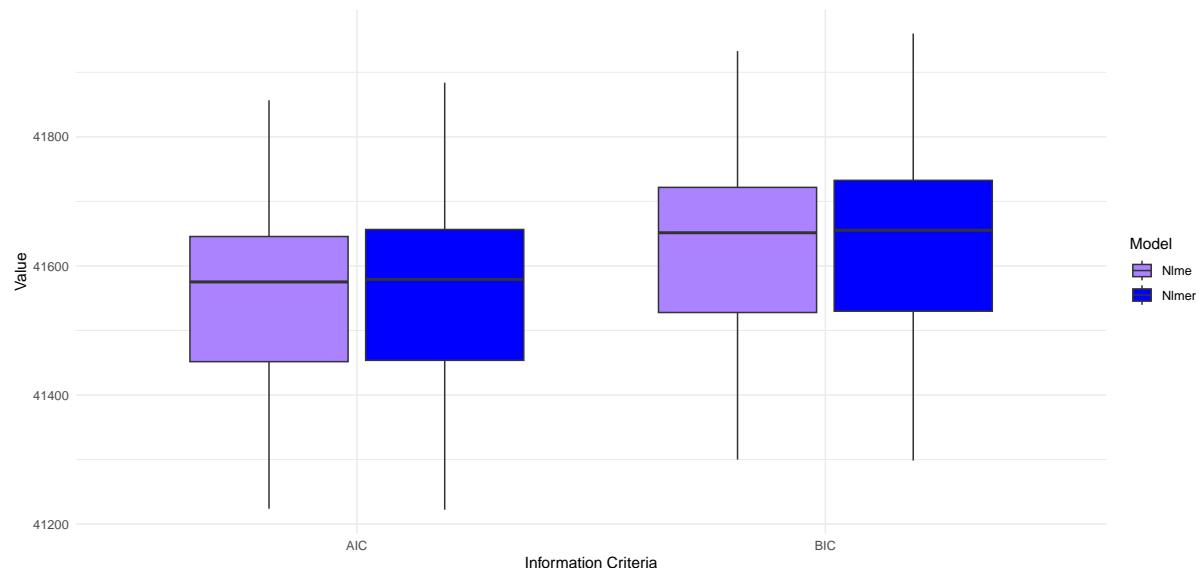


FIGURE 1.10: Comparison of boxplots for the information criteria, AIC and BIC, between the two models.

In Figure 1.10 it can be seen that the median of both the AIC- and BIC values of the 100 `nlme` models are slightly below that of the `nlmer` models. Furthermore, the same applies to the lower and upper quartiles as well as the minimum and maximum scores. The interquartile ranges of the both the AIC- and BIC values for the two models are largely similar, with a subtle elongation observed in the one for the `nlmer` models. All of this indicates that the `nlme` models are slightly better at fitting the data sets they are given. Furthermore, this can also be seen by looking at the mean AIC- and BIC values of the 100 models for each `nlme` and `nlmer`. The mean AIC- and BIC values of the `nlme` models are respectively 41553.54 and 41629.7, where those of the `nlmer` model are 41556.18 and 41632.34. Lastly, we looked into each data simulation and saw that in 61 of the 100 simulation had a better fit based on both the AIC and BIC by the `nlme` model.

To conduct a more thorough examination of overall performance, we examine the parameter estimates of the 100 simulations. The boxplots depicted in the figure below illustrates the bias in parameter estimates across the 100 models for each of the ten parameters, distinguishing between the two types of models.

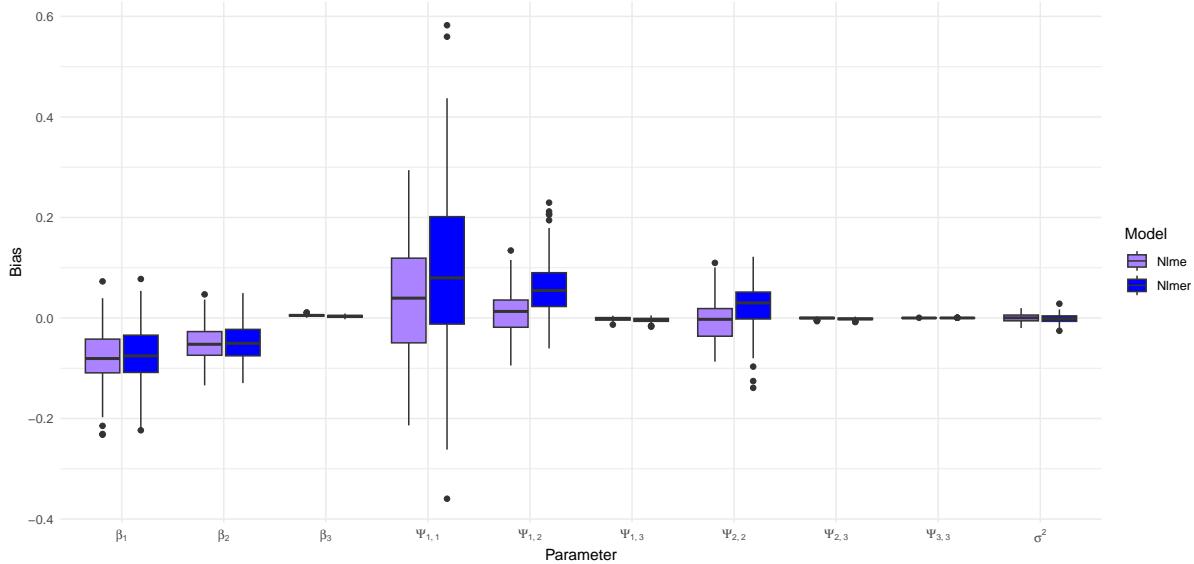


FIGURE 1.11: Boxplots for the bias of the parameter estimates for the two models.

It can be seen in Figure 1.11 that the bias for all the covariance estimates are more dispersed for the nlmer models than for the nlme models. However, the interquartile range and the range between the minimum and maximum score of the fixed effects for the two types of models are very similar. Additionally, we can observe that the median for the three fixed effects are slightly better for the nlmer models compared to that of the nlme models, which indicates that it in general is better at estimating these. However, the coverage of the first- and second fixed effect is better for the nlme models compared to that of the nlmer models. That is, the true parameter value lies within the confidence interval more often for the nlme models than for the nlmer model. The coverage of the third fixed effect is, however, better for the nlmer models. Furthermore, it can be seen that most of the times the two first fixed effects are underestimated, while the third fixed effect is mostly overestimated. Contrary to this, the variances for the first- and second random effect are most of the times overestimated. Moreover, when looking at the bias for the estimates of the covariance matrix, the nlme models, in general, have a lower bias than the nlmer models. This can especially be seen in the bias for the variance for the first random effect, where the bias of the estimate for the nlmer models are notably more dispersed and has larger median.

There has been fitted 100 of each models to the 100 data sets, and hence 1000 parameter estimates has been made. Comparing the estimates between the two models for each data set we observe that 519 of the total parameter estimates are better for the nlme models, compared to the nlmer models. Hence, the results again shows that the performance of the two model types remains fairly equivalent, which also can be seen in the boxplots for the bias of each of the parameters which are quite similar for the two models.

Lastly, we want to compare the two estimation methods by their prediction abilities. The process involved comparing the mean data at each time point with the predictions from each of the models, and this comparison was conducted across all 100 simulations. The MAE was computed for each time point across the 100 simulations for both types of models. The resulting MAEs for the two models across the 50 time points are depicted in Figure 1.12.

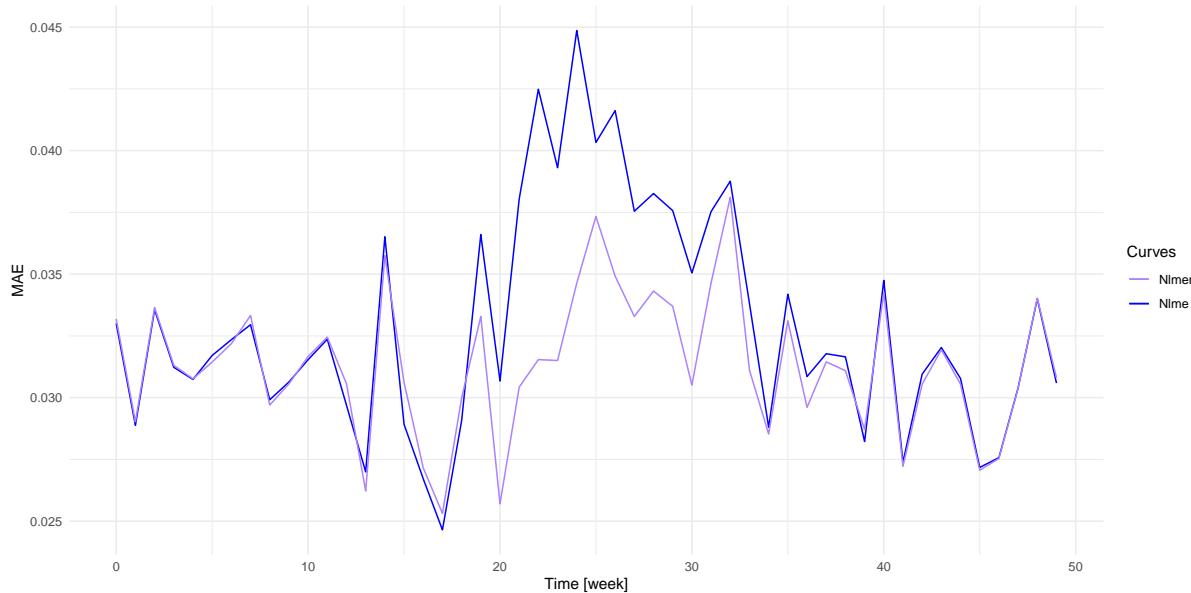


FIGURE 1.12: MAE for predictions of mean trajectory of the data for the two models.

Figure 1.12 shows that the predictions of the first 20 weeks mean trajectory for the two models have approximately the same MAE. However, between week 20 and 30 there is a larger difference, where the nlmer models seem to predict the mean trajectory of the data better than the nlme model. The last 20 weeks the two types of models seem to again predict very similarly.

This indicates that the nlme model type has a better overall performance with regards to parameter estimates of the covariances and describing the variation in the data, while nlmer models are better at predicting the mean trajectory of the data. Here, the last ability, is very important in the application, where this analysis of the two models suggest the use of the nlmer model contrary to the nlme model.

However, this analysis has only been conducted for data sets where both the random effects and errors follow a normal distribution. Since, we can not ensure that the condition is fulfilled in the application, we want to look into how robust the two model types/methods are when these conditions are violated.

1.2 Deviations From Normality

This section will focus on analysing the performance of the non-linear mixed model's estimation method when the random effects and errors are normally distributed, log-normally distributed, gamma distributed or some combination of the three. Hence, a similar simulation-and model fitting process, as the one presented in the former section, is applied to all eight remaining combinations of the distributions for the random effects and errors. The simulations for different combinations of distributions will be referred to with abbreviations based on the distributions. That is, NG has normally distributed random effects and gamma distributed errors, LL is the one where both the random effects and errors are log-normally distributed, for GL the random effects are gamma distributed and the errors are log-normally distributed, and so forth.

The log-normal random effects and errors will be simulated as normal distributions which are then appropriately transformed into log-normal distributions using the exponential function. The covariance of the log-normal distribution should match the one in (1.3), where distribution is then translated such that the it has mean 0. The gamma distributed random effects will be simulated using the `lcmix` package which can simulate correlated multivariate gamma distributions. The univariate gamma distribution used for the errors will be simulated using the `rgamma` function. In all cases, the shape parameter is 1 whilst the rate parameter is chosen as its respective variance. The distribution is then translated such that the it has mean 0.

In Figure 1.13 and Figure 1.14, the distributions of the simulated gamma and log-normal random effects, and errors are presented - simulation GG and LL. Furthermore, the blue curve represents the distribution simulated from.

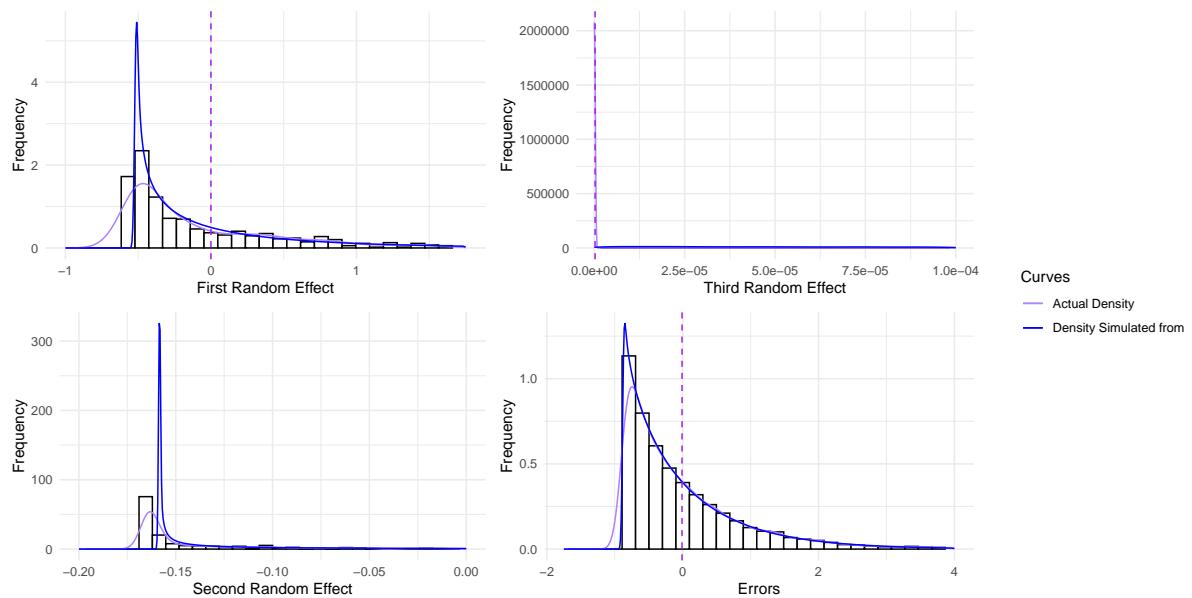


FIGURE 1.13: Histograms of the gamma distributed random effects and errors for one simulation, including their densities (purple curve) and the density they are simulated for (blue curve) with mean zero and standard deviation from Ψ .

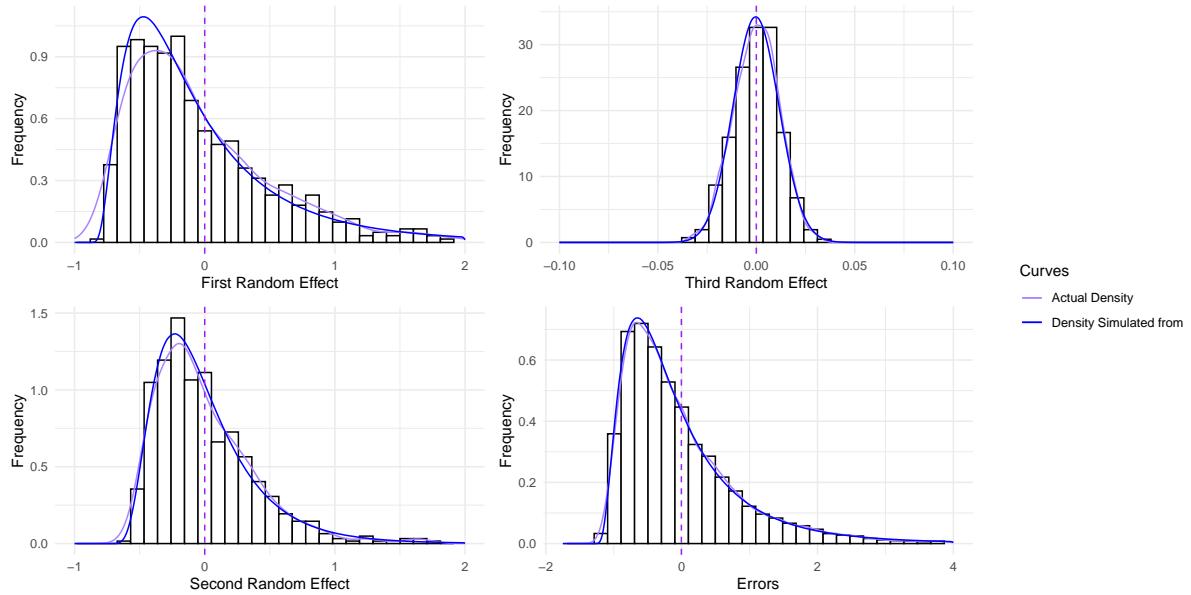


FIGURE 1.14: Histograms of the log-normally distributed random effects and errors for one simulation, including their densities (purple curve) and the density they are simulated for (blue curve) with mean zero and standard deviation from Ψ .

Figure 1.13 and Figure 1.14 shows that both the log-normally and gamma distributed random effects and errors are right-skewed compared to the normal distribution, except for the third random effect in the log-normally distributed random effect, which is slightly left-skewed. Furthermore, when looking at the skewness and kurtosis of this exact random effect it indicates that it follows a normal distribution. The kurtosis of the random effect for the two different distributions show that the log-normally distributed random effects resembles a normal distribution more than those simulated for the gamma distribution, however, still differing quite a lot from a normal distribution. However, looking at the kurtosis of the errors, the gamma distributed errors are closer to a normal distribution than those of the log-normally distributed errors. The contrast of these two cases will help give insight into how deviations from normality will affect the estimation methods, where if the condition of normally distributed random effects and errors are important for the two methods one might expect models based on data including log-normally distributed random effects to outperform those with the gamma distributed random effects. Contrary, since the gamma distributed errors are closer to the normal distributed than those who are log-normally distributed it could be expected that models based on data with these are better.

To gain a better understanding of how robust the estimation methods are to deviations from normality in the random effects and errors, we again analyse the AIC- and BIC values, the bias of the parameter estimates, and the MAE of the predictions. For all different simulations a boxplot of how the AIC- and BIC values of the 100 models are distributed similar to that for the NN simulation, Figure 1.10, which can be found in Section A.1. From this it can be seen that the minimum and maximum score of both the AIC and BIC respectively decreases and increases when the distribution of either the random effect or errors differ from normality. Furthermore, the interquartile ranges of the both the AIC- and BIC values also increase when the distribution of the errors differ from normality. Especially, when the errors are log-normally distributed the AIC- and BIC values are clearly higher over all compared to both the normally- and gamma distributed errors. However, given the non-identical data sets across

the nine simulations, direct comparisons of the AIC- and BIC values are not feasible. Instead, this analysis serves to highlight general trends. Lastly, it can be seen in these illustrations of the AIC- and BIC values, that the two estimation methods are affected in the same way by changes in the distributions of the random effects and errors.

Moreover, some of the same trends, as seen in the boxplots for the AIC- and BIC values, can be observed in the boxplots for the bias of each of the ten parameter estimates for the two models over the nine different simulations, which can be found in Section A.1. It can be seen that the distribution of the errors affects the bias of the parameter estimates more than that of the random effects. That is, there are no clear difference in the distribution of the bias of the parameter estimates when changing the distribution of the random effects. On the contrary we see that when the distribution of the errors change to a gamma distribution the minimum and maximum scores respectively decrease and increase, where when changing to the log-normal distribution, the interquartile ranges also increase. The larger effect on the bias of the parameter estimates when changing the distribution of the errors to a log-normal compared to gamma distribution could be caused by the fact that the errors generated from the gamma distribution are closer to a normal distribution according to the kurtosis. Furthermore, it can also be seen that when the errors are log-normally distributed, the models, in general, have a higher bias of the standard deviation of the errors, compared to the two other distributions. The reason that the different distributions of the random effects does not appear to have any clear affect on the bias of the parameter estimates, could be because the random effects are very small or that the two estimation methods are not as affected by deviations in the random effects compared to the errors. Furthermore, the MAE of the bias is for all nine simulations smaller for the covariance parameters for the nlme models compared to that of the nlmer models. However, the MAE of the bias is for all nine simulations smaller for the fixed effects for the nlmer models compared to that of the nlme models.

These boxplots, for both the AIC- and BIC values, and the bias of the parameter estimates, indicate that the nlme models, in general, are better at describing the variation in the data and estimating the covariance parameters in the model. However, there are only small differences in the AIC- and BIC values in the boxplots. Comparing the two model types for each of the 100 data sets in all nine simulations, we observe that approximately 65% of the time, the AIC- and BIC values for the nlme models are smaller than those for the nlmer models. This suggests that nlme is slightly better than the nlmer model.

Lastly we have looked at how the model predictions are affected by the change in the distributions of the random effects and errors. Below the MAE of the predictions from the two types of models for two of the simulations are presented, those for the rest of the simulations can be found in Section A.2.

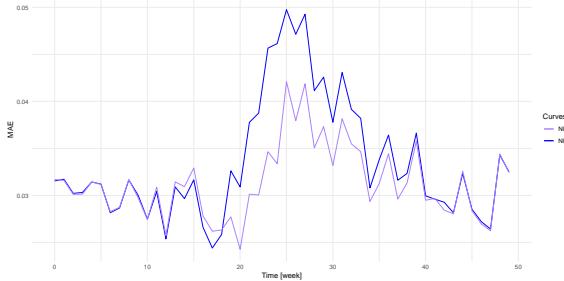


FIGURE 1.15: MAE for predictions of the mean trajectory of the data for the two models in GG.

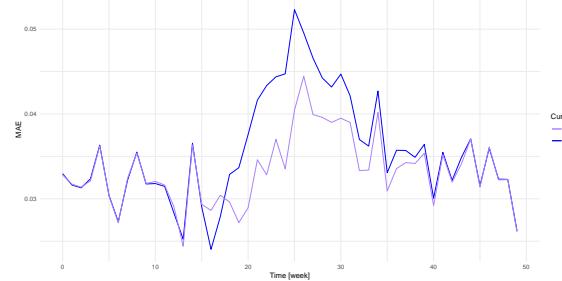


FIGURE 1.16: MAE for predictions of the mean trajectory of the data for the two models in LL.

In general over all nine simulations we see the same trend, that is, the two models approximately have the same MAE for the predictions until week 20 and again after week 30. However, they differ more between week 20 and 30, just as we saw for the NN simulation. Additionally, when considering the average MAE across all time points of the predictions, it becomes evident that simulations with normally distributed errors outperform those with gamma- and log-normally distributed errors. Moreover, simulations with gamma distributed errors exhibit better performance than those with log-normally distributed errors. Furthermore, simulations featuring normally distributed random effects demonstrate superior predictive capabilities compared to those with gamma- and log-normally distributed random effects. Additionally, the predictions are more accurate when the random effects follow a log-normal distribution as opposed to a gamma distribution. This also aligns with the fact that the random effects that are log-normally distributed resemble normal distributions more closely than those with gamma distributions, and vice versa for the errors. This could indicate that the deviations from normality affect the performance of the prediction.

We have also looked at the estimated random effects from the models, and compared them to those from the data. In the two figures below, the distribution of the models random effects for one of the nlme models are plotted with the distribution those in the data are simulated from. This is for the GG and LL simulations.

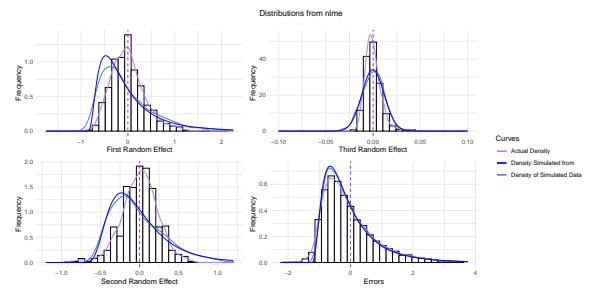
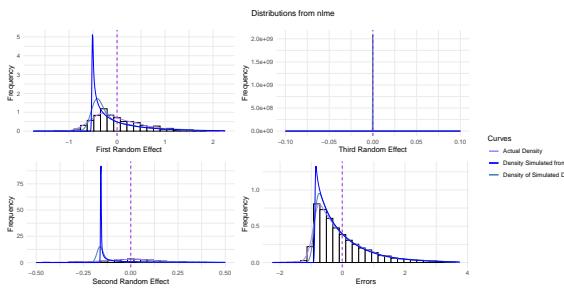


FIGURE 1.17: Histograms of the three random effects and the error term from a nlme model from GG (left) and LL (right), including their densities (purple curve), the density (blue curve) used to simulate the data and the sampled random effects from the data. The dashed line represents the mean of the model values.

Here it can also be seen that the random effects of models in general are more symmetrical than those used in the data. That is, they resemble a normal density more than the real

random effects, and here it is also clear that the estimates of random effects are closer to the in the LL simulation than in the GG simulation to the random effects from the data. However, it can be seen that the errors are quite right-skewed for both the LL- and GG model, just like those the data are based upon. However, these deviations we see in the prediction across the nine simulation are very small.

Lastly, we see for all simulations that the nlmer models perform slightly better at predicting the mean trajectory regardless of the distribution of errors and random effects. This agrees with the fact that we are predicting the mean trajectory, and that the nlmer models in general where seen to estimate the fixed effects better than the nlme models. However, it should be noted that this is a very small difference we see in the MAE of the predictions.

1.3 Using REML

In the former section the `nlme`- and `nlmer` functions were compared by, among other things, the AIC- and BIC values. To do so we opted to use ML method in the two functions, since this was the only option for the `nlmer` function. However, the `nlme` function also has the opportunity of using the REML method. In this section, we will briefly present the difference this makes in the bias of the parameter estimates as well as analyse whether this makes a difference in the performance in the predictions. Using the REML method for one of the model types and not the other one makes the data set they each are based upon different and hence we can no longer compare AIC- and BIC values from the two models. These simulations will be conducted for the nine different compositions of distributions for the random effects and errors as in the former section. Figure 1.18 illustrates the distribution of the bias of the parameters for 100 simulation using the REML method in the `nlme` function together with those from the `nlmer` function still using the ML method. Here the simulations are based upon normally distributed random effects and errors, just as in Subsection 1.1.1. The same type of plots for the other eight simulations can be found in Section A.3.

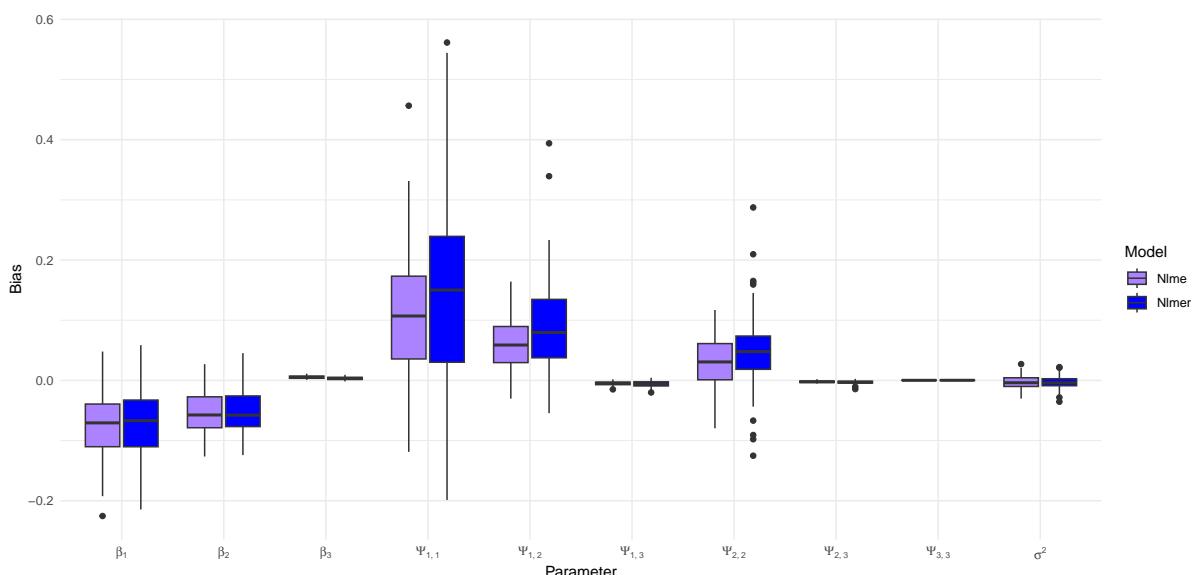


FIGURE 1.18: Boxplots for the bias of the parameter estimates for 100 simulations using REML in `nlme` models and ML in `nlmer` models.

Figure 1.18 shows the same tendencies as when using the ML method for both of the model types. That is, the nlmer models are better at estimating the fixed effects whilst the nlme models are better at estimating the covariance of the random effects. When changing the distributions of the random effects and errors we also see the same tendencies as before. Looking at the absolute mean of these bias' of the parameter estimates and the ones where we use ML for both types of models, the differences between the models are approximately the same. It should, however, be noted that the data used in these simulations and the ones where using the ML method for both models are not the same. Hence, we can not conclude whether the REML method in general has less bias than the ML method from this.

As mentioned, we are also interested in how the change to REML affects the predictions. From Figure 1.18 we expect that we will get similar results as when using the ML methods for both of the models. Figure 1.19 illustrates the MAE of the prediction from the 100 nlme- and nlmer models, where the nlme models are based upon REML and the nlmer model still are based upon the ML method. Again, we only present the results for the NN simulation, whereas the rest can be found in Section A.4.

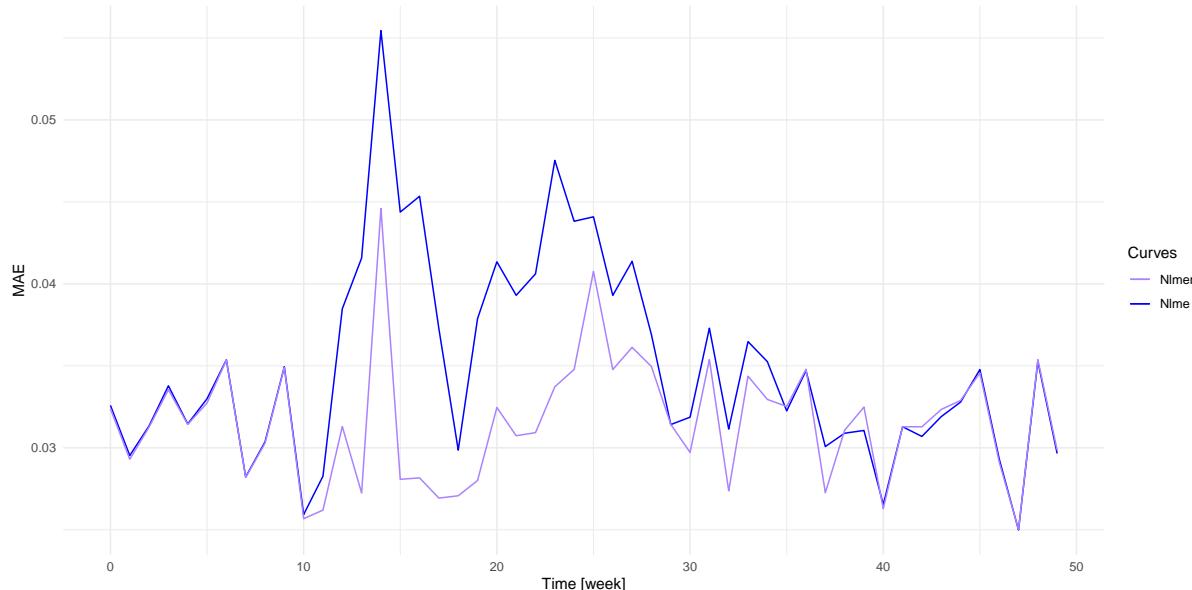


FIGURE 1.19: MAE for predictions of mean trajectory of the data for the two models in NN when using REML in nlme models and ML in nlmer models.

Figure 1.19, as expected, shows results very similar to those where we used the ML method, both in regards to how the two models compare and how the predictions differ when changing the distributions of the random effects and errors. Because of both the similarity in the bias of the parameter estimates and the predictions we will not go further into these results, but can come to the same conclusion as in the former section, Section 1.2.

1.4 Change in number of subject and/or observations

It could be concluded from the former section that the nlme and nlmer models each have some downfalls with the given model specifications. The former section assumed that there were 600 subjects each with 25 visits. It can, however, not always be ensured that there will

be that many subjects with that many visits. This section will explore how variations in the number of subjects and visits impact the estimates of fixed effects, the covariance matrices of the random effects and errors, as well as the predictions of the mean trajectory of the data. This is done for the model presented in (1.1). This is also done such that we can determine if the change in number of subjects or visits affects the estimates more if the distributions of the random effects and errors also deviate from the normal distribution. Consequently, we will modify the nine simulations with 150 subjects and 25 visits, 600 subjects and 6 visits, and 150 subjects and 6 visits when fitting the models. These will be referred to as the 150/25, 600/6, and 150/6 simulations, respectively, where the simulation with 600 subjects and 25 visits will be referred to as the 600/25 simulation. Similar to the previous section, 100 simulations will be performed, and the results will be presented as in the former section. Here it is expected that as the number of subjects or visits decrease the parameter estimates and predictions will worsen due to the decreasing number of points to base the model upon.

1.4.1 Fewer Subjects

First we look at how it affects the models that there are fewer subjects, but the model is still based upon these subjects over a period of 25 weeks. When changing the distributions of the random effects and errors we see the same tendencies of both the AIC- and BIC values along with the bias of the parameter estimates as for the 600/25 simulation. However, the AIC- and BIC values can not be compared in magnitude with those from the former analysis since they are based on data sets that are different in size and hence different degrees of freedom even under the same model. The magnitude of the bias of the parameter estimates can, however, be compared and are in general seen to be larger. The change in number of subjects, however, seems to affect the two estimation methods differently. For the nlmer models the bias of the fixed effects are in general more affected than those of the nlme models when handling fewer subjects. What is meant by this, is that the increase in bias of the fixed effects is in general higher for the nlmer models. Looking at the nine simulations the nlme models generally seem to estimate the covariance of the random effects better than the nlmer models. Furthermore, we now see that the two models estimate the fixed effects even more similarly than before, and in most cases they are equal to each other down to third decimal, which could mean that their predictions of the mean trajectory are closer than before. All boxplots for the AIC- and BIC values along with those for the bias of the estimates for the 150/25 simulation can be found in Subsection A.4.1.

As for the 600/25 simulation we also look at the predictions. In the figures below the MAE of the predictions of the LN simulation from the 150/25 simulation and 600/25 simulation are presented.

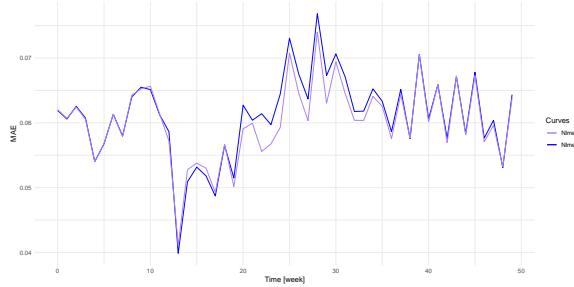


FIGURE 1.20: MAE for predictions of mean trajectory of the data for the two models in LN for the 150/25 simulation.

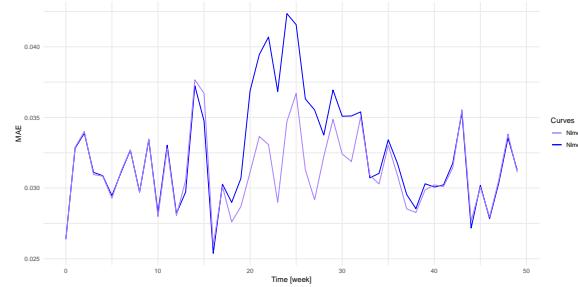


FIGURE 1.21: MAE for predictions of mean trajectory of the data for the two models in LN for the 600/25 simulation.

It can be observed by comparing Figure 1.20 and Figure 1.21 that the difference in MAE of the predictions for the two models is considerably smaller in the 150/25 simulation compared to the difference in the 600/25 simulation. This tendency is also seen in the MAE for the predictions for the remaining eight simulation, which can be found in Subsection A.4.2. Hence, this indicates that the performance of the predictions is more affected by the amount of subjects for the nlmer model compared to the nlme model. We do, however, observe that the predictions for both types of models are, in general, worse due to the smaller amount of subjects.

1.4.2 Fewer Visits

Next, we look at how it affect the results that there are fewer visits in the data. Here we still have 600 subjects over a time period of 50 weeks, but instead of having observations each week, we now only have 12 equidistant observations over the 50 weeks. In Figure 1.22 the data for this simulation can be seen. The model is then fitted to the subjects over the first 6 visits.

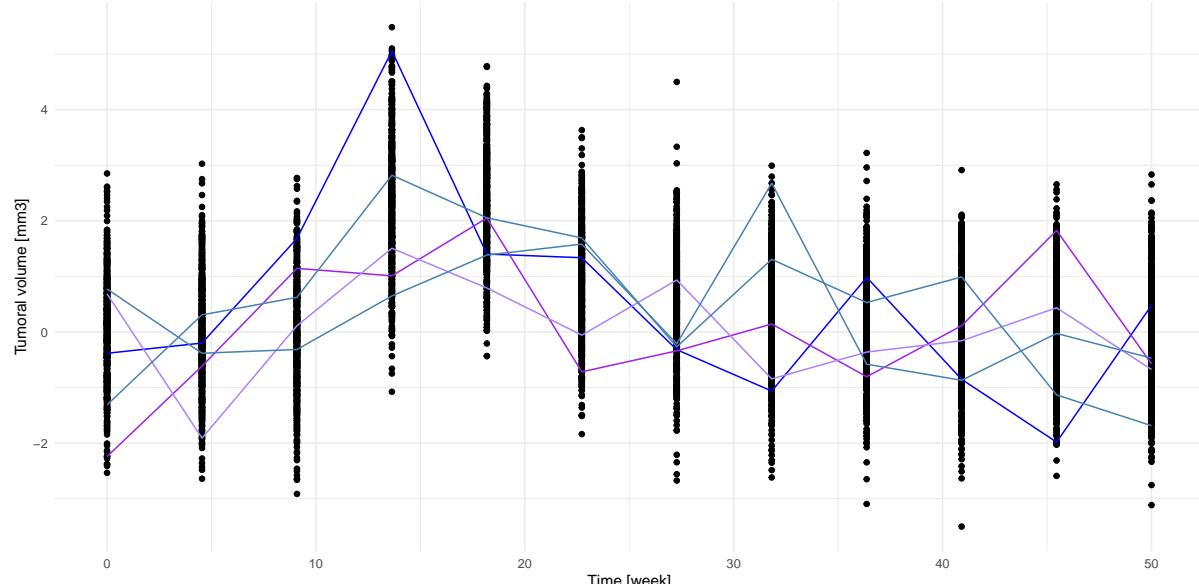


FIGURE 1.22: Simulated data for tumoral volume for 600 subjects for 12 observations over 50 weeks, including the trajectories of five of the subjects.

Looking at the AIC- and BIC values we see that the values for the nlmer models now in general is smaller than those for the nlme models, both seen in a smaller median, interquartile range, and range between the maximum and minimum score. Hence, it seems that the fewer visits affect the nlme models more negatively than the nlmer models in general, since we previously saw a very small difference in the AIC- and BIC values between the two model types/methods. In the bias of the parameter estimates we again see the same tendencies between the distribution as presented for the 600/25 and 150/25 simulations. However, here we see that the bias of the covariance parameters in general are larger than for both the 600/25 and 150/25 simulation as we see the median of them shift further away from 0, whereas the interquartile range and range between the maximum and minimum score remain the same. This is especially seen for the bias of the covariance parameter estimates for the nlmer models, and, furthermore this shift from 0 is most significant for log-normally distributed errors and least for the normally distributed errors. Furthermore, we see that the difference between the models estimates of the fixed effects and the range between the maximum and minimum score increases compared with the 600/25 and 150/25 simulations. Hence, it seem to affect both models more to change the number of visits compared to the number of subjects when looking at the parameter estimates. All boxplots for the AIC- and BIC values along with those for the bias of the estimates for this 600/6 simulation can be found in Subsection A.4.3.

In the figure below the MAE of the predictions of the mean trajectory for the LN, LL and LG simulation for the 600/6 simulation are presented. The MAE of the predictions of the mean trajectory for the NN and GN simulations closely resembles that of LN, the NL and GL simulations that of LL, and the NG and GG simulations that of LG.

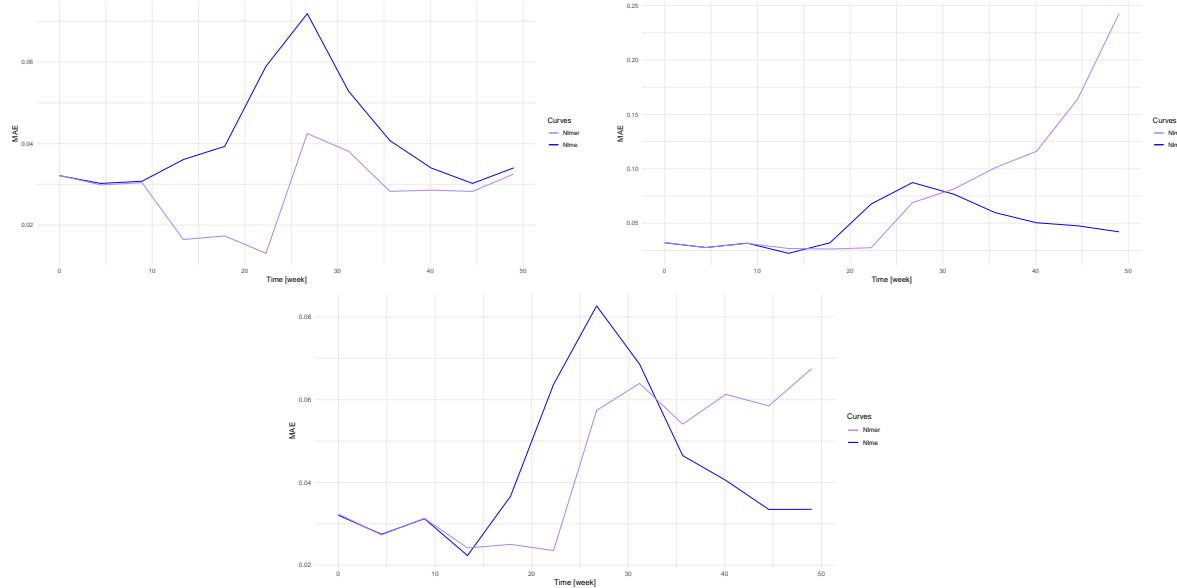


FIGURE 1.23: MAE for predictions of mean trajectory of the data for the two models in LN (left), LL (right) and LG (bottom) for the 600/6 simulation.

It can be seen in all three figures above that they look quite different than those presented for the 600/25 and 150/25 simulations. First of all, we have only predicted 12 points in these plots, and hence they are less granular than the ones with 50 predictions, given the smaller number of data points. Furthermore, we no longer observe that the nlmer models have equally or

better predictions than the nlme models for all the different combinations of distributions of the random effects and errors. We still observe that the predictions up until a bit over week 10 are very similar between the model types/methods, however, the two models exhibit distinct behaviors after this point. In the plots of the MAE of the predictions from the nlme models we observe a consistent trend across the three plots, with values around 0.03 until week 10, then increases until week 27, followed by a decrease until the last week ending up at approximately 0.035. This is in general a bit higher than for the 600/25 simulation, and approximately the same as for the 150/25 simulation. Contrary to that of the nlme models, we observe in the plots of the MAE of the predictions from the nlmer models different trends across the three plots. For all three plots we observe that the predictions are best the first 22 weeks, which are those the model has been fitted to, with a MAE between approximately 0.015 and 0.03. For the normally distributed errors, we still observe that the predictions from the nlmer models in general perform better than those for the nlme model. However, for the log-normally and gamma distributed errors we observe that the predictions from the nlmer models are better until week 30 and 34, respectively. Especially the MAE for predictions in the plots with the log-normally distributed errors from the nlmer models become much worse than those from the nlme models afterwards. Hence, this indicates that the nlme model's mean trajectory prediction is more robust to a decrease in the number of visit, with respect to deviations from normality in the random effects and errors, compared to the nlmer model. However, if the random effects and errors both are normally distributed the nlmer model still seem to predict the best.

1.4.3 Fewer Subjects and Visits

Lastly, we look at how it will affect the models if we have both fewer subject and visits. Specifically, we will analyse a data set containing 150 subjects and 12 visits over the time period of 50 weeks, and fit the models to the first 6 visits. An example of what the data looks in this simulation is presented in the figure below.

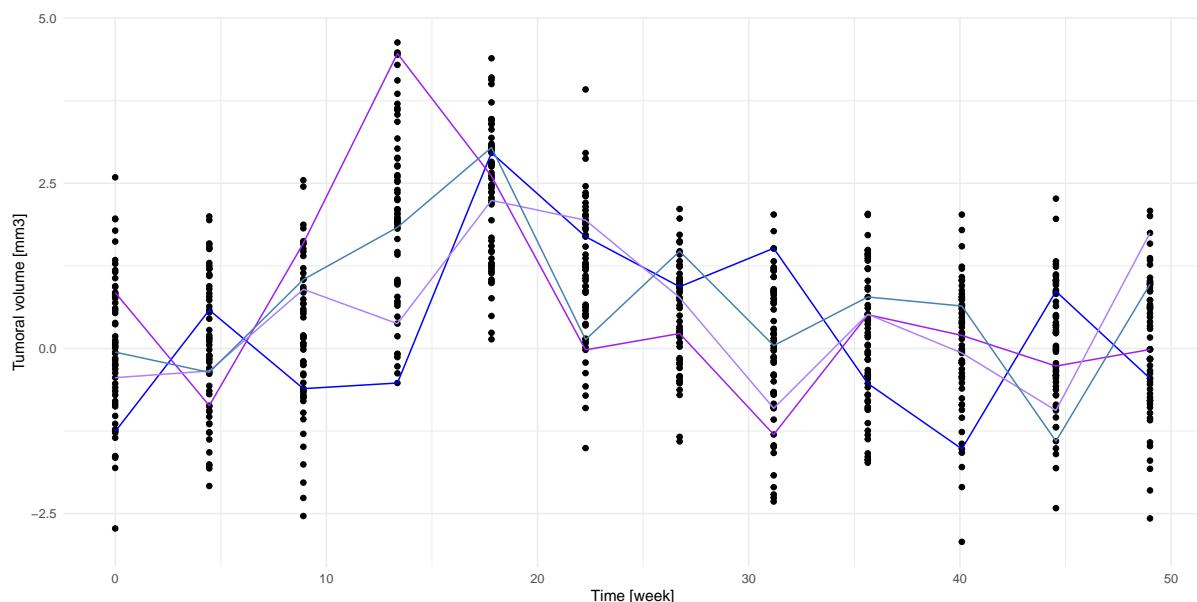


FIGURE 1.24: Simulated data for tumoral volume for 150 subjects and 12 observations over 50 weeks, including the trajectories of five of the subjects.

When looking at the AIC- and BIC values along with the bias of the parameter estimates we observe the same tendencies as when we only decreased the number of visits, however, with a larger dispersion of the parameter estimates. Furthermore, the shift in the bias of the covariance parameter away from 0 is also larger for this simulation in general. Because of the similarity in behavior to the 600/6 simulation we will not go into further details of the AIC, BIC and bias. Again, the MAE of the predictions of the mean trajectory for the LN, LL and LG simulation for the 600/6 simulation are presented in the figure below. The MAE of the predictions of the mean trajectory for the NN and GN simulations closely resembles that of LN, the NL and GL simulations that of LL, and the NG and GG simulations that of LG.

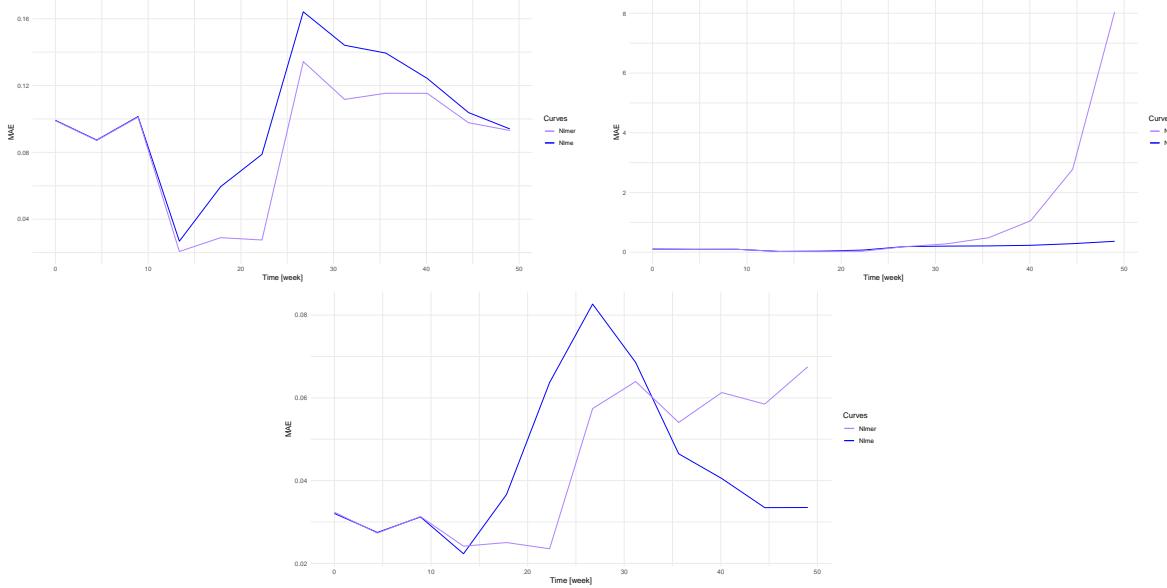


FIGURE 1.25: MAE for predictions of mean trajectory of the data for the two models in LN (left), LL (right) and LG (bottom) for the 150/6 simulation.

Also in these plots, we see the same tendencies as for the 600/6 simulation, however, the MAE is seen to in general be greater than those in Figure 1.23. We will hence not analyse this further.

1.5 Conclusion of the Simulation Study

In this simulation study we have seen that both the `nlme` and `nlmer` function and hence estimation methods each have their downfalls. Based on these we want to conclude which of the two models to use in the application. We saw in all simulations that the `nlme` models in general estimated the fixed effects worse than the `nlmer` models. However, in the 150/25 simulation the parameter estimates of the fixed effects from the estimation methods were almost identical. This presumably also lead to the `nlmer` models being slightly better at predicting the mean trajectory of the data in the 600/25 simulation, but not noticeably better in the 150/25 simulation. Furthermore, we saw that when decreasing the number of visits the `nlme` model's mean trajectory prediction was more robust compared to the `nlmer` models' mean trajectory prediction. Furthermore, we observed that the magnitude of the MAE of the predictions for the `nlme` models were equally affected when the number of subjects and visits decreased together with that the distributions of the random effects and errors changed. On

the contrary, the magnitude of the MAE of the predictions from the nlmer models was very affected when the number of visits decreased and the distributions differed from normality.

Furthermore, we saw that when fitting the nlme- and nlmer models, the optimisation procedure were easier to converge for the nlme models than the nlmer models. This resulted in that we had to change the covariance matrix of the simulated data from the one we originally intended to use, since few to none of the nlmer models converged for this. We have also tried a few other models where we experienced the same tendencies in the optimisation procedure, that is, the nlmer model's optimisation procedure is in general worse at achieving convergence compared to that of the nlme model. These models both differed in complexity and how large the variances of the random effects were. Here the complexity differed from three fixed and random effects in a similar model as (1.1) to one fixed and random effect just added to the time, that is

$$\begin{aligned}y_{i,j} &= t_{i,j} + \nu_{1,i} + \varepsilon_{i,j} \\ \nu_{1,i} &= \beta_1 + U_{1,i}\end{aligned}$$

using the same notation as in (1.1). In all the models the convergence in the optimisation procedure for nlmer models were not the only problem. It also often gave an error when updating the Fisher information matrix of the random effects in the optimisation procedure, which were that it was often not positive definite, which stops the process of fitting the model. Hence, because of these problems with the nlmer models, it could be preferable to use the nlme model, since this can be used for a wider range of models without convergence problems or problems with the Fisher information matrix. However, it generally appears that the choice of which estimation method to choose depends significantly on the data and the type of model, as both have their own advantages and disadvantages.

The nlme model seems preferable in our data analysis in the application, since we cannot ensure normality of the random effects and error along with the fact that we have a data set where only four visits are observed. Lastly, if there are any indications that there is correlation in the errors, the nlmer model cannot be used to directly model this, since it only has the opportunity of modelling the correlation between the random effects.

Appendices

A Simulation Study

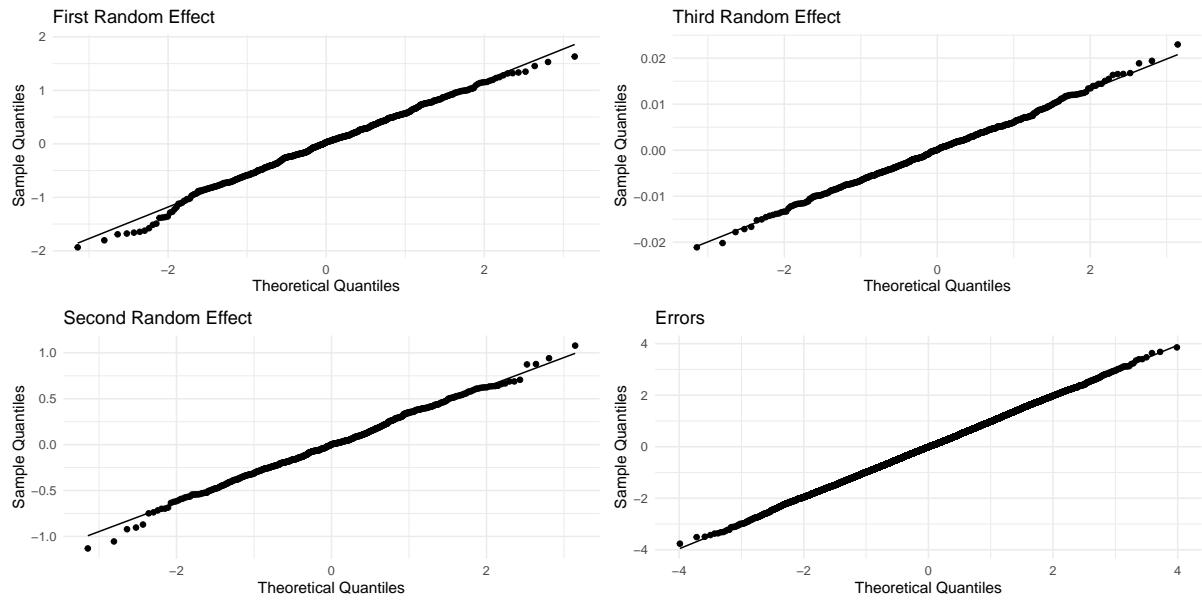


FIGURE A.1: *QQ-plot of the random effects and errors for nlme.*

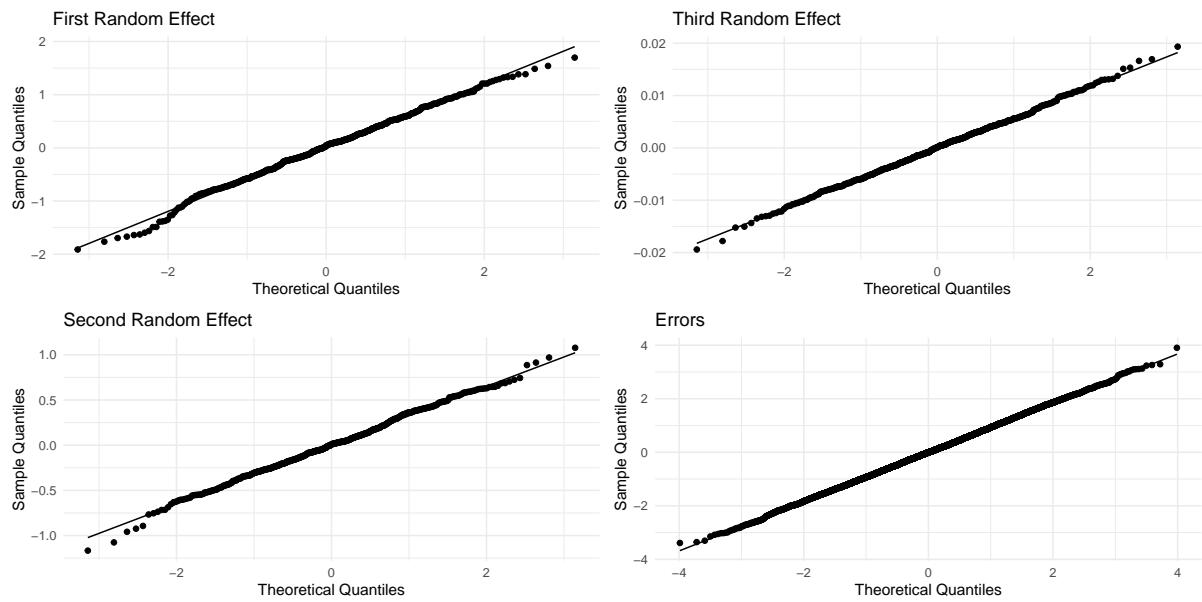


FIGURE A.2: *QQ-plot of the random effects and errors for nlmer.*

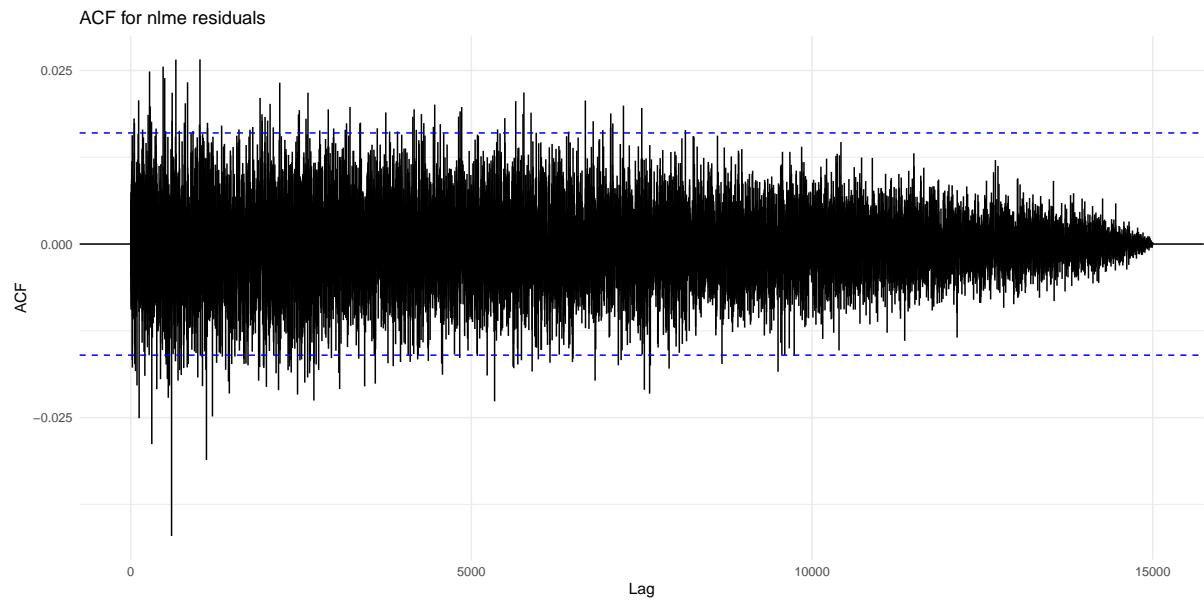


FIGURE A.3: ACF of the residuals for *nlme*.

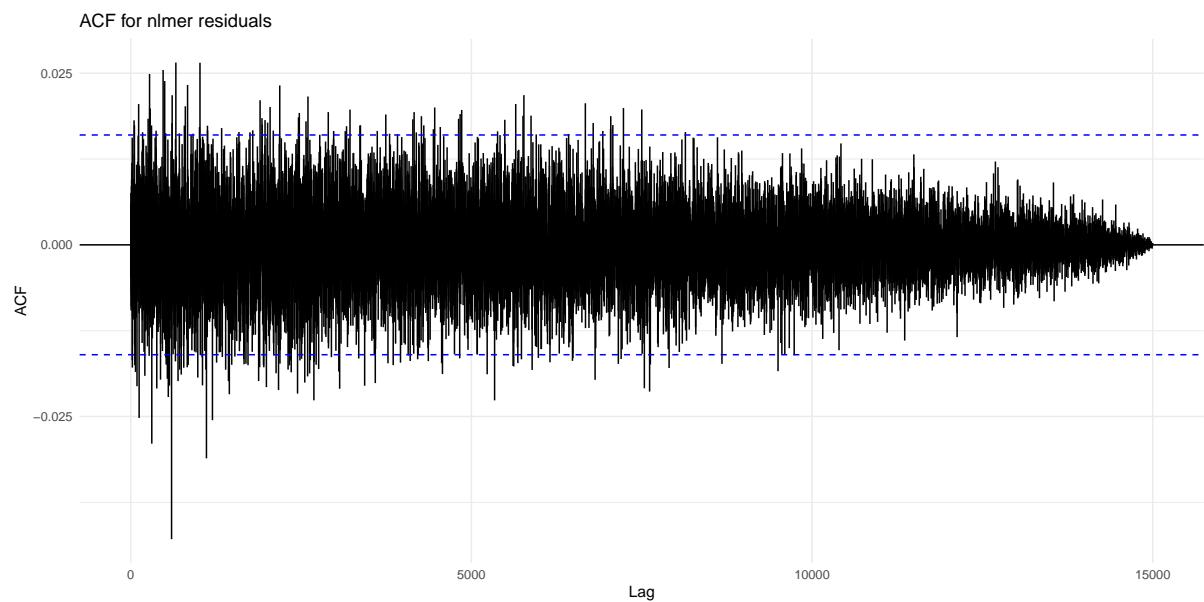


FIGURE A.4: ACF of the residuals for *nlmer*.

A.1 Boxplots for ML

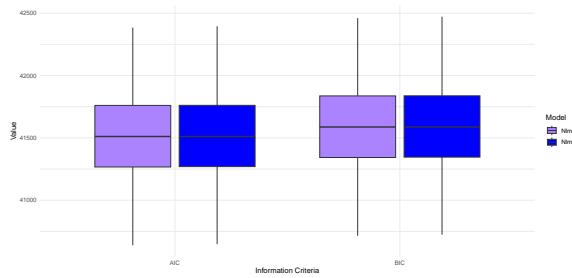


FIGURE A.5: GG

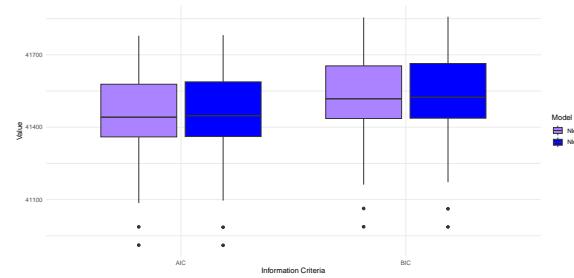


FIGURE A.6: GN

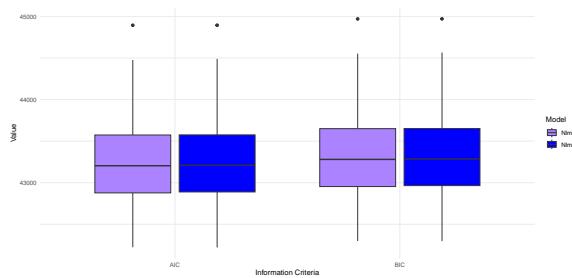


FIGURE A.7: GL

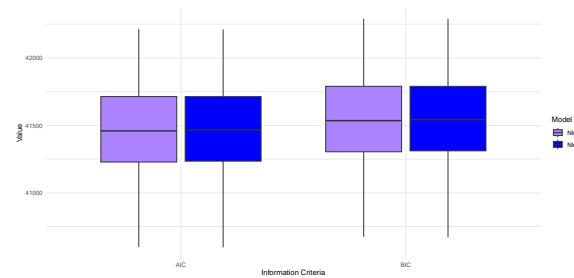


FIGURE A.8: LG

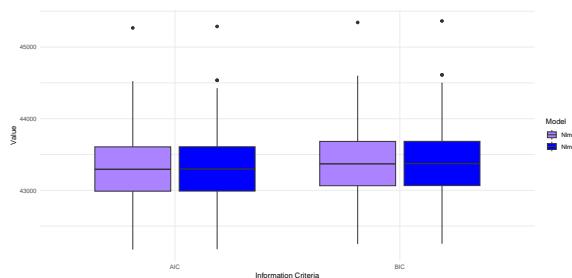


FIGURE A.9: LL

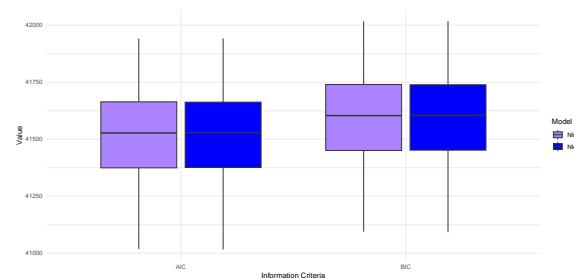


FIGURE A.10: LN

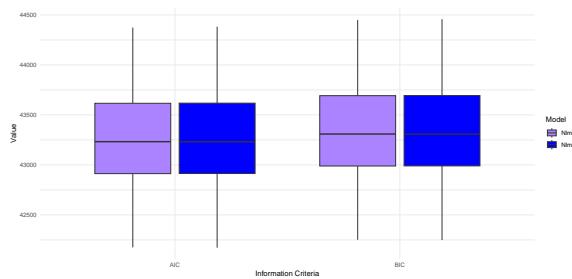


FIGURE A.11: NL

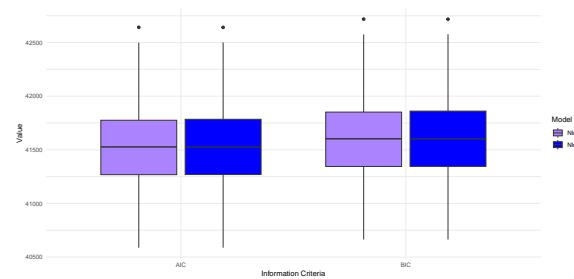
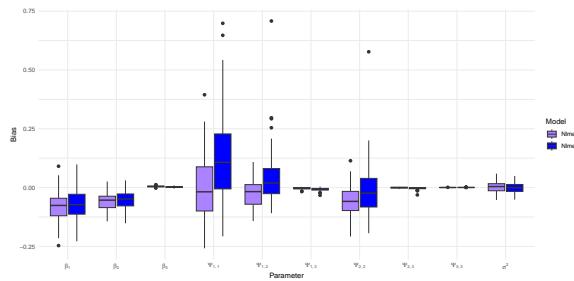
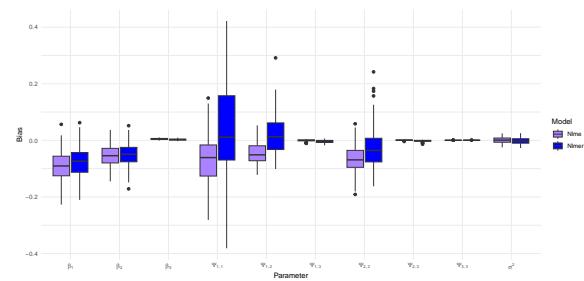
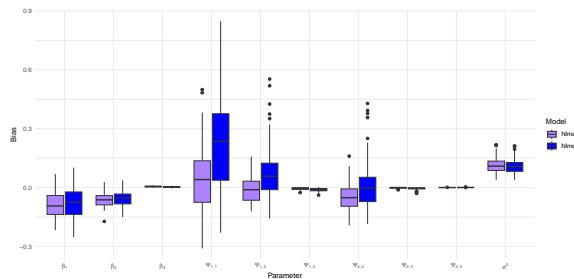
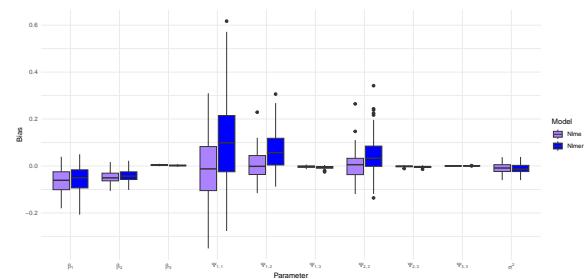
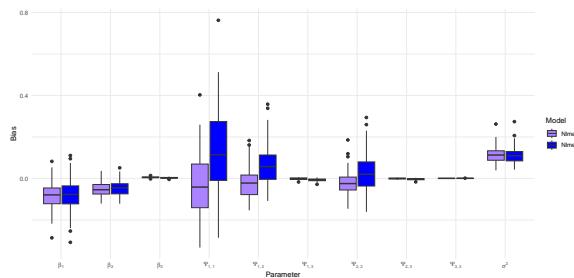
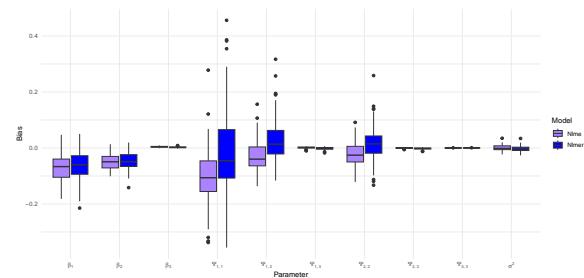
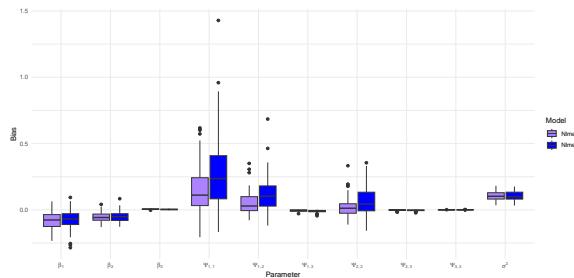
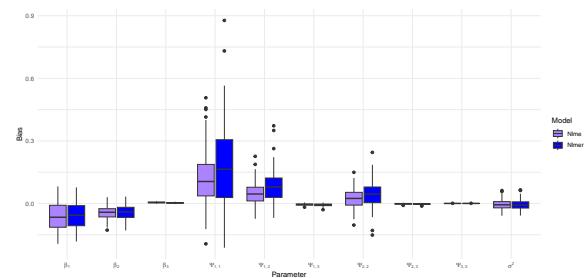
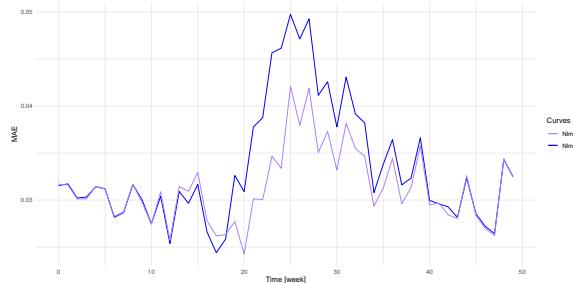
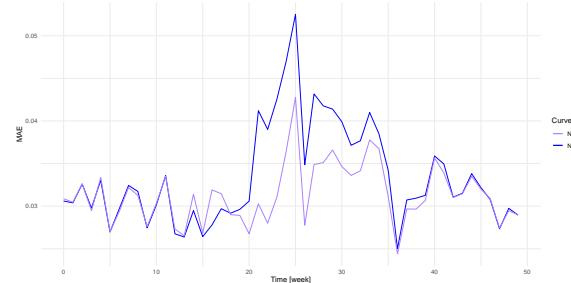
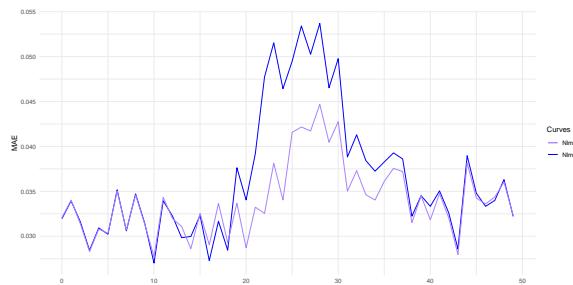
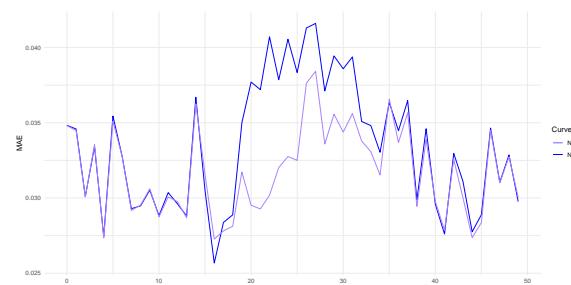
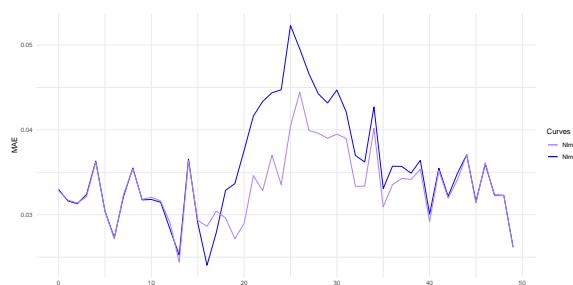
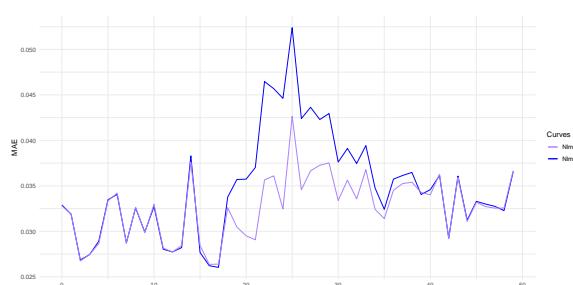
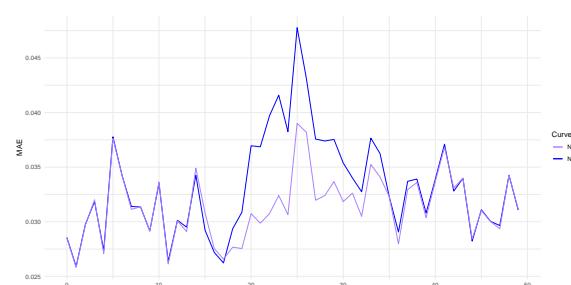


FIGURE A.12: NG

**FIGURE A.13: GG****FIGURE A.14: GN****FIGURE A.15: GL****FIGURE A.16: LG****FIGURE A.17: LL****FIGURE A.18: LN****FIGURE A.19: NL****FIGURE A.20: NG**

A.2 Predictions for ML

**FIGURE A.21: GG****FIGURE A.22: GN****FIGURE A.23: GL****FIGURE A.24: LG****FIGURE A.25: LL****FIGURE A.26: LN****FIGURE A.27: NL****FIGURE A.28: NG**

A.3 Boxplots for REML

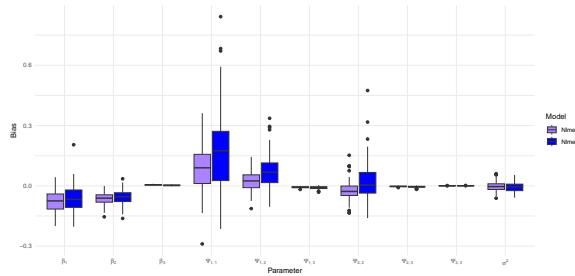


FIGURE A.29: GG

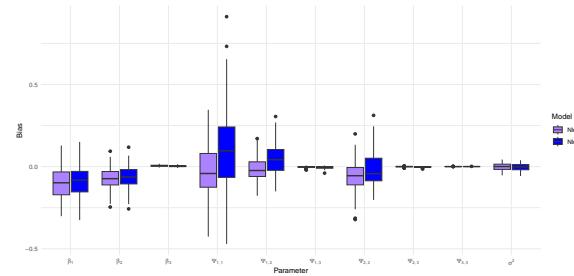


FIGURE A.30: GN

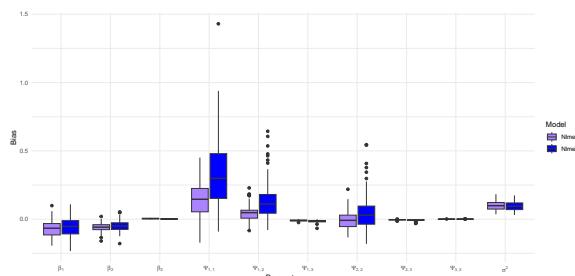


FIGURE A.31: GL

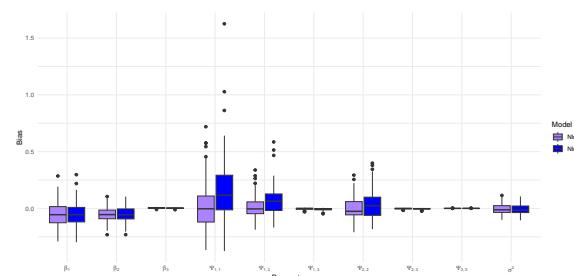


FIGURE A.32: LG

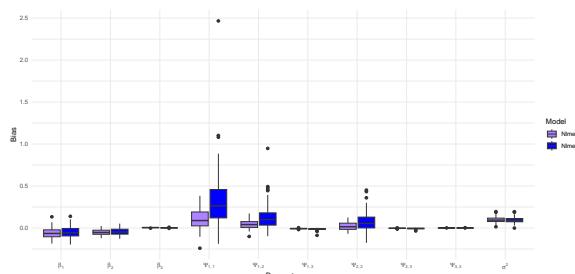


FIGURE A.33: LL

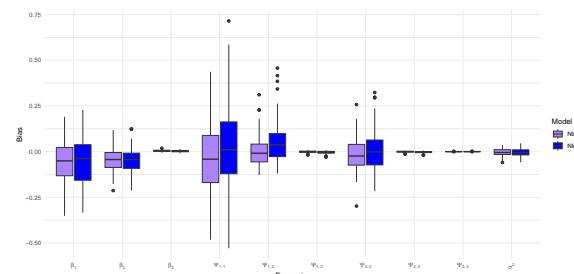


FIGURE A.34: LN

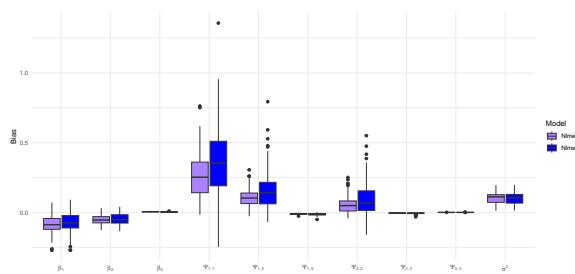


FIGURE A.35: NL

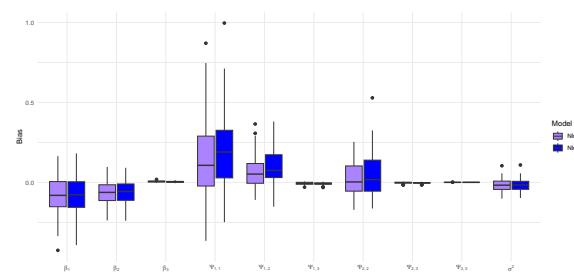


FIGURE A.36: NG

A.4 Predictions for REML

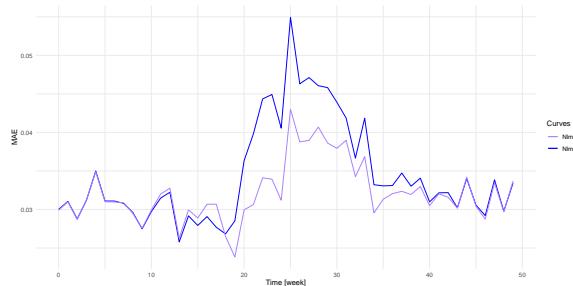


FIGURE A.37: GG

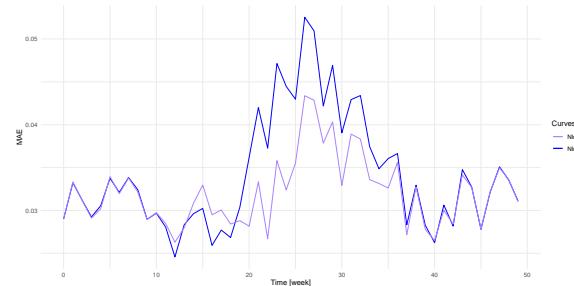


FIGURE A.38: GN

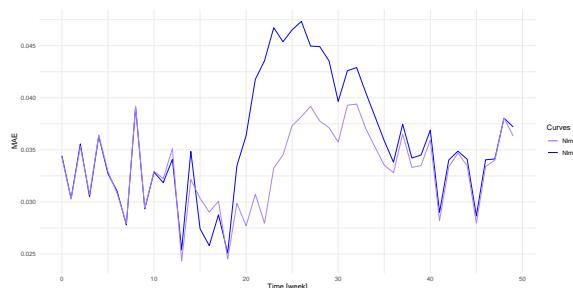


FIGURE A.39: GL

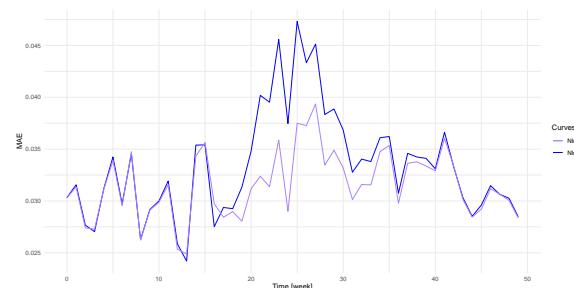


FIGURE A.40: LG

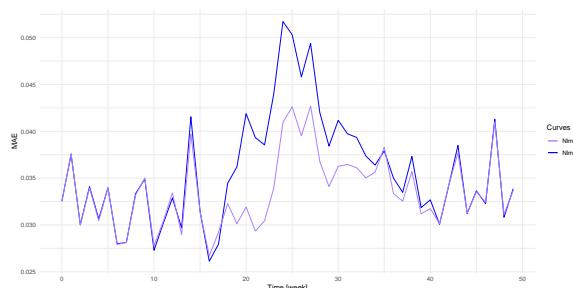


FIGURE A.41: LL

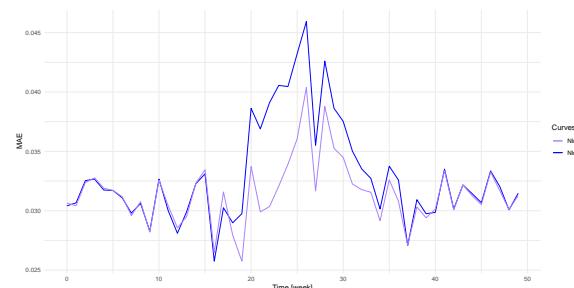


FIGURE A.42: LN

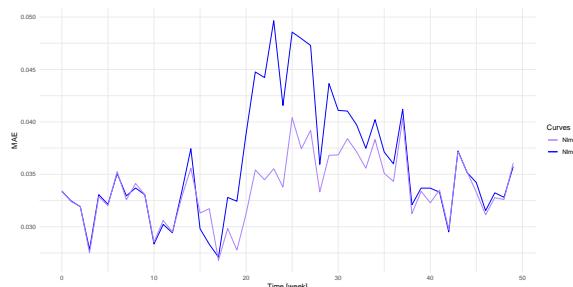


FIGURE A.43: NL

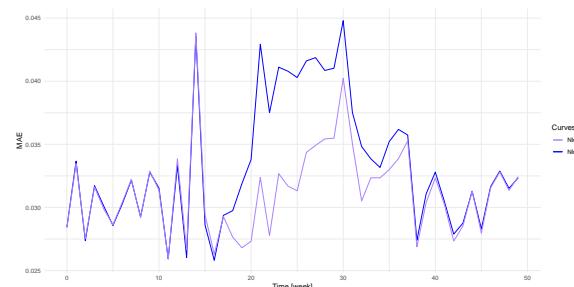


FIGURE A.44: NG

A.4.1 Boxplots for 150/25

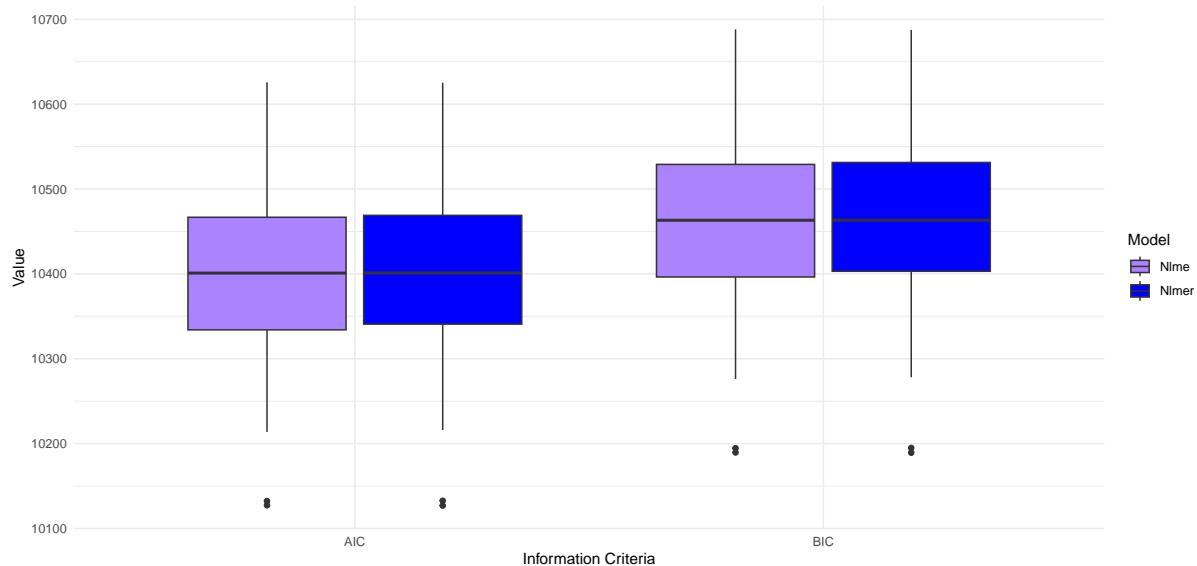


FIGURE A.45: NN

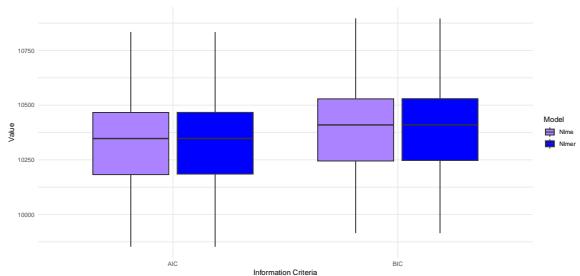


FIGURE A.46: GG

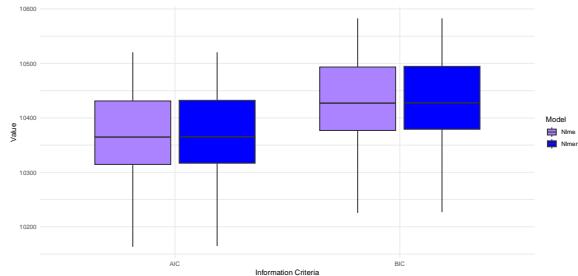


FIGURE A.47: GN

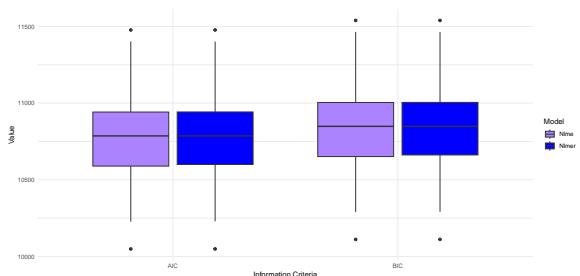


FIGURE A.48: GL

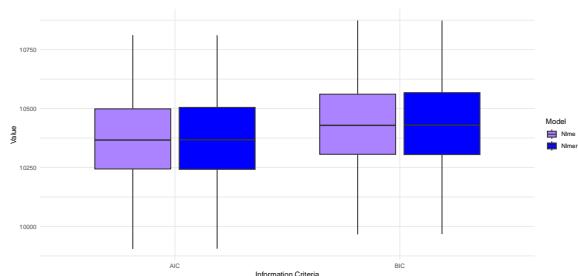
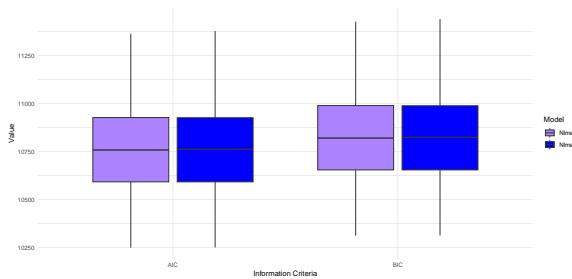
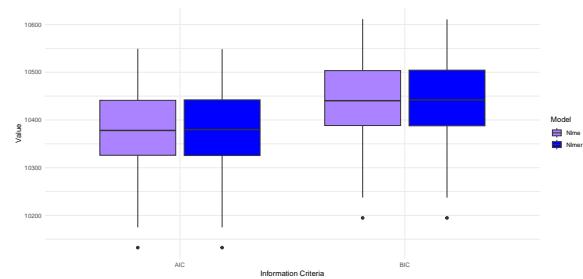
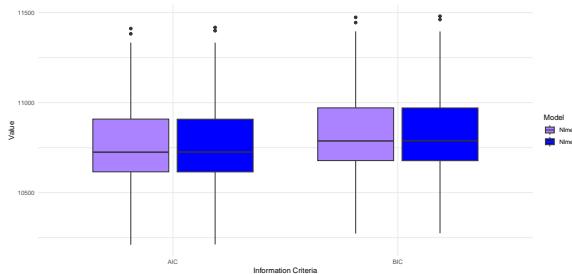
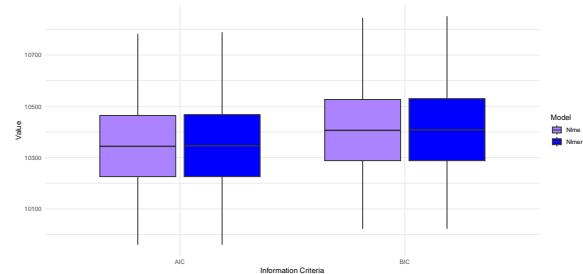
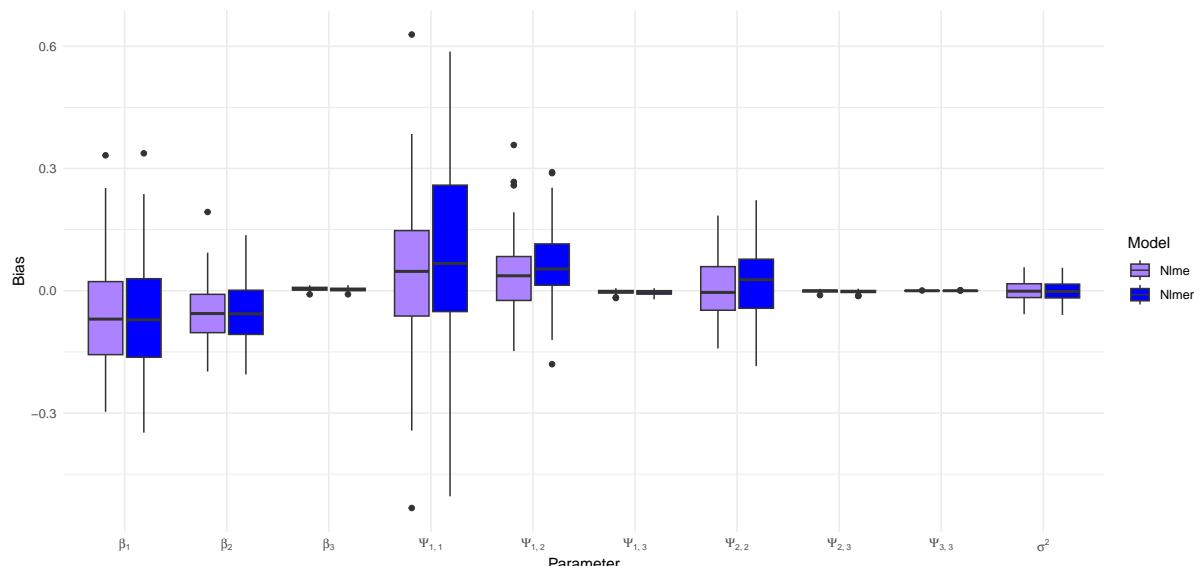
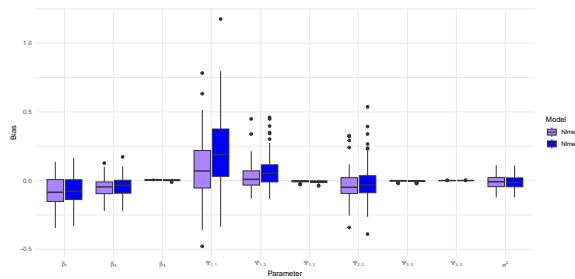
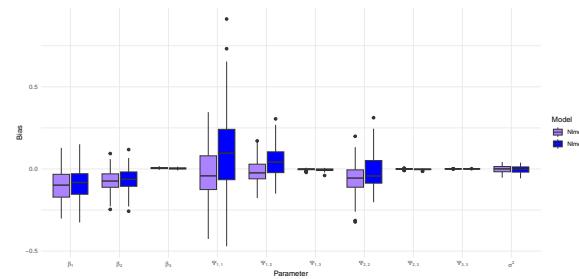
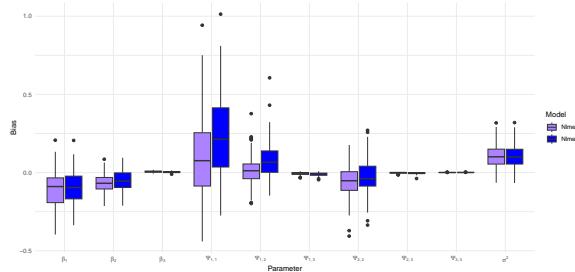
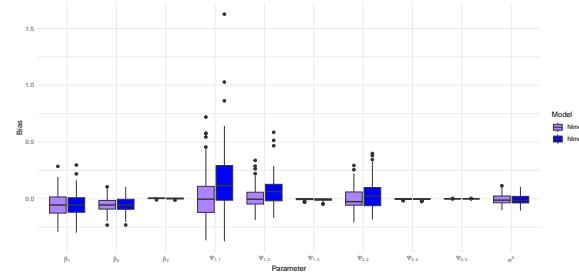
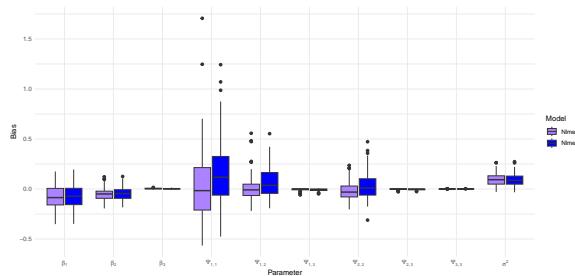
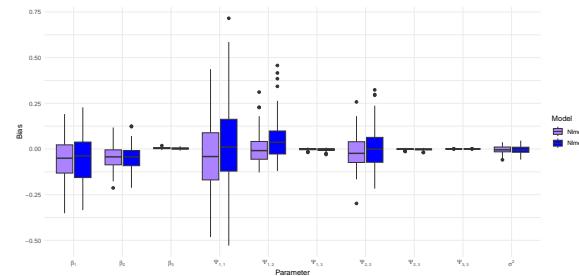
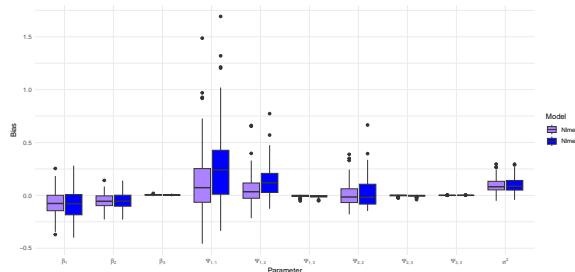
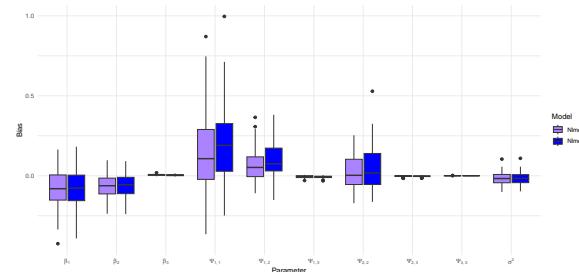
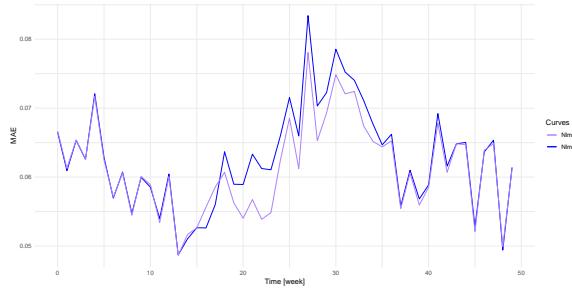
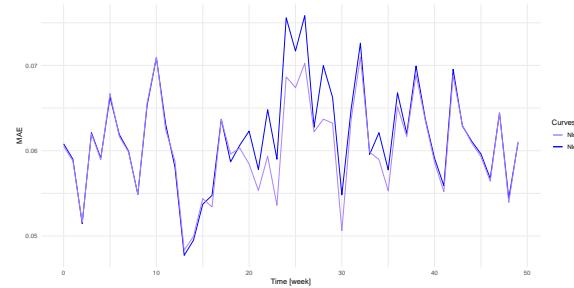
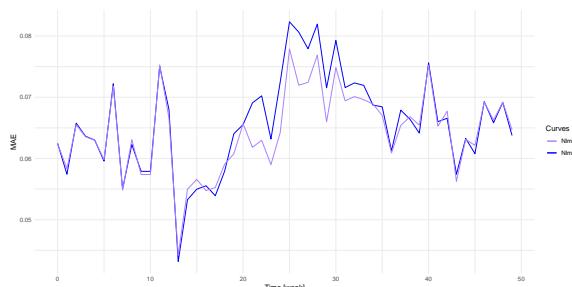
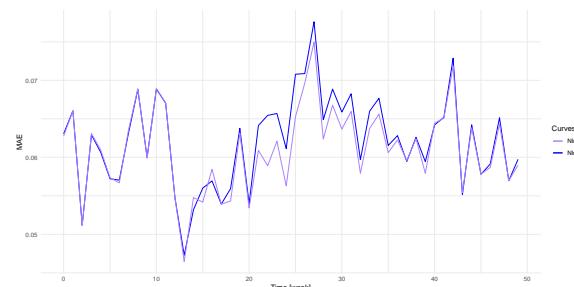
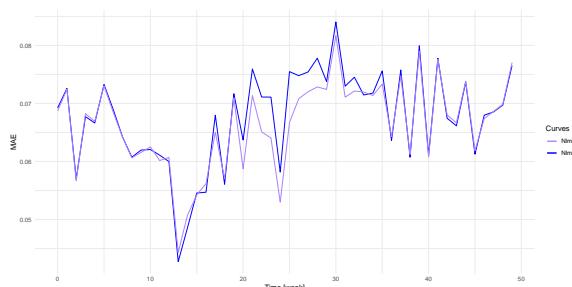
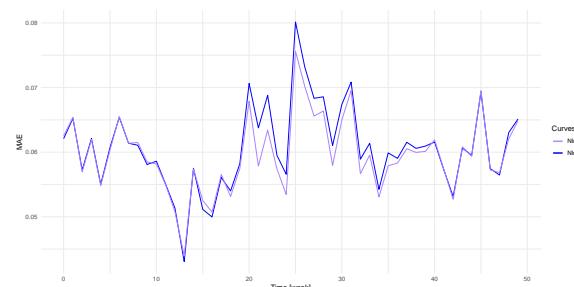
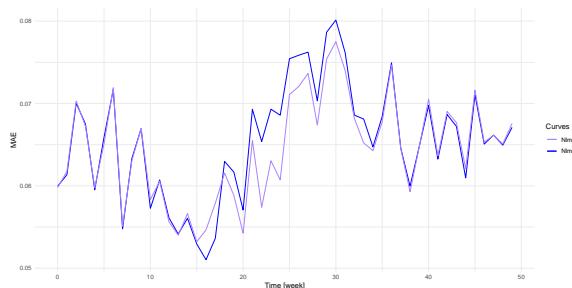
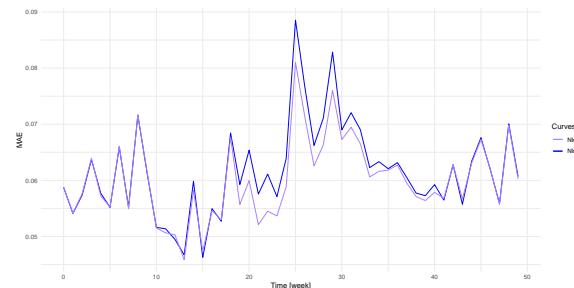


FIGURE A.49: LG

**FIGURE A.50: LL****FIGURE A.51: LN****FIGURE A.52: NL****FIGURE A.53: NG****FIGURE A.54: ddd1**

**FIGURE A.55: GG****FIGURE A.56: GN****FIGURE A.57: GL****FIGURE A.58: LG****FIGURE A.59: LL****FIGURE A.60: LN****FIGURE A.61: NL****FIGURE A.62: NG**

A.4.2 Predictions for 150/25

**FIGURE A.63: GG****FIGURE A.64: GN****FIGURE A.65: GL****FIGURE A.66: LG****FIGURE A.67: LL****FIGURE A.68: NN****FIGURE A.69: NL****FIGURE A.70: NG**

A.4.3 Boxplots for 600/6

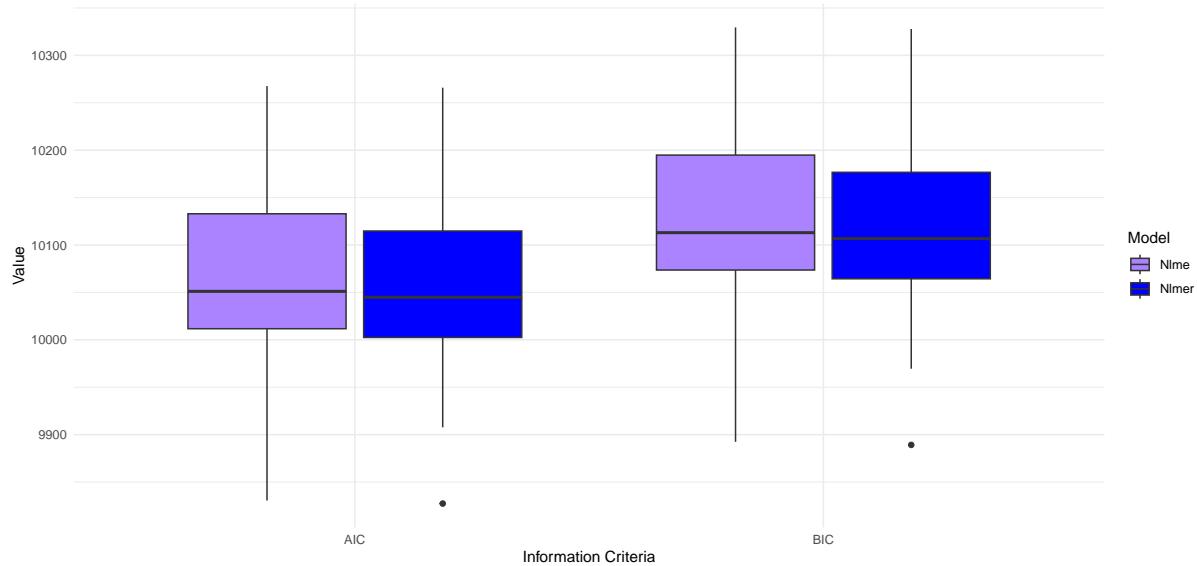


FIGURE A.71: NN

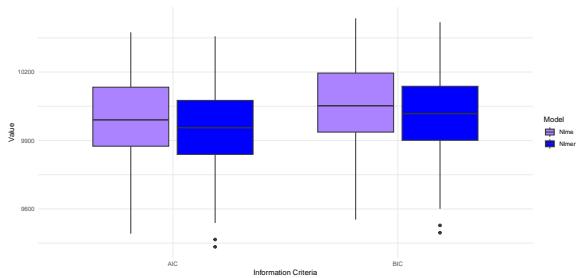


FIGURE A.72: GG

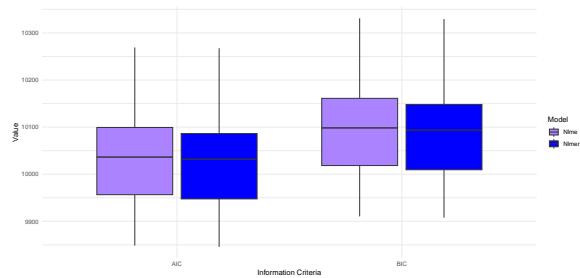


FIGURE A.73: GN

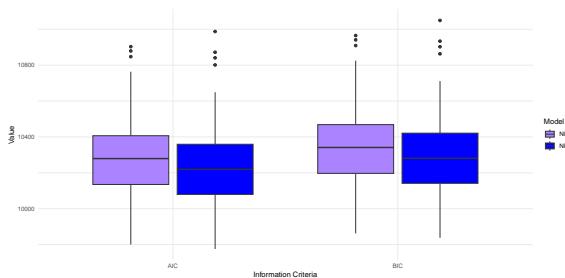


FIGURE A.74: GL

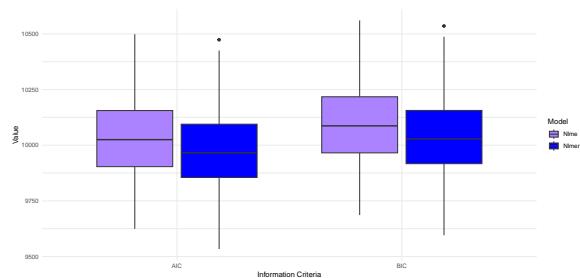
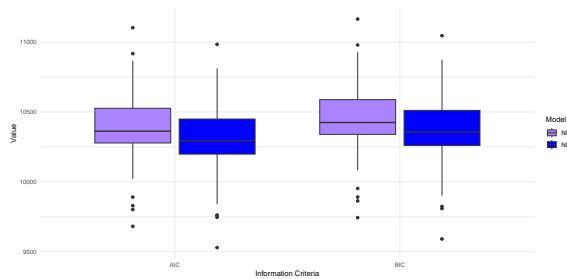
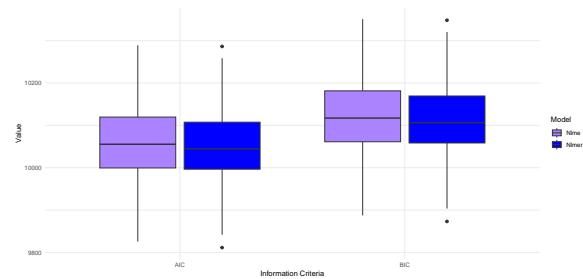
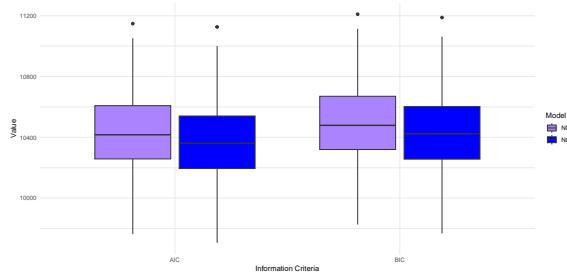
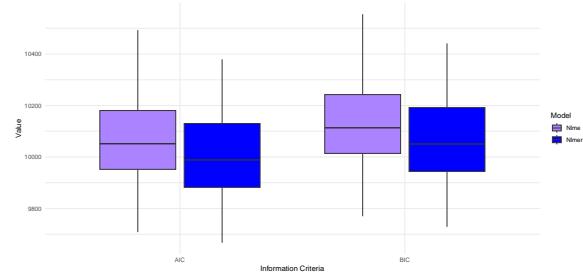
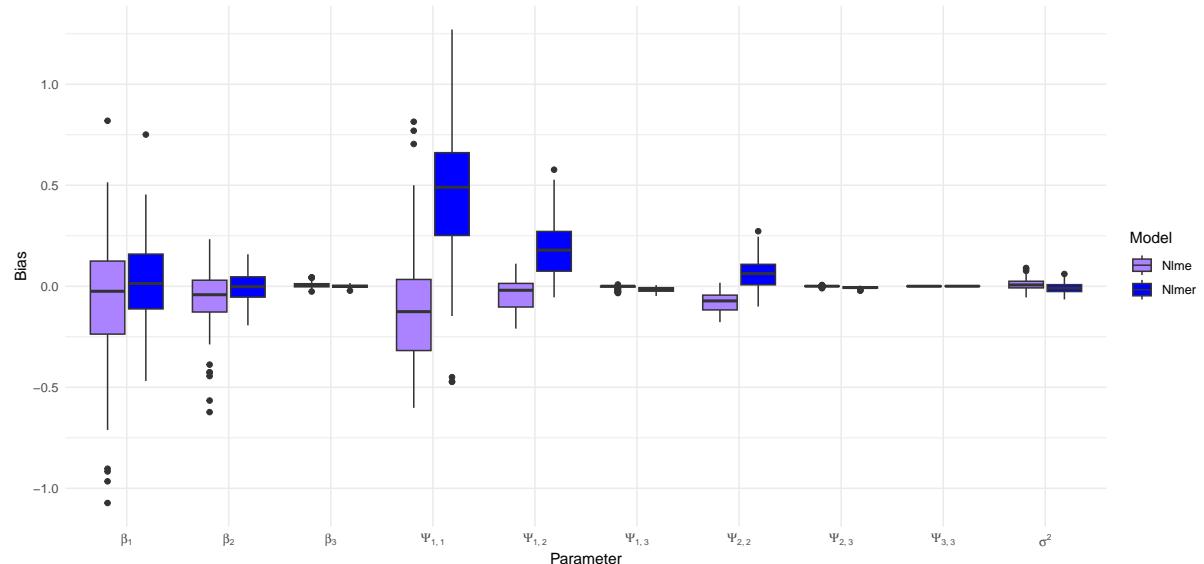
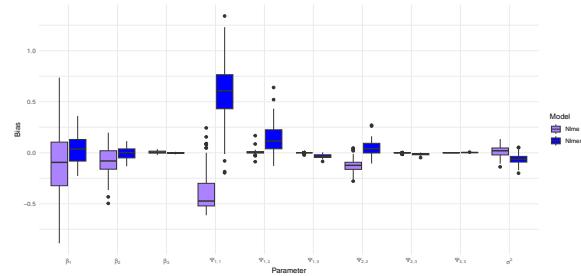
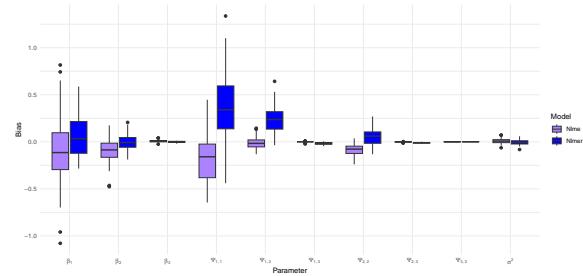
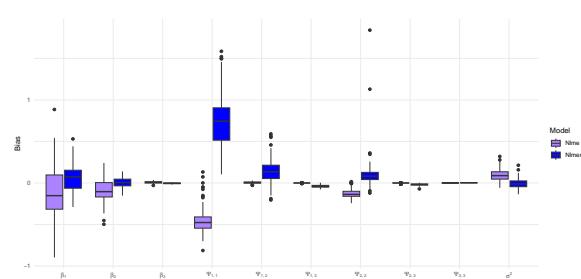
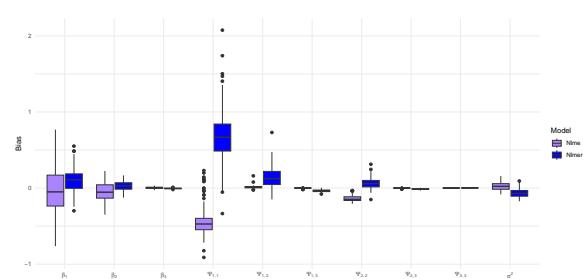
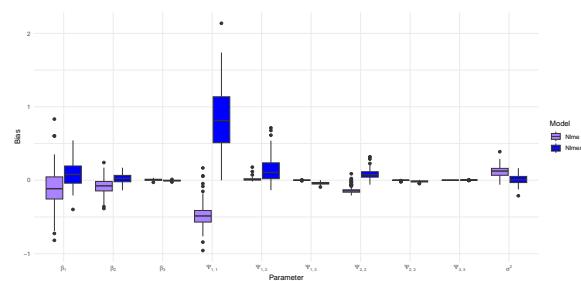
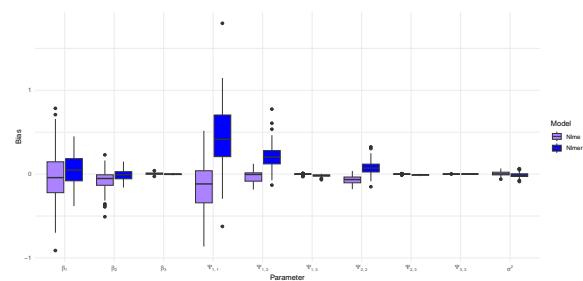
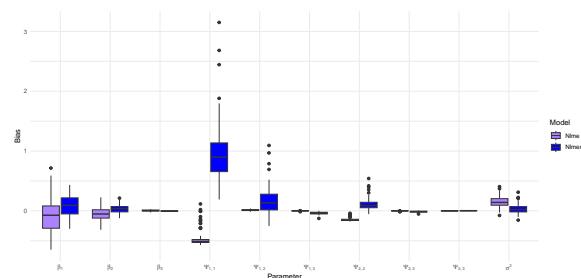
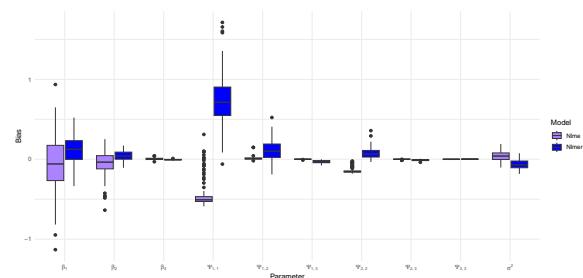


FIGURE A.75: LG

**FIGURE A.76: LL****FIGURE A.77: LN****FIGURE A.78: NL****FIGURE A.79: NG****FIGURE A.80: NN**

**FIGURE A.81: GG****FIGURE A.82: GN****FIGURE A.83: GL****FIGURE A.84: LG****FIGURE A.85: LL****FIGURE A.86: LN****FIGURE A.87: NL****FIGURE A.88: NG**

A.4.4 Predictions for 600/6

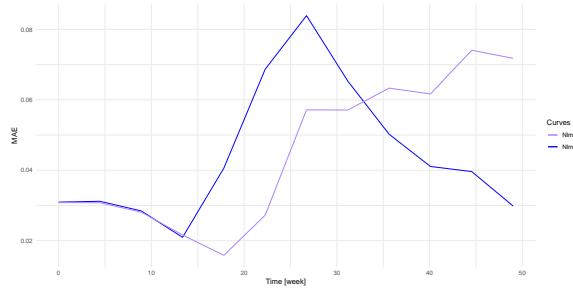


FIGURE A.89: GG

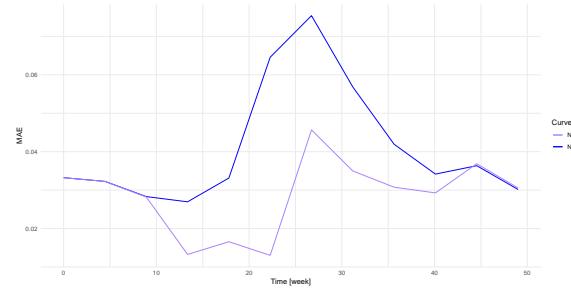


FIGURE A.90: GN

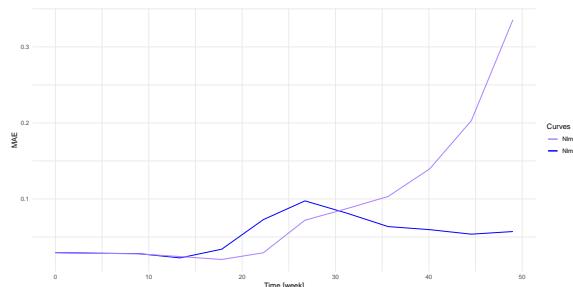


FIGURE A.91: GL

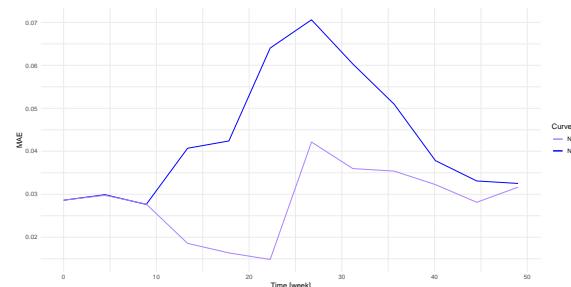


FIGURE A.92: NN

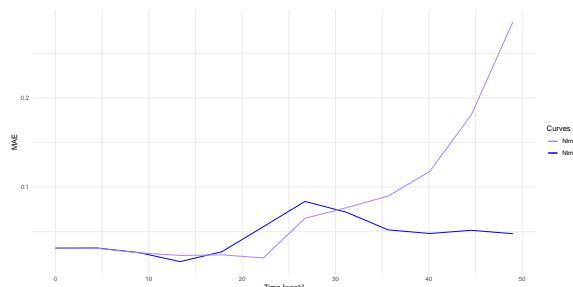


FIGURE A.93: NL

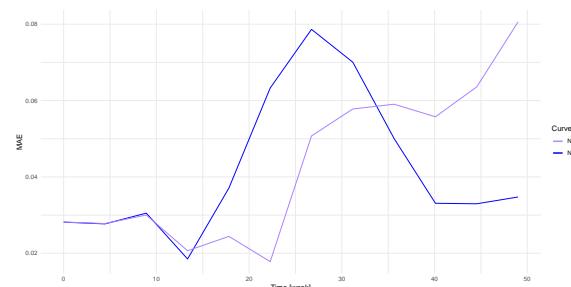


FIGURE A.94: NG

A.4.5 Boxplots for 150/6

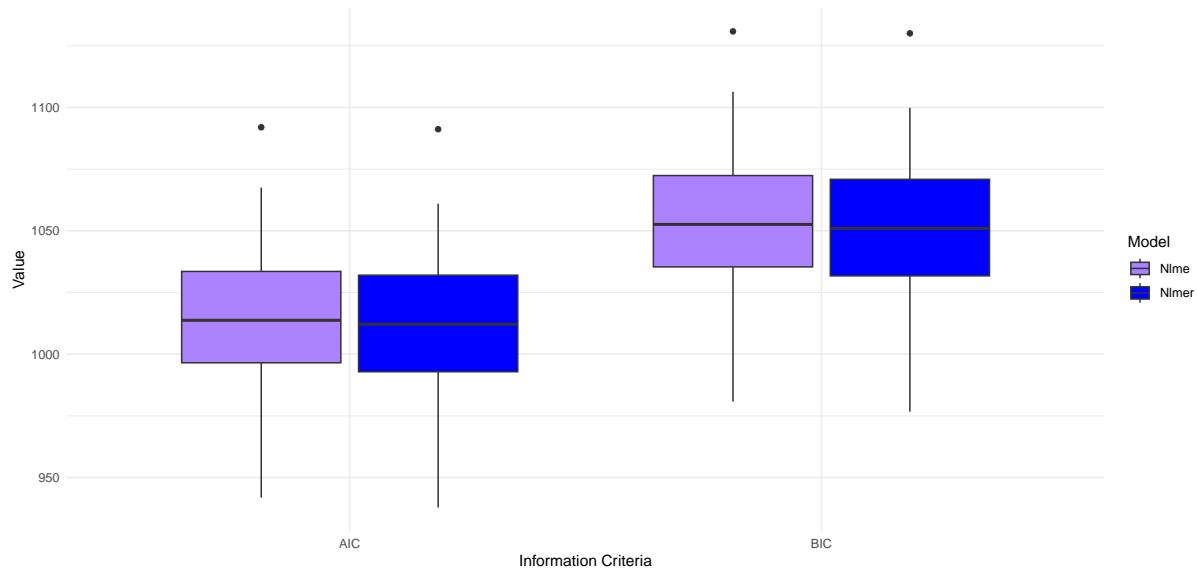


FIGURE A.95: ddd3

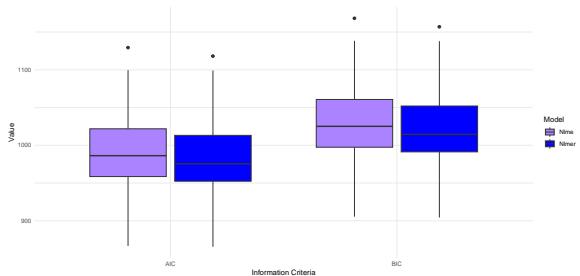


FIGURE A.96: GG

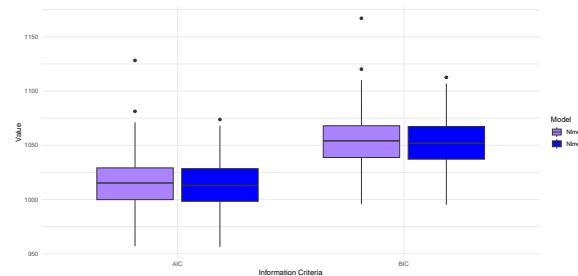


FIGURE A.97: GN

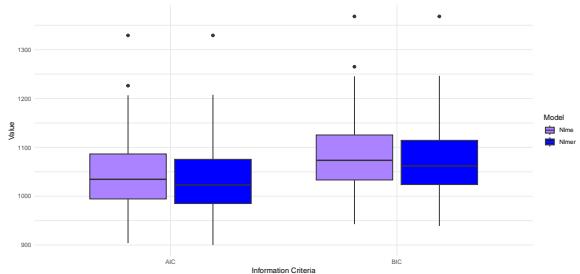


FIGURE A.98: GL

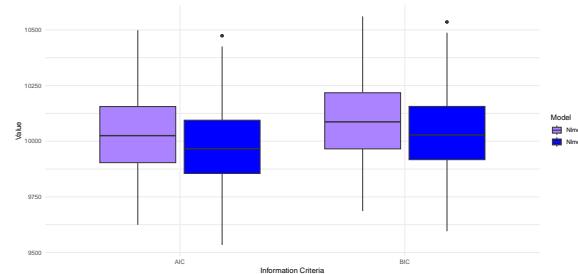
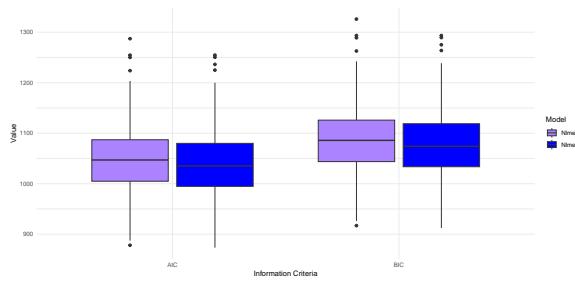
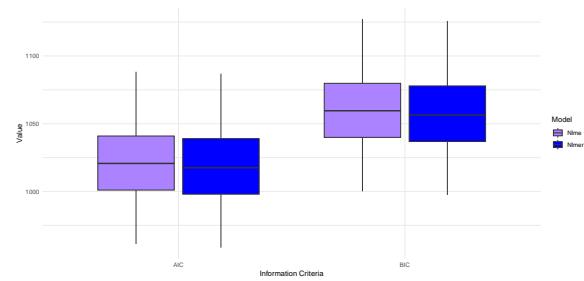
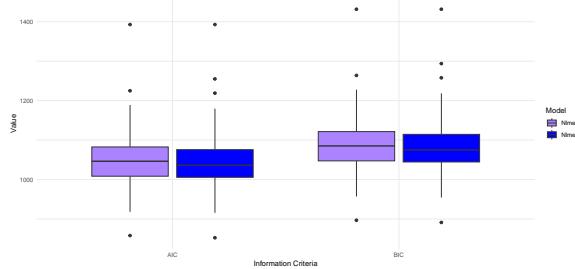
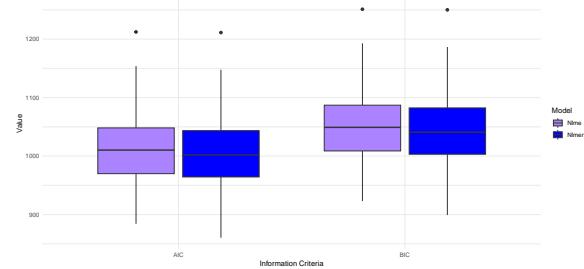
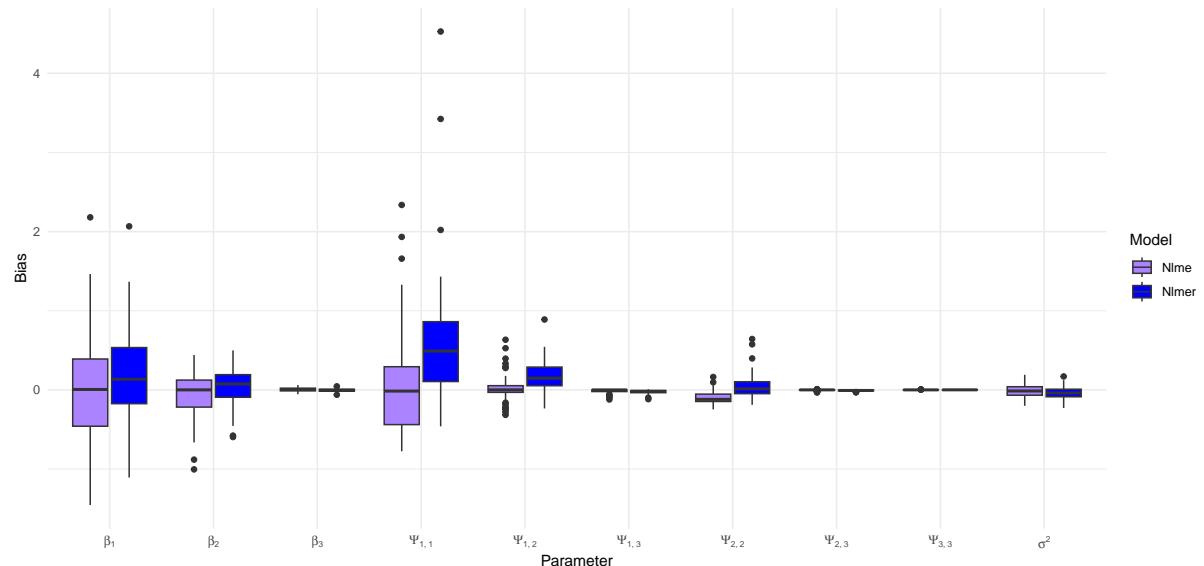
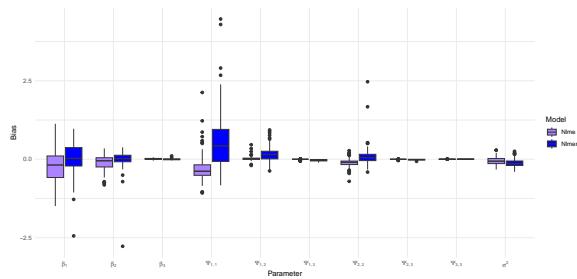
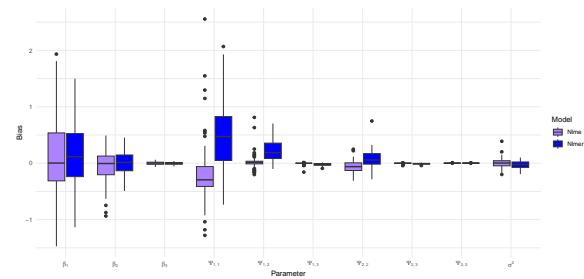
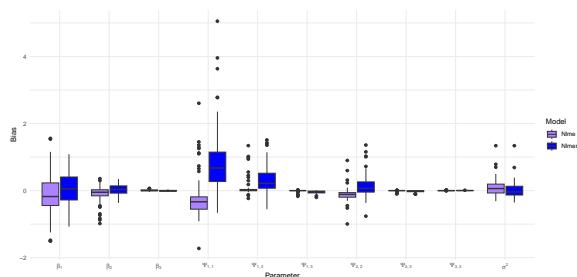
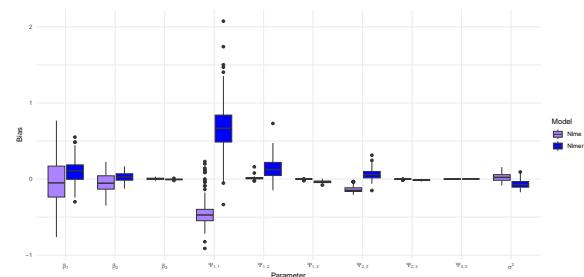
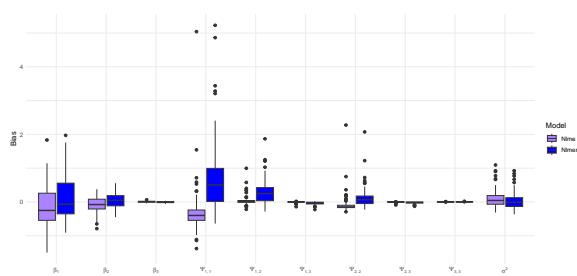
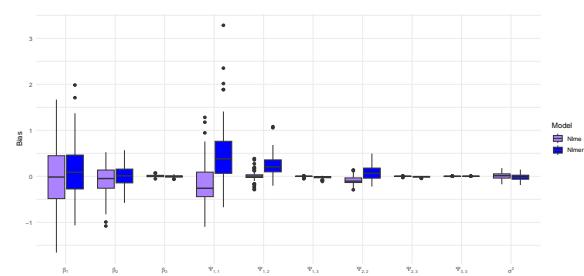
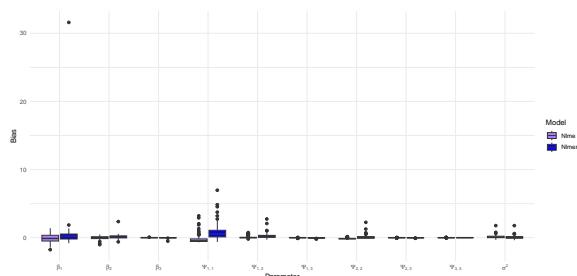
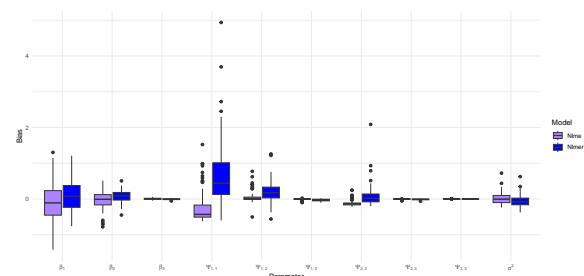


FIGURE A.99: LG

**FIGURE A.100: LL****FIGURE A.101: LN****FIGURE A.102: NL****FIGURE A.103: NG****FIGURE A.104: ddd1**

**FIGURE A.105: GG****FIGURE A.106: GN****FIGURE A.107: GL****FIGURE A.108: LG****FIGURE A.109: LL****FIGURE A.110: LN****FIGURE A.111: NL****FIGURE A.112: NG**

A.4.6 Predictions for 150/6

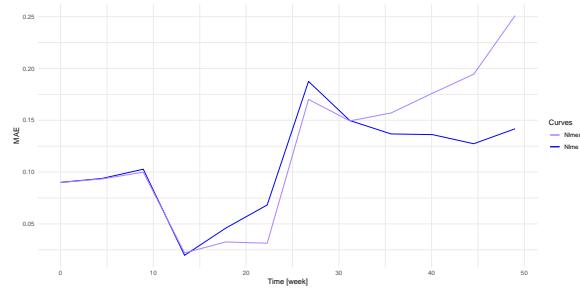


FIGURE A.113: GG

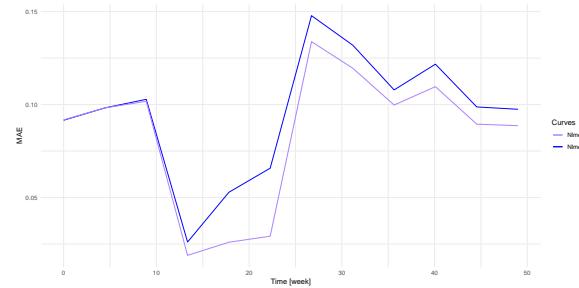


FIGURE A.114: GN

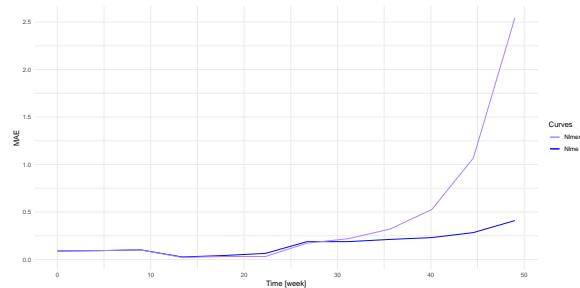


FIGURE A.115: GL

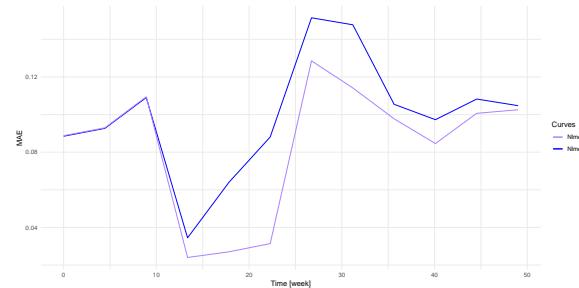


FIGURE A.116: NN

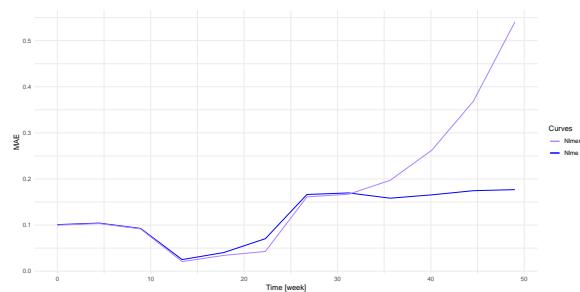


FIGURE A.117: NL

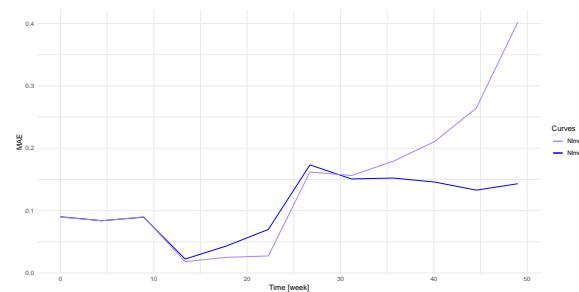


FIGURE A.118: NG

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