Comparison of methods for repeated measures binary data with missing values

by

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Abstract

Missing data is common in health and medical experiments including controlled clinical trials. Using only the complete cases for analysis may cause biased inferences or even controversial results. Assuming that the data are missing at random (MAR), various methods have been developed to handle missing data. Among them, GEE, non-linear mixed effects and multiple imputation (MI-GEE and MI-NLME) methods based on GEEs and NLMEs are considered the most efficient methods. However, these guidelines are too limited to apply generally. We evaluated their performance on various missing data mechanisms with repeated measurement binary data using a simulation study. We considered two different levels of correlation (ρ=0.3, 0.7) with three cases of repeated measures (T=2, 4, 6) with sample sizes of 40, 80, 200 under different missing data mechanisms, MCAR (Missing Completely at Random), MAR (Missing At Random) and MNAR (Missing Not At Random). Based on obtained empirical size control, power level and bias of each method, we conclude that the NLME based multiple imputation (MI-NLME) method performs the best.

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Chapter 1

Introduction

One can classify variables into two categories: continuous or discrete. Continuous data such as height, weight, etc. can take any value in a defined range. On the other hand, discrete data can only take countable values or categories. Due to this difference, different methods should be applied to each data type for analysis. For example, the simple linear regression can be applied to continuous data, while logistic regression can be an appropriate model for binary discrete data [1].

Repeated measures data refers to data that contains repeatedly observed values for subjects and in different conditions of a certain experiment. These observed values are random samples from the population. One of the most prominent types of repeated measures data is longitudinal data. Repeated measures data are often called longitudinal data whenever observed values are ordered by time or a position in space. As a result, these observations cannot be randomly assigned to each time, and results in a correlation within observed values of each subject in the dataset. In other words, the independence assumption in some of the models cannot be satisfied, and therefore these methods will not be applicable to this kind of dataset. There has been some methods that take care of this data type. Among them, we will discuss Nonlinear Mixed Effects (NLME) models and Generalized Estimating Equations (GEE) [2].

In clinical trial studies, subjects go through various phases from the beginning to the end of study [3]:
(i) Enrollment in the study in which subjects will be informed about the study procedure and all the other required information such as possible side effects. The eligibility of the subject for this study will be confirmed via a screening test.
(ii) Treatment will be applied to the subjects taking into account various safety and efficacy considerations.
(iii) Follow up phase: in this period the treated subject will be observed and measured over time.

Any of the following errors may occur to each subject in the study in each phase [3]
(i) Noncompliance to eligibility criteria.
(ii) Noncompliance to treatment.
(iii) Noncompliance to follow up phase.

Noncompliance to eligibility criteria can affect the generalizability of a study. Most investigators resolve this issue by removing subjects who do not qualify for this criteria from the study. Noncompliance to treatments can also alter the study by increasing variability between responses of subjects. This problem may be resolved by conducting intention-to-treat (ITT) analysis. Noncompliance to follow up phase usually refers to situations where the subject withdraws from the study. In such cases, data must be carefully handled using a missing data analysis technique to avoid unwanted bias to the study.

Some of the most popular methods for handling missing data can be classified in the following categories:

1- Case deletion

2- Single imputation

3- Multiple imputation

4- Maximum likelihoood based approaches

5- Quasi likelihood approaches

Currently, the first two methods are mostly being used in empirical studies. However, it has been documented that these two perform poorly in practice. Some of these weaknesses are discussed in this thesis.

The other three methods have been proved to be more efficient [4]. Among these, Non-linear Mixed Effect (NLME) Models and Generalized Estimating Equations(GEE) are discussed in this thesis. These methods can be combined with the multiple imputation method such that after imputation, one can apply these models on each imputed dataset and then combine all the results in order to obtain a more comprehensive result from the data.

Our goal is to make a thorough investigation into all these methods in terms of empirical size, power and bias when applied to binary data.

Chapter 2

Literature Review

2.1 Mising Data Mechanisms

Donald B. Rubin defined three different mechanisms for missing data in his book [5], Missing Completely At Random (MCAR), Missing At Random (MAR) and Missing Not At Random (MNAR). In the following, these different mechanisms have been explained.

2.1.1 Missing Completely At Random (MCAR)

Data are missing completely at random when the probability of missingness on a variable Y is not related to any other variables and to the observed values of the Y variable. Because of this property one can assume that observed values are from a simple random sample extracted from the data set we would have analyzed if all the values were observed. For instance, when an experimentor drops a laboratory sample, the corresponding information of the sample are missed completely at random. Under this mechanism for missingness, almost all the methods of handling missing data work perfectly. However, this situation rarely happens or at least the chance of missingness under two other mechanisms (MAR and MNAR) is higher than MCAR [5].

2.1.2 Missing At Random (MAR)

A missing at random mechanism can be detected when the probability of missingness of variable Y is related to other variables (covariates) but it is not related to the observed values in the same variable (Y). In other words, Missing at random mechanism implies that there is a systematic relationship between the chance of missingness and other variables. Maximum likelihood based methods and also multiple imputation method assume an MAR mechanism [6]. For instance, when asking volunteers to attend a study and show up in a lab to do the experiment for seven days in a row early in the morning, the chance of dropout from the study is higher for people who live further from the lab rather than those people who live close by the lab.

2.1.3 Missing Not At Random (MNAR)

Data are assumed to be missed not at random, when the probability of missingness is related to other variables and also observed values in the variable with missed data. Any data mechanism that does not fit in missing completely at random and missing at random categories, is assumed to be missing not at random [5]. This mechanism is the most common in studies there are a few methods that work well under this assumption when the rate of missingness is not very severe. An example of missing not at random is when a group of people are asked to fill in an electronic form related to the information of their income by a tax related organization. In such a case, the probability that an older person fills in the form is less than the probability for a younger individual as older people are not as comfortable as younger people are with using computers. Also, people with higher income rates have less tendency to report their tax information as the organization which is asking for this information is a tax related organization.

There is another categorization method for different missing data mechanisms in which the first two mechanisms (MCAR and MAR) are called ignorable missing mechanism and the last one (MNAR) is called non-ignorable missing mechanism [5].

2.2 Traditional Methods

There are many conventional methods that are still being used as they are easy to use. Most of these methods come with serious disadvantages. The following methods are the most popular ones among them:

2.2.1 Case Deletion

This method is the most basic method that is used when there is missing data. It can be categorized into two groups: listwise deletion and pairwise deletion. In listwise deletion method, all the cases with any missing value will be discarded from all the calculations. As a result, analysis will be done on the complete cases only. In the pairwise deletion method, cases with a missing value in the variable or variables of interest will be discarded only. In other words, if there is a missing value in a specific variable corresponding to a case and we are not interested in that specific variable but other variables, that case still remains in the study. As all the cases are complete cases, there is no limit for using any standard statistical method to analyze the data. Sometimes deleting some complete subjects will be recommended in order to balance the sample size across treatment groups. This method can be useful when the proportion of missing cases is small and they are not overly influential. Not surprisingly, this method comes with several disadvantages. It can be inefficient when a very high proportion of cases are missing. Also, this method assumes the missing completely at random (MCAR) mechanism for missingness. In practice this assumption is usually violated, so in many cases deletion method distorts the results [7].

2.2.2 Single Imputation

The single imputation approach is a method in which all missing values are replaced by any reasonable value such as the mean, median or even zero depending on the nature of data. Among several single imputation methods, mean imputation, regression imputation and Last Obseravation Carried Forward (LOCF) are the most popular methods.

The mean imputation method replaces all the missing values in a variable by its mean. One advantage is that after the imputation, the mean of the variable does not change. However, this method can become problematic in multivariate cases. Consider a highly correlated multivariate dataset with some missing values. After mean imputation, the correlation between the variables become smaller. In other words, mean imputation may distort the results when estimating the correlation matrix [6].

In the regression imputation method, the missing cases of a variable are being predicted using at least another variable as the predictor on a regression line. Although using some extra information on the other variables in order to estimate missing cases of a specific variable is a very good idea, the method comes with some disadvantages. For example, consider a bivariate scenario with missing cases in only one variable. Assume the variable with missing data is the response and the variable with complete cases is the predictor. After estimating the regression line, the missed cases can be predicted using the corresponding values in the predictor. These predicted values would all fall on a straight line. This implies a perfect correlation. As a result, the regression imputation method can lead to over estimation of correlation between variables [7].

The last Observation Carried Forward (LOCF) method, can be categorized as a single imputation method as well. This method involves replacing missing cases with the last observed value. In data sets with dropouts, the last observed value will be repeated for the rest of dataset. For instance, if there is a study with seven repeated measures and a subject drops out of the study after the third repeated measure, the last four missed measures will be filled in by the third observation of the same subject. This method may change the distribution and relationship between the variables. For example, consider a set of variables with large variations among subjects and also the presence of missing cases. In this situation, replacing the last observed values for missing cases would result in under estimation of the variations of different variables and is inappropriate. Therefore, LOCF can give false results in cases where there are high variations among the subjects of a study [8].

2.3 Generalized Linear Model (GLM)

Components of GLM: Generalized linear models (GLM) are basically an advanced format of ordinary regression models. These models were first introduced by John Nelder and Robert Wedderburn [9]. Generalized linear models can be decomposed into three parts: the random component, the systematic component and the link function. To illustrate these three components, we use the model proposed by Agresti [10]. The random component is basically the response variable and its corresponding distribution. In generalized linear models, it is assumed that responses are independent. These independent responses are assumed to have a distribution from the exponential family. This part can be formulated as:

$$Y = (Y_1, Y_2, ..., Y_n)' \tag{2.1}$$

The systematic component or the linear predictor incorporates the information of the response variable to the model. It also can be considered as a linear combination of covariates and can be written as:

$$\eta_i = \sum_j \beta_j x_{ij} = X_i'\beta, i = 1, 2, ..., n \tag{2.2}$$

in which x_{ij} refers to the j^{th} covariate on the i^{th} subject.

The link function is a function that relates the random component to the systematic component. Suppose that μ_is are the means corresponding to the responses (Y_i) and h(.) is an one-to-one and invertible function. One can write:

$$\mu_i = h(\eta_i) = h(X_i'\beta) \tag{2.3}$$

Then simply, one can write:

$$\eta_i = X_i'\beta = g(\mu_i) \tag{2.4}$$

$g(.) = h^{-1}(.)$ is the link function. There are two different types of link function, the identical link and canonical link. If the link fuction is defined as $g(\mu_i) = \mu_i$, then g(.) is an identical link function. If the function g(.) is such that it transforms μ_is to the natural parameter in the exponential family, then it is called the canonical link. Recall the natural parameter $Q(\theta_i)$ in the exponential family:

$$f(y_i; \theta_i) = a(\theta_i)b(y_i)\text{exp}[y_i Q(\theta_i)] \tag{2.5}$$

Then $g(\mu_i) = Q(\mu_i) = X_i'\beta$ is a canonical link function.

2.4 Non-linear Mixed Effects (NLME) Model

Non-linear mixed effect models are fully parametric models. This model consists of two parts: the fixed effect and the random effect. It models the within subject covariance structure more explicitly. This model is already an acceptable and practical method for analyzing longitudinal data. This model is an extension of linear mixed-effect (LME) models which recognizes and takes into account the variability of within and between responses. In many situations, LMEs are no longer useful as the relationship between responses and covariates cannot be explained in a linear relationship. NLME can be a good solution to these cases [9]. Lindstrom and Bates [2] proposed a non-linear mixed effect model for repeated measures data and defined estimators of NLME's parameters.

Let Y_{ij} be the j^{th} response for the i^{th} individual in the study, then one can write the model as:

$$Y_{ij} = f(\phi_i, x_{ij}) + e_{ij} \tag{2.6}$$

Where x_{ij} is the corresponding vector of independent variable for the j^{th} response of i^{th} individual. $f(.)$ is any non-linear function. The random error part (e_{ij}) is normal, $e_{ij} \sim N(0, \sigma)$. Responses of different individuals are assumed to be independent which implies Cov(e_{ij},$e_{i'j}$)=0 if $i \neq i'$. ϕ_i is a $r \times 1$ vector with the form of:

$$\phi_i = A_i\beta + B_i b_i, \quad b_i \sim N(0, \sigma_b^2 D) \tag{2.7}$$

Where A_i is a $r \times p$ design matrix for the fixed part and B_i is a $r \times q$ design matrix of the random part. β is the mutual vector of parameters of all the subjects in the study, $\beta = (\beta_1, \beta_2, ..., \beta_p)^T$. b_i is the vector of random effects which changes from subject to subject, $b_i = (b_{i1}, b_{i2}, ...b_{iq})^T$. Also, $\sigma_b^2 D$ is the covariance matrix of b_is.

2.5 Generealized Estimating Equations (GEE) Models

2.5.1 Quasi Likelihood

Generalized estimating equations are based on quasi likelihood estimation which is an alternative approach of estimation to maximum likelihood. The only difference between quasi likelihood and maximum likelihood is that the maximum likelihood approach assumes a specific distribution of responses, but quasi likelihood approach only assumes a relationship between the mean and the variance of responses:

$$Var(Y_i) = \nu(\mu_i) \tag{2.8}$$

Thus $\nu(.)$ is a variance function defined in terms of means. Similar to the maximum likelihood score function, a quasi likelihood score function can be defined. The only difference of quasi likelihood score function from the maximum likelihood score function is that it uses $\nu(\mu_i)$ [10].

2.5.2 Generalized Estimating Equations (GEE)

This model has been proposed by Liang and Zeger [11] as an extension of generalized linear models. Similar to NLME, this model also has the ability to account for the correlation within subjects. As metioned in the previous section, estimations are based on quasi likelihood.

Let $Y_i = (y_{i1}, y_{i2}, .., y_{in_i})^T$ be a vector of different measurements on subject i with a mean vector $\mu_i = (\mu_{i1}, \mu_{i2}, .., \mu_{in_i})^T$ and V_i as the corresponding co-variance matrix. Assuming that the $n_i \times p$ matrix of $X_i = (x_{i1}, x_{i2}, .., x_{in_i})^T$ are the corresponding covariates of subject i, one can write $g(\mu_i) = X_i^T \beta$ which is exactly the GLM format. The quasi likelihood score function in this case will be:

$$S(\beta) = \sum_{i=1}^{N} D_i^T V_i^{-1} (Y_i - \mu_i(\beta)) \tag{2.9}$$

where

$$D_i^T = \frac{\partial \mu_i^T}{\partial \beta} = \begin{bmatrix} \frac{x_{i11}}{g(\mu_{i1})^T} & \cdots & \frac{x_{in_i1}}{g(\mu_{in_i})^T} \\ \vdots & \ddots & \vdots \\ \frac{x_{i1p}}{g(\mu_{i1})^T} & \cdots & \frac{x_{in_ip}}{g(\mu_{in_i})^T} \end{bmatrix} \tag{2.10}$$

the formula for V_i is given by

$$V_i = \phi A_i^{\frac{1}{2}} W_i^{\frac{-1}{2}} R(\alpha) W_i^{\frac{-1}{2}} A_i^{\frac{1}{2}} \tag{2.11}$$

where A_i is a $n_i \times n_i$ diagonal matrix. The j^{th} diagonal component of A_i is $\nu(\mu_{ij})$. Also, W_i is the $n_i \times n_i$ potential diagonal weight matrix. Then the $n \times n$ symmetric matrix of $R(\alpha)$ is called the correlation matrix which has to be specified based on properties of responses [12]. There are different defined structures for the correlation matrix such as independet, exchangeable, unstructured and autoregressive. Based on the nature of the study one of these correlation matrices should be chosen. An independent correlation matrix assumes independency between different measurements within a subject. This correlation matrix would not be a proper choice in repeated measures studies. An exchangeable correlation matrix assumes a constant value for the correlation among all different measurements within a subject. A better choice for a correlation matrix is to allow the correlation value to change between different measurements within a subject. However, using such a correlation matrix will acquire more parameter estimations and when the number of repeated measurements is large, it may not be an appropriate correlation matrix to use. Nevertheless, when the measurements are not highly correlated, using any of these correlation structures would result in similar estimates [10].

2.6 Multiple Imputation

The main idea in multiple imputation is to replace missing values with $M > 1$ plausible values. As a result, the uncertainty of the imputed values would be represented better. Estimates from different datasets will be combined after using Rubin's rule which will be introduced in this section. In fact, the multiple imputation procedure can be summarized into these three following phases:

1- Replacing missing values in the dataset M times in order to obtain M datasets.

2- Analyzing each dataset separately using standard methods.

3- Combining results from different datasets all together using Rubin's rule.

In order to explain multiple imputation procedure, a short review of the EM algorithm is necessary as the parameters are estimated using the EM algorithm in a multiple imptation study.

2.6.1 EM algorithm

There are several ways to obtain estimators of maximum likelihood. One of the most well known methods is called the Expectation-Maximization algorithm (EM). The main idea of this method is: if we had the real values for missing subjects, then estimation of the parameters would be clear. On the other hand, if we had the values for parameters of the model, then obtaining an unbiased prediction for the missing subjects would be possible [13].

There are two steps in the EM algorithm. The first step is the Expectation step (E step) in which the conditional expectation of data log likelihood given the observed data and parameter estimates is calculated. The second step is called the maximization step (M step) in which the parameter are estimated such that it maximizes the expectation of the log likelihood obtained in the E step. This procedure will be repeated several times until the system stabilizes.

Suppose there are G specific groups with different missing patterns on multivariate normal data. Then the format of the log likelihood for the observed data has the following form:

$$\log L(\theta|Y_{obs}) = \sum_{g=1}^{G} \log L_g(\theta|Y_{obs}) \tag{2.12}$$

where $\log L_g(\theta|Y_{obs})$ corresponds to g^{th} group and can be decomposed into:

$$logL_g(\theta|Y_{obs}) = -\frac{n_g}{2} log|\sum\nolimits_g| - \frac{1}{2}\sum_{ig}(y_{ig} - \mu_g)' \sum\nolimits_g^{-1}(y_{ig} - \mu_g) \tag{2.13}$$

where n_g is the total number of observations in the g^{th} group, and μ_g and $\sum_g$ are the corresponding mean vector and covariance matrix of the g^{th} group. The results from the EM algorithm are the parameters of the multivariate normal distribution in the multiple imputation method.

2.6.2 MCMC multiple imputation

As mentioned in the previous section, there are three phases for conducting a multiple imputation analysis. In the first phase, missing values are replaced by random values generated from a multivariate normal distribution with parameters obtained by the EM algorithm using an MCMC procedure. This procedure repeats for $M > 1$ times. Due to the fact that it is a random number generation procedure, these datasets and their corresponding estimates will be slightly different from each other. M does not need to be a very large number as three to five imputations are considered sufficient [5].

In the second phase, a statistical analysis method is conducted on each dataset separately. These statistical analyses could be multiple regression, generalized estimating equations (GEE), Non linear mixed effect (NLME) models or any other statistical procedure. In this thesis, GEE and NLME are chosen as appropriate analysis methods because of many of the data properties.

Results obtained from each dataset will be combined in the third phase in order to reach the final estimation of the parameter of interest and its corresponding variance using Rubin's rule.

Let $\hat{\theta}_l$ be the parameter of interest obtained from the l^{th}, $l = 1, ..., M$, dataset and let W_l be the corresponding variance. Then we can write the combined estimate of the parameter of interest $\bar{\theta}_M$ as the following:

$$\bar{\theta}_M = \sum_{l=1}^{M} \frac{\hat{\theta}_M}{M} \tag{2.14}$$

The variability associated with the estimator of the parameter of interest can be decomposed into two parts. First, the average within imputation variance:

$$\bar{W}_M = \sum_{i=1}^{M} \frac{\hat{W}_l}{M} \tag{2.15}$$

Second, the between imputation variance:

$$B_M = \frac{\sum(\hat{\theta}_l - \bar{\theta}_M)^2}{M-1} \tag{2.16}$$

We can then write the total variability associated with the estimator of the parameter of interest as [5]:

$$T_M = \bar{W}_M + \frac{M+1}{M} B_M \tag{2.17}$$

Typically, we can perform inference on θ using a normal distribution with estimated mean $\bar{\theta}_M$ and variance T_M.

2.7 Other Alternatives

2.7.1 Weighted Generalized Estimating Equations (WGEE)

WGEE works similarly to GEE except that a weight w_i is defined as the inverse missingness probability of subject i. A random variable r_{ij} is defined as an indicator if the response is observed. Then the logistic resgression model will be defined as:

$$\text{logit}P(r_{ij=1|X_i}) = \psi_0 + \psi_1 Y_{i,j-1} + \psi_2 X_i \tag{2.18}$$

Where $Y_{i,j-1}$ are the previous observed responses of the same subject and x_i is the covariate of the subject. Then W_i can be modeled as:

$$w_i^{-1} = (\prod_{j=2}^{m-1} \lambda_{ij})(1 - \lambda_{im}) \tag{2.19}$$

Where m is the time of dropout and $\lambda_{ij} = P(r_{ij} = 1|r_{i(j-1)=1}, X_i, Y_{i,j-1})$. Then using the following equation called the weighted GEE equation, β can be estimated from [10]:

$$\sum_i w_i[\frac{\partial \mu_i}{\partial \beta}]'[V_i(\alpha)]^{-1}(Y_i - \mu_i) = 0. \tag{2.20}$$

2.7.2 Penalized Quasi likelihood (PQL)

Penalized Quasi Likelihood (PQL) is developed as another estimation method of GLMs. This method works based on a first order Taylor series approximation. This method is also called pseudo-likelihood and joint maximisation. Recently, this model became popular among statisticians as implementing it is very simple. It has been shown that it performs good in the estimation of mean parameters. However, this technique does not work properly in some certain GLM situations such as small group sizes of binary responses in terms of bias in estimation. Particularly, this method seems to work poorly in the estimation of standard errors of variances in the model [10].

Chapter 3

Simulation Study

3.1 Data Generation

We simulate data using a clinical trial study, which evaluates efficacy of a treatment in comparison to a control group of subjects for a respiratory disorder [14]. The sample size of the generated data is $n = 40, 80, 200$. Half of the subjects are randomly assigned to the treatment group (treatment=1) and the other half are randomly assigned to the placebo group (treatment=0).The y_{ij} is the binary response variable indicating the respiratory condition (0=poor, 1=good) of the subject i at its corresponding j^{th} measurement $i = 1, 2, ..., n$; $j = 1, 2, ..., T$. In this simulation $T = 2, 4, 6$ have been considered repeated measures. Each binary response (y_{ij}) is generated with probability $\pi_{ij} =$

$P(Y_{ij} = 1)$. Therefore the model can be written as:

$$logit(\pi_{ij}) = log(\frac{\pi_{ij}}{1-\pi_{ij}}) = \beta_0 + \beta_1 \times \text{treatment}, i = 1, 2, ..., n, j = 2, 4, 6 \quad (3.1)$$

The probability of observing a subject with a good respiratory disorder condition is assumed to be equal to the probability of observing a subject with poor respiratory disorder condition for the placebo group ($\pi_{ij} = P(Y_{ij} = 1) = 0.5$). In the treatment group it is assumed that the probability of observing a good respiratory disorder condition is more than the probability of observing a subject with a poor disorder respiratory condition. In other words, for the treatment group ($\pi_{ij} = P(Y_{ij} = 1) > 0.5$). In this specific study, we will consider π_{ij}= 0.6, 0.70, 0.80 for the treatment group. It is easy to see $\beta_0 = log(\frac{\pi_{ij}}{1-\pi_{ij}}) = 0$ (treatment=0, $\pi_{ij} = 0.5$). As a result, $\beta_1 = 0.41, 0.85, 1.39$ (treatment=1, $\pi_{ij} = 0.60, 0.70, 0.80$).

For generating correlated binary data, the command "rmvbin" in the R package "bindata" has been used. This command gives the option to choose a correlation structure. In this simulation study, we used an exchangeable correlation matrix with two different correlation coefficients $\rho = 0.3, 0.7$ indicating low and high correlation respectively. After generating data, some data points have to be eliminated in order to generate missing data. 30 percent of the responses are assumed to be missing. For the MCAR mechanism, the 30 percent of responses have been omitted completely at random. In order to create missing data for the MAR mechanism, a 20 percent of reponses with treatment=1 and 10 percent of responses with treatment=0 have been omitted. The MNAR mechanism, works very similarly to MAR mechanism except that among those 20 percent missing responses with treatment=1, we omit 70 percent of reponses with value 1 representing a good respiratory status. Similarly a 10 percent of responses with treatment=0 will be assumed missing.

3.2 Analysis of the Simulated Data

3.2.1 Software Package Introduction

All the analysis of simulatied data have been done using the R software version 3.0.2. The nlme, gee and Amelia packages were used to conduct the analysis for the non-linear mixed effext models, generalized estimating equations and multiple imputations respectively. In this section, we briefly illustrate the analyses steps and commands.

3.2.2 Non-linear Mixed Effects Model

We consider the underlying model which has been discussed in the previous sections:

$$logit(\pi_{ij}) = log(\frac{\pi_{ij}}{1-\pi_{ij}}) = \beta_0 + \beta_1 \times \text{treatment}, i = 1, 2, ..., n, j = 2, 4, 6 \quad (3.2)$$

The R command for conducting this would be:

```
> library(nlme)
> fit1 <- nlme(response ~ exp(1+treatment)/1+exp(1+treatment),
             random=~ 1|id,data=data,
             correlation = "exchangeable", method='ML')
```

Arguments in the nlme command start with defining the general format of the model and then specifying the random part and also the format of the correlation matrix. The maximum likelihood method was chosen for estimating the parameters. The other option for estimation is REML [15].

3.2.3 Generalized Estimating Equations

The following is R code for the GEE model:

```
> library(gee)
> fit2 <- gee(response ~ 1 + treatment,id = id, data = data,
            family = binary, corstr = "exchangeable")
```

Similar to nlme, the first argument in the gee command is to introduce the response and explanatory variables. The "id" argument reprsents a cluster in the dataset. The "family" argument specifies the distribution of the response. The "corstr" argument specifies the structure of the correlation matrix [16].

3.2.4 Multiple Imputation

The following R code was used to conduct multiple imputation:

```
> library(Amelia)
> imp < − amelia(X = data, m = 3, noms = ”response”, ts = visit)
```

The ”X” is the data set that we want to impute, ”m” is the argument indicating number of imputations, the ”noms” argument specifies categorical variables and the ”ts” identifies the variable related to the time change. This command calculates the parameters and covariance matrices using the EM algorithm and imputes the data [16].

3.3 Empirical size, power and bias comparison

Errors that occur in hypothesis testing can be divided into two different kinds: Type I error or Type II error.

Type I error is the probability of rejection of the null hypothesis when the null hypothesis is actually correct (P(Rejection of $H_0|H_0$ is correct)). Type II error occurs when we fail to reject the null hypothesis, when the alternative hypothesis is correct (P(Acceptance of $H_0|H_1$ is correct)). Type I error is considered a more serious kind of error that can happen in practice. Therefore, Type I error will have priority in terms of minimization. This minimization will be done by setting a critical region (C) such that:

$$\alpha = \max P_\theta[(X_1, X_2, ..., X_n) \in C] \tag{3.3}$$

After setting the Type I error, we work to minimize the Type II error. This is often accomplished by maximizing its complement, which is called the power of the test ($\beta = \text{P}(\text{Acceptance of } H_1 | H_1 \text{ is correct})$). Therefore, a reliable test must maintain a low Type I error and a high power.

3.3.1 Claculation of size and power

In this simulation study, the empirical size and power of the different methods have been measured. Based on the definition of the size of a test, the empirical size will be calculated as the proportion of number of rejections over the total number of tests in the simulation when the null hypothesis is correct ($\pi_{ij} = 0.5$). Similarly, power will be calculated as the proportion of number of rejections over the total number of tests during the simulation when null hypothesis is incorrect ($\pi_{ij} = 0.6, 0.7, 0.8$).

When the sample size is large enough, the empirical size follows a normal distribution with mean α_0 which is the estimate of the size of the test and variance $\sigma^2 = \frac{\alpha_0(1-\alpha_0)}{5000}$. A 95% conidence intervel can be obtained using $\alpha_0 \pm 1.96\sigma$. As a result, intervals (0.007, 0.013), (0.044, 0.056) and (0.092, 0.108) are 95% confidence intervals for $\alpha = 0.01, 0.05, 0.1$ respectively. In the following tables, the empirical size has been illustrated for each method with different missing data mechanisms at different levels:

Table 3.1: The Empirical Size in 5000 simulations under the significant level of 0.01

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
rho	T	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
0.3	2	GEE	0.0119	0.0107	0.0122	0.0112	0.0128	0.0113	0.0117	0.0106	0.0112
		NLME	0.0124	0.0103	0.0098	**0.0145**	0.0125	0.0107	0.0124	0.0116	0.0104
		MI-GEE	0.0121	0.0123	0.0104	0.0128	0.0122	0.0112	**0.0145**	0.0128	0.0115
		MI-NLME	0.0105	0.013	0.0089	0.0135	0.0129	0.0114	0.013	0.0108	0.0112
	4	GEE	**0.0168**	0.0102	0.0114	**0.0182**	**0.0151**	0.0126	**0.0173**	**0.0135**	0.0108
		NLME	0.0108	0.0098	0.0087	**0.0134**	0.0116	0.0121	**0.0152**	0.0127	0.0126
		MI-GEE	0.0115	0.0094	0.0108	**0.0162**	**0.0166**	**0.0131**	**0.0171**	0.0102	0.0094
		MI-NLME	0.01	0.0082	0.0117	**0.0148**	**0.0175**	0.0125	**0.019**	0.0108	0.0111
	6	GEE	**0.0165**	0.0119	0.0091	**0.0143**	0.0127	0.0089	**0.0142**	0.0128	0.0098
		NLME	0.01	0.0118	0.0087	**0.0159**	0.0118	0.0099	**0.0153**	**0.0152**	0.0109
		MI-GEE	**0.0163**	0.0109	0.0095	**0.0146**	0.0129	0.0096	**0.0168**	0.0121	0.0103
		MI-NLME	**0.0152**	0.0117	0.0099	**0.0153**	0.0118	0.0094	**0.0184**	**0.0131**	0.011
0.7	2	GEE	0.0112	0.0103	0.0099	0.0124	**0.0134**	0.0127	0.0115	0.0117	0.0108
		NLME	**0.0258**	0.0116	0.0104	**0.0137**	**0.0137**	0.0116	0.0124	**0.0131**	**0.0134**
		MI-GEE	0.0108	0.0105	0.0092	**0.0154**	**0.0143**	**0.0152**	0.0116	0.0105	0.0111
		MI-NLME	0.0119	0.0089	0.0094	**0.0143**	**0.0132**	**0.0164**	0.0123	0.0121	0.0118
	4	GEE	0.0112	0.0096	0.0097	0.0114	0.0126	0.0109	0.0126	0.0122	0.0102
		NLME	0.0094	0.0105	0.0082	**0.0134**	0.0122	0.0114	0.0121	0.0118	0.012
		MI-GEE	0.0116	0.0104	0.0096	**0.0148**	0.0127	0.0106	**0.0137**	**0.0141**	0.0127
		MI-NLME	0.0126	0.012	0.0083	**0.0155**	0.0111	0.0096	0.013	**0.0149**	0.0121
	6	GEE	0.0127	0.0103	0.0089	**0.0136**	0.0119	0.0102	0.0128	0.0115	0.0106
		NLME	0.0076	0.0091	0.0103	**0.0167**	0.0098	0.0101	0.0125	0.0097	0.0104
		MI-GEE	0.0106	0.0097	0.0091	0.0122	0.0094	0.009	0.0109	0.0096	0.0097
		MI-NLME	0.0124	0.0116	0.0098	0.0112	0.009	0.0087	0.0102	0.0108	0.0103

Number of rejections over 5000 simulations with Type I Error=0.01 and a 95% confidence interval=(0.007, 0.013).

Table 3.2: The Empirical Size in 5000 simulations under the significant level of 0.05

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
rho	T	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
0.3	2	GEE	**0.0564**	0.0557	0.0548	**0.0587**	**0.0563**	0.0532	**0.0578**	**0.0585**	**0.057**
		NLME	0.0542	0.0536	0.0518	**0.0571**	0.0545	0.0524	**0.0587**	**0.058**	**0.0571**
		MI-GEE	**0.0561**	0.0558	0.0546	**0.0588**	0.0559	0.0526	**0.0587**	**0.0569**	**0.0564**
		MI-NLME	**0.0577**	0.055	0.0538	**0.0598**	**0.057**	0.051	**0.0577**	0.0556	**0.0574**
	4	GEE	0.0551	0.0549	0.0521	**0.0607**	**0.0601**	0.0529	**0.0601**	0.0545	0.0512
		NLME	0.0539	0.0522	0.0508	**0.0626**	**0.0576**	0.0521	**0.0584**	**0.0588**	0.0525
		MI-GEE	0.0547	0.0544	0.0517	**0.0594**	0.0559	0.0524	0.0524	0.0508	0.0531
		MI-NLME	0.0552	0.0551	0.0522	**0.0575**	**0.0563**	0.0522	0.054	0.0506	0.0546
	6	GEE	0.0548	0.0548	0.0514	**0.0589**	0.0541	0.0514	0.0534	0.0516	0.0504
		NLME	0.0533	0.0515	0.0503	0.0547	0.0516	0.0496	0.0541	0.0544	0.0507
		MI-GEE	0.0545	0.0538	0.0518	**0.0596**	0.0512	0.0489	0.0537	0.0516	0.0481
		MI-NLME	0.054	0.0544	0.0511	**0.0585**	0.0505	0.0474	0.0508	0.0491	0.0529
0.7	2	GEE	**0.057**	0.0551	0.0526	**0.0581**	**0.0562**	0.0531	0.0546	0.0551	0.0537
		NLME	**0.0564**	0.0534	0.0515	**0.0561**	0.0537	0.0519	0.0571	0.0556	0.0516
		MI-GEE	**0.0566**	0.0545	0.0519	0.056	0.0538	0.0524	0.0551	0.0542	0.0519
		MI-NLME	0.0548	0.055	0.0518	**0.0571**	0.0538	0.0512	0.0544	0.0552	0.0524
	4	GEE	**0.0574**	0.0552	0.0527	0.0524	0.0513	0.0507	0.0546	0.0528	0.0512
		NLME	**0.0566**	0.0541	0.0518	0.0518	0.051	0.0501	0.0521	0.0526	0.0502
		MI-GEE	**0.0569**	0.0548	0.0522	0.0532	0.0513	0.0504	0.0528	0.0543	0.0511
		MI-NLME	**0.0587**	0.0548	0.0525	0.055	0.0497	0.0488	0.0526	0.0551	0.0505
	6	GEE	**0.0565**	0.0551	0.0524	**0.0572**	0.0529	0.0488	0.0552	0.0531	0.0499
		NLME	0.0524	0.0506	0.0498	0.0532	0.0517	0.0495	0.0537	0.0504	0.04986
		MI-GEE	0.0556	0.0527	0.0513	0.0547	0.0511	0.0491	0.0516	0.0523	0.0496
		MI-NLME	0.0537	0.053	0.0507	**0.0564**	0.051	0.0471	0.0512	0.0515	0.0492

Number of rejections over 5000 simulations with Type I Error=0.05 and a 95% confidence interval=(0.044, 0.056).

Table 3.3: The Empirical Size in 5000 simulations under the significant level of 0.1

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
rho	T	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
0.3	2	GEE	**0.1096**	0.1052	0.1016	**0.1107**	0.1066	0.1021	**0.1091**	0.1041	0.1016
		NLME	**0.1088**	0.1035	0.1011	**0.1091**	0.1043	0.1051	**0.1083**	0.1067	0.1023
		MI-GEE	**0.1094**	0.1055	0.1008	**0.1103**	**0.1082**	0.1027	0.1077	0.1064	0.1011
		MI-NLME	**0.1094**	0.1054	0.1027	**0.112**	**0.1094**	0.1034	0.1077	0.1046	0.1019
	4	GEE	**0.1099**	0.1053	0.1027	**0.1116**	0.1034	0.1048	0.1069	0.1021	0.107
		NLME	0.1063	0.1021	0.0997	**0.1095**	0.1028	0.1006	**0.1116**	**0.1083**	0.1027
		MI-GEE	**0.1087**	0.1036	0.1002	**0.1081**	0.1026	0.1034	**0.1093**	0.1024	0.1026
		MI-NLME	0.108	0.1033	0.1014	**0.1097**	0.1045	0.1026	**0.109**	0.1027	0.1041
	6	GEE	0.1075	0.1068	0.1011	**0.1084**	0.1044	0.0103	**0.1095**	0.1019	0.1004
		NLME	0.1056	0.1016	0.0999	**0.1097**	0.1016	0.0989	**0.1115**	0.1031	0.0992
		MI-GEE	0.1078	0.1044	0.0991	0.1064	0.0994	0.0992	0.1074	0.1017	0.0995
		MI-NLME	0.1074	0.106	0.0989	0.1057	0.0981	0.0982	0.1058	0.1002	0.1008
0.7	2	GEE	**0.1149**	0.0994	0.1002	**0.1125**	**0.1102**	0.1053	**0.1142**	0.1054	0.1062
		NLME	**0.1153**	0.1012	0.0958	**0.1147**	0.1048	0.1057	**0.1151**	0.1042	0.1051
		MI-GEE	**0.1132**	0.1005	0.0981	**0.1136**	0.1072	0.1064	**0.1084**	0.1071	0.1064
		MI-NLME	**0.1144**	0.0992	0.0969	**0.1152**	0.1067	0.1054	0.1065	0.1064	**0.1082**
	4	GEE	0.1036	0.1008	0.0996	**0.1094**	0.1021	0.1036	**0.1086**	0.0997	0.1007
		NLME	0.1023	0.0989	0.0984	**0.1087**	0.0995	0.1007	0.1055	0.1029	0.1004
		MI-GEE	0.1026	0.0985	0.0985	**0.1104**	0.1042	0.1051	0.1071	0.1002	0.1027
		MI-NLME	0.1031	0.0996	0.0976	**0.1123**	0.1038	0.1062	0.1056	0.102	0.104
	6	GEE	0.1006	0.0984	0.0972	0.1073	0.1013	0.0982	**0.1095**	0.1015	0.0984
		NLME	0.1041	0.0988	0.098	**0.1084**	0.1008	0.1012	0.1076	0.0982	0.0991
		MI-GEE	0.0971	0.0973	0.0965	0.1079	0.0981	0.0997	0.1072	0.0995	0.1002
		MI-NLME	0.0964	0.0983	0.0971	**0.1084**	0.0963	0.0993	0.1066	0.0999	0.0998

Number of rejections over 5000 simulations with Type I Error=0.1 and a 95% confidence interval=(0.092, 0.0108).

As can be seen from the tables, most of the empirical sizes of the different tests are very close to the levels 0.01, 0.05 and 0.1 in each table respectively. This convergence to the level, holds true for all the missing data mechanisms as well as different methods for each level. In general, in cases that sample size is larger ($n = 200$), the empirical size deviates less from the level in comparison with cases where the sample size is smaller. Also, the results do not change drastically by changing the correlation (ρ) from 0.3 to 0.7. It can be observed that the NLME based methods are more conservative than the GEE based methods which are more liberal. Also, the values from the GEE and MI-GEE fall out of the confidence interval more than values for NLME and MINLME. This has been shown in the tables. In the following tables, the power has been illustrated for each method with different missing data mechanisms at different levels:

Table 3.4: The Power in 5000 simulations under the level of 0.01 and $\rho = 0.3$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.0125	0.021	0.0637	0.0143	0.0204	0.0641	0.0192	0.0121	0.0353
		NLME	0.0131	0.0292	0.068	0.0195	0.0273	0.0679	0.0102	0.0144	0.0346
		MI-GEE	0.0147	0.0269	0.0614	0.016	0.0244	0.0666	0.0194	0.0155	0.0393
		MI-NLME	0.0176	0.0287	0.0705	0.0179	0.028	0.0707	0.008	0.0175	0.0318
	0.85	GEE	0.0543	0.1087	0.3927	0.0481	0.1254	0.3974	0.0164	0.065	0.3547
		NLME	0.0304	0.121	0.3965	0.0534	0.1306	0.4078	0.0196	0.0983	0.3594
		MI-GEE	0.0569	0.1476	0.4003	0.0425	0.1304	0.4057	0.0243	0.0813	0.386
		MI-NLME	0.0366	0.1205	0.3987	0.058	0.135	0.4084	0.0202	0.095	0.3617
	1.39	GEE	0.1026	0.3233	0.8259	0.1176	0.3204	0.8112	0.0597	0.2454	0.7611
		NLME	0.0947	0.3676	0.8308	0.1025	0.3675	0.8138	0.0546	0.2784	0.7753
		MI-GEE	0.0938	0.338	0.819	0.0951	0.3035	0.8133	0.0786	0.2748	0.7817
		MI-NLME	0.0979	0.3719	0.8297	0.1082	0.3729	0.8112	0.0556	0.2766	0.7767
4	0.41	GEE	0.0172	0.0212	0.0532	0.0128	0.0203	0.053	0.0167	0.0127	0.0367
		NLME	0.0227	0.0242	0.0541	0.0181	0.0284	0.0573	0.011	0.0128	0.0304
		MI-GEE	0.0201	0.0236	0.0526	0.0135	0.0232	0.0545	0.014	0.015	0.0369
		MI-NLME	0.0261	0.0234	0.053	0.02	0.0345	0.0591	0.0078	0.012	0.0304
	0.85	GEE	0.0523	0.0858	0.2877	0.0525	0.0851	0.2848	0.0282	0.0695	0.2545
		NLME	0.0523	0.0997	0.2996	0.0527	0.0994	0.2972	0.0165	0.7204	0.2674
		MI-GEE	0.0529	0.0953	0.2877	0.0527	0.0856	0.2918	0.0363	0.062	0.2599
		MI-NLME	0.0576	0.1006	0.3037	0.0555	0.0974	0.3015	0.018	0.7217	0.2704
	1.39	GEE	0.1136	0.2663	0.68	0.1176	0.2605	0.6712	0.0672	0.2431	0.6527
		NLME	0.1179	0.2713	0.6889	0.114	0.2609	0.6892	0.0997	0.2307	0.6621
		MI-GEE	0.1159	0.2662	0.6868	0.1119	0.275	0.6805	0.0797	0.2492	0.6477
		MI-NLME	0.1212	0.2721	0.6877	0.1149	0.2633	0.689	0.0974	0.2315	0.6629
6	0.41	GEE	0.0193	0.027	0.0533	0.0192	0.0277	0.0516	0.0112	0.0133	0.0345
		NLME	0.0195	0.0305	0.0549	0.0199	0.0282	0.0517	0.017	0.0198	0.0325
		MI-GEE	0.0199	0.0271	0.0545	0.019	0.0274	0.0511	0.0192	0.0121	0.0365
		MI-NLME	0.0257	0.0287	0.0603	0.0255	0.0287	0.0514	0.0168	0.0166	0.0313
	0.85	GEE	0.047	0.0868	0.2315	0.0496	0.0864	0.2329	0.0198	0.0777	0.2
		NLME	0.0483	0.0897	0.2393	0.0472	0.0876	0.2377	0.0279	0.0726	0.2128
		MI-GEE	0.052	0.0899	0.2321	0.0472	0.0874	0.2367	0.028	0.077	0.2168
		MI-NLME	0.0506	0.0905	0.2438	0.0515	0.0939	0.2383	0.0293	0.0725	0.2102
	1.39	GEE	0.091	0.2386	0.6151	0.105	0.2216	0.6126	0.0616	0.1997	0.5883
		NLME	0.109	0.2398	0.6196	0.1069	0.2293	0.618	0.0705	0.199	0.5997
		MI-GEE	0.0999	0.2333	0.6159	0.1008	0.2213	0.6135	0.081	0.2069	0.5864
		MI-NLME	0.1136	0.2433	0.619	0.1076	0.2356	0.6225	0.0744	0.1989	0.5978

Table 3.5: The Power in 5000 simulations under the level of 0.01 and $\rho = 0.7$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.0077	0.0341	0.0828	0.0074	0.0317	0.0955	0.0055	0.0147	0.069
		NLME	0.0073	0.0384	0.0946	0.0076	0.0357	0.0963	0.0048	0.0118	0.0565
		MI-GEE	0.0079	0.0348	0.0911	0.0072	0.0346	0.0958	0.0058	0.0181	0.0737
		MI-NLME	0.0105	0.0362	0.0936	0.0079	0.0383	0.0986	0.0054	0.0136	0.0558
	0.85	GEE	0.0131	0.1794	0.4803	0.0268	0.1279	0.4662	0.0127	0.1033	0.4152
		NLME	0.0206	0.1887	0.4888	0.0277	0.1703	0.5206	0.0134	0.0857	0.4321
		MI-GEE	0.0264	0.1671	0.4829	0.0233	0.143	0.4814	0.0175	0.1158	0.4341
		MI-NLME	0.0245	0.1925	0.4932	0.0276	0.1702	0.5255	0.0153	0.0837	0.4355
	1.39	GEE	0.1052	0.3451	0.8822	0.0949	0.3373	0.8854	0.0525	0.2067	0.8543
		NLME	0.113	0.4208	0.9136	0.1003	0.3992	0.8909	0.0479	0.238	0.869
		MI-GEE	0.1181	0.3913	0.8983	0.1403	0.3575	0.8832	0.0534	0.2699	0.8552
		MI-NLME	0.1126	0.4201	0.9189	0.1021	0.4052	0.8907	0.0495	0.2349	0.8676
4	0.41	GEE	0.0157	0.0371	0.0771	0.0096	0.0297	0.0776	0.0076	0.0127	0.0552
		NLME	0.0166	0.0395	0.0882	0.0112	0.0385	0.0878	0.0076	0.0188	0.0692
		MI-GEE	0.0245	0.0396	0.0707	0.0112	0.0357	0.0861	0.0073	0.0137	0.0578
		MI-NLME	0.0148	0.0429	0.0878	0.0136	0.0444	0.0866	0.0114	0.0165	0.0688
	0.85	GEE	0.0606	0.1249	0.4358	0.0438	0.1143	0.4479	0.0254	0.0869	0.4034
		NLME	0.0548	0.1494	0.4495	0.0603	0.1553	0.4747	0.0113	0.1009	0.4014
		MI-GEE	0.0581	0.1429	0.4448	0.0595	0.1516	0.4781	0.0225	0.1011	0.4186
		MI-NLME	0.0586	0.1472	0.4543	0.0652	0.1538	0.4799	0.0093	0.1021	0.4022
	1.39	GEE	0.1053	0.3301	0.8721	0.1043	0.3632	0.8675	0.0604	0.26	0.836
		NLME	0.1162	0.3794	0.8933	0.1683	0.4223	0.8912	0.0536	0.3133	0.8331
		MI-GEE	0.1414	0.3564	0.8972	0.1633	0.4074	0.8628	0.0678	0.2919	0.8592
		MI-NLME	0.1167	0.3769	0.8908	0.1694	0.4267	0.891	0.0522	0.314	0.8353
6	0.41	GEE	0.0192	0.0255	0.0817	0.0145	0.0307	0.0864	0.0063	0.0102	0.061
		NLME	0.0213	0.0382	0.0881	0.0114	0.0347	0.0899	0.0088	0.0169	0.0534
		MI-GEE	0.0202	0.0331	0.0849	0.0247	0.0384	0.0851	0.0074	0.0168	0.0649
		MI-NLME	0.0223	0.0397	0.0851	0.0164	0.0325	0.0925	0.0104	0.015	0.0561
	0.85	GEE	0.0671	0.1422	0.448	0.0409	0.1517	0.4505	0.0172	0.088	0.4103
		NLME	0.0677	0.148	0.4338	0.0437	0.1587	0.4588	0.0238	0.0795	0.3931
		MI-GEE	0.0309	0.1306	0.436	0.0539	0.1407	0.4546	0.0149	0.0793	0.4141
		MI-NLME	0.0699	0.1454	0.4326	0.0429	0.1616	0.4572	0.0249	0.0755	0.3933
	1.39	GEE	0.1226	0.3525	0.857	0.1671	0.3654	0.8526	0.0647	0.2845	0.8425
		NLME	0.1503	0.4359	0.877	0.1675	0.3872	0.8673	0.0558	0.2895	0.8473
		MI-GEE	0.1336	0.3933	0.8535	0.1651	0.3877	0.8698	0.0981	0.2546	0.851
		MI-NLME	0.1554	0.4393	0.8821	0.1733	0.3862	0.8679	0.0539	0.2858	0.8487

Table 3.6: The Power in 5000 simulations under the level of 0.05 and $\rho = 0.3$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.083	0.1137	0.2004	0.0836	0.1103	0.1986	0.0752	0.0961	0.1759
		NLME	0.0832	0.1172	0.2082	0.0845	0.1296	0.2117	0.0867	0.1194	0.1748
		MI-GEE	0.0832	0.1152	0.2016	0.0833	0.1124	0.1989	0.0733	0.1102	0.1828
		MI-NLME	0.0877	0.1137	0.2089	0.0882	0.134	0.2171	0.0843	0.1184	0.1782
	0.85	GEE	0.1834	0.3156	0.6157	0.1534	0.2981	0.6235	0.1378	0.0671	0.5872
		NLME	0.1426	0.3148	0.6271	0.17	0.3089	0.6242	0.1327	0.0861	0.5854
		MI-GEE	0.1829	0.3142	0.6164	0.1583	0.3051	0.6231	0.1364	0.0804	0.6064
		MI-NLME	0.142	0.3162	0.6314	0.1732	0.3108	0.6229	0.1311	0.0887	0.5842
	1.39	GEE	0.3358	0.6184	0.9413	0.295	0.5927	0.9475	0.2696	0.5642	0.9222
		NLME	0.3415	0.6491	0.9737	0.3065	0.5997	0.9495	0.2661	0.5575	0.9339
		MI-GEE	0.3367	0.6175	0.9561	0.2901	0.6093	0.949	0.2731	0.5593	0.9385
		MI-NLME	0.3477	0.6524	0.9724	0.3048	0.603	0.951	0.269	0.556	0.9368
4	0.41	GEE	0.0833	0.1154	0.2013	0.0842	0.0894	0.1637	0.0526	0.0669	0.1544
		NLME	0.0837	0.1182	0.2102	0.0818	0.0918	0.1682	0.0633	0.0793	0.1567
		MI-GEE	0.0827	0.1159	0.2013	0.0819	0.092	0.1634	0.0627	0.0798	0.1587
		MI-NLME	0.0841	0.1166	0.2087	0.085	0.0917	0.1681	0.0635	0.0832	0.1543
	0.85	GEE	0.1556	0.2583	0.5137	0.1427	0.2438	0.5134	0.1345	0.2172	0.4985
		NLME	0.1429	0.2597	0.5234	0.1463	0.2584	0.5148	0.1313	0.2216	0.4929
		MI-GEE	0.1569	0.2593	0.5148	0.1466	0.2596	0.5173	0.1215	0.2205	0.4978
		MI-NLME	0.1477	0.2571	0.522	0.1478	0.2578	0.5128	0.1288	0.2202	0.4948
	1.39	GEE	0.2779	0.5064	0.8659	0.2765	0.4964	0.863	0.2323	0.4678	0.8304
		NLME	0.2843	0.5147	0.8742	0.2766	0.498	0.8665	0.2361	0.4784	0.8352
		MI-GEE	0.2829	0.5049	0.8715	0.2737	0.4921	0.8609	0.2357	0.4777	0.8396
		MI-NLME	0.2818	0.5217	0.8743	0.2802	0.5038	0.8671	0.2397	0.4792	0.8315
6	0.41	GEE	0.0936	0.1163	0.2115	0.0746	0.0947	0.1502	0.0521	0.0757	0.136
		NLME	0.0937	0.119	0.2142	0.075	0.0954	0.1591	0.0622	0.0741	0.1483
		MI-GEE	0.0953	0.1162	0.2119	0.0752	0.0947	0.1515	0.0602	0.0777	0.1374
		MI-NLME	0.0949	0.1237	0.218	0.0796	0.0937	0.1638	0.0584	0.0772	0.1455
	0.85	GEE	0.1405	0.2272	0.452	0.1495	0.2439	0.5145	0.1258	0.2077	0.4457
		NLME	0.142	0.2275	0.4589	0.1495	0.2554	0.52	0.1354	0.2077	0.4371
		MI-GEE	0.1416	0.2223	0.4537	0.1465	0.2529	0.5117	0.1398	0.2196	0.4418
		MI-NLME	0.1437	0.2245	0.4655	0.1466	0.2609	0.5187	0.1369	0.206	0.4362
	1.39	GEE	0.2438	0.4481	0.8093	0.2745	0.492	0.8609	0.2262	0.4368	0.7959
		NLME	0.2482	0.4498	0.8183	0.2716	0.4974	0.8654	0.2263	0.43	0.8015
		MI-GEE	0.2408	0.4403	0.8134	0.278	0.4996	0.8628	0.2313	0.4389	0.8089
		MI-NLME	0.2518	0.454	0.8194	0.2726	0.5034	0.8655	0.226	0.4276	0.8053

Table 3.7: The Power in 5000 simulations under the level of 0.05 and $\rho = 0.7$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.0195	0.1434	0.2436	0.0234	0.1394	0.2371	0.0286	0.1249	0.2138
		NLME	0.0262	0.1456	0.2583	0.0253	0.1573	0.2545	0.0241	0.1367	0.2073
		MI-GEE	0.0202	0.1436	0.2441	0.0228	0.1425	0.238	0.0256	0.1385	0.2269
		MI-NLME	0.027	0.1506	0.2577	0.0235	0.1591	0.2541	0.027	0.1327	0.2078
	0.85	GEE	0.07892	0.3373	0.7045	0.0863	0.314	0.7266	0.0496	0.273	0.771
		NLME	0.08172	0.3495	0.7159	0.0794	0.3498	0.7284	0.0482	0.2819	0.7271
		MI-GEE	0.07263	0.3341	0.7183	0.073	0.3739	0.7111	0.0505	0.2784	0.7497
		MI-NLME	0.082	0.3483	0.7205	0.0807	0.3496	0.7334	0.0482	0.2816	0.7303
	1.39	GEE	0.3317	0.6632	0.9657	0.3024	0.643	0.9631	0.2075	0.5959	0.9436
		NLME	0.3359	0.6646	0.9662	0.2681	0.6491	0.9647	0.2173	0.5715	0.9404
		MI-GEE	0.3311	0.6802	0.9656	0.3716	0.6838	0.9628	0.2085	0.5961	0.9491
		MI-NLME	0.3332	0.67	0.9669	0.268	0.6527	0.9711	0.2155	0.5728	0.9403
4	0.41	GEE	0.0456	0.1534	0.2436	0.0726	0.1198	0.2268	0.0503	0.0945	0.2049
		NLME	0.0462	0.1556	0.257	0.0837	0.1252	0.2281	0.0474	0.0909	0.2019
		MI-GEE	0.0455	0.1536	0.2444	0.0841	0.1244	0.2267	0.049	0.0958	0.2065
		MI-NLME	0.0525	0.1573	0.2609	0.0813	0.1311	0.2263	0.0447	0.0934	0.2054
	0.85	GEE	0.1801	0.3086	0.696	0.1649	0.3362	0.7047	0.127	0.25	0.6621
		NLME	0.2197	0.3495	0.6956	0.1917	0.344	0.6941	0.1223	0.2581	0.6833
		MI-GEE	0.2029	0.3012	0.6818	0.1603	0.3127	0.6957	0.1377	0.2652	0.6872
		MI-NLME	0.2199	0.3539	0.6987	0.195	0.3471	0.6944	0.1185	0.2615	0.6838
	1.39	GEE	0.3344	0.6332	0.9638	0.3413	0.6613	0.9639	0.2608	0.5836	0.9472
		NLME	0.3069	0.6702	0.977	0.322	0.6386	0.9676	0.255	0.6043	0.9407
		MI-GEE	0.3161	0.6677	0.9633	0.3215	0.6787	0.9654	0.2622	0.5823	0.9499
		MI-NLME	0.3057	0.667	0.9822	0.3282	0.645	0.9728	0.2527	0.6038	0.941
6	0.41	GEE	0.0443	0.1136	0.2541	0.0766	0.1195	0.2206	0.044	0.0946	0.2008
		NLME	0.0458	0.1538	0.2579	0.0752	0.1207	0.2299	0.0437	0.0919	0.2007
		MI-GEE	0.0435	0.1447	0.255	0.0774	0.1041	0.2218	0.0465	0.0989	0.2178
		MI-NLME	0.0469	0.1593	0.2624	0.0785	0.1219	0.2337	0.0471	0.0915	0.1992
	0.85	GEE	0.1801	0.3012	0.6818	0.2093	0.3239	0.6839	0.1247	0.2661	0.6761
		NLME	0.2197	0.3495	0.6956	0.1844	0.3377	0.6819	0.1406	0.2738	0.6502
		MI-GEE	0.2029	0.3086	0.696	0.2177	0.3484	0.6853	0.1286	0.2718	0.6793
		MI-NLME	0.2167	0.3544	0.7004	0.1868	0.3353	0.6839	0.1404	0.2755	0.6505
	1.39	GEE	0.3161	0.6332	0.9633	0.3603	0.6327	0.9649	0.2671	0.571	0.9348
		NLME	0.3069	0.6702	0.977	0.3819	0.6475	0.9657	0.2653	0.5965	0.9251
		MI-GEE	0.3344	0.6677	0.9638	0.3719	0.6405	0.9632	0.2639	0.5863	0.9445
		MI-NLME	0.312	0.6702	0.9749	0.3844	0.6479	0.9668	0.269	0.5935	0.922

Table 3.8: The Power in 5000 simulations under the level of 0.1 and $\rho = 0.3$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.1457	0.17	0.3144	0.1331	0.1828	0.3128	0.1219	0.1532	0.3041
		NLME	0.1332	0.1852	0.3152	0.1491	0.1816	0.3179	0.1217	0.1674	0.3038
		MI-GEE	0.1474	0.174	0.315	0.1365	0.1718	0.3163	0.1285	0.1657	0.311
		MI-NLME	0.1384	0.1847	0.3162	0.1529	0.1787	0.3196	0.1218	0.171	0.3057
	0.85	GEE	0.2623	0.4241	0.7409	0.2522	0.4255	0.7405	0.214	0.4148	0.7141
		NLME	0.2676	0.4275	0.7479	0.2432	0.4257	0.747	0.2127	0.4184	0.7175
		MI-GEE	0.2595	0.4238	0.7419	0.2603	0.4301	0.7467	0.2146	0.413	0.7138
		MI-NLME	0.2744	0.4267	0.7491	0.2427	0.4292	0.7515	0.2128	0.4192	0.7196
	1.39	GEE	0.4599	0.7135	0.9605	0.4365	0.711	0.965	0.4138	0.6939	0.9435
		NLME	0.4359	0.7178	0.967	0.4564	0.716	0.9669	0.4257	0.6919	0.9445
		MI-GEE	0.4329	0.7145	0.965	0.4483	0.7148	0.9636	0.4118	0.7099	0.9478
		MI-NLME	0.4418	0.7256	0.9691	0.4543	0.7162	0.9672	0.4291	0.6909	0.9438
4	0.41	GEE	0.1435	0.1541	0.2623	0.1318	0.1558	0.2626	0.1228	0.1477	0.254
		NLME	0.1447	0.1581	0.2637	0.1399	0.1573	0.2674	0.1237	0.1408	0.2594
		MI-GEE	0.1493	0.1544	0.2628	0.1349	0.1527	0.2642	0.1223	0.1485	0.255
		MI-NLME	0.1507	0.156	0.261	0.1401	0.1629	0.2667	0.1236	0.1435	0.2613
	0.85	GEE	0.2308	0.364	0.6335	0.2393	0.3633	0.6325	0.2171	0.3463	0.6183
		NLME	0.2377	0.3694	0.6375	0.2312	0.3698	0.6366	0.2135	0.3422	0.6186
		MI-GEE	0.2385	0.365	0.6371	0.2371	0.3622	0.6345	0.2175	0.3483	0.6185
		MI-NLME	0.2421	0.3764	0.6388	0.2331	0.371	0.6379	0.2106	0.3427	0.6212
	1.39	GEE	0.3863	0.6183	0.9248	0.3833	0.6127	0.92	0.3777	0.6986	0.927
		NLME	0.3822	0.6186	0.9251	0.386	0.6171	0.9284	0.37	0.699	0.9479
		MI-GEE	0.3803	0.6145	0.9251	0.386	0.6178	0.9264	0.3787	0.6994	0.9441
		MI-NLME	0.38	0.6224	0.9263	0.3885	0.6215	0.9347	0.3673	0.6993	0.9491
6	0.41	GEE	0.139	0.151	0.2429	0.1304	0.1549	0.2442	0.1142	0.1459	0.2278
		NLME	0.1334	0.1579	0.248	0.1353	0.1567	0.2498	0.118	0.1497	0.2266
		MI-GEE	0.1386	0.1527	0.2442	0.1326	0.1547	0.2432	0.1129	0.1476	0.2281
		MI-NLME	0.1382	0.1616	0.2529	0.1357	0.1582	0.2504	0.1205	0.1532	0.2259
	0.85	GEE	0.2226	0.3266	0.5823	0.2242	0.3218	0.5822	0.2021	0.3088	0.5645
		NLME	0.2297	0.3277	0.5868	0.228	0.3281	0.5879	0.2068	0.3042	0.5666
		MI-GEE	0.2259	0.3255	0.5821	0.2292	0.3247	0.5863	0.2023	0.3091	0.564
		MI-NLME	0.2325	0.33	0.5867	0.2279	0.3312	0.5914	0.2067	0.3032	0.5665
	1.39	GEE	0.3583	0.574	0.8813	0.3556	0.5767	0.883	0.3339	0.5578	0.8679
		NLME	0.3542	0.5775	0.8897	0.3568	0.5792	0.8868	0.3494	0.5513	0.898
		MI-GEE	0.3676	0.5766	0.8819	0.3651	0.5731	0.8864	0.3327	0.588	0.8678
		MI-NLME	0.3542	0.5776	0.8958	0.3629	0.5803	0.8851	0.3487	0.5515	0.8952

Table 3.9: The Power in 5000 simulations under the level of 0.1 and $\rho = 0.7$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.0421	0.2219	0.3617	0.04225	0.1925	0.3695	0.0225	0.1744	0.3235
		NLME	0.0427	0.2216	0.3733	0.04179	0.2038	0.3701	0.0266	0.1838	0.3083
		MI-GEE	0.0418	0.2173	0.3651	0.04235	0.2154	0.3794	0.0208	0.1843	0.3073
		MI-NLME	0.0464	0.2254	0.3712	0.0419	0.208	0.3731	0.0273	0.184	0.3088
	0.85	GEE	0.1315	0.462	0.8226	0.1273	0.4496	0.8228	0.1034	0.4275	0.8065
		NLME	0.1321	0.5104	0.8375	0.1275	0.472	0.8241	0.0925	0.4086	0.7911
		MI-GEE	0.1166	0.4649	0.8335	0.1113	0.5016	0.8226	0.1075	0.4717	0.7973
		MI-NLME	0.1299	0.5095	0.8385	0.1249	0.4722	0.823	0.0954	0.4065	0.794
	1.39	GEE	0.4385	0.7531	0.9806	0.4344	0.7105	0.9877	0.3623	0.6	0.9557
		NLME	0.412	0.7943	0.9848	0.4994	0.7792	0.9891	0.3772	0.6555	0.9757
		MI-GEE	0.5004	0.7248	0.9843	0.5045	0.761	0.9856	0.3791	0.6043	0.9701
		MI-NLME	0.4164	0.8013	0.9815	0.4987	0.782	0.9936	0.3766	0.6545	0.9794
4	0.41	GEE	0.12	0.1857	0.3472	0.1386	0.1838	0.3402	0.117	0.1648	0.31
		NLME	0.1217	0.2057	0.3485	0.1291	0.1957	0.3419	0.1144	0.1578	0.3027
		MI-GEE	0.1422	0.2001	0.3401	0.1336	0.2038	0.3404	0.1002	0.1707	0.3237
		MI-NLME	0.1197	0.2109	0.3506	0.1297	0.1963	0.3395	0.1161	0.1615	0.3016
	0.85	GEE	0.2657	0.4345	0.8035	0.2573	0.4641	0.8017	0.2235	0.4049	0.789
		NLME	0.2913	0.4695	0.809	0.2785	0.4647	0.8074	0.2234	0.4103	0.7915
		MI-GEE	0.2796	0.4467	0.8034	0.3061	0.4312	0.8055	0.229	0.4089	0.7957
		MI-NLME	0.2933	0.4666	0.8082	0.2769	0.4636	0.8108	0.2267	0.4066	0.7916
	1.39	GEE	0.4762	0.758	0.9836	0.4884	0.7493	0.9827	0.379	0.7151	0.9587
		NLME	0.4572	0.7714	0.9847	0.4652	0.758	0.9876	0.3744	0.7122	0.9692
		MI-GEE	0.4711	0.7629	0.9898	0.4574	0.7495	0.9867	0.3993	0.7259	0.9638
		MI-NLME	0.4555	0.7726	0.9899	0.4687	0.7622	0.9917	0.3734	0.7118	0.9689
6	0.41	GEE	0.1291	0.1987	0.3434	0.1324	0.1986	0.3408	0.1027	0.1692	0.306
		NLME	0.1313	0.2092	0.3476	0.1279	0.1999	0.3412	0.1067	0.1601	0.3
		MI-GEE	0.1394	0.2038	0.3414	0.1491	0.1912	0.3414	0.1152	0.1513	0.3152
		MI-NLME	0.1313	0.2147	0.3461	0.1327	0.2036	0.34	0.1074	0.1569	0.298
	0.85	GEE	0.272	0.45	0.7924	0.2851	0.4507	0.7995	0.227	0.4115	0.7719
		NLME	0.2421	0.4652	0.7985	0.2546	0.4745	0.7995	0.2148	0.4112	0.7743
		MI-GEE	0.2569	0.456	0.7961	0.2544	0.4599	0.7914	0.2223	0.4238	0.7761
		MI-NLME	0.2404	0.4706	0.7967	0.2556	0.4797	0.8044	0.2116	0.4098	0.775
	1.39	GEE	0.4787	0.7513	0.9868	0.4902	0.755	0.9824	0.3869	0.7326	0.9538
		NLME	0.4997	0.7541	0.9875	0.5015	0.7646	0.9828	0.3872	0.7282	0.9584
		MI-GEE	0.4792	0.7529	0.9867	0.4784	0.759	0.9824	0.3902	0.7299	0.9673
		MI-NLME	0.5053	0.7588	0.9861	0.4998	0.771	0.987	0.3838	0.7261	0.9544

When the empirical size of each method does not deviate too much from the nominal level, comparison of methods based on their power is advisable. Otherwise, some adjustments would be needed. In our simulations, it can be seen that the empirical sizes do not deviate from each other by a large amount.

In general, the NLME has a higher power than the GEE in most of the cases under MAR and MCAR. It seems that the multiple imputation method helps to increase the power of both the GEE and NLME methods. It can be seen that by implementing multiple imputation, the NLME method still slightly performs better in comparison with the GEE. As the sample size increases all the tests become more powerful. Power increases as the value of β increases too. Note that to make an inference, one should check the corresponding empirical size as well. If the corresponding empirical size falls out of the bounds of the 95% confidence interval, conclusions are not valid anymore. In cases where the MNAR mechanism is used,we cannot say if any of the methods is performing better than the rest. Of course, the effect of multiple imputation in increasing the power is obvious.

3.3.2 Bias

The relative bias of each method was also measured. As making conclusions only based on power may not be wise, a specific method can consistently give a higher power in comparison with other methods, but its estimates may be biased. Therefore, regardless of the power of a method, further investigation is needed.

In this simulation study, bias is calculated as the diference between the average of estimated coefficients over the total number of simulations and the true parameter estimates ($\beta_1 = 0.41, 0.85, 1.39$) [3].

In the following tables, bias has been estimated for each method with different missing data mechanisms at different levels:

Table 3.10: The Bias in 5000 simulations under the level of 0.01 and $\rho = 0.3$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	-0.0059	-0.0319	0.0172	-0.0156	0.0286	0.0022	0.0354	-0.0317	-0.0101
		NLME	-0.0111	0.0168	0.0128	-0.0376	0.0316	-0.0114	0.0565	0.0046	-0.0141
		MI-GEE	-0.0246	-0.0269	-0.0024	0.017	0.026	-0.0067	0.0407	0.0003	-0.0021
		MI-NLME	0.0431	-0.0169	-0.0032	0.0281	0.0183	-0.0072	-0.0449	0.0028	-0.0016
	0.85	GEE	0.0168	-0.0294	0.0152	0.009	-0.0339	0.0134	0.0389	-0.029	-0.0198
		NLME	0.0424	-0.0294	-0.0016	-0.0399	0.026	0.0182	-0.0126	-0.0272	-0.006
		MI-GEE	0.0077	0.0066	-0.0042	0.0153	-0.0152	-0.0072	0.0192	-0.0031	-0.0093
		MI-NLME	-0.0296	0.0157	-0.0014	0.0398	0.0091	-0.004	-0.0289	0.0026	-0.0075
	1.39	GEE	0.0217	0.028	-0.0064	0.0381	-0.0221	-0.0121	0.032	0.0355	-0.016
		NLME	0.0527	0.0193	-0.0118	0.0471	0.0325	-0.0078	-0.0118	0.007	0.005
		MI-GEE	0.0118	-0.0117	-0.0099	0.0125	0.0132	-0.0048	-0.0429	0.0203	-0.0011
		MI-NLME	0.0117	-0.0288	-0.0034	-0.0383	-0.0165	-0.0004	-0.0092	-0.0263	-0.0064
4	0.41	GEE	0.0461	-0.0309	-0.0157	-0.0588	-0.0124	0.0031	-0.025	0.0375	-0.0182
		NLME	-0.0267	0.0315	-0.0033	-0.0207	-0.0111	-0.0065	-0.0307	-0.025	0.002
		MI-GEE	-0.0497	0.0089	-0.0086	0.0368	-0.0214	-0.0065	-0.0419	-0.022	-0.0069
		MI-NLME	-0.0173	-0.0293	-0.0087	0.0027	0.01	-0.0032	0.0406	0.0017	-0.0052
	0.85	GEE	-0.0363	-0.0148	-0.0157	0.0524	0.0328	0.0197	-0.0479	-0.0038	0.0152
		NLME	-0.0125	0.0085	0.0102	0.0314	0.0343	-0.0082	-0.0524	-0.0214	-0.0088
		MI-GEE	0.0309	0.0047	-0.0079	0.0442	0.0171	-0.001	0.0281	0.027	-0.0067
		MI-NLME	0.0418	0.0138	-0.0051	0.0388	0.0102	-0.0072	-0.0167	0.0109	-0.0003
	1.39	GEE	-0.0017	0.0164	0.0148	0.0046	0.0202	-0.0117	-0.0164	-0.0378	-0.0111
		NLME	0.0482	0.0094	-0.0136	-0.0024	0.0156	-0.0155	-0.0182	-0.0387	-0.0165
		MI-GEE	0.0041	-0.0267	-0.0042	0.0028	-0.0102	-0.0047	-0.036	0.0206	-0.0095
		MI-NLME	-0.0401	-0.0052	-0.0065	0.0387	-0.0195	-0.0093	0.0093	-0.0046	-0.01
6	0.41	GEE	-0.0036	0.0335	0.0085	0.0299	-0.0327	-0.003	-0.029	0.0277	0.0184
		NLME	0.0545	0.0149	0.0196	-0.0586	0.0169	0.0117	-0.0418	-0.032	-0.0019
		MI-GEE	-0.0427	-0.0174	-0.0005	-0.0326	-0.0295	-0.0032	-0.03	-0.0058	-0.0039
		MI-NLME	0.0102	0.0004	-0.0072	-0.0195	-0.0015	-0.0061	0.0322	-0.0218	-0.0031
	0.85	GEE	-0.0425	-0.0121	0.0126	-0.0287	-0.0247	0.0182	-0.0203	-0.0134	0.02
		NLME	-0.0144	-0.0352	0.0073	0.0354	0.0147	0.0195	0.0446	0.0265	0.0069
		MI-GEE	0.0305	-0.0085	-0.0083	0.0233	0.028	-0.01	-0.0231	-0.0083	-0.0029
		MI-NLME	0.0057	0.0016	-0.0082	-0.0469	0.007	-0.0069	-0.0233	0.0233	-0.0056
	1.39	GEE	-0.0509	0.006	-0.0057	0.0402	0.0283	-0.01	-0.0312	0.0214	-0.0023
		NLME	0.0402	0.0363	0.0101	0.0106	0.036	0.012	0.0249	-0.0104	0.0012
		MI-GEE	0.0444	0.0131	-0.0066	-0.0373	-0.027	-0.0068	0.0134	-0.0275	-0.0066
		MI-NLME	-0.0137	-0.0176	-0.0041	-0.0319	0.01	-0.0003	0.0205	-0.0242	-0.0061

Table 3.11: The Bias in 5000 simulations under the level of 0.01 and $\rho = 0.7$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	-0.0488	-0.0028	-0.0146	-0.0089	-0.0214	0.006	-0.018	-0.0104	0.0194
		NLME	0.0454	-0.0355	0.001	0.0504	0.0384	-0.0035	0.0038	-0.0324	0.0094
		MI-GEE	0.0109	-0.0181	-0.0052	0.0174	0.0274	-0.0097	-0.0117	0.0175	-0.004
		MI-NLME	0.044	-0.0154	-0.0082	0.042	0.0242	-0.0026	-0.0145	0.0251	-0.0083
	0.85	GEE	-0.0423	-0.0095	0.0005	-0.0193	0.0084	-0.0045	-0.0567	0.0304	-0.0114
		NLME	0.0031	0.0307	-0.0181	0.0524	0.0242	0.0004	0.0054	-0.0244	-0.0149
		MI-GEE	0.0404	0.0087	-0.0075	0.0192	0.0243	-0.0077	0.0092	0.003	-0.0002
		MI-NLME	0.0376	0.0177	-0.0054	-0.0048	-0.0163	-0.0058	-0.0147	0.0218	-0.0077
	1.39	GEE	0.0593	0.0334	0.0013	-0.0367	-0.0225	-0.002	-0.0085	0.0071	0.0186
		NLME	-0.0156	0.0341	-0.0186	0.0565	0.0214	0.0031	0.0044	-0.0003	-0.0137
		MI-GEE	0.014	0.0097	-0.0099	0.043	-0.0298	-0.0087	0.0203	0.0098	-0.008
		MI-NLME	0.0152	-0.0066	-0.0015	-0.0365	0.0143	-0.0099	-0.0484	0.024	-0.0069
4	0.41	GEE	-0.0484	0.0335	0.0015	-0.0182	-0.03	-0.0145	-0.0075	0.0095	-0.0053
		NLME	0.024	-0.0034	0.0147	-0.0069	0.0019	-0.0097	-0.0504	-0.0034	0.0118
		MI-GEE	0.0167	-0.0142	-0.0053	-0.022	0.0266	-0.0013	-0.0105	-0.0206	-0.0006
		MI-NLME	0.0405	0.0272	-0.0025	-0.0214	0.0025	-0.0062	0.0342	-0.0104	-0.0081
	0.85	GEE	-0.0291	0.007	-0.0091	0.0526	-0.0199	0.0113	0.0377	-1E-04	-0.0168
		NLME	-0.028	-0.0229	-0.0165	-0.0551	-0.0038	-0.0055	0.0358	0.0072	0.0123
		MI-GEE	-0.0121	-0.0134	-0.0015	0.0073	0.0029	-0.001	0.0497	-0.0113	-0.0073
		MI-NLME	-0.0088	-0.0205	-0.0032	0.0089	0.0206	-0.0034	0.0017	-0.0014	-0.0013
	1.39	GEE	0.0327	-0.0127	0.009	-0.0442	0.0354	-0.0164	0.0255	-0.0189	0.0011
		NLME	-0.0525	0.0059	-0.0065	0.0229	0.0055	0.0129	0.0473	0.036	0.0049
		MI-GEE	-0.0336	0.0112	-0.006	0.0385	-0.0027	-0.0007	0.0364	0.0046	-0.009
		MI-NLME	-0.0384	0.025	-0.004	-0.0381	0.0038	-0.0067	0.0418	-0.0036	-0.0051
6	0.41	GEE	0.0332	0.0354	-0.0188	-0.0122	-0.0127	-0.0159	0.0492	-0.0319	-0.0015
		NLME	0.0059	0.0319	-0.0127	-0.0137	-0.0065	0.0192	0.0305	0.0378	0.0169
		MI-GEE	-0.0016	-0.0013	-0.0032	-0.0018	-0.0132	-0.0035	0.0079	0.0027	-0.0033
		MI-NLME	0.0477	-0.0253	-0.0025	-0.0394	-0.0002	-0.0047	0.0268	0.0135	-0.0043
	0.85	GEE	-0.0069	0.025	-0.0146	-0.0014	-0.0396	0.0026	-0.0482	-0.0387	-0.0176
		NLME	0.0333	-0.0315	-0.0152	0.0362	0.0078	-0.0094	0.0115	0.0313	0.0158
		MI-GEE	-0.0323	-0.0159	-0.0045	-0.0204	0.0201	-0.0031	0.0336	0.0038	-0.0011
		MI-NLME	0.0106	-0.0016	-0.0008	0.0493	0.0048	-0.0056	-0.0482	0.0068	-0.0022
	1.39	GEE	0.0544	0.0395	0.0143	-0.0208	0.0215	-0.0035	-0.0069	-0.0199	-0.0075
		NLME	-0.0324	-0.0019	-0.0053	0.0556	-0.0343	-0.0023	-0.0585	0.0039	0.0017
		MI-GEE	-0.041	0.0127	-0.0081	-0.0459	0.026	-0.0057	-0.043	0.0132	-0.0043
		MI-NLME	0.0206	0.0089	-0.008	0.0405	0.0106	-0.002	0.0073	0.0201	-0.0099

Table 3.12: The Bias in 5000 simulations under the level of 0.05 and $\rho = 0.3$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.0002	0.0087	0.0145	0.0293	0.0243	-0.0091	-0.0071	-0.0318	0.0172
		NLME	0.0205	-0.0222	0.011	-0.0289	-0.033	0.0182	0.0181	-0.0374	0.0168
		MI-GEE	-0.0224	-0.0089	-0.007	0.0305	-0.0243	-0.0074	0.0174	0.0169	-0.0075
		MI-NLME	-0.0478	-0.0188	-0.0002	-0.0128	0.0185	-0.0005	0.0343	0.029	-0.0077
	0.85	GEE	0.0495	-0.04	-0.0115	0.0582	-0.0388	-0.0024	-0.013	-0.0272	0.0048
		NLME	0.0299	0.0293	-0.0166	-0.0274	0.0186	0.0141	-0.0012	-0.0051	-0.0155
		MI-GEE	-0.0021	0.0178	-0.0063	-0.0415	0.0082	-0.0077	-0.049	0.0096	-0.0019
		MI-NLME	0.0269	0.0038	-0.0019	0.0014	0.0064	-0.0038	-0.0062	0.0118	-0.005
	1.39	GEE	-0.0331	-0.0006	0.0099	0.0123	0.0162	0.0135	0.0581	-0.0272	0.0059
		NLME	0.0173	0.0367	-0.0065	-0.0308	-0.0351	0.0002	0.0586	0.0333	0.0016
		MI-GEE	-0.0193	0.0049	-0.0097	-0.0466	-0.0289	-0.0031	-0.0339	-0.0284	-0.0018
		MI-NLME	-0.0444	0.0164	-0.0002	-0.0256	0.0277	-0.0069	-0.0246	-0.0277	-0.0029
4	0.41	GEE	0.0477	-0.0152	0.0162	0.0011	-0.0263	-0.0143	-0.045	-0.0261	-0.0047
		NLME	-0.0269	0.0099	-0.0052	-0.001	-0.0237	0.018	-0.0351	-0.0369	-0.0165
		MI-GEE	-0.017	-0.0058	-0.0051	0.0301	-0.0146	-0.0095	0.0167	-0.018	-0.0064
		MI-NLME	-0.0471	-0.0286	-0.0089	0.0331	-0.0057	-0.0061	0.0316	0.021	-0.006
	0.85	GEE	-0.0352	-0.0029	-0.0064	-0.01	-0.0157	0.0129	0.0244	-0.0071	-0.0181
		NLME	0.0121	0.0072	0.0022	0.0086	0.0354	0.0104	-0.0367	-0.0021	0.0092
		MI-GEE	-0.037	0.0179	-0.0065	-0.0353	0.0117	-0.0048	-0.0176	0.0176	-0.0009
		MI-NLME	0.0412	-0.0103	-0.0038	0.0341	-0.0252	-0.0058	0.0396	0.0243	-0.0026
	1.39	GEE	-0.0489	-0.0023	0.0097	-0.0422	-0.0376	-0.0126	-0.0205	-0.0123	-0.0073
		NLME	-0.005	-0.0334	0.0012	-0.0347	-0.0039	-0.0004	0.0221	0.0047	0.003
		MI-GEE	-0.0005	-0.0187	-1E-04	0.0148	0.0161	-0.0079	-0.0004	0.0067	-0.0084
		MI-NLME	0.035	0.0206	-0.0085	0.0418	-0.0161	-0.0009	-0.0274	-0.0264	-0.0065
6	0.41	GEE	-0.0162	-0.0158	0.004	-0.0558	0.0024	0.0197	0.0524	0.0201	0.0129
		NLME	-0.0509	-0.0082	-0.0099	-0.0299	-0.0012	0.0025	-0.0148	-0.0386	-0.0173
		MI-GEE	0.0026	-0.0066	-1E-04	-0.0267	-0.0045	-0.0054	0.0473	0.0211	-0.0039
		MI-NLME	-0.0162	0.0076	-0.0072	0.0454	-0.0193	-0.0089	0.0088	0.0288	-0.0022
	0.85	GEE	-0.0332	0.0375	-0.0159	0.0087	-0.0051	-0.0092	-0.0317	0.0232	0.0015
		NLME	-0.0318	-0.0359	-0.013	0.0442	0.023	-0.0058	0.0302	0.014	-0.0061
		MI-GEE	-0.0082	-0.0068	-0.0053	-0.0019	0.03	-0.0038	-0.0201	0.0026	-0.0027
		MI-NLME	0.0067	-0.0075	-0.0069	0.0188	0.0022	-0.0031	0.0126	0.0006	-0.0077
	1.39	GEE	0.0372	-0.0319	0.0182	-0.058	-0.0046	0.0159	0.0088	0.0285	-0.0118
		NLME	0.047	0.0064	-0.0159	-0.0315	0.0173	-0.0148	0.0105	0.0065	-0.0135
		MI-GEE	-0.002	0.0084	-0.0018	0.0149	-0.0182	-0.0076	0.0363	-0.0145	-0.0074
		MI-NLME	0.0478	-0.0227	-0.0055	-0.0345	-0.012	-0.0019	-0.0175	-0.0115	-0.0003

Table 3.13: The Bias in 5000 simulations under the level of 0.05 and $\rho = 0.7$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	-0.0052	0.0209	-0.0198	0.0249	0.026	-0.0125	-0.0256	0.0038	-0.0137
		NLME	0.0033	0.0128	0.0176	-0.0245	-0.0148	-0.0026	-0.0561	0.0034	-0.015
		MI-GEE	0.0217	0.0065	-0.0022	0.0203	-0.0014	-0.0038	-0.0029	-0.0057	-0.0064
		MI-NLME	0.0132	0.0078	-0.0068	0.0476	-0.0202	-0.0071	-0.0241	0.0161	-0.0064
	0.85	GEE	-0.0046	0.0205	0.0001	-0.0068	0.0018	0.002	0.0291	-0.0307	-0.0012
		NLME	0.006	-0.0081	0.0121	-0.0083	-0.0373	0.019	0.0299	-0.0005	0.0106
		MI-GEE	0.047	0.0118	-0.0026	-0.0261	0.0277	-0.0028	-0.0391	0.0034	-0.0009
		MI-NLME	-0.044	-0.0208	-0.0002	0.0444	0.0056	-0.0025	0.015	-0.0037	-0.0066
	1.39	GEE	0.0515	-0.0279	-0.0008	-0.0125	0.0113	0.0147	0.0366	0.0294	0.0163
		NLME	0.0533	-0.013	0.0008	0.0349	-0.0336	-0.0112	-0.007	0.0377	0.0087
		MI-GEE	0.0477	-0.0174	-0.0047	0.0252	0.0214	-0.0087	-0.0225	0.0162	-0.0099
		MI-NLME	0.0306	0.0227	-0.0048	-0.0467	-0.0122	-0.0086	-0.0204	-0.0098	-0.0063
4	0.41	GEE	-0.0133	-0.0358	-0.0169	0.0453	-0.0072	0.0086	-0.0207	-0.012	-0.0052
		NLME	0.0017	-0.0341	0.0132	-0.0274	-0.0382	-0.0112	0.0554	0.0212	0.0191
		MI-GEE	-0.0363	0.0231	-0.0087	-0.0315	0.0142	-0.0013	-0.0295	0.007	-0.0062
		MI-NLME	-0.0481	0.0196	-0.01	-0.0267	-0.0039	-0.0079	0.0031	-0.019	-0.0019
	0.85	GEE	0.0477	-0.0224	-0.0151	-0.0292	0.0321	-0.0069	-0.0169	-0.0266	-0.011
		NLME	0.0025	0.0321	0.0165	-0.0549	-0.0312	0.0098	-0.0234	-0.0217	0.0022
		MI-GEE	0.0468	0.0151	-0.0032	0.0344	0.026	-0.0086	-0.0212	-0.0073	-0.0014
		MI-NLME	0.0435	-0.026	-0.0043	-0.0063	0.0019	-0.0072	0.0242	0.0197	-0.0058
	1.39	GEE	0.0423	0.0145	-0.0127	0.0033	-0.037	0.008	0.0594	-0.0174	0.004
		NLME	0.0284	-0.0285	-0.0151	0.035	-0.0355	0.0155	-0.0344	0.0284	-0.0044
		MI-GEE	0.0196	-0.0117	-0.0041	0.0298	-0.0165	-0.0022	-0.032	-0.0036	-0.0073
		MI-NLME	0.0014	-0.0211	-0.0019	0.0313	-0.0162	-0.0029	-0.0492	0.0066	-0.0069
6	0.41	GEE	-0.0328	0.0052	0.0161	0.0384	0.0275	-0.0119	-0.0586	0.0104	0.0157
		NLME	0.0256	0.0192	0.0156	0.0221	0.0333	-0.0136	0.0062	0.0377	-0.017
		MI-GEE	0.0191	-0.0203	-0.0097	0.0402	-0.0211	-0.0026	0.0184	-0.0109	-0.0075
		MI-NLME	0.0172	0.0052	-0.0052	-0.0018	0.0139	-0.0084	-0.0314	-0.009	-0.0078
	0.85	GEE	0.0461	0.0398	0.0114	-0.0591	0.02	-0.0099	0.0164	0.0182	0.0136
		NLME	0.0558	0.0101	-0.0046	0.012	0.037	0.0012	0.0292	-0.022	0.0051
		MI-GEE	0.005	0.0123	-0.001	0.0311	0.0227	-0.0026	0.0354	-0.0111	-0.003
		MI-NLME	0.0414	-0.0184	-0.0003	-0.0145	-0.0065	-0.0062	0.0084	0.0299	-0.0013
	1.39	GEE	0.0338	0.029	0.0077	0.0522	0.0155	-0.007	0.0208	-0.0006	0.0097
		NLME	0.0116	-0.0067	0.0156	-0.0154	0.0194	0.0148	0.0174	0.0135	-0.0143
		MI-GEE	0.0286	0.0178	-0.0056	-0.0252	-0.0183	-0.0065	0.0064	-0.0013	-0.0063
		MI-NLME	-0.0122	-0.0183	-0.0019	-0.0044	-0.0166	-0.0052	0.0313	0.017	-0.0094

Table 3.14: The Bias in 5000 simulations under the level of 0.1 and $\rho = 0.3$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	-0.015	-0.0149	-0.0165	-0.0369	-0.0248	0.0108	0.0303	0.0122	-0.009
		NLME	-0.04	0.0015	0.0141	0.0102	0.0352	0.0049	-0.0537	0.0004	0.0123
		MI-GEE	-0.0377	-0.0168	-0.0068	-0.0037	-0.0136	-0.0054	0.0287	0.0113	-0.0055
		MI-NLME	0.0367	-0.0072	-0.0024	-0.0354	-0.0087	-0.0059	-0.0414	0.016	-0.0055
	0.85	GEE	0.0589	0.0138	-0.0195	0.0167	-0.0293	-0.0103	0.0354	0.0032	-0.015
		NLME	0.0327	-0.0343	-0.0161	-0.0438	0.0302	-0.0154	-0.017	-0.0104	-0.0183
		MI-GEE	0.0009	-0.0039	-0.0051	-0.0027	-0.0262	-0.003	-0.027	-0.0092	-0.0056
		MI-NLME	-0.0004	-0.0234	-0.004	0.0032	-1E-04	-0.0088	0.0492	0.0046	-0.0072
	1.39	GEE	-0.024	0.0178	-0.0164	-0.0441	-0.0367	0.0046	0.039	0.0045	0.0143
		NLME	-0.0562	0.0386	-0.0094	0.005	0.0113	-0.0006	0.0035	0.0098	-0.0117
		MI-GEE	0.0444	-0.0071	-0.0065	-0.0376	-0.023	-0.0003	-0.0487	-0.0186	-0.0005
		MI-NLME	0.003	0.0208	-0.003	0.0256	0.0271	-0.0078	0.0422	0.0201	-0.0006
4	0.41	GEE	0.0332	0.0231	0.0112	0.0419	-0.008	0.0045	0.0271	-0.0164	0.0054
		NLME	-0.0566	0.0097	-0.0019	-0.0581	0.029	-0.0184	0.0206	-0.0122	0.0025
		MI-GEE	-0.0229	0.0181	-0.0077	-0.0464	0.014	-0.0074	0.0194	-0.0068	-0.0088
		MI-NLME	-0.0352	-0.0019	-0.0043	0.0299	-0.0281	-0.0002	0.0102	0.0207	-0.009
	0.85	GEE	-0.0363	0.0047	-0.0081	0.058	-0.0339	0.0145	0.0195	-0.0079	0.0062
		NLME	0.0512	-0.0106	-0.0116	-0.0443	0.0038	0.0147	-0.0111	0.0278	-0.0132
		MI-GEE	0.0253	0.0131	-0.0022	0.0323	-0.01	-0.0094	0.0101	0.0259	-0.0078
		MI-NLME	0.043	-0.0117	-0.0054	-0.034	-0.0224	-0.0052	-0.0078	-0.0299	-0.0032
	1.39	GEE	-0.038	0.0133	0.0173	-0.0117	0.0071	0.0194	0.0489	-0.003	-0.0162
		NLME	-0.0368	-0.0167	-0.0038	-0.0249	-0.0215	0.001	0.0549	0.0025	-0.0039
		MI-GEE	-0.0137	-0.0181	-0.0008	-0.0471	-0.0126	-0.0021	-0.0324	0.0082	-0.0085
		MI-NLME	0.0032	0.0144	-0.0016	0.0299	0.0207	-0.0004	-0.046	0.0202	-0.0056
6	0.41	GEE	0.0209	-0.0315	0.0119	-0.0089	0	-0.0166	-0.0163	0.0152	-0.0146
		NLME	-0.0385	-0.0235	0.0131	0.0518	0.0045	0.0001	-0.0235	-0.0329	0.0031
		MI-GEE	0.0331	-0.0188	-0.0009	0.0018	-0.0211	-0.0028	-0.0267	-0.0145	-0.0005
		MI-NLME	0.0146	0.0273	-0.0042	0.0471	-0.0003	-0.0085	0.0419	0.0192	-0.0032
	0.85	GEE	-0.0468	0.003	-0.0075	0.0415	0.0003	-0.0021	-0.0399	0.036	-0.0046
		NLME	0.06	-0.014	-0.0043	-0.0392	0.0098	0.0113	-0.0525	-0.018	0.0086
		MI-GEE	-0.0034	0.0238	-0.0095	-0.0098	-0.0031	-0.004	-0.0493	0.0155	-0.0031
		MI-NLME	-0.0145	0.0137	-0.0012	0.0378	0.0266	-0.0058	0.0418	0.0282	-0.0014
	1.39	GEE	0.0375	-0.0197	-0.0194	-0.0574	-0.0352	-0.0143	0.0252	-0.0037	0.0072
		NLME	-0.0079	-0.0262	-0.0039	-0.0353	0.0269	0.0119	-0.0599	-0.0233	-0.0103
		MI-GEE	0.0105	-0.0016	-0.0076	0.0164	-0.0141	-0.0044	0.0124	0.0265	-0.0007
		MI-NLME	0.0295	-0.0174	-0.0005	0.0324	0.0017	-0.009	0.0474	0.0029	-0.0042

Table 3.15: The Bias in 5000 simulations under the level of 0.1 and $\rho = 0.7$

			MAR	MAR	MAR	MCAR	MCAR	MCAR	MNAR	MNAR	MNAR
T	Beta	Method	n=40	n=80	n=200	n=40	n=80	n=200	n=40	n=80	n=200
2	0.41	GEE	0.045	-0.0339	0.0079	-0.0115	-0.0154	0.0154	0.0542	0.0222	-0.01
		NLME	-0.0026	0.0053	-0.009	-0.0047	-0.0326	0.006	-0.0352	-0.0338	0.0123
		MI-GEE	-0.0032	-0.025	-0.0089	0.0043	0.0009	-0.0035	0.0437	-0.0002	-0.0051
		MI-NLME	0.0423	-0.0008	-0.0082	0.0359	-0.0108	-0.0092	0.0478	0.0078	-0.0043
	0.85	GEE	-0.029	-0.0049	0.0185	-0.0414	0.0219	-0.0161	-0.0304	-0.0179	0.0125
		NLME	0.0117	0.0021	-0.013	-0.0032	-0.0177	-0.0075	-0.0416	0.0291	-0.003
		MI-GEE	0.0026	-0.0127	-0.0017	-0.0084	-0.0105	-0.0064	0.0136	-0.0227	-0.0075
		MI-NLME	0.002	0.0285	-0.0049	-0.0186	-0.0075	-0.0065	0.0064	-0.0093	-0.0068
	1.39	GEE	-0.0205	-0.0281	0.0142	0.0259	-0.0233	0.0069	-0.0124	-0.0302	-0.0177
		NLME	0.0195	-0.0029	-0.0186	0.0237	0.0225	0.0109	0.0221	-0.0223	0.0058
		MI-GEE	0.0341	-0.02	-0.0008	-0.0309	0.0111	-0.0045	0.0436	0.0028	-0.0026
		MI-NLME	0.021	0.0155	-0.004	-0.0311	-0.0133	-0.0037	0.0125	0.0264	-0.0032
4	0.41	GEE	-0.0509	0.0282	0.0157	0.0236	0.0232	0.0062	-0.009	-0.0108	0.0154
		NLME	-0.0076	0.0146	0.0014	-0.053	-0.0254	0.0054	-0.0207	-0.0305	-0.0088
		MI-GEE	-0.0126	-0.0029	-0.0079	-0.0023	-0.0169	-0.0022	-0.0322	-0.0048	-0.0025
		MI-NLME	-0.0387	-0.0152	-0.0052	0.0339	-0.0112	-0.006	0.0361	0.0167	-0.0083
	0.85	GEE	-0.045	-0.008	-0.0036	0.0224	-0.0236	-0.0059	0.0582	-0.0116	-0.0016
		NLME	0.0374	-0.0091	0.0194	0.0529	0.0026	-0.0167	0.0333	0.0228	0.0106
		MI-GEE	-0.0451	-0.0061	-0.0006	-0.0255	-0.0185	-0.0047	0.0349	0.0139	-0.0031
		MI-NLME	0.0439	0.0211	-0.0093	0.047	0.0069	-0.0072	0.0216	-0.0179	-0.0006
	1.39	GEE	-0.0282	-0.02	-0.0068	-0.0032	-0.0021	0.0024	0.0119	-0.0383	-0.0199
		NLME	-0.0324	-0.0333	-0.0176	-0.0248	0.0318	-0.0071	-0.0511	-0.0108	0.0025
		MI-GEE	0.0145	0.0241	-0.0097	0.0033	0.0194	-0.0008	0.0444	-0.0125	-0.0021
		MI-NLME	0.0175	0.0271	-0.0071	0.0453	-0.0255	-0.0076	-0.0244	0.0296	-0.0056
6	0.41	GEE	0.0496	-0.0152	-0.0098	0.0569	-0.0287	0.0049	0.0504	-0.0029	0.0014
		NLME	-0.0583	-0.0123	0.0188	0.0522	-0.0257	0.0049	0.0027	-0.0131	0.0197
		MI-GEE	-0.0036	-0.0249	-0.0021	0.0033	0.0178	-0.0048	-0.0228	-1E-04	-0.0004
		MI-NLME	-0.0487	-0.0038	-0.006	-0.0341	-0.02	-0.0036	0.0295	0.0092	-0.0069
	0.85	GEE	0.0493	-0.0287	0.0168	0.0472	0.015	0.0155	-0.0321	-0.0356	-0.0184
		NLME	-0.0262	-0.0395	-0.0072	-0.0191	0.0373	-0.0161	-0.053	0.0307	0.0118
		MI-GEE	0.0042	0.0291	-0.0074	-0.0422	-0.0234	-0.0004	0.0014	-0.0278	-0.0041
		MI-NLME	-0.0297	-0.0096	-0.0045	0.0491	0.0133	-0.0005	-0.002	-0.0053	-0.0034
	1.39	GEE	-0.0054	0.0138	-0.0066	-0.036	0.0126	0.0186	0.0571	0.024	0.0106
		NLME	0.0207	-0.0121	0.0018	-0.0226	-0.0056	0.0051	-0.0205	-0.0073	0.0069
		MI-GEE	-0.0315	0.001	-0.0042	0.0406	-0.0122	-0.0075	-0.0388	-0.0059	-1E-04
		MI-NLME	-0.0392	-0.0018	-0.0094	0.0097	-0.0149	-0.0035	-0.0398	-0.0231	-0.0038

Overally, the bias for all the methods is fairly small. Also no trend or priority can be found among the different methods, although bias has a tendency to get smaller as the sample size increases for each method. Since the estimate is obtained by calculating an average over all the estimates in the simulation study, it might not be the best statistic for comparing the performance of the methods. In particular, there can be some estimates with big differences (both underestimation and over estimation) from the observed value. However, by averaging over all of them, those big differences will cancel each other out and the user will only see a small value for the bias.

Chapter 4

Data Analysis

4.1 Data Description

A dataset has been used to illustrate the missing data analysis and the impact of using one missing mechanism to another. This dataset is from a clinical trial in which two different treatments (active treatment and placebo) for a respiratory disorder has been treated. There are 56 participants from center 1 and the rest are from center 2 out of total 111 participants. All these subjects have been randomly assigned to receive one of the possible treatments. The binary response variable, which is the respiratory status, has been measured at four different times for each subject during the study. A good respiratory status is coded as 1 and a poor respiratory status is coded as 0. Explanatory variables in the study are the center, the treatment, gender, age and a baseline. In this study, 33 subjects are assumed to have no responses for their third and fourth responses (30 percent missingness). This missigness mechanism is believed to be the MAR mechanism as 22 of missed subjects are people who received the active treatment and the rest are people who received the placebo regardless of their responses in the first two visits.

A partial data set can be found in the following table:

Table 4.1: The partial data set for the respiratory disorder clinical trial

Center	ID	Treat	Sex	Age	Baseline	Visit 1	Visit 2	Visit 3	Visit 4
1	1	P	M	46	0	0	0	0	0
1	2	P	M	28	0	0	0	NA	NA
1	3	A	M	23	1	1	1	NA	NA
1	4	P	M	44	1	1	1	1	0
1	5	P	F	13	1	1	1	1	1

P: placebo A: active treatment

The underlying GEE model can be written as:

$$\text{logit}(\mu_{ij}) = \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2} + \beta_3 x_{ij3} + \beta_4 x_{ij4} + \beta_5 x_{ij5} \tag{4.1}$$

Where x_{ij1} is the center variable (center1=0, center2=1), x_{ij2} is the treatment (treatment=1, Placebo=0), x_{ij3} is sex (male=0, female=1), x_{ij4} is the continuous variable of age and x_{ij5} is the baseline variable (poor=0, good=1). Also, $\mu_{ij} = E(Y_i)$ is the mean of the response variable. An extra random term would be added to this model to construct the non-linear mixed effect model.

4.2 Parameter Estimation

Parameter estimates were found and are shown in the following tables:

4.2.1 Parameter Estimation via GEE

Table 4.2: The Parameter Estimates by GEE

Parameter	Estimate	SE	LCL	UCL	Z	P-Value
Intercept	-0.1566	1.4628	-3.0239	2.7106	-0.1070	0.9147
Center	0.5647	0.3621	-0.1451	1.2745	1.5593	0.1189
Treatment	1.3136	0.3497	0.6281	1.9991	3.7561	0.0001
Sex	-0.1588	0.4549	-1.0504	0.7327	-0.3491	0.7269
Age	-0.0199	0.0130	-0.0454	0.0055	-1.5331	0.1252
Baseline	1.8026	0.3551	1.1066	2.4987	5.0761	3.85e-07

For the GEE method, the variables treatment and baseline seem to be statistically significant with p-values of 0.0001 and $3.85e^{-7}$. According to these estimates, the odds of having a good respiratory status for a subject in the treatment group are 3.7195(=exp(1.3136)) times higher than those in the placebo group. The corresponding 95% confidence interval is (exp(0.6281), exp(1.9991)) which can be written as (1.8740, 7.3824).

4.2.2 Parameter Estimation via NLME

Table 4.3: The Parameter Estimates by NLME

Parameter	Estimate	SE	LCL	UCL	Z	P-Value
Intercept	-0.1248	1.2551	-2.5848	2.3351	-0.099	0.9207
Center	0.7556	0.3117	0.1447	1.3666	2.424	0.0153
Treatment	1.7815	0.3583	1.0791	2.4838	4.971	6.64e-07
Sex	-0.0722	0.4202	-0.8958	0.7514	-0.172	0.8636
Age	-0.0214	0.0126	-0.0463	0.0033	-1.694	0.0902
Baseline	2.0612	0.3682	1.3394	2.7830	5.597	2.18e-08

For the NLME model, the variables, center, treatment and baseline, are statistically significant at 5% significance level with p-values of 0.0153, $6.64e^{-7}$ and $2.18e^{-8}$. According to this model, the odds of having a good respiratory status for a subject in the treatment group is 5.9387(=exp(1.7815)) times higher than the odds of a good respiratory status for a subject in the placebo group. The corresponding 95% confidence interval is CI=(exp(1.0791), exp(2.4838)) which can be written as (2.9420, 11.9867).

4.2.3 Parameter Estimation via MI-GEE

Table 4.4: The Parameter Estimates from MI-GEE

Parameter	Estimate	Within	Between	SE	LCL	UCL	Z	P-Value
Intercept	-0.3259	1.7798	0.1589	1.4112	-3.0920	2.4401	-0.23096	0.8173
Center	0.6041	0.1099	0.0211	0.3716	-0.1243	1.3326	1.6253	0.1040
Treatment	1.1182	0.0955	0.0041	0.3179	0.4950	1.7413	3.5170	0.0004
Sex	-0.0888	0.1748	0.0010	0.4198	-0.9117	0.7341	-0.2115	0.8324
Age	-0.0222	0.0001	7.68e-06	0.0126	-0.0471	0.0026	-1.7502	0.0800
Baseline	1.6350	0.0997	0.0322	0.3778	0.8944	2.3756	4.3272	1.50e-05

For the MI-GEE model, the variables, treatment and baseline are statistically significant at 5% significance level with p-values of 0.0004 and $1.50e^{-5}$. According to this model, the odds of having a good respiratory status for a subject in the treatment group are 3.0593(=exp(1.1182)) times higher than the odds of a good respiratory status for a subject in the placebo group. The corresponding 95% confidence interval is CI=(exp(0.4950), exp(1.7413)) which can be written as (1.6405, 5.7047).

4.2.4 Parameter Estimation via MI-NLME

Table 4.5: The Parameter Estimates from MI-NLME

Parameter	Estimate	Within	Between	SE	LCL	UCL	Z	P-Value
Intercept	-0.1307	1.1517	0.2589	1.2235	-2.5289	2.2673	-0.1068	0.9148
Center	0.7435	0.0714	0.0501	0.3718	0.0146	1.4723	1.9994	0.0455
Treatment	1.4586	0.0887	0.0085	0.3166	0.8380	2.0791	4.6071	4.08e-06
Sex	-0.0838	0.1339	0.0114	0.3863	-0.8409	0.6733	-0.2169	0.8282
Age	-0.0231	0.0001	4.82e-06	0.01136	-0.0454	-0.0009	-2.0398	0.0413
Baseline	1.7739	0.0949	0.0771	0.4447	0.9023	2.6455	3.9889	6.63e-05

For the MI-NLME model, the variables, center, treatment and baseline, are statistically significant at 5% significance level with p-values of 0.0455, $4.08e^{-6}$ and $6.63e^{-5}$. According to this model, the odds of having a good respiratory status for a subject in the treatment group are 4.2999(=exp(1.4586)) times higher than the odds of a good respiratory status for a subject in the placebo group. The corresponding 95% confidence interval is CI=(exp(0.8380), exp(2.0791)) which can be written as (2.3117, 7.9973).

4.3 Goodness of fit

In order to evaluate the goodness of fit of each model, classification tables have been obtained. with a classification table, the predicted values can be compared with observed values. In the following analysis, it has been assumed that the predicted value for any subject with $\hat{\pi}_{ij} > 0.5$ is 1 and zero otherwise.

Useful methods to assess the performance of these methods are the sensitivity and specificity of the different methods. Sensitivity is the probability of a test giving positive results given the observed values are actually positive. Specificity is the probability of a test giving negative results given the observed values are actually negative [17]. It is easy to see that sensitivity and power are the same concepts. Also, the misclassification rate can be obtained by dividing the number of incorrect classifications by the total number of classifications. Classification tables of different methods are listed below:

Table 4.6: The classification table for GEE

	Truth +	Truth -	Total
Predit +	177	75	252
Predict -	40	86	126
Total	217	161	378

For the GEE method, the sensitivity (power) is 0.8156 and specificity is 0.5341. Also, the misclassification rate for this model is 0.3042.

Table 4.7: The classification table for NLME

	Truth +	Truth -	Total
Predit +	188	47	235
Predict -	29	114	143
Total	217	161	378

For the NLME method, the sensitivity (power) is 0.8663 and specificity is 0.7080. Also, the misclassification rate for this model is 0.2010.

Table 4.8: The classification table for MI-GEE

	Truth +	Truth -	Total
Predit +	630	213	843
Predict -	136	353	489
Total	766	566	1332

For the MI-GEE method, the sensitivity (power) is 0.8224 and specificity is 0.6236. Also, the misclassification rate for this model is 0.2620.

Table 4.9: The classification table for MI-NLME

	Truth +	Truth -	Total
Predit +	668	143	811
Predict -	98	423	521
Total	766	566	1332

Finally, for the MI-NLME method, the sensitivity (power) is 0.8721 and specificity is 0.7473. Also, the misclassification rate for this model is 0.1809. Overall, it can be concluded that the MI-NLME method is performing the best in terms of both sensitivity and specificity. The corresponding misclassification of this method is relatively lower than the other methods as well.

In general, a slight advantage of the NLME based models can be seen in comparison with the GEE based models. Also, results show that multiple imputation actually improves the performance of both GEE and NLME models, although it may be considered as a rather trivial improvement.

Chapter 5

Conclusions and Limitations

5.1 Conclusion

In this study, we compare the performance of four different methods to analyze repeated measures binary responses data with missing values. Methods that have been compared are the generalized estimating equations, non-linear mixed effects models and combination of each of these with a multiple imputation method called MI-GEE and MI-NLME. We evaluated the performance of these methods by comparing them in terms of empirical size, power and bias in parameter estimates.

Results for empirical size show that all these methods fairly maintain the nominal level and converges more and more to the nominal size of the test as the sample size increases.

The power comparison reveals that the NLME method works better than GEE in general. Also implementing multiple imputation on these two methods increases their performances. However, these differences among the power of the different methods are really small and in a sense it can be stated that all these four methods are showing a very good performance in terms of power.

Comparing bias in estimaton of the coefficients for each method using the underlying model shows very small deviation from the theoretical value. Therefore, it can be stated that none of the methods used in this study are biased when it comes to estimation.

Two different levels of correlation ($\rho = 0.3, 0.7$) have been assumed for the simulated study representing the low and high correlation among data points and the performances of these methods do not seem to change significantly by changing the correlation level. Also, it can be stated that the empirical size gets better as the number of repeated mesures (T) increases. By increasing T, larger powers are obtained. Power increases as the β values increase too. All the methods are performing fairly well. Maximum likelihood based methods work slightly better than quasi likelihood based methods and multiply imputating separate datasets helps both methods to improve their performances. Bias, power and empirical sizes become more ideal as the sample size increases. Specifically, when the sample size is $n = 200$ under the MAR assumption, the empirical size is really close to the size of a test, power is at its highest and the bias is almost zero.

5.2 Limitation

As a limitation it can be mentioned that all these properties hold true under MAR and MCAR missing mechanisms only. Under MNAR missing data mechanism, it cannot be decided which method works the best. The empirical size of MNAR deviates more from the size of a test in comparison with MAR and MCAR situation. This especially can be seen when the sample size gets large. This can also be seen in comparison with powers and biases between different missing data mechanisms. It may be due to the assumption of ignorability of missingness which is the assumption behind the most of the methods used in this study. In general, MAR and MCAR missing data mechanisms show a higher power and smaller bias than MNAR missing data mechanism although all these differences are rather small.

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