

Handling Missing Data in the Multivariate Growth Curve Model: Comparative Evaluations Using Extensive Simulations

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

The multivariate growth curve models (GCMs) are generalized multivariate analysis of variance (GMANOVA) models useful in analyzing of longitudinal data, growth curves or other datasets involving response curves. Unlike the MANOVA model and traditional linear models (eg. generalized linear mixed models), the GCM allows a structured mean. That is the mean trajectory for each group is expressed as a function of and is assumed to be represented by a polynomials with appropriate degree. Therefore, the GCM involves two design matrices: the within-individual design matrix capturing the mean structure as a function of time and the between-individual design matrix representing group membership coded as dummy variables. Several extensions are made to accommodate clustered longitudinal data, high-dimensional data as well as data that do not follow the multivariate normal distribution. Models that allow structured covariances (eg. compound symmetry, autoregressive, etc) are also available.

A critical challenge we encounter in data analysis is presence of missing data, which is relatively more common in studies involving longitudinal data. Approaches for handling missing longitudinal data do exist and are used in practical applications. However, applications involving the GCM are limited to data with no missing values or complete data analysis, where individuals with missing data are deleted. This leads to either the GCM not being used in practice (because of its demonstrated optimality, in particular in when sample size is small) or loss of information, hence suboptimal inference.

We performed a comprehensive literature review and identified three multivariate methods for handling missing data, developed under the framework of GCMs, taking advantage of the bilinear nature of the model. However, our literature review also revealed that implementations and practical applications of these methods are limited. This is because of a combination of many factors including perhaps the complexity of the proposed approaches and lack of software readily available to implement the methods, despite the methods being available for several decades. Moreover, performances of the methods have not yet been investigated and compared. In this study, we considered the three multivariate methods: Kleinbaum's (1973) method based on the generalized growth curve model (GGCM), Liski's (1984) Bayesian method and Liski's (1985) EM algorithm.

We implemented these methods in R, allowing flexible adaptations to different settings. We also made some extensions to allow generalization of the methods to any number of time points, groups and sample size. We conducted extensive simulations to evaluate and compare performance of these methods in estimation of the mean and variance-covariance parameters of the GCM, we also identified limitations and methodological gaps, some of which we addressed in this thesis. The methods are compared by considering element-wise and aggregated bias and mean squared error (MSE) as well as by comparing them to the gold-standard (assuming no missing data) and complete case analysis (list-wise deletion of missing data, which is not current practice in applications involving the GCM).

Our simulation results show that complete case analysis (ignoring missing data) is not desirable in most of the scenarios considered, but in particular when the sample size is small and the missing percentage is high as well as when the missingness mechanism is

non-ignorable. Even when the missingness percentage is small and the mechanism is missing completely at random (MCAR) (which is considered ignorable), the methods developed under the GCM framework provided uniformly smaller MSE values than the complete case analysis. Overall, the simulation results also show that the Liski's EM algorithm and Liski's Bayesian method overall showed comparable performance as gold-standard in estimating both the mean and variance-covariance parameters. However, these methods become unstable in estimating the variance-covariance matrix in scenarios where the missing percentage is high. This is the case even when the missing mechanism is MCAR or missing at random (MAR). Kleinbaum's GGCM method is unreliable for estimating the mean parameter estimators of the GCM, while it remains stable for estimating the variance-covariance matrix. In fact, in most scenarios, Kleinbaum's method is the most optimal approach for estimating the variance-covariance matrix.

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I am immensely thankful to my parents, Peng Wang and Hongyan Wu, whose love and unwavering support have sustained my academic journey. Without you, I could not have pursued this higher degree.

Finally, I extend my heartfelt thanks to everyone who has supported me in both life and study.

Dedication

This is dedicated to my parents, to all who love me, and to everyone who has come into my life and helped me become a better person.

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Chapter 1

Introduction and Objectives

1.1 Introduction

Missing data is common problem, especially in studies involving longitudinal designs [1]. Presence of missing data leads to challenges when building statistical models or performing data analysis [2]. Complete data analysis, where we remove individuals with missing observations, can lead to inaccurate and imprecise inference [3]. On the other hand, imputing data using inappropriate methods can also introduce bias and uncertainty in our inference [4]. Therefore, it is crucial to develop or choose methods that allow us to accurately predict the missing observations and lead to optimal inference.

Before designing the approaches to estimate the missing data, researchers need to learn the mechanism behind the cause of the missing observations, which is often referred to as the missingness mechanism [5]. Rubin (1976) categorized missingness mechanism into three different types: Missing Completely at Random (MCAR), Missing at Random (MAR), and Missing Not at Random (MNAR). In practical applications, the missingness mechanism is often mixed [6, 7].

Methods for handling missing data can vary from the simplest approach involving deletion to create a complete data set to more complex ones [8, 9, 10], such as maximum likelihood methods [11], the expectation maximization (EM) algorithm [12], Bayesian methods [13], or other imputation techniques [14, 15, 16].

In the analysis of longitudinal data, where repeated measurements from each individual are required, missing data are a problem arising more commonly [17]. The mechanisms generating missing data in longitudinal studies vary. Depending on the study and its settings, the missingness mechanisms can be MCAR, MAR, or NMAR, with the most common and complicated case being a mixed mechanism. Nevertheless, researchers usually assume the mechanism generating the missing data to be MCAR, which is a valid assumption in most realistic settings [6, 4, 18, 19].

The most commonly used approaches to handle missing data in longitudinal studies include complete data analysis, the EM algorithm and multiple imputation techniques based often on linear models [8, 4, 12, 18]. Complete analysis deletes any individual with a

missing value and analysis involves only observed data. The EM algorithm is an iterative approach consisting of two steps: expectation step and maximization step. The method first estimates parameters using complete data by applying list-wise deletion and uses the parameter estimates to predict the missing data. The parameters are then re-estimated and the missing data are predicted again, and this is repeated until convergence is reached [12]. The multiple imputation techniques replace each missing item with two or more acceptable values, representing a distribution of possibilities [14, 15, 16].

In this thesis, we consider analysis of longitudinal data using the multivariate growth curve models (GCMs), and in the presence of missing data. The GCMs are generalized analysis of variance (GMANOVA) models, demonstrated to be optimal in the analysis of longitudinal data and other response curves, including dose-response curves, where repeated measurements for a continuous dependent (response) variable are modeled as a function of a continuous exposure (independent) variable, adjusted for other covariates [20, 21, 22]. The model is proven to be particularly optimal in scenarios where sample sizes are limited, including high dimensional data where the number of repeated measurements (eg. number of time points) are much higher than the sample size.

The GCM is a bilinear regression model consisting of two design matrices: the between-individual matrix representing group differences and within-individual matrix capturing the mean structure (with respect to time or other continuous exposure variables) [23, 24, 20, 21]. Such bilinear regression models are often used to: 1) estimate the mean profile (or response curve) for various groups; 2) test whether the mean profiles differ between two or more groups; 3) predict response (dependent variable) at a specific time, treatment dose or other relevant exposure variable [25]. The model was first introduced by Potthoff and Roy [20], and subsequently studied by many prominent statisticians including Khatri [21], Rao [26], Grizzle and Allen [27], Lee and Geisser [28], and von Rosen [22, 29]. Since then, many theoretical aspects of the model and its implementations have been considered extensively, and the model is extended to accommodate structured covariances, skewed distributions, and high-dimensional data [24, 30, 24, 31].

1.2 Rationale and Objectives

The GCM requires complete data and observations measured at the same time (eg. for longitudinal data) and dose (eg. dose-response curves) or same values of the exposure variable of interest [32]. Hence, missing data can be more problematic, for instance, than those encountered with univariate approaches to analyzing longitudinal data, which can utilize irregular time points [33]. On the other hand, the GCMs have many advantages, especially when the sample size is limited, where it is shown to lead to more optimal estimators and powerful tests [34]. Moreover, the GCM allows for a structured mean and, therefore, allowing the mean response curve to be estimated more effectively while incorporating the correlation between repeated observations [35]. Most importantly, the least squares and likelihood approaches (under the assumption of multivariate normality) lead to explicit solutions, which allows extensions to high-dimensional data [24, 31]. The method has also been extended to accommodate clustered longitudinal data, where different

groups (eg. treatment group vs. controls) follow different mean trajectories over time [36]. As such, overcoming missing data problems so that the method can be applicable in the presence of missing data is of importance.

Methods for handling missing data in GCMs do exist [37, 38, 39, 40]. However, there is limited to none literature indicating the attempt to implement or use these methods in practical applications. This is perhaps because of the mathematical complexity of the methods and the lack of software readily available statistical software or packages. Moreover, to our knowledge, evaluations of the different methods and their comparative performance have not been previously investigated. As such, it is important to perform comparative evaluations of these methods as well as facilitate the methodological uptake by implementing the algorithms in the R statistical software.

The objectives of this thesis are to identify existing multivariate methods for handling missing longitudinal data and conduct comparative evaluations of their performance in estimating the model parameters. We will consider methods that are specifically developed under the GCM framework, where the mean is assumed to be structured as a function of time.

1.3 Thesis Contributions

To address our objective, we first performed extensive literature review, with the aim of identifying all available methods developed for handling missing data under the GCM. We identified three methods: 1) Kleinbaum’s approach based on the generalized growth curve model (GGCM) [37]; 2) Liski’s EM algorithm [39]; and 3) Liski’s Bayesian approach [38, 41, 42].

We implemented the algorithms corresponding to these three methods in the R statistical software and performed comparative evaluations of their performance in estimating the model parameters (both the mean and covariance parameters). We used extensive simulations, where the true parameters are generated to reflect real-life scenarios. We compared the estimators with respect of bias, mean square error (MSE). We also compared performance of the methods to what we refer to as the gold-standard (assuming no missing data) as well as to complete data analysis, where individuals with missing observations are deleted. Since we are estimating matrix parameters, we considered element-wise bias, MSE and RMSE as well as using appropriate aggregations of these well-established optimality criteria for estimators.

Our extensive simulation studies included different missingness mechanisms, various percentages of missing data, small and large sample sizes as well as different numbers of time points. We also used real data sets to illustrate the methods and to empirically compare usefulness, validity, and optimality of the different methods, and to demonstrate applications in biomedical sciences.

In addition to the extensive simulations, we have also made novel contributions by generalizing the methods to accommodate real-life scenarios. First, we would like to highlight

that the above three approaches we identified are highly technical and rely on a sequence of other advanced methods developed in earlier years. The papers lack detailed theoretical presentations. Moreover, the papers rarely provided discussions of the algorithms and their implementations (programming). Furthermore, the papers corresponding to two of the methods do not give any computational examples. As such, we synthesized all the theoretical and computational aspects of the methods and presented complete and step-by-step descriptions along with detailed numerical illustrations. Second, the theoretical and numerical illustrations (when provided) were limited to one group, and a linear mean structure over time. As such, we extended all of the computational algorithms to accommodate multiple groups, different sample sizes, different time points (hence different dimensions of the covariance matrix) and different mean structures (hence different number of mean parameters). This also means that our implementation of the computational algorithms in the R statistical software was programmed in such a way that it allows general conditions. Third, the existing methods did not consider missingness mechanisms and patterns. As such, we extended the existing computational algorithms to accommodate different missingness mechanisms and patterns, and we automated the R programs to allow general conditions. This automation is done so that it is valid for any sample size, number of time points, number of groups as well as different mean trajectories over time.

1.4 Thesis Organization

In **Chapter 1**, we provide a brief introduction, present the rationale and objectives and highlight thesis contributions. In **Chapter 2**, we present the background material on the research topic summarized from an extensive literature review we performed. This includes the methodological background on univariate as well as multivariate analysis of variance models (ANOVA and MANOVA), discuss analysis of longitudinal data, introduce growth curve models (GCMs) and present the mathematical formulation of the model and illustrate the matrices involved. We also discuss missing data and missingness mechanisms in **Chapter 2**. Throughout the chapter, we also identify and discuss the existing methodological and computational gaps and as well highlight the rationale and significance of our study. In **Chapter 3**, we synthesized and presented existing literature on the three multivariate methods for handling missing data within the framework of multivariate GCMs. In this chapter, we present the mathematical formulations and the corresponding computational algorithms. Meanwhile, we use the numerical example to illustrate methods. In **Chapter 4**, we present the settings of the simulation studies we perform. Our simulation involves gold-standard inference (no missing data), complete case analysis (deleting individuals with missing data) as well as using the multivariate methods for handling missing data. We also illustrated extended implementations of the existing algorithms by considering two groups, different number of time points and non-linear mean structures. We also present the results of the simulation studies in this chapter. In **Chapter 5**, we exhibit how the methods work using the real data sets as motivating examples and obtain element-wise estimates and confidence intervals. Summary and discussions of the thesis, and potential future directions are provided in **Chapter 6**.

Chapter 2

Background

2.1 Univariate Analysis of Variance Model

Consider a continuous outcome (eg. blood pressure, blood sugar level, etc) measured from n individuals, denoted by $y_1, y_2, \dots, y_n$, across k groups where n_j individuals belong to the j^{th} group. Suppose that the objective is to estimate and compare the mean across these different groups. If assumptions of normality can be made, we can use the univariate analysis of variance model (ANOVA) to make statistical inference. To put this model in a general mathematical and statistical framework, that can later be generalized to multivariate linear and bilinear models, consider the following ANOVA model

$$y_{ij} = \mu_j + \epsilon_{ij}, \quad \text{where} \quad \epsilon_{ij} \stackrel{\text{i.i.d.}}{\sim} N(0, \sigma^2)$$

where μ_j denotes the mean value for j th group, $j = 1, 2, 3, \dots, k$ and $i = 1, 2, 3, \dots, n_j$; ϵ_{ij} represents a random error (also referred to as the error term), which is assumed to be normally distributed and the symbol $\stackrel{\text{i.i.d.}}{\sim}$ denotes independent and identically distributed. Note that the total sample size n is $n_1 + n_2 + n_3 + \dots + n_k$. We can also consider to use the matrix formulation, which presents the ANOVA model as the linear regression model, where group membership is incorporated as dummy variable covariates:

$$\mathbf{y} = \mathbf{B}\mathbf{X} + \boldsymbol{\epsilon}, \quad \text{where} \quad \boldsymbol{\epsilon} \sim N_n(\mathbf{0}, \sigma^2 \mathbf{I}) \quad (2.1)$$

where $\mathbf{y}$ denotes a row vector of length n representing the outcome (dependent) variable, $\mathbf{B}$ is a row vector of length k containing of unknown parameters representing the population mean for the k groups, $\mathbf{X}$ is a $k \times n$ matrix consisted of 0s and 1s, indicating group membership (i.e. k rows of dummy variables). The matrix $\mathbf{X}$ is often referred to as the between-individual design matrix. The error vector $\boldsymbol{\epsilon}$ is a row vector of length n consisting of n independent univariate normal random variables with mean 0 and variance σ^2 . As such, $\boldsymbol{\epsilon}$ follows a multivariate normal distribution with mean $\mathbf{0}$ and variance-covariance matrix $\sigma^2 \mathbf{I}$, where $\mathbf{I}$ denotes the $n \times n$ identity matrix.

Inference for the ANOVA model can be done through the linear model presented in

Equation (2.1), and using traditional statistical approaches including likelihood inference, which we will discuss in the next subsection, since ANOVA is a special case of the multivariate analysis of variance model.

2.2 Multivariate Analysis of Variance Model

In most real-life scenarios, particularly in biomedical sciences, outcomes are correlated (dependent) with each other. For instance, if a researcher wants to assess the cardiovascular health of an individual, they have to consider several cardiovascular markers and risk factors (eg. blood pressure, lipid levels, age etc). In physics and engineering, if one wants to compare performance of an equipment, they need to consider several performance related outcomes as well. In such circumstances, a multivariate model that allows us to compare groups of individuals or items with respect to multiple outcomes, while incorporating the inherent correlation in the data (due to multiple measurements taken from the same individuals or items).

Consider, for instance, the data structure presented in Table 2.1 below, where p repeated measurements of the same outcome or single measurements from p continuous outcomes were taken from each individual or item in the k groups:

Table 2.1: Data structure corresponding to a MANOVA model, where p repeated measurements from the same continuous outcome or a single measurement from p multiple continuous outcomes, are observed from individuals across k groups.

Group 1	Group 2	...	Group k
$y_{111}, y_{112}, \dots, y_{11p}$	$y_{121}, y_{122}, \dots, y_{12p}$	...	$y_{1k1}, y_{1k2}, \dots, y_{1kp}$
$y_{211}, y_{212}, \dots, y_{21p}$	$y_{221}, y_{222}, \dots, y_{22p}$	...	$y_{2k1}, y_{2k2}, \dots, y_{2kp}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$
$y_{n_111}, y_{n_112}, \dots, y_{n_11p}$	$y_{n_221}, y_{n_222}, \dots, y_{n_22p}$	...	$y_{n_kk1}, y_{n_kk2}, \dots, y_{n_kkp}$

For a study producing such a multivariate data set, inference can be done through the multivariate analysis of variance (MANOVA) model, which can be written as

$$\mathbf{Y} = \mathbf{B}\mathbf{X} + \mathbf{E}, \quad \text{where} \quad \mathbf{E} = (\boldsymbol{\epsilon}_1, \boldsymbol{\epsilon}_2, \dots, \boldsymbol{\epsilon}_n) \quad \text{and} \quad \boldsymbol{\epsilon}_j \sim N_p(\mathbf{0}, \boldsymbol{\Sigma}) \quad (2.2)$$

where $\mathbf{Y}$ is the $p \times n$ matrix of responses (outcome measures), $\mathbf{B}$: $p \times k$ is the matrix of unknown regression coefficients, where column j of $\mathbf{B}$ represents the mean vectors corresponding to group j , and $\mathbf{X}$ is a $k \times n$ between-individual design matrix representing group membership, which is the same as in the ANOVA model presented in Equation 2.1. The vector $\boldsymbol{\epsilon}_j$ denotes the j^{th} column of the random error matrix $\mathbf{E}$, $j = 1, 2, \dots, n$, and are assumed to be independently and identically distributed as a p -variate normal distribution with mean vector $\mathbf{0}$ and an unknown positive definite variance-covariance matrix $\boldsymbol{\Sigma}$, often

written as $N_p(\mathbf{0}, \mathbf{\Sigma})$, Alternatively, the distribution of the matrix of error terms can be described as a matrix normal distribution, which is often denoted by $\mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_n)$ or $\mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma} \otimes \mathbf{I})$, and the notations indicate that the columns of $\mathbf{E}$ are independent but the rows are dependent, with the dependency represented by $\mathbf{\Sigma}$. This corresponds to the assumption that measurements from different individuals or items are independent but measurements from the same individuals or items are dependent, which is a reasonable assumption to make in most real-life scenarios leading to multivariate data.

We would like to highlight that in the MANOVA model, the mean profile is unstructured, meaning there is no functional relationship among the elements of the mean vector. However, for longitudinal studies and studies involving response curves, the mean often has a functional form (a structure) with respect to time or the relevant continuous independent variable. Since MANOVA ignores the mean structure, it is important to extend the model to account for functional relationship between the dependent and independent variables, which leads us to the generalized analysis of variance (GMANOVA) model, which is briefly presented in subsequent subsections. In this thesis, we focus on longitudinal data, hence we will consider one continuous dependent variable measured at p different time points. Hence, our presentation of the GMANOVA model is presented, without loss of generality, in the context of longitudinal studies.

2.3 The Growth Curve Model

Longitudinal studies involve a design by which repeated measurements of the same outcome is collected at different time points. Longitudinal studies are also referred to as panel studies in sociology and economics literature [43, 44]. Longitudinal data can be collected in two different ways: 1) individuals are recruited at the start of the study and are followed over time. Such studies can be randomized control trials (RCTs) involving relatively short period of time or cohort studies, where individuals are followed for a long period of time. Cohort studies may or may not involve treatments [45, 46, 44]; 2) data is collected retrospectively, by extracting multiple measurements on each person from historical records (for instance, hospital records) [44, 47, 48].

A key feature of longitudinal data is the presence of repeated measurements from the same individuals, which allows direct investigation of the change over time. Analyzing such data requires specialized statistical methods and models, that account for the inherent within individual (across time) correlation. In most studies involving longitudinal data, the relationship between the dependent variable and time (eg. investigating how the outcomes change over time for treated and untreated individuals) is often one of the primary objectives. As such, models that incorporate this relationship (sometimes referred to as time dependency) are more appropriate as they take advantage of the existing mean structure over time.

Consider the blood pressure example again, and suppose we record a continuous outcome of blood pressure measured from 50 individuals in 2 groups of patients (female and male), where 23 female patients belong to group 1 and 27 male patients belong to group

2. And patients are measured repeatedly through time, a total of ten measurements are taken, with an interval of one hour between each measurement. The blood pressure data set can be considered as the longitudinal data. Suppose that the mean is structured, i.e., the mean has a functional form with respect to time and can be expressed as a polynomial function. We can construct the growth curve model (GCM), which is also referred to as generalized multivariate analysis of variance model (GMANOVA). We will use another two examples from real life scenarios to discuss the GCM as examples with different sample size, different numbers of time points, different degrees of freedom of polynomial functions.

Consider the data structure presented in Table 2.1 and suppose that the data was generated from a longitudinal study involving a continuous outcome measured at p time points. We assume that the mean profile (trajectory) as a function of time (the conditional mean given t) for the j^{th} group can be expressed as a polynomial function of degree $q - 1$:

$$\mu_j = \beta_{0j} + \beta_{1j}t + \beta_{2j}t^2 + \cdots + \beta_{(q-1)j}t^{q-1}, \quad (2.3)$$

where $j = 1, 2, \dots, k$. The generalized multivariate analysis of variance (GMANOVA) model, which is often referred to as the growth curve model (GCM) is given by [20]:

$$\mathbf{Y} = \mathbf{ZBX} + \mathbf{E}, \quad \text{where } \mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_n), \quad (2.4)$$

where $\mathbf{Y} : p \times n$ is a matrix consisting of the repeated measurements of the response variable (dependent variable) :

$$\mathbf{Y} = \begin{pmatrix} Y_{11} & Y_{12} & Y_{13} & \cdots & Y_{1n} \\ Y_{21} & Y_{22} & Y_{23} & \cdots & Y_{2n} \\ Y_{31} & Y_{32} & Y_{33} & \cdots & Y_{3n} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ Y_{p1} & Y_{p2} & Y_{p3} & \cdots & Y_{pn} \end{pmatrix}.$$

For instance, the i^{th} column of $\mathbf{Y}$ represents the p observations corresponding to the i^{th} individual. Note that $n = n_1 + n_2 + \dots + n_k$, where k is the total number of groups in the study. We often put the first n_1 observations (from the first group) as the first n_1 columns of $\mathbf{Y}$, followed by n_2 elements from group 2 so on, where the last n_k columns of $\mathbf{Y}$ are the n_k elements from group k . The parameter matrix $\mathbf{B} : q \times k$ consists of the coefficients of polynomial representing the mean structure over time and is given by:

$$\mathbf{B} = \begin{pmatrix} b_{01} & b_{02} & b_{03} & \cdots & b_{0k} \\ b_{11} & b_{12} & b_{13} & \cdots & b_{1k} \\ b_{21} & b_{22} & b_{23} & \cdots & b_{2k} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ b_{(q-1)1} & b_{(q-1)2} & b_{(q-1)3} & \cdots & b_{(q-1)k} \end{pmatrix}.$$

The design matrix $\mathbf{Z} : p \times q$ represents the time dependency and is often referred to as the

within-individual design matrix:

$$\mathbf{Z} = \begin{pmatrix} 1 & t_1 & t_1^2 & \cdots & t_1^{q-1} \\ 1 & t_2 & t_2^2 & \cdots & t_2^{q-1} \\ 1 & t_3 & t_3^2 & \cdots & t_3^{q-1} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & t_p & t_p^2 & \cdots & t_p^{q-1} \end{pmatrix}.$$

This design matrix represents the assumed functional form of the assumed mean profile with respect to time. Preliminary data analysis, often involving exploratory graphical investigation, is done as a first step to identify an appropriate functional form that represents the data. This can be later tests formally using appropriate statistical tests. Note that the first column of the matrix $\mathbf{Z}$ is a vector of 1s corresponding to the intercept term in the polynomial function that represents the mean trajectory over time.

The design matrix $\mathbf{X} : k \times n$ is the same between-individual design matrix specified in the ANOVA and MANOVA models, which simply indicates which observations come from which group:

$$\mathbf{X} = \begin{pmatrix} \mathbf{1}_{n_1} & \mathbf{0}_{n_2} & \mathbf{0}_{n_3} & \cdots & \mathbf{0}_{n_k} \\ \mathbf{0}_{n_1} & \mathbf{1}_{n_2} & \mathbf{0}_{n_3} & \cdots & \mathbf{0}_{n_k} \\ \mathbf{0}_{n_1} & \mathbf{0}_{n_2} & \mathbf{1}_{n_3} & \cdots & \mathbf{0}_{n_k} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0}_{n_1} & \mathbf{0}_{n_2} & \mathbf{0}_{n_3} & \cdots & \mathbf{1}_{n_k} \end{pmatrix},$$

where, $\mathbf{1}_{n_1}$ is a row vector of length n_1 with all its elements as 1. This vector indicates that the first n_1 elements of $\mathbf{Y}$. On the other hand, $\mathbf{0}_{n_1}$ is a row vector of length n_1 with all its elements as 0. The design matrix $\mathbf{X}$ can also be viewed as a collection of k dummy variables representing group membership.

Similar to the MANOVA model, $\mathbf{E}$ is the error matrix and its columns are assumed to be identically and independently distributed as a p -variate normal distribution with mean zero and an unknown positive definite covariance matrix Σ . That is, $\mathbf{E} \sim N_{p,n}(\mathbf{0}, \Sigma, \mathbf{I}_n)$, which implies that $\mathbf{Y} \sim N_{p,n}(\mathbf{ZBX}, \Sigma, \mathbf{I}_n)$. In addition, for the GCM presented in Equation 2.4, it is assumed that $p \geq q$ and $n \geq \rho(\mathbf{X}) + p$, to avoid singularity problems. This assumption has been related to accommodating singularity, which is useful in high-dimensional scenarios, which we will not consider in this thesis [20, 24, 49].

Next, we provide two motivating examples to illustrate the GCM. The first example is the classical dental data, first analyses by Potthoff and Roy and subsequently re-analyzed by many [20]. Data consisted of four repeated dental measurements taken at ages 8, 10, 12, and 14 from 11 girls and 16 boys. That is, a total sample size of $n = 27$, $k = 2$, $p = 4$. Figure 2.1 displays both the individual and mean profiles over time for the two groups.

As can be seen in the above figure, it appears that the group means for both boys and girls can be modeled using linear functions of time, that is a structured mean with a polynomial of degree $q - 1 = 1$, hence $q = 2$. The observation matrix $\mathbf{Y}$ is of dimension 4×27 (representing $p = 4$ repeated measurements collected from $n = 27$ individuals), the

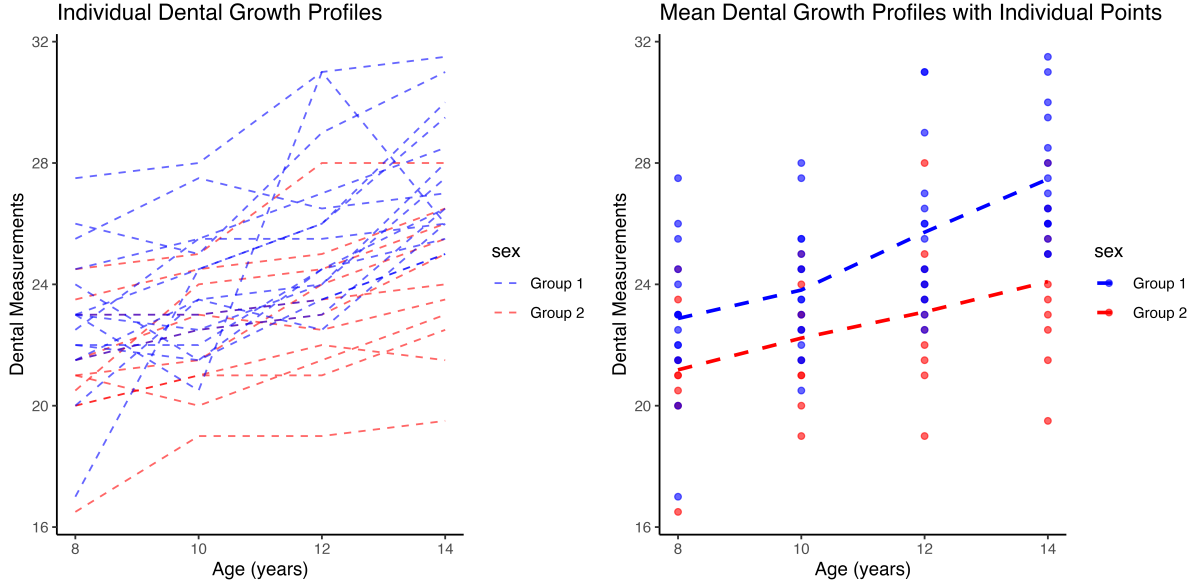


Figure 2.1: Individual and mean profile Plots for the Potthoff and Roy dental data

within-individual design matrix $\mathbf{Z}$ is of dimension 4×2 and is given by

$$\mathbf{Z} = \begin{pmatrix} 1 & 8 \\ 1 & 10 \\ 1 & 12 \\ 1 & 14 \end{pmatrix}.$$

The between-individual matrix $\mathbf{X}$ is of dimension 2×27 and is given by:

$$\mathbf{X} = \begin{pmatrix} \mathbf{1}_{11} & \mathbf{0}_{16} \\ \mathbf{0}_{11} & \mathbf{1}_{16} \end{pmatrix},$$

The matrix $\mathbf{B}$: 2×2 contains the unknown intercepts and slopes for the two groups (boys and girls):

$$\mathbf{B} = \begin{pmatrix} 17.42 & 15.92 \\ 0.48 & 0.81 \end{pmatrix}.$$

The error columns of matrix $\mathbf{E}$ are independent and are assumed to follow 4-variate multivariate normal distribution with mean vector $\mathbf{0}$ of length 4 and a 4×4 unknown positive definite variance-covariance matrix $\mathbf{\Sigma}$. We will use this data set later in Chapter 5, to illustrate the different multivariate methods for handling missing data. The estimates of the mean and covariance parameters from this data set were also used to generate simulations mimicking real-life scenarios.

The second motivating example was obtained from a glucose tolerance test and includes 8 repeated measurements of glucose tolerance outcome (plasma inorganic phosphate) that were taken 1, 1.5, 2.0, 2.5, 3, 3.5, 4 and 4.5 hours after administration of oral glucose. The measurements were collected from 29 controls (non-obese individuals) and 21 obese

individuals ($n = 50$, $k = 2$, $p = 8$). Figure 2.2 shows individual and mean profiles for the two groups.

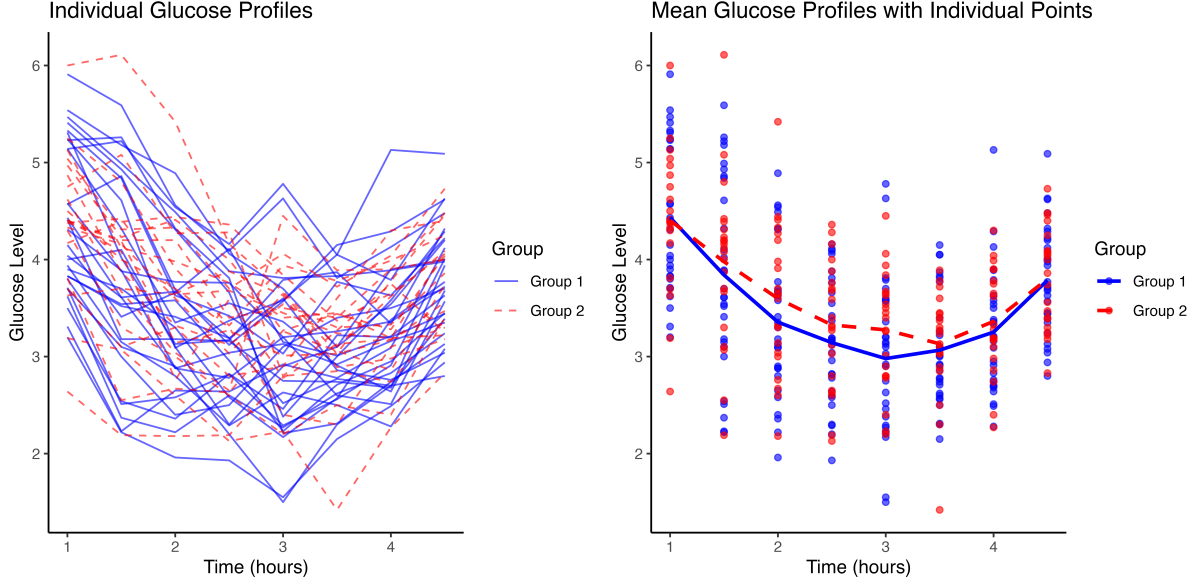


Figure 2.2: Individual and mean profile plots for the glucose data

We can see from Figure 2.2, that a quadratic curve over time may appropriately represent the group means for both groups. That is, the structured mean follows a polynomial of degree $q - 1 = 2$, hence $q = 3$. The observation matrix $\mathbf{Y}$ is of dimension 8×50 (representing $p = 8$ repeated measurements collected from $n = 50$ individuals), the within-individual design matrix $\mathbf{Z}$ is of dimension 8×3 and is given by

$$\mathbf{Z} = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 1.5 & 2.25 \\ 1 & 2 & 4 \\ 1 & 2.5 & 6.25 \\ 1 & 3 & 9 \\ 1 & 3.5 & 12.25 \\ 1 & 4 & 16 \\ 1 & 4.5 & 20.25 \end{pmatrix}.$$

The between-individual matrix $\mathbf{X}$ is of dimension: 2×50 and is given by:

$$\mathbf{X} = \begin{pmatrix} \mathbf{1}_{29} & \mathbf{0}_{21} \\ \mathbf{0}_{29} & \mathbf{1}_{21} \end{pmatrix},$$

The matrix $\mathbf{B}$: 3×2 contains the unknown intercepts and slopes for the two groups (non-

obesed and obesed):

$$\mathbf{B} = \begin{pmatrix} 6.032 & 5.696 \\ -2.067 & -1.749 \\ 0.349 & 0.293 \end{pmatrix}.$$

The error columns of matrix $\mathbf{E}$ are independent and are assumed to follow 8-variate multivariate normal distribution with mean vector $\mathbf{0}$ of length 8 and a 8×8 unknown positive definite variance-covariance matrix $\mathbf{\Sigma}$. We will return to this data set in Chapter 5 to show how different multivariate methods handle missing data, and the mean and covariance estimates obtained from it will be applied for the real-life-style simulations in Chapter 4.

2.3.1 Inference for the Growth Curve Model

The GCM, using matrix representation as a GMANOVA model, was formally introduced by Potthoff and Roy [20]. The authors proposed transformations of the model to the MANOVA model and use established likelihood based methods to conduct statistical inference involving the model parameters. Their approach was criticized because of an arbitrary matrix involved in the transformation (references). Since then, the GCM have been studied by many and the techniques for both parameter estimations and hypothesis testing have been developed very well and there is considerable literature on the theory. In this thesis, we only consider estimation, hence we present a brief literature review on estimation of the model parameters of the GCM. The hypothesis testing for the GCMs is discussed, among others, by Khatri [21, 50], Fujikoshi [51, 52, 53], Srivastava [54], Krishnaiah [55, 56], Hamid [57, 58, 23]. Model diagnostics for the GCM has also been studied extensively [59, 60, 61, 62].

Consider first the MANOVA model given by $\mathbf{Y} = \mathbf{BX} + \mathbf{E}$, where $\mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_n)$, which also includes ANOVA model as a special case (when we suppose $p = 1$). The Maximum Likelihood Estimator (MLE) which is also the Least Squares Estimator (LSE) for $\mathbf{B}$ [63, 64, 65] is given by

$$\hat{\mathbf{B}} = \mathbf{YX}'(\mathbf{XX}')^{-1},$$

which leads to the following estimated (predicted) mean and residuals, respectively:

$$\begin{aligned} \hat{\mathbf{Y}} &= \hat{\mathbf{B}}\mathbf{X} = \mathbf{YX}'(\mathbf{XX}')^{-1}\mathbf{X}, \\ \mathbf{R} &= \mathbf{Y} - \hat{\mathbf{Y}} = \mathbf{Y}(\mathbf{I} - \mathbf{X}'(\mathbf{XX}')^{-1}\mathbf{X}). \end{aligned}$$

Similar to linear regression models, under the normality assumption, the MLE for $\mathbf{\Sigma}$ is given by

$$\hat{\mathbf{\Sigma}} = \frac{\mathbf{RR}'}{n} = \frac{(\mathbf{Y} - \hat{\mathbf{B}}\mathbf{X})(\mathbf{Y} - \hat{\mathbf{B}}\mathbf{X})'}{n} = \frac{\mathbf{Y}(\mathbf{I} - \mathbf{X}'(\mathbf{XX}')^{-1}\mathbf{X})\mathbf{Y}'}{n}.$$

In practice, we often use the unbiased estimator, given in Equation 2.5 below, which can

also be shown to be equivalent to the pooled sample variance-covariance matrix [22, 59].

$$\hat{\Sigma}^* = \frac{(\mathbf{Y} - \hat{\mathbf{B}}\mathbf{X})(\mathbf{Y} - \hat{\mathbf{B}}\mathbf{X})'}{n - k} = \frac{\mathbf{R}\mathbf{R}'}{n - k} \quad (2.5)$$

Now, consider the GCM under the multivariate normality assumption: $\mathbf{Y} = \mathbf{Z}\mathbf{B}\mathbf{X} + \mathbf{E}$, where $\mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_n)$. Potthoff & Roy [20] performed inference for the model by using an approach involving a linear transformation of the GCM to the MANOVA model, where they pre-multiplied each term in the GCM by the matrix $(\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{V}^{-1}$, where $\mathbf{V}$ is an arbitrary non-singular matrix. The transformation leads to the MANOVA model:

$$\mathbf{Y}^* = \mathbf{B}\mathbf{X} + \mathbf{E}^*,$$

where $\mathbf{Y}^* = (\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Y}$ and $\mathbf{E}^* = (\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{V}^{-1}\mathbf{E}$. Note that the columns of both $\mathbf{Y}^*$ and $\mathbf{E}^*$ are linear combinations of a multivariate normal random variables, hence follow the multivariate normal distribution. Therefore, the least square or maximum likelihood procedures can be used on the transformed model, which leads to the following estimator for $\mathbf{B}$:

$$\hat{\mathbf{B}} = \mathbf{Y}^*\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1} = (\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}.$$

The corresponding predicted values and residuals, respectively, are given by

$$\begin{aligned} \hat{\mathbf{Y}} &= \mathbf{Z}\hat{\mathbf{B}}\mathbf{X} = \mathbf{Z}(\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}\mathbf{X} \\ \mathbf{R} &= \mathbf{Y} - \hat{\mathbf{Y}} = \mathbf{Y} - \mathbf{Z}(\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}\mathbf{X}, \end{aligned}$$

which leads to the following MLE estimator for $\mathbf{\Sigma}$

$$\hat{\Sigma} = \frac{1}{n}\mathbf{R}\mathbf{R}'.$$

The likelihood of the GCM was tackled directly by Khatri (1966) (under some full rank assumptions) and von Rosen (1989) (under general conditions) and explicit solutions for the MLEs of $\mathbf{B}$ and $\mathbf{\Sigma}$ were provided. Khatri directly used the likelihood function and, with the help of results from standard multivariate analysis of variance, derived the maximum likelihood estimator for $\mathbf{B}$:

$$\hat{\mathbf{B}} = (\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{S}^{-1}\mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}, \text{ where } \mathbf{V} = \mathbf{Y}(\mathbf{I} - \mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}\mathbf{X})\mathbf{Y}'.$$

von Rosen obtained the MLE by solving the likelihood equations:

$$\begin{aligned} \mathbf{Z}'\Sigma^{-1}(\mathbf{Y} - \mathbf{Z}\mathbf{B}\mathbf{X})\mathbf{X}' &= \mathbf{0} \\ n\Sigma &= (\mathbf{Y} - \mathbf{Z}\mathbf{B}\mathbf{X})(\mathbf{Y} - \mathbf{Z}\mathbf{B}\mathbf{X})' \end{aligned}$$

We would like to highlight again that the GCM, like most multivariate models, requires that we have a complete data. However, in practical applications, we encounter missing

data problems. Moreover, in longitudinal studies, the observations for individuals are required to be taken at the same time points. That leads to more missing data in particular in both prospective and retrospective observational studies. Therefore, approaches to handle missing data are important, which we will briefly discuss in the next subsection.

2.4 Missing Data and Missingness Mechanisms

Missing data is a common problem in practical applications, and ignoring it (by deleting individuals with missing data and using only observed data) may lead to serious consequences and may lead to misleading conclusions [4, 5, 66]. Longitudinal studies are more susceptible to missing data and their analysis often impacted by the way the missing data is handled [67, 68]. Thus, it is a crucial topic for researchers to consider how to deal with the missing data appropriately. Careful considerations should be made in terms of whether they should choose to delete the missing data (is the missingness ignorable) or replace the missing data by some imputed values, as well as choice of optimal imputation techniques [5, 69, 66].

Many decades of research in the topic demonstrates that, before we develop or choose the methods to handle the missing data, we need to understand the potential causes missing data and the mechanism by which the observations are missing [4, 6, 70].

There are various reasons for missing data, and it is defined how to illustrate which type of missing data it is conceptually and in the form of mathematical formulations. In 1976, Rubin introduced the concept of missingness mechanisms for the first time, where the authors categorize missing data into three different mechanisms: missing completely at random (MCAR), missing at random (MAR), and not missing at random (MNAR) [6]. Since then, missingness mechanisms as well as methods to handle missing data has been studied extensively [6, 4, 71].

Missing Completely at Random (MCAR) refers to a missingness mechanism in which the probability of missingness is unrelated to any observed or unobserved data. As such, the missingness indicator is independent of all variables, so the observed data is an unbiased subsample of the full data set [6]. Missing at random (MAR) is a mechanism in which the probability of missingness depends only on observed data, but not on the missing values themselves [4, 6]. For instance, considering a blood pressure level study as an example, there are 50 individuals in 2 groups of patients (female and male), where 23 female patients belong to group 1 and 27 male patients belong to group 2. We track monthly measurements over a 1-year period for two groups of patients, with each individual expected to contribute 12 repeated observations. Due to unpredictable technical issues with the blood pressure measurement device, for instance, random equipment failure or data entry errors, some measurements are missing at random time points. These missing values are not associated with the patient’s blood pressure levels at other unobserved time points, sex, or any other measured variables or the missing measurements. The mechanism for such missing data can be considered as MCAR. On the other hand, suppose that male patients, or patients in older age groups, are more likely to miss clinic visits. For instance, older individuals

may face mobility issues, transportation barriers, or chronic health conditions that make regular follow-up more difficult. Thus, the missingness related to blood pressure readings is associated with observed variables such as sex or age, but not with the missing blood pressure data. The mechanism for such missing data can be considered as MAR.

Missing Not at Random (MNAR) refers to a missingness mechanism such that the probability of missingness depends on the unobserved value itself and possibly also on observed data [6, 4, 5]. Reconsidering blood pressure level data, patients with abnormally high blood pressure may intentionally skip visits out of concerns about being prescribed additional medication, facing increased healthcare expenses, or receiving restrictions related to work or daily activities. Since the chance of missing data is higher when blood pressure is elevated, but these values are not observed, which represents a non-ignorable missing data mechanism.

There are no tests to detect MNAR (non-ignorable) missingness, so we have to apply our understanding and former experience of biological systems to make a decision as to whether the mechanism of missingness here is MNAR or not [72]. In contrast to MNAR, MCAR and MAR are classed as ignorable, since when the parameters for the data itself are separate from those for the missing-data process, the joint likelihood splits into two parts. Due to this split, we can rely on the likelihood from the observed data alone and draw valid conclusions, without having to model the missingness mechanism. However, for MNAR, which is non-ignorable, because the probability of missingness depends on the unobserved value, the joint likelihood cannot be separated [6, 4, 5, 68].

Several approaches for handling missing data have been proposed and the methods depend on the objective at hand, the statistical models used as well as the missingness mechanisms [3, 4, 69]. In this thesis, we focus on parameter estimation involving analysis of longitudinal data using the multivariate GCM, a scenario in which missing data is usually unavoidable and nonignorable. As such, choosing an appropriate technique that leads to accurate and efficient estimators is important. In the next section, we will provide a brief overview of methods developed for handling missing data, with a focus on longitudinal studies. In Chapter 3, we will provide a detailed presentation of multivariate methods developed under the GCM framework, and provide numerical illustrations using the motivating examples we discussed in Chapter 5.

2.4.1 Methods for Handling Missing Longitudinal Data

Because missing data often occur in longitudinal studies, many papers have been written on methods for dealing with them [67]. Frequently used approaches in the analysis of longitudinal data are list-wise deletion (eg. using only observed data) and imputation methods (single or multiple imputations). For instance, in the list-wise deletion method, we first select which variables we are interested in, and we omit every individual with missing values. Since we do the analysis on the observed complete data, this list-wise deletion method is also referred to as complete case analysis.

On the other hand, when handling missing data using any of the imputation methods, we take advantage of the features of the data and to use the information we collected

from the observed data, combined with imputed techniques, to handle missing data. Such approaches are often needed when the missingness mechanism is MNAR (non-ignorable), the list-wise deletion (complete case analysis) leads analysis to be biased and under-powered [73, 4]. For instance, multiple imputation draws several plausible values for each missing entry, and final estimates and confidence intervals properly reflect the extra uncertainty introduced by missingness [18, 5, 68, 67].

Imputation methods can be categorized into two different types: single imputation and multiple imputation. Single imputation methods replace each missing value with a single estimated value, such as the mean, median, predicted values from a regression model, last observed value, next observed value etc, choices made depending on specific scenarios. While these approaches are simple and straightforward to implement and maintain the structure of the original data set, they fail to account for the uncertainty associated with the imputed values and tend to underestimate variability [5, 4].

Multiple imputation provides a statistically reliable solution to handle missing data problems [73, 66, 4]. Instead of filling in each missing value just once, multiple imputation approach generates several complete data sets by imputing missing values multiple times using a stochastic model [73, 69, 71]. We perform inference (analysis) on each complete data set separately, and the results are then combined to produce appropriate estimates that reflect both the variation within each data set and the differences between them [73, 4, 71]. Thus, the multiple imputation approach preserves the natural uncertainty caused by missing values and provides more accurate and robust inference, particularly under the assumption that the missingness mechanism is MNAR [4, 73, 5, 66, 18].

Several statistical methods are proposed to provide imputation solutions to missing longitudinal data problems [67, 18, 69]. For instance, the EM algorithm, which is a step-by-step iterative likelihood-based method used to estimate model parameters when the original data set has missing values, is developed for obtaining maximum-likelihood estimates from incomplete data set [12, 74, 71]. It works in two iterative steps: the expectation step estimates the missing data conditional on the current observed values of the data, and the maximization step updates the parameter estimates to make the data fit the model better. We repeat these two steps until the results converge to a pre-specified threshold. The EM algorithm a commonly used likelihood approach, even when data is complete (no missing data), but the method is especially useful when dealing with incomplete data [12]. This is because it allows us to make full use of all available information without having to remove missing cases, which usually leads to optimal estimates of the model parameters [4]. EM algorithm can also convert to a multiple imputation method by adding stochastic step, which conduct random draw for model parameters and missing values, and this method is referred to be as EM-posterior-draw (EMPD) [73, 71, 4]. While an alternative that re-samples the observed data and reruns EM on each bootstrap replicate is known as EM-plus-bootstrap (EMB) [75, 76].

Another method proposed to handle missing longitudinal data is a Bayesian approach, proposed by Tanner et al., Ibrahim et al., and Daniels et al. [77, 78, 79]. Bayesian method can handle missing data by treating unknown values as additional random variables. Instead of filling in missing values with fixed and single guesses, Bayesian methods

use probability distributions to describe the uncertainty corresponding to both the missing values and the unknown model parameters. By combining earlier assumptions with the information from the observed data through the Bayesian theorem, the approach generates a full posterior distribution that reflects all sources of uncertainty [80, 79, 78, 81]. This is usually done using computational methods such as Markov Chain Monte Carlo (MCMC) method [80, 81], which allows for estimation of parameters and imputation of missing values at the same time. As a result, the Bayesian method naturally incorporates uncertainty and provides valid inference, even in complex models or small sample settings [4]. Bayesian data-augmentation approaches via MCMC method are multiple imputation methods, because each posterior draw of the missing values generates one valid imputed data set and combining inferences over many such draws yields estimates that follow Rubin’s multiple-imputation combining rules [73, 71, 77].

The methods discussed above are commonly used to handle missing data in longitudinal studies. And in applications, complete case deletion method is the most common approach [82, 83, 84]. Nevertheless, the methods are developed under general frameworks and are not limited to longitudinal studies [4, 73, 71, 69]. As such, they may lack optimality when applied to certain specific scenarios or models. For example, such methods often ignore the inherent mean structure in longitudinal data (eg. the relationship between the outcome and time) or the within individual (across-time) correlations, which play important roles in achieving optimal inference in GCMs. Therefore, it is essential to consider more specialized multivariate approaches that are specifically developed under the GCM framework, and have the potential to effectively handle missing longitudinal data. We performed extensive literature review to identify such methods and details on the methods and the computational algorithms, along with numerical illustrations are provided in Chapter 3.

Chapter 3

Multivariate Methods for Handling Missing Longitudinal Data

As indicated in the previous chapter, the GCM, and multivariate models in general, do not allow missing data. That is, the model, as originally formulated, requires analysis to be conducted on a complete data set, where measurements for all individuals are observed at all time points. However, in practical applications, it is nearly impossible to avoid missing values in longitudinal data [4, 85]. Simply deleting individuals with missing observations may lead to serious consequences on inference, in particular when we have small sample sizes (both for large and small number of time points). Even when we have a relatively large sample size, deletion can be consequential when the number of time points is small and/or when individuals have missing observations at more than one time point.

Several approaches for handling longitudinal missing data do exist, including simple methods involving single and multiple imputations as well as more complex methods, based on the generalized linear mixed model (GLMM) [68, 44]. Nevertheless, these commonly used approaches do not account for the inherent time dependency (the mean trajectory or structure with respect to time) that exists in most longitudinal designs, hence may be subjected to loss of information. Some of the methods (eg. imputing missing data using means) may even ignore the correlation structure that exists in the data [45, 86, 85]. Therefore, it is important to explore methods that account for both the correlation and the mean structures.

In this chapter, we present multivariate methods for handling missing longitudinal data. We performed extensive literature reviews to identify such methods, and found three, which we will discuss in more detail in subsequent sections. We use numerical examples, using a real data set, to illustrate the steps involved in the methods and the corresponding computational algorithms. All the three methods were specifically developed under the GCM (and the GMANOVA model) framework, where the mean is assumed to be structured and observations from the same subjects are correlated.

Although all the three methods were proposed many decades ago, there is little to none literature available on their implementations or applications. In this thesis, we fill this computational gap, which perhaps led to the lack of methodological uptake in practical

applications. Although the theoretical foundations were established for general cases, the computational algorithms, for all the three methods, were developed and illustrated for longitudinal data involving only one group, limited number of time points, and a very simple case of a missing pattern. We extended the algorithms and implemented them using the R statistical software, where the R programs are automated to allow more than one group, any number of time points, different missingness mechanisms, as well as different mean trajectories over time.

3.1 Liski's EM Algorithm

This approach was introduced by Liski in 1985 [39] and is based on the GCM framework, where longitudinal measurements of a continuous outcome are modeled using two design matrices. Although this thesis focuses on longitudinal data, the proposed method is applicable for any continuous outcome with a structured mean (eg. modeling dose-response relationships). The method is a likelihood-based approach and was developed under the assumption of multivariate normality.

The expectation maximization (EM) algorithm is an iterative computational method used to obtain maximum-likelihood estimates (MLEs) from incomplete data set. The algorithm consists of two steps: the expectation step, where missing data are estimated conditional on observed data and the maximization step, where the model parameters are updated to improve inference and model fit. These steps are repeated until convergence is achieved, which is determined based on a predefined threshold [12, 74, 71].

In order to facilitate the presentation of Liski's EM approach for handling missing longitudinal data under the GCM framework, we will use a numerical example involving Potthoff & Roy's dental data, which we discussed in Section 2.3. Without loss of generality, consider only one group (the girls) and a simple missing pattern identified as NA in Table 3.1.

Now, recall that the GCM with the multivariate normal assumption :

$$\mathbf{Y} = \mathbf{ZBX} + \mathbf{E}, \quad \text{where } \mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_n)$$

For the dental data involving only the girls, the observation matrix $\mathbf{Y}$ is of dimension 4×11 ($p = 4$ repeated measurements collected from $n = 11$ girls), the within-individual design matrix $\mathbf{Z}$ is of dimension 4×2 (representing a linear mean structure) and is given by

$$\mathbf{Z} = \begin{pmatrix} 1 & 8 \\ 1 & 10 \\ 1 & 12 \\ 1 & 14 \end{pmatrix}.$$

Note that the first column of $\mathbf{Z}$ corresponds to the intercept and the second column corresponds to linear component of time. The between-individual matrix $\mathbf{X}$ is of dimension: $1 \times$

11 (highlighting all of the individuals belong to one group) and is given by:

$$\mathbf{X} = (\mathbf{1}_{11}),$$

where $(\mathbf{1}_{11})$ denotes a row vector with all its elements equal to one.

Table 3.1: Potthoff and Roy dental data (Females only) with missing data created manually, where "NA" denotes the missing observations.

ID	Sex	Age (years)			
		8	10	12	14
1	F	21.0	20.0	21.5	23.0
2	F	21.0	21.5	24.0	25.5
3	F	20.5	24.0	NA	26.0
4	F	NA	24.5	25.0	26.5
5	F	NA	NA	22.5	23.5
6	F	20.0	21.0	21.0	22.5
7	F	21.5	22.5	23.0	25.0
8	F	23.0	23.0	NA	NA
9	F	20.0	21.0	22.0	21.5
10	F	16.5	19.0	19.0	19.5
11	F	24.5	25.0	28.0	28.0

We denote the MLE of the mean parameters ($\mathbf{B}$) and the unbiased estimator of the variance-covariance matrix (Σ) obtained by using a complete sample (where individuals with missing data are deleted) by $\mathbf{B}^*$ and Σ^* , respectively. Note that throughout the thesis, an estimator with a superscript "*" represents an estimator obtained from a complete data, where individuals with missing observations are deleted. We also refer to such estimators as "complete data" estimators.

We set Σ^* and $\mathbf{B}^*$ from the complete data set, as our initial values $\Sigma^{(0)}$ and $\mathbf{B}^{(0)}$ for the EM algorithm, which for the dental data presented in Table 3.1 are given by:

$$\hat{\Sigma}^* = \begin{bmatrix} 4.84 & 3.55 & 5.37 & 5.38 \\ 3.55 & 3.17 & 4.44 & 4.22 \\ 5.37 & 4.44 & 6.91 & 6.49 \\ 5.38 & 4.22 & 6.49 & 6.82 \end{bmatrix},$$

$$\hat{\mathbf{B}}^* = [16.37 \quad 0.48].$$

Liski's EM algorithm relies on the following conditional expectation [39]:

$$\begin{aligned} \hat{\mathbf{y}}_{(m)i} &= E \left(\tilde{\mathbf{y}}_{(m)i} \mid \mathbf{O}_i; \tilde{\boldsymbol{\mu}}_i^*, \hat{\Sigma}^* \right) \\ &= \tilde{\boldsymbol{\mu}}_{(m)i}^* + \Sigma_{(mo)i}^* \Sigma_{(oo)i}^{*-1} (\tilde{\mathbf{y}}_{(o)i} - \tilde{\boldsymbol{\mu}}_{(o)i}^*) \end{aligned} \quad (3.1)$$

where $\hat{\mathbf{y}}_{(m)i}$ is a $p \times 1$ column vector, containing the estimated missing values, and zero else where, and "m" in the brackets represents "missing"; $\mathbf{O}_i$ denotes the set of variables

observed for the i th individual; $\tilde{\boldsymbol{\mu}}_{(m)i}^*$ is a $p \times 1$ column vector, which assumes expectations to missing components, but zero for else where; $\boldsymbol{\Sigma}_{(mo)i}^*$ is a $p \times p$ matrix consisting of the covariances between missing and observed components in the positions corresponding to the values of index (j, k) , where j refers to a missing observation and k to an observed component and zero elsewhere, and "o" in the brackets represents "observed"; For instance, $\boldsymbol{\Sigma}_{(oo)i}^*$ is a $p \times p$ matrix denoting covariance between the observed data and zeros elsewhere; $\tilde{\mathbf{y}}_{(o)i}$ is a $p \times 1$ column vector consisting of the observed values for individual i ; $\tilde{\boldsymbol{\mu}}_{(o)i}^*$ is a $p \times 1$ column vector consisting of the estimated mean for the components corresponding to observed values and zeros elsewhere. Note that the estimated mean trajectory is calculated from the GCM using. At the initial stage, the estimated mean trajectory is given by

$$\mathbf{M}^* = \mathbf{Z} \hat{\mathbf{B}}^* \mathbf{X} = [\tilde{\mathbf{y}}_1^* \quad \tilde{\mathbf{y}}_2^* \quad \dots \quad \tilde{\mathbf{y}}_r^*],$$

where r is the number of individuals with no-missing data. Note that each individual within the same group is represented by one mean trajectory over time, hence the matrix $\mathbf{M}^*$ consists of k distinct columns of length p . For the dental data presented in Table 3.1, we have one group ($k = 1$), hence $\mathbf{M}^*$ consists of 11 columns of the same mean vector of length $p = 4$, which is given by

$$\tilde{\mathbf{y}}_i^* = [20.64 \quad 21.43 \quad 22.64 \quad 23.57]^T.$$

Now, the missing observations for the dental data (identified as NA in Table 3.1) can be estimated according to the formula provided in Equation 3.1. Consider $\hat{\mathbf{y}}_{(m)3}$ as an example, which corresponds to the 3rd individual and the missing observation at time point 3. This missing observation is estimated (at the first iteration) as follows:

$$\begin{aligned} \hat{\mathbf{y}}_{(m)3} &= \begin{bmatrix} 0 \\ 0 \\ 22.64 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 5.37 & 4.44 & 0 & 6.49 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} 1.98 & -0.75 & 0 & -1.10 \\ -0.75 & 2.07 & 0 & -0.68 \\ 0 & 0 & 0 & 0 \\ -1.10 & -0.68 & 0 & 1.44 \end{bmatrix} \left(\begin{bmatrix} 20.50 \\ 24.00 \\ 0 \\ 26.00 \end{bmatrix} - \begin{bmatrix} 20.64 \\ 21.43 \\ 0 \\ 23.57 \end{bmatrix} \right) \\ &= \begin{bmatrix} 0 \\ 0 \\ 25.33 \\ 0 \end{bmatrix} \end{aligned}$$

Since the 3rd individual has a single missing observation at time point 3, $\tilde{\boldsymbol{\mu}}_{(m)i}^*$ its third element (corresponding to time point 3) is set to the estimated mean at that particular time point and zero elsewhere. The initial values for the covariance (denoted by $\boldsymbol{\Sigma}_{(mo)i}^* = \boldsymbol{\Sigma}_{(om)i}^{*'}$) are obtained from the covariance estimates (without the variance) corresponding to the 3rd time point (i.e. from $\hat{\boldsymbol{\Sigma}}^*$, we retain only the covariance estimates corresponding to time point 3) and the remaining elements of the matrix set to 0. The third row of $\hat{\boldsymbol{\Sigma}}^*$ is replaced by a zero vector and the resulting matrix is inverted to obtain $\boldsymbol{\Sigma}_{(oo)i}^{*-1}$. The vector $\tilde{\mathbf{y}}_{(o)i}$ consists of the observed data points for the third individual and the missing observation at time point 3 replaced by 0. Finally, the vector $\tilde{\boldsymbol{\mu}}_{(o)i}^*$ consists of the estimated mean

values for time point 1, 2, 4 and assigned to zero for time point 3 (for the missing data point). Once we calculate $\hat{\mathbf{y}}_{(m)3}$ at the first iteration, the resulting value will replace the missing observation for the 3rd individual. Similarly, the imputed vectors corresponding to individuals 4, 5, and 8 are given by:

$$\hat{\mathbf{y}}_{(m)4} = \begin{bmatrix} 23.15 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \hat{\mathbf{y}}_{(m)5} = \begin{bmatrix} 20.56 \\ 21.34 \\ 0 \\ 0 \end{bmatrix}, \quad \hat{\mathbf{y}}_{(m)8} = \begin{bmatrix} 0 \\ 0 \\ 25.12 \\ 26.12 \end{bmatrix}$$

We would like to note here that the 5th and 8th individuals have missing data at 2 time points, the non-zero imputed values calculated above will replace the corresponding missing observations for these individuals.

The next step for Liski's EM algorithm is to estimate the matrix $\mathbf{V}^k$, which will be used as a weight in the iterative estimation of $\mathbf{B}$ and $\mathbf{\Sigma}$. Let $\mathbf{V}_i$ denote a $p \times p$ matrix consisting of conditional covariances between the missing observations and takes on a value zero elsewhere. The procedure used to calculate the conditional component of the covariance can be mathematically described as:

$$\begin{aligned} \mathbf{V}_i &= \text{cov} \left(\tilde{\mathbf{y}}_i | \mathbf{O}_i; \tilde{\boldsymbol{\mu}}_i^*, \hat{\boldsymbol{\Sigma}}^* \right) \\ &= \boldsymbol{\Sigma}_{(mm)i}^* - \boldsymbol{\Sigma}_{(mo)i}^* \boldsymbol{\Sigma}_{(oo)i}^{*-1} \boldsymbol{\Sigma}_{(om)i}^* \end{aligned}$$

where $\tilde{\mathbf{y}}_i$ denotes an individual i from the original data set with missing observations; $\boldsymbol{\Sigma}_{(mm)i}^*$ is a $p \times p$ matrix consisting of covariances between the missing observations and 0 elsewhere. For instance, for the dental data presented in Table 3.1, the conditional covariance matrices between 3rd, 4th, 5th, and 8th individuals are denoted by $\mathbf{V}_3$, $\mathbf{V}_4$, $\mathbf{V}_5$ and $\mathbf{V}_8$, respectively. Consider $\mathbf{V}_3^{(1)}$ (i.e. $\mathbf{V}_3$ at the first iteration) as an example. It is calculated as follows

$$\begin{aligned} \mathbf{V}_3^{(1)} &= \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 6.91 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} - \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 5.37 & 4.44 & 0 & 6.49 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} 1.98 & -0.76 & 0 & -1.10 \\ -0.76 & 2.07 & 0 & -0.68 \\ 0 & 0 & 0 & 0 \\ -1.01 & -0.68 & 0 & 1.44 \end{bmatrix} \begin{bmatrix} 0 & 0 & 5.37 & 0 \\ 0 & 0 & 4.44 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 6.49 & 0 \end{bmatrix} \\ &= \begin{bmatrix} 0 & 0 & 0.0 & 0 \\ 0 & 0 & 0.0 & 0 \\ 0 & 0 & 0.40 & 0 \\ 0 & 0 & 0.0 & 0 \end{bmatrix}, \end{aligned}$$

where $\boldsymbol{\Sigma}_{(mm)i}^*$ retains only the variance estimate (from $\hat{\boldsymbol{\Sigma}}^*$) corresponding to time point 3, and is set to 0 elsewhere; $\boldsymbol{\Sigma}_{(mo)i}^*$ and $\boldsymbol{\Sigma}_{(oo)i}^{*-1}$ are as before. Similarly, $\mathbf{V}_4^{(1)}$, $\mathbf{V}_5^{(1)}$, and $\mathbf{V}_8^{(1)}$

can be calculated:

$$\mathbf{V}_4^{(1)} = \begin{bmatrix} 0.49 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \mathbf{V}_5^{(1)} = \begin{bmatrix} 0.50 & 0.07 & 0 & 0 \\ 0.07 & 0.32 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \mathbf{V}_8^{(1)} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0.50 & 0.27 \\ 0 & 0 & 0.27 & 0.70 \end{bmatrix}.$$

Next, we calculate $\mathbf{V}^{(k)}$, which is obtained by adding the conditional covariances corresponding to each individual with missing observations. That is,

$$\mathbf{V}^{(k)} = \sum_{i=1}^n cov\left(\tilde{\mathbf{y}}_i; \tilde{\boldsymbol{\mu}}_i^{(k-1)}, \hat{\boldsymbol{\Sigma}}^{(k-1)}\right) = \sum_{i=1}^n \mathbf{V}_i^{(k)}$$

where $\tilde{\boldsymbol{\mu}}_i^{(k-1)}$ denotes the i th column of $\mathbf{M}^{(k-1)} = \mathbf{Z}\hat{\mathbf{B}}^{(k-1)}\mathbf{X}$. For the dental data presented in Table 3.1, $\mathbf{V}^{(1)}$ is given by

$$\mathbf{V}^{(1)} = \mathbf{V}_3^{(1)} + \mathbf{V}_4^{(1)} + \mathbf{V}_5^{(1)} + \mathbf{V}_8^{(1)} = \begin{bmatrix} 0.99 & 0.07 & 0.00 & 0.00 \\ 0.07 & 0.32 & 0.00 & 0.00 \\ 0.00 & 0.00 & 0.90 & 0.27 \\ 0.00 & 0.00 & 0.27 & 0.70 \end{bmatrix}$$

The iterative steps of the EM algorithm for the GCM lead to the following estimators for $\mathbf{B}$

$$\hat{\mathbf{B}}^{(k)} = (\mathbf{X}\mathbf{X}')^{-1}\mathbf{X}\left(\hat{\mathbf{Y}}_1 - \hat{\boldsymbol{\gamma}}^{(k)}\hat{\mathbf{Y}}_2\right)$$

$$\hat{\boldsymbol{\gamma}}^{(k)} = \left(\hat{\mathbf{Y}}_2'\mathbf{P}\hat{\mathbf{Y}}_2 + \mathbf{H}_2'\mathbf{V}\mathbf{H}_2\right)^{-1}\left(\hat{\mathbf{Y}}_2'\mathbf{P}\hat{\mathbf{Y}}_1 + \mathbf{H}_2'\mathbf{V}\mathbf{H}_1\right),$$

where $\mathbf{P}$ is the projection matrix corresponding to the between individual design matrix and is given by $\mathbf{I} - \mathbf{X}'(\mathbf{X}\mathbf{X}')\mathbf{X}$. The other matrices in the above iterative formulas are:

$$\hat{\mathbf{Y}}_1 = \hat{\mathbf{Y}}'\mathbf{H}_1,$$

where $\mathbf{H}_1 = \mathbf{Z}(\mathbf{Z}'\mathbf{Z})^{-1}$. The matrix $\mathbf{H}_2$ is chosen as a column basis of $\mathbf{I} - \mathbf{Z}(\mathbf{Z}'\mathbf{Z})^{-1}\mathbf{Z}'$ with dimension $p \times (p - q)$ and is used to provide the estimator denoted by $\hat{\mathbf{Y}}_2$:

$$\hat{\mathbf{Y}}_2 = \mathbf{Y}'\hat{\mathbf{H}}_2$$

To find the column basis for calculating $\mathbf{H}_2$, we choose the first two eigenvectors of $\mathbf{I} - \mathbf{Z}(\mathbf{Z}'\mathbf{Z})^{-1}\mathbf{Z}'$, which for the dental data is given by:

$$\mathbf{H}_2 = \begin{bmatrix} 0.2982956 & -0.05533407 & -0.7842185 & 0.54125705 \\ 0.4593689 & -0.83482821 & 0.2915498 & 0.08390953 \end{bmatrix}$$

Note that $\mathbf{H}_1$ and $\mathbf{H}_2$ are related to the within individual design matrix $\mathbf{Z}$ and can be considered as "constant", in the sense that their values do not change throughout the procedure.

Consider next the matrix $\hat{\mathbf{Y}}$ (which is needed to calculate $\hat{\mathbf{Y}}_1$ and $\hat{\mathbf{Y}}_2$), it represents the original data, where missing values are filled by the estimates $\hat{\mathbf{y}}_{(m)i}$ (the imputed values) which, as illustrated above, are obtained from Equation 3.1. Using matrix formulations, $\hat{\mathbf{Y}}$ can be written as the following conditional expectation:

$$\hat{\mathbf{Y}}^{(k)} = E\left(\mathbf{Y} | \mathbf{O}_Z, \hat{\mathbf{M}}^{(k-1)}, \hat{\mathbf{\Sigma}}^{(k-1)}\right)$$

where $\hat{\mathbf{M}}^{(k-1)} = \mathbf{Z}\hat{\mathbf{B}}^{(k-1)}\mathbf{X}$ and $\mathbf{O}_Z$ denotes the total set of measurements observed. For the dental data presented in Table 3.1, where colored units denote imputed values, $\hat{\mathbf{Y}}^{(1)}$ is given by

$$\hat{\mathbf{Y}}^{(1)} = \begin{bmatrix} 21.00 & 20.00 & 21.50 & 23.00 \\ 21.00 & 21.50 & 24.00 & 25.50 \\ 20.50 & 24.00 & 25.33 & 26.00 \\ 23.15 & 24.50 & 25.00 & 26.50 \\ 20.56 & 21.34 & 22.50 & 23.50 \\ 20.00 & 21.00 & 21.00 & 22.50 \\ 21.50 & 22.50 & 23.00 & 25.00 \\ 23.00 & 23.00 & 25.12 & 26.12 \\ 20.00 & 21.00 & 22.00 & 21.50 \\ 16.50 & 19.00 & 19.00 & 19.50 \\ 24.50 & 25.00 & 28.00 & 28.00 \end{bmatrix}^T$$

The iterative formula to obtain the adjusted sample variance-covariance matrix $\hat{\mathbf{\Sigma}}^{(k)}$ used when in updated iteration, is given by:

$$\hat{\mathbf{\Sigma}}_S^{(k)} = \frac{1}{n} \left(\hat{\mathbf{Y}} \mathbf{P} \hat{\mathbf{Y}}' + \mathbf{V}^{(k)} \right)$$

The iterative formula to get the MLE for $\mathbf{\Sigma}$ is not the traditional MLE and we denote it as $\hat{\mathbf{\Sigma}}_{EMML}$, which is given by:

$$\hat{\mathbf{\Sigma}}_{EMML}^{(k)} = \frac{1}{n} \left[\left(\hat{\mathbf{Y}} - \mathbf{Z}\hat{\mathbf{B}}^{(k)}\mathbf{X} \right) \left(\hat{\mathbf{Y}} - \mathbf{Z}\hat{\mathbf{B}}^{(k)}\mathbf{X} \right)' + \mathbf{V}^{(k)} \right]$$

The iterative procedure is performed until the algorithm converges, where convergence is established by setting a fixed threshold for $\hat{\mathbf{B}}^{(k)}$.

For the dental data example (with $k = 1$), we get the following estimates at the first iteration:

$$\hat{\mathbf{\Sigma}}_S^{(1)} = \begin{bmatrix} 4.07 & 2.99 & 4.17 & 4.31 \\ 2.99 & 3.31 & 4.03 & 3.97 \\ 4.17 & 4.03 & 5.75 & 5.47 \\ 4.31 & 3.97 & 5.47 & 5.80 \end{bmatrix}, \hat{\mathbf{B}}^{(1)} = [16.63 \quad 0.53], \hat{\mathbf{\Sigma}}_{EMML}^{(1)} = \begin{bmatrix} 4.09 & 3.01 & 4.21 & 4.33 \\ 3.01 & 3.32 & 4.06 & 3.99 \\ 4.21 & 4.06 & 5.82 & 5.52 \\ 4.33 & 3.99 & 5.52 & 5.83 \end{bmatrix}$$

After 10 iterations, we obtain the final results, where

$$\hat{\mathbf{B}} = \begin{bmatrix} 16.53 & 0.55 \end{bmatrix},$$

$$\hat{\Sigma}_{EMML} = \begin{bmatrix} 3.83 & 2.74 & 4.02 & 4.09 \\ 2.74 & 3.31 & 3.89 & 3.95 \\ 4.02 & 3.89 & 5.50 & 5.33 \\ 4.09 & 3.95 & 5.33 & 5.77 \end{bmatrix}$$

As you can see from the above numerical illustrations, the calculations involved in Liski's iterative algorithm are very tedious. Moreover, the many matrices involved in the calculations depend on the location of the missing data points, the number of groups, the number of time points as well as the within group and total sample sizes. To our knowledge, the algorithm is not implemented in any statistical software. This might have led to the lack of methodological uptake. Therefore, one of the significant contributions of this thesis is generalizing the algorithm and implementing it in R. Our algorithm and the corresponding R program works for any sample, any number of groups, any number of time points, linear and non-linear mean structures as well as any sample sizes.

3.2 Kleinbaum's Generalized Growth Curve Model

Generalized Growth Curve Model (GGCM) was introduced by Kleinbaum in 1973 and is considered to be the first multivariate approach allowing missing data under the GCM framework, where the mean is allowed to be structured unlike the MANOVA model [37]. The author showed that the estimators proposed in his paper are best asymptotically normal (BAN).

Consider again the GCM under the multivariate normal assumptions:

$$\mathbf{Y} = \mathbf{ZBX} + \mathbf{E}, \quad \text{where } \mathbf{E} \sim N_{p,n}(\mathbf{0}, \Sigma, \mathbf{I}_n)$$

The expectation of $\mathbf{Y}$ (the systematic component of the model) and the variance of $\mathbf{E}$ (the random component of the model) are given by $E(\mathbf{Y}) = \mathbf{ZBX}$ and $Var(\mathbf{Y}) = \mathbf{I}_n \otimes \Sigma$, respectively. To avoid high-dimensional problems, the rank of $\mathbf{X}$ (the between individual design matrix) is assumed to be less than the number of groups k , that is $Rank(\mathbf{X}) = r \leq k$ and $\mathbf{Z}$ (the within individual design matrix) is also assumed to be of full rank. That is $Rank(\mathbf{Z}) = q$, where $q - 1$ is the degrees of polynomial representing the mean structure.

In order to handle the missing data, missing either by chance or by design, Kleinbaum defines a model they referred to as the Generalized Growth Curve Model (GGCM). This model is given by:

$$E(\mathbf{Y}_t) = \mathbf{G}_t \mathbf{ZBX}_t, \quad t = 1, \dots, u$$

$$Var(\mathbf{Y}_t) = \mathbf{I}_{n_t} \otimes \mathbf{G}_t \Sigma \mathbf{G}_t, \quad t = 1, \dots, u$$

where $\mathbf{Y}_t$ has dimensions $(p_t \times n_t)$; $\mathbf{X}_t$ has dimensions $(m \times n_t)$; $\mathbf{G}_t$ is an incidence matrix of 0's and 1's and has dimensions $(p_t \times p)$; and $\mathbf{Z}$, $\mathbf{B}$, $\mathbf{\Sigma}$ are as defined in the traditional GCM. Note that the within individual design matrices are modified implicitly through the incidence matrices and depending on the missing data pattern. On the other hand, different between individual matrices are created for different subsets of the data, which again depends on the missingness pattern. Note also that we assume that there are n experimental units (eg. individuals) and p time points $(t_1, t_2, \dots, t_p)$ at which measurements are taken. The p time points correspond to p repetitive measurements $V_1, V_2, \dots, V_p$. The n individuals are divided into u disjoint sets of individuals $S_1, S_2, \dots, S_u$ where S_j contains n_t individuals. For each individual in S_t , measurements are taken on $p_t (p_t \leq p)$ time points, leading to the response variates $V_{t1}, V_{t2}, \dots, V_{tp_t}$. No two distinct sets, S_t and $S_{t'}$, can have measurements at the same p_t time points (although two sets may have the same number of measurements, that is, $p_t = p_{t'}$). Furthermore, it is assumed, similar to the GCM, that $\mathbf{Y}_t$ and $\mathbf{Y}_{t'}$ are independent if $t \neq t'$, and that the columns of $\mathbf{Y}_t$, for any t , are independent and follow a multivariate normal distribution [37].

To illustrate the GGCM, consider the dental data presented in Table 3.1. We observe that there are 5 subsets with different data structures (with respect to whether or not the individuals have missing values at the same time points). As such, we need to create 5 different sets of data matrices (denoted by $\mathbf{Y}_t$) along with the corresponding incidence matrices (denoted by $\mathbf{G}_t$) and between-individual matrices (denoted by $\mathbf{X}_t$). The first subset involves individuals with complete data points (i.e. measurements at all time points), and the 3 matrices for this subset is given by:

$$\mathbf{Y}_1 = \begin{bmatrix} 21.0 & 20.0 & 21.5 & 23.0 \\ 21.0 & 21.5 & 24.0 & 25.5 \\ 20.0 & 21.0 & 21.0 & 22.5 \\ 21.5 & 22.5 & 23.0 & 25.0 \\ 20.0 & 21.0 & 22.0 & 21.5 \\ 16.5 & 19.0 & 19.0 & 19.5 \\ 24.5 & 25.0 & 28.0 & 28.0 \end{bmatrix}^T, \mathbf{G}_1 = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \mathbf{X}_1 = [1 \ 1 \ 1 \ 1 \ 1 \ 1 \ 1]^T.$$

$\mathbf{Y}_2$, $\mathbf{G}_2$ and $\mathbf{X}_2$ are for the subset consisting of only individual 3 (i.e. the only individual with a missing observation at time 3):

$$\mathbf{Y}_2 = [20.5 \ 24.0 \ 26.0]^T, \mathbf{G}_2 = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \mathbf{X}_2 = [1].$$

Note that the incidence matrix $\mathbf{G}_2$ is constructed by deleting the 3rd row of $\mathbf{G}_1$ (the incidence matrix corresponding to complete data) by the zero vector (i.e. the row corresponding to the third time point is deleted).

The matrices $\mathbf{Y}_3$, $\mathbf{G}_3$ and $\mathbf{X}_3$ correspond to a subset consisting of only individual 4, the only individual with missing observation at time point 1:

$$\mathbf{Y}_3 = [24.5 \quad 25.0 \quad 26.5]', \mathbf{G}_3 = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \mathbf{X}_3 = [1].$$

Same as above, the incidence matrix $\mathbf{G}_3$ is constructed by deleting the 1st row of $\mathbf{G}_1$. The other two subsets also consist of single observations. However, they both have missing data at 2 time points, and the corresponding matrices are given by

$$\mathbf{Y}_4 = [22.5 \quad 23.5]', \mathbf{G}_4 = \begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}, \mathbf{X}_4 = [1],$$

and

$$\mathbf{Y}_5 = [23.0 \quad 23.0]', \mathbf{G}_5 = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix}, \mathbf{X}_5 = [1].$$

The MLE for $\mathbf{B}$ for the GCM is $\hat{\mathbf{B}} = (\mathbf{Z}'\mathbf{S}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{S}^{-1}\mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}$, where $\mathbf{S} = \mathbf{Y}(\mathbf{I} - \mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}\mathbf{X})\mathbf{Y}'$. This leads to an estimator for the mean trajectory over time ($E[\mathbf{Y}|\mathbf{X}, \mathbf{Z}] = \mathbf{Z}\mathbf{B}\mathbf{X}$), which is often referred to as the fitted (predicted) model or the estimated meas, and is given by

$$\hat{\mathbf{Y}} = \mathbf{Z}\hat{\mathbf{B}}\mathbf{X} = \mathbf{Z}(\mathbf{Z}'\mathbf{S}^{-1}\mathbf{Z})^{-1}\mathbf{Z}'\mathbf{S}^{-1}\mathbf{Y}\mathbf{X}'(\mathbf{X}\mathbf{X}')^{-1}\mathbf{X} = \mathbf{P}_Z\mathbf{Y}\mathbf{P}_X,$$

where $\mathbf{P}_Z$ and $\mathbf{P}_X$, are projections with respect to the within and between design matrices, respectively. Because of this bilinear projection, the GCM is often referred to as a bilinear regression mode. Observe that $\mathbf{Z}\mathbf{B}\mathbf{X}$ is an estimable linear function, which Kleinbaum exploited in their inference involving the GGCM [37]. Such estimable linear functions are also important in general linear hypotheses, where tests (eg. likelihood ratio test) involving the mean parameters of the GCM are established.

Consider the GGCM and sets of estimable linear functions of the form $\mathbf{C}\mathbf{B}\mathbf{D}$, where $\mathbf{C}$ and $\mathbf{D}$ are known matrices of dimensions $g \times q$ and $k \times v$, respectively. We first vectorize the matrix $\mathbf{C}\mathbf{B}\mathbf{D}$ ($g \times v$) and put it into the $gv \times 1$ column vector of form $g(\mathbf{B}) = \mathbf{H}'\text{Vec}(\mathbf{B})$, where $\mathbf{H}' = \mathbf{D}' \otimes \mathbf{C}$ and $\text{Vec}(\mathbf{B}) = (\tilde{\mathbf{B}}_1, \tilde{\mathbf{B}}_2, \dots, \tilde{\mathbf{B}}_q)'$, where $\tilde{\mathbf{B}}_s$ is the s^{th} row of $\mathbf{B}$. On the other hand, we define $\mathbf{y}_t$ ($n_t p_t \times 1$), $t = 1, \dots, u$ by vectorizing $\mathbf{Y}_t$. The BAN estimator of an estimable linear set $\mathbf{H}'\text{Vec}(\mathbf{B})$ is given by Kleinbaum [37]:

$$\mathbf{H}'\text{Vec}(\hat{\mathbf{B}}) = (\mathbf{D}' \otimes \mathbf{C})\text{Vec}(\hat{\mathbf{B}})$$

which can be expanded as

$$\mathbf{H}'\text{Vec}(\hat{\mathbf{B}}) = \mathbf{H}' \left[\sum_{t=1}^u \mathbf{Z}'\mathbf{G}'_t(\mathbf{G}_t\hat{\Sigma}\mathbf{G}'_t)^{-1}\mathbf{G}_t\mathbf{Z} \otimes \mathbf{X}_t\mathbf{X}'_t \right]^{-1} \bullet \sum_{t=1}^u \left[\mathbf{Z}'\mathbf{G}'_t(\mathbf{G}_t\hat{\Sigma}\mathbf{G}'_t)^{-1} \otimes \mathbf{X}_t \right] \mathbf{y}_t.$$

Next, we introduce the matrices $\mathbf{D}$ and $\mathbf{\Omega}$ to help us establish the computational

algorithm. The estimator in Equation 3.2 can be rewritten as

$$\mathbf{H}'Vec(\hat{\mathbf{B}}) = \mathbf{H}'(\mathbf{D}'\hat{\mathbf{\Omega}}^{-1}\mathbf{D})^{-1}\mathbf{D}'\hat{\mathbf{\Omega}}^{-1}\mathbf{y}$$

where $\mathbf{y} = [\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_u]'$ denotes the $N \times 1$ column vector obtained by stacking all the observed data for each individual, and $\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_u$ are column vectors for each individual with their observed data. $N = p_1n_1 + \dots + p_un_u$ is the number of all the observed measurements for each individual.

In the dental example presented in Table 3.1, $\mathbf{y}$ is

$$\mathbf{y} = \begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \\ \mathbf{y}_3 \\ \vdots \\ \mathbf{y}_9 \\ \mathbf{y}_{10} \\ \mathbf{y}_{11} \end{bmatrix} = \begin{bmatrix} 21.0 \\ 21.0 \\ 20.0 \\ \vdots \\ 23.5 \\ 23.0 \\ 23.0 \end{bmatrix} \quad (3.2)$$

which is a 38×1 column vector, containing 38 observations. Therefore, $Vec(\hat{\mathbf{B}})$ is given by

$$Vec(\hat{\mathbf{B}}) = (\mathbf{D}'\hat{\mathbf{\Omega}}^{-1}\mathbf{D})^{-1}\mathbf{D}'\hat{\mathbf{\Omega}}^{-1}\mathbf{y},$$

where $\mathbf{D}$ is given by

$$\mathbf{D} (N \times kq) = \begin{bmatrix} \mathbf{G}_1\mathbf{Z} \otimes \mathbf{X}'_1 \\ \vdots \\ \mathbf{G}_u\mathbf{Z} \otimes \mathbf{X}'_u \end{bmatrix}$$

For the dental example, the $\mathbf{D}$ is given by

$$\mathbf{D} = \begin{bmatrix} \mathbf{G}_1\mathbf{Z} \otimes \mathbf{X}'_1 \\ \mathbf{G}_2\mathbf{Z} \otimes \mathbf{X}'_2 \\ \mathbf{G}_3\mathbf{Z} \otimes \mathbf{X}'_3 \\ \mathbf{G}_4\mathbf{Z} \otimes \mathbf{X}'_4 \\ \mathbf{G}_5\mathbf{Z} \otimes \mathbf{X}'_5 \end{bmatrix} = \begin{bmatrix} 1 & 8 \\ 1 & 8 \\ 1 & 8 \\ \vdots & \vdots \\ 1 & 14 \\ 1 & 8 \\ 1 & 10 \end{bmatrix}$$

which is a matrix of dimensions 38×2 . Note that this represents a within individual design matrix corresponding to the 38 measurements from individuals with complete data. The weight matrix $\mathbf{\Omega}$ is given by

$$\mathbf{\Omega} = \begin{bmatrix} (\mathbf{G}_1\mathbf{\Sigma}\mathbf{G}'_1) \otimes \mathbf{I}_{n_1} & & \\ & \ddots & \\ & & (\mathbf{G}_u\mathbf{\Sigma}\mathbf{G}'_u) \otimes \mathbf{I}_{n_u} \end{bmatrix},$$

where n_u is the number of individuals in the u^{th} subset, and is estimated by replacing Σ by its estimator $\hat{\Sigma}$:

$$\hat{\Omega} = \begin{bmatrix} (G_1 \hat{\Sigma} G_1') \otimes I_{n_1} & & \\ & \ddots & \\ & & (G_u \hat{\Sigma} G_u') \otimes I_{n_u} \end{bmatrix}$$

For the dental data, with the 5 subsets we described above, $\hat{\Omega}$ is given by

$$\hat{\Omega} = \begin{bmatrix} (G_1 \hat{\Sigma} G_1') \otimes I_{n_1} & & \\ & \ddots & \\ & & (G_5 \hat{\Sigma} G_5') \otimes I_{n_5} \end{bmatrix}$$

$$= \begin{bmatrix} 4.86 & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 4.86 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & 4.86 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 6.60 & 0 & 0 \\ 0 & 0 & 0 & \cdots & 0 & 4.86 & 3.39 \\ 0 & 0 & 0 & \cdots & 0 & 3.39 & 3.95 \end{bmatrix}$$

which is a 38×38 sparse matrix.

The straightforward unbiased and consistent estimator of $\hat{\Sigma}$ can be obtained by forming the usual pooled estimate of σ_{rs} (the rs^{th} element of Σ) from individuals for whom the measurements V_r and V_s are both observed (i.e. using pair-wise complete data) and is written using matrix formulations as follows:

$$\hat{\sigma}_{rs} = \frac{1}{N_{rs} - \text{Rank}(\mathbf{D}_{rs})} \mathbf{y}_{rs} \left(\mathbf{I} - \mathbf{D}_{rs}' (\mathbf{D}_{rs} \mathbf{D}_{rs}')^{-1} \mathbf{D}_{rs} \right) \mathbf{y}_{sr}',$$

where $\hat{\sigma}_{rs}$ represents the rs^{th} elements of $\hat{\Sigma}$ for $r, s = 1, \dots, p$; N_{rs} is the number of individuals contributing to the calculations of $\hat{\sigma}_{rs}$; $\mathbf{y}_{rs}$ is a row vector of length N_{rs} consisting of observation row vector on V_r that corresponds to the experimental units on which both V_r and V_s are observed; $\mathbf{y}_{sr}$ is the $1 \times N_{sr}$ observation row vector on V_s that corresponds to the experimental units on which both V_s and V_r are observed; $\mathbf{D}_{rs}$ is the $k \times N_{rs}$ design matrix, consisting of a row of $\mathbf{X}_t$ matrix, corresponding to $\mathbf{y}_{rs}$.

For instance, for the dental data presented in Table 3.1, $\hat{\sigma}_{11}$ and $\hat{\sigma}_{12} = \hat{\sigma}_{21}$ are calculated as:

$$\hat{\sigma}_{11} = \frac{1}{N_{11} - \text{Rank}(\mathbf{D}_{11})} \mathbf{y}_{11} \left(\mathbf{I} - \mathbf{D}_{11}' (\mathbf{D}_{11} \mathbf{D}_{11}')^{-1} \mathbf{D}_{11} \right) \mathbf{y}_{11}'$$

where $N_{11} = 9$, $\mathbf{D}_{11} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix}$, $\text{Rank}(\mathbf{D}_{11}) = 1$, $\mathbf{I}$ is a 9×9 identity matrix and $\mathbf{y}_{11} = \begin{bmatrix} 21 & 21 & 20.5 & 20 & 21.5 & 23 & 20 & 16.5 & 24.5 \end{bmatrix}$.

$$\hat{\sigma}_{12} = \frac{1}{N_{12} - \text{Rank}(\mathbf{D}_{12})} \mathbf{y}_{12} \left(\mathbf{I} - \mathbf{D}'_{12} (\mathbf{D}_{12} \mathbf{D}'_{12})^{-1} \mathbf{D}_{12} \right) \mathbf{y}'_{21}$$

where $N_{12} = 9$, $\mathbf{D}_{12} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \end{bmatrix}$, $\text{Rank}(\mathbf{D}_{12}) = 1$, and $\mathbf{I}$ is a 9×9 identity matrix, $\mathbf{y}_{12} = \begin{bmatrix} 21 & 21 & 20.5 & 20 & 21.5 & 23 & 20 & 16.5 & 24.5 \end{bmatrix}$ and $\mathbf{y}_{21} = \begin{bmatrix} 20 & 21.5 & 24 & 21 & 22.5 & 23 & 21 & 19 & 25 \end{bmatrix}$.

Similarly, we can compute the remaining elements of $\hat{\Sigma}$ to get:

$$\hat{\Sigma} = \begin{bmatrix} 4.86 & 3.39 & 6.27 & 5.34 \\ 3.39 & 3.95 & 5.34 & 5.18 \\ 6.27 & 5.34 & 6.67 & 6.45 \\ 5.34 & 5.18 & 6.45 & 6.60 \end{bmatrix}$$

Therefore, $\text{Vec}(\hat{\mathbf{B}})$ is given by

$$\text{Vec}(\hat{\mathbf{B}}) = (\mathbf{D}' \hat{\Omega}^{-1} \mathbf{D})^{-1} \mathbf{D}' \hat{\Omega}^{-1} \mathbf{y} = \begin{bmatrix} 16.33 \\ 0.56 \end{bmatrix}$$

Similar to Liski's EM algorithm, Kleinbaum's approach involves several cumbersome matrix specifications and calculations. Moreover, the specifications of the various matrices involved depend on many characteristics of the data and the missingness pattern. Some of the factors, for instance, are the matrices corresponding to the dependent variables in each subset, the incidence matrices, the various between individual design matrices as well as the number of groups, sample size, the number of time points and the degree of the polynomial representing the mean structure. To our knowledge, this method is limitedly implemented in PC program by Guo et al. compiled using GAUSS386i, version 3.0 several decades ago and it may not be feasible anymore [87]. And another numerical example (quadratic mean structure and designed missing pattern) can be found in that paper as well. Moreover, the algorithm was illustrated only using one, linear mean structure and a simple case of missing pattern in the thesis. As part of this thesis work, we generalized the computational algorithm and implemented the algorithm in the R statistical software in such a way that the algorithm is automated for general scenarios.

3.3 Liski's Bayesian Approach

The Bayesian approach for handling missing longitudinal data under the GCM framework was introduced by Liski in 1984 [38]. This paper relies heavily on two methods proposed earlier: the first approach they used is proposed by Lindley and Smith [42], and the second is proposed by Fearn [41]. In this thesis, we chose the second approach, which is not iterative and hence computationally faster and easier [41].

The main idea behind Liski's Bayesian method is to estimate the missing values using individual growth curves, and fill the incomplete data with the estimates obtained. Inference is then conducted using the traditional GCM using completed data consisting of the observed and imputed values. Suppose each individual follows a unique univariate growth curve model with respect to time, which for the i^{th} individual in group j is given by:

$$\tilde{\mathbf{y}}_{ij} = \mathbf{Z}_{ij}\tilde{\boldsymbol{\beta}}_{ij} + \tilde{\boldsymbol{\epsilon}}_{ij}, \text{ where } \tilde{\boldsymbol{\epsilon}}_{ij} \sim N(0, \sigma_j^2 \mathbf{I})$$

$$\tilde{\mathbf{y}}_{ij} \sim N(\mathbf{Z}_{ij}\tilde{\boldsymbol{\beta}}_{ij}, \mathbf{Z}_{ij}\mathbf{C}\mathbf{Z}_{ij}' + \sigma_j^2 \mathbf{I}), \tilde{\boldsymbol{\beta}}_{ij} \sim N(\boldsymbol{\beta}_j, \mathbf{C})$$

where $i = 1, 2, \dots, n_j$ and $j = 1, 2, \dots, m$; $\tilde{\mathbf{y}}_{ij}$ is a $q_{ij} \times 1$ column vector consisting of the measurements corresponding to individual i in group j . For example, $\tilde{y}_{34}$ denotes the observations for the 3rd individual from the 4th group. The design matrix $\mathbf{Z}_{ij}$ is of dimension $q_{ij} \times p$, where $q_{ij} - 1$ is the degrees of the polynomial representing the mean trajectory over time, $\tilde{\boldsymbol{\beta}}_{ij}$ is a row vector of length p representing the coefficients of the polynomials and $\tilde{\boldsymbol{\epsilon}}_{ij}$ represents columns vector of length q_{ij} consisting of the error terms.

Consider first a frequentist inference, the coefficients of the polynomials are estimated from individual growth curves using weighted least square (which leads to the same solutions as the maximum likelihood procedure with the normality assumption with correlated errors):

$$\hat{\boldsymbol{\beta}}_{ij}^* = (\mathbf{Z}_{ij}'\mathbf{S}_{ij}^{-1}\mathbf{Z}_{ij})^{-1}\mathbf{Z}_{ij}'\mathbf{S}_{ij}^{-1}\mathbf{y}_{ij}$$

where $\mathbf{y}_{ij}$ is a column vector corresponding to the observed measurements of individual i in group j ; $\mathbf{S}_{ij}$ is subset of the pooled sample variance-covariance matrix from observed data, which provides an estimate for the variance-covariance between the within individual (across-time) measurements. Note that the dimension of $\mathbf{S}_{ij}$ often varies because of the differences in the number and type of missing observations for a given individual. For instance, for the dental data presented in Table 3.1, the 3rd individual has missing observation at time point 3, hence $\mathbf{S}_{13}$ is a 3×3 covariance matrix obtained by deleting the 3rd row and the 3rd column of $\mathbf{S}^*$, which is calculated as follows using the complete data

$$\mathbf{S}^* = \mathbf{Y}^{*'}(\mathbf{I} - \mathbf{X}^{*'}(\mathbf{X}^*\mathbf{X}^{*'})^{-1}\mathbf{X}^*)\mathbf{Y}^*$$

where $\mathbf{Y}^*$ denotes the data set without missing data, where individual with missing data has been removed. The design matrix $\mathbf{Z}_{ij}$ also depends on the number and pattern of missing data. For example, for the dental data, the 5th individual involving missing data at time points 1 and 2, hence $\mathbf{Z}_{15}$ is constructed by removing the first row and the second row of $\mathbf{Z}$, which is the original within individual design matrix in the GCM and is given by (assuming a linear relationship with time): $\mathbf{Z}$ and $\mathbf{S}$ are given as follows:

$$\mathbf{Z} = \begin{bmatrix} 1 & 8 \\ 1 & 10 \\ 1 & 12 \\ 1 & 14 \end{bmatrix}$$

For the dental data, $\mathbf{S}^*$ is the unbiased sample variance-covariance estimator from complete data, given by

$$\mathbf{S}^* = \begin{bmatrix} 5.64 & 4.14 & 6.27 & 6.28 \\ 4.14 & 3.70 & 5.18 & 4.92 \\ 6.27 & 5.18 & 8.06 & 7.57 \\ 6.28 & 4.92 & 7.57 & 7.95 \end{bmatrix}$$

To illustrate the estimation of the $\tilde{\boldsymbol{\beta}}_{ij}$ vectors, we will use the third individual who has a missing observation at time point 3. For instance, the estimate of $\tilde{\boldsymbol{\beta}}_{13}$ is calculated as follows:

$$\begin{aligned} \hat{\boldsymbol{\beta}}_{31}^* &= (\mathbf{Z}_{31}' \mathbf{S}_{31}^{-1} \mathbf{Z}_{31})^{-1} \mathbf{Z}_{31}' \mathbf{S}_{31}^{-1} \mathbf{y}_{31} \\ &= \left(\begin{bmatrix} 1 & 1 & 1 \\ 8 & 10 & 14 \end{bmatrix} \begin{bmatrix} 5.64 & 4.14 & 6.28 \\ 4.14 & 3.70 & 4.92 \\ 6.28 & 4.92 & 7.95 \end{bmatrix} \begin{bmatrix} 1 & 8 \\ 1 & 10 \\ 1 & 14 \end{bmatrix} \right)^{-1} \begin{bmatrix} 1 & 1 & 1 \\ 8 & 10 & 14 \end{bmatrix} \begin{bmatrix} 5.64 & 4.14 & 6.28 \\ 4.14 & 3.70 & 4.92 \\ 6.28 & 4.92 & 7.95 \end{bmatrix}^{-1} \begin{bmatrix} 20.5 \\ 24.0 \\ 26 \end{bmatrix} \\ &= \begin{bmatrix} 15.40 \\ 0.97 \end{bmatrix}, \end{aligned}$$

where 15.40 and 0.97 represent the intercept and slope for the estimated mean trajectory (growth curve) over time. That is, the mean for this individual, as a function of time, is given by

$$\mu_{31} = 15.40 + 0.97t$$

We can calculate the estimated mean trajectory for the remaining 10 individuals in a similar fashion.

The next step is to estimate the missing observations themselves (denoted by $\tilde{\mathbf{y}}_{ij}^f$). They are estimated using the estimated model parameters and appropriate within individual design matrix, which we denoted by $\tilde{\mathbf{y}}_{ij}^{f(v)}$:

$$\tilde{\mathbf{y}}_{ij}^{f(v)} = \mathbf{Z}_{ij}^f \hat{\boldsymbol{\beta}}_{ij}^{(v)}, \text{ where } \hat{\boldsymbol{\beta}}_{ij}^* \text{ is the initial value.} \quad (3.3)$$

Consider again the 3rd individual in the dental data. The single missing observation (at time point 3) is estimated by:

$$\tilde{\mathbf{y}}_{31}^{(f)} = \mathbf{Z}_{31}^{(f)} \tilde{\boldsymbol{\beta}}_{31}^* = \begin{bmatrix} 1 & 12 \end{bmatrix} \begin{bmatrix} 15.40 \\ 0.97 \end{bmatrix} = \begin{bmatrix} 27.04 \end{bmatrix}$$

Note that $\mathbf{Z}_{31}^{(f)}$ is constructed by selecting the values of the within individual design matrix ($\mathbf{Z}$) corresponding to the missing observation. In this case, the individual has a missing observation at time point 3 (age=12). Note also that the first element of $\mathbf{Z}_{31}^{(f)}$ corresponds to the intercept. Similarly, we can compute $\mathbf{Z}_{41}^{(f)} = \begin{bmatrix} 24.03 \end{bmatrix}$, $\mathbf{Z}_{51}^{(f)} = \begin{bmatrix} 20.5 & 21.5 \end{bmatrix}$, $\mathbf{Z}_{81}^{(f)} = \begin{bmatrix} 23 & 23 \end{bmatrix}$.

Next, we combine the original data for these individuals (individuals with missing observations) and the imputed values. This combined vector is given by

$$\dot{\mathbf{y}}_{ij}^{(v)} = \left(\tilde{\mathbf{y}}_{ij}^{(v)'} , \left(\tilde{\mathbf{y}}_{ij}^f \right)^{(v)'} \right)'$$

which is assumed to follow a normal distribution similar to the individuals with no missing data. Moreover, we denote $\mathbf{Z}_{ij} = \left(\mathbf{Z}_{ij}', (\mathbf{Z}_{ij}^f)' \right)'$ as the design matrix corresponding to the i th individual in the j th group.

For instance, for the dental data presented in Table 3.1, the completed (original and imputed) data for individuals 3, 4, 5 and 8 are given by $\dot{\mathbf{y}}_{31} = [20.50 \ 24.00 \ 27.00 \ 26.00]$, $\dot{\mathbf{y}}_{41} = [24.03 \ 24.50 \ 25.00 \ 26.50]$, $\dot{\mathbf{y}}_{51} = [20.5 \ 21.5 \ 22.5 \ 23.5]$, $\dot{\mathbf{y}}_{81} = [23 \ 23 \ 23 \ 23]$.

These vectors combined with the vector of measurements for the remaining 7 girls in the data (with no missing observations) will then be used to provide initial values for the iterative Bayesian algorithm we will present next.

We first introduce the parameter $\hat{\beta}_{ij}^{(v)}$, which is an estimator for $\tilde{\beta}_{ij}^{(v)}$ at the v th iteration and summarize the steps needed in above iterative algorithm, which is given by

$$\hat{\beta}_{ij}^{(v)} = \mathbf{w}_{ij} \hat{\beta}_{ij}^{(v-1)} + (I - \mathbf{w}_{ij}) \left(\sum_{k=1}^{n_j} \mathbf{w}_{kj} \right)^{-1} \left(\sum_{k=1}^{n_j} \mathbf{w}_{kj} \hat{\beta}_{kj}^{(v-1)} \right), \quad (3.4)$$

where

$$\hat{\beta}_{ij}^{(v-1)} = (\mathbf{Z}'\mathbf{Z})^{-1} \mathbf{Z}' \dot{\mathbf{y}}_{ij}^{(v-1)} \quad (3.5)$$

$$\mathbf{w}_{ij} = \left(\frac{\mathbf{Z}'\mathbf{Z}}{s_j^2} + \hat{\mathbf{C}}^{-1} \right)^{-1} \frac{\mathbf{Z}'\mathbf{Z}}{s_j^2}$$

Note that, in the above formula, it is assumed that every individual from the same group shares the same weight calculated from all individuals in that group. Note also that the above steps as well as the steps presented in Equation 3.5 are iterative, and the estimates are updated at each iteration until convergence.

In order to calculate the weight $\mathbf{w}_{ij}$, we need the values of s_j^{-2} and $\hat{\mathbf{C}}^{-1}$, which are calculated using a method proposed by Fearn [41], where a Bayesian approach is used. And we take the variance s_j^2 to be equal to s^2 , where s_j^2 is the estimate of σ^2 , and $i = 1, 2, \dots, n_j$, $j = 1, 2, \dots, m$.

In practice the variances σ_j^2 and the covariance matrix $\mathbf{C}$ for parameters from polynomial function for the assumed mean trajectory over time are unknown, Fearn's approach estimates them using a Bayesian approach, where, following the Lindley and Smith ([42]) assumes that $\mathbf{C}^{-1}$ has an inverted wishart distribution with ρ degrees of freedom and matrix $\mathbf{R}$ (that is, $\mathbf{C}$ has a Wishart distribution). Hence, the following representation for the

posterior distribution can be done [41]

$$p(\mathbf{C}^{-1}|\rho, \mathbf{R}) \propto |\mathbf{C}|^{-\frac{1}{2}(\rho-q-1)} \exp\left(-\frac{1}{2}\text{tr}(\mathbf{C}^{-1}\mathbf{R})\right). \quad (3.6)$$

The variance of the observations (across time) for the individuals is assumed to be the same (i.e. $\sigma_j^2 = \sigma^2$ for all j), and thus we only need to specify a prior distribution for σ^2 . It is assumed that $\nu\lambda/\sigma^2$ has a χ^2 distribution with ν degrees of freedom. Hence, we have

$$p(\sigma^2|\nu, \lambda) \propto |\sigma^2|^{-\frac{1}{2}(\nu+2)} \exp\left(-\frac{1}{2}\nu\lambda/\sigma^2\right).$$

This leaves the problem of how to choose the hyper-parameters ν , λ , ρ and $\mathbf{R}$ (the parameters of the prior distributions). The usual situation is that the prior knowledge about the variance is vague, hence we use a non-informative prior by using a very large value. To achieve this, there are no significant objections to setting $\nu = \lambda = 0$, which results in the standard improper vague prior for the within-individual (across time) variance σ^2 . The parameter ρ measures the prior precision concerning $\mathbf{C}^{-1}$, with the minimum value ensuring convergence of distribution Equation 3.6 being $\rho = q$, where $q - 1$ is the degree of the polynomial representing the mean structure (q can also be viewed as the number of parameters). Additionally, we can use the relationship between the expected value of $\mathbf{C}^{-1}$ and $\mathbf{R}^{-1}$, that is $E(\mathbf{C}^{-1}) = \rho\mathbf{R}^{-1}$ [38]. Therefore, $\mathbf{R}$ can be computed from the following approximation:

$$E[\mathbf{C}^{-1}] = \rho\mathbf{R}^{-1} \Rightarrow \mathbf{R} \approx \rho\mathbf{C}, \quad \rho = q$$

$$s_j^2 = \frac{S_j + \nu\lambda}{N_j + \nu - n_jq + 2} \quad (3.7)$$

$$S_j = \sum_{i=1}^{n_j} (\mathbf{y}_{ij} - \mathbf{Z}_{ij}\hat{\boldsymbol{\beta}}_{ij})'(\mathbf{y}_{ij} - \mathbf{Z}_{ij}\hat{\boldsymbol{\beta}}_{ij}) \quad (3.8)$$

$$\hat{\mathbf{C}} = \frac{\sum_{j=1}^m \mathbf{S}_{\beta_j} + \mathbf{R}}{n + \rho - q - 1 - m} \quad (3.9)$$

$$\mathbf{S}_{\beta_j} = \sum_{i=1}^{n_j} (\hat{\boldsymbol{\beta}}_{ij} - \hat{\boldsymbol{\beta}}_i)(\hat{\boldsymbol{\beta}}_{ij} - \hat{\boldsymbol{\beta}}_i)' \quad (3.10)$$

$$\hat{\boldsymbol{\beta}}_j = \frac{\sum_{i=1}^{n_j} \hat{\boldsymbol{\beta}}_{ij}}{n_j} \quad (3.11)$$

where $i = 1, 2, \dots, n_j$, $j = 1, 2, \dots, m$. For the meaning and the values of several defined parameter in Equation (3.7) to (3.11), N_j is the number of observations in j^{th} group, ν and λ are assumed as 0, n_j is the number of individuals in j^{th} group, q is the degree of the polynomial plus 1, m is the number of groups, ρ is equal to q .

For the dental data example, $q = 2$ (representing the slope and intercept in the assumed mean trajectory over time. The following values are used in Fearn's paper [41], which we

use in our simulations as well:

$$\mathbf{C} = \begin{bmatrix} 1.00 & 0.00 \\ 0.00 & 0.10 \end{bmatrix} \Rightarrow \mathbf{R} = 2\mathbf{C} = \begin{bmatrix} 2.00 & 0.00 \\ 0.00 & 0.20 \end{bmatrix}$$

Note that we have $n = 11$ individuals in the data one group ($m = 1$). Following Fearn's paper, we will also make an assumption that $\lambda = \nu = 0$ [41]. Therefore, using the initial values we computed earlier, we can now obtain the following numerical for the dental data:

$$\hat{\beta}_1 = \frac{\sum_{i=1}^{n_j} \hat{\beta}_{ij}}{n_i} = \frac{\sum_{i=1}^{n_1} \hat{\beta}_{i1}}{11} = \begin{bmatrix} 17.20 \\ 0.49 \end{bmatrix}$$

$$\begin{aligned} \mathbf{S}_{\beta_1} &= \sum_{i=1}^{n_j} (\hat{\beta}_{ij} - \hat{\beta}_i)(\hat{\beta}_{ij} - \hat{\beta}_i)' = \sum_{j=1}^{11} (\hat{\beta}_{i1} - \hat{\beta}_1)(\hat{\beta}_{i1} - \hat{\beta}_1)' \\ &= \begin{bmatrix} 66.95 & -4.56 \\ -4.56 & 0.64 \end{bmatrix} \end{aligned}$$

$$\hat{\mathbf{C}} = \frac{\sum_{j=1}^m \mathbf{S}_{\beta_j} + \mathbf{R}}{n + \rho - p - 1 - m} = \frac{\sum_{j=1}^1 \mathbf{S}_{\beta_j} + \mathbf{R}}{n + \rho - p - 1 - m} = \begin{bmatrix} 7.66 & -0.51 \\ -0.51 & 0.09 \end{bmatrix},$$

$$S_1 = \sum_{i=1}^{n_j} (\mathbf{y}_{ij} - \mathbf{Z}_{ij}\hat{\beta}_{ij})'(\mathbf{y}_{ij} - \mathbf{Z}_{ij}\hat{\beta}_{ij}) = \sum_{i=1}^{11} (\mathbf{y}_{i1} - \mathbf{Z}_{i1}\hat{\beta}_{i1})'(\mathbf{y}_{i1} - \mathbf{Z}_{i1}\hat{\beta}_{i1}) = 108.87$$

$$s_1^2 = \frac{S_j + \nu\lambda}{N_j + \nu - n_jp + 2} = \frac{S_1 + \nu\lambda}{N_1 + \nu - n_1p + 2} = 6.05$$

We can now compute $\mathbf{w}_{i1}$, which is the fixed weight parameter for all individuals in the same group (in this case the single group) :

$$\begin{aligned} \mathbf{w}_{i1} &= \left(\frac{\mathbf{Z}'\mathbf{Z}}{s_1^2} + \hat{\mathbf{C}}^{-1} \right)^{-1} \frac{\mathbf{Z}'\mathbf{Z}}{s_1^2} \\ &= \left(\frac{1}{6.05} \begin{bmatrix} 1 & 1 & 1 & 1 \\ 8 & 10 & 12 & 14 \end{bmatrix} \begin{bmatrix} 1 & 8 \\ 1 & 10 \\ 1 & 12 \\ 1 & 14 \end{bmatrix} + \begin{bmatrix} 7.66 & -0.51 \\ -0.51 & 0.09 \end{bmatrix} \right) \\ &\quad \times \left(\frac{1}{6.05} \right) \begin{bmatrix} 1 & 1 & 1 & 1 \\ 8 & 10 & 12 & 14 \end{bmatrix} \begin{bmatrix} 1 & 8 \\ 1 & 10 \\ 1 & 12 \\ 1 & 14 \end{bmatrix} = \begin{bmatrix} 0.32 & 1.82 \\ 0.05 & 0.68 \end{bmatrix} \end{aligned}$$

Now, we can use the initial imputed data (which we denoted by $\dot{\mathbf{y}}_{ij}^{(0)}$) and apply Equation (3.5) to compute initial values for the parameters $\hat{\boldsymbol{\beta}}_{ij}^{(0)}$ corresponding to each individual. Note that that only the estimates for individuals with missing data changes (since the procedure only updates the imputed values), The updated estimates for individuals 3, 4, 5 and 8 in the dental data are given by

$$\hat{\boldsymbol{\beta}}_{31}^{(0)} = \begin{bmatrix} 13.65 \\ 0.98 \end{bmatrix}, \hat{\boldsymbol{\beta}}_{41}^{(0)} = \begin{bmatrix} 20.67 \\ 0.39 \end{bmatrix}, \hat{\boldsymbol{\beta}}_{51}^{(0)} = \begin{bmatrix} 16.50 \\ 0.50 \end{bmatrix}, \hat{\boldsymbol{\beta}}_{81}^{(0)} = \begin{bmatrix} 23.00 \\ 0.00 \end{bmatrix}$$

At each iteration, we can also compute the MLEs of $\hat{\mathbf{B}}$ and $\hat{\boldsymbol{\Sigma}}$ (using the GCM and the completed data with the missing observations imputed) until convergence, where convergence is determined using a threshold set for $\hat{\mathbf{B}}$.

For instance, for the dental data, the estimates at the first iteration are:

$$\hat{\mathbf{B}}^{(1)} = \begin{bmatrix} 17.04 \\ 0.51 \end{bmatrix} \quad \text{and} \quad \hat{\boldsymbol{\Sigma}}^{(1)} = \begin{bmatrix} 3.84 & 2.89 & 3.79 & 3.86 \\ 2.89 & 3.25 & 3.76 & 3.79 \\ 3.79 & 3.76 & 5.15 & 5.02 \\ 3.86 & 3.79 & 5.02 & 5.40 \end{bmatrix}.$$

After 12 iterations, the estimates are

$$\hat{\mathbf{B}}^{(12)} = \begin{bmatrix} 16.78 \\ 0.53 \end{bmatrix} \quad \text{and} \quad \hat{\boldsymbol{\Sigma}}^{(12)} = \begin{bmatrix} 3.71 & 2.78 & 3.90 & 3.97 \\ 2.78 & 3.26 & 3.73 & 3.89 \\ 3.90 & 3.73 & 5.08 & 5.02 \\ 3.97 & 3.89 & 5.02 & 5.51 \end{bmatrix}.$$

Chapter 4

Simulations

We performed extensive simulations to evaluate and compare the performance of the multivariate approaches for handling missing data under the GCM framework (Kleinbaum’s GGCM method, Liski’s Bayesian approach and Liski’s EM algorithm). We also compared these methods with complete case analysis, where list-wise deletion of individuals with missing observations is done as well as the gold-standard, where we used the full data with no missing observations. Since this thesis considers an estimation problem, we used empirical bias and empirical mean square error (MSE) as optimality measures for our performance evaluations. The parameters involved in the estimation are matrices, as such considered element-wise bias and MSE as well as aggregated bias and MSE, where the average of the absolute bias and average of MSE across the elements within a matrix estimator. We provided these aggregated optimality measures separately for $\hat{\mathbf{B}}$ (estimators corresponding to the mean) and $\hat{\mathbf{\Sigma}}$ (variance-covariance estimators). The results of our simulation studies are presented graphically and in Tables, and interpretations of the results and some discussions of the simulation results are also provided in this chapter.

4.1 Simulation Settings

Our simulations involved more than 2,000 scenarios, where each scenario is replicated 1000 times to account for random variation, and to allow calculations of bias and MSE empirically. Without loss of generality, and to mimic real-life scenarios, we used estimators from two real data sets as our true values for both the mean and covariance parameters of the GCM: the dental data first analyzed by Potthoff & Roy [20] and the glucose data (seen in Table A.1 and Table A.2, appendix), both data sets are discussed in Chapter 2. In our simulations, we considered different missingness mechanisms, different percentages of missing values, and a wide range of sample sizes. Details on the simulation specifications that we used to generate our scenarios are provided in Table 4.1.

The following GCM was used to generate the longitudinal data for our simulations:

$$\mathbf{Y} = \mathbf{ZBX} + \mathbf{E}, \quad \text{where } \mathbf{E} \sim N_{p,n}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_n)$$

Table 4.1: Parameters and specifications used to generate data used in our simulation

Parameters	Values
Mean Trajectory	Linear ($q = 2$), Quadratic ($q = 3$)
Number of Time Points	$p = 4, 8$
Number of Groups	$k = 2$
Range of Sample Sizes	$n = 27, 30 - 120$ (<i>interval 2</i>)
Missingness Mechanism	MCAR, MAR, MNAR
Percentage of Missingness	5%, 10%, 20%
Distribution	Multivariate Normal
Total Number of Scenarios	2,214

where, we first generated the error matrix $\mathbf{E}$ with appropriate dimensions from a multivariate normal distribution with mean $\mathbf{0}$ and variance-covariance matrix $\mathbf{\Sigma}$, which is of dimension $p \times p$. Details on the true values of $\mathbf{\Sigma}$ (which we will denote by $\mathbf{\Sigma}_0$) corresponding to each scenario will be provided in the results sections of the chapter. Once we generated the error matrix, we specified appropriate within and between individual design matrices (i.e. we specified $\mathbf{Z}$ and $\mathbf{X}$). The within individual design matrix depends on the values of time at which the observations are collected, the number of time points and as well as the assumed the mean structure (eg. linear or quadratic growth curve). On the other hand, the between individual design matrix depends on the total sample size, the number of groups and the sample size corresponding to each group. Next, we specified the true values of $\mathbf{B}$ (the coefficients of the polynomial representing the mean structure), which we will denote by $\mathbf{B}_0$.

The next step in our simulation is to create the missing data. We used three different missingness mechanisms: MCAR, MAR and MNAR. For each missingness mechanism, we created 5%, 10% and 20% missing data. We made the assumption, for all groups in each scenario, that there is at least one individual with full data (i.e. observed at all time points). We also assumed that there is no one individual without any observation. For the MCAR scenarios, we simply replace a random selection of data points as missing value. For the MAR cases, we assumed that the likelihood that an observation is missing depended on group membership. We set different fixed probabilities for observations to be missing, which may be different for different groups. For the MNAR mechanism, we assumed that missingness depended on the value of the missing observation itself, where we set the observations greater than a fixed value to be missing with a fixed probability, while those at or below that fixed value are made missing with another different fixed probability. Such approaches for creating MCAR, MAR and MNAR are proposed by [6, 69, 88].

After generating missing data, we computed the estimators $\hat{\mathbf{B}}$ and $\hat{\mathbf{\Sigma}}$ using the three multivariate methods for handling missing data., We also used the gold-standard approach (assuming no missing data) and complete case analysis (deleting individuals with missing data). The empirical bias and MSE were then calculated based on 1000 simulations of each scenario. In order to show the distribution of bias, we generated 100 samples (of the same scenario). That is, we calculated 100 biases for each scenario, and the results from these 100 samples are presented using scatter plots and tables. For MSE, we replicated

each scenario (of 1000 simulations) for various sample sizes, and the results are plotted with respect to sample size to establish consistency of the estimators empirically.

For the first scenario, we provided detailed results including element-wise bias and MSE. However, presenting the results element by element produces lots of figures and tables. To overcome this challenge, we aggregated the bias and MSE matrices, where bias is aggregated using average of absolute bias, and we considered average MSE across all the elements of the matrix estimators. The aggregation was done separately for the mean and covariance parameters. To allow concise presentation of the simulation results, we will present the aggregated bias and MSE. However, we still discuss the element-wise results, which we have still documented, narratively in paragraphs.

Finally, we will use the following abbreviations in tables and figures: for the gold-standard (data set generalized with no missing data), we will use **GS**; **CCA** to denote complete case analysis (with list-wise deletion done); **KB** for Kleinbaum's GGCM approach; **LBS** for Liski's Bayesian approach; and **LEM** represents Liski's EM algorithm.

4.2 Simulation Results

4.2.1 Experiment 1

This experiment involves all scenarios, where we used the dental data to generate the true values of the parameters [20]. We first fitted the growth curve model to the data, where a linear growth curve is assumed to represent the mean trajectory over time for both the girls and the boys. That is, we fitted

$$\mathbf{Y} = \mathbf{Z}\mathbf{B}\mathbf{X} + \mathbf{E}, \quad \text{where } \mathbf{E} \sim N_{4,27}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_{27})$$

where $\mathbf{Y}$ is 4×27 matrix, $\mathbf{Z}$ is 4×2 matrix, $\mathbf{B}$ is 2×2 matrix, $\mathbf{X}$ is 2×27 matrix, $\mathbf{E}$ is 4×27 matrix, and $\mathbf{\Sigma}$ is 4×4 matrix, the details on these matrices are provided in Chapter 2. Note also that the assumption of a linear growth curve to represent the mean for both groups is made after a preliminary graphical investigation, as shown in Figure 2.1.

The true parameter values (for $\mathbf{B}$ and $\mathbf{\Sigma}$) for scenarios under this experiment are set to be the MLEs, where we used the full data set (no missing data), which are given by:

$$\mathbf{B}_0 = \begin{pmatrix} 17.42 & 15.92 \\ 0.48 & 0.81 \end{pmatrix}, \quad \mathbf{\Sigma}_0 = \begin{pmatrix} 5.93 & 3.29 & 4.88 & 4.04 \\ 3.29 & 4.65 & 3.86 & 4.53 \\ 4.88 & 3.86 & 7.94 & 6.20 \\ 4.04 & 4.53 & 6.20 & 7.65 \end{pmatrix}.$$

4.2.1.1 Missing Completely at Random

Here, we considered two groups ($k = 2$), $p = 4$ ($t = 8, 10, 12, 14$) and $n = 27$ ($n_1 = 11$ and $n_2 = 16$), which is a scenario created to mimic the dental data itself. Despite the sample size being small, we generated 5%, 10% and 20% missing values with the MCAR mechanism, which we implemented by simply replacing a random selection of data points as missing value.

The element-wise bias and MSE corresponding to the scenario with 5% MCAR are presented in Table 4.2. As we can see from the table, the three methods seem to produce reasonably accurate estimators for the parameters of the GCM (i.e. small bias is observed). The results indeed show that Liski’s Bayesian method and the EM algorithms are comparable to the gold-standard, and perform much better than Kleinbaum’s GGCM approach. Considering that the missingness here is ignorable and that missingness percentage is relatively small, it is reasonable to expect the complete case analysis to have relatively good performance. We would like to highlight here that these results are quite promising, especially considering that the sample size is very small.

In order to investigate the nature of bias further, we plotted bias for the 100 samples, and corresponding to all the methods considered. From Figure 4.1, we see that bias in estimating $\mathbf{B}$ seems to be randomly distributed around zero for the gold-standard, complete case analysis as well as Liki’s Bayesian method. For the gold-standard, this is to be expected, since we can in fact mathematically show that the MLE of $\mathbf{B}$ is in fact unbiased. From the the results presented in Figure 4.1, we also see that this is true for complete case analysis and the Bayesian approach, despite the limited sample size. On the other hand, Liski’s EM algorithm tends to under estimate $\mathbf{B}$. However, bias still appears to be small, and the estimator has relatively small variability, seen in Figure 4.1 and also in the MSE values presented in Table 4.2.

Table 4.2: Bias and MSE for a scenario involving 5% MCAR, where $n = 27$, $k = 2$, $q = 2$ and the MLEs for the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$.

	Methods				
Parameter	GS	CCA	KB	LBS	LEM
Bias					
b_{01}	0.01463	0.01601	-0.05186	0.00924	-0.05750
b_{02}	0.00095	0.00053	0.06379	0.00323	0.04991
b_{11}	-0.00126	-0.00136	0.01527	-0.00059	0.00689
b_{12}	0.00009	0.00015	-0.01229	-0.00031	-0.00557
σ_{11}	-0.29569	-0.34436	0.33088	-0.52039	-0.28111
σ_{12}	-0.27155	-0.31778	0.52607	-0.35362	-0.26743
σ_{13}	-0.25476	-0.29422	0.71768	-0.46619	-0.25034
σ_{14}	-0.24104	-0.27918	0.91013	-0.36448	-0.23643
σ_{22}	-0.28256	-0.33294	0.83607	-0.41354	-0.27560
σ_{23}	-0.30475	-0.35357	1.13459	-0.37650	-0.30100
σ_{24}	-0.32266	-0.37758	1.44482	-0.46624	-0.31994
σ_{33}	-0.36342	-0.42356	1.54317	-0.64056	-0.35385
σ_{34}	-0.41856	-0.48642	1.96382	-0.63514	-0.41521
σ_{44}	-0.50475	-0.59167	2.49620	-0.75068	-0.48762
MSE					
b_{01}	1.52082	1.90093	441.63844	1.62005	1.50492
b_{02}	0.99537	1.24138	30.87809	1.06376	1.01134
b_{11}	0.01322	0.01680	7.99491	0.01403	0.01311
b_{12}	0.00854	0.01082	0.55551	0.00917	0.00868
σ_{11}	2.70500	3.25843	3.27502	2.79684	2.86139
σ_{12}	1.40879	1.68919	2.35897	1.40139	1.47062
σ_{13}	2.73883	3.33727	4.45945	2.68449	2.81246
σ_{14}	2.22304	2.77543	4.63989	2.18432	2.34218
σ_{22}	1.59796	1.95012	3.20255	1.65343	1.66529
σ_{23}	1.93642	2.32079	4.50860	1.88553	1.98275
σ_{24}	2.01740	2.44314	5.94450	2.02612	2.07754
σ_{33}	5.03045	6.14432	9.93669	5.13184	5.09371
σ_{34}	3.77551	4.58756	11.06179	3.77452	3.83823
σ_{44}	4.27254	5.26653	14.94091	4.50468	4.40623

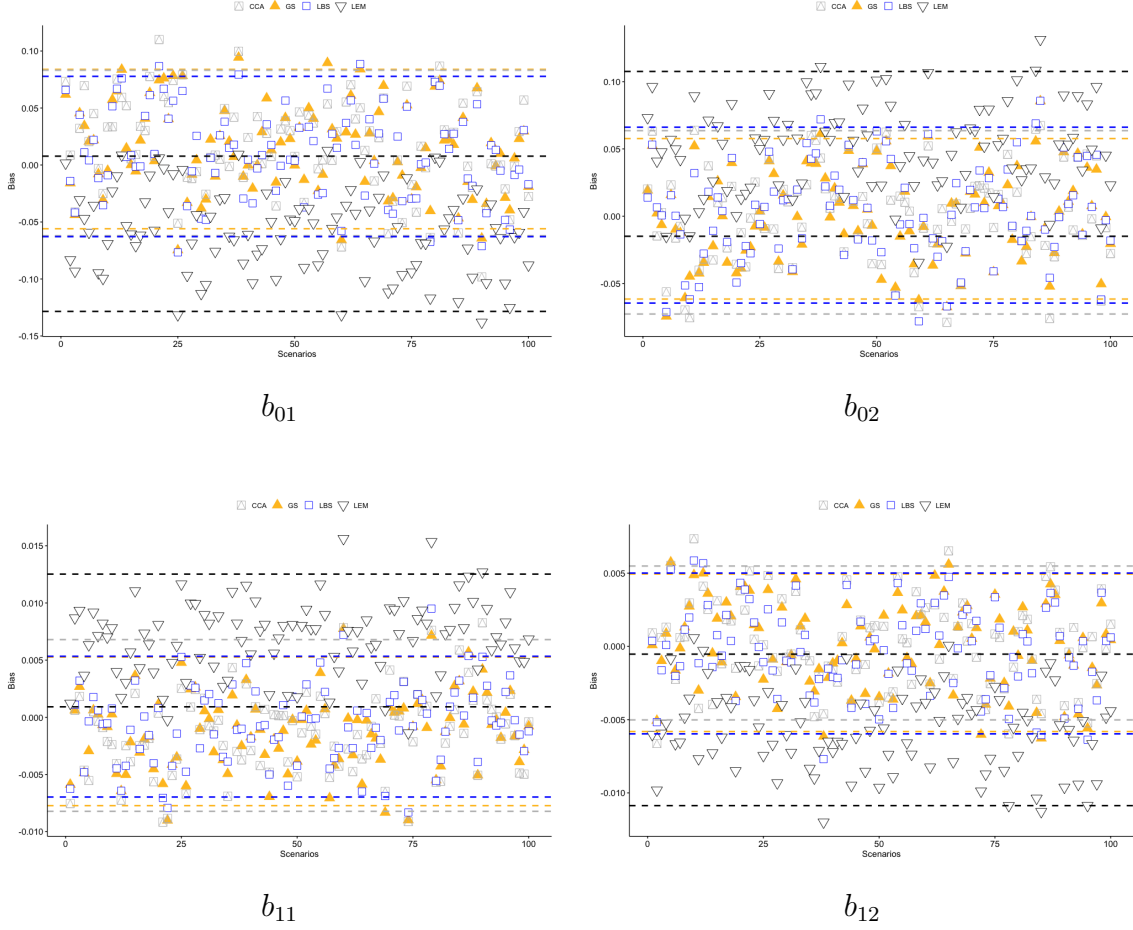


Figure 4.1: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Note that Kleinbaum's GGCM approach is not included in Figure 4.1, this is because of the high variability associated with the estimator (see Figure B.1, Appendix). Although Figure B.1 shows that the method seems to produce an unbiased estimator, the high variability makes it less desirable. This is also reflected in the very high MSE values we observed in Table 4.2.

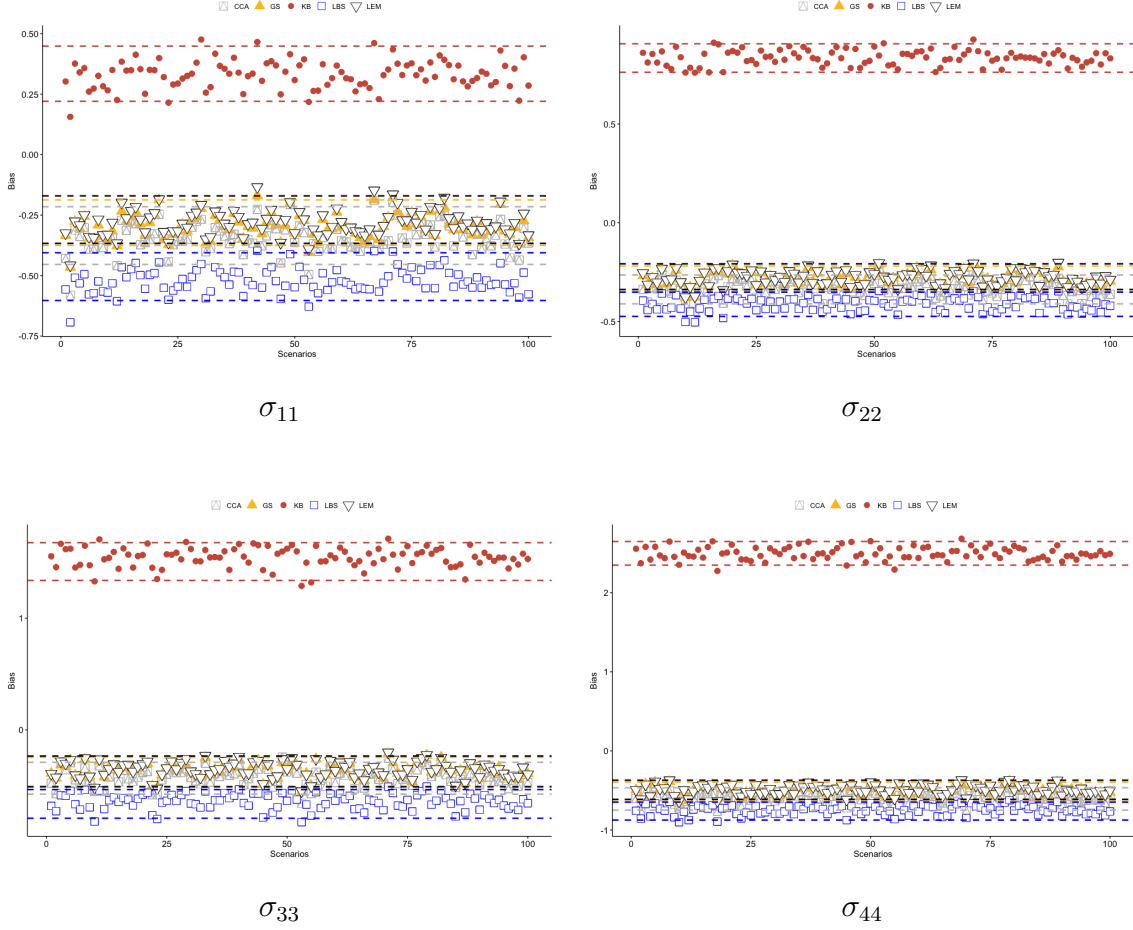


Figure 4.2: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

From Figure 4.2, we can see that Liski’s EM algorithm is comparable to the gold-standard in estimating the within-individual (across-time) variances (the diagonal elements of $\mathbf{\Sigma}$). The negative bias we observe in Figure 4.2 is to be expected, since it can be mathematically shown that the MLE underestimates the true variance-covariance matrix. Kleinbaum’s method seems to overestimate the true variances, while the Bayesian method underestimates the variances. However, unlike the results we saw for $\mathbf{B}$, Kleinbaum’s methods seems to be relatively stable (less variability is observed). Similar results are observed for covariance estimates (Figure 4.3)

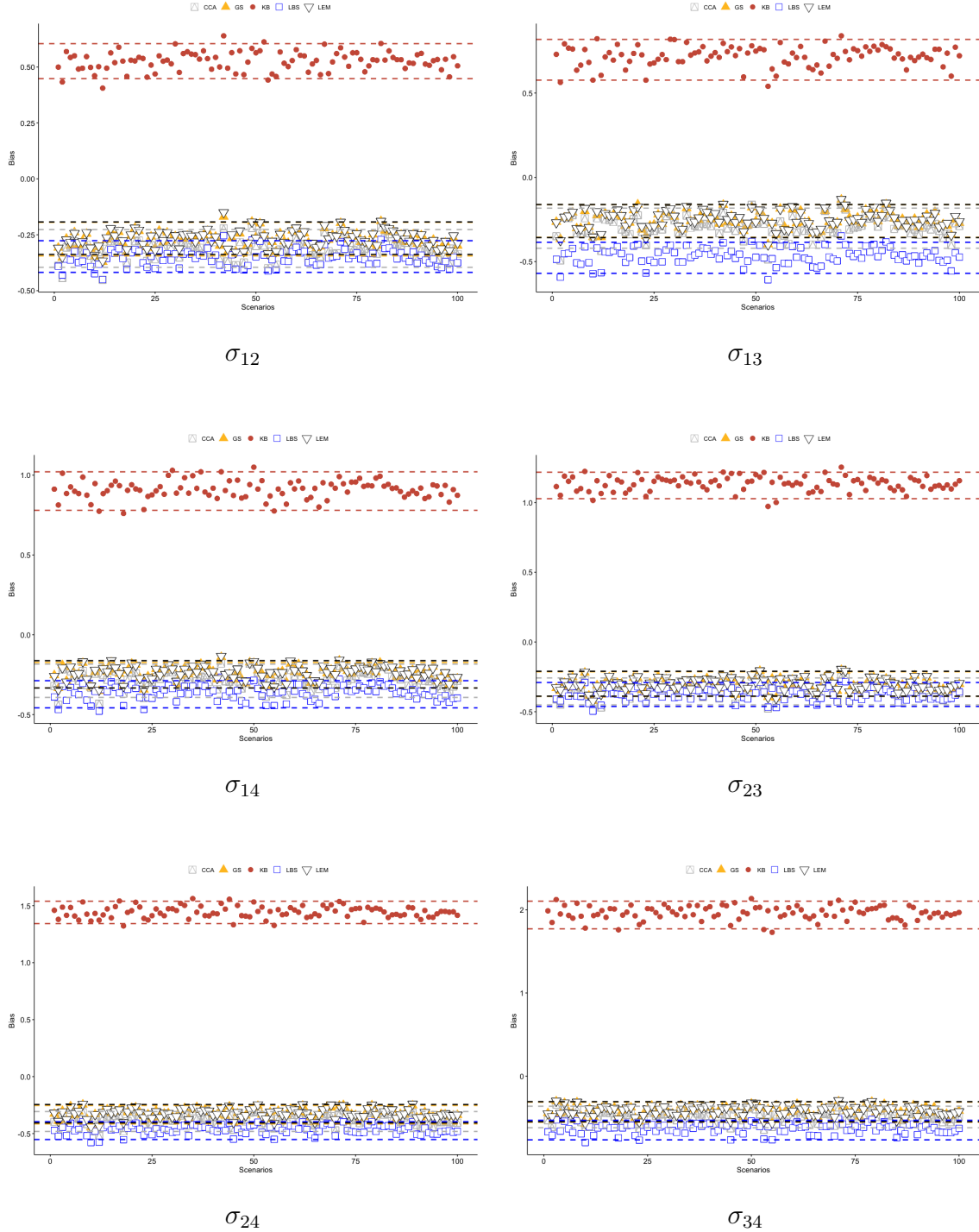


Figure 4.3: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Consider now the MCAR scenarios with 10% and 20% missing data. Although we still provide figures for element-wise bias, to make the presentations concise, we will provide bias and MSE aggregated across all the elements, but separately for $\mathbf{B}$ and $\mathbf{\Sigma}$.

Table 4.3: Aggregated bias and MSE for scenarios with 10% and 20% MCAR, where $n = 27$, $p = 4$, $q = 2$, and the MLEs from the dental data are used as true values of $\mathbf{B}$ and $\mathbf{\Sigma}$. Bias across the elements of matrix estimators are aggregated using average absolute bias and MSE is aggregated as an average of the element-wise MSEs.

		Methods				
		GS	CCA	KB	LBS	LEM
10%						
Bias	$\mathbf{B}$	0.0042	0.0029	1.0623	0.0023	0.0730
	$\mathbf{\Sigma}$	0.3260	0.4621	1.1937	0.7247	0.3060
MSE	$\mathbf{B}$	0.6345	1.0302	321.1110	0.7112	0.6311
	$\mathbf{\Sigma}$	2.7706	4.4492	6.9261	2.9884	3.0298
20%						
Bias	$\mathbf{B}$	0.0042	0.0053	0.8387	0.0077	0.1590
	$\mathbf{\Sigma}$	0.3260	0.5608	1.1975	1.1901	0.2517
MSE	$\mathbf{B}$	0.6345	1.9470	49.3417	0.8244	0.7310
	$\mathbf{\Sigma}$	2.7706	9.1883	7.8232	3.6780	3.4444

For scenario with 10% MCAR, we see from Table 4.3 that Liski’s Bayesian method and complete case analysis are more accurate choices (smaller average absolute bias) for estimating $\mathbf{B}$. On the other hand, Liski’s EM algorithm seems to be the most accurate method when estimating $\mathbf{\Sigma}$. Looking at the aggregated MSE values, we observe that Liski’s Bayesian method and Liski’s EM algorithm are two comparable approaches that can be used for estimating both $\hat{\mathbf{B}}$ and $\hat{\mathbf{\Sigma}}$. Although the aggregated bias for Kleinbaum’s method is very small (it is in fact randomly distributed around zero when estimating the mean parameters, indicating unbiasedness), the method is still unstable and produces very large variance, and hence the large MSE values observed in Table 4.3. Similar conclusions can be made for the 10% MCA, however, with increasing the missing percentage, we observe that both bias and MSE for most of the methods increase, which is to be expected. Nevertheless, Kleinbaum’s GGCM approach seems to produce unexpected results (less bias and less MSE for estimating $\mathbf{B}$, as the missingness percentage increases), which perhaps is because of its instability.

From the element-wise bias plots (Figure 4.4), we see that bias in estimating $\mathbf{B}$ seems to be randomly distributed around zero for the gold-standard (as expected). From the results presented in Figure 4.1, we also see that this is true for complete case analysis and the Bayesian approach, despite the limited sample size presence of missing data. On the other hand, Liski’s EM algorithm tends to underestimate some elements of $\mathbf{B}$ and overestimate others. However, bias still appears to be very small and a reasonably small

variability was also observed, seen in Figure 4.4 and also in the MSE values presented in Table 4.3. Similar conclusions can be drawn for 20% MCAR (Figure 4.5), . However, we observe that element-wise bias and MSE increase as the missingness percentage increases, which again is to be expected.

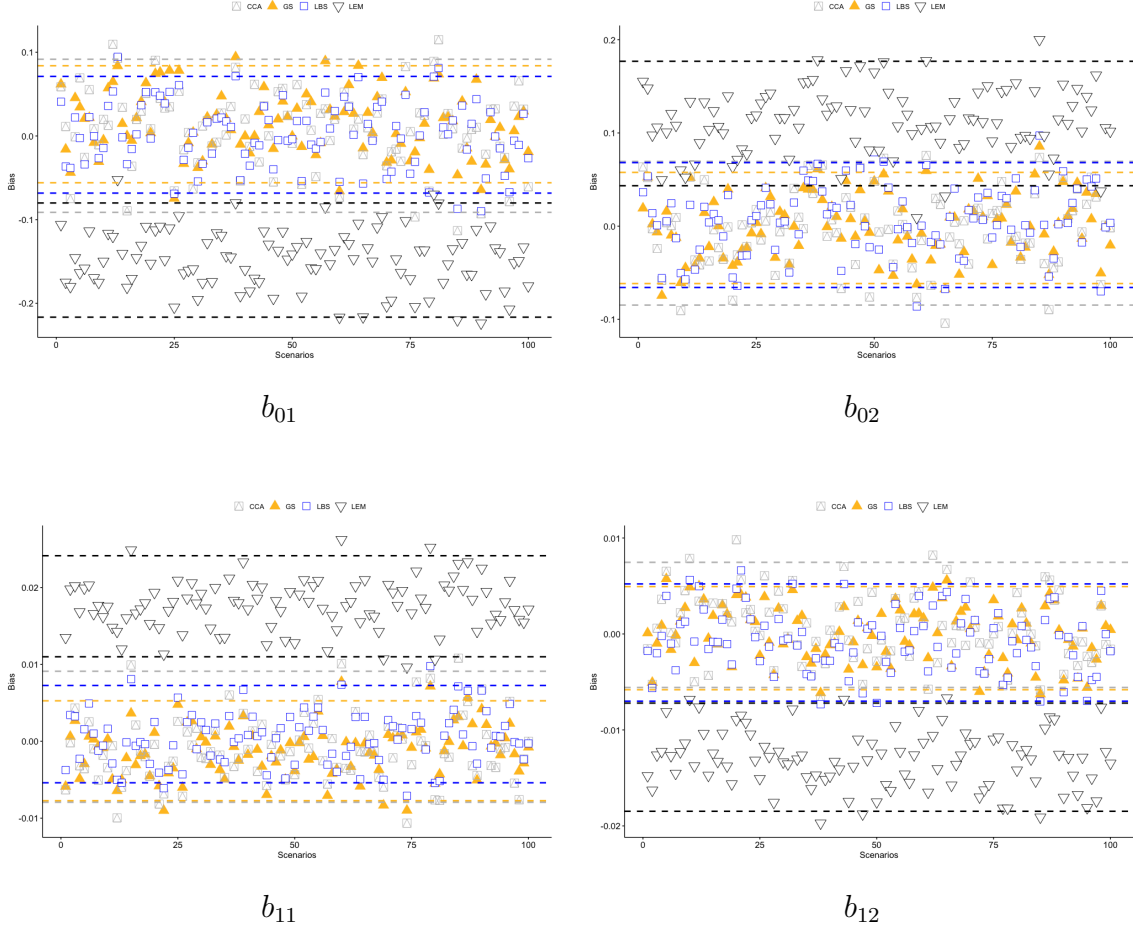


Figure 4.4: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

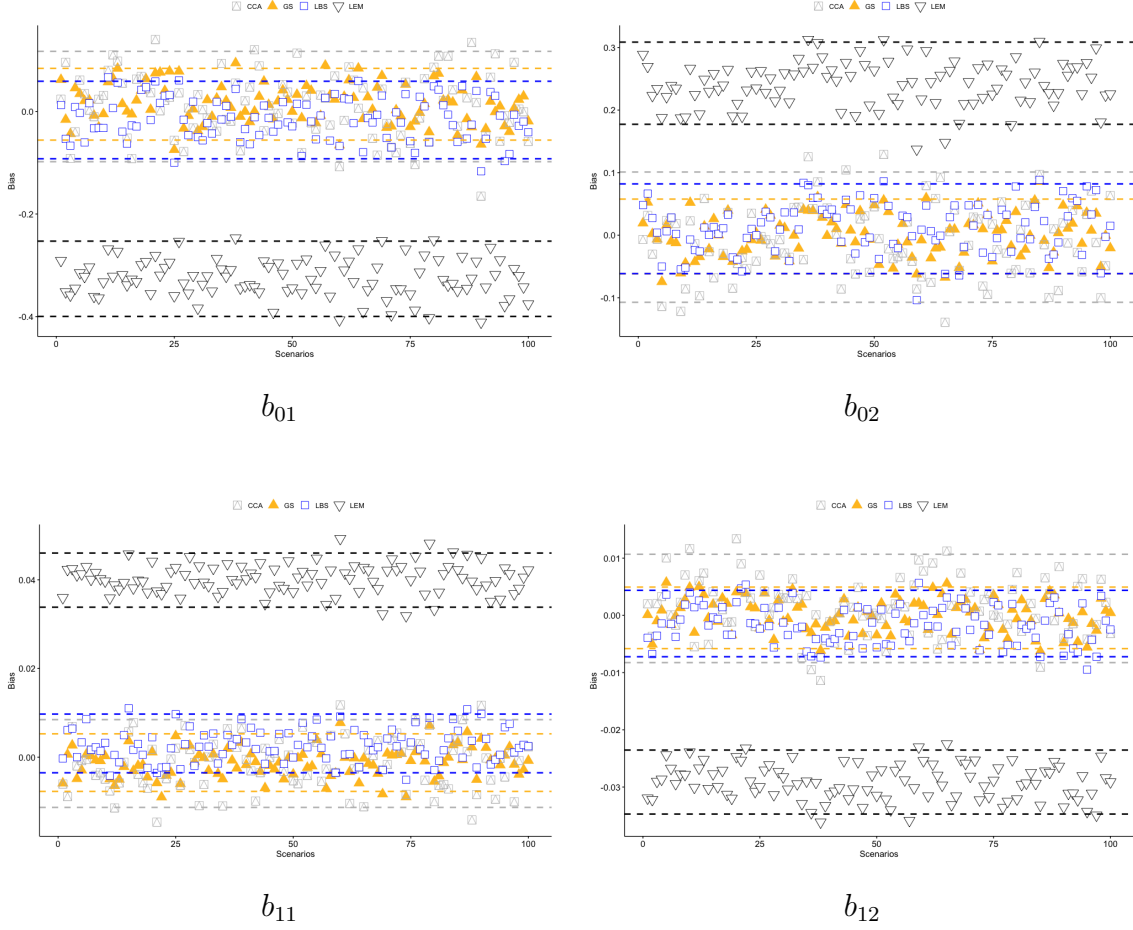


Figure 4.5: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Similar to the scenarios with 5% MCAR, we can see that Liski's EM algorithm for 10% MCAR is comparable to the gold-standard in estimating the within-individual (across-time) variances (the diagonal elements of $\mathbf{\Sigma}$) (Figure 4.6). Kleinbaum's method seems to overestimate the true variances, while the Bayesian method underestimates the variances. Kleinbaum's methods seems to be relatively stable (less variability is observed) in estimating the variances and covariances, as we saw earlier for 5% MCAR. Similar results are observed for covariance estimates (Figure 4.7) and for 20% MCAR scenarios (Figures 4.8 and 4.9).

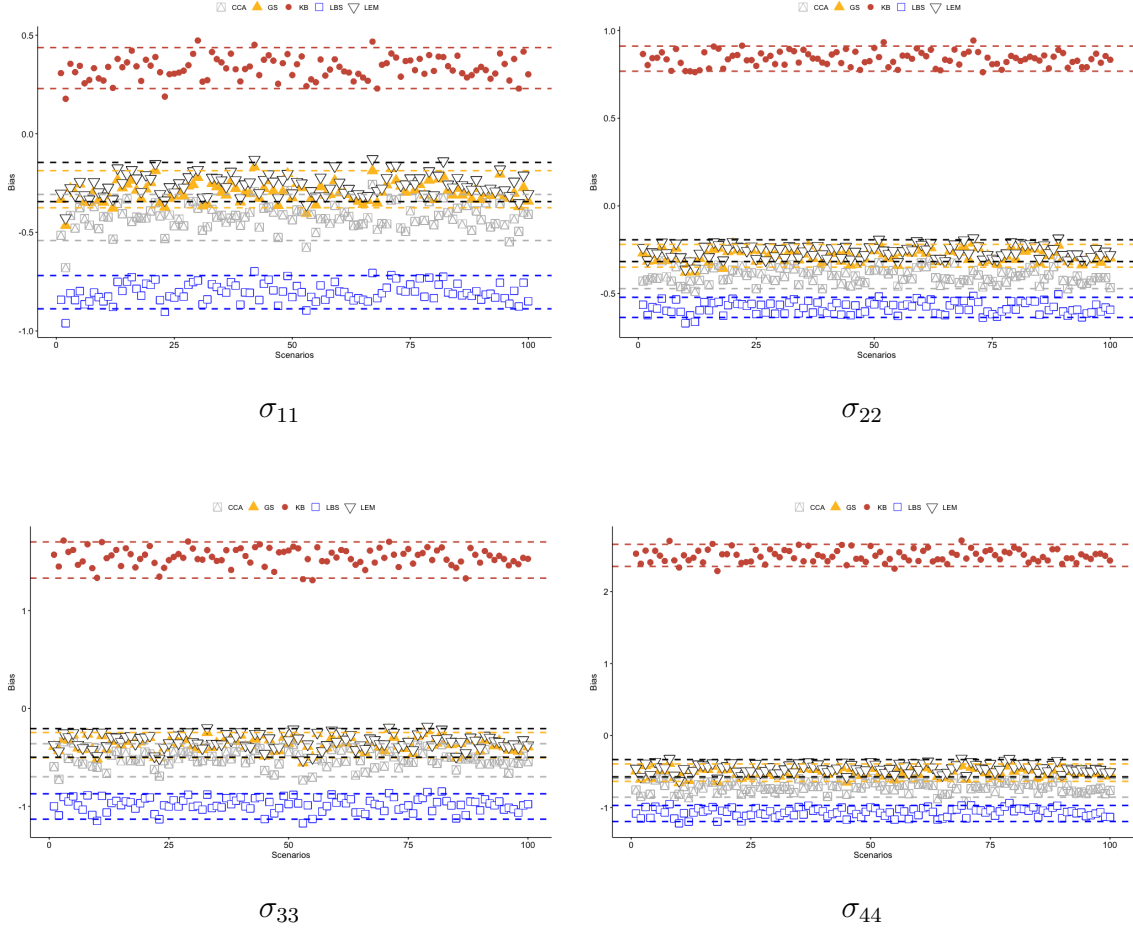


Figure 4.6: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

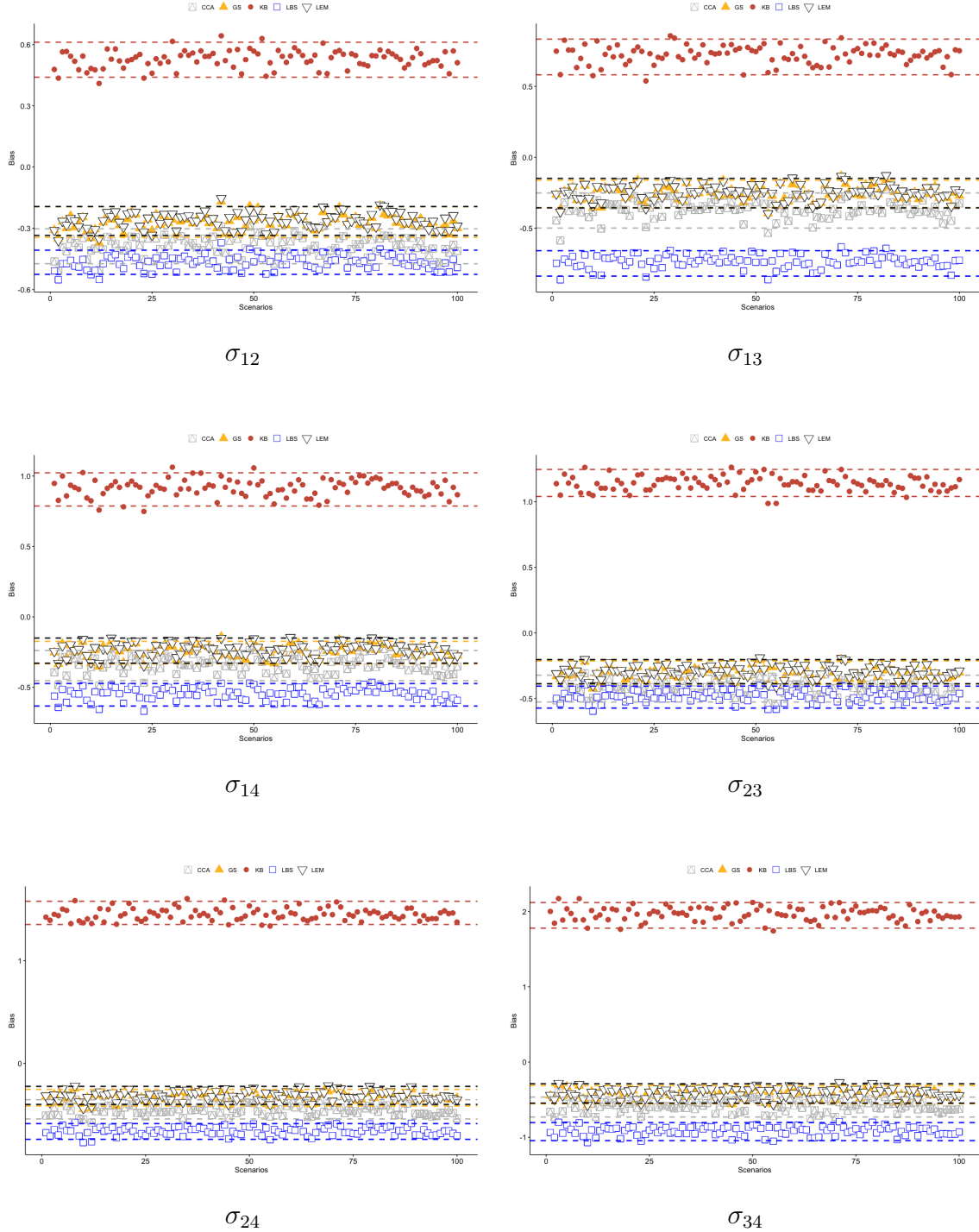


Figure 4.7: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

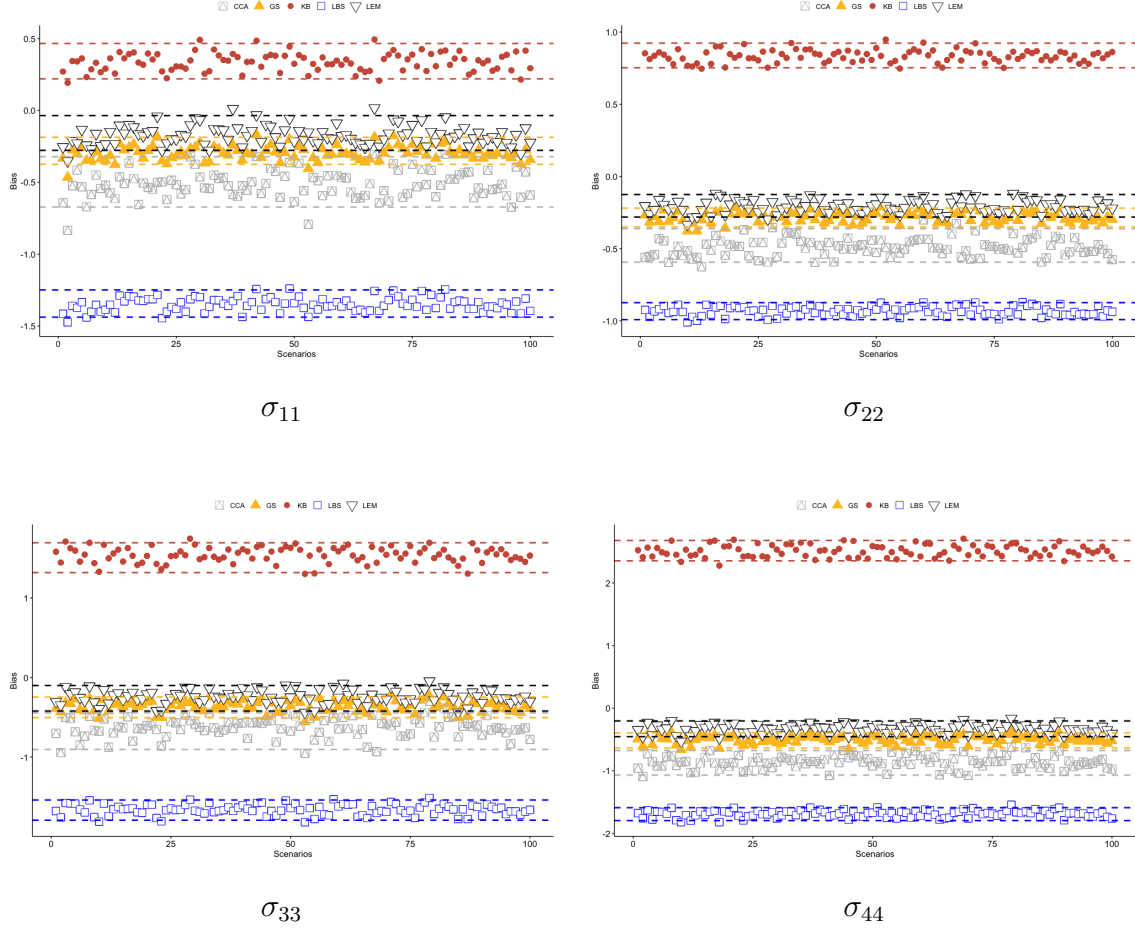


Figure 4.8: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

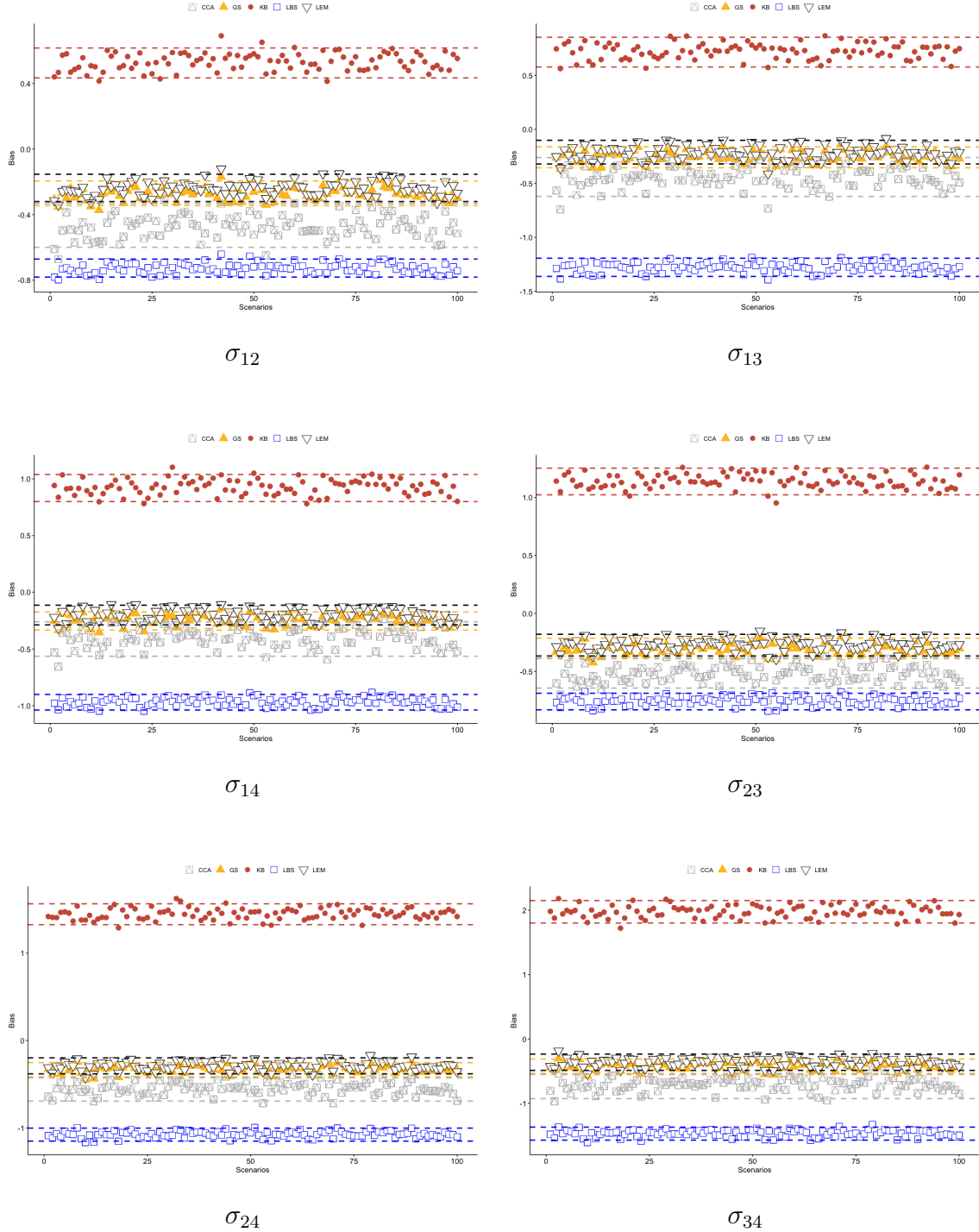


Figure 4.9: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

4.2.1.2 Missing at Random

In this section, we present the simulation results, where we still consider two groups ($k = 2$), $p = 4$ ($t = 8, 10, 12, 14$) and $n = 27$ ($n_1 = 11$ and $n_2 = 16$). However, in this case we consider MAR mechanism with 5%, 10% and 20% percentages of the data missing. We implemented the MAR mechanism by assuming missingness to depend on group membership. In our simulations, we generated the data such that the missingness probability for an observation in Group 1 is 0.1 (10%) and missingness probability of 0.3 (30%) for observations in Group 2. We generated both element-wise and aggregated bias and MSE, which are presented in Tables and Figures.

Table 4.4: Aggregated bias and MSE for scenarios with 5%, 10% and 20% MAR, where $n = 27$, $p = 4$, $q = 2$, and the MLEs from the dental data are used as true values of $\mathbf{B}$ and $\mathbf{\Sigma}$. Bias across the elements of matrix estimators are aggregated using average absolute bias and MSE is aggregated as an average of the element-wise MSEs.

		Methods				
		GS	CCA	KB	LBS	LEM
5%						
Bias	$\mathbf{B}$	0.0042	0.0048	0.1910	0.0038	0.0246
	$\mathbf{\Sigma}$	0.3260	0.3797	1.2045	0.5007	0.3172
MSE	$\mathbf{B}$	0.6345	0.7393	1.0250	0.6552	0.6353
	$\mathbf{\Sigma}$	2.7706	3.3906	6.5911	2.8148	2.8616
10%						
Bias	$\mathbf{B}$	0.0042	0.0040	0.0475	0.0047	0.0623
	$\mathbf{\Sigma}$	0.3260	0.4551	1.2216	0.7319	0.3039
MSE	$\mathbf{B}$	0.6345	0.9461	27.9691	0.7061	0.6449
	$\mathbf{\Sigma}$	2.7706	4.3094	7.2285	2.9600	3.0143
20%						
Bias	$\mathbf{B}$	0.0042	0.0051	3.0856	0.0037	0.1413
	$\mathbf{\Sigma}$	0.3260	0.5599	1.2358	1.2275	0.2559
MSE	$\mathbf{B}$	0.6345	1.8574	4216.3326	0.8406	0.7590
	$\mathbf{\Sigma}$	2.7706	6.9634	8.3385	3.7319	3.5514

From the bias presented in Table 4.4 and Figures 4.10, 4.11 and 4.12, we can see that, in nearly all scenarios involving MAR, complete case analysis and the Bayesian approach led to comparable performance as the gold-standard for estimating $\mathbf{B}$. However, we also observe that the performance of the complete case analysis decreased slightly as the missingness percentage increases. In fact, we can see from Figure 4.10 that element-wise bias for the complete case analysis and Bayesian approach are randomly distributed around zero (as is for the gold-standard). On the other hand, the EM algorithm produced estimators with slightly higher biases, and the bias seems to go in both directions as we can see from Figure 4.10. This indicates that the EM algorithm overestimates or underestimates

elements of $\mathbf{B}$. However, bias associated with the EM algorithm is still very small, and the performance of this method seems to be relatively well for data with small percentage of MAR.

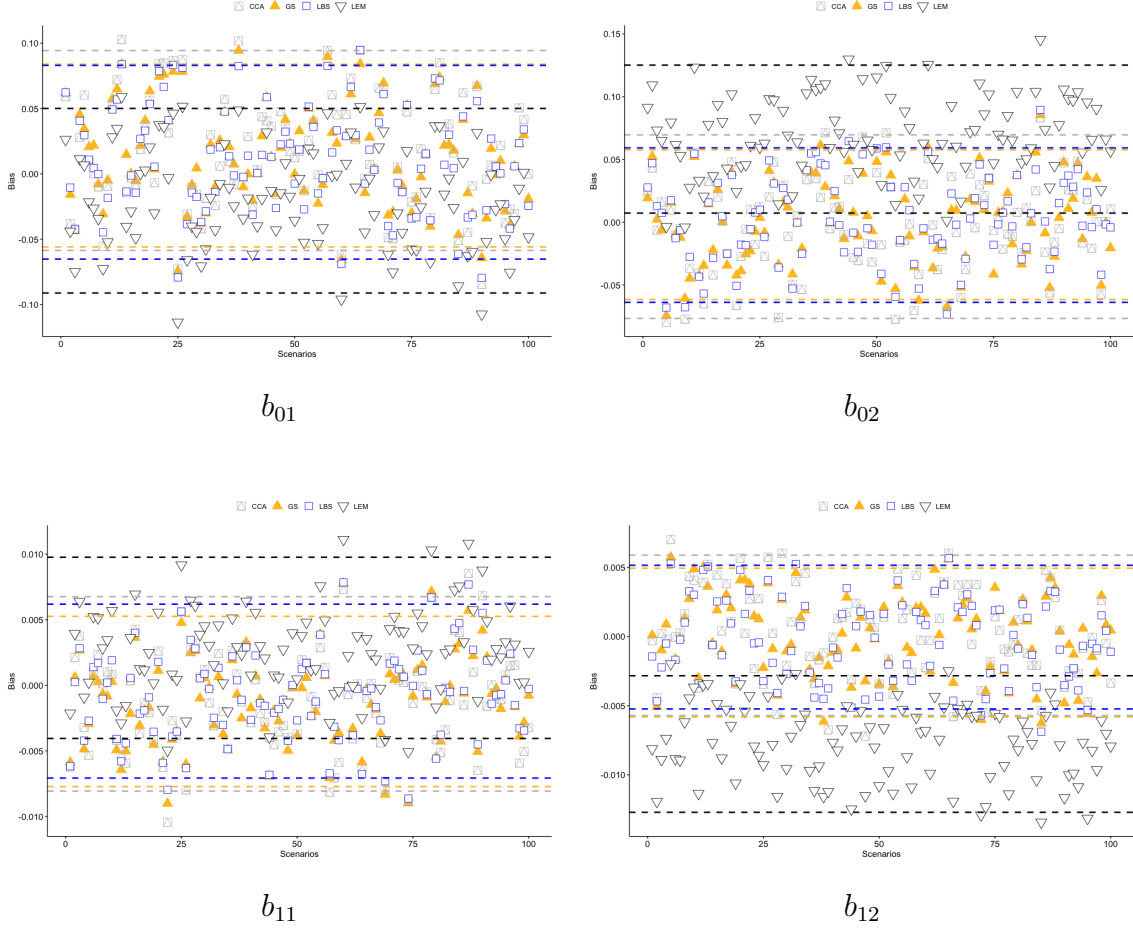


Figure 4.10: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Looking at the values of MSE in Table 4.4, we can see that the EM algorithm is comparable in performance as the gold-standard, and leading to an overall smaller MSE value than the complete case analysis, especially when the missing percentage is higher. On the other hand, our simulation results show that Kleinbaum's GGCM led to the highest bias in estimating $\mathbf{B}$. We can also see from the MSE values that the same instability (high-variability) we observed for the MCAR scenarios were observed for the MAR scenarios. Despite this large MSE value, the element-wise bias associated with $\hat{\mathbf{B}}$ for Kleinbaum's method is still randomly distributed around zero for all the scenarios involving MAR.

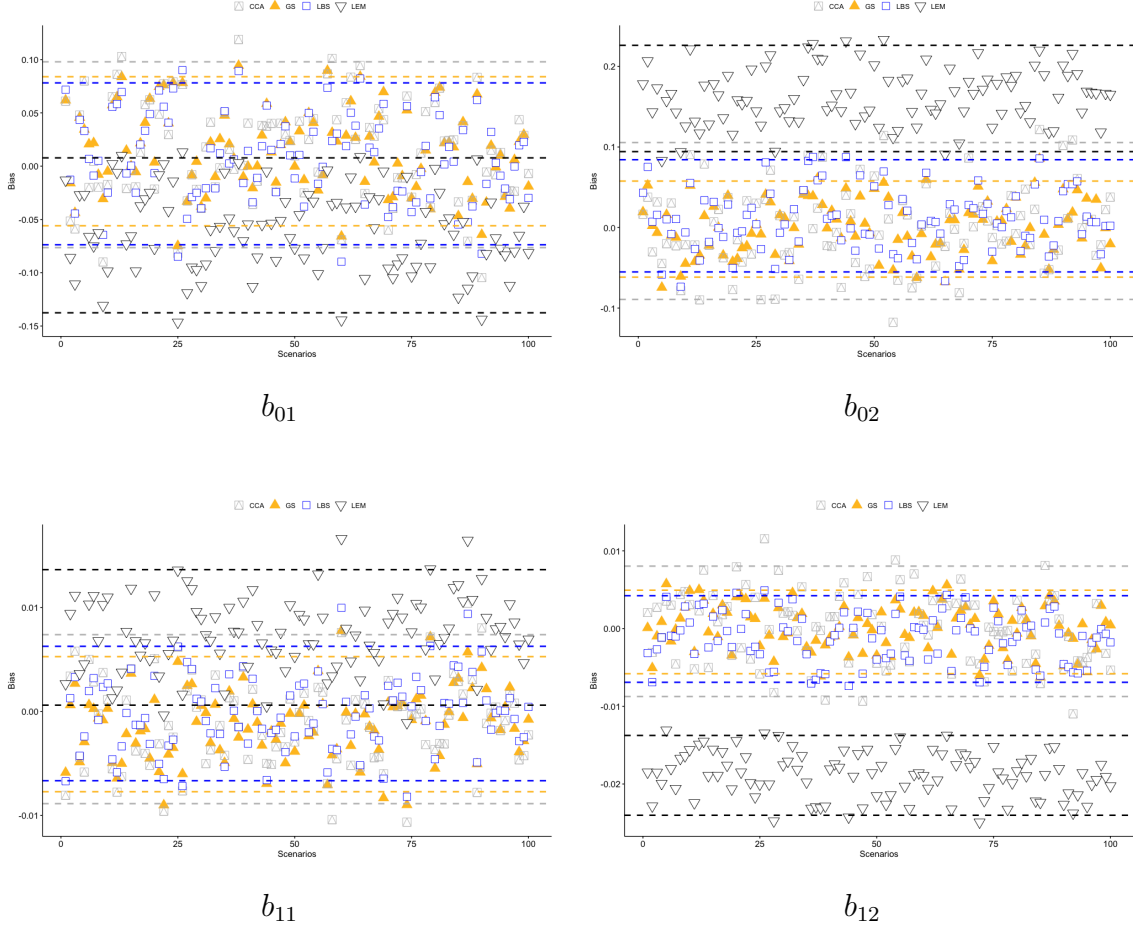


Figure 4.11: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Bias corresponding to the EM algorithm still appears to be small when the percentage of missing data increases. However, an increase in bias is observed as the percentage of missing data increases as it is clearly seen in Figures 4.11 and 4.12, where we observe a significant difference in the accuracy of the EM algorithm, complete case analysis and the Bayesian approach. Nevertheless, the estimator of $\mathbf{B}$ from the EM algorithm still has a reasonably small bias and show small variability across all the scenarios involving MAR, as seen in Figures 4.10, 4.11 and 4.12 as well as in the aggregated MSE values presented in Table 4.4. The results presented in Figures 4.11, 4.12 also show that element-wise bias for the gold-standard (as expected), Bayesian method and complete case analysis still produce unbiased estimators. However, we can observe that the variability associated with the estimator from the complete case analysis is higher, which is also reflected in the aggregated MSE values.

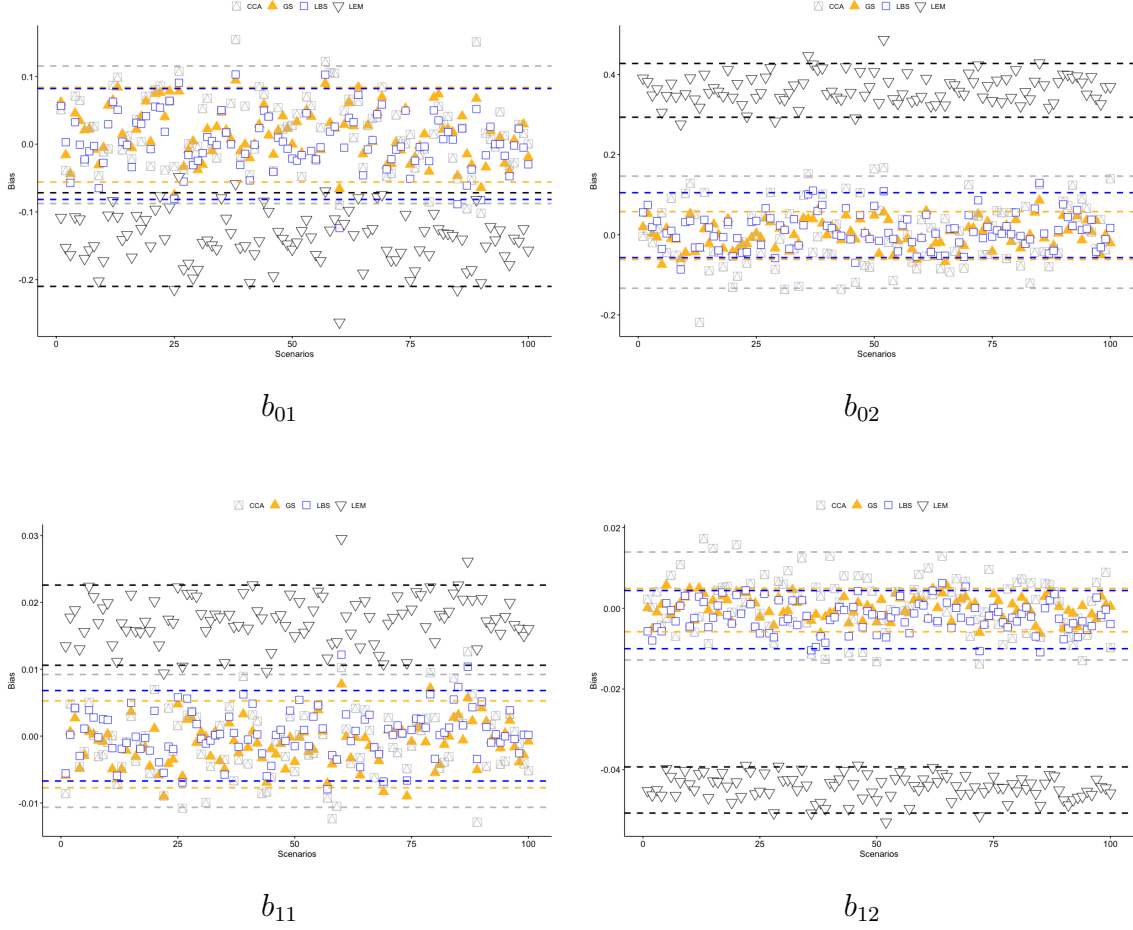


Figure 4.12: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

From Figure 4.13, we can see that Liski's EM algorithm and complete case analysis are comparable to the gold-standard in estimating the within-individual (across-time) variances (the diagonal elements of Σ). As indicated earlier, the negative bias we observe in Figure 4.13 is to be expected, since the MLE underestimates the true variance-covariance matrix. Kleinbaum's method seems to overestimate the true variances, while the Bayesian method under estimates the variances. However, the results show that the magnitude of bias associated with Kleinbaum's method is significantly higher than the Bayesian method. Unlike the results we saw for $\mathbf{B}$, Kleinbaum's method seems to be relatively stable (less variability is observed) in estimating within individual variances. This is also observed in all the scenarios involving MCAR. Similar results are observed for covariance estimates (Figure 4.14), where EM and complete case analysis providing estimators comparable to the gold-standard, and the Bayesian and Kleinbaum underestimating and overestimating, respectively.

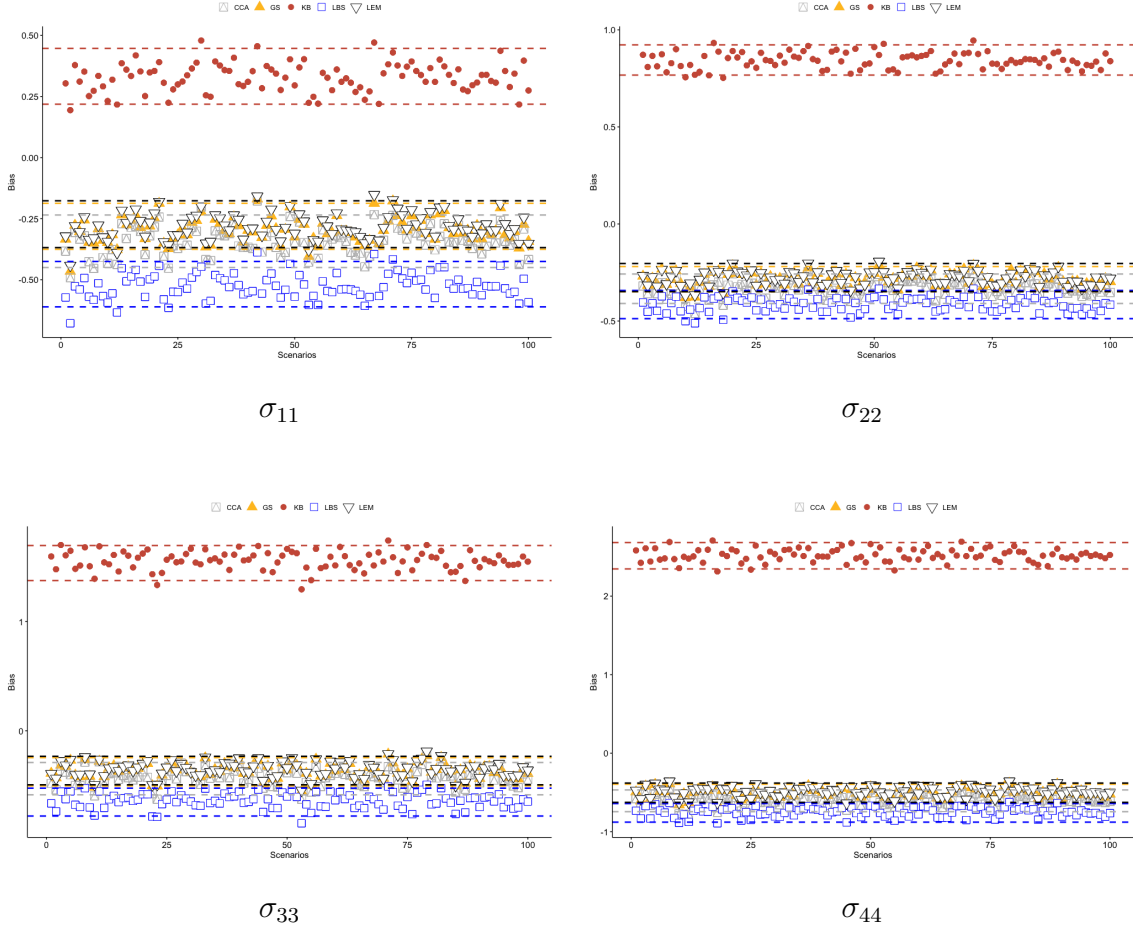


Figure 4.13: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

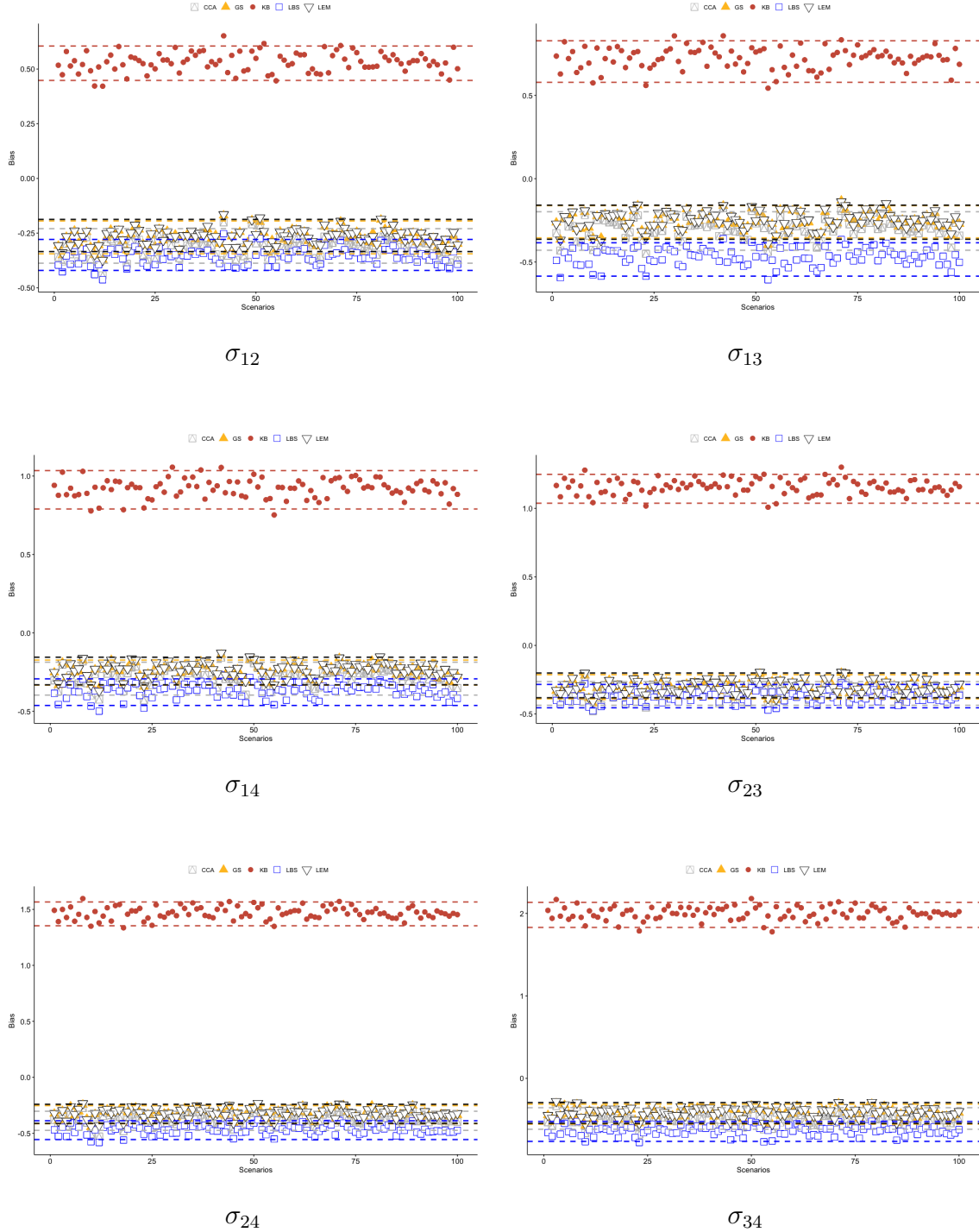


Figure 4.14: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

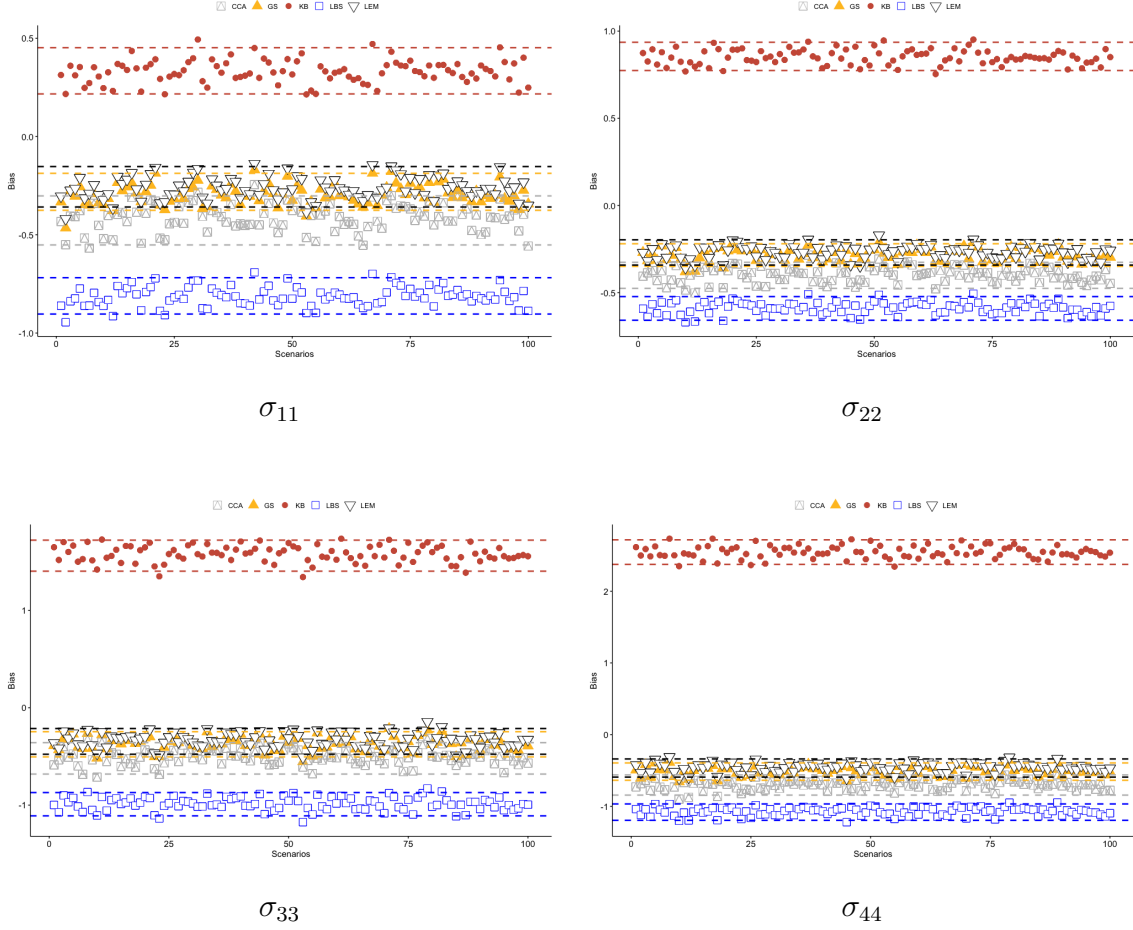


Figure 4.15: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

From Figure 4.15, we can see that Liski’s EM algorithm, when used for data with 10% MAR, is comparable to the gold-standard in estimating the within-individual (across-time) variances (the diagonal elements of $\mathbf{\Sigma}$). We also observe that complete case analysis leads to an estimator with increased negative bias and a relatively higher variability. The increase in bias for the complete case analysis seems to be more pronounced as the percentage of missingness increases (Figure 4.16).

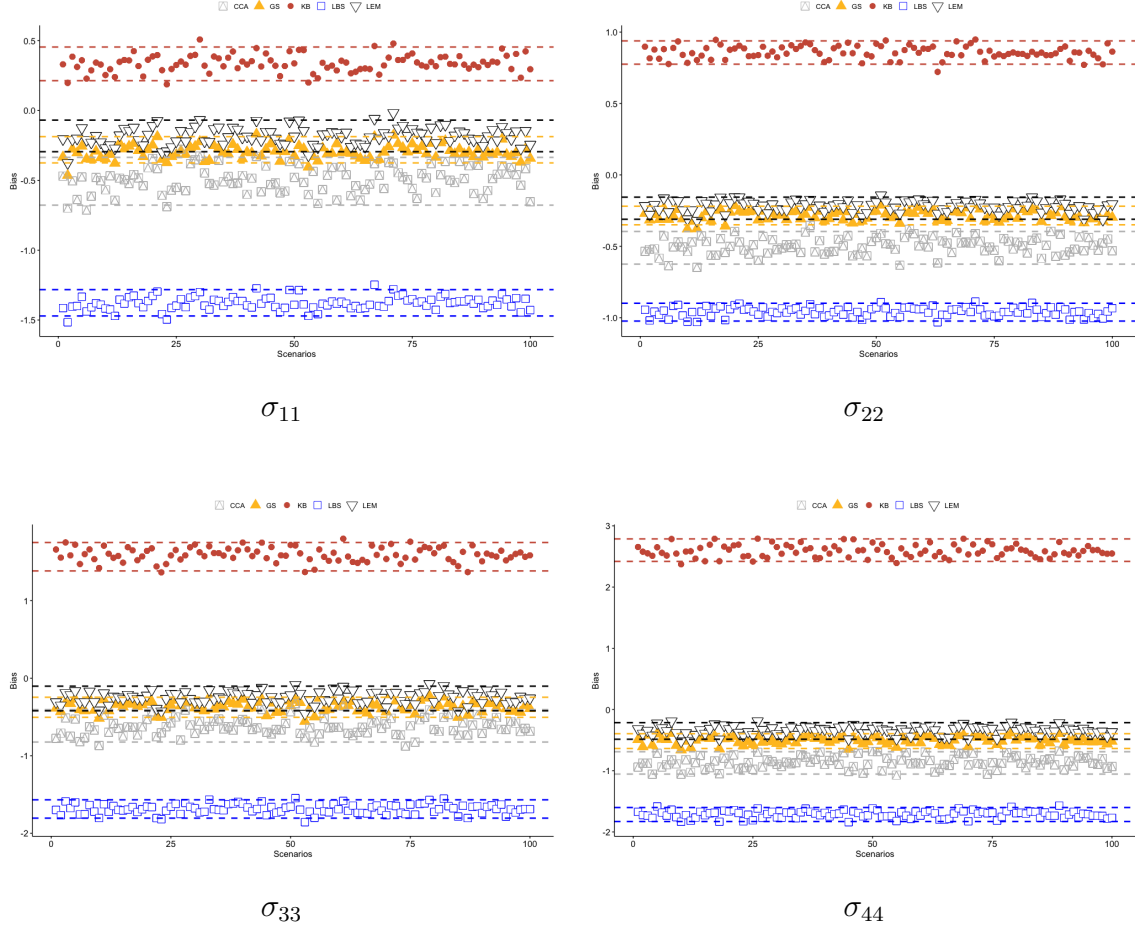


Figure 4.16: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Kleinbaum's method seems to overestimate the true variances significantly, Bias from this also increases as the percentage of missingness increases. However, unlike the results we saw for $\mathbf{B}$, Kleinbaum's method seems to be relatively stable (less variability is observed) in estimating the within-individual variances, this is consistently the case in all the scenarios involving MAR. Similar results were observed for the covariance estimates (Figures 4.17 and 4.18).

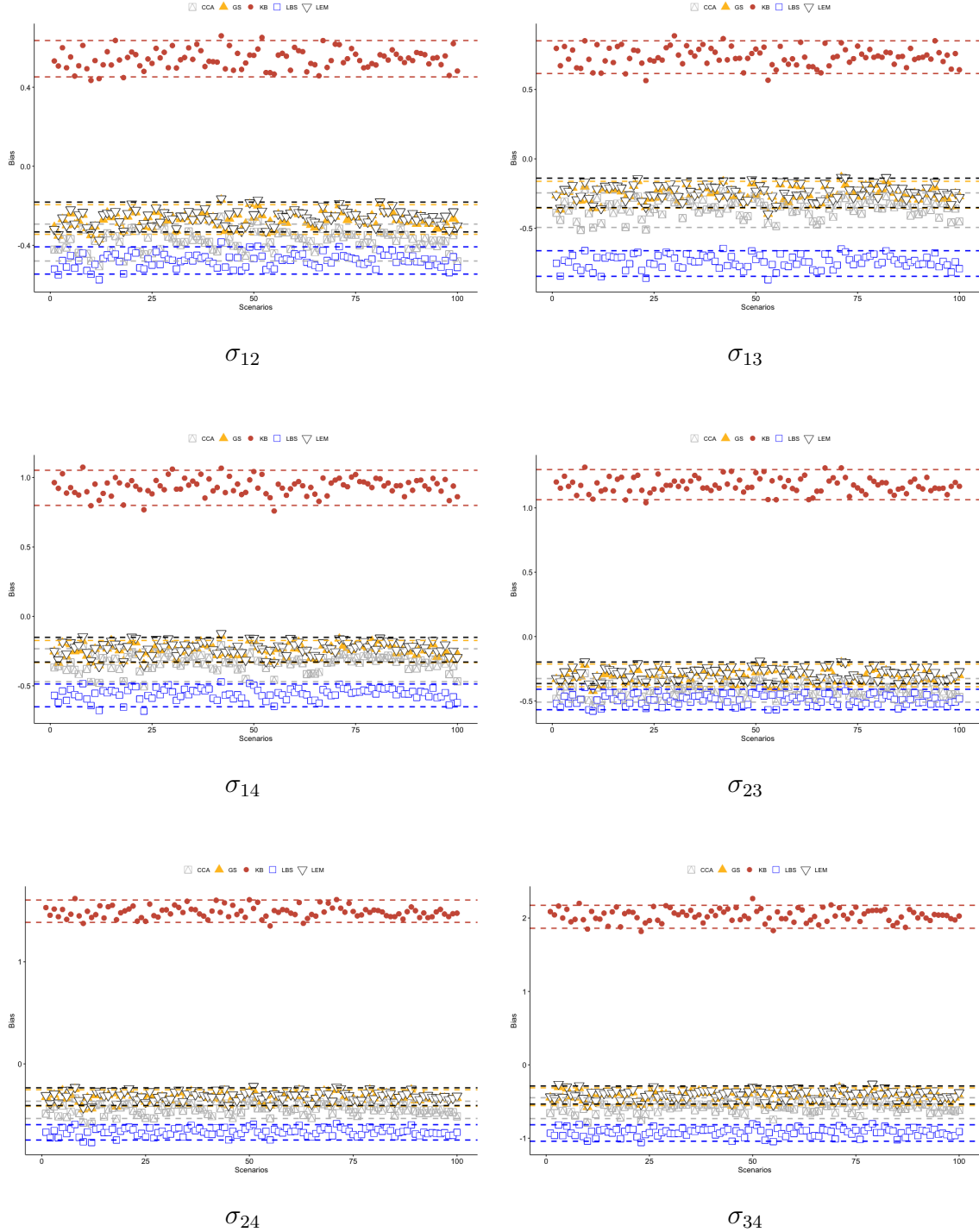


Figure 4.17: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

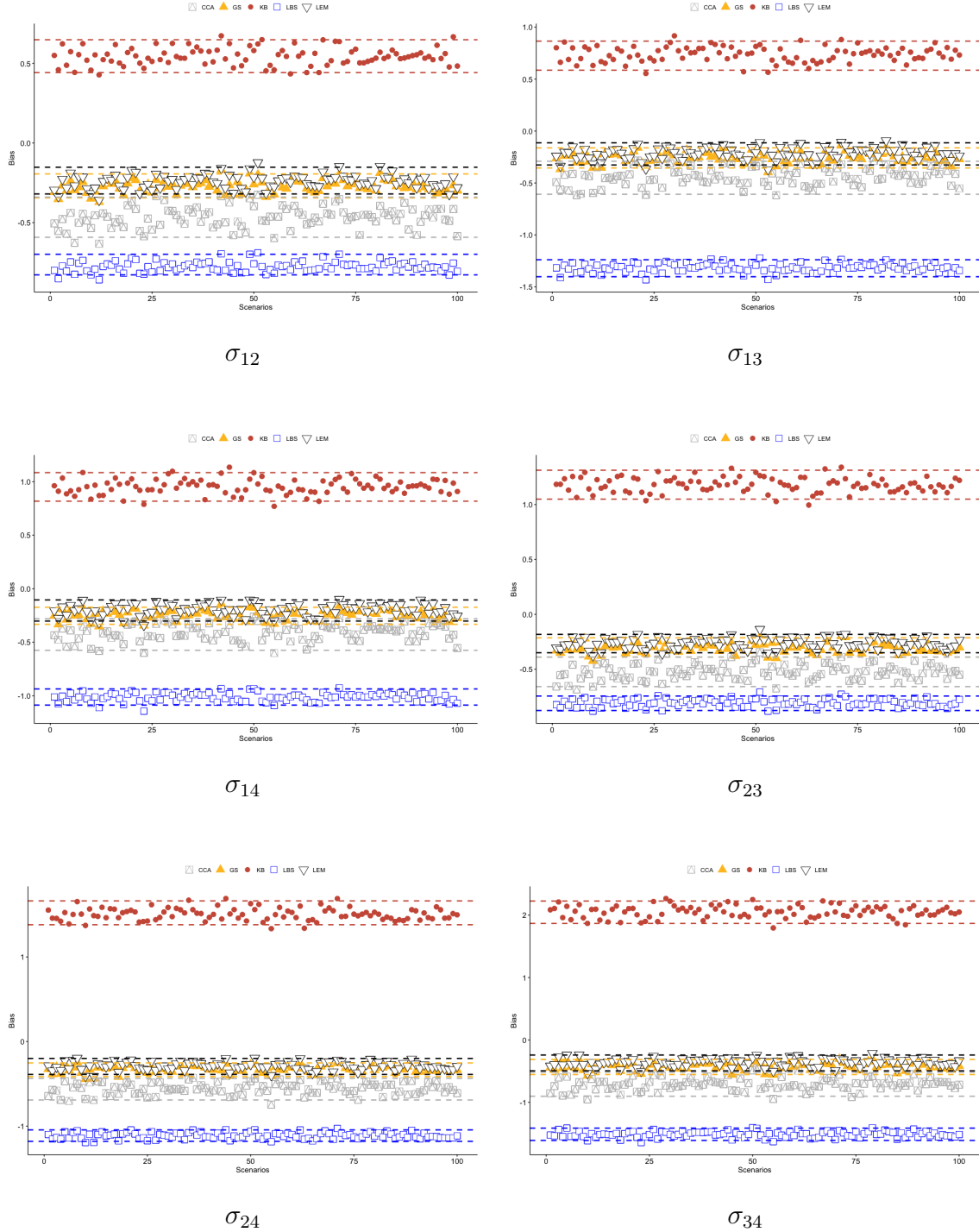


Figure 4.18: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

We would like to highlight here that complete case analysis, the Bayesian method and the EM algorithm led to reasonably good estimators, with a relatively small element-wise and aggregated bias and MSE. This is quite promising, especially considering that the sample size is very small. Moreover, note that the number of time points (p) for the scenarios considered under Experiment 1 is also small, which, when missing data is introduced, might have led to very limited data to estimate both the mean trajectory and within individual variance-covariance matrix. We would also like to note here that the negative bias associated with estimating the variance-covariance matrix is inherent to the likelihood method, and can be corrected by adjusting the denominator. Nevertheless, this adjustment comes at the cost of increased variance. We will show in Experiment 2 that MSE, overall, converges to zero as $n \rightarrow \infty$, hence showing MSE consistency of the estimators, which also means bias goes to zero as $n \rightarrow \infty$, indicating asymptotic unbiasedness.

4.2.1.3 Missing Not at Random

Consider now the MNAR scenarios with 5%, 10% and 20% missing data. We generate missingness by assuming that observations greater than 22.00 are made missing with a 60% probability, while those at or below 22.00 are made missing with a 40% probability. We provide scatter plots of element-wise bias, and to make the presentations concise, we also will provide aggregated bias and MSE values.

From the results presented in Table 4.5, we can see that the biases obtained from the complete case analysis and Bayesian approach in estimating $\mathbf{B}$ are still relatively small for 5% MNAR, where the Bayesian method is shown to perform slightly better than the complete case analysis. However, unlike the MCAR and MAR scenarios, we observed that bias significantly increases as the missingness percentage increases. With respect to bias, the Bayesian estimator performs better than complete case analysis for all the scenarios of MNAR considered. Moreover, the results show that the variability of the estimators from these two methods also increased as the missingness percentage increases, especially for the estimator from complete case analysis. On the other hand, Liski's EM algorithm led to slightly higher bias than the Bayesian method and complete case analysis, across all the scenarios of MNAR. However, the EM algorithm led to smaller variability, as reflected in the aggregated MSE values.

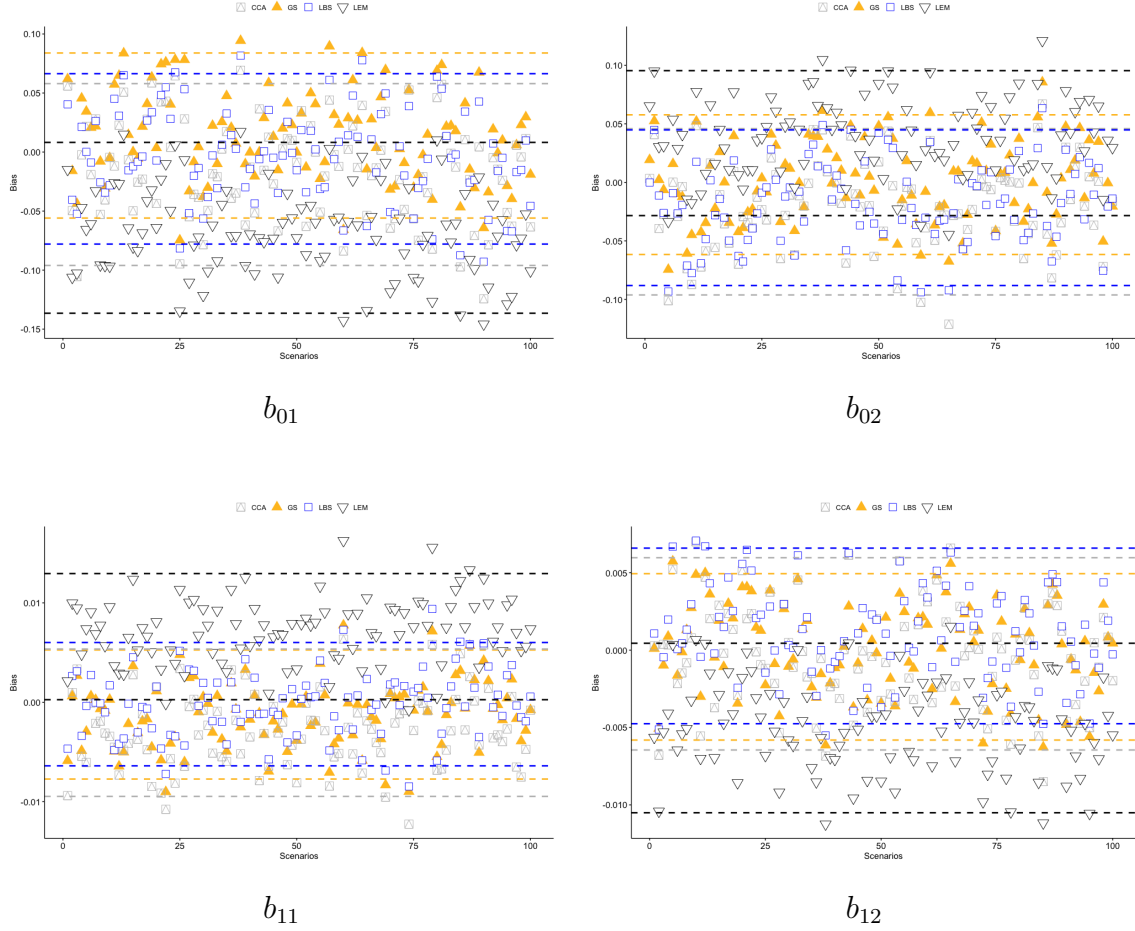


Figure 4.19: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Table 4.5: Aggregated bias and MSE for scenarios with 5%, 10% and 20% MNAR, where $n = 27$, $p = 4$, $q = 2$, and the MLEs from the dental data are used as true values of $\mathbf{B}$ and $\mathbf{\Sigma}$. Bias across the elements of matrix estimators are aggregated using average absolute bias and MSE is aggregated as an average of the element-wise MSEs.

		Methods				
		GS	CCA	KB	LBS	LEM
5%						
Bias	$\mathbf{B}$	0.0042	0.0099	0.0671	0.0057	0.0293
	$\mathbf{\Sigma}$	0.3260	0.3447	1.2218	0.4891	0.3111
MSE	$\mathbf{B}$	0.6345	0.7848	1.0034	0.6738	0.6352
	$\mathbf{\Sigma}$	2.7706	3.3609	6.4899	2.8100	2.8574
10%						
Bias	$\mathbf{B}$	0.0042	0.0264	1.9412	0.0186	0.0714
	$\mathbf{\Sigma}$	0.3260	0.3820	1.2634	0.7033	0.2868
MSE	$\mathbf{B}$	0.6345	1.0247	2931.8915	0.7248	0.6477
	$\mathbf{\Sigma}$	2.7706	4.3132	7.1017	2.9674	2.9635
20%						
Bias	$\mathbf{B}$	0.0042	0.0601	0.9029	0.0502	0.1520
	$\mathbf{\Sigma}$	0.3260	0.4108	1.3471	1.1444	0.2083
MSE	$\mathbf{B}$	0.6345	2.0031	4142585.0000	0.8570	0.7503
	$\mathbf{\Sigma}$	2.7706	7.8536	8.4890	3.5510	3.3420

The scatter plots of element-wise bias displayed in Figure 4.20 show that bias in estimating $\mathbf{B}$ is randomly distributed around zero for the gold-standard (as expected). However, unlike the MCAR and MAR scenarios, for the MAR scenarios complete case analysis and the Bayesian approach seem to slightly underestimate the true parameters of $\mathbf{B}$. On the other hand, Liski's EM algorithm led to a relatively higher bias for all the elements of $\mathbf{B}$, and the bias seems to be in both directions (it overestimates sometimes and it underestimates sometimes depending on which mean parameter we are looking at). We also observe that bias associated with the EM is relatively larger, compared to what we observed for MCAR and MAR 5% scenarios.

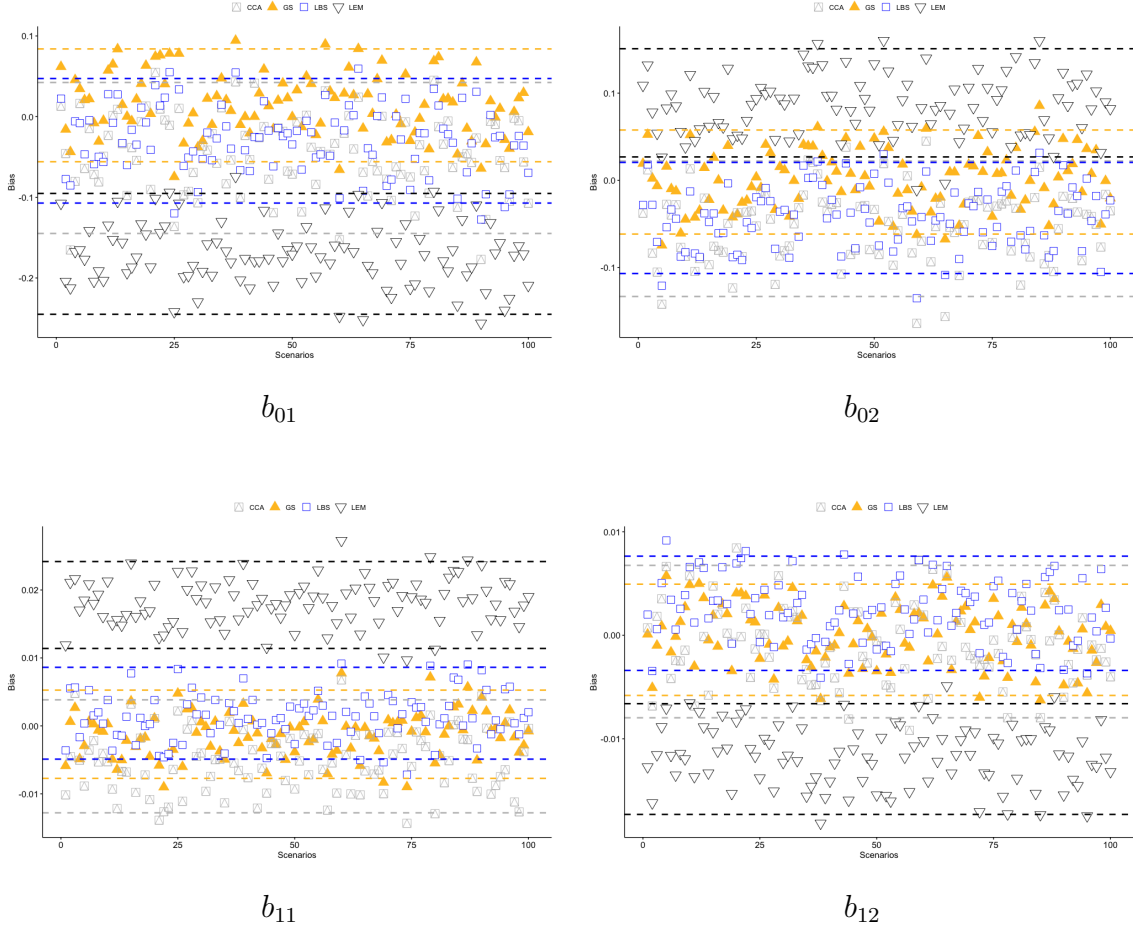


Figure 4.20: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

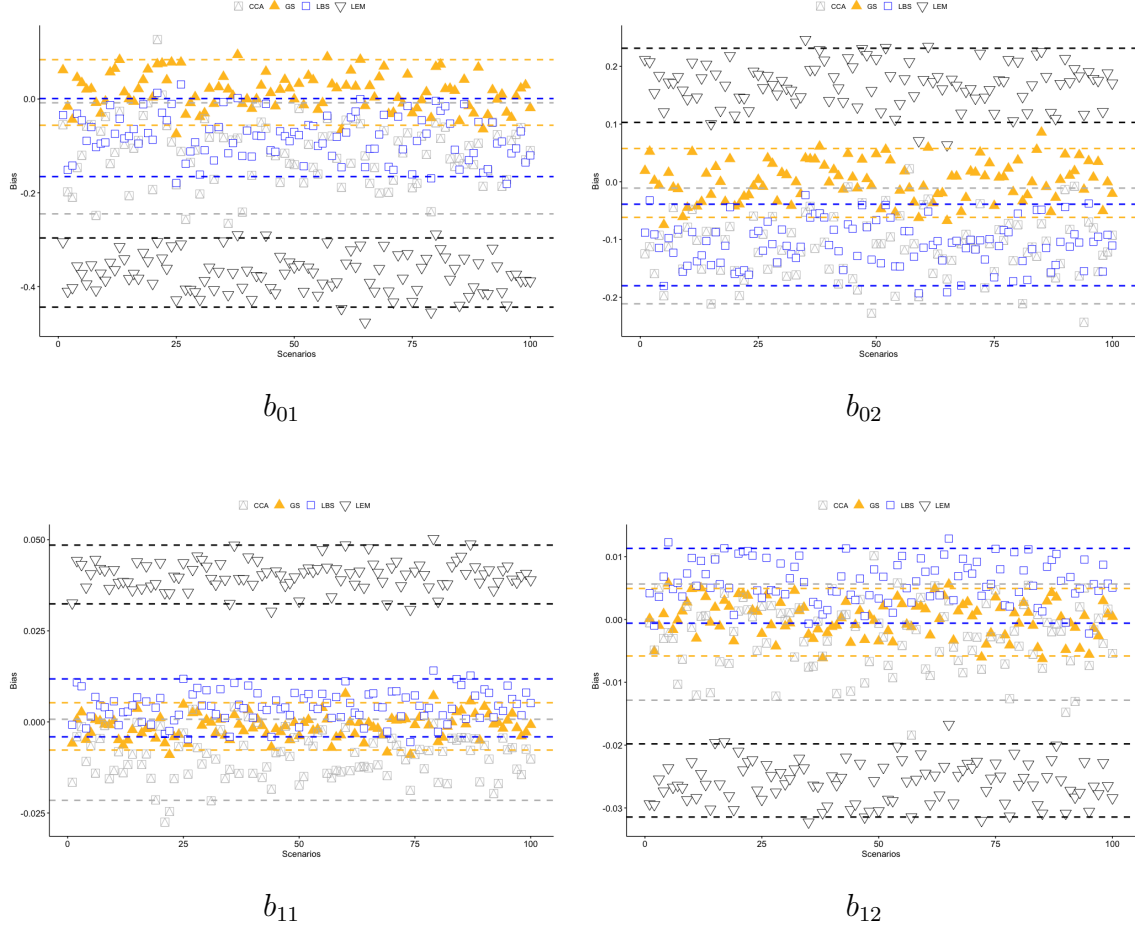


Figure 4.21: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Similar conclusions can be drawn for MAR 20% (Table 4.5, Figure 4.21). We can also see from these figures that, bias increased for all the four methods (complete case analysis, Kleinbaum's GGCM method, Liski's Bayesian method and Liski's EM algorithm) as the percentage of missing values increased. The bias increase for the EM algorithm seems to be more pronounced than the other methods. However, the variance of the estimator from complete case analysis increased significantly more than the other approaches, which can also be seen from the significant increase in the aggregated MSE values for the complete case analysis as the missingness percentage increases. Kleinbaum's approach seems to be unstable for all the scenarios considered under the MNAR scenarios, leading to very large variability, hence is not a reliable method for handling data with MNAR or higher percentages of missing percentages involving MCAR or MAR.

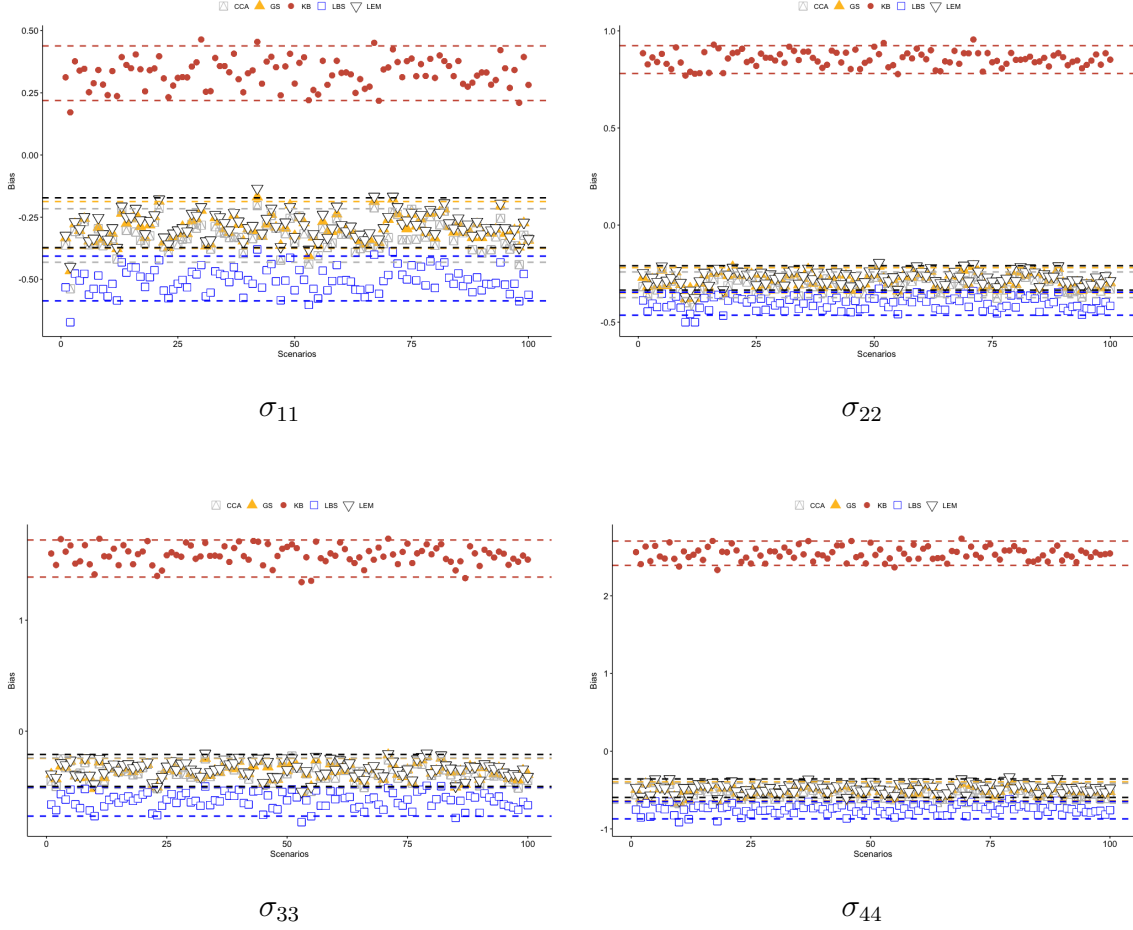


Figure 4.22: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

When estimating the $\mathbf{\Sigma}$ for data with MNAR, the empirical bias from our simulation results show that (Table 4.5, Figures 4.22 and 4.23) Liski's EM algorithm and complete case analysis are comparable to the gold-standard. The Bayesian method seems to consistently underestimate the elements of $\mathbf{\Sigma}$, but this negative bias is relatively small. On the other hand, Kleinbaum's method seems to overestimate both the variances and covariances, and the bias associated with this method appears to be relatively larger. However, similar to the scenarios with MCAR and MAR scenarios, we see that Kleinbaum's method when the missingness mechanism is MNAR is relatively stable when estimating $\mathbf{\Sigma}$. From the aggregated MSE presented in Table 4.5, we can see that complete case analysis still provides reasonably good estimates for $\mathbf{\Sigma}$ for scenarios with MNAR, except when the missingness percentage is high.

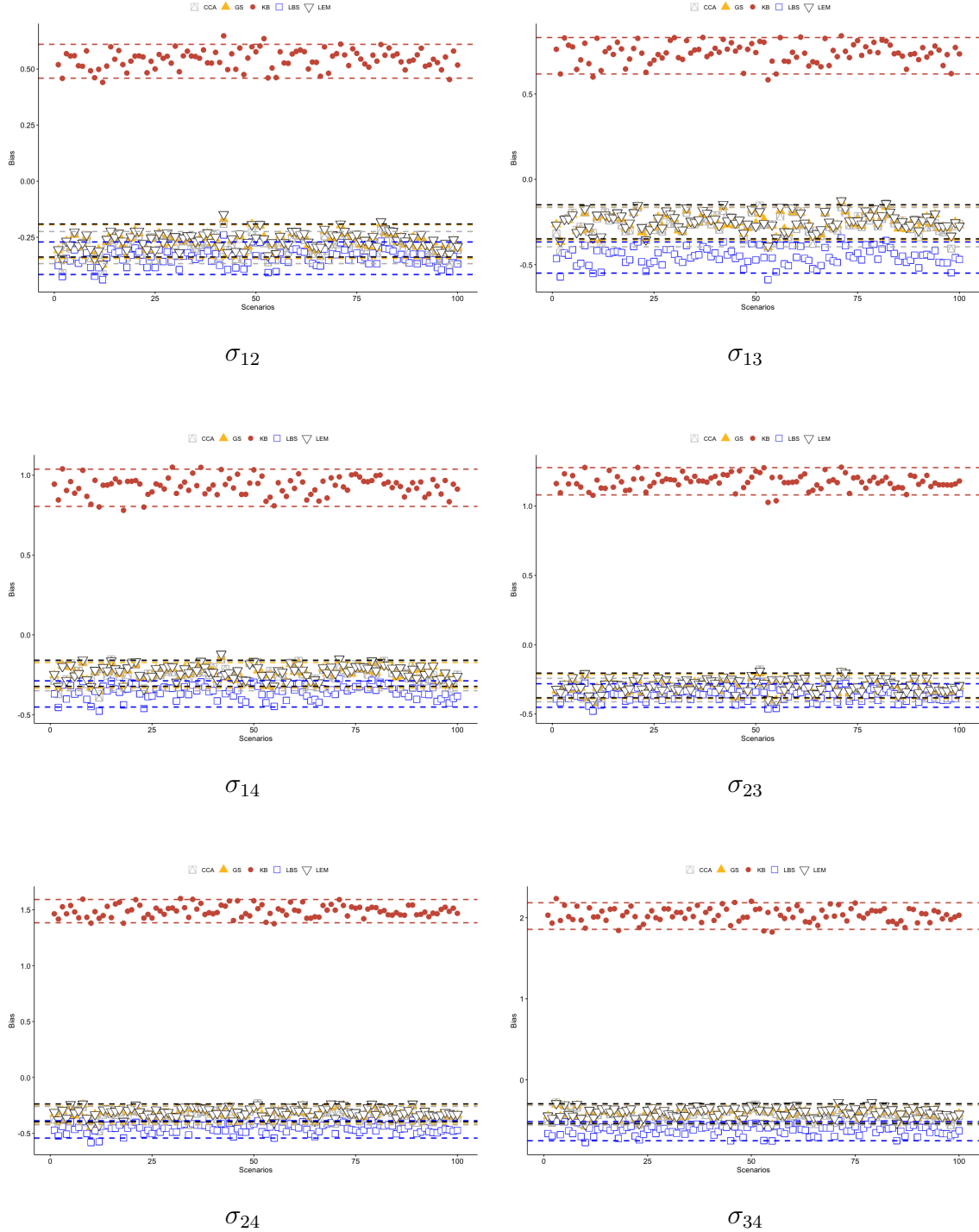


Figure 4.23: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

We can draw similar conclusions from Figures 4.24, 4.25, 4.26 and 4.27 in the sense that Liski's EM algorithm and complete case analysis in general led to comparable results to the gold-standard in estimating Σ . However, the EM algorithm starts to overestimate slightly as the missingness percentage increases, while complete case analysis seems to underestimate slightly. Moreover, the bias associated with the Bayesian and Kleinbaum's methods seem to increase significantly with increase in percentage of missing data, while the direction of bias for both methods stayed the same.

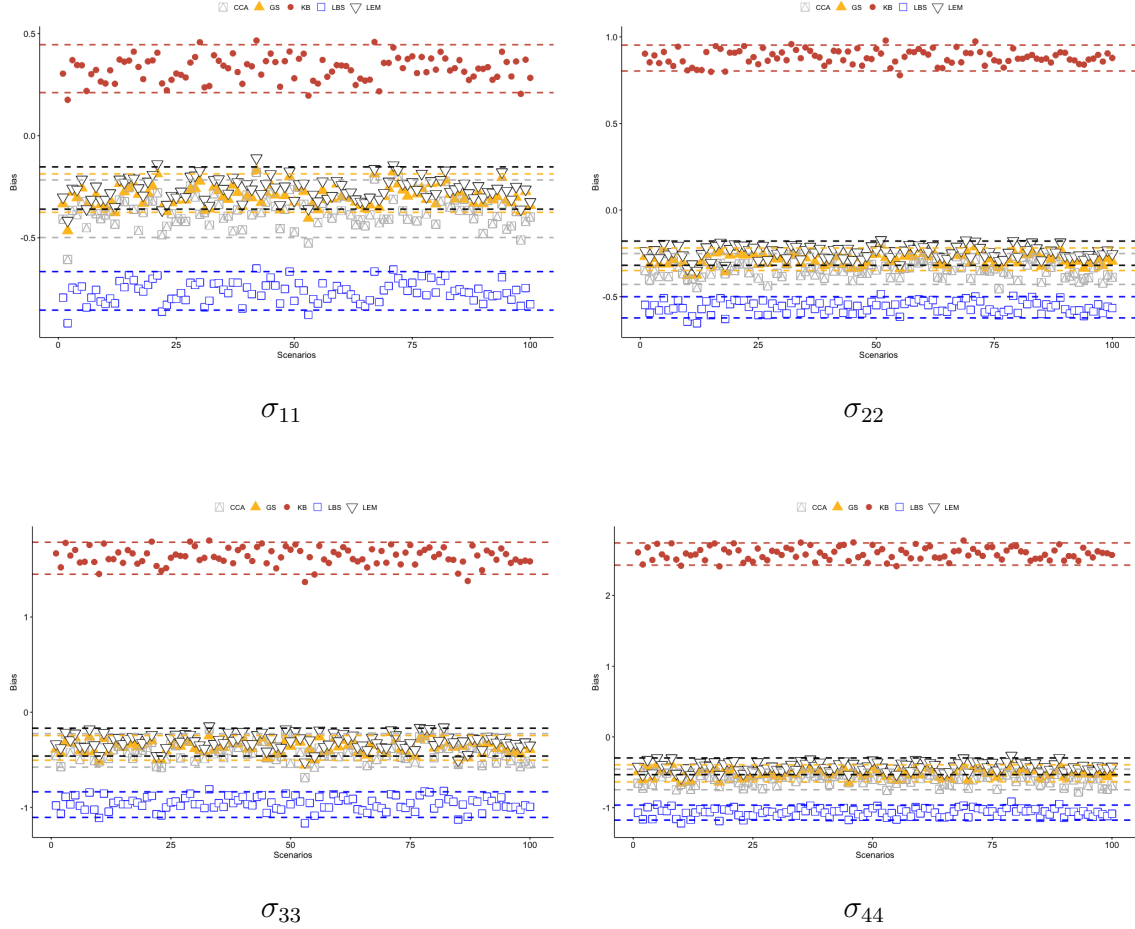


Figure 4.24: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

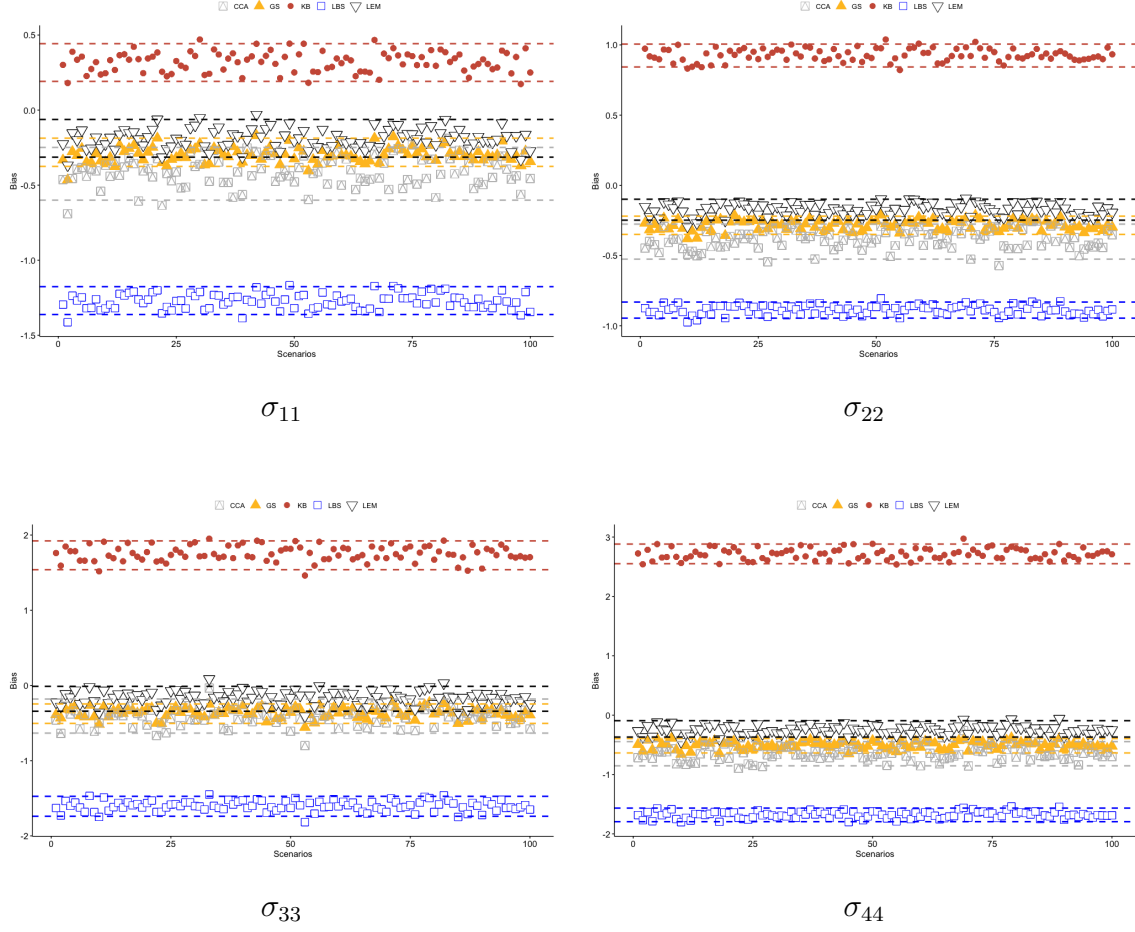


Figure 4.25: Element-wise bias in estimating the within individual (across-time) variances, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

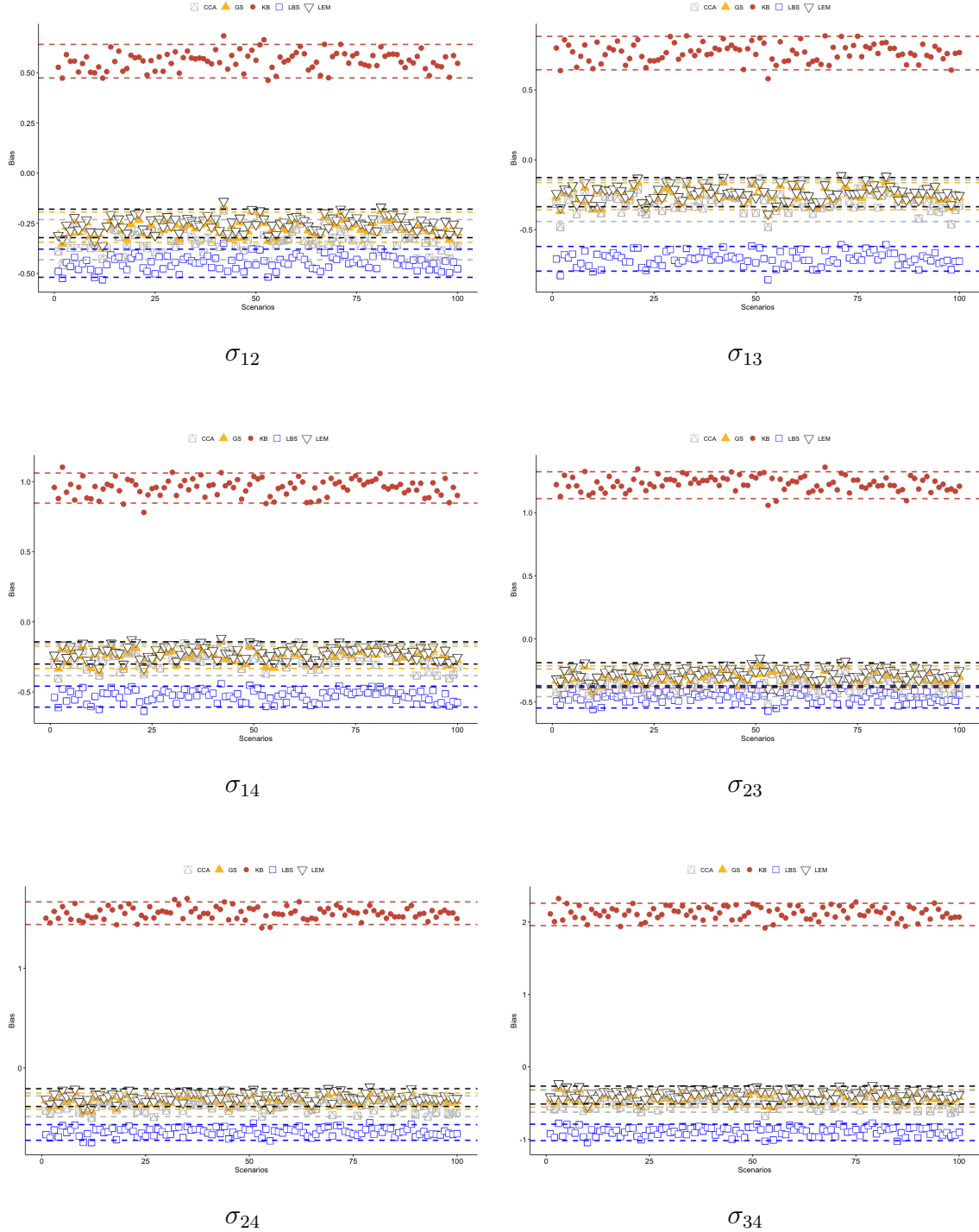


Figure 4.26: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 10% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

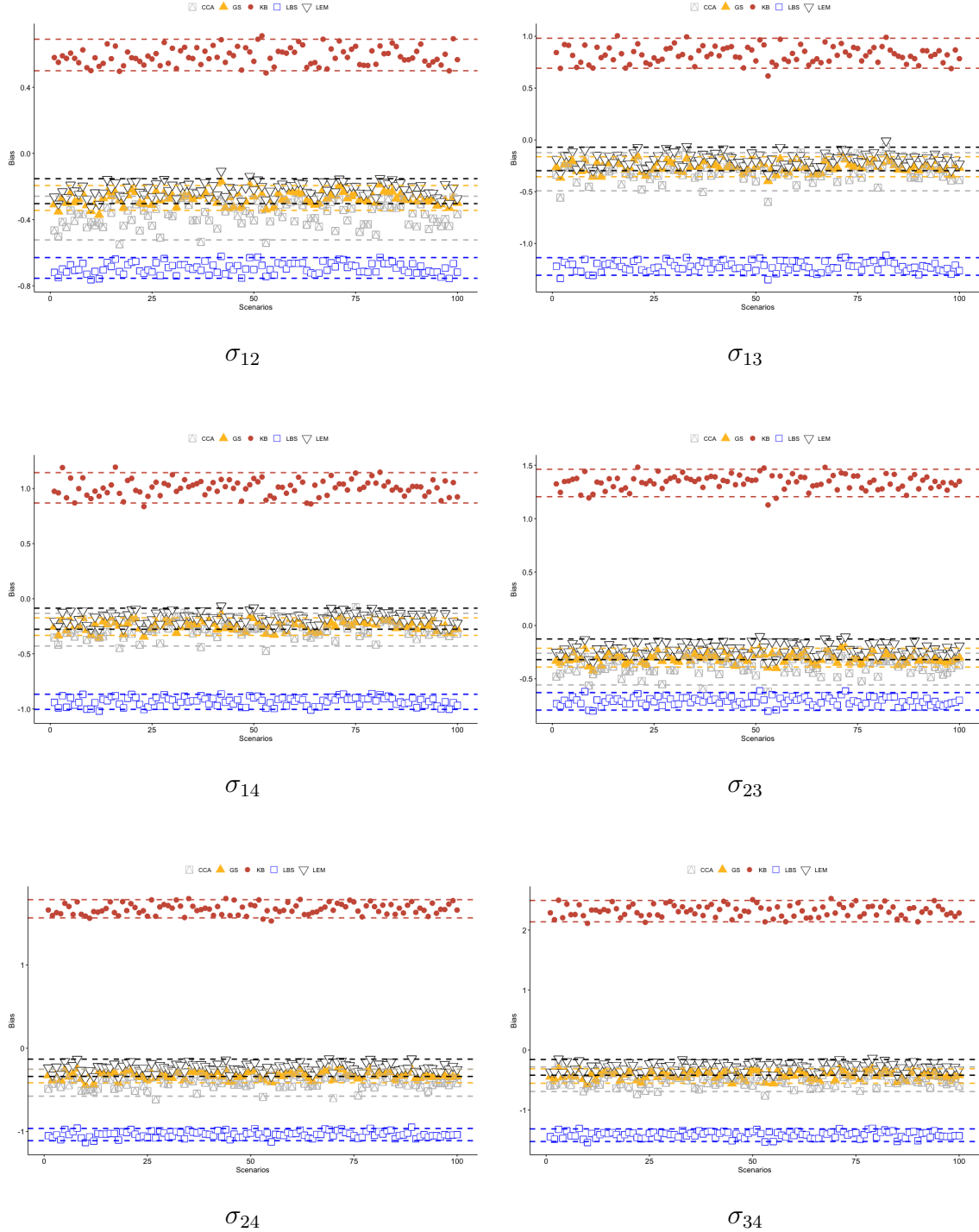


Figure 4.27: Element-wise bias in estimating the covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 20% missing with MNAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

4.2.2 Experiment 2

In this experiment, we consider the glucose data (presented in Chapter 2) to generate our true parameters. The data consists of slightly larger number of time points ($p = 8$, $t = 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5$). As illustrated in Chapter 2 (using profile plots), the glucose data seems to have non-linear mean trajectory over time for both of the groups. As such, this experiment involves scenarios where the mean structure is assumed to be quadratic ($q = 3$) for both groups. Moreover, for scenarios under this experiment, we consider various sample sizes (ranging from small to large), to establish asymptotic unbiasedness and/or consistency of the estimators.

We started by fitting the GCM to the original glucose data and obtained the MLE estimators for both $\mathbf{B}$ and $\mathbf{\Sigma}$:

$$\mathbf{Y} = \mathbf{Z}\mathbf{B}\mathbf{X} + \mathbf{E}, \quad \text{where } \mathbf{E} \sim N_{8,50}(\mathbf{0}, \mathbf{\Sigma}, \mathbf{I}_{50})$$

where $\mathbf{Y}$ is 8×50 matrix, $\mathbf{Z}$ is 8×3 matrix, $\mathbf{B}$ is 3×2 matrix, $\mathbf{X}$ is 2×50 matrix, $\mathbf{E}$ is 8×50 matrix, and $\mathbf{\Sigma}$ is 8×8 matrix. Details on these matrices are provided in Chapter 2. The true parameter values (for $\mathbf{B}$ and $\mathbf{\Sigma}$) for scenarios under this experiment are set to be the MLEs, where we used the full data set (without missing data):

$$\mathbf{B}_0 = \begin{pmatrix} 6.032 & 5.696 \\ -2.067 & -1.749 \\ 0.349 & 0.293 \end{pmatrix},$$

$$\mathbf{\Sigma}_0 = \begin{pmatrix} 0.568 & 0.620 & 0.443 & 0.344 & 0.311 & 0.219 & 0.203 & 0.215 \\ 0.620 & 0.869 & 0.621 & 0.458 & 0.369 & 0.237 & 0.298 & 0.214 \\ 0.443 & 0.621 & 0.592 & 0.416 & 0.293 & 0.151 & 0.215 & 0.167 \\ 0.344 & 0.458 & 0.416 & 0.410 & 0.258 & 0.147 & 0.146 & 0.114 \\ 0.311 & 0.369 & 0.293 & 0.258 & 0.523 & 0.314 & 0.286 & 0.268 \\ 0.219 & 0.237 & 0.151 & 0.147 & 0.314 & 0.316 & 0.273 & 0.238 \\ 0.203 & 0.298 & 0.215 & 0.146 & 0.286 & 0.273 & 0.353 & 0.260 \\ 0.215 & 0.214 & 0.167 & 0.114 & 0.268 & 0.238 & 0.260 & 0.291 \end{pmatrix}.$$

4.2.2.1 Missing Completely at Random

In this section, we consider longitudinal data involving two groups ($k = 2$), $p = 8$ and $n = 50$ ($n_1 = 29$ and $n_2 = 21$), a scenario created to mimic the glucose data itself. We generated 5%, 10% and 20% MCAR, by simply replacing a random selection of data points as missing. We calculated both element-wise and aggregated bias and MSE. The results are presented in Figures and Tables.

The results are similar to MCAR scenarios in Experiment 1, where the approach using complete case analysis and the Bayesian method show comparable accuracy (i.e. comparable bias) as the gold-standard (Table 4.6, Figure 4.28). The accuracy of the complete case

analysis starts to decrease as the percentage of missingness increases, but still the method provides a good estimator. We can also see that the EM algorithm leads to an estimator with a slightly larger bias but with less variability consistently for all the scenarios under the MCAR mechanism that we considered under Experiment 2. However, the results also show that the variance for the Liski's EM algorithm starts to increase as the missingness percentage increases.

Table 4.6: Aggregated bias and MSE for scenarios with 5%, 10% and 20% MCAR, where $n = 50$, $p = 8$, $q = 3$, and the MLEs from the glucose data are used as true values of $\mathbf{B}$ and $\mathbf{\Sigma}$. Bias across the elements of matrix estimators are aggregated using average absolute bias and MSE is aggregated as an average of the element-wise MSEs.

		Methods				
		GS	CCA	KB	LBS	LEM
5%						
Bias	$\mathbf{B}$	0.00095	0.00076	0.06479	0.00052	0.00688
	$\mathbf{\Sigma}$	0.00765	0.00992	0.00124	0.01509	0.00737
MSE	$\mathbf{B}$	0.02099	0.03563	274.79884	0.02380	0.02136
	$\mathbf{\Sigma}$	0.00812	0.01214	0.00891	0.00808	0.00825
10%						
Bias	$\mathbf{B}$	0.00095	0.00063	0.29530	0.00052	0.01530
	$\mathbf{\Sigma}$	0.00765	0.01205	0.00125	0.02297	0.00698
MSE	$\mathbf{B}$	0.02099	0.06034	78.89277	0.02516	0.02216
	$\mathbf{\Sigma}$	0.00812	0.01994	0.00975	0.00832	0.00842
20%						
Bias	$\mathbf{B}$	0.00095	0.01905	0.52194	0.00156	0.03871
	$\mathbf{\Sigma}$	0.00765	0.05543	0.00136	0.03679	0.32069
MSE	$\mathbf{B}$	0.02099	0.41993	66.27408	0.02850	0.04559
	$\mathbf{\Sigma}$	0.00812	0.10975	0.01206	0.00948	31.97636

Again similar to the MCAR results we presented for Experiment 1, the results in Figure 4.28 show that bias in estimating $\mathbf{B}$ is randomly distributed around zero for the gold-standard, complete case analysis and the Bayesian method. Liski's EM algorithm also tends to underestimate or overestimate $\mathbf{B}$, similar to what we saw for the MCAR scenarios in Experiment 1. Kleinbaum's GGCM approach is highly unstable and leads to a very large variability, hence we did not include this method in Figure 4.28 (to maintain margin of plots that allow clear display of the bias corresponding to the other methods). This instability in Kleinbaum's approach is also observed in Experiment 1, indicating that the results related to accuracy of the various methods is consistent for different p , mean trajectory (linear, non-linear), mean values, variance-covariance values and sample size.

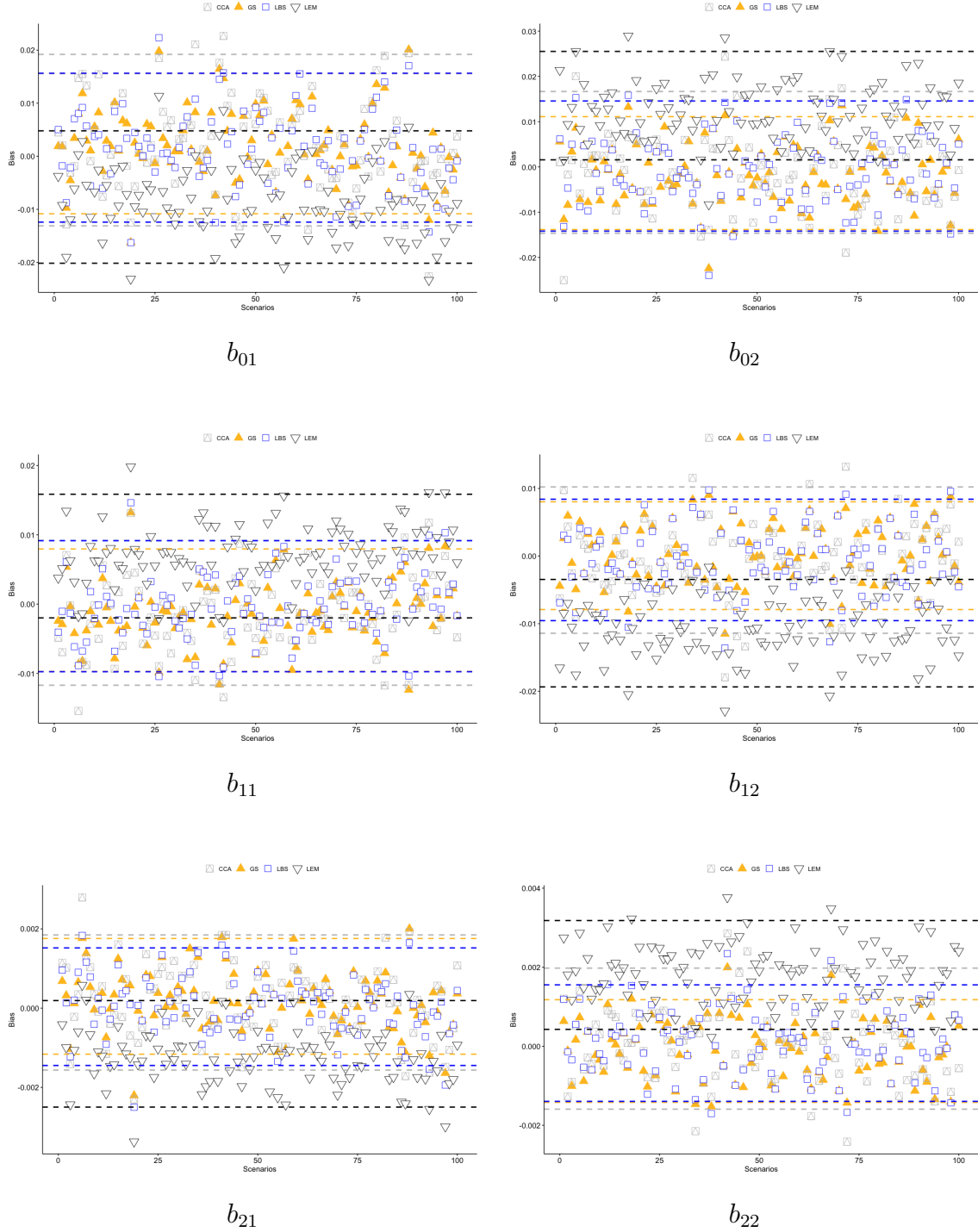


Figure 4.28: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$, 5% missing with MCAR mechanism and the MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

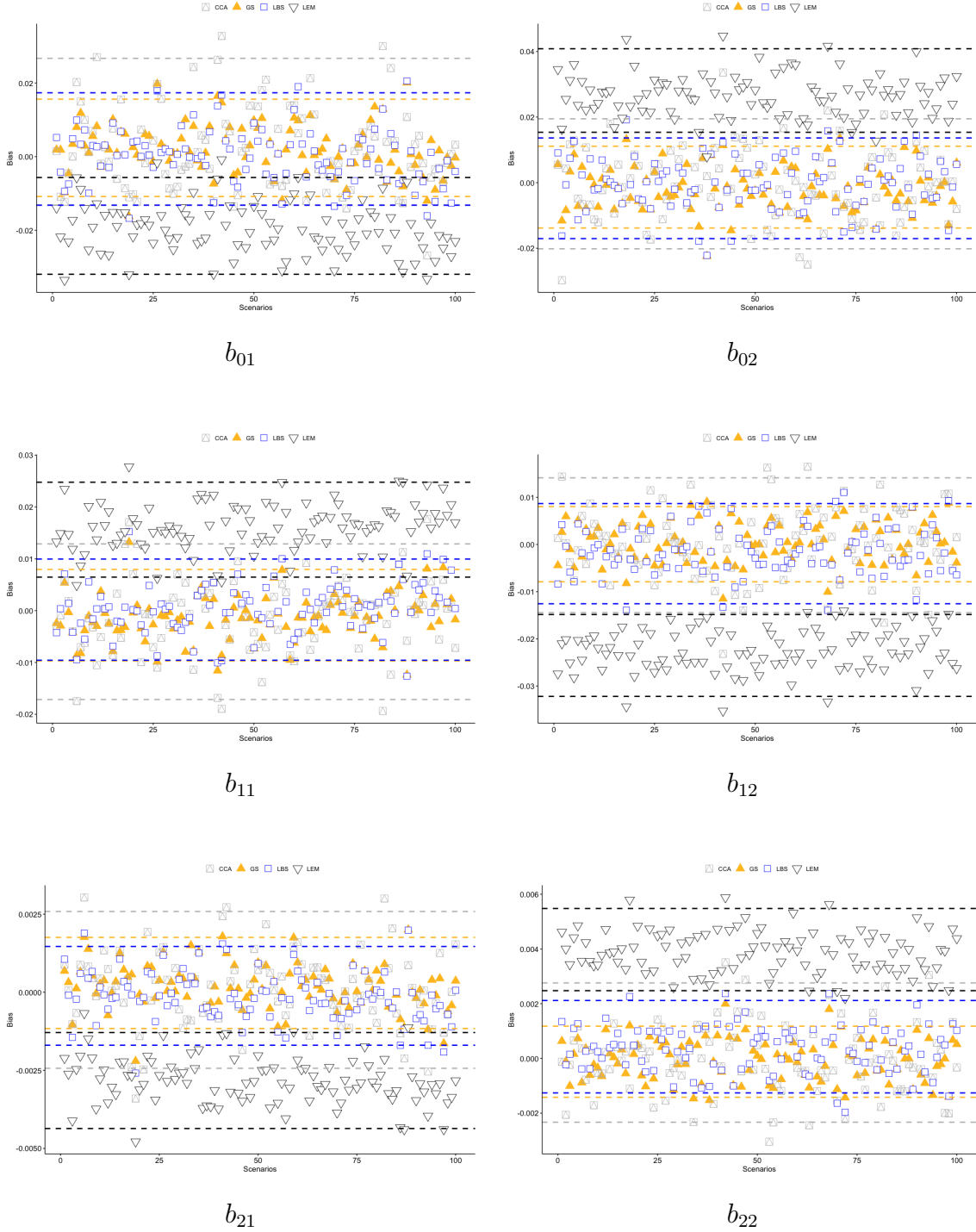


Figure 4.29: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$, 10% missing with MCAR mechanism and the MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

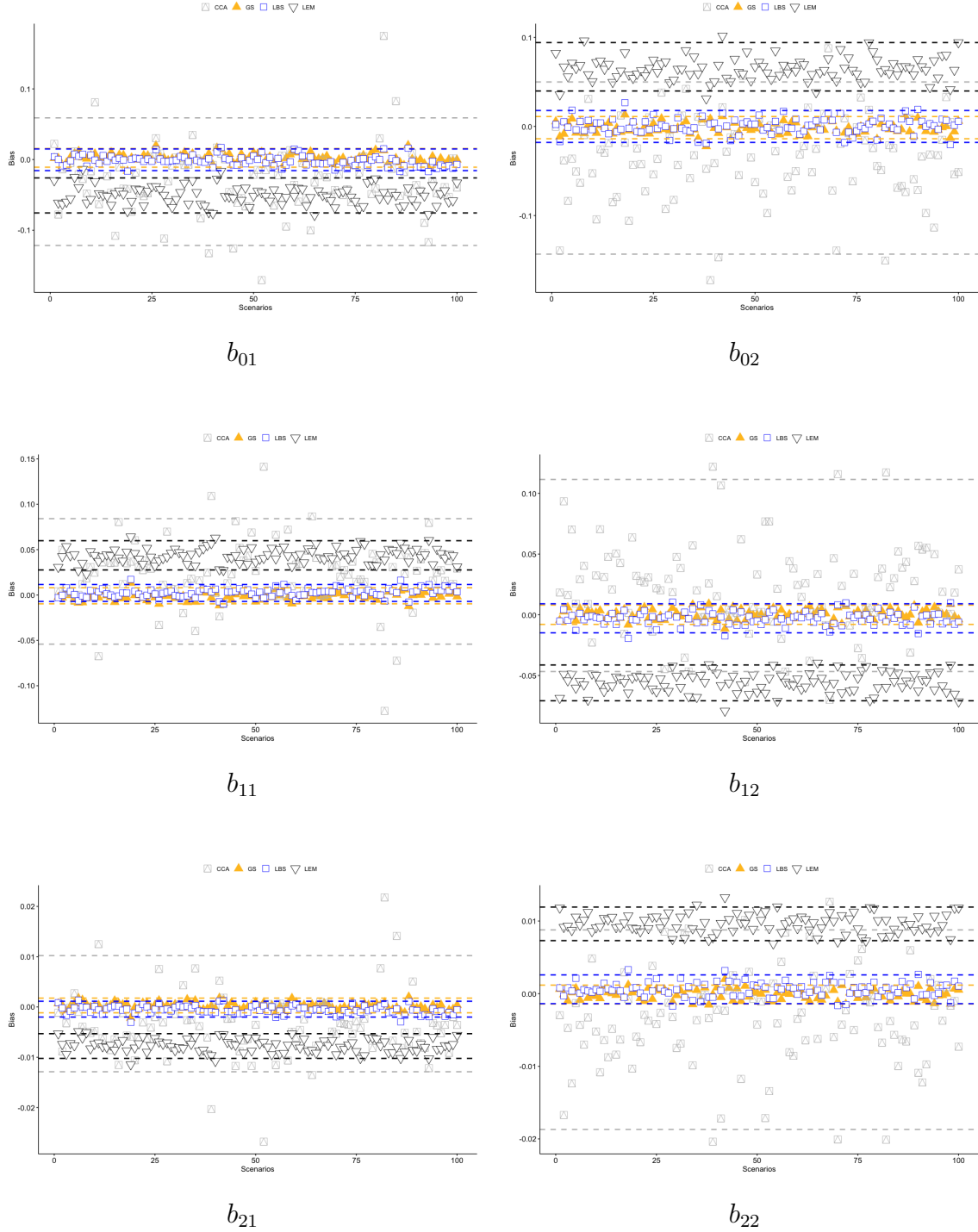


Figure 4.30: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$, 20% missing with MCAR mechanism and the MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

The element-wise bias scatter plots, corresponding to estimation of $\mathbf{B}$, presented in Figures 4.29 and 4.30 are also similar to those obtained from the MCAR scenarios of Experiment 1, where bias seems to increase as the percentage of missingness increases. Moreover, we also see that complete case analysis, the Bayesian method and the EM algorithm still produce reasonably good estimators for $\mathbf{B}$ when the missingness mechanism is MCAR. The results also show that Kleinbaum’s method is unstable for estimating $\mathbf{B}$ regardless of the missingness mechanism or percentage.

The element-wise bias plots for selected elements of $\mathbf{\Sigma}$ under scenarios of 5%, 10% and 20% MCAR are presented in Figures B.2 to B.7 in the Appendix. The figures show similar results as in scenarios for MCAR of Experiment 1. For instance, complete case analysis and the Bayesian approach provide comparable performance as the gold-standard, the EM produces estimators with slightly higher bias (in both directions) and Kleinbaum’s method significantly overestimates $\mathbf{\Sigma}$, but it is stable.

Now consider the MSE for estimating $\mathbf{B}$ and $\mathbf{\Sigma}$. To allow us study the distribution of MSE with respect to sample size, and establish consistency of the estimators (or lack thereof), we performed simulations with varying sample sizes. We calculated both element-wise and aggregated MSE values, and present the results in Tables and Figures. Since $\mathbf{\Sigma}$ has too many unique elements and the conclusions drawn, in terms of comparative performance are consistent, we present plots of element-wise MSE for selected variance and covariance parameters.

We start with the 5% MCAR scenario and the plot of element-wise MSE for all the 6 elements of $\mathbf{B}$, presented in Figure 4.31. We would like to first note that Kleinbaum’s approach is not included in the study of the MSE for $\hat{\mathbf{B}}$, because of its instability. Hence, the discussion we have here about MSE of $\hat{\mathbf{B}}$ involves the other methods. The first clear result we can observe from Figure 4.31 is that MSE for all the methods decreases monotonically as the sample size increases. This indicates that all the methods considered produce MSE consistent estimators for $\mathbf{B}$, which also implies asymptotic unbiasedness and variance consistency (variance also goes to zero as $n \rightarrow \infty$).

Moreover, we see from Figure 4.31 that the EM algorithm and the Bayesian approach produce almost the same performance as the gold-standard, with slightly less MSE values for very small sample sizes. This seems to be the case for all the elements of $\mathbf{B}$. The results show that complete case analysis performs uniformly poorly across all sample sizes. In summary, the results presented in this Figure relay the message that the Bayesian approach and the EM algorithm are very good techniques we can use when the missingness mechanism is MCAR and the percentage of missing data is small.

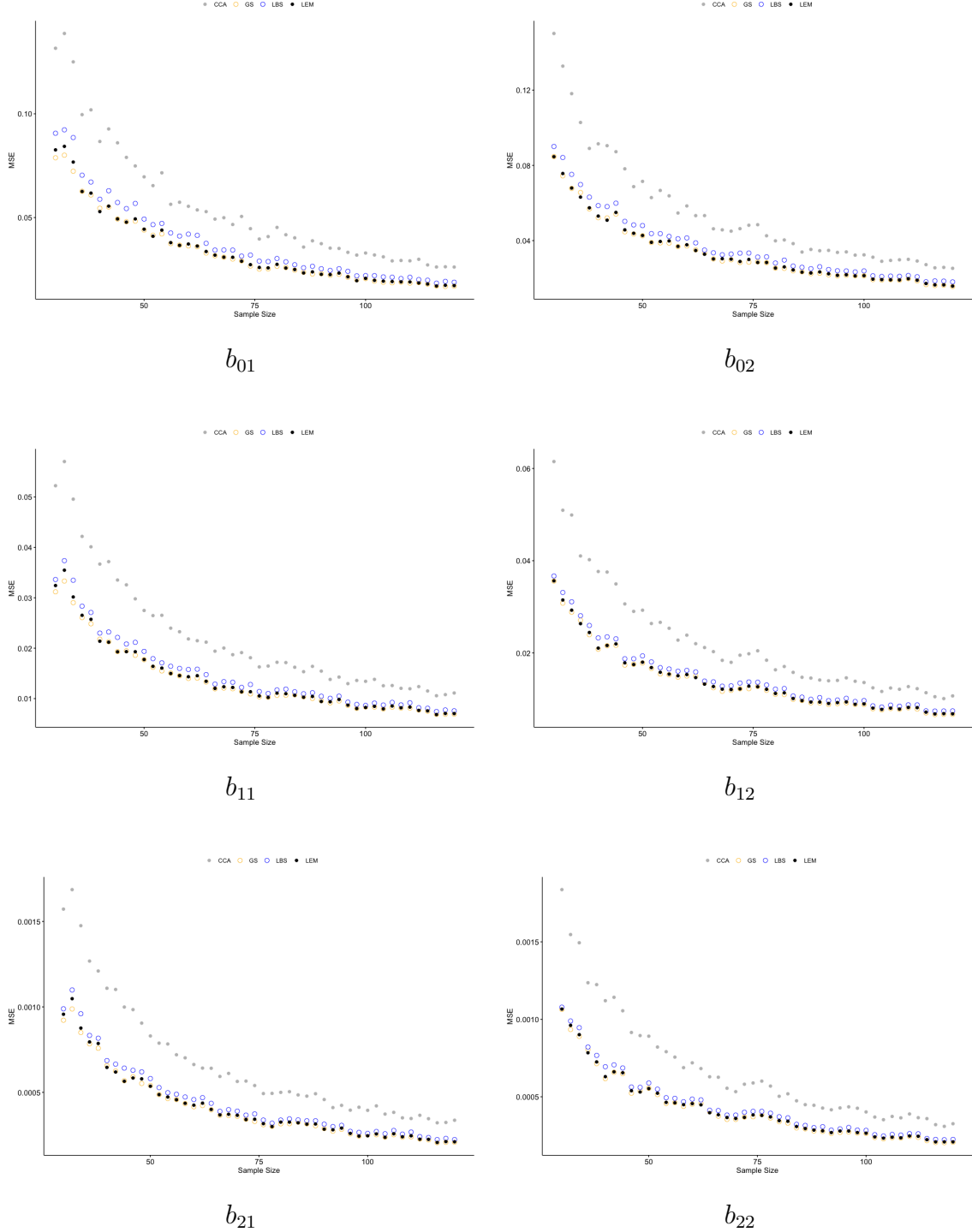


Figure 4.31: Element-wise MSE corresponding to $\hat{\mathbf{B}}$, where scenarios consisting of data with different sample size (ranging from $n = 30$ to $n = 120$) are considered. The scenarios still have $p = 8$ measurements, $k = 2$ groups, quadratic mean structure for both groups ($q = 3$) and 5% MCAR is used. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate the empirical MSEs plotted here.

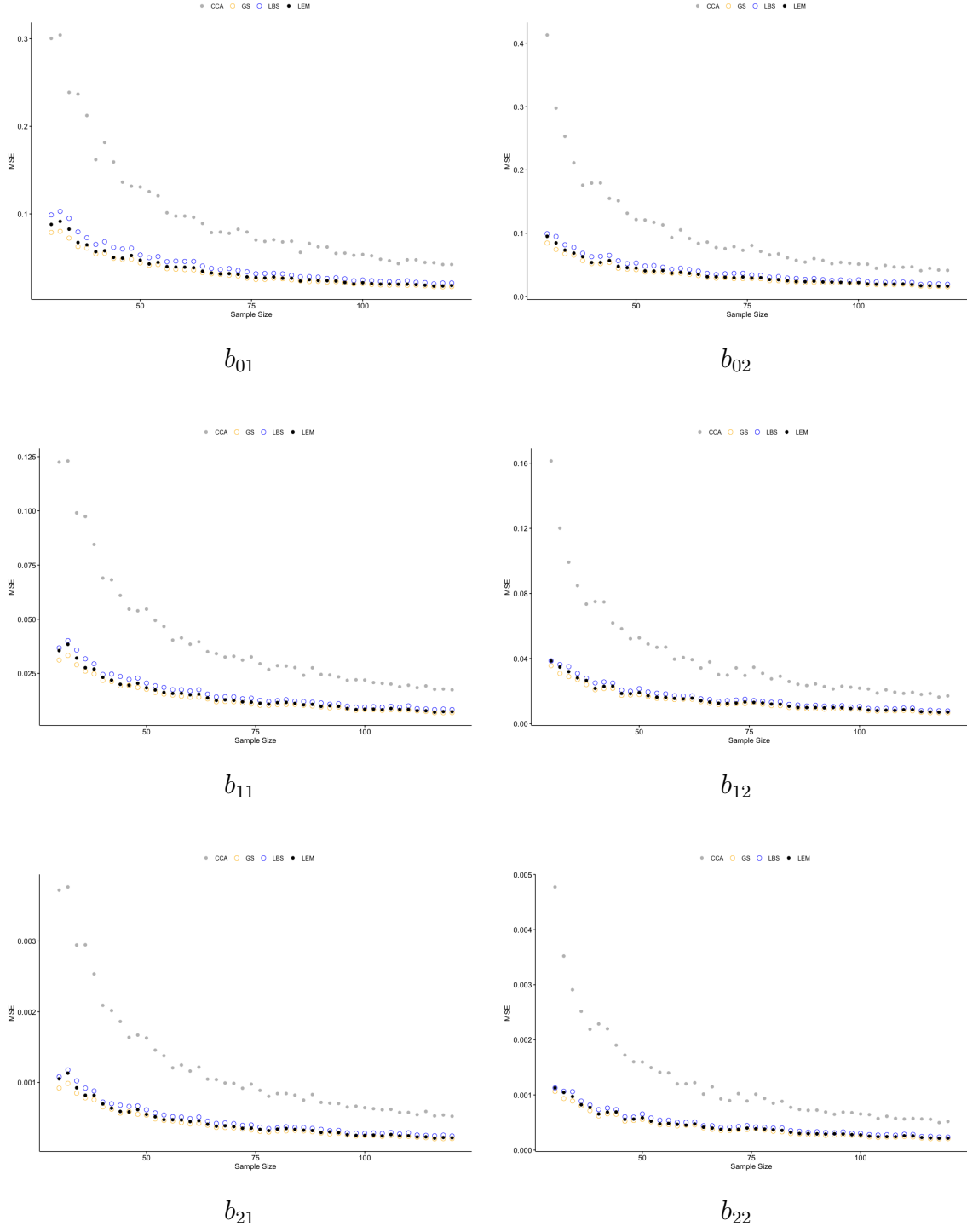


Figure 4.32: Element-wise MSE corresponding to $\hat{\mathbf{B}}$, where 46 scenarios consisting of data with different sample size (ranging from $n = 30$ to $n = 120$) are considered. The scenarios still have $p = 8$ measurements, $k = 2$ groups, quadratic mean structure for both groups ($q = 3$) and 10% MCAR is used. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate the empirical MSEs plotted here.

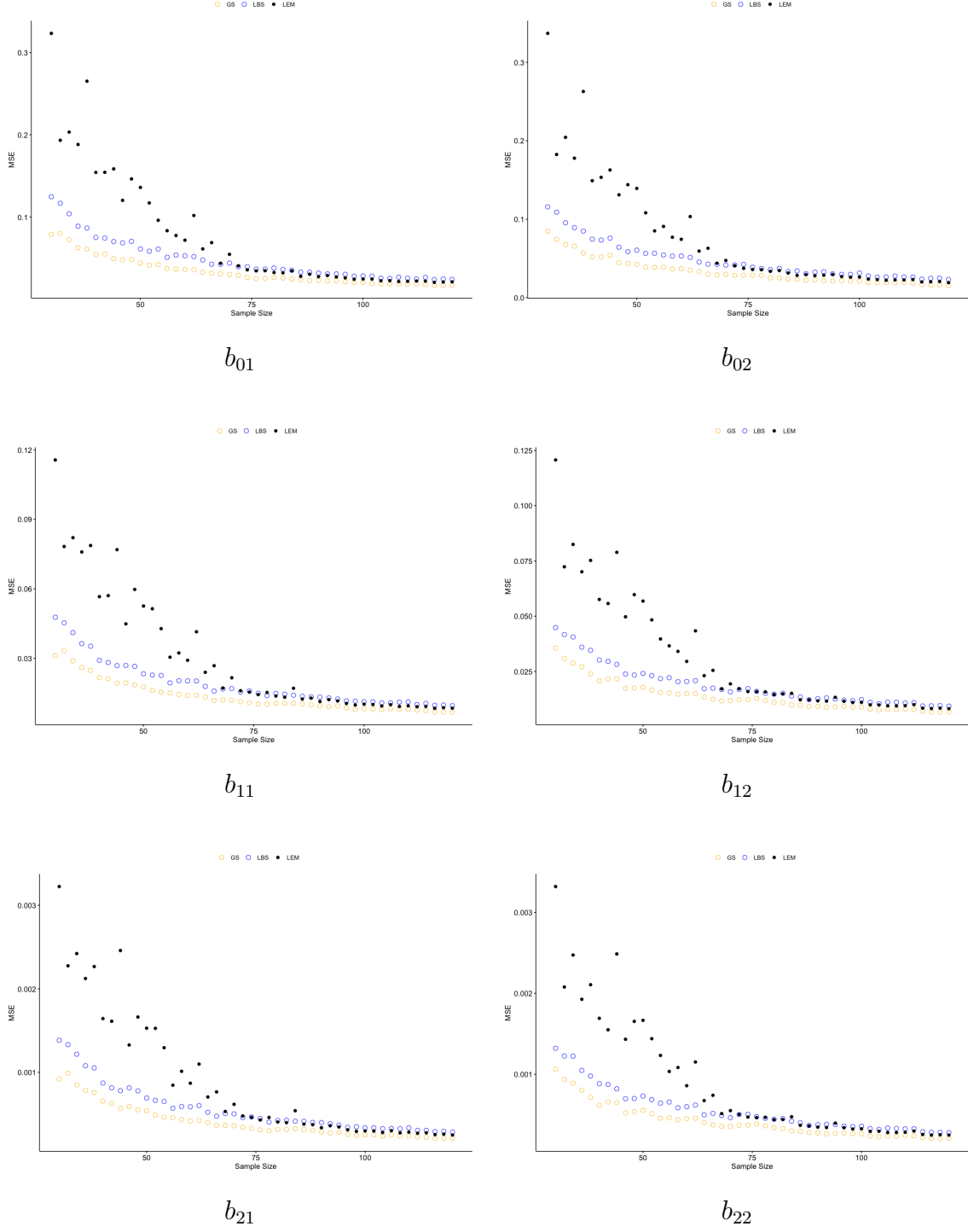


Figure 4.33: Element-wise MSE corresponding to $\hat{\mathbf{B}}$, where 46 scenarios consisting of data with different sample size (ranging from $n = 30$ to $n = 120$) are considered. The scenarios still have $p = 8$ measurements, $k = 2$ groups, quadratic mean structure for both groups ($q = 3$) and 20% MCAR is used. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate the empirical MSEs plotted here.

We see similar results when the percentage of missing data is increased to 10%, where the EM algorithm and the Bayesian approach still show comparable performance (Figure 4.32) across all the sample sizes. The results from Figure 4.32 also show that the performance of the complete case analysis deteriorated as the percentage of missingness is increased to 10%, where the MSE corresponding to the complete case analysis is significantly larger than what we observed for 5% MCAR.

When the missingness percentage is increased to 20%, we see that the EM algorithm performs poorly for small sample sizes but performs comparably to the gold-standard for larger sample sizes (Figure 4.33). On the other hand, the Bayesian approach shows a relatively better performance across all the sample sizes, with almost the same performance as the sample size increases. For small sample sizes and 20% MCAR, the MSE from the Bayesian method is uniformly larger than the gold-standard. Therefore, from the MSE plots shown in Figures 4.31, 4.32 and 4.33 that the Bayesian method is a reasonably good approach, and when the missingness is very small the EM algorithm is the better alternative. Finally, we would like to highlight that the results from Figures 4.31, 4.32 and 4.33 also show that all the methods, including complete case analysis, produce MSE consistent estimators for $\mathbf{B}$ when the missingness mechanism is MCAR, and regardless of missingness percentage.

Let us now examine the element-wise MSE plots corresponding to $\hat{\Sigma}$. Without loss of generality, we will only display plots corresponding to selected elements of the matrix estimators. Note also that Kleinbaum's method is consistent here, since it leads to a stable estimator for Σ . Consider first the results for the scenarios with 5%, presented in Figure 4.34. As we can see from the figure, the MSE corresponding to all methods decrease monotonically with respect to sample size, indicating that the methods produce MSE consistent estimators for Σ . The figure also shows that both the Bayesian method and the EM algorithm perform very well, almost the same performance as the gold-standard. Kleinbaum's method also performs well, with comparative performance as the gold-standard for the variance parameters (diagonal elements of Σ) but a slightly larger MSE values when estimating the covariances (off-diagonal elements) compared to the Bayesian approach and EM algorithm. Similar to estimators of $\mathbf{B}$, the complete case analysis performs poorly in estimating Σ .

As the missingness percentage increased, the complete case analysis led to very poor estimators for Σ . The MSE values are much larger than the other methods, hence the results could not be presented with the other methods in the same plot. As such, we removed the complete case analysis from Figures 4.35 and 4.36, corresponding to 10% MCAR and 20% MCAR, respectively. Overall, the results presented in these two figures show that all the methods led to MSE consistent estimators, regardless of the missingness percentages. Moreover,

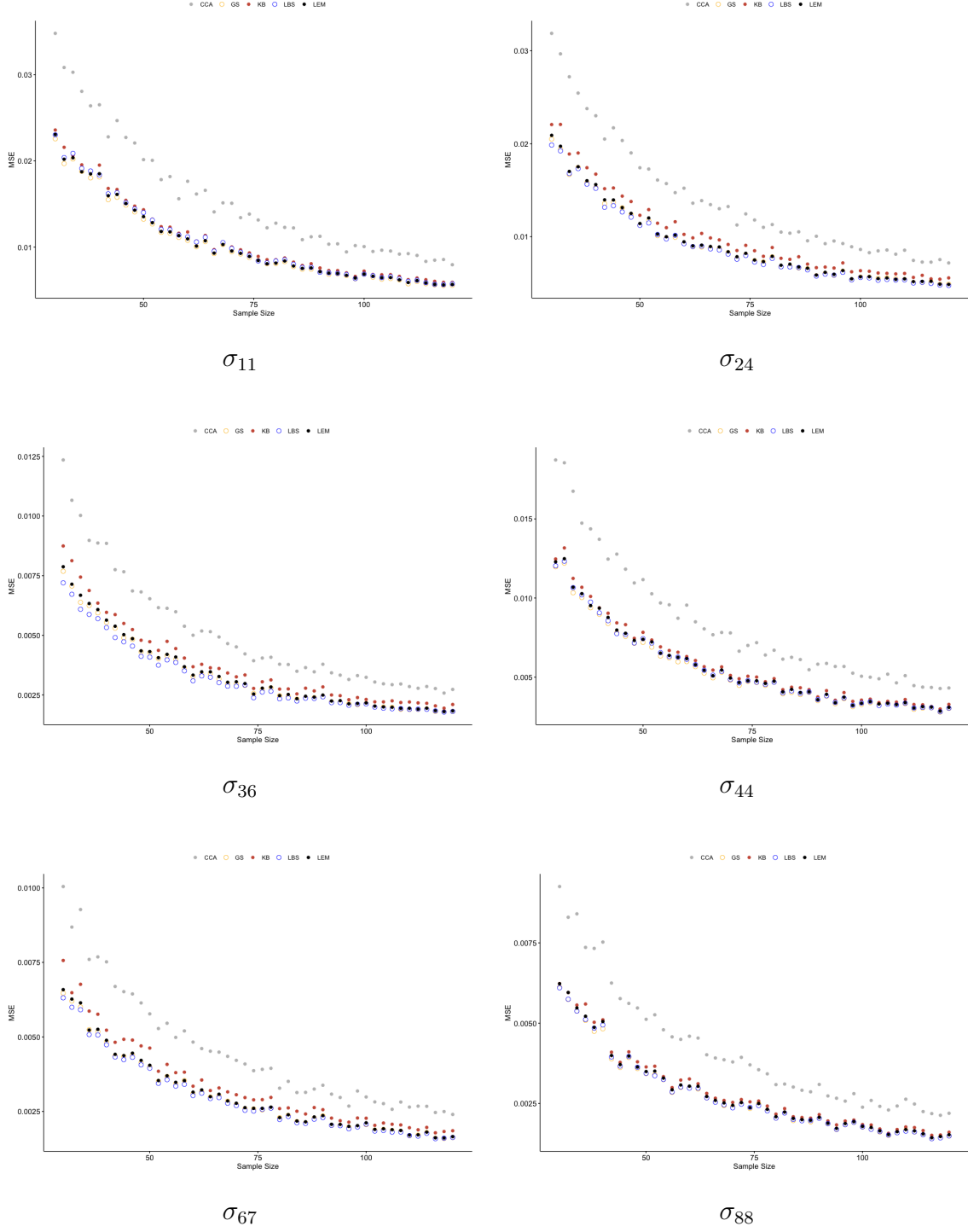


Figure 4.34: Element-wise MSE values for selected elements of $\hat{\Sigma}$, where scenarios with varying sample sizes (ranging from $n = 30$ to $n = 120$) are considered. All scenarios consist of $k = 2$ groups, $p = 8$ time points, quadratic mean structure ($q = 3$) for both groups and 5% MCAR. The MLEs from the glucose data were used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate empirical the MSEs.

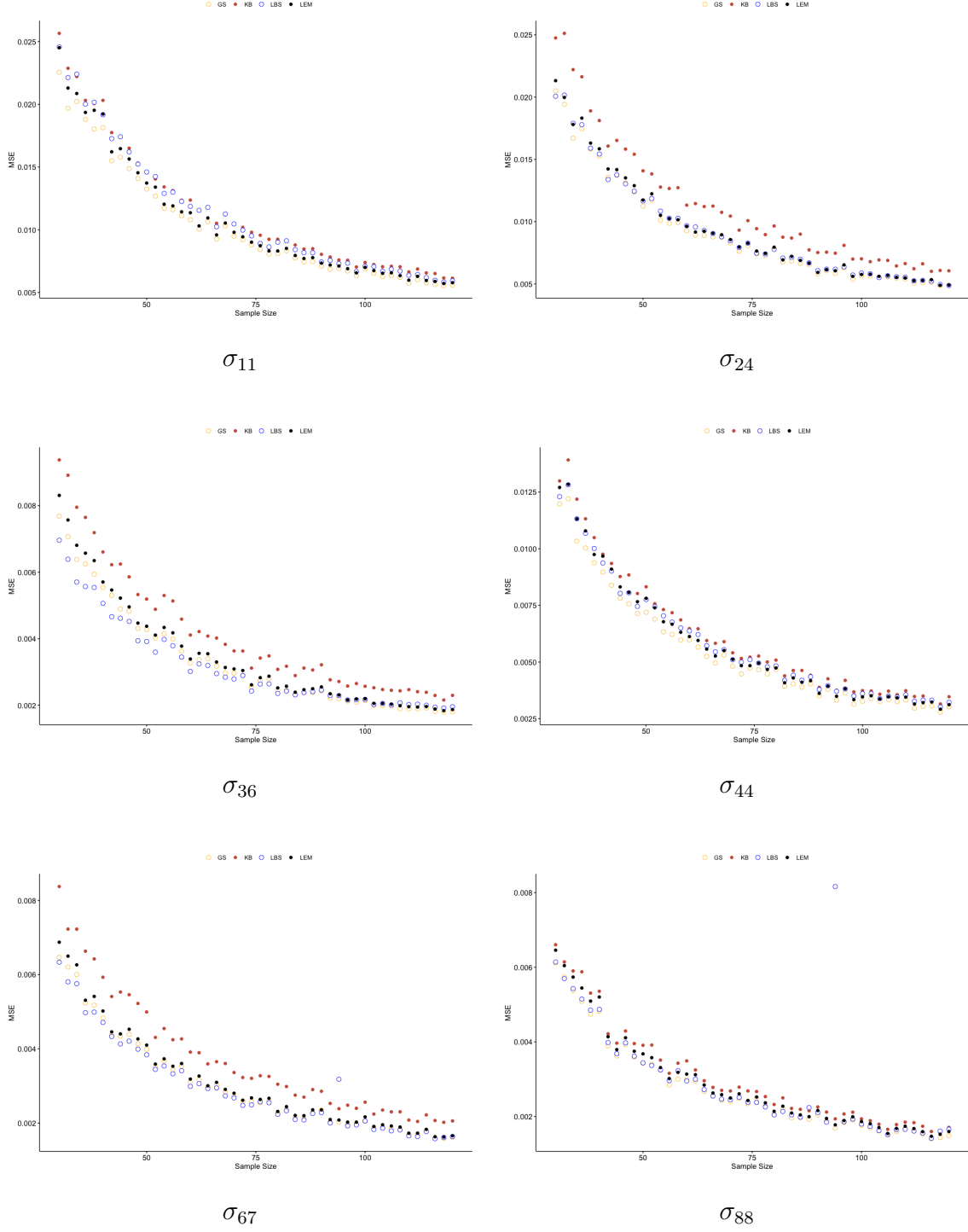


Figure 4.35: Element-wise MSE values for selected elements of $\hat{\Sigma}$, where scenarios with varying sample sizes (ranging from $n = 30$ to $n = 120$) are considered. All scenarios consist of $k = 2$ groups, $p = 8$ time points, quadratic mean structure ($q = 3$) for both groups and 10% MCAR. The MLEs from the glucose data were used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate empirical the MSEs

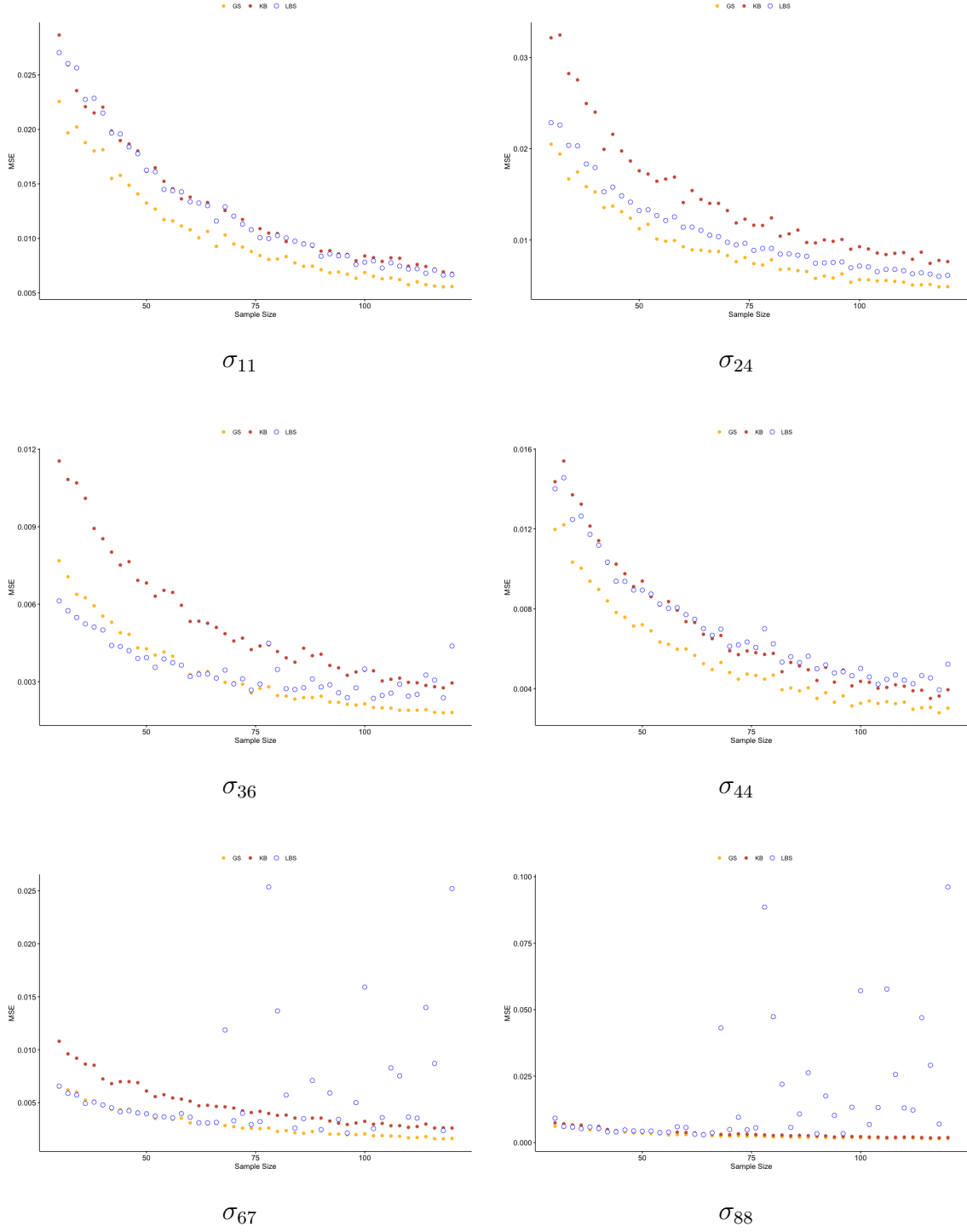


Figure 4.36: Element-wise MSE values for selected elements of $\hat{\Sigma}$, where scenarios with varying sample sizes (ranging from $n = 30$ to $n = 120$) are considered. All scenarios consist of $k = 2$ groups, $p = 8$ time points, quadratic mean structure ($q = 3$) for both groups and 20% MCAR. The MLEs from the glucose data were used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate empirical the MSEs.

4.2.2.2 Missing at Random

In this section, we present the results of the simulation studies involving longitudinal data with $k = 2$ groups, $p = 8$ time points and various sample sizes. The missing data were generated using the MAR mechanism with 5%, 10% and 20% of the data missing. Similar to Experiment 1, we generated the MAR missingness by setting 10% missing possibility for observations in Group 1 and 30% missing possibility for observations in Group 2. We calculated element-wise and aggregated bias and, and the results are presented in tables and figures.

Table 4.7: Aggregated bias and MSE for scenarios with 5%, 10% and 20% MAR, where $n = 50$, $p = 8$, $q = 3$, and the MLEs from the glucose data are used as true values of $\mathbf{B}$ and $\mathbf{\Sigma}$. Bias across the elements of matrix estimators are aggregated using average absolute bias and MSE is aggregated as an average of the element-wise MSEs.

		Methods				
		GS	CCA	KB	LBS	LEM
5%						
Bias	$\mathbf{B}$	0.00095	0.00107	0.02028	0.00054	0.00819
	$\mathbf{\Sigma}$	0.00765	0.01043	0.00117	0.01520	0.00748
MSE	$\mathbf{B}$	0.02099	0.03723	17.76600	0.02317	0.02106
	$\mathbf{\Sigma}$	0.00812	0.01165	0.00893	0.00807	0.00832
10%						
Bias	$\mathbf{B}$	0.00095	0.00130	0.23847	0.00086	0.01847
	$\mathbf{\Sigma}$	0.00765	0.01221	0.00107	0.02340	0.00721
MSE	$\mathbf{B}$	0.02099	0.07688	816.78656	0.02551	0.02172
	$\mathbf{\Sigma}$	0.00812	0.01736	0.00981	0.00838	0.00849
20%						
Bias	$\mathbf{B}$	0.00095	0.00434	0.21073	0.00131	0.04200
	$\mathbf{\Sigma}$	0.00765	0.01025	0.00103	0.04019	0.04119
MSE	$\mathbf{B}$	0.02099	0.41472	58.69719	0.03169	0.03564
	$\mathbf{\Sigma}$	0.00812	0.05470	0.01191	0.01107	0.99406

The aggregated bias and MSE presented results in Table 4.7 as well as the element-wise bias plots presented in Figures B.8, B.9 and B.10 (Appendix) show that the findings are similar to the corresponding scenarios in Experiment 1. This indicates that the Bayesian and EM algorithm have comparable accuracy as the gold-standard in estimating $\mathbf{B}$, regardless of the values of p , k , sample size and mean structure. The performance of the Bayesian and EM are quite good, even when the percentage of missingness increases. However, we observe that bias increases as the missingness percentage increases, which is to be expected. The results also show that complete case analysis has a good performance for 5% MAR, however, its bias and MSE increase significantly as the percentage of missingness increases, which we have also seen the MAR scenarios in Experiment 1.

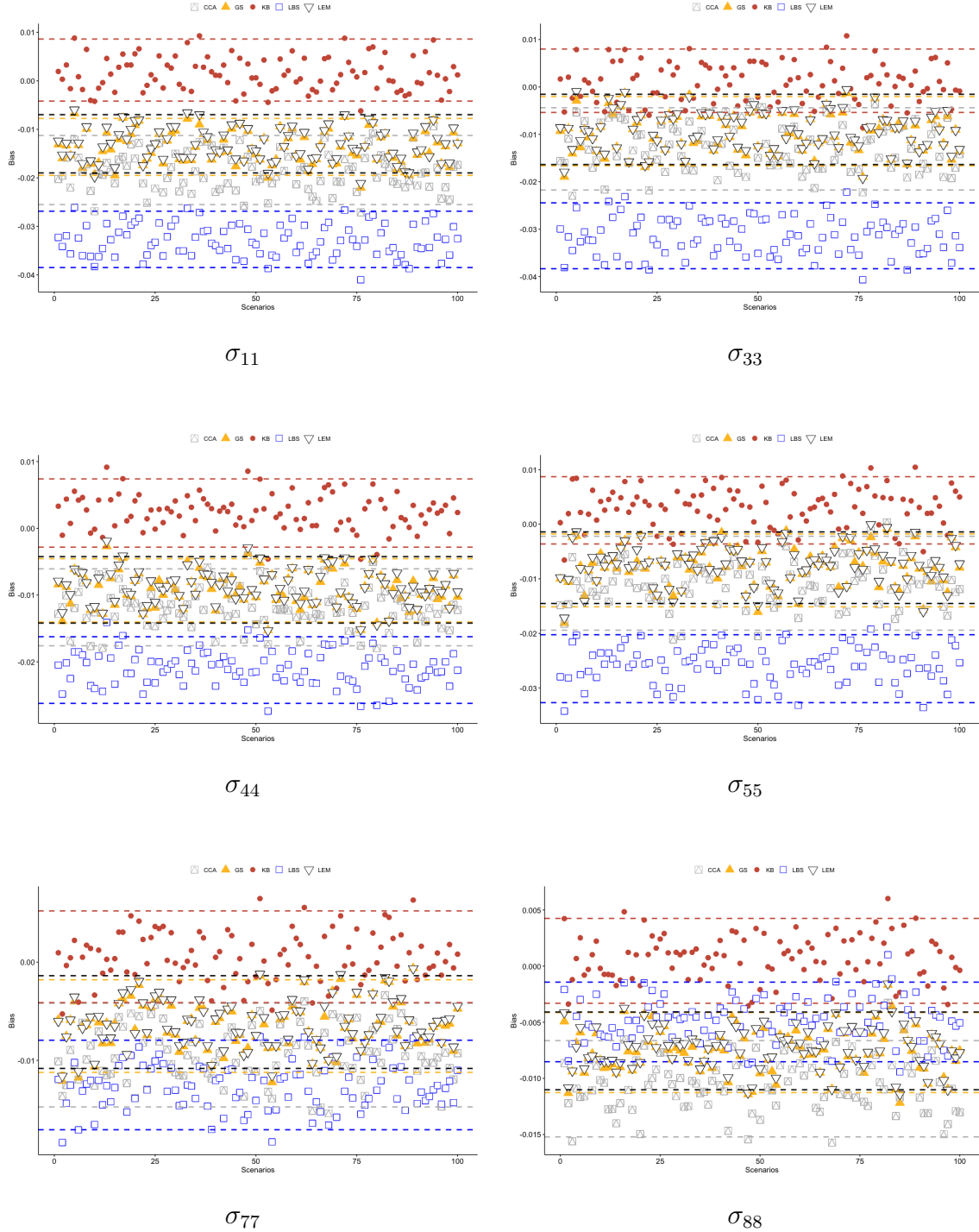


Figure 4.37: Element-wise bias for selected estimators of variances (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% missing with MAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

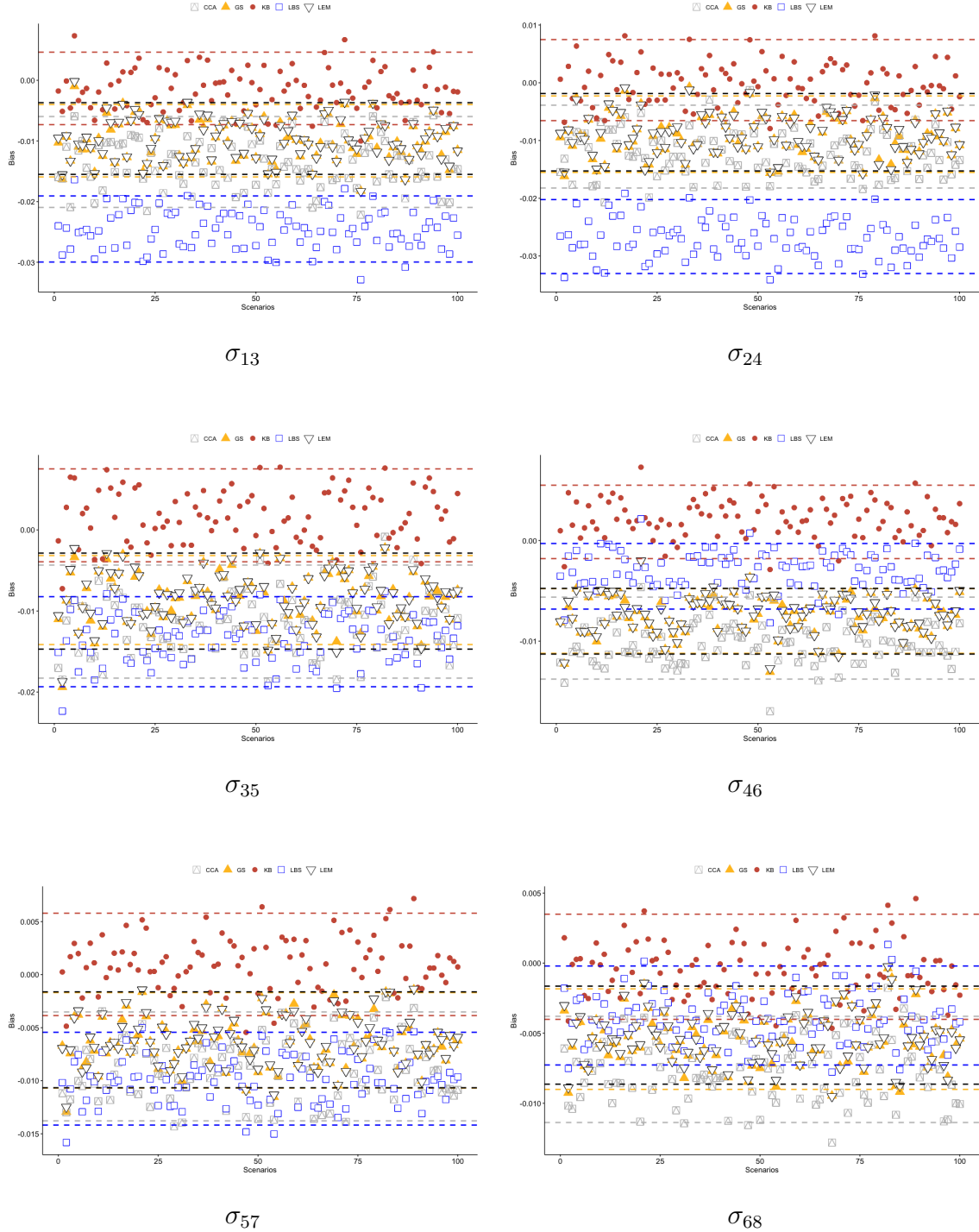


Figure 4.38: Element-wise bias for selected estimators of covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% MAR mechanism. The MLEs from the glucose data are used as true values for B and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Figures B.8 and B.9 also show that the complete case analysis and the Bayesian approach, when the missingness percentage is relatively small, produce unbiased estimators, where element-wise bias is seen to fluctuate randomly around zero. However, this is no longer true for 20% MAR, where the complete case analysis is shown to produce biased estimators for $\mathbf{B}$ (Figure B.10). The EM algorithm produced biased estimators for some of the elements of $\mathbf{B}$, and the bias is seen to go both directions (i.e. it overestimates or underestimates some of the elements of the matrix).

Overall, element-wise bias plots for variance and covariance estimators (Figures 4.37 and 4.39) show that the results for 5% MAR lead to similar conclusions as the corresponding scenarios of Experiment 1, where the EM algorithm and gold-standard have similar performance in terms of accuracy. However, the EM algorithm shows relatively higher variability than the gold-standard in some scenarios, which will be investigated further using element-wise MSEs.

Kleinbaum’s method, although it produces positively biased estimators similar to the results we saw for MAR scenarios in Experiment 1, the bias we observe in Experiment 2 for this approach seems to be relatively smaller (Figures 4.37 and 4.38). In fact, we see later in the MSE plots that Kleinbaum’s method is the most optimal approach when estimating Σ , even when the percentage of missingness is large. This may be due to the fact that we encounter less sparsity in Experiment 2, since the number of time points (p) is relatively larger.

Overall, the results show that the complete case analysis led to estimators with poor performance, even when the missingness percentage is small (Figures 4.37, 4.38, 4.39 and 4.40). As the percentage of missingness increases to 20%, we see that the complete case analysis method and the EM algorithm led to unstable variance estimators (Figure 4.41), as such the bias associated with these two methods could not be presented in the same plot as the other methods. On the other hand, the EM algorithm seems to work very well in estimating the covariances for data with 20% missing, in some cases with comparable performance as the gold-standard (Figure 4.42).

The Bayesian method led to negative bias in estimating both the variance and the covariances in Σ (Figures 4.37 and 4.38). In some cases biases associated with this method are large and in some cases small. As the percentage of missingness increases, the magnitude of bias increased in most cases (Figures 4.39, 4.40, 4.41 and 4.42). However, in some cases, the Bayesian method seems to be working well, leading to a much smaller bias. Nevertheless, this might be due to its instability as we can see later in the MSE plots.

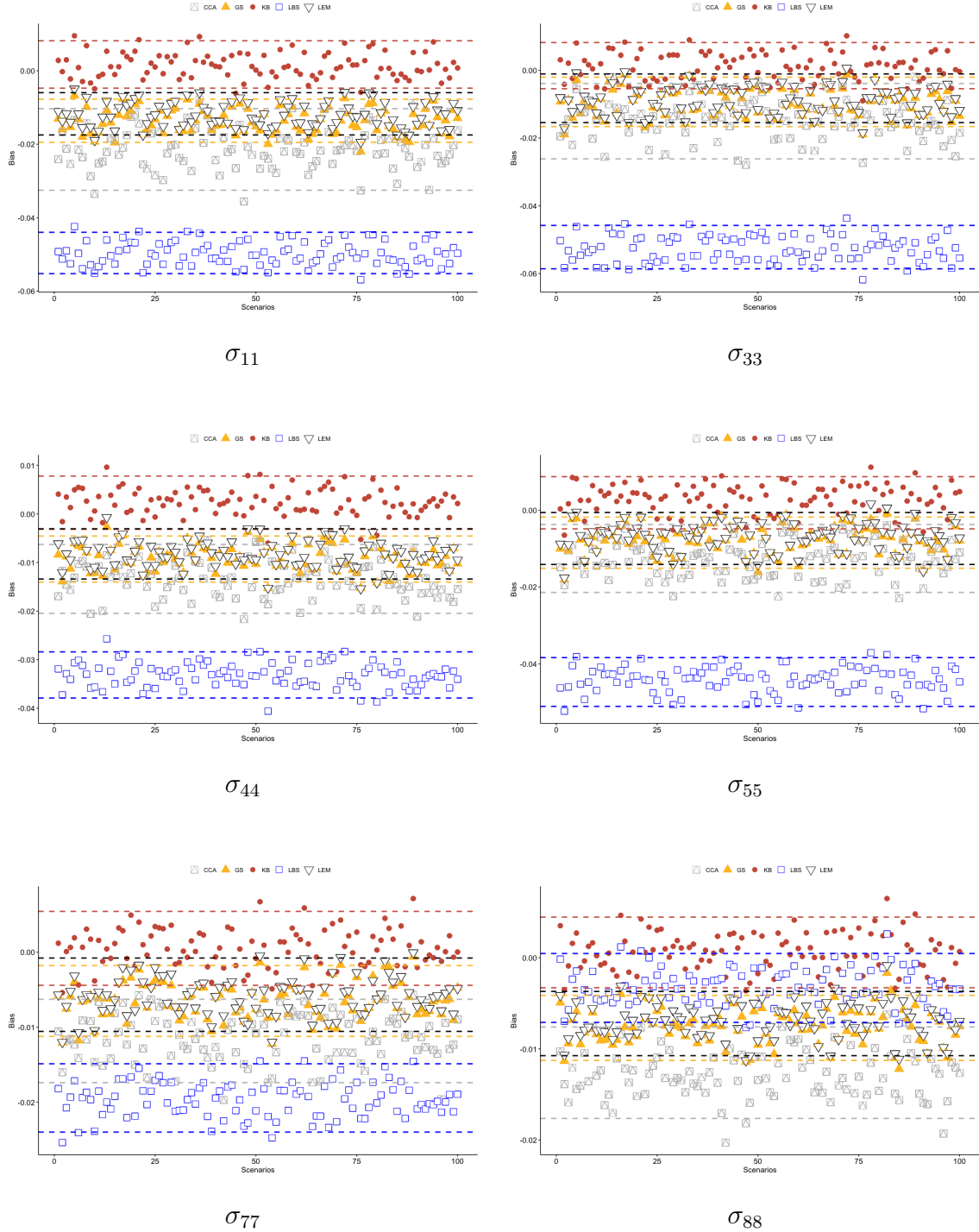


Figure 4.39: Element-wise bias for selected estimators of variances (diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% MAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

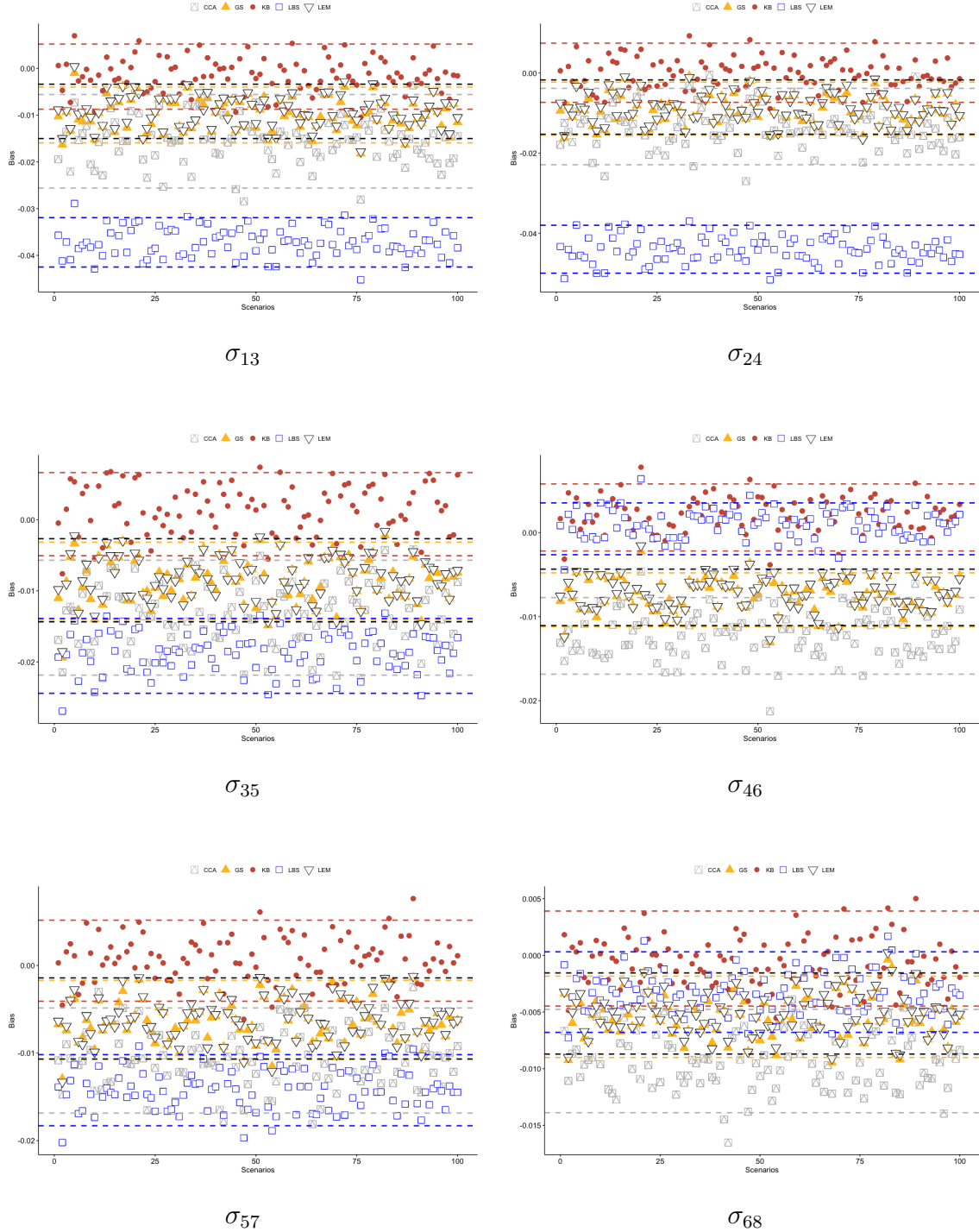


Figure 4.40: Element-wise bias for selected estimators of covariances (off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% MAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the empirical bias is calculated and plotted in the graphs.

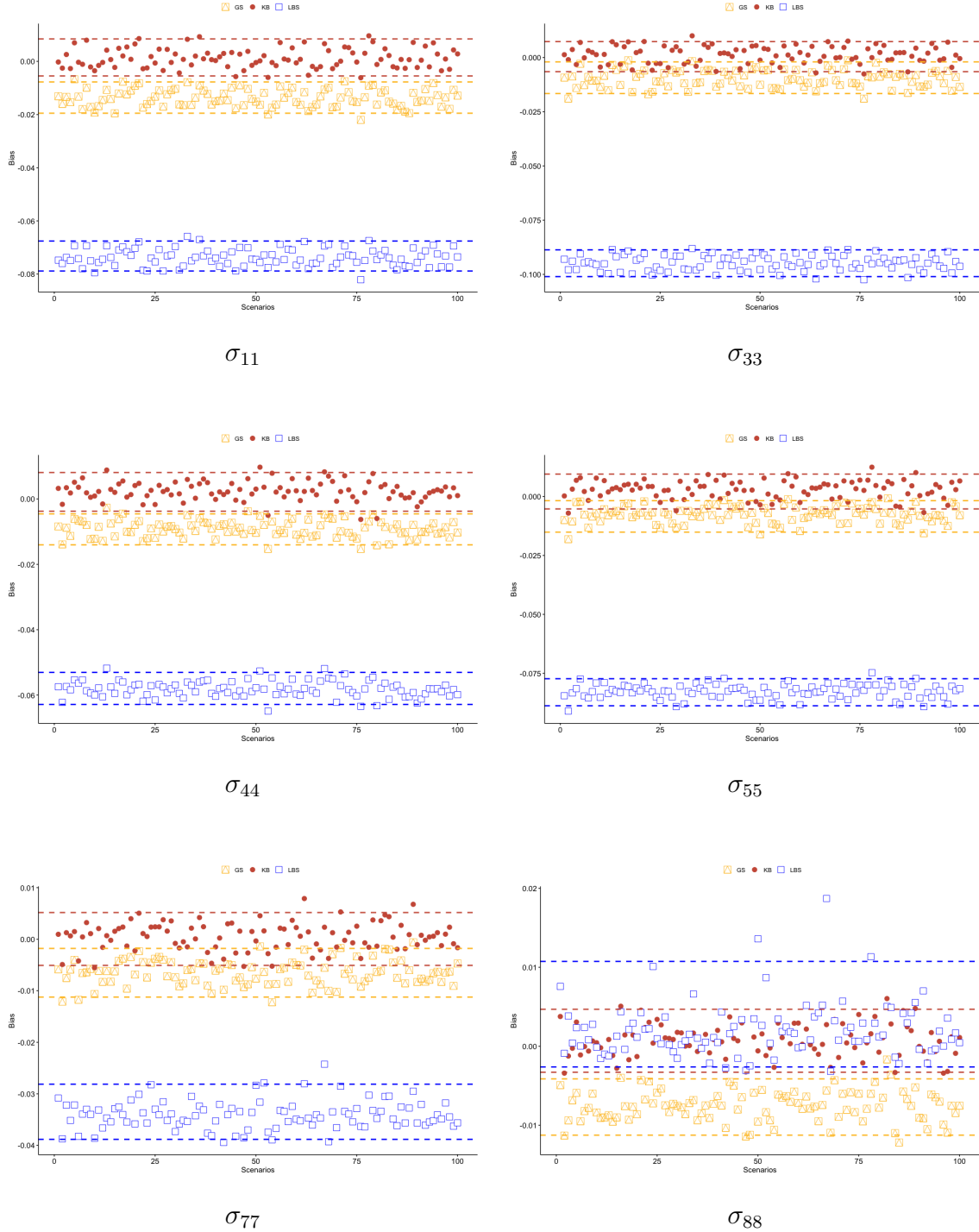


Figure 4.41: Element-wise bias for selected estimators of variances (diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% MAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

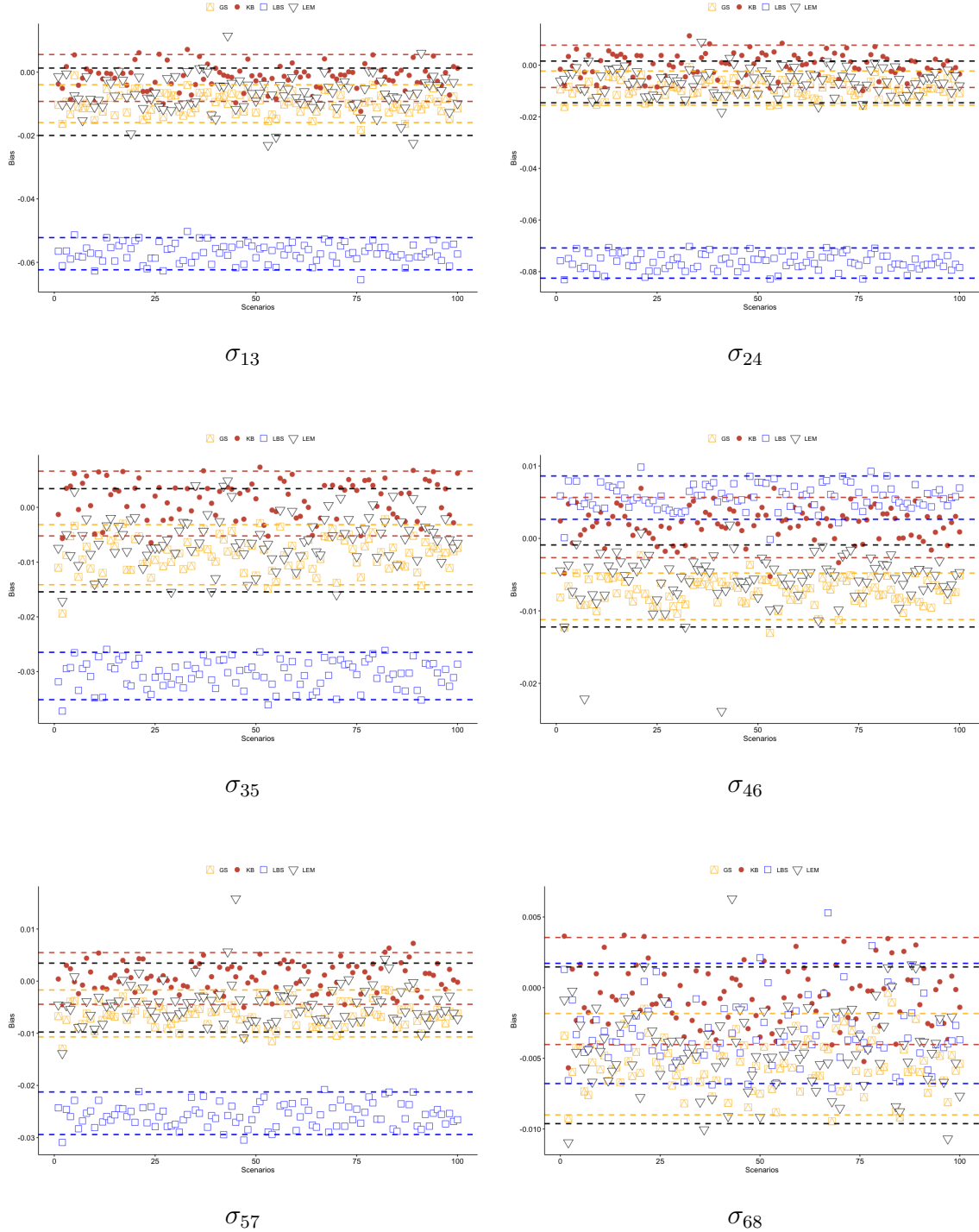


Figure 4.42: Element-wise bias for selected estimators of covariances (off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% MAR mechanism. The MLEs from the glucose data are used as true values for B and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

For 5% MAR, the plots of the element-wise MSE show that the EM algorithm has a comparable performance as the gold-standard in estimating all the elements of $\mathbf{B}$ (Figure 4.43). The Bayesian method led to a uniformly higher MSE values across all the sample sizes, however, the difference seems to be very small. Hence, the results indicate that for 5% MAR, the EM algorithm and the Bayesian approaches lead to good estimators for the mean parameters of the GCM. On the other hand, complete case analysis produced estimators with uniformly higher MSE values across all the sample sizes. From the figure, we can also see that the MSE for all the methods considered decreased monotonically as $n \rightarrow \infty$, hence demonstrating MSE consistency of the estimators. Kleinbaum's method led to unstable estimators with very large variability, hence very large MSE values, hence could not be shown in the same plot as the other methods.

Similar results were observed as the missingness percentage increases to 10% (Figure 4.44), but the MSE corresponding to complete case analysis increased indicating further loss of optimality, which is to be expected. On the other hand, when the missingness increased to 20%, the performance of the other methods started to deteriorate as well (Figure 4.45). For instance, the MSE for the EM algorithm was significantly larger than the gold-standard for small sample sizes. However, the performance of the Bayesian method, despite a slight increase in MSE, is still good across all sample sizes. For large sample size, both the EM and the Bayesian methods perform reasonably well. For 20% MAR, the complete case analysis led to estimators with very high MSE, hence could not be presented in the same plots as the other methods.

Looking at element-wise MSE in estimating Σ when data involves 5% MAR, the EM algorithm, the Bayesian method and Kleinbaum's approach led to comparable performance as the gold-standard (Figure 4.46). We can also observe that Kleinbaum's method has a slightly higher, but negligible, MSE compared to the Bayesian and EM algorithm. The complete case analysis led to estimators with uniformly higher MSE values across all the sample sizes, and the difference in performance is more pronounced for smaller sample sizes.

When the missingness percentage increased to 10%, we also observe the same results where the EM algorithm, Kleinbaum's method and the Bayesian approach performing relatively well (Figure 4.47). However, in some cases we see that the Bayesian method corrects the bias in the gold-standard, but we see also some variability (instability) for larger sample sizes. Kleinbaum's method is seem to produce estimators with slightly higher MSE values in some cases as well. From Figures 4.46 and 4.47, we observe that all the methods led to MSE consistent estimators except in a few instances where the Bayesian method showing some instability for large sample size. As the missingness percentage increases to 20%, we see this instability in the Bayesian approach more pronounced (Figure 4.48). Moreover, the EM algorithm led to very unstable results in estimating Σ with very large MSE value, hence could not be presented in the same plot as the other methods. The results show that Kleinbaum's method is the strongest, for data with large percentage of missingness with the MAR mechanism.

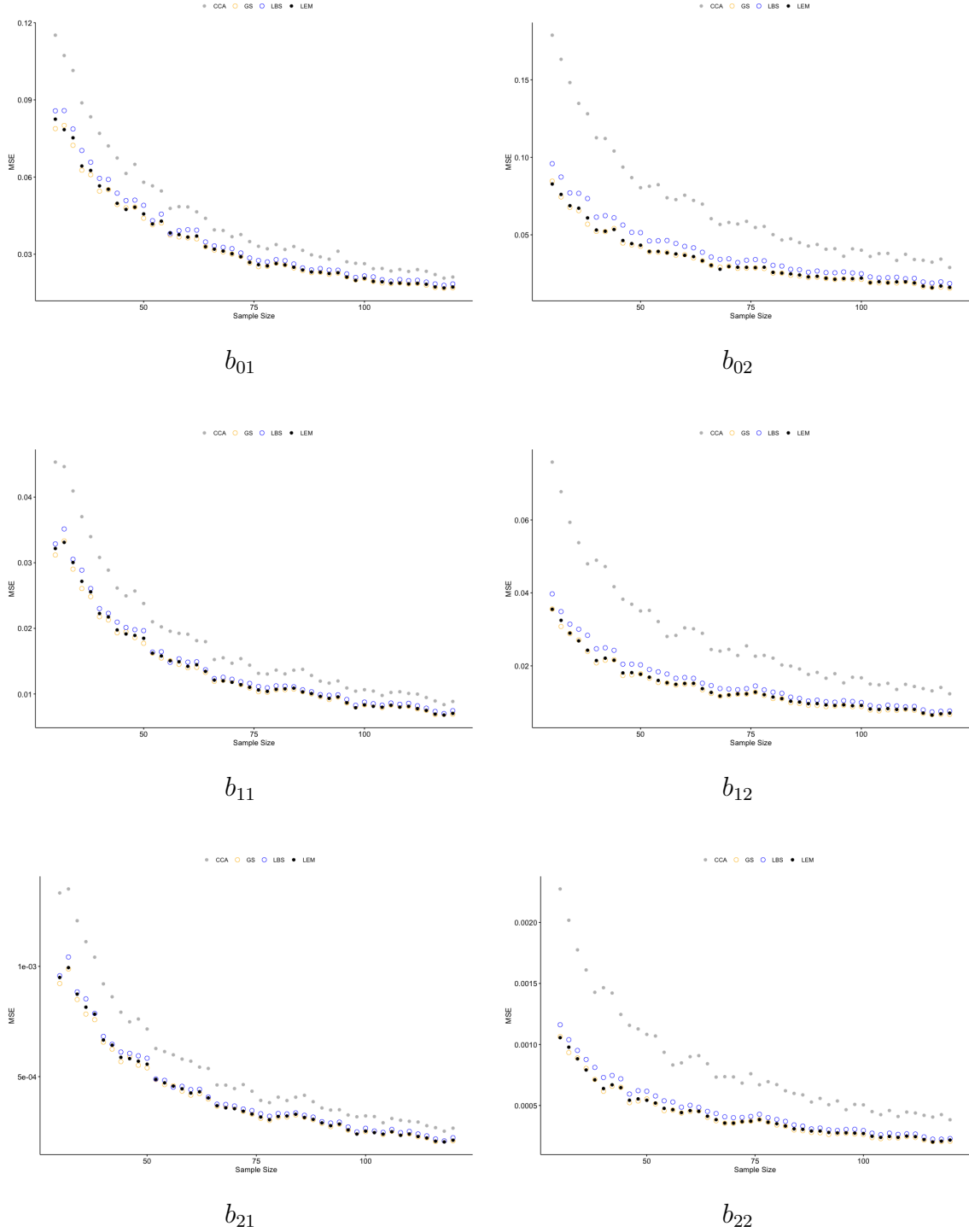


Figure 4.43: Element-wise MSE corresponding to $\hat{\mathbf{B}}$, where 46 scenarios with varying sample sizes (ranging from $n = 30$ to $n = 120$) are considered. Data consisted of $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 5% MAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate MSE empirically.

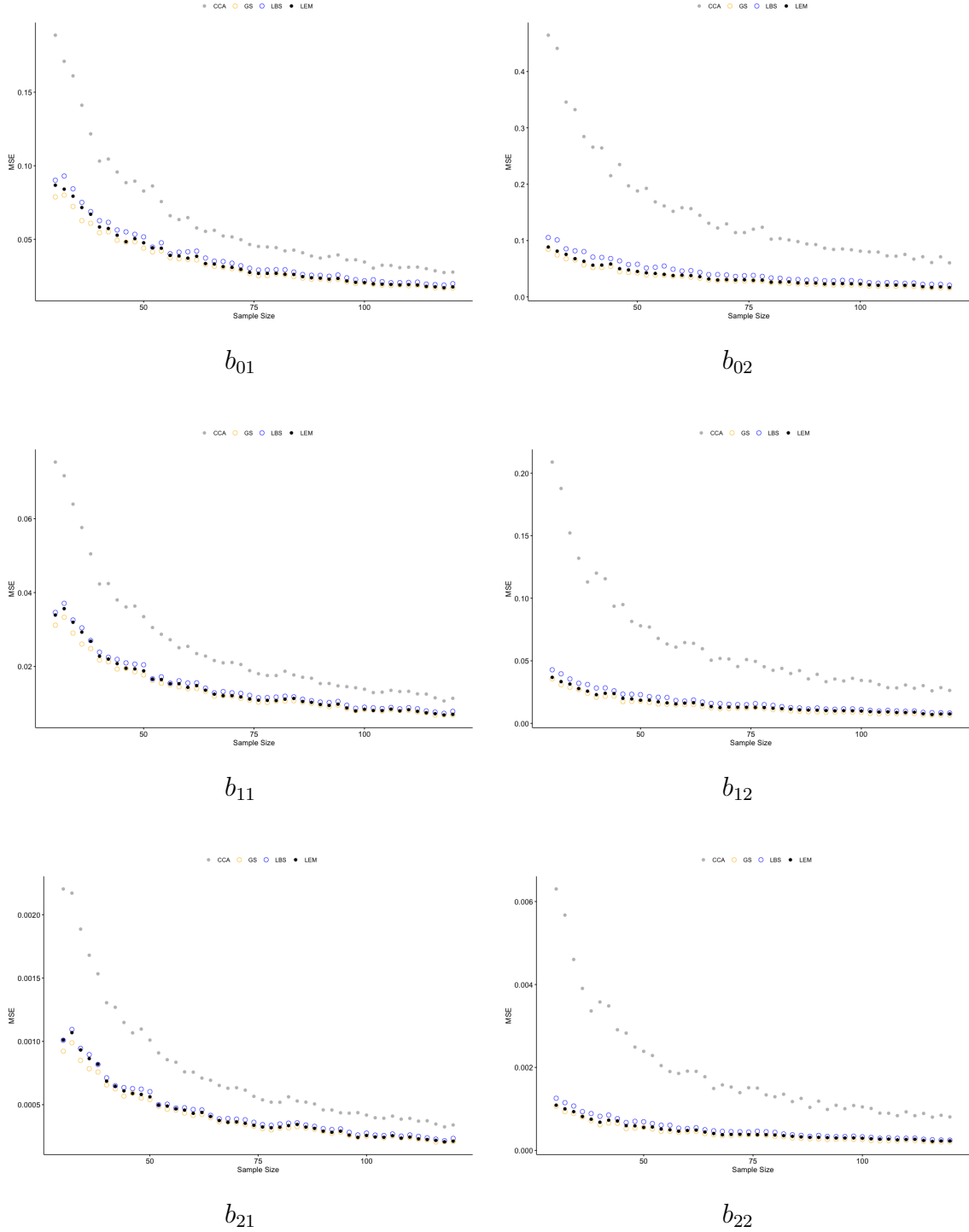


Figure 4.44: Element-wise MSE corresponding to $\hat{\mathbf{B}}$, where 46 scenarios with varying sample sizes (ranging from $n = 30$ to $n = 120$) are considered. Data consisted of $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 10% MAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate MSE empirically.

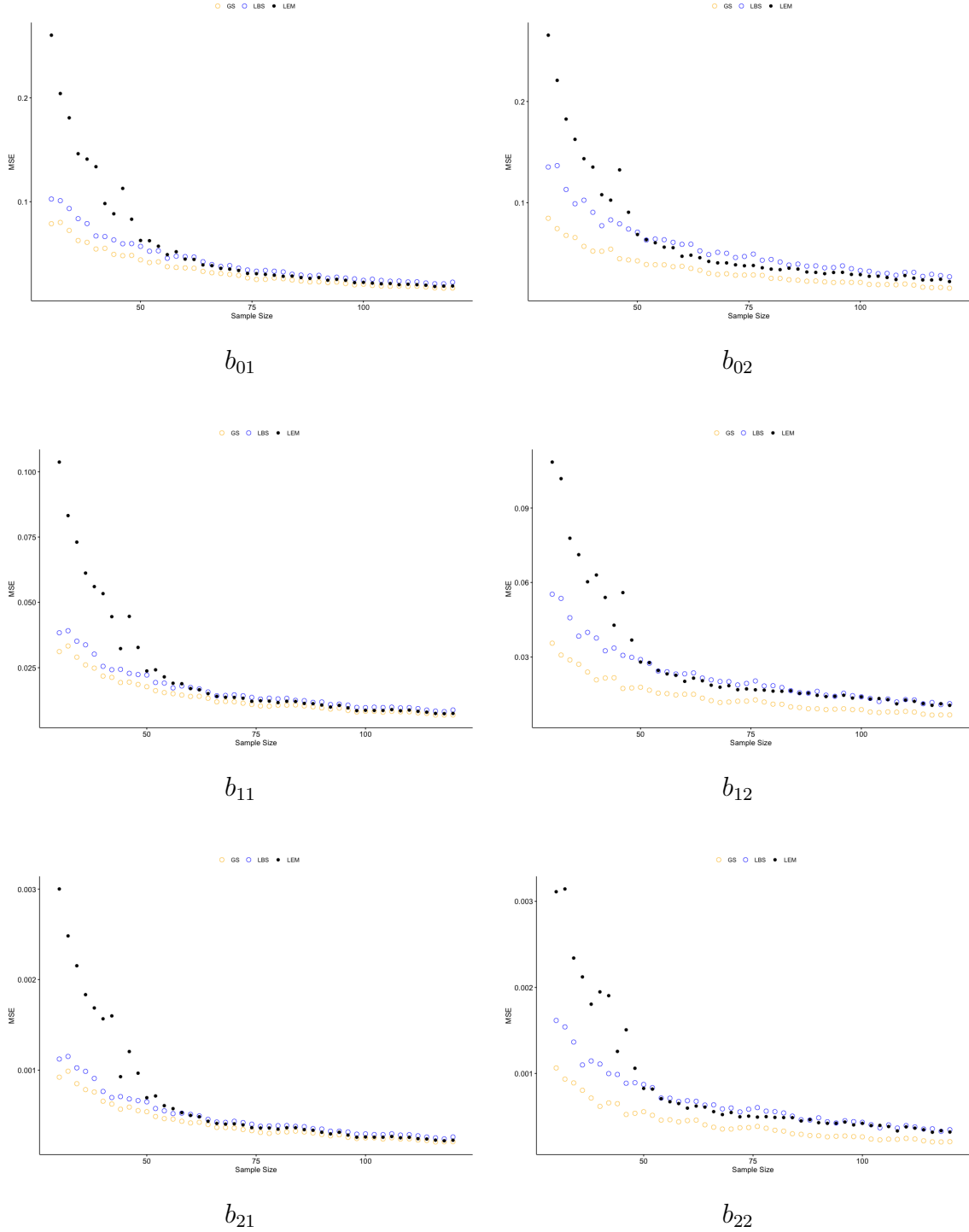


Figure 4.45: Element-wise MSE corresponding to $\hat{\mathbf{B}}$, where 46 scenarios with varying sample sizes (ranging from $n = 30$ to $n = 120$) are considered. Data consisted of $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 20% MAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate MSE empirically.

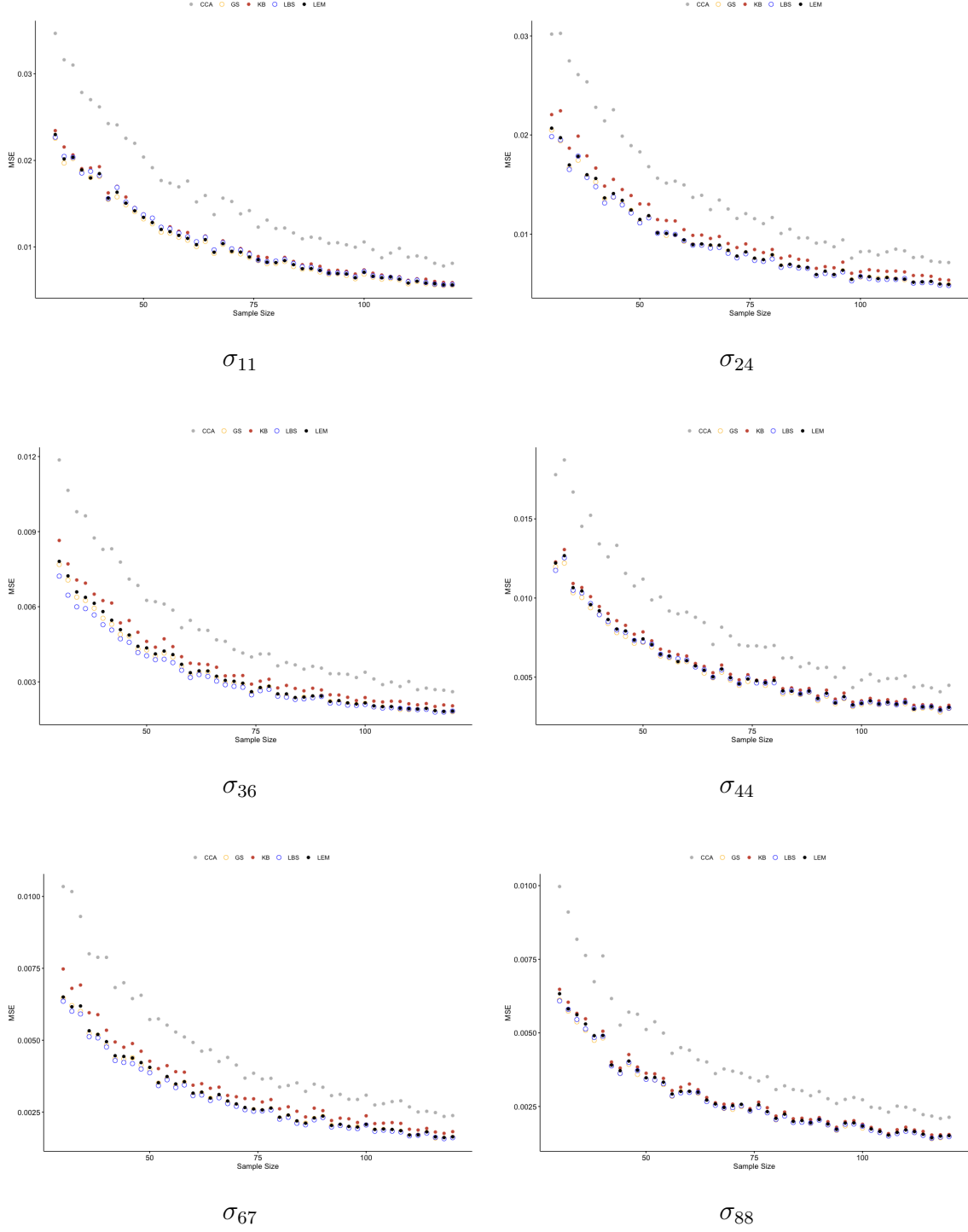


Figure 4.46: Element-wise MSE for selected elements of $\hat{\Sigma}$, where 46 scenarios of varying sample size (ranging from $n = 30$ to $n = 120$) are considered. The simulated data consisted of $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 5% MAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and the calculate empirical MSE plotted in the graphs.

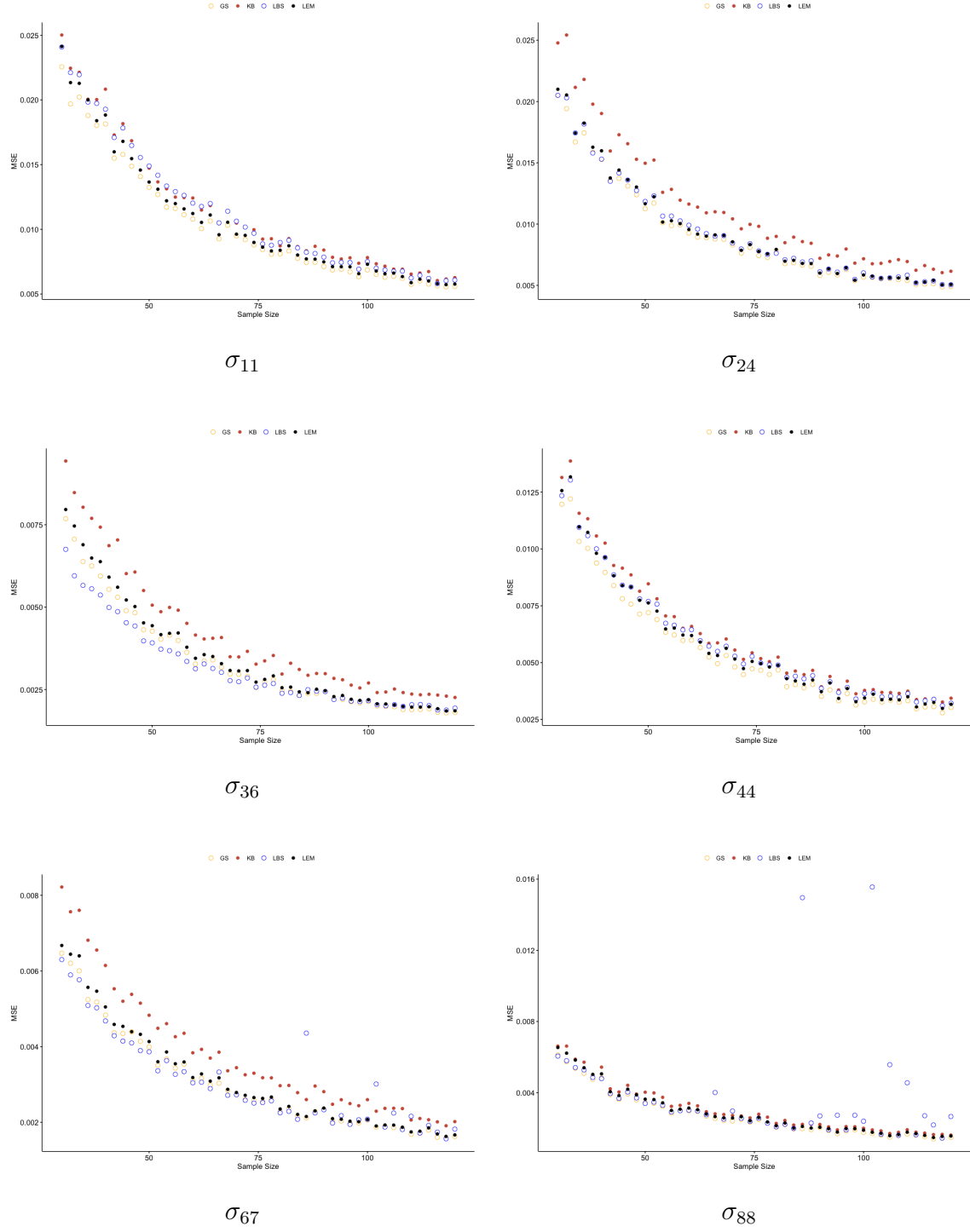


Figure 4.47: Element-wise MSE for selected elements of $\hat{\Sigma}$, where 46 scenarios of varying sample size (ranging from $n = 30$ to $n = 120$) are considered. The simulated data consisted of $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 10% MAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and the calculate empirical MSE plotted in the graphs.

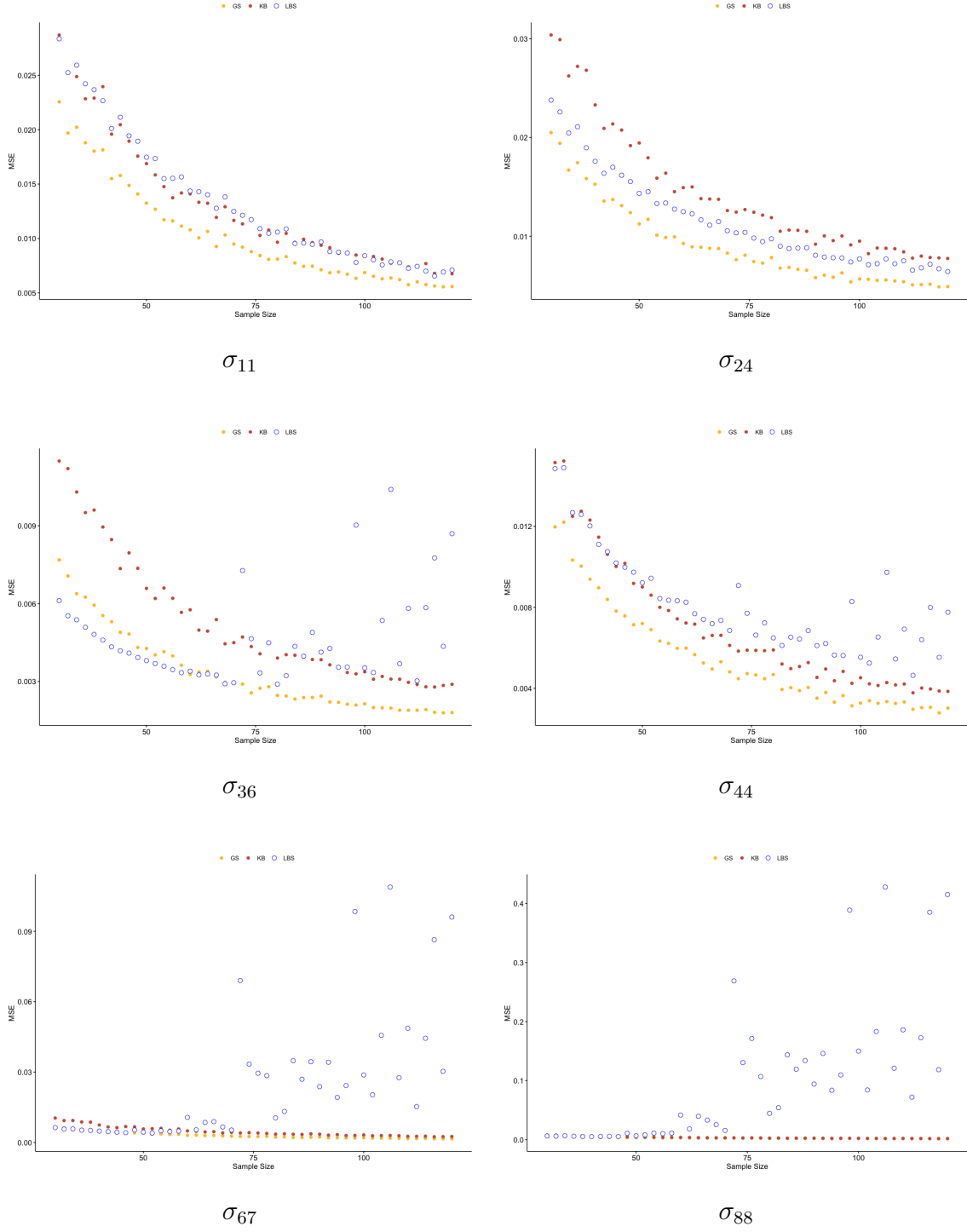


Figure 4.48: Element-wise MSE for selected elements of $\hat{\Sigma}$, where 46 scenarios of varying sample size (ranging from $n = 30$ to $n = 120$) are considered. The simulated data consisted of $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 20% MAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and the calculate empirical MSE plotted in the graphs.

4.2.2.3 Missing Not at Random

Here, we present the simulation results for the scenarios, where the missing data is generated according to the MNAR mechanism. In these simulations, we generated longitudinal data measured at $p = 8$ time points and evaluated performance when 5%, 10% and 20% of the data is missing. We considered various sample sizes, two groups ($k = 2$) and quadratic mean structure ($q = 3$) for both groups. The MLEs from the glucose data were used as the true parameters for $\mathbf{B}$ and $\mathbf{\Sigma}$. We created the MNR missingness by letting observations greater than 3.00 to be missing with a 60% probability, while those at or below 3.00 were missing with a 50% probability. We calculated element-wise and aggregated bias and MSE and presented the results in tables and figures.

Table 4.8: Aggregated bias and MSE for scenarios with 5%, 10% and 20% MNAR, where $n = 50$, $p = 8$, $q = 3$, and the MLEs from the glucose data are used as true values of $\mathbf{B}$ and $\mathbf{\Sigma}$. Bias across the elements of matrix estimators are aggregated using average of the absolute bias and MSE is aggregated as an average of the element-wise MSEs.

		Methods				
		GS	CCA	KB	LBS	LEM
5%						
Bias	$\mathbf{B}$	0.00095	0.00268	0.08998	0.00177	0.00686
	$\mathbf{\Sigma}$	0.00765	0.00840	0.00139	0.01486	0.00728
MSE	$\mathbf{B}$	0.02099	0.03527	3.73280	0.02333	0.02104
	$\mathbf{\Sigma}$	0.00812	0.01234	0.00890	0.00809	0.00829
10%						
Bias	$\mathbf{B}$	0.00095	0.00540	0.50051	0.00309	0.01539
	$\mathbf{\Sigma}$	0.00765	0.00894	0.00198	0.02242	0.00675
MSE	$\mathbf{B}$	0.02099	0.06712	1049.03000	0.02512	0.02240
	$\mathbf{\Sigma}$	0.00812	0.01966	0.00987	0.00828	0.00846
20%						
Bias	$\mathbf{B}$	0.00095	0.02888	0.26427	0.00639	0.03876
	$\mathbf{\Sigma}$	0.00765	0.05096	0.00361	0.03539	0.33527
MSE	$\mathbf{B}$	0.02099	0.48817	277.75675	0.02983	0.05868
	$\mathbf{\Sigma}$	0.00812	0.29563	0.01215	0.00924	1840.42600

From Table 4.8, we can see that the complete case analysis still provides reasonable estimators when the percentage of missing data is small. Nevertheless, the estimators from this approach overall seem to have uniformly larger MSE values, hence there is loss of precision when using this method for handling missing data when the mechanism is MNAR. As the percentage of missing data increases, both the bias and MSE from the complete case analysis increase. On the other hand, the Bayesian method, in most cases, provides estimators with a comparable performance as the gold-standard. However, we observed some instability in this method when the missingness percentage is large, which we will investigate further using MSE plots with respect to sample size. The EM algorithm seems to work reasonably well for small percentage of missingness, especially considering MSE which is

comparable to the gold-standard. However, this method provided estimators with slightly higher bias than the gold-standard. As the percentage of missingness increases, the EM algorithm becomes unstable and produces estimators with high MSE values. Surprisingly, Kleinbaum’s method seems to correct the bias in estimating Σ and provided estimators that are less biased than even the gold-standard. What was more surprising is that the bias correction did not come at the expense of increased variance, since we observe that the MSE for this method is comparable to the gold-standard. Nevertheless, Kleinbaum’s method is unstable for estimating $\mathbf{B}$ and should not be used, not only in scenarios with MNAR but in general, since we have seen this behavior in most of the simulation scenarios we considered.

From the element-wise plots for 5% MNAR provided in Figure 4.49, we see that bias in estimating $\mathbf{B}$ indeed is randomly distributed around zero for the gold-standard, complete case analysis as well as the Bayesian method. As mentioned earlier, for the gold-standard, this is to be expected, since it can be mathematically shown that the MLE of $\mathbf{B}$ is unbiased. We also observe from Figure 4.49 that EM algorithm tends to underestimate or overestimate the elements of $\mathbf{B}$. However, the method still produces estimators with a relatively small bias and comparable variability with the gold-standard.

When the missingness percentages increase to 10% MNA, we observe that the element-wise bias for complete case analysis still randomly fluctuates around zero for some elements, while showing some negative bias for others (Figure 4.50). Moreover, we see that the variability of the estimators for the complete case analysis increased. The Bayesian method seems to still work very well for 10% MNAR, in some cases maintaining its unbiasedness. We also observe that the Bayesian method maintains small variability, which is compared to the gold-standard. The bias for the EM algorithm seems to be more pronounced for 10% MNAR, compared to 5% MNA. We also observe that the direction of bias (overestimate or underestimate) has not changed as the percentage of missingness increased. Moreover, the variability of the estimators from the EM algorithm seems to stay similar as the percentage of missingness increases.

When the percentage of missingness increased to 20% MNAR, the performance of the estimators from the complete case analysis deteriorated significantly, where both bias and variability increased significantly (Figure 4.51). In some cases, we observe element-wise bias that seems to be randomly distributed around zero, however, the variability is very high. Overall, Figure 4.51 shows that the Bayesian method has the closest performance to the gold-standard, with respect to the magnitude of bias and variability of the estimators. We also observe that the method overestimates in some cases and underestimates in others, however, the difference from the gold-standard (which is unbiased) is quite small. The EM algorithm seems to have larger bias for scenarios with 20% MNAR, compared to 5% and 10%, however, the method produces estimators with a relatively small variability. However, the variability in the EM algorithm seems to be slightly larger than that of the gold-standard and the Bayesian approach (Figure 4.51).

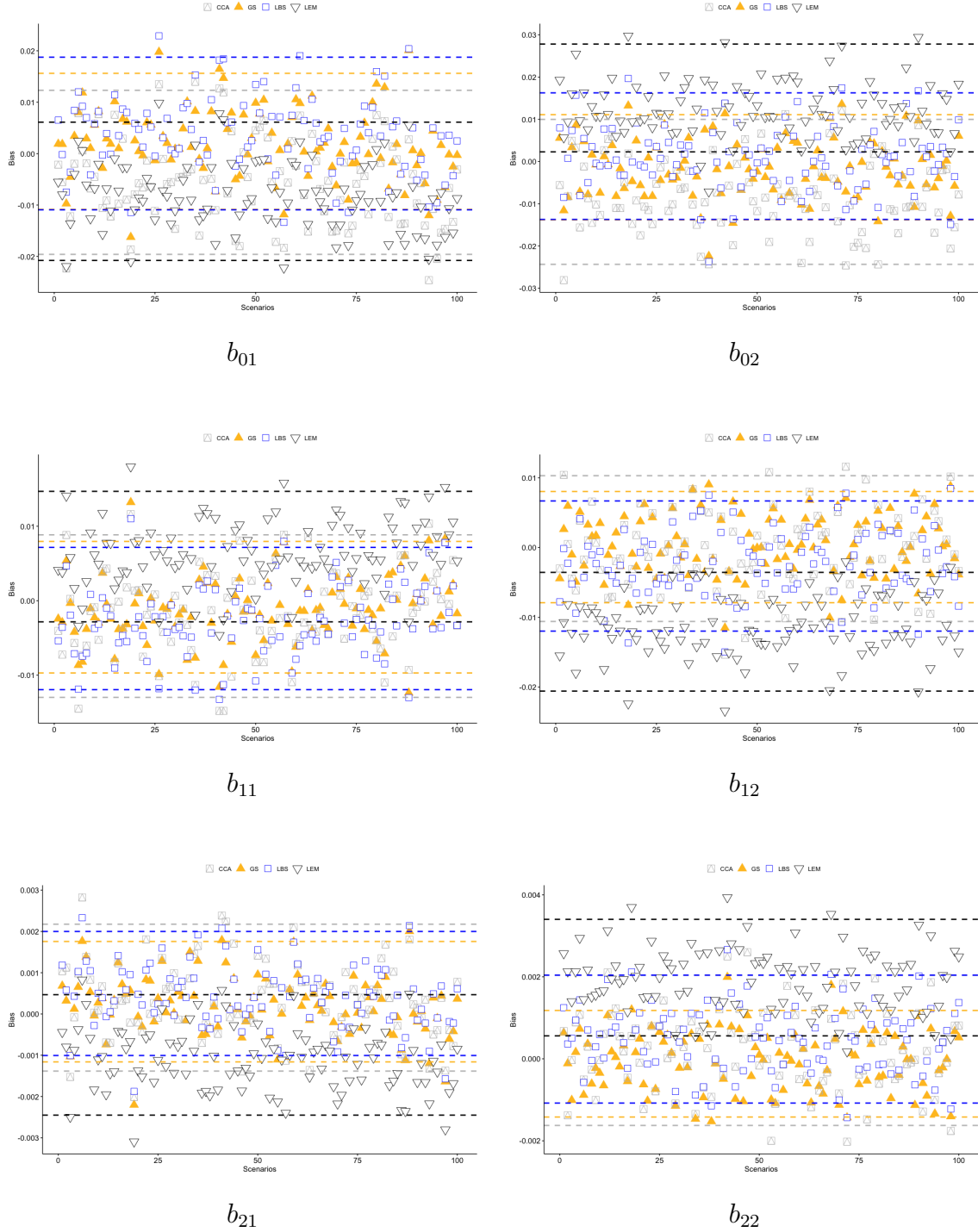


Figure 4.49: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% MNAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

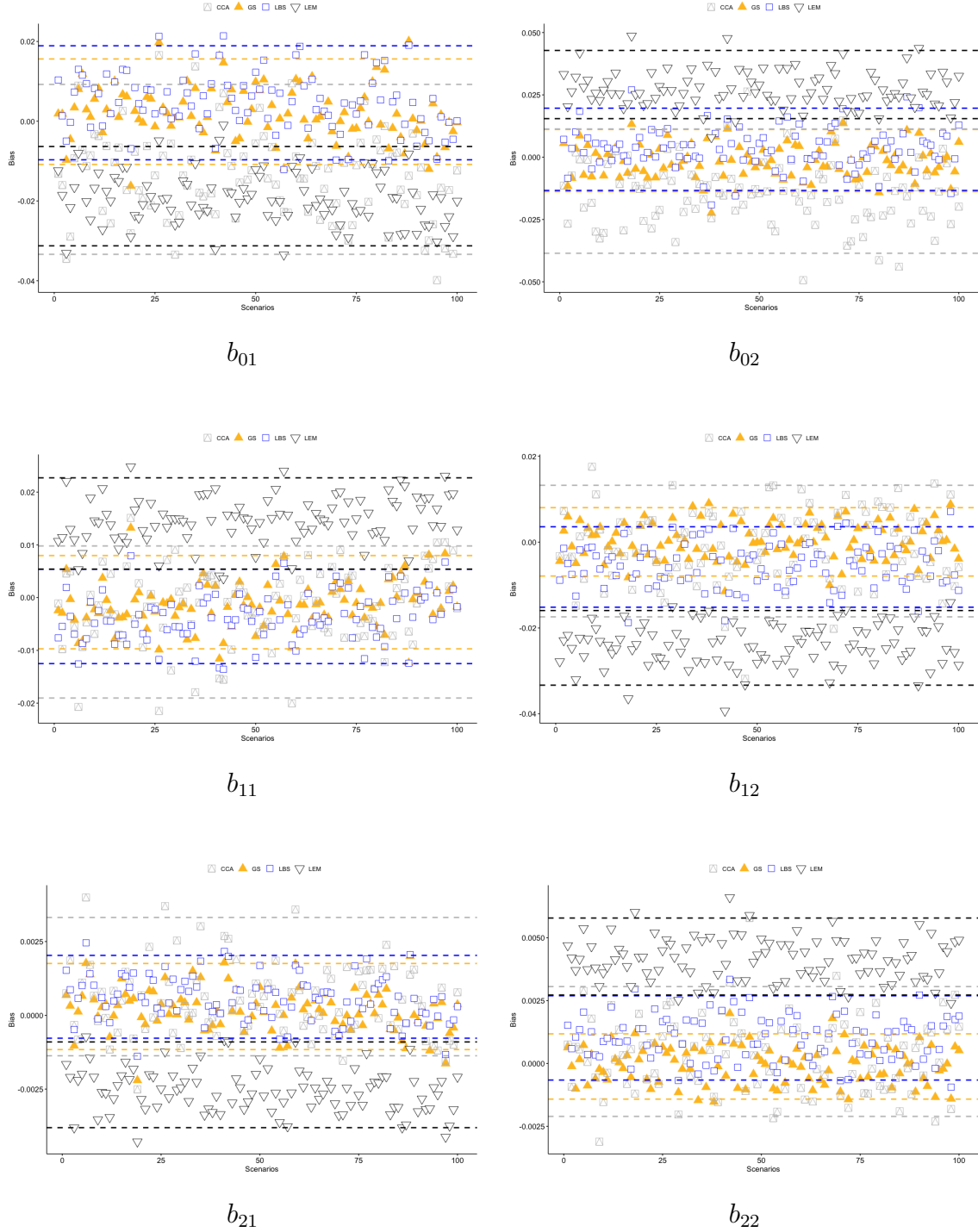


Figure 4.50: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% MNAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

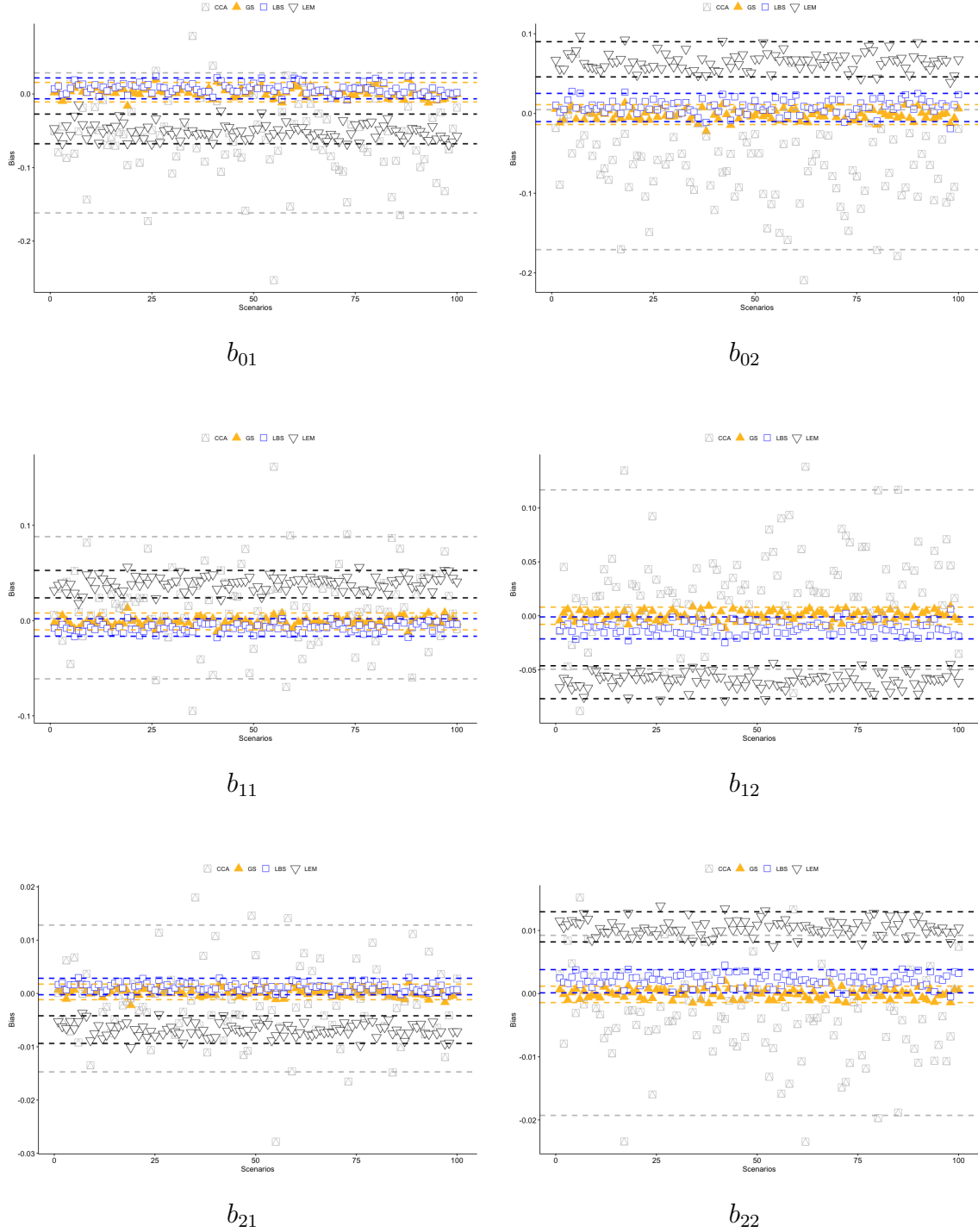


Figure 4.51: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% MNAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

From the element-wise bias plots corresponding to the estimators of within individual variance (diagonal elements of Σ), we observe that the EM algorithm produces estimators with comparable performance for 5% MNAR, both in terms of the magnitude of bias and variability of estimators (Figure 4.52). Note that the gold-standard, being the MLE, is expected to be negatively biased. Similar to the MNAR scenarios in Experiment 1, we see that Kleinbaum’s method produces estimators with a very small positive bias, however, in some cases we see that the method seems to even correct the bias perfectly, leading to bias that is randomly distributed around zero (Figure 4.52).

On the other hand, the Bayesian approach produces estimators with a negative bias that seems to be significantly larger than the gold-standard and the EM algorithm. For 5% MNAR, complete case analysis also seems to provide reasonable estimators in most cases (Figure 4.52). We also observe from this figure that, in general, all methods seem to have comparable variability for 5% MNAR with few outliers here and there. For covariance (off-diagonal elements of Σ) estimators in scenarios with 5% MNAR, we observe a similar pattern as variance estimators in some cases. However, in some cases, it appears that the Bayesian method produces estimators with comparable performance as the gold-standard and the EM algorithm (Figure 4.53).

When the missingness increases to 10% MNAR, the EM algorithm continues to produce variance estimators that are comparable to the gold-standard (Figure 4.54). We can also see from the figure that the Bayesian approach led to a significantly higher negative bias compared to the gold-standard and the EM algorithm. The behavior of the Bayesian method is not consistent in the sense that in a few cases, it seems to produce variance estimators with small positive bias. On the other hand, Kleinbaum’s approach is quite stable and consistently produces variance estimators with small positive bias (Figure 4.54). In fact, it appears that Kleinbaum’s method corrects the negative bias in the gold-standard and EM algorithm.

The complete case analysis also produced variance estimators with a slightly higher negative bias, but with larger variance as well. From Figure 4.55, we see the same pattern as the variance estimators, where the EM algorithm still seems to produce covariance estimators that are comparable to the gold-standard, when the missingness increases to 10% MNAR. In a few cases, the Bayesian method seems to be performing similar to Kleinbaum’s method and produces covariance estimators with a small positive bias. In general, for scenarios with 10% MNAR, the performance of the complete case analysis in estimating the covariance parameters is not very good. However, in some instances, we see that the method leads to a similar bias as the gold-standard, but with higher variability (Figure 4.55).

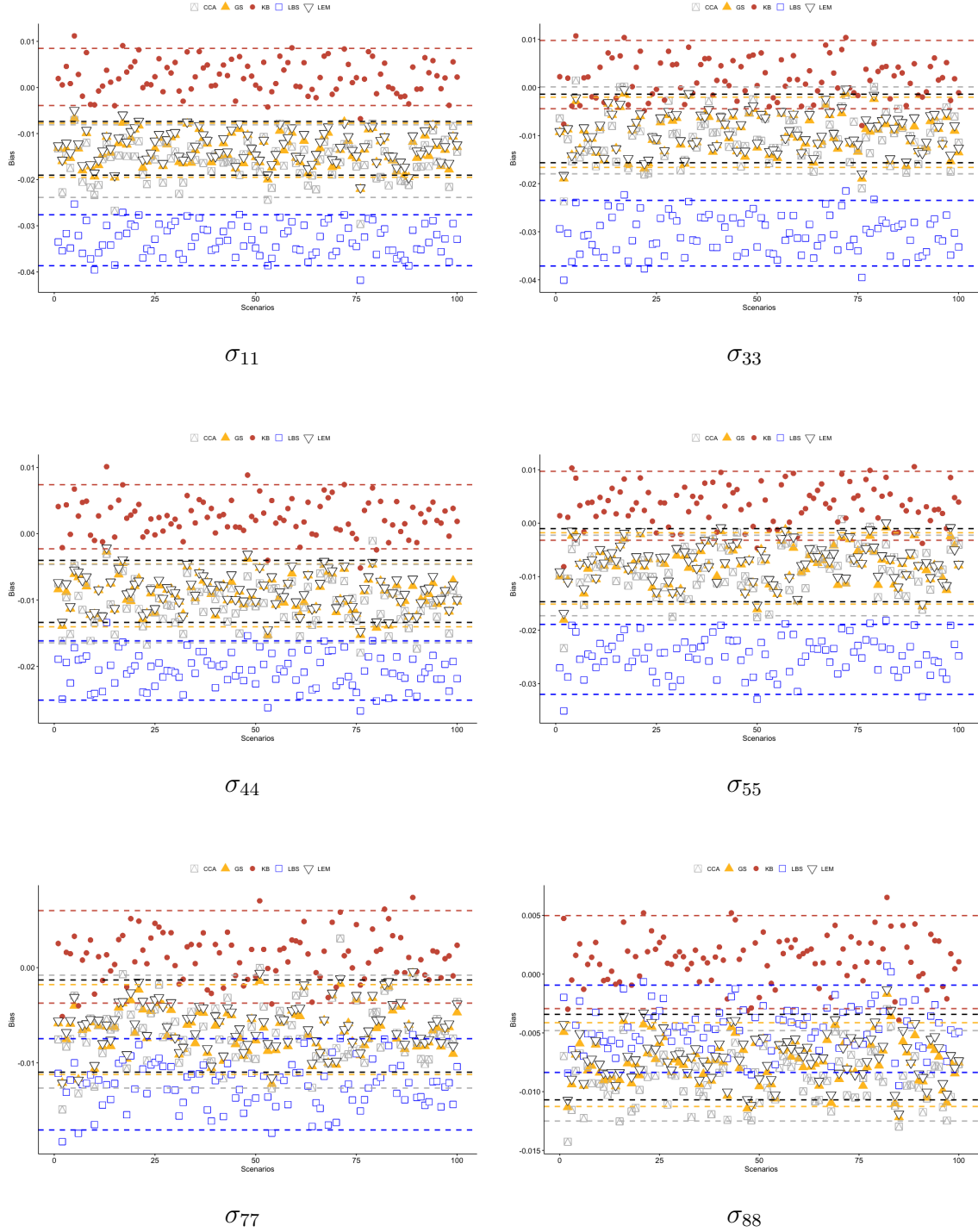


Figure 4.52: Element-wise bias for selected variance parameters (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

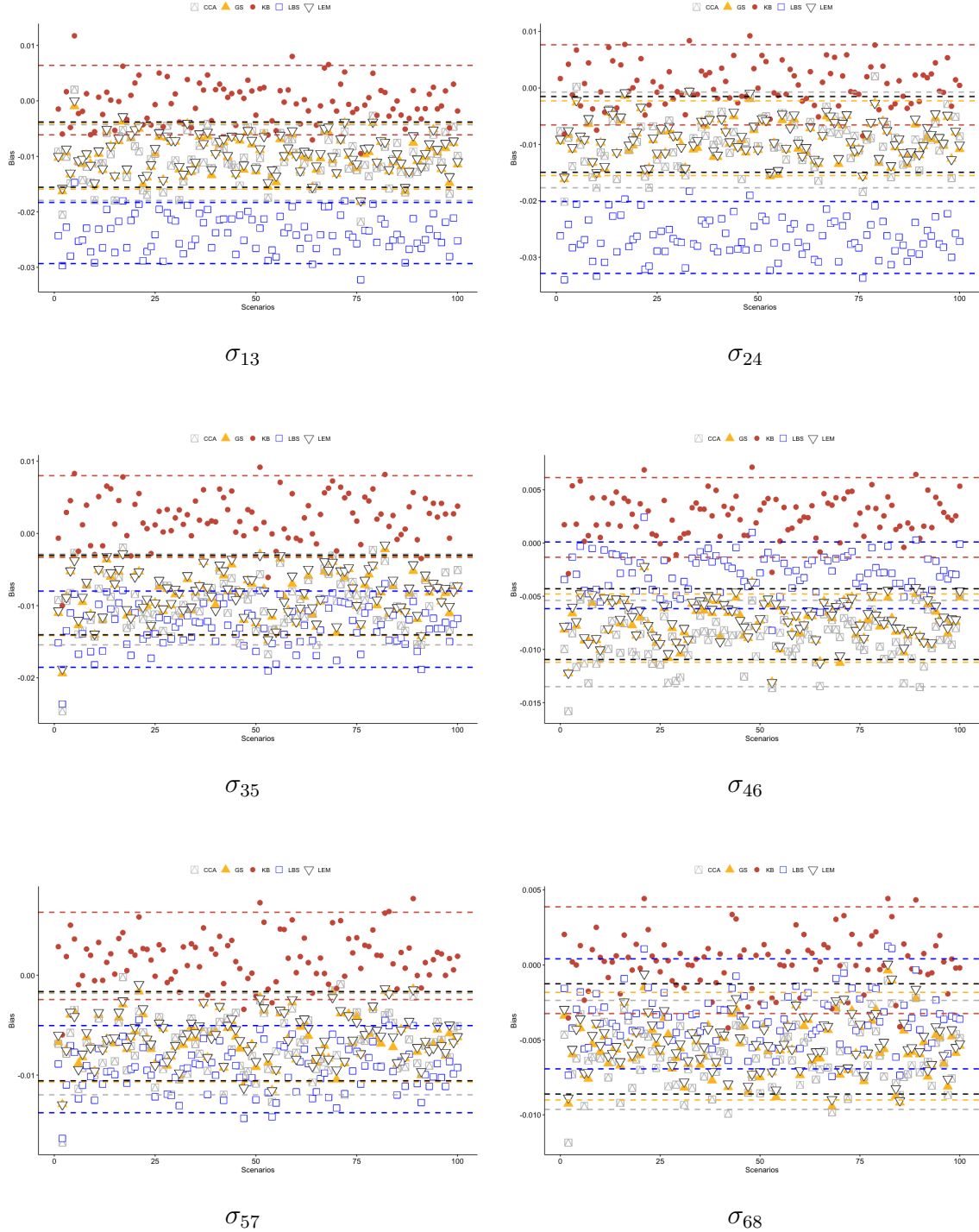


Figure 4.53: Element-wise bias for selected covariance parameters (off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

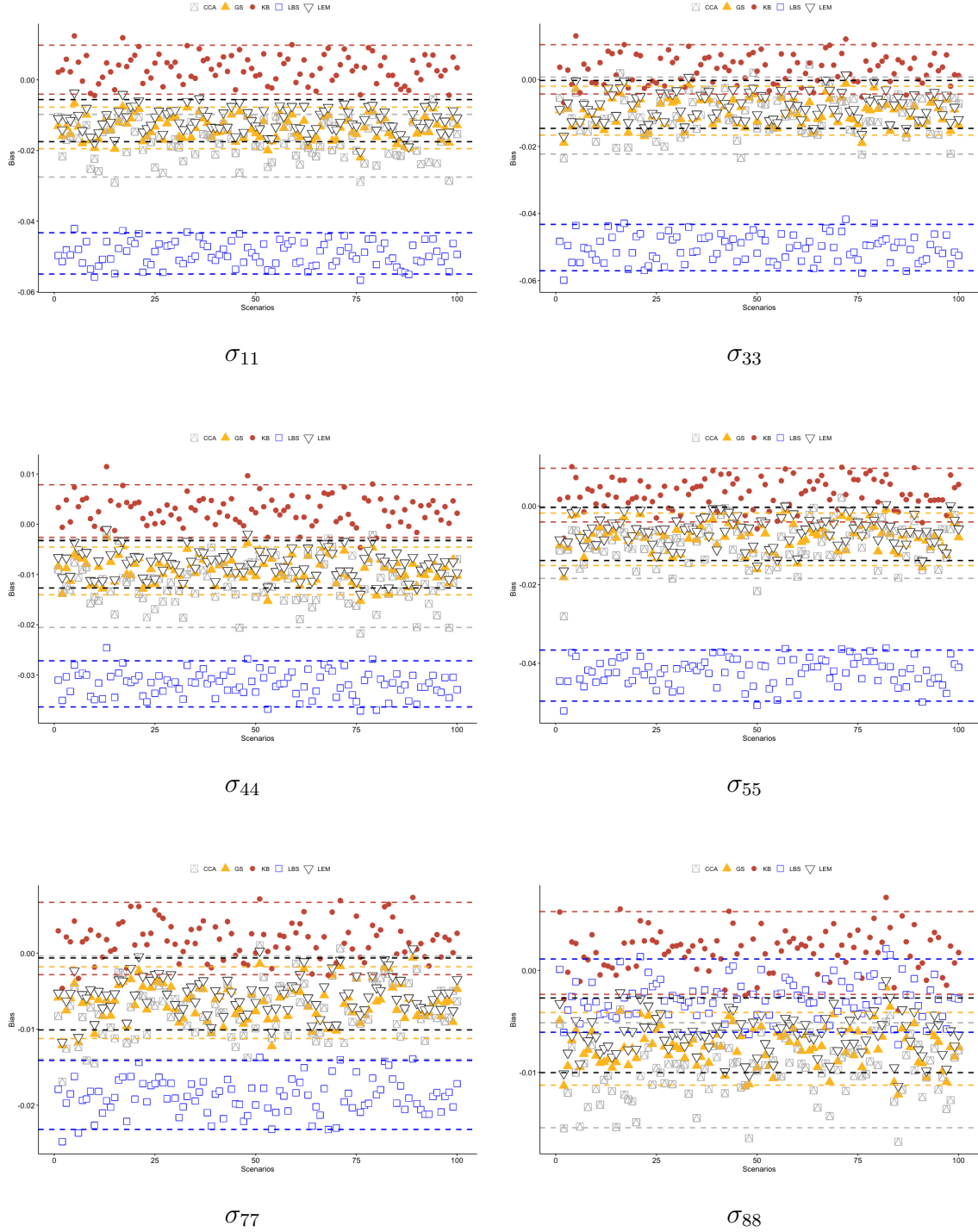


Figure 4.54: Element-wise bias for selected variance parameters (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

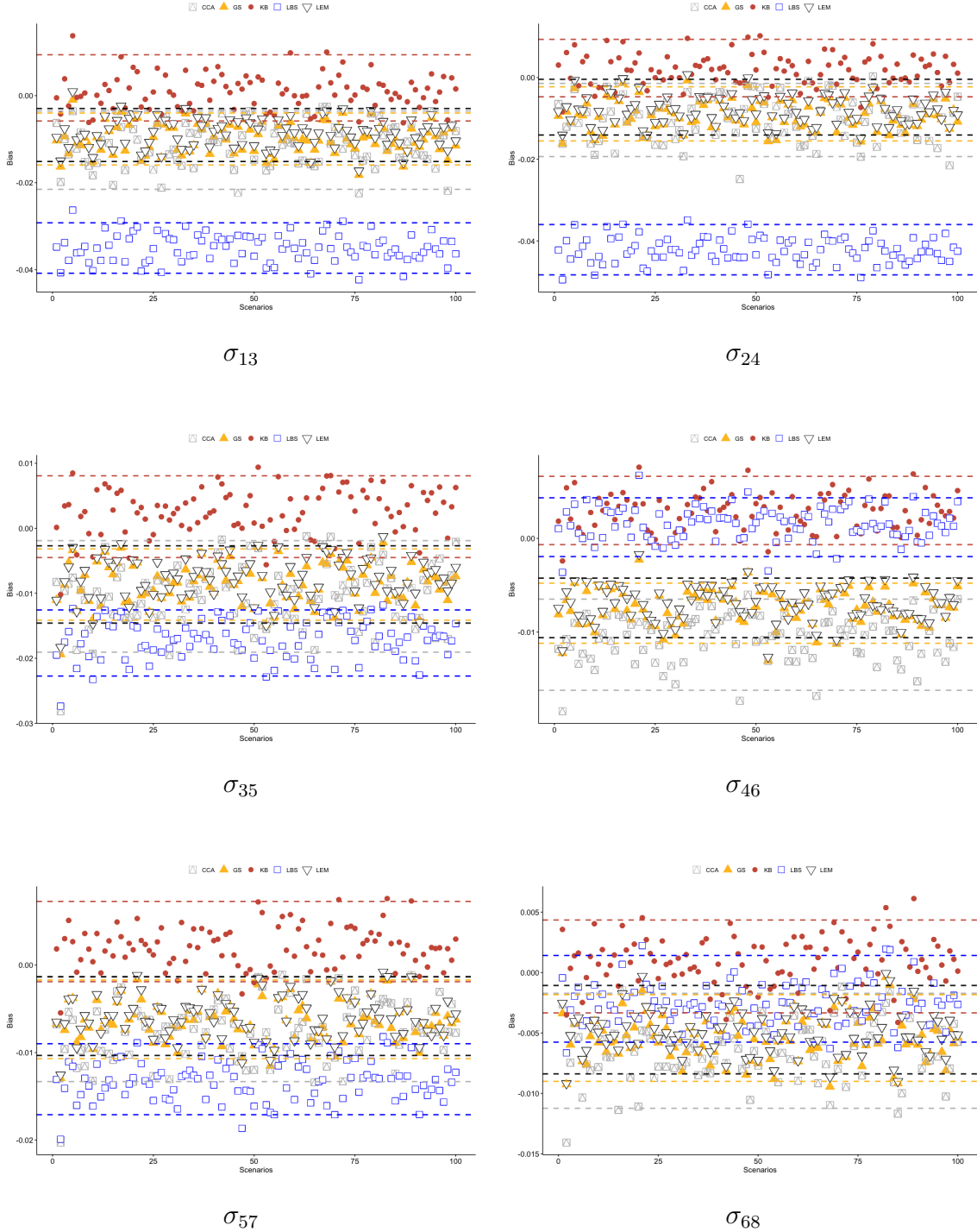


Figure 4.55: Element-wise bias for selected covariance parameters (off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

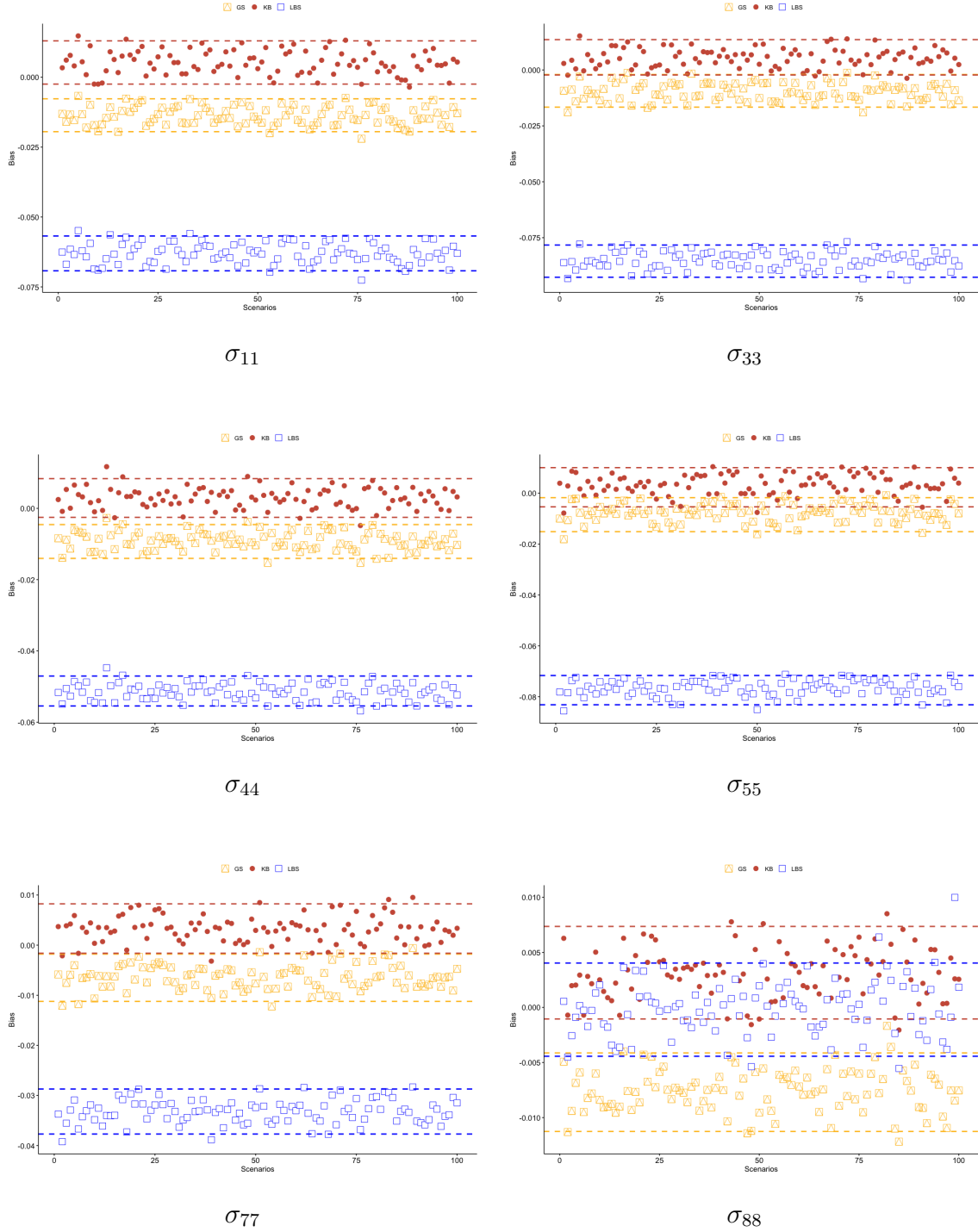


Figure 4.56: Element-wise bias for selected variance parameters (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

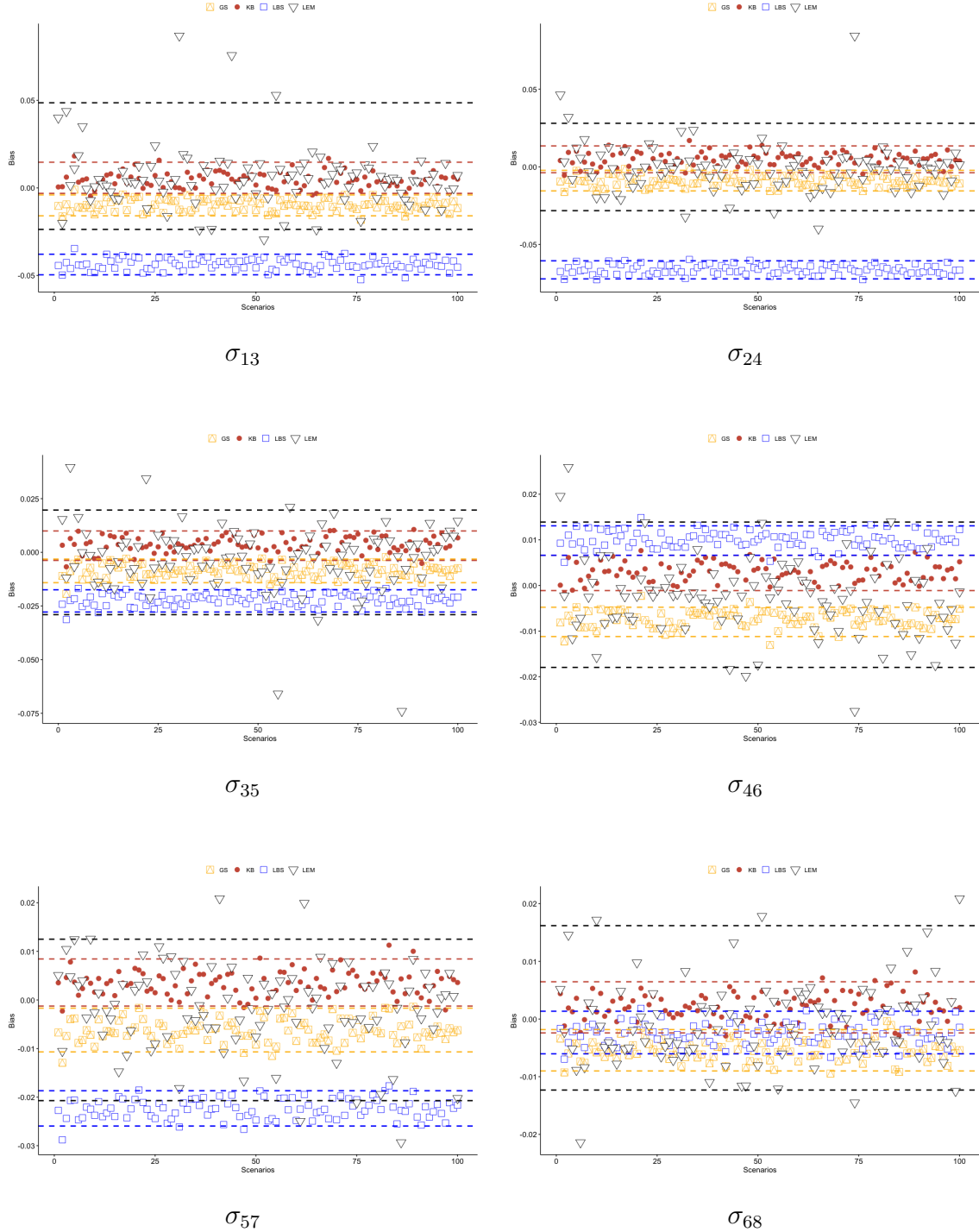


Figure 4.57: Element-wise bias for selected covariance parameters (off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

When the percentage of missingness increased to 20% MNAR, both the EM algorithm and complete case analysis broke down, leading to variance estimators that are unstable. As such, these two methods are not included in bias comparison for variance estimators presented in Figure 4.56. The figure shows that Kleinbaum’s method still works well, producing estimators with similar magnitude of bias as the gold-standard. However, we also observe that Kleinbaum’s method slightly overestimates the true within individual variance while the gold-standard underestimates the true variance. The Bayesian method, in most cases, produces variance estimators with significantly larger negative bias. However, in a few scenarios, we see that bias for the Bayesian approach seems to be randomly distributed around zero (Figure 4.56).

For covariance estimators in scenarios with 20% MNAR, we also observe that Kleinbaum’s method produces estimators with the same magnitude of bias as the gold-standard (Figure 4.57). Covariance estimators from the Bayesian approach behave similar to the variance estimators, and led to estimators with a relatively larger bias. We were still able to plot bias corresponding to the EM algorithm, however, the method is still unstable and produces estimators with high variability (Figure 4.57), which we will explore further using MSE calculated for various sample sizes. complete case analysis was highly unstable and produced covariance estimators with significantly higher variability than any of the other methods, hence could not be presented in the same plot.

Finally, let us investigate element-wise MSE, which provides us with an optimality criteria that combines bias and variance of the estimators. Moreover, MSE makes interpretation of the results relatively easier and allows us to have a better understanding of the comparative performance of the different methods.

Let us first start with estimators of the mean parameters of the GCM (i.e. $\mathbf{B}$). For 5% MNAR, we see from Figure 4.58 that the EM algorithm performs the same as the gold-standard. The Bayesian method produces estimators with uniformly higher MSE values across all the elements of $\mathbf{B}$. However, the difference seems to be negligible. Therefore, for 5% MNAR, both the Bayesian and EM algorithm are very good methods to estimate the mean parameters of the GCM. Figure 4.58 shows that MSE of estimators from complete case analysis is significantly higher than the gold-standard, the EM algorithm and the Bayesian method. The difference is more pronounced in scenarios with smaller sample sizes. Therefore, when the missingness mechanism is MNAR, the complete case analysis should not be used to estimate $\mathbf{B}$. The results in Figure 4.58 show that all the methods (including the complete case analysis) lead to estimators that are MSE consistent. Note that Kleinbaum’s method is not included in Figure 4.58, because of its instability in estimating $\mathbf{B}$, which was also the case in the majority of the scenarios we considered earlier.

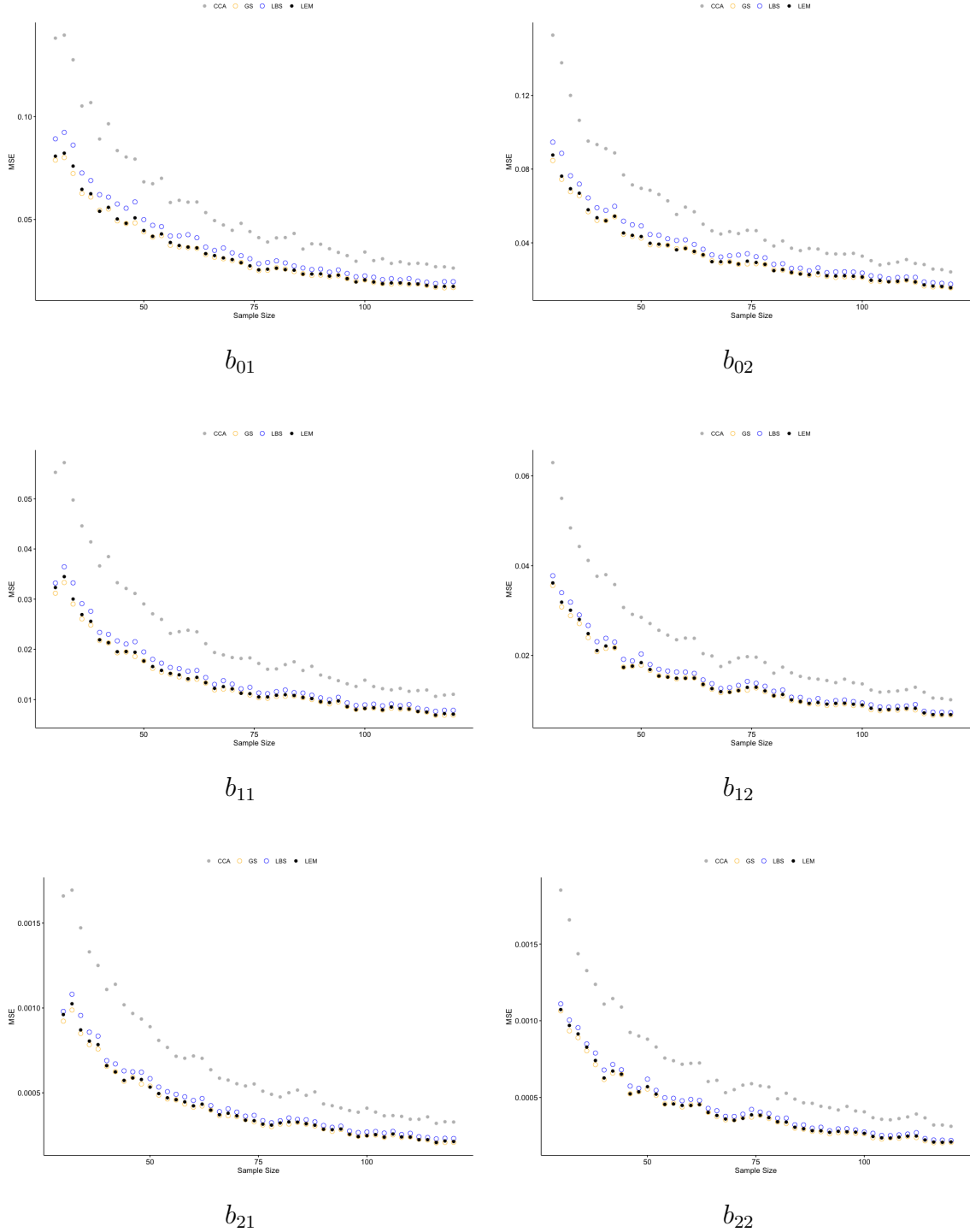


Figure 4.58: Element-wise MSE for estimators of $\mathbf{B}$, where 46 scenario of the different sample sizes (ranging from $n = 30$ to $n = 120$) are considered. We used two groups ($k = 2$), $p = 8$ measurements, quardartic mean structure ($q = 3$) for both groups and 5% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate empirical MSE.

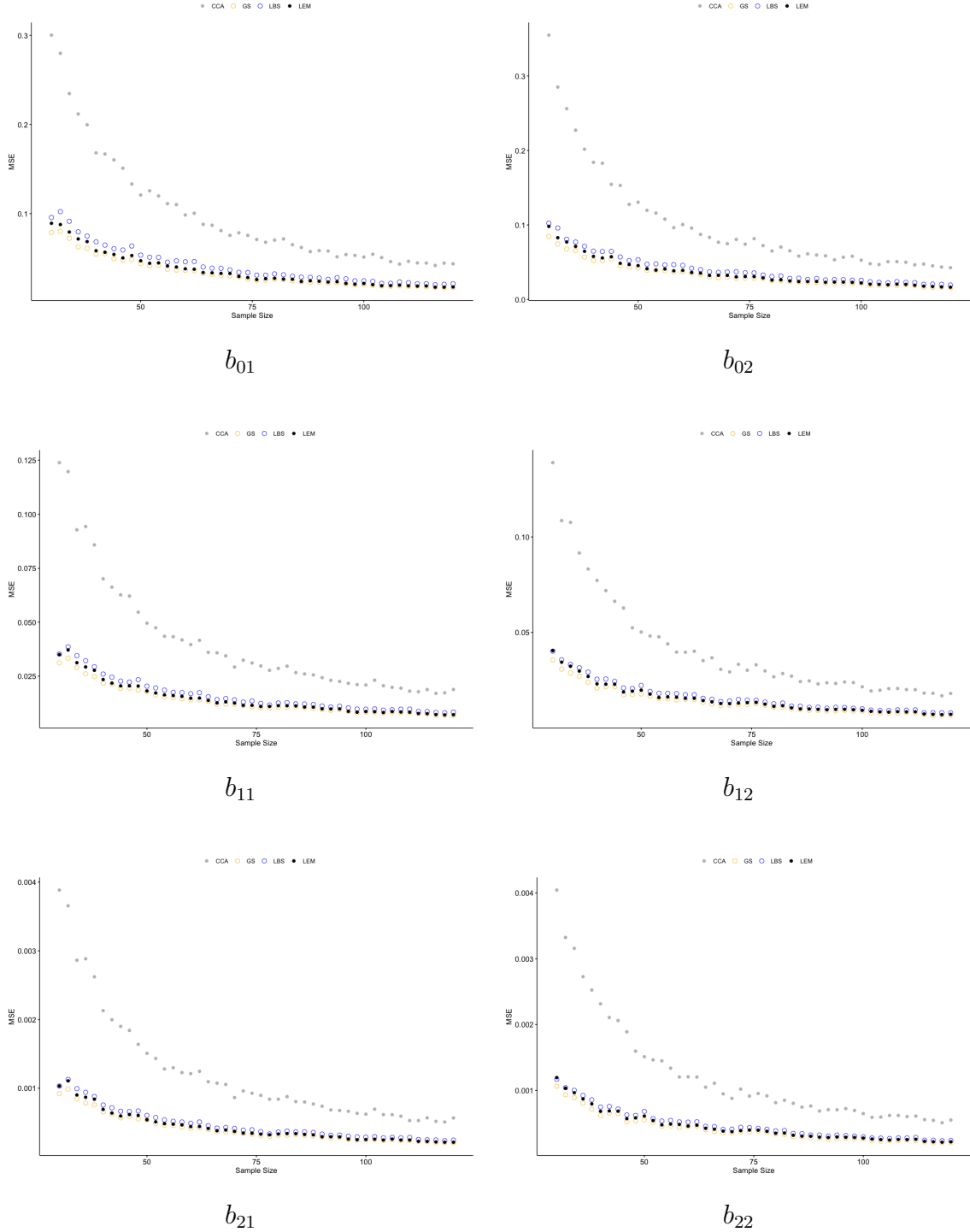


Figure 4.59: Element-wise MSE for estimators of $\mathbf{B}$, where 46 scenario of the different sample sizes (ranging from $n = 30$ to $n = 120$) are considered. We used two groups ($k = 2$), $p = 8$ measurements, quartic mean structure ($q = 3$) for both groups and 10% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate empirical MSE.

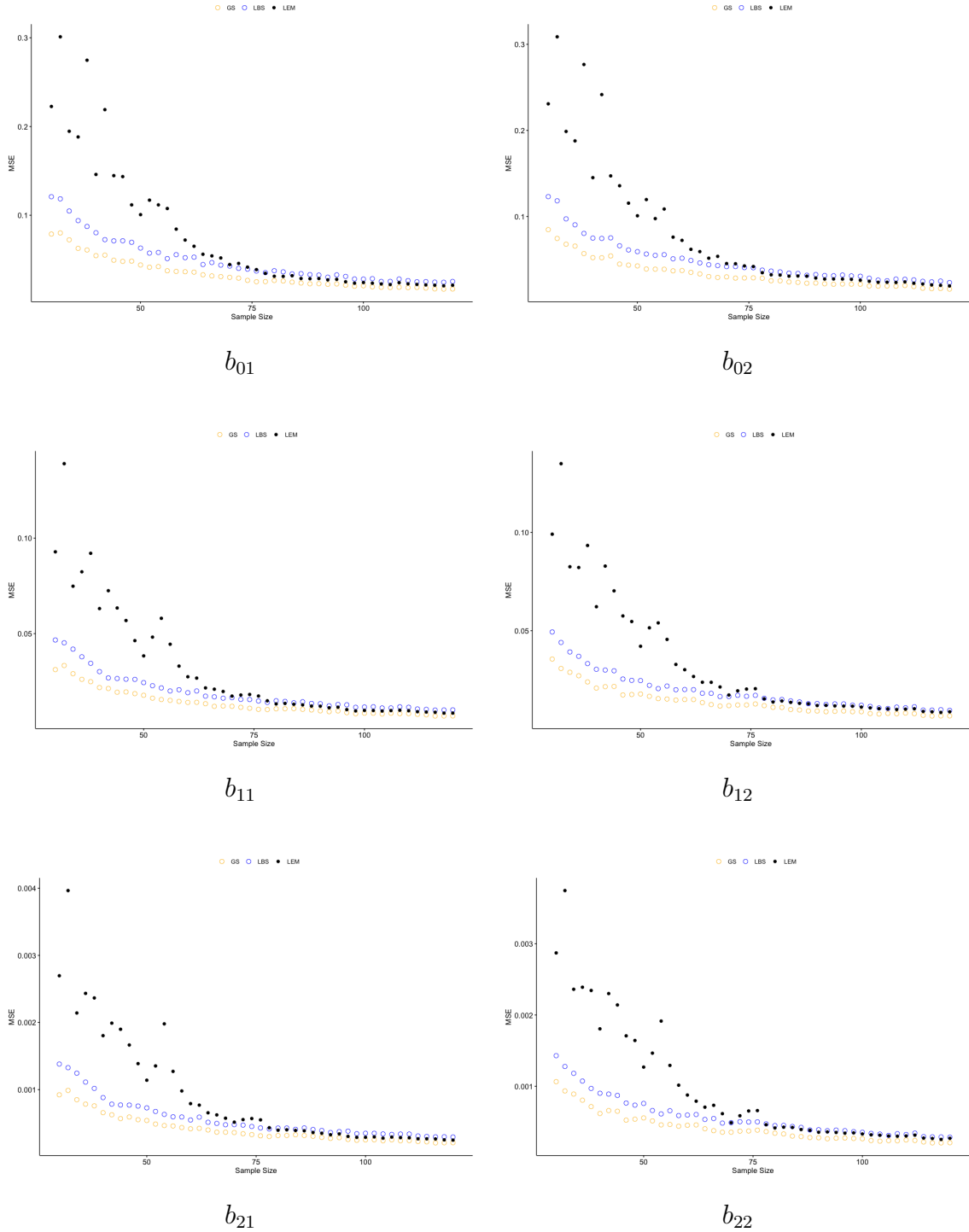


Figure 4.60: Element-wise MSE for estimators of $\mathbf{B}$, where 46 scenario of the different sample sizes (ranging from $n = 30$ to $n = 120$) are considered. We used two groups ($k = 2$), $p = 8$ measurements, quartic mean structure ($q = 3$) for both groups and 20% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each scenario was generated 1000 times to account for random variation and to calculate empirical MSE.

We see similar results when the missingness increased to 10% MNAR, where the EM algorithm and the Bayesian methods still seem to perform as good as the gold-standard (Figure 4.59). However, the performance of the complete case analysis declined further, leading to a much higher MSE values, especially for smaller sample sizes. The results shown in Figure 4.59 also show that all the methods considered here (including the complete case analysis) lead to MSE consistent estimators for the mean parameters of the GCM, even when the missingness is 10% MNAR.

However, for scenarios involving 20% MNAR, the performance of both the Bayesian and EM algorithm declined, leading to uniformly larger MSE values than the gold-standard (Figure 4.60) for scenarios with small sample size. The results also show that the Bayesian approach is significantly better than the EM algorithm for scenarios involving small sample sizes. For larger sample sizes, both the Bayesian and EM algorithm perform comparably to the gold-standard. The results also show that all the methods considered here provide MSE consistent estimators. Note that the complete case analysis is not included in Figure 4.60, because of its high MSE value, which did not fit within the same margin as the other methods. Therefore, our results show that the Bayesian method is a better alternative to the EM algorithm, when we have a small sample size and a high percentage of missing data with the MNAR mechanism. Nevertheless, the Bayesian method still leads to biased estimators and higher variance (loss of precision).

We see relatively different results for estimators of Σ , especially when the missingness percentage is large. For scenarios with 5% MNAR, we observe that all the 3 multivariate methods for handling missing data perform comparably with the gold-standard (Figure 4.61), uniformly across all the sample sizes we considered. However, complete case analysis seems to provide estimators with uniformly higher MSE values. The results also show that all the methods (including complete case analysis) produce MSE consistent estimators.

For scenarios involving 10% MNAR, the complete case analysis started to fall apart, and produced estimators with significantly larger MSE values, hence could not be presented within the same margin as the other methods. As we can see from Figure 4.62, the 3 methods (Kleinbaum, Bayesian and EM) still perform very well for scenarios with 10% MNAR. However, we also observe that for covariance parameters (off-diagonal elements of Σ , Kleinbaum's approach provides estimators with slightly higher MSE values, uniformly across all the sample sizes considered. On the other hand, the three methods still seem to perform similar to the gold-standard when estimating the within individual variances (diagonal elements of Σ). The results in Figure 4.62 also shows that the estimators from all the methods are MSE consistent.

As the missingness increases to 20%, both Kleinbaum and Bayesian produce estimators with higher MSE values than the gold-standard (Figure 4.63). The EM algorithm and complete case analysis are instable and could not be included in the figure. In Figure 4.63, we also observe that the Bayesian method is unstable, especially when the sample size is large (Figure 4.63). Kleinbaum's approach is very stable in estimating Σ , and seems to be the most optimal choice (among those we considered) for 20% MNAR.

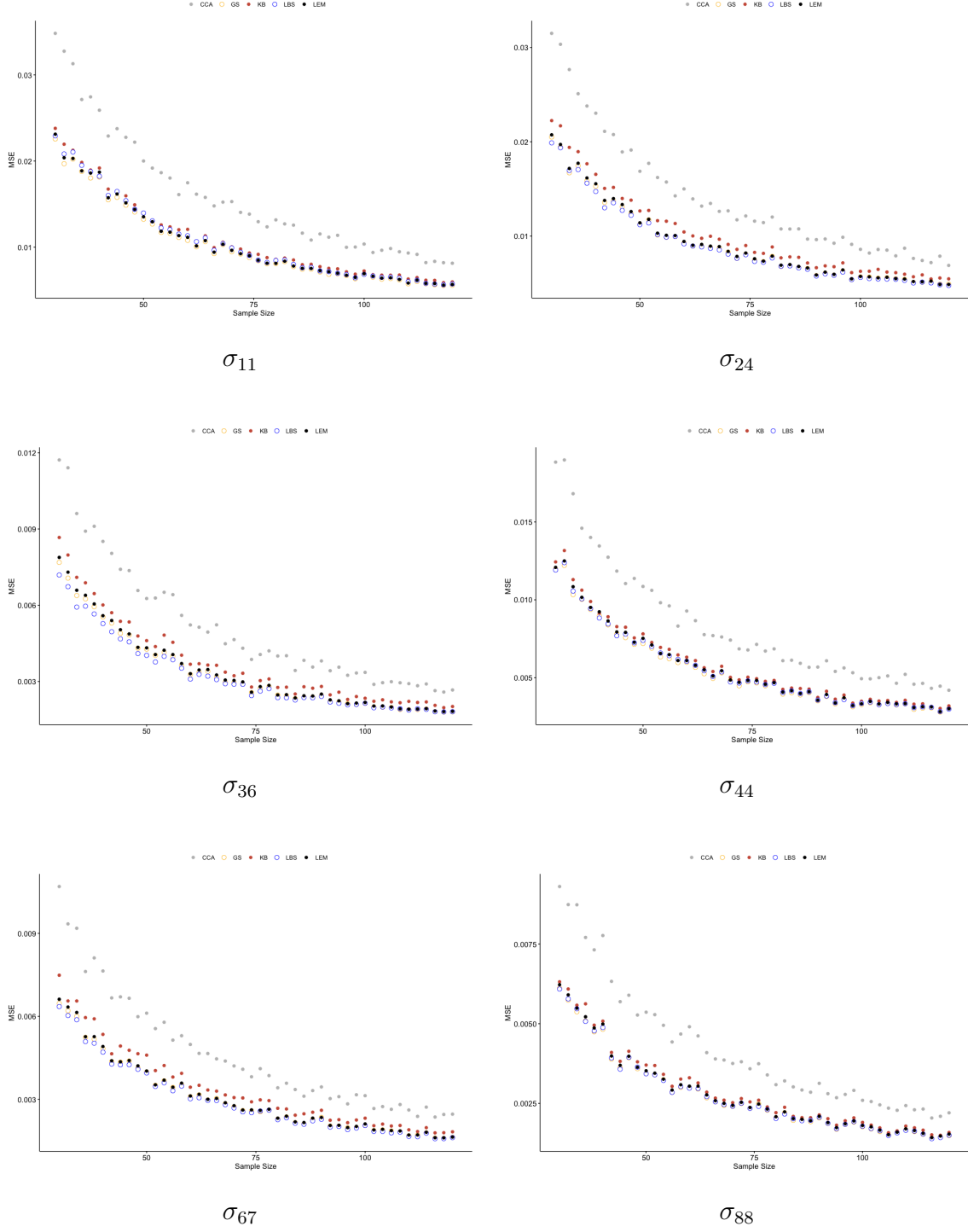


Figure 4.61: Element-wise MSE for selected elements of $\hat{\Sigma}$, where 46 scenarios with varying sample size (ranging from $n = 30$ to 120) were generated. We considered $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 5% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate the empirical MSE displayed in the graphs.

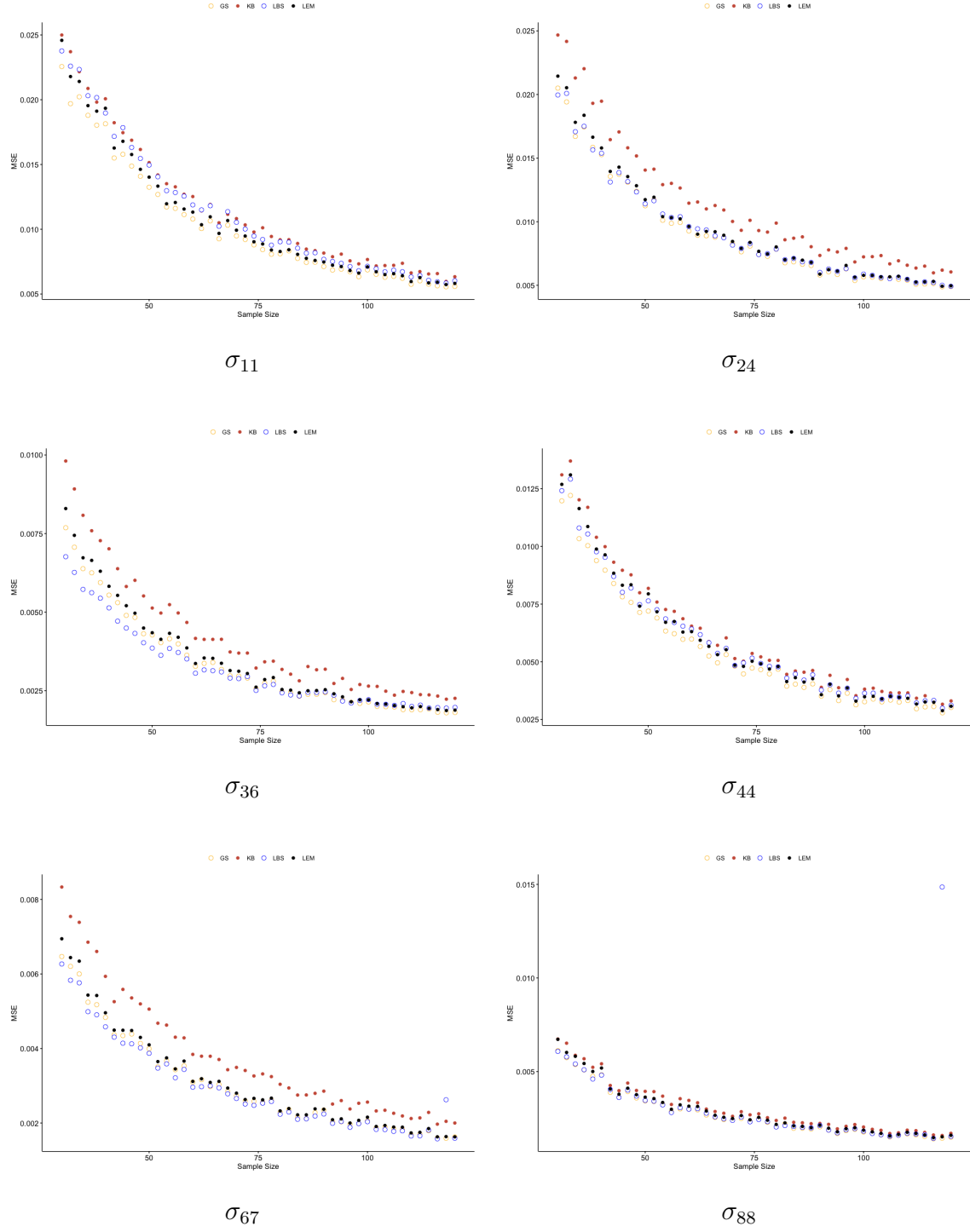


Figure 4.62: Element-wise MSE for selected elements of $\hat{\Sigma}$, where 46 scenarios with varying sample size (ranging from $n = 30$ to 120) were generated. We considered $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 10% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate the empirical MSE displayed in the graphs.

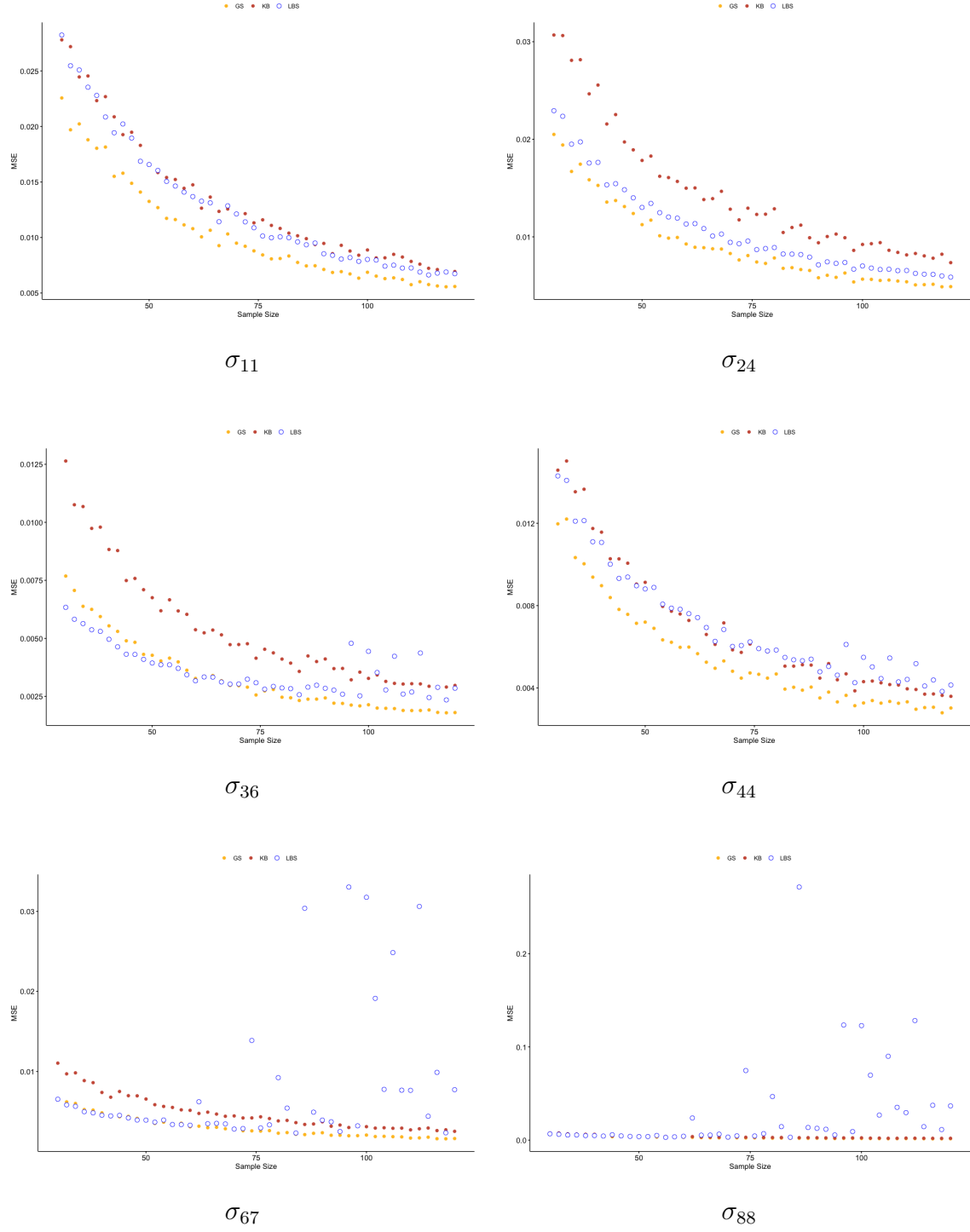


Figure 4.63: Element-wise MSE for selected elements of $\hat{\Sigma}$, where 46 scenarios with varying sample size (ranging from $n = 30$ to 120) were generated. We considered $k = 2$ groups, $p = 8$ measurements, quadratic mean structure ($q = 3$) and 20% MNAR. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each scenario was generated 1000 times to account for random variation and to calculate the empirical MSE displayed in the graphs.

Chapter 5

Illustrations Using Real Data

In this chapter, we illustrate how the different methods can be used in practical applications. We used the two data sets presented in Chapter 2: the dental data and the glucose data, both involving 2 groups. There are no missing observations in the two data sets, this was done purposefully to allow comparison with the gold-standard. We created missing data using the three mechanisms (MCAR, MAR and MNAR), as we did in our simulations. Established methods for providing confidence intervals (CIs) in the traditional GCM do not exist. Moreover, CIs were not discussed in any of the 3 multivariate methods for handling missing data. Therefore, we used bootstrapping to calculate element-wise CIs.

When performing the bootstrapping of data involving missing observations, we made an assumption that there exists at least one individual with complete data for each group. This assumption was required for the methods to work and was also implemented in the simulations. We generated 1000 bootstrap samples, from which we calculated the mean and 95% CI for the elements of $\hat{\mathbf{B}}$, which provides an empirical measure for precision of the estimators.

5.1 Dental Data

This data consists of 4 repeated dental measurements (at ages 8, 10, 12, 14) taken from 11 girls and 16 boys (i.e. $n = 27$, $k = 2$, $p = 4$). The individual and mean profile plots are provided in Figure 2.1, Chapter 2. As we can see from the profile plots, both groups seem to have linear mean structures, as such we will use $q = 2$ (i.e. a polynomial of degree $q - 1 = 1$). The within and between individual design matrices, assuming a linear mean profile overtime, are given in Chapter 4.

5.1.1 Missing Completely at Random

The results corresponding to the mean parameter matrix $\mathbf{B}$ are provided in Table 5.1. The results show that with only 5% MCAR, every method gives estimates close to gold-standard, however, their CIs already differ. CIs for Kleinbaum's GGCM method are the

widest, showing that this method is less precise. This is consistent with our simulation results since this method was shown to be unstable in estimating $\mathbf{B}$. Liski's Bayesian method and Liski's EM algorithm have intervals almost as narrow as the gold-standard, demonstrating that they are clearly better than complete case analysis. We would like to highlight here that, although the missing percentage is small, the sample size is also very small. As such, it is quite an impressive performance to observe the performance of these two methods.

Table 5.1: Estimates and 95% confidence intervals for the mean parameters of the GCM (elements of $\mathbf{B}$). The dental data with 5%, 10% and 20% MCAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
b_{01}	17.42 (15.87, 19.02)	17.71 (15.88, 19.57)	17.67 (13.49, 22.29)	17.65 (15.90, 19.32)	17.66 (16.20, 19.27)
b_{02}	15.92 (13.18, 19.76)	15.80 (13.12, 19.92)	15.81 (3.34, 30.72)	15.94 (13.65, 19.76)	15.83 (13.28, 19.77)
b_{11}	0.48 (0.34, 0.62)	0.43 (0.29, 0.58)	0.46 (-0.28, 1.15)	0.46 (0.32, 0.64)	0.46 (0.33, 0.58)
b_{12}	0.81 (0.52, 1.05)	0.83 (0.51, 1.07)	0.82 (-0.63, 2.03)	0.81 (0.48, 1.00)	0.82 (0.51, 1.04)
10%					
b_{01}	17.42 (15.87, 19.02)	17.15 (15.03, 19.40)	17.52 (-0.01, 35.28)	17.49 (15.71, 19.18)	17.53 (15.92, 19.22)
b_{02}	15.92 (13.18, 19.76)	15.59 (12.45, 19.42)	15.18 (-33.01, 63.70)	15.62 (13.26, 19.34)	15.20 (12.74, 19.58)
b_{11}	0.48 (0.34, 0.62)	0.46 (0.29, 0.63)	0.47 (-0.53, 1.45)	0.47 (0.33, 0.66)	0.47 (0.33, 0.60)
b_{12}	0.81 (0.52, 1.05)	0.90 (0.55, 1.16)	0.90 (-2.99, 4.75)	0.86 (0.52, 1.05)	0.90 (0.53, 1.10)
20%					
b_{01}	17.42 (15.87, 19.02)	17.27 (3.90, 29.30)	17.56 (-1733.45, 1827.78)	17.22 (15.64, 18.59)	17.13 (15.10, 19.69)
b_{02}	15.92 (13.18, 19.76)	16.08 (-7.62, 37.49)	16.14 (-122.18, 161.71)	15.49 (12.95, 19.30)	16.88 (14.01, 20.80)
b_{11}	0.48 (0.34, 0.62)	0.38 (-0.68, 1.59)	0.46 (-151.36, 147.28)	0.48 (0.36, 0.66)	0.49 (0.31, 0.65)
b_{12}	0.81 (0.52, 1.05)	0.73 (-1.24, 2.88)	0.79 (-12.92, 13.77)	0.86 (0.51, 1.08)	0.71 (0.40, 0.95)

When the missingness increases to 10% MCAR and 20% MCAR, the CIs corresponding to the complete case analysis became wider, and we see that the method provides results that are different from the gold-standard, this is to be expected because deleting incomplete individuals wastes information. Although Kleinbaum's GGCM method obtain estimates

close to gold-standard, it still becomes unstable: some of its CIs become extremely wide, so its results are not dependable. In contrast, the Bayesian method and the EM algorithm still provided estimates close to the gold-standard, despite the high percentage of missing for such a small sample size. The width of the CIs produced by the Bayesian method and the EM algorithm are also close to the gold-standard. These results are in line with our findings from the simulation studies, and suggest that the Bayesian and the EM algorithm are the best choices for estimating the mean parameters of the GCM in the presence of missing data with the MCAR mechanism.

Table 5.2: Estimates and 95% confidence intervals for variance parameters (diagonal elements of Σ) The dental data with 5%, 10% and 20% MCAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
σ_{11}	5.93 (1.62, 7.96)	5.63 (1.75, 8.78)	6.16 (2.00, 9.70)	5.06 (1.55, 8.10)	5.31 (1.65, 8.25)
σ_{22}	4.65 (2.03, 5.70)	3.99 (1.92, 5.85)	4.72 (2.08, 7.02)	3.68 (1.82, 5.56)	3.79 (1.91, 5.46)
σ_{33}	7.94 (2.72, 8.91)	6.57 (2.98, 9.79)	8.48 (3.30, 12.84)	5.94 (2.63, 9.50)	6.22 (2.88, 9.12)
σ_{44}	7.65 (2.24, 6.42)	4.81 (2.18, 6.80)	7.65 (3.13, 11.42)	4.62 (2.13, 7.81)	4.62 (2.23, 6.45)
10%					
σ_{11}	5.93 (1.62, 7.96)	6.95 (1.74, 11.29)	6.16 (2.00, 9.71)	5.04 (1.54, 8.13)	5.32 (1.67, 8.22)
σ_{22}	4.65 (2.03, 5.70)	3.94 (1.44, 5.93)	5.29 (2.36, 7.81)	3.63 (1.78, 5.56)	4.10 (2.08, 5.89)
σ_{33}	7.94 (2.72, 8.91)	7.08 (2.14, 11.23)	8.83 (3.50, 13.30)	5.80 (2.52, 9.50)	6.09 (2.70, 9.23)
σ_{44}	7.65 (2.24, 6.42)	5.59 (1.72, 8.69)	8.26 (3.40, 12.35)	4.57 (2.15, 7.91)	4.82 (-9.67, 20.11)
20%					
σ_{11}	5.93 (1.62, 7.96)	3.72 (-76.93, 95.97)	6.74 (2.06, 10.65)	4.68 (1.30, 7.77)	5.31 (-6.68, 18.16)
σ_{22}	4.65 (2.03, 5.70)	2.51 (-4.95, 11.51)	4.84 (2.20, 6.97)	3.32 (1.62, 5.14)	4.27 (-2.38, 11.74)
σ_{33}	7.94 (2.72, 8.91)	3.29 (-11.11, 19.77)	9.15 (3.51, 13.81)	5.86 (2.48, 9.54)	10.22 (-667.16, 717.24)
σ_{44}	7.65 (2.24, 6.42)	3.32 (-94.59, 114.85)	8.39 (3.15, 12.79)	4.01 (1.69, 7.24)	6.44 (-372.51, 419.75)

Table 5.3: Estimates and 95% confidence intervals for covariance parameters (off-diagonal elements of the Σ). The dental data with 5%, 10% and 20% MCAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
σ_{12}	3.29 (0.34, 4.36)	2.96 (0.68, 4.97)	3.74 (0.67, 6.60)	2.73 (0.60, 4.81)	2.79 (0.71, 4.62)
σ_{13}	4.88 (0.95, 6.07)	4.18 (1.22, 6.87)	5.46 (1.33, 9.16)	3.80 (1.05, 6.63)	3.89 (1.21, 6.31)
σ_{14}	4.04 (-0.06, 4.85)	2.99 (0.16, 5.47)	4.41 (0.15, 8.38)	2.81 (0.08, 5.72)	2.83 (0.23, 5.12)
σ_{23}	3.86 (0.04, 5.26)	2.81 (-0.28, 5.72)	4.12 (0.54, 7.43)	2.61 (0.01, 5.43)	2.68 (-0.06, 5.23)
σ_{24}	4.53 (1.15, 4.58)	3.06 (0.94, 4.71)	4.67 (1.52, 7.41)	2.91 (0.98, 5.01)	2.96 (1.06, 4.44)
σ_{34}	6.20 (1.11, 6.13)	4.07 (0.95, 6.74)	6.63 (2.15, 10.51)	3.80 (1.12, 6.98)	3.87 (1.12, 6.20)
10%					
σ_{12}	3.29 (0.34, 4.36)	3.53 (0.42, 6.19)	4.23 (0.76, 7.41)	2.70 (0.60, 4.79)	2.79 (0.71, 4.60)
σ_{13}	4.88 (0.95, 6.07)	5.41 (1.05, 9.27)	5.68 (1.45, 9.44)	3.68 (0.96, 6.58)	3.76 (1.14, 6.20)
σ_{14}	4.04 (-0.06, 4.85)	4.19 (0.21, 7.80)	4.68 (0.11, 8.91)	2.91 (0.23, 5.90)	3.01 (0.33, 5.20)
σ_{23}	3.86 (0.04, 5.26)	4.70 (1.31, 7.47)	4.83 (0.67, 8.59)	2.53 (0.04, 5.32)	2.70 (0.04, 5.11)
σ_{24}	4.53 (1.15, 4.58)	3.83 (0.82, 6.19)	5.34 (1.49, 8.64)	2.70 (0.71, 5.02)	2.72 (-0.20, 5.51)
σ_{34}	6.20 (1.11, 6.13)	5.79 (1.56, 9.21)	7.58 (2.58, 11.75)	4.32 (1.81, 7.42)	4.74 (-0.21, 8.18)
20%					
σ_{12}	3.29 (0.34, 4.36)	2.27 (-20.09, 28.38)	3.51 (-0.06, 6.69)	2.30 (0.39, 4.34)	2.82 (-0.60, 6.23)
σ_{13}	4.88 (0.95, 6.07)	3.08 (-35.55, 37.23)	6.95 (1.90, 11.20)	3.55 (0.93, 6.37)	6.29 (-10.16, 20.81)
σ_{14}	4.04 (-0.06, 4.85)	3.27 (-98.25, 92.74)	5.27 (-0.83, 10.84)	2.49 (0.09, 5.38)	3.01 (-2.97, 8.38)
σ_{23}	3.86 (0.04, 5.26)	2.41 (-9.02, 12.83)	3.74 (0.10, 6.95)	2.35 (-0.02, 5.00)	2.65 (-2.20, 7.43)
σ_{24}	4.53 (1.15, 4.58)	2.27 (-26.17, 27.55)	4.60 (1.15, 7.32)	2.63 (0.78, 4.80)	4.64 (-7.52, 15.79)
σ_{34}	6.20 (1.11, 6.13)	2.49 (-34.39, 44.69)	7.50 (1.74, 12.41)	3.99 (1.49, 7.08)	1.71 (-14.89, 18.04)

In estimating the variance parameters (diagonal elements of Σ), the results presented in Table 5.2 show that when the missing percentage is 5% MCAR, all methods provided estimates close to the gold-standard. However, we also observe the estimators from Kleinbaum's are relatively higher than the gold-standard (confirming the direction of bias that we saw in our simulations). Nevertheless, we would like to highlight again that the gold-standard is also negatively biased (being an MLE of variances and covariances), as such the true value is somewhere in between., and the fact that the CIs overlap shows that Kleinbaum's approach works well in estimating Σ . The Bayesian approach is also a good alternative to Kleinbaum's approach.

As the percentage of missing data increases to 10% MCAR and 20% MCAR, we see that the EM algorithm is not working well. However, Kleinbaum and Bayesian still provided estimators with reasonable precision (Table 5.2). We see similar results (Table 5.3) for covariance parameters (off-diagonal elements of Σ), where Kleinbaum and Bayesian provide reasonable approaches for estimating Σ in the presence of moderate to high percentage of MCAR.

5.1.2 Missing at Random

From Table 5.4, we can see that the Bayesian method and the EM algorithm are desirable for estimating $\mathbf{B}$, including when the missingness percentage is high, where we can see that these methods still provided estimates that are relatively close to gold-standard. These methods also provided CIs that are closer to gold-standard, even when the missingness percentage is moderate to high. complete case analysis works well when the missingness percentage is low, but its CI for some parameters widens when the missing percentage is high. Kleinbaum's GGCM is not considerable, since it provides extremely wide CIs revealing is instability, which we also observed in the simulation studies.

From Table 5.5, we can see that when the missing percentage is low, all the methods perform well in estimating variances. However, when missingness percentage increases, we observe that the complete case analysis and the EM algorithm do not provide valid approaches. We also observe that the CIs cross the 0 point, which means that these two methods have large variation, this is especially the case for Liski's EM algorithm. On the other hand, Kleinbaum's approach remains stable in estimating the within individual variances in the GCM. Similar conclusions can be made for the covariance estimates provided in Table C.1 in the Appendix.

Table 5.4: Estimates and 95% confidence intervals for the mean parameters of the GCM (elements of $\mathbf{B}$). The dental data with 5%, 10% and 20% MAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
b_{01}	17.42 (15.87, 19.02)	17.50 (15.79, 19.22)	17.48 (7.65, 27.54)	17.48 (15.77, 19.05)	17.49 (15.86, 19.15)
b_{02}	15.92 (13.18, 19.76)	16.80 (13.58, 20.76)	16.33 (-0.07, 33.32)	16.53 (14.41, 19.26)	16.79 (14.35, 19.55)
b_{11}	0.48 (0.34, 0.62)	0.47 (0.33, 0.62)	0.47 (-0.04, 1.01)	0.47 (0.34, 0.66)	0.47 (0.33, 0.62)
b_{12}	0.81 (0.52, 1.05)	0.81 (0.47, 1.08)	0.80 (-0.01, 1.49)	0.78 (0.53, 0.96)	0.76 (0.53, 0.98)
10%					
b_{01}	17.42 (15.87, 19.02)	16.95 (15.11, 18.82)	16.83 (5.20, 29.00)	17.10 (15.68, 18.61)	17.10 (15.59, 18.72)
b_{02}	15.92 (13.18, 19.76)	19.55 (16.01, 22.59)	19.97 (-37.15, 69.35)	17.43 (15.40, 19.47)	17.58 (15.58, 19.89)
b_{11}	0.48 (0.34, 0.62)	0.51 (0.36, 0.66)	0.53 (-0.33, 1.35)	0.51 (0.39, 0.65)	0.51 (0.37, 0.63)
b_{12}	0.81 (0.52, 1.05)	0.61 (0.34, 0.90)	0.45 (-4.25, 5.96)	0.70 (0.53, 0.84)	0.69 (0.51, 0.85)
20%					
b_{01}	17.42 (15.87, 19.02)	17.25 (12.82, 21.28)	16.46 (-91.55, 121.95)	17.07 (15.30, 18.87)	16.81 (14.29, 19.98)
b_{02}	15.92 (13.18, 19.76)	19.76 (9.07, 27.89)	1570.89 (-18906.21, 19564.65)	17.13 (14.76, 19.60)	17.29 (14.30, 21.37)
b_{11}	0.48 (0.34, 0.62)	0.49 (0.12, 0.90)	0.56 (-8.11, 9.41)	0.51 (0.37, 0.69)	0.55 (0.30, 0.76)
b_{12}	0.81 (0.52, 1.05)	0.64 (-0.13, 1.59)	-163.54 (-673.57, 653.37)	0.72 (0.52, 0.88)	0.71 (0.39, 0.92)

Table 5.5: Estimates and 95% confidence intervals for the variance parameters (diagonal elements of Σ). The dental data with 5%, 10% and 20% MAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
σ_{11}	5.93 (1.62, 7.96)	5.78 (1.67, 9.32)	5.93 (2.06, 9.24)	5.03 (1.58, 8.27)	5.02 (1.53, 8.02)
σ_{22}	4.65 (2.03, 5.70)	3.90 (1.90, 5.59)	4.86 (2.12, 7.28)	3.26 (1.65, 4.98)	3.90 (-22.17, 30.79)
σ_{33}	7.94 (2.72, 8.91)	5.70 (2.06, 8.82)	8.58 (3.45, 12.97)	5.80 (2.57, 9.42)	5.98 (2.69, 8.90)
σ_{44}	7.65 (2.24, 6.42)	4.97 (2.46, 6.83)	7.65 (3.16, 11.46)	4.62 (2.14, 7.72)	4.62 (2.27, 6.34)
10%					
σ_{11}	5.93 (1.62, 7.96)	3.60 (0.69, 6.30)	5.43 (1.67, 8.77)	3.50 (1.14, 6.09)	3.67 (1.34, 5.77)
σ_{22}	4.65 (2.03, 5.70)	5.02 (2.13, 7.29)	5.08 (2.21, 7.60)	3.29 (1.66, 5.05)	4.22 (1.69, 6.82)
σ_{33}	7.94 (2.72, 8.91)	5.74 (1.95, 8.92)	9.11 (3.59, 13.85)	5.44 (2.18, 9.18)	5.94 (2.52, 9.12)
σ_{44}	7.65 (2.24, 6.42)	5.62 (2.24, 8.43)	7.65 (3.13, 11.52)	4.65 (2.03, 7.98)	4.64 (2.20, 6.55)
20%					
σ_{11}	5.93 (1.62, 7.96)	1.58 (-6.28, 10.48)	6.11 (1.85, 9.83)	3.56 (1.10, 6.19)	4.17 (-652.85, 686.19)
σ_{22}	4.65 (2.03, 5.70)	3.29 (-3.30, 10.01)	4.15 (1.67, 6.31)	3.04 (1.45, 4.72)	3.97 (-43.94, 57.11)
σ_{33}	7.94 (2.72, 8.91)	2.89 (-5.41, 11.49)	9.94 (3.98, 14.97)	5.29 (2.04, 9.21)	6.76 (-17.74, 32.46)
σ_{44}	7.65 (2.24, 6.42)	3.05 (-6.48, 13.99)	6.75 (2.94, 9.92)	3.83 (1.72, 6.87)	4.54 (-26.50, 37.73)

5.1.3 Missing Not at Random

Despite the missingness mechanism being MNAR, we see from Table 5.6 that all methods provide an estimate very close to the gold-standard when the missingness percentage is small. However, we observe that Kleinbaum’s method provides wider CI, highlighting its imprecision. When the missingness percentage increases, we observe that complete case analysis and Kleinbaum’s GGCM method become not dependable due to high variation in the estimates they provide, which is reflected in the wide the corresponding CIs.

Table 5.6: Estimates and 95% confidence intervals for $\mathbf{B}$. The dental data with 5%, 10% and 20% MNAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
b_{01}	17.42 (15.87, 19.02)	17.54 (15.79, 19.28)	17.40 (13.27, 21.42)	17.44 (15.60, 18.97)	17.45 (15.84, 19.06)
b_{02}	15.92 (13.18, 19.76)	14.97 (12.42, 18.80)	15.43 (6.12, 26.32)	15.31 (13.08, 18.91)	15.14 (12.70, 19.04)
b_{11}	0.48 (0.34, 0.62)	0.46 (0.31, 0.62)	0.48 (0.25, 0.72)	0.48 (0.34, 0.68)	0.48 (0.34, 0.62)
b_{12}	0.81 (0.52, 1.05)	0.90 (0.58, 1.13)	0.86 (0.12, 1.45)	0.87 (0.55, 1.06)	0.89 (0.58, 1.09)
10%					
b_{01}	17.42 (15.87, 19.02)	16.07 (13.78, 18.16)	17.28 (-6.88, 41.58)	16.99 (15.21, 18.36)	16.96 (15.48, 18.49)
b_{02}	15.92 (13.18, 19.76)	13.70 (10.96, 18.25)	14.90 (-41.65, 72.67)	14.96 (12.72, 18.69)	14.53 (12.01, 18.81)
b_{11}	0.48 (0.34, 0.62)	0.50 (0.25, 0.75)	0.48 (-0.63, 1.63)	0.51 (0.38, 0.71)	0.51 (0.37, 0.65)
b_{12}	0.81 (0.52, 1.05)	1.02 (0.67, 1.25)	0.92 (-3.52, 5.16)	0.91 (0.58, 1.09)	0.95 (0.61, 1.15)
20%					
b_{01}	17.42 (15.87, 19.02)	15.83 (3.64, 27.88)	17.10 (-83.86, 120.42)	17.71 (15.49, 19.24)	16.89 (14.48, 19.06)
b_{02}	15.92 (13.18, 19.76)	13.28 (-43.80, 70.54)	15.60 (-64.45, 95.02)	14.73 (12.42, 18.62)	14.05 (11.36, 18.37)
b_{11}	0.48 (0.34, 0.62)	0.54 (-0.55, 1.65)	0.50 (-6.90, 7.74)	0.44 (0.29, 0.68)	0.52 (0.32, 0.76)
b_{12}	0.81 (0.52, 1.05)	1.03 (-3.97, 6.03)	0.83 (-5.68, 7.34)	0.92 (0.55, 1.11)	0.97 (0.58, 1.21)

Table 5.7: Estimates and 95% confidence intervals for variance parameters (diagonal elements of Σ). The dental data with 5%, 10% and 20% MNAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
σ_{11}	5.93 (1.62, 7.96)	5.60 (1.53, 8.79)	6.03 (2.02, 9.42)	5.15 (1.65, 8.10)	5.30 (1.67, 8.20)
σ_{22}	4.65 (2.03, 5.70)	3.74 (1.69, 5.49)	4.65 (2.11, 6.90)	3.90 (1.96, 5.81)	3.90 (1.97, 5.61)
σ_{33}	7.94 (2.72, 8.91)	6.80 (2.89, 10.22)	8.83 (3.48, 13.29)	5.86 (2.54, 9.48)	6.18 (2.84, 9.10)
σ_{44}	7.65 (2.24, 6.42)	5.18 (2.37, 7.31)	7.93 (3.24, 11.88)	4.66 (2.17, 7.83)	4.79 (2.37, 6.58)
10%					
σ_{11}	5.93 (1.62, 7.96)	5.97 (1.08, 9.73)	6.25 (1.95, 9.92)	4.75 (1.40, 7.70)	5.35 (1.46, 8.66)
σ_{22}	4.65 (2.03, 5.70)	3.57 (-0.06, 7.32)	5.04 (2.35, 7.39)	3.88 (1.98, 5.81)	4.05 (2.13, 5.80)
σ_{33}	7.94 (2.72, 8.91)	6.73 (2.36, 10.85)	9.22 (3.68, 13.85)	5.82 (2.56, 9.52)	6.28 (2.94, 9.23)
σ_{44}	7.65 (2.24, 6.42)	4.68 (1.65, 7.20)	8.26 (3.46, 12.36)	4.57 (2.13, 7.83)	4.79 (2.41, 6.61)
20%					
σ_{11}	5.93 (1.62, 7.96)	6.42 (-583.05, 648.13)	6.48 (2.01, 10.28)	4.71 (1.38, 7.70)	5.59 (-219.75, 242.28)
σ_{22}	4.65 (2.03, 5.70)	3.11 (-119.34, 134.81)	4.19 (1.64, 6.43)	3.25 (1.38, 5.01)	3.52 (-1.19, 8.42)
σ_{33}	7.94 (2.72, 8.91)	7.24 (-11.01, 26.20)	10.09 (3.57, 15.61)	4.59 (1.65, 8.39)	6.04 (-121.64, 139.98)
σ_{44}	7.65 (2.24, 6.42)	5.00 (-317.15, 353.95)	7.84 (2.69, 12.19)	3.69 (1.51, 6.88)	5.57 (-1.70, 13.00)

From Table 5.7, we can see that the Bayesian method, the EM algorithm and Kleinbaum's method provide comparable estimates to the gold-standard, when the missingness percentage is small (5%). Moreover, despite the missingness being MNAR, for small percentage of missing, the complete case analysis also provides good estimates for the variance parameters. estimating the within individual variance. However, as the missingness percentage increases, the EM algorithm is not dependable anymore. The complete case analysis also provides relatively wide CIs. Keinbaum's approach still provides good estimators when the missingness is moderate to large, however, it has relatively wider CIs than the gold-standard. On the other hand, the Bayesian method is the best alternative, providing estimates comparable to the gold-standard (CIs overlap), and with good precision. Similar conclusions can be drawn from the covariance estimates in Table C.2 in the Appendix.

5.2 Glucose Data

In this section, we use the glucose data to illustrate practical use of the different methods considered in this thesis. The data consists of 8 repeated measurements (at times 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 hours post administration of oral glucose) taken from 29 controls (non-obese individuals) and 21 obese individuals ($n = 50$, $k = 2$, $p = 8$). The individual and mean profile plots for this data are provided in Figure 2.2, Chapter 2. As you can see from the profile plots, the mean trajectory overtime, for both groups, is non-linear. Therefore, we will fit the GCM with $q = 3$, quadratic function of time. The within and between individual design matrices for are provided in Chapter 4.

We would like to highlight that this data does not contain any missing observations. We purposefully use it so that we can illustrate the performance of the methods when the mean structure is non-linear, and performance will be evaluated by comparing the estimates to the gold-standard. We provide element-wise estimates for both $\mathbf{B}$ and $\mathbf{\Sigma}$, with the corresponding CIs, calculated using bootstrap samples. Below, we only present the results corresponding to $\mathbf{B}$. For the results corresponding to $\mathbf{\Sigma}$, refer to Tables C.3 to C.20 in the Appendix.

5.2.1 Missing Completely at Random

Similar to the dental data, we see from Table 5.8 that, when the missingness percentage is low, all methods perform well and the estimates and CIs are close to that of the gold-standard. Indicating that all these approaches, regardless of the number of time points and mean structure, can be used for estimating mean parameters of the GCM, when data consists of small percentage of MCAR. Similar to what we saw for the dental data, and as demonstrated in our simulation studies, Kleinbaum's method is not a stable method for estimating the mean parameters of the GCM, when the missingness percentage is moderate to high. As such, this method should not be used in practical applications involving large missing data, even when the missingness mechanism is MCAR. However, we will see below that it is one of the best choices when estimating $\mathbf{\Sigma}$. On the other hand, the results in Table 5.8 show that, in scenarios with large percentage of MCAR, the Bayesian method and the EM algorithm are desirable for estimating $\mathbf{B}$.

We can see from Tables C.3 C.4 in the Appendix that all methods also work well in estimating $\mathbf{\Sigma}$, when the missingness percentage is small and the mechanism is MCAR. Even when we increased the missingness percentage to 10%, which is not a low percentage considering that the sample size is only 50, these the multivariate methods developed to handle missing data still provide what appears to be valid estimates for $\mathbf{\Sigma}$. However, complete case analysis leads to estimators with relatively wider CIs when the missingness percentage is 10% (See Tables C.5 and C.6 in the Appendix). When missingness is 20%, complete case analysis becomes unstable in estimating $\mathbf{\Sigma}$, hence not a reliable approach. Among three multivariate methods, we observe that Kleinbaum's method and the Bayesian approach provide CIs relatively closer to gold-standard than the EM algorithm (See Tables C.7 and C.8 in the Appendix).

Table 5.8: Estimates and 95% confidence intervals for $\mathbf{B}$. The glucose data with 5%, 10%, and 20% MCAR is used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
b_{01}	6.03 (5.71, 6.37)	6.01 (5.53, 6.50)	6.13 (2.66, 9.54)	6.08 (5.68, 6.41)	6.07 (5.72, 6.43)
b_{02}	5.70 (5.15, 6.20)	5.77 (5.27, 6.26)	5.72 (4.39, 6.99)	5.60 (5.14, 6.18)	5.68 (5.24, 6.15)
b_{11}	-2.07 (-2.28, -1.88)	-1.99 (-2.29, -1.71)	-2.13 (-3.49, -0.72)	-2.07 (-2.26, -1.84)	-2.08 (-2.30, -1.87)
b_{12}	-1.75 (-2.06, -1.40)	-1.81 (-2.10, -1.51)	-1.80 (-2.56, -1.07)	-1.72 (-2.08, -1.43)	-1.75 (-2.06, -1.45)
b_{21}	0.35 (0.31, 0.39)	0.34 (0.29, 0.39)	0.36 (0.15, 0.56)	0.35 (0.31, 0.38)	0.35 (0.31, 0.39)
b_{22}	0.29 (0.24, 0.34)	0.31 (0.26, 0.36)	0.31 (0.16, 0.46)	0.29 (0.24, 0.35)	0.30 (0.24, 0.35)
10%					
b_{01}	6.03 (5.71, 6.37)	6.01 (5.44, 6.61)	6.13 (-254.38, 258.49)	6.23 (5.76, 6.58)	6.14 (5.74, 6.58)
b_{02}	5.70 (5.15, 6.20)	6.06 (5.36, 6.79)	5.51 (-10.04, 20.46)	5.60 (5.15, 6.18)	5.62 (5.15, 6.21)
b_{11}	-2.07 (-2.28, -1.88)	-2.00 (-2.34, -1.71)	-2.15 (-261.90, 266.01)	-2.14 (-2.33, -1.87)	-2.11 (-2.37, -1.87)
b_{12}	-1.75 (-2.06, -1.40)	-2.03 (-2.34, -1.73)	-1.70 (-8.13, 4.73)	-1.69 (-2.06, -1.42)	-1.72 (-2.08, -1.42)
b_{21}	0.35 (0.31, 0.39)	0.34 (0.29, 0.40)	0.36 (-48.11, 47.33)	0.36 (0.31, 0.39)	0.35 (0.31, 0.40)
b_{22}	0.29 (0.24, 0.34)	0.35 (0.30, 0.39)	0.30 (-0.87, 1.48)	0.29 (0.24, 0.35)	0.29 (0.24, 0.35)
20%					
b_{01}	6.03 (5.71, 6.37)	2.91 (-10.84, 14.86)	7.90 (-34.26, 46.01)	6.11 (5.51, 6.50)	6.11 (5.23, 6.84)
b_{02}	5.70 (5.15, 6.20)	5.10 (-6.59, 11.98)	7.53 (-205.51, 209.88)	5.59 (5.20, 6.29)	5.71 (4.93, 6.58)
b_{11}	-2.07 (-2.28, -1.88)	0.09 (-10.62, 11.26)	-3.00 (-22.73, 17.87)	-2.07 (-2.35, -1.66)	-2.11 (-2.53, -1.61)
b_{12}	-1.75 (-2.06, -1.40)	-1.23 (-7.58, 7.71)	-2.47 (-144.71, 146.11)	-1.67 (-2.12, -1.42)	-1.82 (-2.32, -1.37)
b_{21}	0.35 (0.31, 0.39)	0.01 (-2.08, 1.97)	0.43 (-2.90, 3.75)	0.35 (0.28, 0.40)	0.35 (0.27, 0.43)
b_{22}	0.29 (0.24, 0.34)	0.20 (-1.58, 1.52)	0.36 (-31.36, 30.92)	0.28 (0.24, 0.35)	0.31 (0.24, 0.39)

5.2.2 Missing at Random

From Table 5.9, we can see that when the missingness percentage is low, all methods, except Kleinbaum's, perform well in estimating $\mathbf{B}$, and the estimates and CIs that are close to the gold-standard. The results show that when the missingness mechanism is MAR, Kleinbaum's method led to wide CIs even when the percentage of missing is small. When the missingness percentage increases, complete case analysis also led to wider CIs than the Bayesian method and the EM algorithm. Similar to the MCAR, we can conclude that, in the presence of large percentage of MAR, the Bayesian method and the EM algorithm are desirable techniques for estimating $\mathbf{B}$, and they produce estimates and CIs comparable to gold-standard. Note that we also reached to the same conclusion when using the dental data, which has smaller number of time points, smaller sample size and linear mean structure. The findings from our simulation studies also support this conclusion.

From Tables C.9 and C.10 (provided in the Appendix), we can see that all methods works well for estimating Σ when missingness percentage is small. As we increase the missingness percentage to 10%, complete case analysis led to estimators with a slightly wider CIs. We can also clearly see that the EM algorithm led to a much wider CIs for several variance parameters, compared to Kleinbaum's method and the Bayesian method (Tables C.11 and C.12, Appendix). When missingness is high reaching 20%, complete case analysis also led to a much wider CIs, hence this approach is not reliable in estimating Σ . Among three multivariate methods considered in this thesis, we can observe that Kleinbaum's method and the Bayesian method are the best choices and lead to estimates and CIs that are relatively closer to gold-standard. We have seen this finding for the dental data as well as in our simulation studies. Therefore, we can safely conclude that when data involve a moderate to large percentage of data with mechanism MAR, Kleinbaum's approach and the Bayesian method provide optimal methods. This is especially important for studies with small sample size. However, the EM algorithm is also a good alternative in most cases.

5.2.3 Missing Not at Random

Similar to the dental data and our simulation findings, Kleinbaum's method is unstable in estimating $\mathbf{B}$, hence should not be used (Table 5.10). The other methods, including complete case analysis, seem to work well when the missingness is 5%. When the missingness percentage increases, complete case analysis led to wider CIs compared to the Bayesian method and the EM algorithm. Therefor, these two methods are the best approaches for estimating the mean parameters of the GCM in the presence of missing data, extending our conclusions for MCAR and MAR above to MNAR.

Table 5.9: Estimates and 95% confidence intervals for $\mathbf{B}$. The glucose data with 5%, 10%, and 20% MAR is used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
b_{01}	6.03 (5.71, 6.37)	6.02 (5.55, 6.62)	6.16 (-3.49, 15.67)	6.11 (5.66, 6.46)	6.07 (5.68, 6.48)
b_{02}	5.70 (5.15, 6.20)	5.76 (5.69, 6.84)	5.75 (-21.36, 32.65)	5.50 (5.48, 6.50)	5.98 (5.53, 6.45)
b_{11}	-2.07 (-2.28, -1.88)	-2.03 (-2.36, -1.85)	-2.16 (-9.96, 5.69)	-2.11 (-2.25, -1.81)	-2.04 (-2.25, -1.85)
b_{12}	-1.75 (-2.06, -1.40)	-1.89 (-2.36, -1.55)	-1.82 (-44.61, 41.76)	-1.64 (-2.16, -1.56)	-1.84 (-2.15, -1.56)
b_{21}	0.35 (0.31, 0.39)	0.34 (0.31, 0.39)	0.36 (-1.10, 1.80)	0.36 (0.30, 0.37)	0.34 (0.31, 0.37)
b_{22}	0.29 (0.24, 0.34)	0.32 (0.25, 0.38)	0.31 (-7.62, 8.07)	0.28 (0.26, 0.35)	0.30 (0.26, 0.35)
10%					
b_{01}	6.03 (5.71, 6.37)	6.18 (5.27, 6.98)	5.90 (-31.89, 44.82)	6.11 (5.63, 6.45)	6.11 (5.69, 6.57)
b_{02}	5.70 (5.15, 6.20)	5.66 (5.28, 8.20)	5.40 (-14.92, 26.64)	5.53 (5.45, 6.50)	6.12 (5.65, 6.65)
b_{11}	-2.07 (-2.28, -1.88)	-2.06 (-2.57, -1.70)	-1.88 (-27.03, 22.21)	-2.09 (-2.22, -1.79)	-2.05 (-2.28, -1.84)
b_{12}	-1.75 (-2.06, -1.40)	-1.95 (-3.14, -1.39)	-1.46 (-14.21, 10.41)	-1.58 (-2.18, -1.56)	-1.96 (-2.30, -1.68)
b_{21}	0.35 (0.31, 0.39)	0.34 (0.28, 0.42)	0.31 (-3.84, 4.66)	0.35 (0.30, 0.37)	0.34 (0.30, 0.37)
b_{22}	0.29 (0.24, 0.34)	0.34 (0.22, 0.51)	0.24 (-1.74, 2.37)	0.26 (0.26, 0.36)	0.32 (0.27, 0.37)
20%					
b_{01}	6.03 (5.71, 6.37)	6.26 (0.78, 10.91)	6.50 (-674.82, 709.59)	6.26 (5.56, 6.40)	6.24 (4.85, 7.10)
b_{02}	5.70 (5.15, 6.20)	5.65 (-1.69, 13.06)	4.79 (-37.07, 50.47)	5.75 (5.51, 6.54)	6.12 (4.77, 7.10)
b_{11}	-2.07 (-2.28, -1.88)	-2.09 (-5.76, 2.25)	-2.15 (-130.31, 122.34)	-2.17 (-2.19, -1.73)	-2.17 (-2.75, -1.30)
b_{12}	-1.75 (-2.06, -1.40)	-1.56 (-7.22, 4.63)	-1.77 (-23.39, 19.18)	-1.66 (-2.25, -1.55)	-1.96 (-2.69, -1.15)
b_{21}	0.35 (0.31, 0.39)	0.35 (-0.42, 1.00)	0.37 (-2.33, 3.01)	0.36 (0.29, 0.36)	0.35 (0.21, 0.46)
b_{22}	0.29 (0.24, 0.34)	0.26 (-0.85, 1.29)	0.22 (-2.80, 3.46)	0.27 (0.26, 0.37)	0.31 (0.18, 0.45)

Table 5.10: Estimates and 95% confidence intervals for $\mathbf{B}$. The glucose data with 5%, 10%, and 20% MNAR is used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
b_{01}	6.03 (5.71, 6.37)	6.13 (5.37, 6.37)	6.15 (-1002.86, 981.47)	6.15 (5.50, 6.40)	6.05 (5.64, 6.48)
b_{02}	5.70 (5.15, 6.20)	5.69 (5.18, 6.47)	5.59 (-4.91, 16.95)	5.57 (5.25, 6.29)	5.89 (5.40, 6.38)
b_{11}	-2.07 (-2.28, -1.88)	-2.07 (-2.23, -1.73)	-2.12 (-1363.63, 1405.72)	-2.11 (-2.24, -1.76)	-2.06 (-2.29, -1.84)
b_{12}	-1.75 (-2.06, -1.40)	-1.75 (-2.31, -1.47)	-1.69 (-9.88, 6.06)	-1.67 (-2.07, -1.38)	-1.77 (-2.10, -1.47)
b_{21}	0.35 (0.31, 0.39)	0.35 (0.29, 0.37)	0.36 (-183.92, 178.53)	0.35 (0.30, 0.37)	0.34 (0.30, 0.38)
b_{22}	0.29 (0.24, 0.34)	0.29 (0.25, 0.39)	0.29 (-0.61, 1.21)	0.28 (0.23, 0.34)	0.29 (0.24, 0.34)
10%					
b_{01}	6.03 (5.71, 6.37)	5.79 (4.56, 6.29)	5.64 (-60.35, 70.58)	6.16 (5.48, 6.40)	6.01 (5.57, 6.45)
b_{02}	5.70 (5.15, 6.20)	5.68 (4.60, 6.66)	5.89 (-424.69, 450.56)	5.61 (5.22, 6.33)	5.94 (5.38, 6.48)
b_{11}	-2.07 (-2.28, -1.88)	-1.84 (-2.34, -1.22)	-1.95 (-49.30, 47.03)	-2.10 (-2.22, -1.75)	-2.04 (-2.28, -1.79)
b_{12}	-1.75 (-2.06, -1.40)	-1.68 (-2.63, -1.17)	-1.61 (-75.66, 74.48)	-1.69 (-2.07, -1.38)	-1.81 (-2.16, -1.47)
b_{21}	0.35 (0.31, 0.39)	0.32 (0.21, 0.41)	0.36 (-5.88, 6.33)	0.35 (0.29, 0.37)	0.34 (0.29, 0.38)
b_{22}	0.29 (0.24, 0.34)	0.29 (0.19, 0.46)	0.27 (-46.53, 45.63)	0.29 (0.22, 0.34)	0.29 (0.23, 0.35)
20%					
b_{01}	6.03 (5.71, 6.37)	6.83 (-2.54, 4.83)	6.80 (-1174.19, 1224.39)	6.11 (5.45, 6.60)	6.03 (4.99, 7.03)
b_{02}	5.70 (5.15, 6.20)	5.39 (-3.90, 7.53)	27.74 (-73.61, 83.24)	5.61 (5.33, 6.44)	5.97 (4.96, 6.93)
b_{11}	-2.07 (-2.28, -1.88)	-2.49 (-1.93, 2.31)	-3.11 (-1134.30, 1094.53)	-2.13 (-2.36, -1.72)	-2.04 (-2.51, -1.52)
b_{12}	-1.75 (-2.06, -1.40)	-1.68 (-3.11, 3.59)	-18.55 (-45.25, 42.90)	-1.74 (-2.17, -1.44)	-1.86 (-2.38, -1.30)
b_{21}	0.35 (0.31, 0.39)	0.43 (-0.37, 0.64)	0.51 (-215.63, 223.39)	0.36 (0.28, 0.39)	0.34 (0.25, 0.40)
b_{22}	0.29 (0.24, 0.34)	0.28 (-0.60, 0.92)	2.32 (-5.33, 5.75)	0.30 (0.23, 0.36)	0.29 (0.20, 0.38)

Finally, we see from the results presented in Tables C.15 and C.16 (provided in the Appendix) that, when estimating Σ in the presence of small percentage of missing data, all methods perform well. This was also the case for the dental data, hence providing additional evidence and strengthening the conclusions made. As we increase the missingness percentage to 10% MNAR, the complete case analysis and the EM algorithm led to wider CIs for several estimates of variance and covariance parameters (Tables C.17 and C.18, Appendix). When high percentage of missingness (reaching 20%) is considered, the complete case analysis and the EM algorithm became unreliable choices. Therefore, these two methods should not be used in estimating Σ when data consists of moderate to high MNAR. On the other hand, Kleinbaum's method and the Bayesian approach provide reliable estimates and CIs, even when the missingness mechanism is MNAR (Tables C.19 and C.20, Appendix). This conclusion is also supported by our results for the dental data and our simulation findings.

Chapter 6

Summary and Future Directions

6.1 Summary and Discussions

The GCM, which is a GCMANOVA model, has been demonstrated to be useful in the analysis of longitudinal data, growth curves as well as other response curves. Inference in the model involves bilinear projections, unlike the traditional linear models, therefore earning a name bilinear regression models. The GCM, in addition to accounting the correlation between measurements from the same unit, the model also incorporates the mean structure, contributing to its optimality for studies involving longitudinal data analysis. The explicit likelihood solutions make the model also desirable, in particular for allowing extensions including to high-dimensional data. However, one of the limitations is that it does not allow missing data. Missing data is a common problem in practice, in particular in studies involving longitudinal data. Therefore, when using the GCM, handling missing data is crucial.

Our extensive literature review revealed three multivariate methods for handling missing data (Liski's EM algorithm, Liski's Bayesian method and Kleinbaum's generalized GCM approach). These methods are specifically developed under the GCM framework, allowing structured mean. Despite their availability for several decades, we found no single article involving their use, hence applications of these methods are non-existent. This is mainly because these methods have not been implemented in any of the statistical software. Moreover, the numerical examples provided in the papers, if any, are very limited.

In this thesis, we implemented the algorithms in the R statistical software. In our implementation, we generalized and automated the algorithms such that our R programs allow any p (number of time points), n (sample size), k (number of groups), q (degree of polynomial representing the mean structure) and different missingness patterns. We also extended some of the assumptions and parameter settings, when they did not allow generalization and automation.

We conducted extensive simulations involving more than 2,000 scenarios, with sample sizes ranging from small to large. The true model parameters were specified to mimic real-life scenarios. We compared the methods using bias and MSE, using both element-wise

and aggregated values. We also compared the estimators with the gold-standard (using the full data with no missing values) as well as complete case analysis (list-wise deletion of individuals with missing data). We also provided detailed illustrations using real data sets. In our real data analysis, we provided CIs calculated using the bootstrap algorithm.

The findings from our simulation studies and real data examples show that Liski's EM algorithm is uniformly better than the other methods in estimating the mean parameters ($\mathbf{B}$) of the GCM, across most of the scenarios considered including MNAR scenarios. In most cases, this method produced estimators with similar MSE values as the gold-standard, which can serve as benchmark for what we could have achieved with no missing data. However, the EM algorithm is shown to be unstable for estimating Σ when the missingness percentage is high, for MCAR, MAR and MNAR scenarios. Liski's Bayesian method matched Liski's EM algorithm performance in estimating Σ when the missing percentage is not too high. In fact, the Bayesian method produced slightly smaller MSE values for several parameters of Σ , indicating that there is no uniformly better approach. To facilitate comparison in such cases, since we are estimating matrix parameters, we used aggregated values of bias and MSE. The Bayesian method also becomes unstable when the percentage of missing data is high and the missingness mechanism is MNAR.

Complete case analysis remained unbiased when the percentage of missing data is small, for both MCAR and MAR scenarios. The method quickly lost efficiency with increasing missing percentage. For scenarios with MNAR, complete case analysis still provided estimators with reasonable bias, however, variability was observed to be high even when the percentage of missingness is small. However, we would like to highlight that, even for scenarios with low percentage of missingness and MCAR mechanism, complete case analysis led to estimators with uniformly lower MSE than the EM algorithm and Bayesian method.

The Kleinbaum's method was numerically unstable in estimating $\mathbf{B}$, hence should not be used in practical applications. However, Kleinbaum's gave stable estimates for Σ in all scenarios. In fact, our simulation results show that this approach is the best some scenarios involving MAR and in most scenarios involving MNAR. This is a significant finding for this approach, especially considering that MAR and MNAR are the mechanisms that generate most of missing data we encounter in real life scenarios.

The results we obtained from dental and glucose data were consistent with our simulation findings. We observed that the EM algorithm and the Bayesian method almost reproduced the estimates obtained using the full data sets. Complete case analysis provided CIs that are wider than the gold-standard, and in most cases wider than the EM algorithm and the Bayesian method. The CIs we calculated from the real data analysis also confirmed that Kleinbaum's method is unstable in estimating $\mathbf{B}$, but also confirmed that the method remained reliable for estimating Σ .

6.2 Future Directions

Despite the promising results obtained in this thesis, several methodological limitations remain. For instance, Liski’s EM algorithm relies on a complete case estimate of the variance–covariance matrix ($\hat{\Sigma}$), which can be inefficient when the percentage of missing data is high and/or the missingness is non-ignorable. Liski’s Bayesian method makes strong assumptions of $\Sigma = \sigma_j^2 \mathbf{I}_p$ (i.e. sample variance within each group j and independence between measurements from the same unit), which are both unrealistic assumptions in practical applications involving longitudinal data. Therefore, forcing independence of repeated measures and within group constant variance might have led to some of the poor performances and instabilities. The Bayesian method also involves choice of priors and hyper-parameters, as such their choice will impact performance. Moreover, in Kleinbaum’s approach, parameter estimates are obtained in a single pass (no iterations), which may limit accuracy for some missing patterns. Furthermore, all the three multivariate methods considered in this thesis do not take missingness mechanisms into account nor do they involve multiple imputations.

Although we performed extensive simulations, the simulations are still not extensive enough to evaluate other important factors. As such, the simulations can be expanded to evaluate the performance of the existing methods (and emerging ones) with respect to different covariance structures (compound symmetry, autoregressive, or unstructured), different levels of dependency (independent as well as weak, moderate and high within individual correlations) as well as in high-dimensional settings, both in near singular $p \approx n$ and truly high dimensional $p > n$ settings. The simulations can also be expanded to evaluate robustness (or lack of) the methods when the multivariate-normal assumption is violated.

One possible future direction is to improve the EM algorithm by adopting a more information-efficient covariance estimators in the algorithm. A simple strategy, for instance, is to use pairwise deletion instead of list-wise deletion that the algorithm currently uses. The algorithm can also be improved to account for modeling error, an error that can arise because of model mis-specification. For Kleinbaum’s method, extending the estimation process as an iterative procedure (alternating between fixed-effects and random-effects updates) could increase the precision when estimating $\mathbf{B}$. For the Bayesian method, further investigation surrounding the prior distributions and their hyper-parameters can be done, which may allow us to provide better choices for the matrix $\mathbf{C}$. Relaxing the independence assumption and the within group constant variance assumption in the Bayesian method is also another important research direction that may allow improved performance of the Bayesian method.

Beyond algorithmic refinements highlighted above, extending all three methods to allow analysis of clustered longitudinal data is a natural step. This can be achieved by considering the Extended Growth Curve Model (EGCM), which allows different groups (clusters) to have different mean structures. Another possible extension could involve MANOVA-type models, where we have multivariate data representing multiple outcomes from the same individuals but unstructured mean (eg. blood pressure, cholesterol, blood sugar level etc. measured from the same individuals). Moreover, all the models GCM, EGCM and

MANOVA can be extended to include additional covariates. This will allow additional variables (some auxiliary and not included in the model) to inform both the mean structure and missing-data mechanisms. Another future direction is hypothesis testing using the GCM, where presence of missing data still causes the problem. Some of the methods we evaluated in this thesis can be easily extended and their performance evaluated, because they complete the data (by estimating the missing data) as an intermediate step. As such, hypothesis testing using available test statistic can be done using the completed data (the original and imputed).

Finally, the methods evaluated in this thesis are currently implemented as a single-imputation procedures. Embedding the methods within a multiple-imputation framework may improve inference. This will also allow comparisons with other available multiple imputation techniques for longitudinal data to be compared. If mathematically feasible, incorporating explicit assumptions about the missing-data mechanism into the methods is another promising future direction.

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APPENDICES

Appendix A

Glucose Data Set

Table A.1: Glucose data set from a glucose tolerance test and includes 8 repeated measurements of glucose tolerance outcome (plasma inorganic phosphate) that were taken 1, 1.5, 2.0, 2.5, 3, 3.5, 4 and 4.5 hours after administration of oral glucose. The measurements were collected from 29 controls (non-obese individuals) and 21 obese individuals ($n = 50$, $k = 2$, $p = 8$). (Part 1)

ID	1	1.5	2	2.5	3	3.5	4	4.5	Group
1	3.70	3.10	2.90	2.20	1.50	2.30	2.70	2.80	1
2	4.41	3.18	3.18	3.16	2.75	2.74	2.68	3.94	1
3	3.71	2.51	2.58	2.82	2.29	2.56	2.91	4.01	1
4	5.33	4.84	3.63	3.42	3.03	3.77	3.63	4.22	1
5	3.80	3.00	2.40	2.50	3.10	3.40	3.50	3.70	1
6	3.31	2.23	2.65	2.64	2.92	2.78	3.09	4.12	1
7	4.58	3.88	3.77	3.76	3.20	2.60	2.51	3.57	1
8	5.47	4.99	4.49	3.88	3.81	3.83	3.89	3.98	1
9	5.14	5.22	4.54	4.16	4.78	4.05	5.13	5.09	1
10	3.83	3.54	3.58	2.96	2.23	2.71	2.95	3.45	1
11	4.04	3.61	3.67	3.19	3.60	2.86	2.76	3.04	1
12	5.14	4.32	3.35	3.55	3.36	2.91	2.64	3.68	1
13	5.23	5.26	4.32	3.81	2.21	2.31	2.74	3.13	1
14	3.20	2.22	1.96	1.93	1.55	2.15	2.49	2.94	1
15	4.43	3.61	2.88	2.78	3.20	3.26	3.36	3.72	1
16	5.91	5.59	4.56	4.09	4.63	3.81	4.13	4.48	1
17	3.90	3.70	3.30	2.58	2.17	2.57	3.38	3.77	1
18	3.62	2.37	2.22	2.60	2.27	2.62	2.83	3.24	1
19	5.24	4.61	3.09	3.37	3.58	4.05	3.79	4.63	1
20	3.50	2.54	2.36	2.82	2.46	3.22	3.20	3.44	1
21	4.15	3.41	3.66	4.11	3.15	3.01	3.21	3.63	1
22	5.54	5.18	4.89	4.06	3.70	3.10	3.54	4.20	1

Table A.2: Glucose data set from a glucose tolerance test and includes 8 repeated measurements of glucose tolerance outcome (plasma inorganic phosphate) that were taken 1, 1.5, 2.0, 2.5, 3, 3.5, 4 and 4.5 hours after administration of oral glucose. The measurements were collected from 29 controls (non-obese individuals) and 21 obese individuals ($n = 50$, $k = 2$, $p = 8$). (Part 2)

ID	1	1.5	2	2.5	3	3.5	4	4.5	Group
23	4.31	3.89	2.88	3.04	3.13	2.92	3.16	3.35	1
24	3.94	3.15	2.80	2.29	2.63	2.50	2.28	3.08	1
25	4.00	4.10	3.10	2.30	2.90	3.10	3.90	4.00	1
26	4.57	4.86	3.69	3.12	3.57	4.15	4.29	4.62	1
27	5.31	4.02	3.13	3.17	3.79	3.87	3.34	4.32	1
28	5.41	4.93	4.31	3.66	2.38	3.00	3.58	4.29	1
29	3.83	3.52	3.41	3.19	2.52	2.77	2.70	3.39	1
30	4.97	4.23	4.41	4.00	3.26	3.06	2.86	3.74	2
31	4.50	4.00	3.70	3.30	2.40	2.30	3.10	3.30	2
32	4.41	4.08	2.76	3.59	2.78	3.13	3.18	3.47	2
33	4.33	4.16	3.60	3.03	3.65	3.03	3.78	4.46	2
34	5.25	4.80	3.91	3.32	3.94	3.78	3.99	4.25	2
35	4.87	3.87	3.32	3.12	3.54	3.30	3.33	3.86	2
36	5.13	4.12	3.98	3.76	3.40	3.45	3.19	4.08	2
37	4.30	3.30	3.00	2.60	2.20	2.50	2.40	3.40	2
38	3.81	2.55	2.67	2.63	3.27	3.44	3.28	4.04	2
39	4.17	4.39	4.44	4.36	3.84	3.37	3.65	4.06	2
40	6.00	6.11	5.42	4.16	3.67	3.10	3.62	4.09	2
41	4.38	4.42	3.65	3.88	3.63	2.89	2.98	3.18	2
42	2.64	2.19	2.18	2.19	2.80	2.85	2.74	3.39	2
43	3.19	3.07	2.60	2.13	2.23	1.42	2.27	2.83	2
44	4.40	4.20	4.20	3.40	3.50	3.40	3.90	4.00	2
45	5.04	4.31	4.33	3.70	4.06	3.72	4.04	4.73	2
46	4.38	4.19	3.14	3.27	3.01	3.03	3.17	3.56	2
47	3.70	3.10	3.30	2.80	2.90	3.60	4.30	4.40	2
48	4.62	3.67	3.04	2.65	4.45	3.89	3.90	4.48	2
49	3.63	3.70	3.64	3.68	3.45	3.24	3.19	3.22	2
50	4.75	5.08	4.27	4.28	2.80	3.27	3.75	3.25	2

Appendix B

Figures for Chapter 4

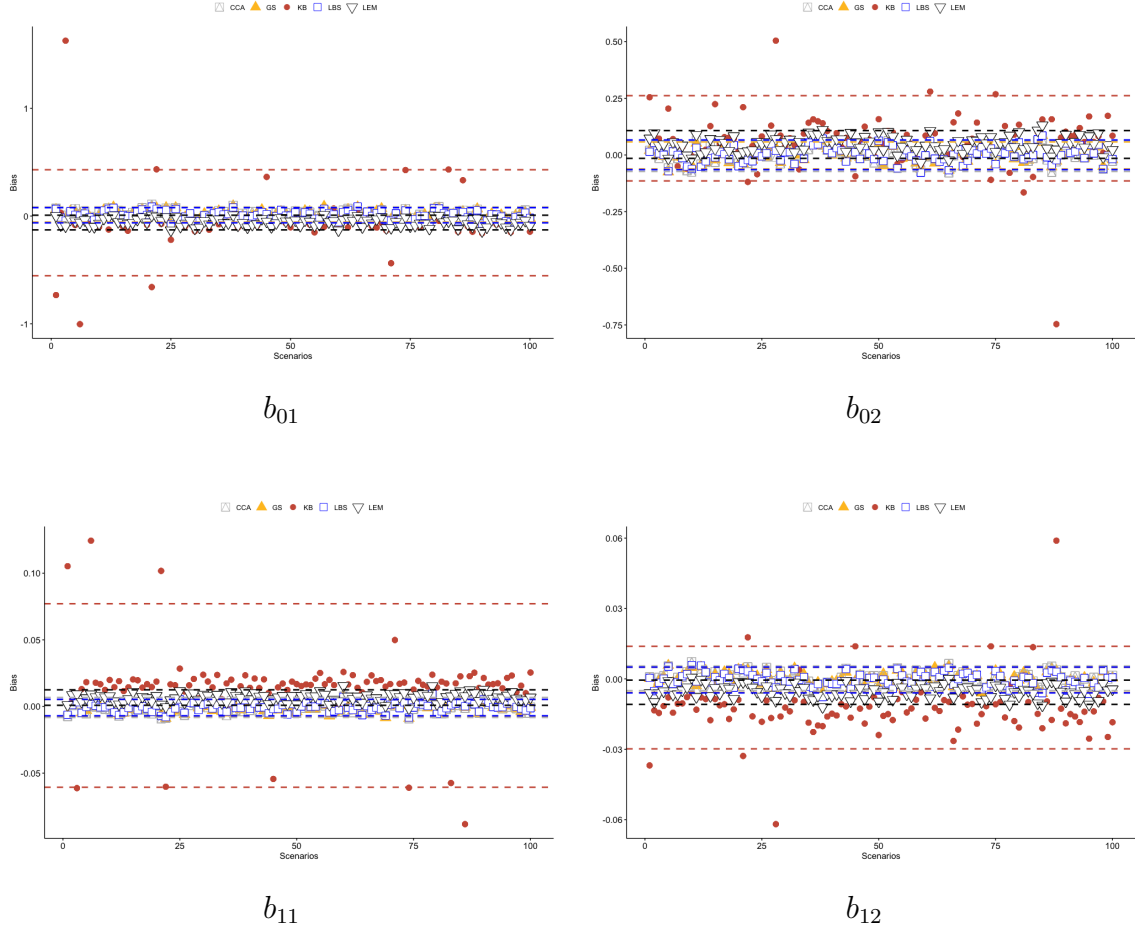


Figure B.1: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 27$, $p = 4$, $q = 2$, 5% missing with MCAR mechanism and the MLEs from the dental data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs (Kleinbaum's GGCM method is included in the plots to show the huge variation).

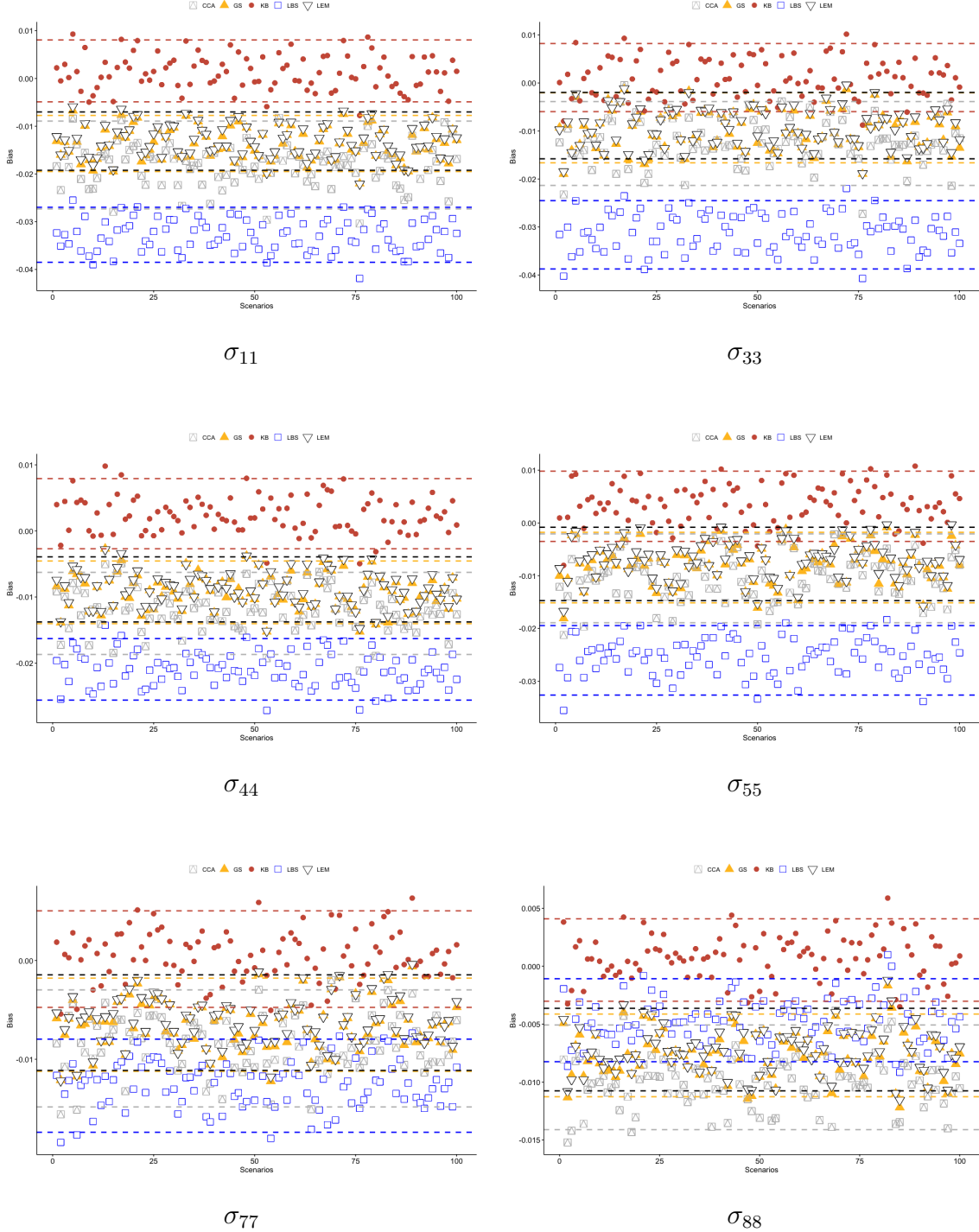


Figure B.2: Element-wise bias for selected estimators of variances (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% missing with MCAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

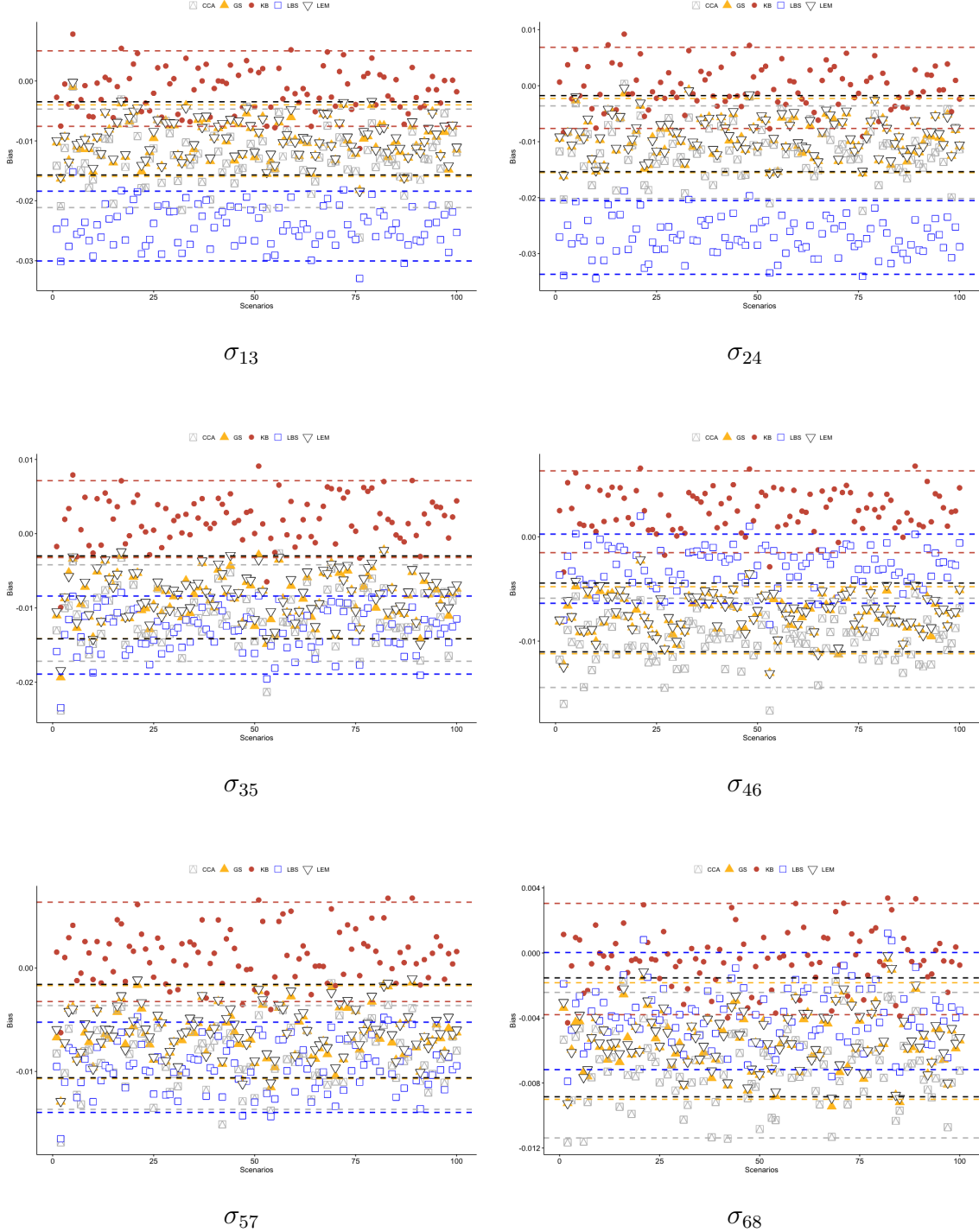


Figure B.3: Element-wise bias for selected estimators of covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 5% MCAR mechanism. The MLEs from the glucose data are used as true values for B and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

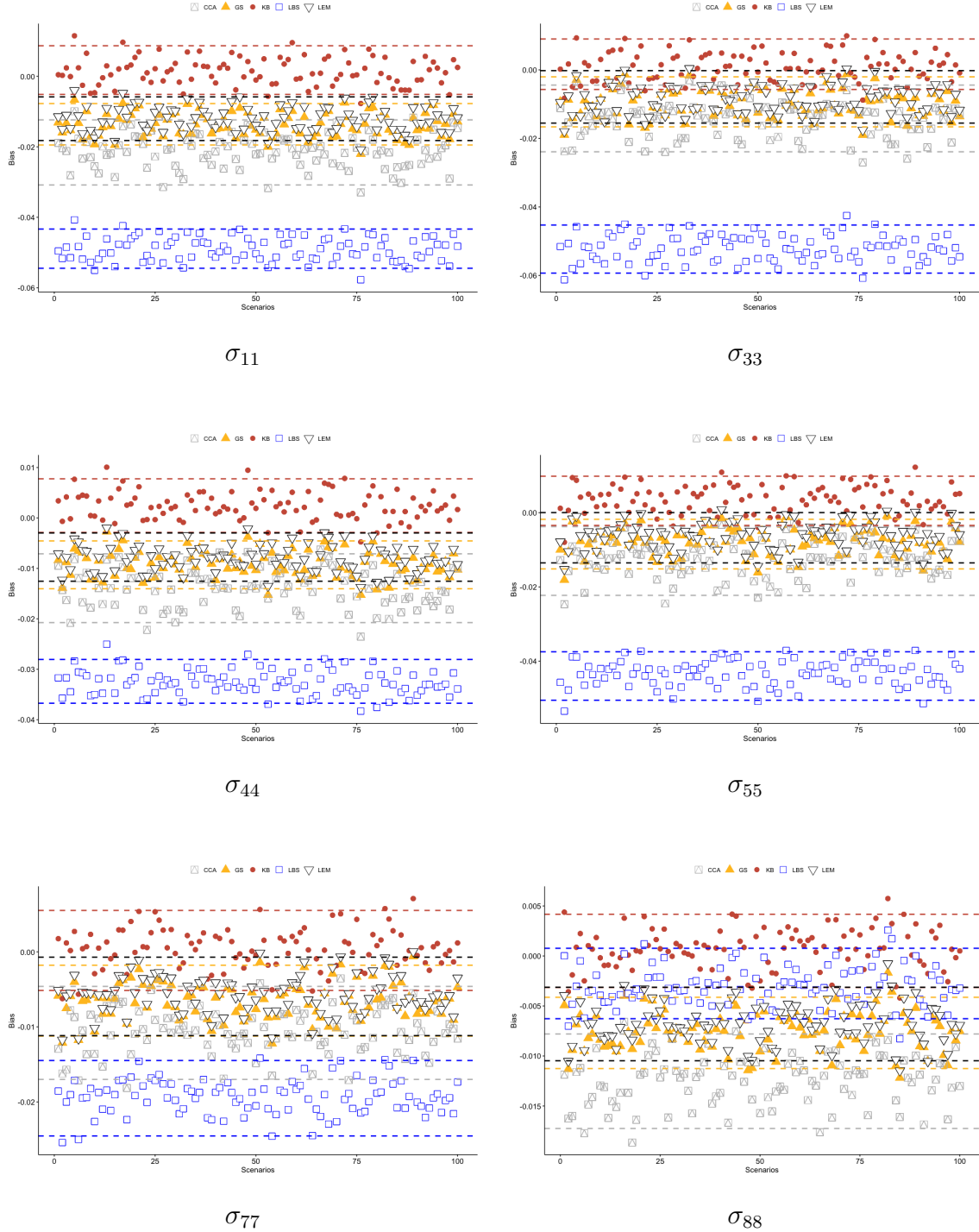


Figure B.4: Element-wise bias for selected estimators of variances (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% missing with MCAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

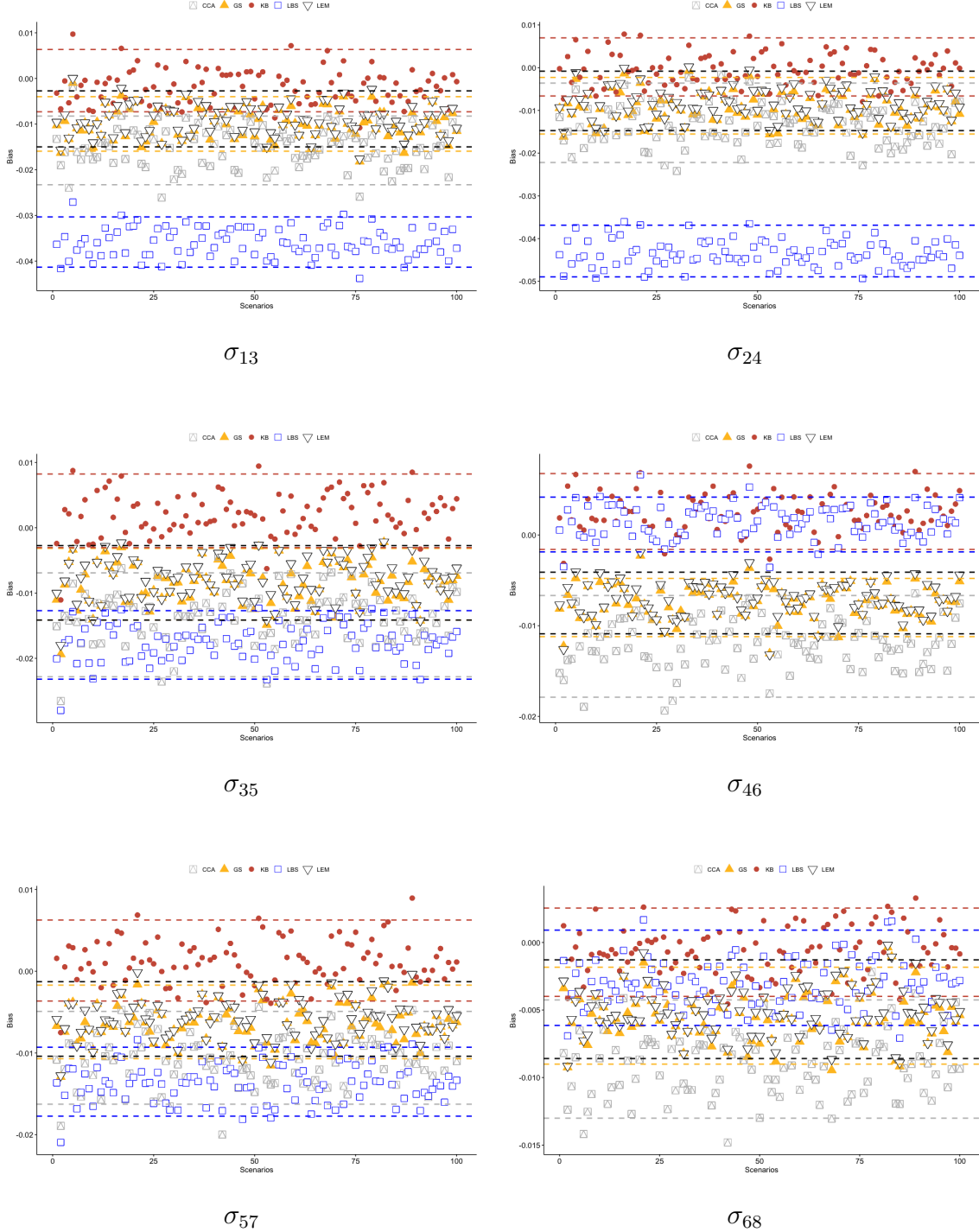


Figure B.5: Element-wise bias for selected estimators of covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 10% MCAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

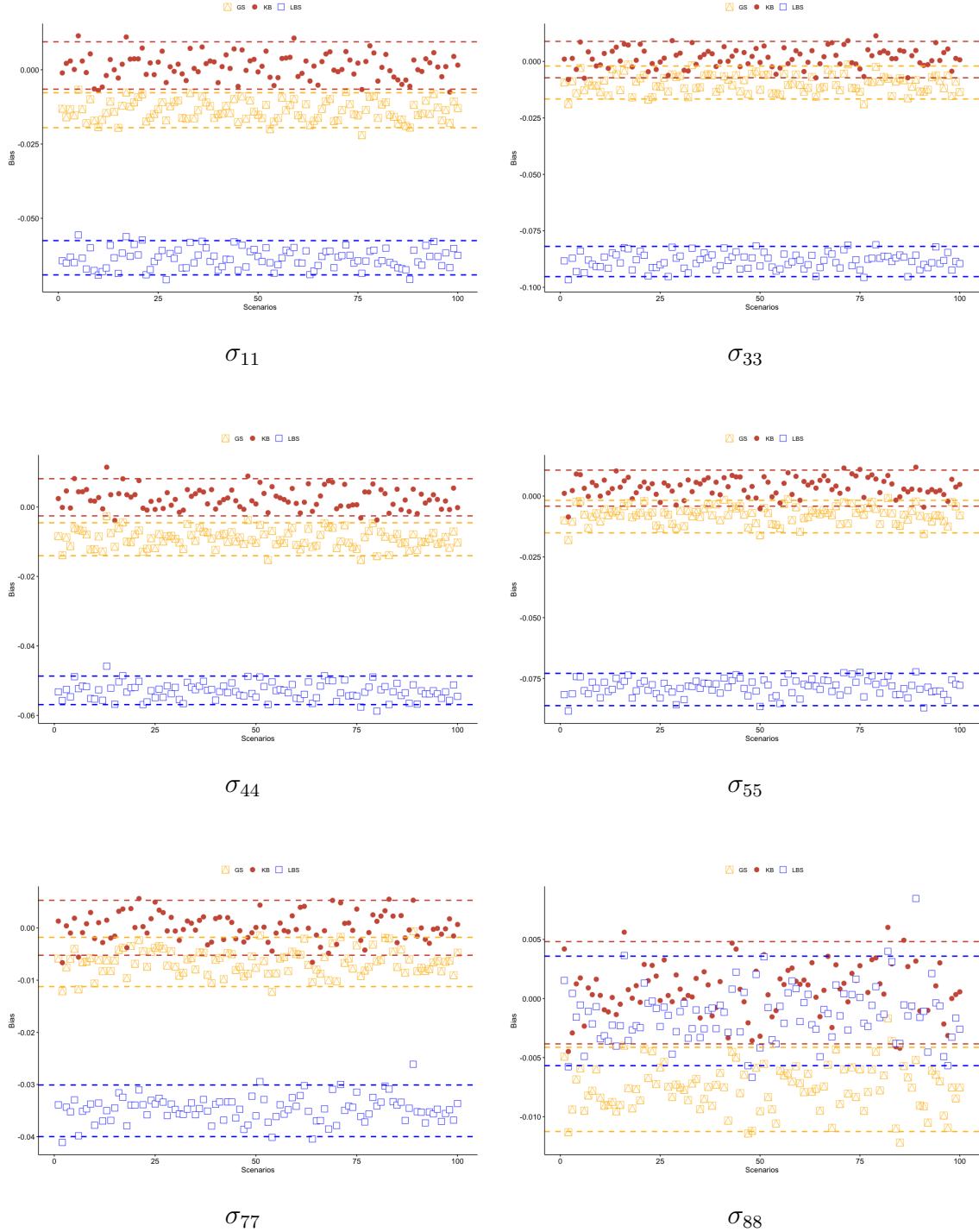


Figure B.6: Element-wise bias for selected estimators of variances (diagonal elements of Σ , where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% missing with MCAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and to calculate empirical bias.

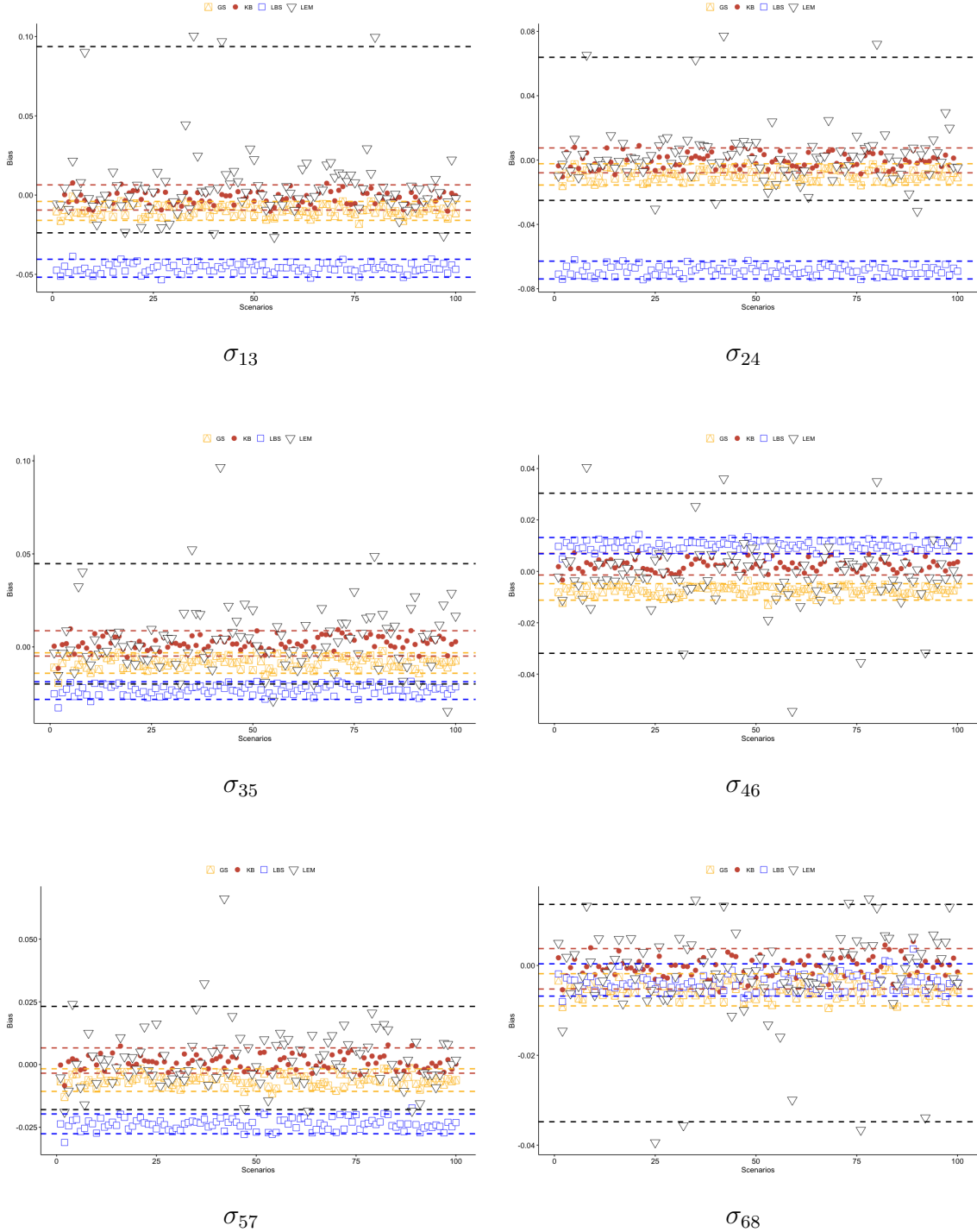


Figure B.7: Element-wise bias for selected estimators of covariances (the off-diagonal elements of Σ), where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$ and 20% MCAR mechanism. The MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

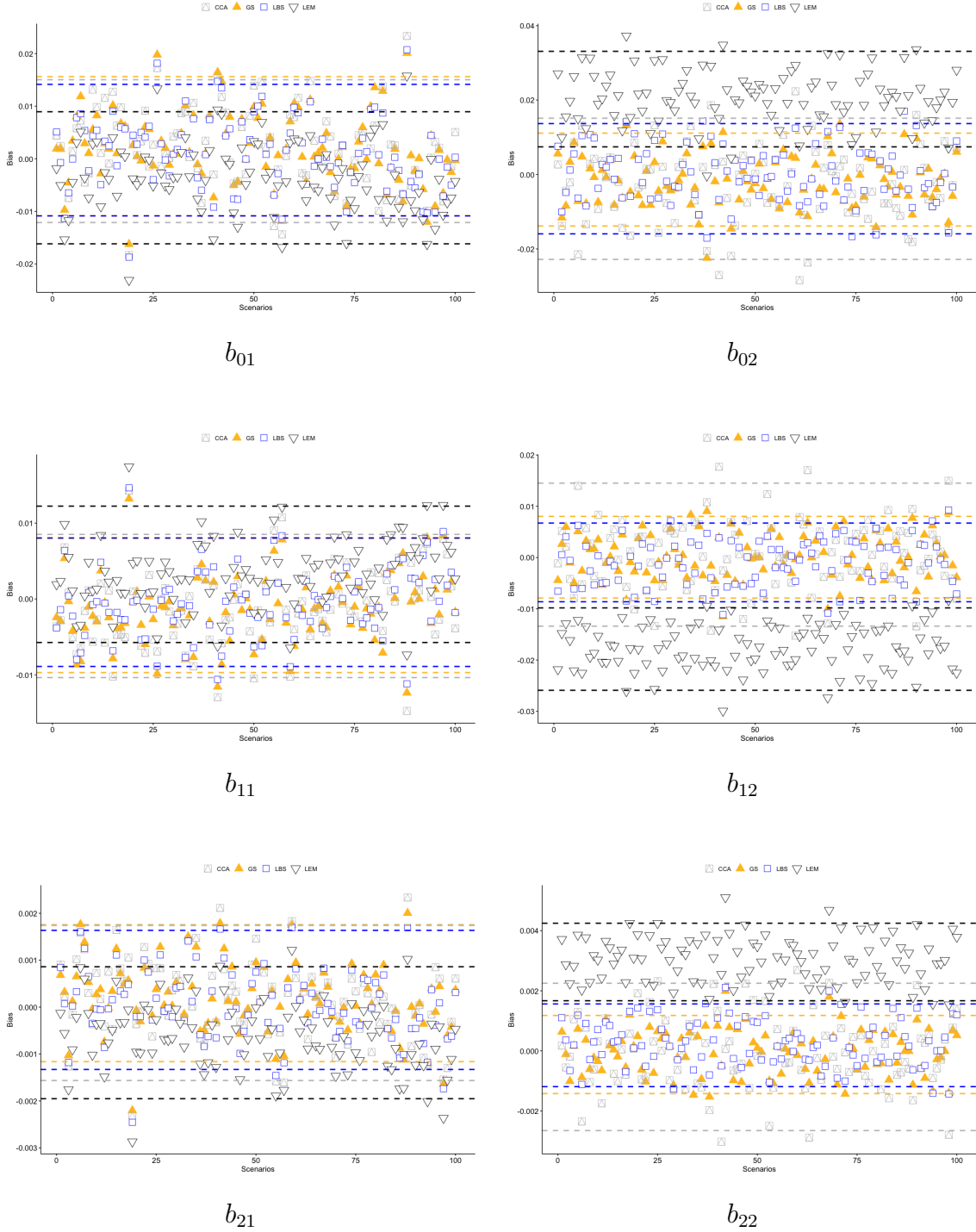


Figure B.8: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$, 5% missing with MAR mechanism and the MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

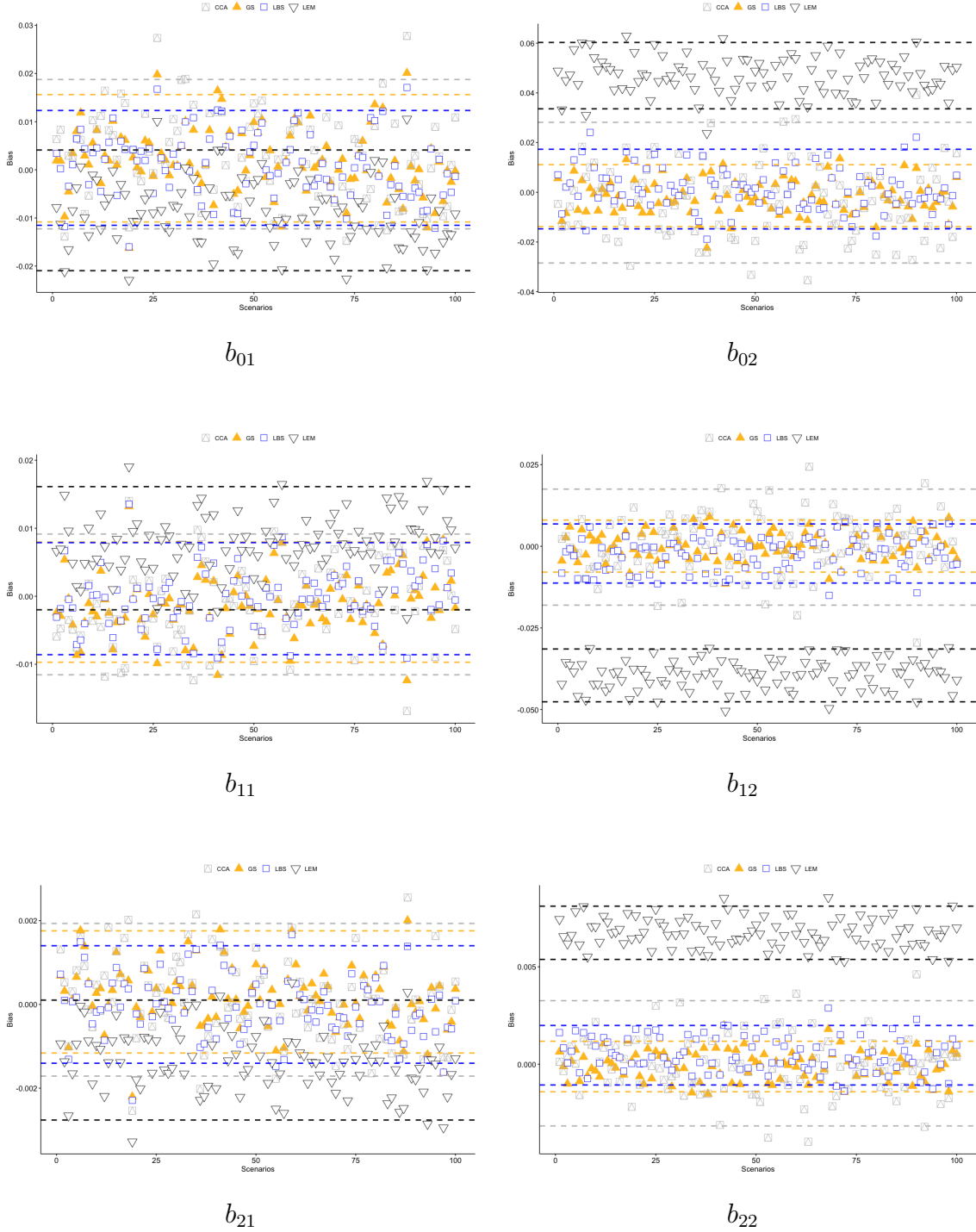


Figure B.9: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$, 10% missing with MAR mechanism and the MLEs from the glucose data are used as true values for $\mathbf{B}$ and Σ . Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

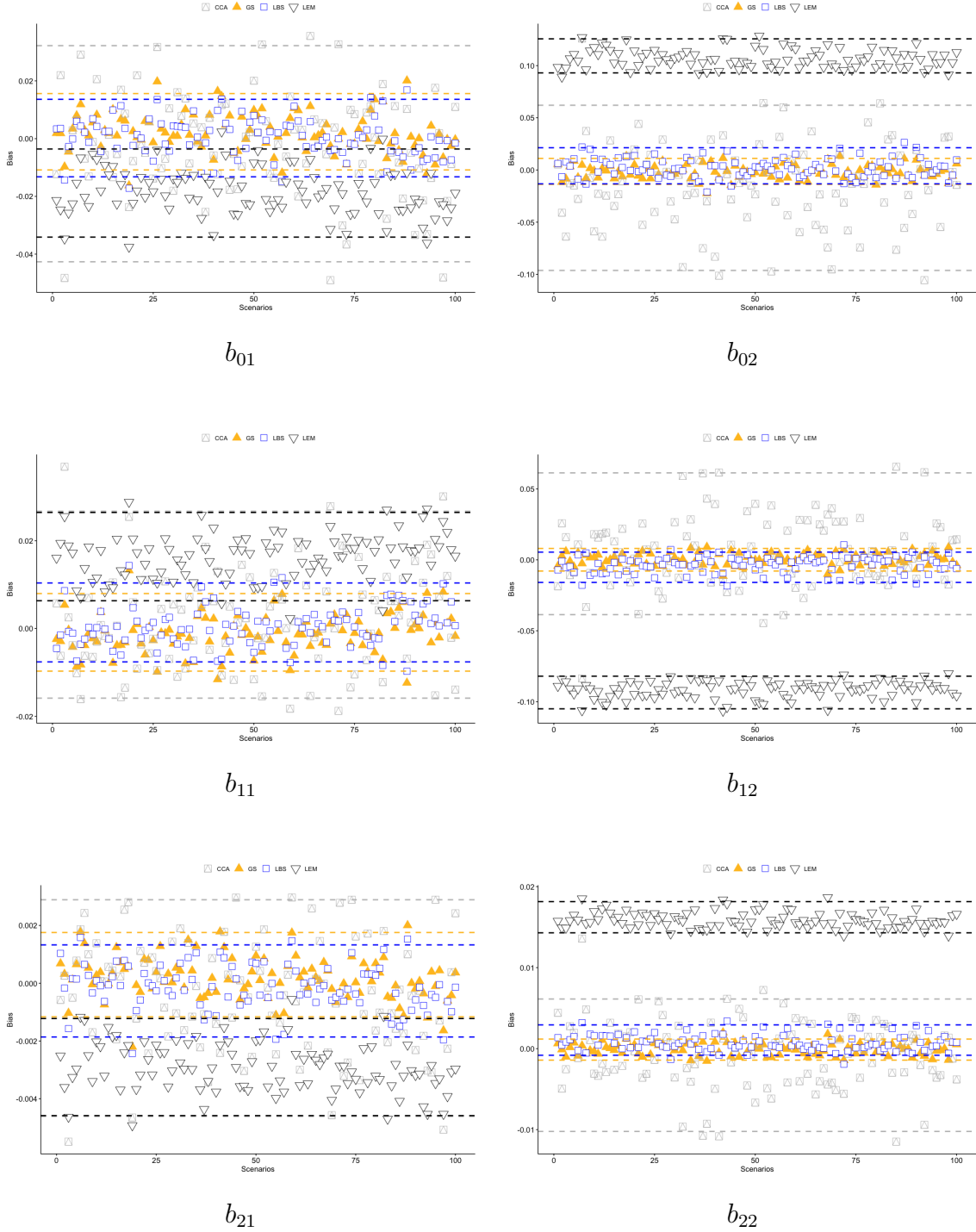


Figure B.10: Element-wise bias corresponding to $\hat{\mathbf{B}}$, where 100 samples of the same scenarios are generated with $n = 50$, $p = 8$, $q = 3$, 20% missing with MAR mechanism and the MLEs from the glucose data are used as true values for $\mathbf{B}$ and $\mathbf{\Sigma}$. Each sample was generated 1000 times to account for random variation and the calculate empirical bias plotted in the graphs.

Appendix C

Tables for Chapter 5

Table C.1: Estimates and 95% confidence intervals for covariance parameters (off-diagonal elements of Σ). The dental data with 5%, 10% and 20% MAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
σ_{12}	3.29 (0.34, 4.36)	2.90 (0.62, 4.89)	3.82 (0.62, 6.78)	2.47 (0.46, 4.54)	2.50 (0.52, 4.20)
σ_{13}	4.88 (0.95, 6.07)	4.17 (1.06, 7.01)	5.26 (1.34, 8.79)	3.50 (0.86, 6.38)	3.55 (0.93, 5.93)
σ_{14}	4.04 (-0.06, 4.85)	2.96 (0.18, 5.49)	4.04 (0.11, 7.70)	2.51 (-0.11, 5.54)	2.51 (-0.01, 4.78)
σ_{23}	3.86 (0.04, 5.26)	3.96 (1.53, 6.00)	5.36 (1.91, 8.35)	3.40 (1.49, 5.60)	4.06 (1.07, 6.79)
σ_{24}	4.53 (1.15, 4.58)	3.21 (1.11, 4.85)	5.12 (1.77, 8.05)	2.69 (0.90, 4.83)	2.66 (0.70, 4.27)
σ_{34}	6.20 (1.11, 6.13)	4.68 (1.76, 6.99)	6.77 (2.41, 10.55)	3.82 (1.25, 6.94)	3.84 (1.18, 6.04)
10%					
σ_{12}	3.29 (0.34, 4.36)	3.23 (0.86, 5.14)	4.94 (1.16, 8.32)	2.41 (0.59, 4.47)	2.59 (0.63, 4.41)
σ_{13}	4.88 (0.95, 6.07)	4.04 (0.87, 6.80)	6.67 (1.89, 10.89)	3.20 (0.76, 6.09)	3.40 (0.92, 5.75)
σ_{14}	4.04 (-0.06, 4.85)	3.58 (0.32, 6.50)	5.44 (1.17, 9.27)	3.01 (0.57, 5.95)	3.07 (0.65, 5.12)
σ_{23}	3.86 (0.04, 5.26)	4.51 (1.60, 6.86)	5.80 (2.02, 9.08)	3.34 (1.42, 5.58)	4.31 (1.87, 6.51)
σ_{24}	4.53 (1.15, 4.58)	3.77 (0.99, 6.13)	5.35 (1.84, 8.43)	2.67 (0.83, 4.91)	2.70 (0.76, 4.34)
σ_{34}	6.20 (1.11, 6.13)	5.11 (1.67, 7.99)	7.39 (2.67, 11.50)	3.73 (1.09, 7.00)	3.75 (1.08, 6.08)
20%					
σ_{12}	3.29 (0.34, 4.36)	1.54 (-4.27, 7.53)	4.64 (0.86, 7.86)	2.52 (0.77, 4.45)	3.13 (-18.48, 26.04)
σ_{13}	4.88 (0.95, 6.07)	1.57 (-4.52, 7.28)	7.44 (2.13, 12.04)	3.30 (0.82, 6.25)	4.07 (-17.61, 26.94)
σ_{14}	4.04 (-0.06, 4.85)	0.93 (-6.67, 8.15)	4.74 (1.10, 7.96)	2.69 (0.60, 5.28)	3.08 (-20.87, 27.79)
σ_{23}	3.86 (0.04, 5.26)	2.23 (-5.03, 9.63)	4.73 (1.67, 7.23)	3.03 (1.18, 5.22)	4.43 (-20.61, 30.40)
σ_{24}	4.53 (1.15, 4.58)	1.10 (-6.06, 8.88)	3.34 (1.20, 5.06)	2.13 (0.63, 4.01)	2.49 (-24.36, 30.35)
σ_{34}	6.20 (1.11, 6.13)	2.20 (-6.08, 11.34)	6.67 (2.22, 10.48)	3.17 (0.94, 6.19)	3.78 (-23.36, 32.01)

Table C.2: Estimates and 95% confidence intervals for covariances (off-diagonal elements of Σ). The dental data with 5%, 10% and 20% MNAR was used in the analysis.

	GS	CCA	KB	LBS	LEM
5%					
σ_{12}	3.29 (0.34, 4.36)	2.55 (0.17, 4.59)	3.54 (0.59, 6.30)	2.69 (0.54, 4.78)	2.71 (0.57, 4.59)
σ_{13}	4.88 (0.95, 6.07)	4.19 (0.98, 7.00)	5.46 (1.36, 9.09)	3.69 (0.94, 6.52)	3.75 (1.07, 6.21)
σ_{14}	4.04 (-0.06, 4.85)	3.16 (0.11, 5.87)	4.29 (0.08, 8.21)	2.90 (0.19, 5.81)	3.00 (0.32, 5.21)
σ_{23}	3.86 (0.04, 5.26)	2.90 (-0.22, 5.71)	4.30 (0.64, 7.67)	2.68 (0.13, 5.38)	2.72 (-0.01, 5.26)
σ_{24}	4.53 (1.15, 4.58)	3.47 (1.25, 5.17)	4.55 (1.41, 7.29)	3.29 (1.28, 5.35)	3.40 (1.28, 4.88)
σ_{34}	6.20 (1.11, 6.13)	4.44 (1.24, 7.14)	7.22 (2.42, 11.30)	3.91 (1.29, 7.05)	3.97 (1.23, 6.21)
10%					
σ_{12}	3.29 (0.34, 4.36)	1.93 (-1.18, 4.94)	4.02 (0.49, 7.29)	2.47 (0.41, 4.58)	2.55 (0.29, 4.68)
σ_{13}	4.88 (0.95, 6.07)	3.96 (0.38, 7.22)	5.91 (1.21, 10.05)	3.34 (0.81, 6.14)	3.61 (0.78, 6.39)
σ_{14}	4.04 (-0.06, 4.85)	2.68 (-0.61, 5.79)	4.78 (0.04, 9.21)	2.68 (0.18, 5.55)	2.94 (0.25, 5.29)
σ_{23}	3.86 (0.04, 5.26)	2.38 (-1.64, 6.36)	4.90 (0.77, 8.63)	2.68 (0.17, 5.42)	2.83 (0.09, 5.42)
σ_{24}	4.53 (1.15, 4.58)	3.43 (0.49, 6.04)	5.20 (1.75, 8.20)	3.43 (1.48, 5.46)	3.73 (1.62, 5.13)
σ_{34}	6.20 (1.11, 6.13)	3.69 (0.17, 6.97)	7.93 (2.79, 12.31)	3.86 (1.27, 7.09)	3.95 (1.21, 6.28)
20%					
σ_{12}	3.29 (0.34, 4.36)	0.94 (-259.44, 283.42)	3.57 (-0.32, 7.20)	1.96 (0.01, 4.03)	2.14 (-1.40, 5.66)
σ_{13}	4.88 (0.95, 6.07)	3.77 (-93.71, 93.99)	6.91 (1.29, 11.84)	2.95 (0.55, 5.77)	3.44 (-0.88, 7.63)
σ_{14}	4.04 (-0.06, 4.85)	2.25 (-453.92, 420.61)	3.63 (-1.14, 8.07)	2.04 (-0.32, 4.96)	2.97 (-2.00, 7.76)
σ_{23}	3.86 (0.04, 5.26)	1.08 (-37.15, 36.22)	4.71 (-0.92, 9.89)	1.89 (-0.39, 4.38)	2.30 (-1.13, 5.67)
σ_{24}	4.53 (1.15, 4.58)	3.24 (-183.72, 174.23)	4.08 (0.99, 6.72)	2.74 (1.01, 4.48)	3.81 (0.45, 6.68)
σ_{34}	6.20 (1.11, 6.13)	3.51 (-69.61, 81.53)	7.17 (1.34, 12.14)	2.80 (0.74, 5.82)	3.97 (-1.39, 9.23)

Table C.3: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 5% MCAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.55 (0.30, 0.80)	0.58 (0.37, 0.76)	0.58 (0.36, 0.76)	0.57 (0.37, 0.76)
σ_{12}	0.62 (0.37, 0.87)	0.65 (0.32, 0.97)	0.61 (0.37, 0.83)	0.62 (0.37, 0.84)	0.66 (0.39, 0.91)
σ_{13}	0.44 (0.23, 0.66)	0.44 (0.16, 0.71)	0.46 (0.23, 0.67)	0.45 (0.22, 0.65)	0.46 (0.24, 0.66)
σ_{14}	0.34 (0.20, 0.50)	0.33 (0.15, 0.51)	0.38 (0.22, 0.52)	0.37 (0.21, 0.50)	0.36 (0.20, 0.49)
σ_{15}	0.31 (0.14, 0.48)	0.31 (0.09, 0.52)	0.31 (0.14, 0.46)	0.31 (0.13, 0.47)	0.32 (0.14, 0.48)
σ_{16}	0.22 (0.08, 0.33)	0.19 (0.02, 0.36)	0.21 (0.08, 0.32)	0.20 (0.07, 0.32)	0.20 (0.08, 0.32)
σ_{17}	0.20 (0.06, 0.31)	0.15 (-0.01, 0.31)	0.20 (0.07, 0.31)	0.20 (0.06, 0.32)	0.20 (0.06, 0.32)
σ_{18}	0.22 (0.09, 0.32)	0.18 (0.03, 0.32)	0.21 (0.10, 0.30)	0.22 (0.10, 0.33)	0.21 (0.09, 0.32)
σ_{22}	0.87 (0.55, 1.19)	0.93 (0.50, 1.35)	0.88 (0.54, 1.17)	0.85 (0.52, 1.15)	0.93 (0.58, 1.28)
σ_{23}	0.62 (0.35, 0.89)	0.62 (0.26, 0.97)	0.62 (0.32, 0.88)	0.59 (0.32, 0.84)	0.64 (0.36, 0.91)
σ_{24}	0.46 (0.28, 0.64)	0.44 (0.21, 0.66)	0.50 (0.30, 0.66)	0.46 (0.28, 0.63)	0.49 (0.30, 0.66)
σ_{25}	0.37 (0.14, 0.59)	0.40 (0.11, 0.67)	0.38 (0.15, 0.60)	0.37 (0.13, 0.58)	0.38 (0.14, 0.59)
σ_{26}	0.24 (0.07, 0.37)	0.19 (-0.00, 0.38)	0.23 (0.06, 0.37)	0.21 (0.06, 0.36)	0.23 (0.07, 0.37)
σ_{27}	0.30 (0.11, 0.44)	0.23 (0.01, 0.44)	0.27 (0.10, 0.42)	0.27 (0.09, 0.43)	0.29 (0.10, 0.46)
σ_{28}	0.21 (0.05, 0.36)	0.18 (-0.02, 0.37)	0.20 (0.04, 0.33)	0.23 (0.06, 0.39)	0.23 (0.07, 0.38)
σ_{33}	0.59 (0.35, 0.80)	0.60 (0.29, 0.88)	0.60 (0.36, 0.81)	0.56 (0.32, 0.78)	0.59 (0.36, 0.80)
σ_{34}	0.42 (0.25, 0.56)	0.39 (0.18, 0.58)	0.45 (0.28, 0.60)	0.41 (0.24, 0.56)	0.42 (0.26, 0.56)
σ_{35}	0.29 (0.09, 0.47)	0.30 (0.07, 0.50)	0.31 (0.11, 0.48)	0.29 (0.10, 0.47)	0.29 (0.10, 0.46)
σ_{36}	0.15 (0.02, 0.25)	0.09 (-0.06, 0.23)	0.13 (-0.00, 0.25)	0.13 (0.01, 0.24)	0.13 (0.01, 0.24)
σ_{37}	0.21 (0.05, 0.33)	0.15 (-0.03, 0.31)	0.19 (0.06, 0.31)	0.20 (0.05, 0.33)	0.20 (0.05, 0.34)

Table C.4: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 5% MCAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.13 (-0.02, 0.27)	0.14 (0.02, 0.25)	0.18 (0.04, 0.30)	0.17 (0.04, 0.29)
σ_{44}	0.41 (0.28, 0.53)	0.37 (0.20, 0.53)	0.43 (0.30, 0.55)	0.41 (0.27, 0.53)	0.41 (0.28, 0.53)
σ_{45}	0.26 (0.08, 0.41)	0.26 (0.06, 0.44)	0.27 (0.10, 0.42)	0.26 (0.09, 0.41)	0.25 (0.08, 0.40)
σ_{46}	0.15 (0.02, 0.24)	0.10 (-0.05, 0.24)	0.14 (0.01, 0.25)	0.14 (0.02, 0.24)	0.13 (0.01, 0.24)
σ_{47}	0.15 (-0.01, 0.25)	0.09 (-0.08, 0.24)	0.16 (0.03, 0.27)	0.15 (0.01, 0.27)	0.14 (-0.00, 0.27)
σ_{48}	0.11 (-0.00, 0.22)	0.10 (-0.05, 0.24)	0.12 (0.00, 0.22)	0.14 (0.02, 0.25)	0.12 (0.00, 0.23)
σ_{55}	0.52 (0.28, 0.71)	0.48 (0.21, 0.74)	0.52 (0.31, 0.71)	0.51 (0.29, 0.72)	0.50 (0.28, 0.71)
σ_{56}	0.31 (0.16, 0.43)	0.28 (0.12, 0.44)	0.31 (0.17, 0.43)	0.30 (0.16, 0.42)	0.30 (0.16, 0.42)
σ_{57}	0.29 (0.10, 0.43)	0.27 (0.06, 0.47)	0.27 (0.12, 0.42)	0.28 (0.10, 0.44)	0.28 (0.10, 0.44)
σ_{58}	0.27 (0.12, 0.40)	0.26 (0.08, 0.44)	0.25 (0.11, 0.37)	0.27 (0.11, 0.41)	0.26 (0.11, 0.40)
σ_{66}	0.32 (0.17, 0.43)	0.35 (0.17, 0.53)	0.31 (0.18, 0.43)	0.31 (0.17, 0.43)	0.31 (0.17, 0.44)
σ_{67}	0.27 (0.15, 0.37)	0.29 (0.13, 0.43)	0.26 (0.14, 0.36)	0.27 (0.15, 0.38)	0.27 (0.15, 0.38)
σ_{68}	0.24 (0.13, 0.33)	0.26 (0.12, 0.39)	0.23 (0.12, 0.33)	0.24 (0.13, 0.34)	0.23 (0.13, 0.33)
σ_{77}	0.35 (0.19, 0.49)	0.36 (0.15, 0.55)	0.35 (0.19, 0.49)	0.36 (0.19, 0.50)	0.35 (0.18, 0.51)
σ_{78}	0.26 (0.13, 0.36)	0.27 (0.11, 0.41)	0.26 (0.14, 0.37)	0.27 (0.14, 0.38)	0.26 (0.13, 0.38)
σ_{88}	0.29 (0.19, 0.37)	0.30 (0.17, 0.41)	0.28 (0.18, 0.37)	0.29 (0.18, 0.40)	0.28 (0.18, 0.38)

Table C.5: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 10% MCAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.55 (0.25, 0.87)	0.61 (0.39, 0.80)	0.56 (0.35, 0.74)	0.58 (-4.17, 5.49)
σ_{12}	0.62 (0.37, 0.87)	0.68 (0.32, 1.05)	0.67 (0.39, 0.90)	0.58 (0.34, 0.80)	0.66 (0.36, 0.93)
σ_{13}	0.44 (0.23, 0.66)	0.46 (0.18, 0.73)	0.50 (0.25, 0.71)	0.44 (0.23, 0.64)	0.46 (0.21, 0.69)
σ_{14}	0.34 (0.20, 0.50)	0.35 (0.15, 0.56)	0.29 (0.16, 0.41)	0.33 (0.20, 0.45)	0.37 (0.16, 0.56)
σ_{15}	0.31 (0.14, 0.48)	0.39 (0.07, 0.70)	0.32 (0.14, 0.49)	0.32 (0.14, 0.47)	0.33 (0.11, 0.53)
σ_{16}	0.22 (0.08, 0.33)	0.15 (-0.04, 0.35)	0.16 (0.05, 0.27)	0.17 (0.06, 0.27)	0.18 (0.06, 0.29)
σ_{17}	0.20 (0.06, 0.31)	0.15 (-0.07, 0.37)	0.21 (0.07, 0.33)	0.20 (0.07, 0.32)	0.20 (0.06, 0.33)
σ_{18}	0.22 (0.09, 0.32)	0.14 (-0.06, 0.34)	0.22 (0.10, 0.33)	0.22 (0.09, 0.33)	0.22 (0.08, 0.33)
σ_{22}	0.87 (0.55, 1.19)	1.00 (0.54, 1.48)	0.92 (0.56, 1.23)	0.80 (0.48, 1.10)	0.93 (0.16, 1.71)
σ_{23}	0.62 (0.35, 0.89)	0.65 (0.31, 1.01)	0.68 (0.35, 0.96)	0.57 (0.31, 0.82)	0.65 (0.37, 0.92)
σ_{24}	0.46 (0.28, 0.64)	0.46 (0.21, 0.73)	0.45 (0.28, 0.59)	0.43 (0.26, 0.57)	0.50 (0.28, 0.70)
σ_{25}	0.37 (0.14, 0.59)	0.46 (0.04, 0.88)	0.39 (0.11, 0.64)	0.36 (0.13, 0.57)	0.38 (0.13, 0.61)
σ_{26}	0.24 (0.07, 0.37)	0.18 (-0.09, 0.46)	0.18 (0.00, 0.34)	0.17 (0.03, 0.31)	0.19 (0.04, 0.33)
σ_{27}	0.30 (0.11, 0.44)	0.26 (-0.06, 0.59)	0.30 (0.10, 0.47)	0.26 (0.09, 0.42)	0.28 (0.09, 0.47)
σ_{28}	0.21 (0.05, 0.36)	0.17 (-0.12, 0.46)	0.19 (0.02, 0.34)	0.21 (0.05, 0.37)	0.22 (0.05, 0.39)
σ_{33}	0.59 (0.35, 0.80)	0.54 (0.27, 0.82)	0.60 (0.36, 0.80)	0.55 (0.33, 0.76)	0.59 (0.20, 0.98)
σ_{34}	0.42 (0.25, 0.56)	0.34 (0.13, 0.56)	0.35 (0.22, 0.46)	0.37 (0.23, 0.51)	0.43 (0.24, 0.60)
σ_{35}	0.29 (0.09, 0.47)	0.31 (-0.00, 0.62)	0.28 (0.07, 0.46)	0.29 (0.10, 0.45)	0.30 (0.07, 0.50)
σ_{36}	0.15 (0.02, 0.25)	0.07 (-0.11, 0.26)	0.09 (-0.03, 0.21)	0.11 (0.00, 0.22)	0.12 (-0.01, 0.24)
σ_{37}	0.21 (0.05, 0.33)	0.17 (-0.07, 0.41)	0.20 (0.06, 0.32)	0.20 (0.06, 0.33)	0.21 (0.04, 0.36)

Table C.6: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 10% MCAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.14 (-0.07, 0.35)	0.14 (0.02, 0.25)	0.17 (0.04, 0.30)	0.18 (0.04, 0.30)
σ_{44}	0.41 (0.28, 0.53)	0.31 (0.14, 0.49)	0.37 (0.26, 0.48)	0.37 (0.25, 0.48)	0.43 (0.27, 0.59)
σ_{45}	0.26 (0.08, 0.41)	0.26 (-0.02, 0.54)	0.19 (0.03, 0.33)	0.23 (0.08, 0.37)	0.26 (0.05, 0.44)
σ_{46}	0.15 (0.02, 0.24)	0.07 (-0.09, 0.23)	0.06 (-0.04, 0.15)	0.10 (0.01, 0.19)	0.11 (-0.00, 0.21)
σ_{47}	0.15 (-0.01, 0.25)	0.10 (-0.13, 0.32)	0.15 (0.02, 0.28)	0.14 (0.01, 0.26)	0.14 (-0.01, 0.28)
σ_{48}	0.11 (-0.00, 0.22)	0.10 (-0.10, 0.29)	0.11 (-0.01, 0.22)	0.13 (0.01, 0.24)	0.12 (-0.00, 0.24)
σ_{55}	0.52 (0.28, 0.71)	0.63 (0.23, 1.03)	0.53 (0.31, 0.74)	0.49 (0.28, 0.70)	0.53 (0.23, 0.84)
σ_{56}	0.31 (0.16, 0.43)	0.36 (0.14, 0.57)	0.31 (0.17, 0.44)	0.27 (0.15, 0.40)	0.29 (0.14, 0.43)
σ_{57}	0.29 (0.10, 0.43)	0.37 (0.05, 0.68)	0.29 (0.11, 0.45)	0.28 (0.11, 0.44)	0.29 (0.10, 0.47)
σ_{58}	0.27 (0.12, 0.40)	0.37 (0.11, 0.63)	0.25 (0.10, 0.38)	0.27 (0.12, 0.41)	0.27 (0.11, 0.42)
σ_{66}	0.32 (0.17, 0.43)	0.32 (0.17, 0.47)	0.25 (0.16, 0.34)	0.25 (0.16, 0.33)	0.26 (0.15, 0.37)
σ_{67}	0.27 (0.15, 0.37)	0.29 (0.11, 0.46)	0.23 (0.13, 0.32)	0.25 (0.14, 0.34)	0.26 (0.14, 0.36)
σ_{68}	0.24 (0.13, 0.33)	0.25 (0.09, 0.41)	0.20 (0.11, 0.29)	0.22 (0.13, 0.31)	0.22 (0.12, 0.31)
σ_{77}	0.35 (0.19, 0.49)	0.39 (0.11, 0.67)	0.36 (0.20, 0.50)	0.35 (0.19, 0.50)	0.37 (0.19, 0.54)
σ_{78}	0.26 (0.13, 0.36)	0.29 (0.07, 0.50)	0.27 (0.15, 0.39)	0.27 (0.14, 0.38)	0.28 (0.14, 0.39)
σ_{88}	0.29 (0.19, 0.37)	0.30 (0.12, 0.49)	0.29 (0.19, 0.37)	0.30 (0.19, 0.40)	0.29 (0.17, 0.40)

Table C.7: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 20% MCAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.75 (-23.41, 38.85)	0.59 (0.37, 0.78)	0.53 (0.31, 0.68)	0.59 (0.01, 1.26)
σ_{12}	0.62 (0.37, 0.87)	0.31 (-9.13, 17.01)	0.66 (0.33, 0.94)	0.57 (0.27, 0.74)	0.65 (0.13, 1.23)
σ_{13}	0.44 (0.23, 0.66)	0.14 (-18.34, 22.06)	0.61 (0.29, 0.88)	0.46 (0.21, 0.61)	0.47 (0.02, 0.96)
σ_{14}	0.34 (0.20, 0.50)	0.16 (-29.59, 32.10)	0.31 (0.16, 0.45)	0.35 (0.17, 0.44)	0.37 (-0.01, 0.80)
σ_{15}	0.31 (0.14, 0.48)	-0.05 (-34.04, 36.20)	0.28 (0.11, 0.44)	0.29 (0.10, 0.41)	0.32 (-0.00, 0.68)
σ_{16}	0.22 (0.08, 0.33)	-0.19 (-34.41, 38.27)	0.18 (0.05, 0.29)	0.17 (0.05, 0.24)	0.21 (-0.04, 0.49)
σ_{17}	0.20 (0.06, 0.31)	-0.28 (-37.20, 44.23)	0.14 (0.01, 0.25)	0.18 (0.04, 0.27)	0.20 (-0.05, 0.45)
σ_{18}	0.22 (0.09, 0.32)	0.14 (-49.31, 63.66)	0.21 (0.07, 0.33)	0.18 (0.06, 0.29)	0.23 (-0.03, 0.51)
σ_{22}	0.87 (0.55, 1.19)	0.50 (-8.90, 15.47)	0.91 (0.52, 1.25)	0.76 (0.41, 1.04)	0.89 (0.38, 1.51)
σ_{23}	0.62 (0.35, 0.89)	0.31 (-11.36, 17.23)	0.73 (0.32, 1.07)	0.57 (0.27, 0.79)	0.67 (0.21, 1.17)
σ_{24}	0.46 (0.28, 0.64)	0.34 (-15.52, 22.36)	0.48 (0.28, 0.63)	0.44 (0.23, 0.59)	0.54 (0.15, 0.97)
σ_{25}	0.37 (0.14, 0.59)	0.02 (-20.05, 27.35)	0.37 (0.09, 0.61)	0.36 (0.13, 0.54)	0.37 (0.01, 0.76)
σ_{26}	0.24 (0.07, 0.37)	-0.05 (-25.16, 34.01)	0.18 (-0.01, 0.34)	0.19 (0.07, 0.30)	0.18 (-0.08, 0.48)
σ_{27}	0.30 (0.11, 0.44)	-0.08 (-31.25, 42.05)	0.23 (0.05, 0.38)	0.21 (0.06, 0.33)	0.24 (-0.01, 0.50)
σ_{28}	0.21 (0.05, 0.36)	-0.13 (-39.45, 53.76)	0.17 (-0.00, 0.31)	0.19 (0.03, 0.31)	0.20 (-0.06, 0.49)
σ_{33}	0.59 (0.35, 0.80)	0.42 (-12.79, 21.24)	0.65 (0.37, 0.88)	0.54 (0.30, 0.74)	0.61 (0.19, 1.08)
σ_{34}	0.42 (0.25, 0.56)	0.28 (-17.80, 28.77)	0.36 (0.20, 0.49)	0.38 (0.20, 0.52)	0.47 (0.10, 0.88)
σ_{35}	0.29 (0.09, 0.47)	0.10 (-22.11, 35.05)	0.34 (0.11, 0.54)	0.32 (0.13, 0.48)	0.31 (-0.03, 0.67)
σ_{36}	0.15 (0.02, 0.25)	-0.03 (-27.30, 42.10)	0.13 (-0.02, 0.27)	0.14 (0.04, 0.24)	0.12 (-0.12, 0.39)
σ_{37}	0.21 (0.05, 0.33)	-0.06 (-34.69, 51.35)	0.15 (0.01, 0.28)	0.17 (0.04, 0.28)	0.19 (-0.04, 0.42)

Table C.8: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 20% MCAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	-0.06 (-47.34, 66.64)	0.14 (0.01, 0.26)	0.17 (0.03, 0.28)	0.17 (-0.04, 0.41)
σ_{44}	0.41 (0.28, 0.53)	0.31 (-25.03, 40.56)	0.38 (0.25, 0.49)	0.37 (0.23, 0.48)	0.45 (0.13, 0.83)
σ_{45}	0.26 (0.08, 0.41)	0.03 (-30.28, 49.06)	0.19 (0.01, 0.35)	0.26 (0.09, 0.40)	0.28 (-0.04, 0.62)
σ_{46}	0.15 (0.02, 0.24)	-0.04 (-35.92, 58.01)	0.04 (-0.06, 0.15)	0.13 (0.04, 0.22)	0.11 (-0.12, 0.36)
σ_{47}	0.15 (-0.01, 0.25)	-0.09 (-45.41, 70.54)	0.12 (-0.02, 0.24)	0.13 (0.01, 0.23)	0.13 (-0.09, 0.36)
σ_{48}	0.11 (-0.00, 0.22)	-0.09 (-63.87, 92.63)	0.12 (-0.03, 0.25)	0.12 (0.00, 0.22)	0.13 (-0.07, 0.34)
σ_{55}	0.52 (0.28, 0.71)	0.06 (-36.94, 61.21)	0.54 (0.30, 0.76)	0.49 (0.27, 0.69)	0.54 (0.22, 0.92)
σ_{56}	0.31 (0.16, 0.43)	0.05 (-45.28, 74.78)	0.36 (0.18, 0.50)	0.27 (0.14, 0.39)	0.30 (0.06, 0.55)
σ_{57}	0.29 (0.10, 0.43)	0.03 (-57.97, 92.73)	0.22 (0.08, 0.34)	0.24 (0.10, 0.37)	0.26 (0.05, 0.49)
σ_{58}	0.27 (0.12, 0.40)	-0.01 (-80.05, 120.80)	0.27 (0.11, 0.41)	0.26 (0.10, 0.39)	0.27 (0.06, 0.49)
σ_{66}	0.32 (0.17, 0.43)	0.15 (-57.82, 95.35)	0.26 (0.16, 0.35)	0.23 (0.15, 0.32)	0.27 (0.07, 0.51)
σ_{67}	0.27 (0.15, 0.37)	0.13 (-74.63, 120.78)	0.19 (0.09, 0.27)	0.21 (0.11, 0.30)	0.24 (0.07, 0.41)
σ_{68}	0.24 (0.13, 0.33)	-0.04 (-99.62, 155.77)	0.20 (0.11, 0.27)	0.19 (0.09, 0.28)	0.22 (0.07, 0.39)
σ_{77}	0.35 (0.19, 0.49)	0.17 (-95.46, 154.93)	0.29 (0.19, 0.38)	0.30 (0.18, 0.42)	0.33 (0.15, 0.53)
σ_{78}	0.26 (0.13, 0.36)	-0.06 (-124.19, 199.57)	0.24 (0.14, 0.32)	0.23 (0.12, 0.34)	0.25 (0.10, 0.40)
σ_{88}	0.29 (0.19, 0.37)	0.14 (-159.16, 259.47)	0.30 (0.19, 0.39)	0.27 (0.15, 0.40)	0.28 (0.13, 0.45)

Table C.9: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 5% MAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.49 (0.30, 0.66)	0.57 (0.36, 0.70)	0.57 (0.35, 0.69)	0.53 (0.35, 0.69)
σ_{12}	0.62 (0.37, 0.87)	0.60 (0.25, 0.71)	0.62 (0.37, 0.84)	0.63 (0.33, 0.78)	0.58 (0.35, 0.81)
σ_{13}	0.44 (0.23, 0.66)	0.41 (0.15, 0.48)	0.45 (0.23, 0.52)	0.46 (0.21, 0.49)	0.36 (0.21, 0.49)
σ_{14}	0.34 (0.20, 0.50)	0.33 (0.13, 0.41)	0.36 (0.16, 0.38)	0.37 (0.17, 0.39)	0.29 (0.16, 0.40)
σ_{15}	0.31 (0.14, 0.48)	0.35 (0.09, 0.40)	0.31 (0.12, 0.38)	0.33 (0.11, 0.36)	0.24 (0.11, 0.36)
σ_{16}	0.22 (0.08, 0.33)	0.23 (0.04, 0.28)	0.23 (0.06, 0.28)	0.24 (0.05, 0.26)	0.16 (0.04, 0.26)
σ_{17}	0.20 (0.06, 0.31)	0.24 (-0.08, 0.23)	0.26 (-0.01, 0.25)	0.22 (-0.03, 0.24)	0.10 (-0.05, 0.24)
σ_{18}	0.22 (0.09, 0.32)	0.23 (-0.03, 0.20)	0.21 (-0.01, 0.19)	0.21 (-0.02, 0.18)	0.08 (-0.02, 0.18)
σ_{22}	0.87 (0.55, 1.19)	0.88 (0.42, 1.05)	0.87 (0.57, 1.18)	0.87 (0.53, 1.13)	0.88 (0.57, 1.18)
σ_{23}	0.62 (0.35, 0.89)	0.60 (0.27, 0.69)	0.64 (0.38, 0.77)	0.62 (0.34, 0.70)	0.54 (0.35, 0.71)
σ_{24}	0.46 (0.28, 0.64)	0.48 (0.18, 0.50)	0.47 (0.24, 0.54)	0.46 (0.24, 0.51)	0.39 (0.25, 0.53)
σ_{25}	0.37 (0.14, 0.59)	0.50 (0.08, 0.48)	0.38 (0.13, 0.45)	0.38 (0.12, 0.43)	0.29 (0.12, 0.45)
σ_{26}	0.24 (0.07, 0.37)	0.33 (0.07, 0.35)	0.26 (0.07, 0.33)	0.28 (0.07, 0.32)	0.20 (0.07, 0.33)
σ_{27}	0.30 (0.11, 0.44)	0.39 (0.04, 0.41)	0.37 (0.07, 0.38)	0.30 (0.06, 0.38)	0.24 (0.07, 0.41)
σ_{28}	0.21 (0.05, 0.36)	0.30 (-0.04, 0.24)	0.24 (-0.02, 0.22)	0.23 (-0.02, 0.22)	0.10 (-0.02, 0.22)
σ_{33}	0.59 (0.35, 0.80)	0.56 (0.30, 0.63)	0.59 (0.33, 0.62)	0.59 (0.31, 0.59)	0.46 (0.32, 0.59)
σ_{34}	0.42 (0.25, 0.56)	0.42 (0.17, 0.46)	0.43 (0.20, 0.44)	0.41 (0.20, 0.42)	0.32 (0.20, 0.42)
σ_{35}	0.29 (0.09, 0.47)	0.38 (0.07, 0.35)	0.29 (0.10, 0.31)	0.29 (0.10, 0.30)	0.21 (0.10, 0.31)
σ_{36}	0.15 (0.02, 0.25)	0.20 (-0.01, 0.21)	0.16 (0.01, 0.19)	0.18 (0.02, 0.19)	0.10 (0.00, 0.19)
σ_{37}	0.21 (0.05, 0.33)	0.26 (0.03, 0.30)	0.25 (0.05, 0.28)	0.20 (0.04, 0.27)	0.16 (0.04, 0.27)

Table C.10: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 5% MAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.22 (-0.00, 0.19)	0.18 (-0.00, 0.16)	0.17 (-0.00, 0.16)	0.08 (-0.00, 0.16)
σ_{44}	0.41 (0.28, 0.53)	0.44 (0.21, 0.51)	0.42 (0.23, 0.47)	0.42 (0.23, 0.46)	0.35 (0.23, 0.46)
σ_{45}	0.26 (0.08, 0.41)	0.34 (0.05, 0.33)	0.29 (0.05, 0.26)	0.29 (0.06, 0.26)	0.17 (0.05, 0.27)
σ_{46}	0.15 (0.02, 0.24)	0.17 (-0.00, 0.20)	0.17 (0.00, 0.16)	0.18 (0.01, 0.17)	0.08 (-0.00, 0.16)
σ_{47}	0.15 (-0.01, 0.25)	0.19 (-0.03, 0.21)	0.19 (-0.02, 0.17)	0.16 (-0.02, 0.17)	0.08 (-0.02, 0.18)
σ_{48}	0.11 (-0.00, 0.22)	0.16 (-0.04, 0.14)	0.13 (-0.05, 0.10)	0.14 (-0.04, 0.10)	0.03 (-0.04, 0.10)
σ_{55}	0.52 (0.28, 0.71)	0.56 (0.29, 0.69)	0.52 (0.31, 0.63)	0.51 (0.29, 0.60)	0.46 (0.30, 0.61)
σ_{56}	0.31 (0.16, 0.43)	0.30 (0.11, 0.40)	0.33 (0.15, 0.39)	0.31 (0.13, 0.36)	0.25 (0.13, 0.36)
σ_{57}	0.29 (0.10, 0.43)	0.33 (0.09, 0.41)	0.31 (0.13, 0.38)	0.29 (0.12, 0.36)	0.25 (0.12, 0.37)
σ_{58}	0.27 (0.12, 0.40)	0.29 (0.10, 0.39)	0.28 (0.11, 0.34)	0.27 (0.13, 0.35)	0.24 (0.12, 0.34)
σ_{66}	0.32 (0.17, 0.43)	0.28 (0.12, 0.37)	0.33 (0.16, 0.35)	0.32 (0.15, 0.34)	0.25 (0.15, 0.34)
σ_{67}	0.27 (0.15, 0.37)	0.28 (0.12, 0.37)	0.30 (0.15, 0.34)	0.27 (0.14, 0.33)	0.25 (0.15, 0.35)
σ_{68}	0.24 (0.13, 0.33)	0.22 (0.08, 0.28)	0.26 (0.09, 0.26)	0.24 (0.10, 0.26)	0.18 (0.10, 0.26)
σ_{77}	0.35 (0.19, 0.49)	0.38 (0.22, 0.51)	0.36 (0.23, 0.45)	0.33 (0.23, 0.46)	0.37 (0.24, 0.50)
σ_{78}	0.26 (0.13, 0.36)	0.28 (0.11, 0.34)	0.28 (0.13, 0.31)	0.25 (0.14, 0.31)	0.23 (0.14, 0.32)
σ_{88}	0.29 (0.19, 0.37)	0.31 (0.12, 0.32)	0.30 (0.13, 0.28)	0.28 (0.14, 0.30)	0.22 (0.13, 0.30)

Table C.11: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 10% MAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.60 (-0.13, 1.30)	0.59 (0.37, 0.72)	0.55 (0.35, 0.70)	0.53 (0.30, 0.76)
σ_{12}	0.62 (0.37, 0.87)	0.73 (-0.04, 1.19)	0.66 (0.38, 0.89)	0.60 (0.33, 0.78)	0.57 (0.33, 0.81)
σ_{13}	0.44 (0.23, 0.66)	0.48 (-0.07, 0.91)	0.48 (0.22, 0.49)	0.44 (0.21, 0.48)	0.36 (0.20, 0.50)
σ_{14}	0.34 (0.20, 0.50)	0.38 (-0.04, 0.72)	0.40 (0.16, 0.39)	0.36 (0.18, 0.40)	0.29 (0.16, 0.42)
σ_{15}	0.31 (0.14, 0.48)	0.45 (-0.07, 0.68)	0.33 (0.12, 0.36)	0.30 (0.11, 0.34)	0.24 (-0.16, 0.62)
σ_{16}	0.22 (0.08, 0.33)	0.29 (-0.13, 0.43)	0.24 (0.07, 0.31)	0.24 (0.03, 0.27)	0.17 (0.03, 0.29)
σ_{17}	0.20 (0.06, 0.31)	0.30 (-0.32, 0.41)	0.26 (-0.02, 0.27)	0.23 (-0.04, 0.24)	0.09 (-0.08, 0.25)
σ_{18}	0.22 (0.09, 0.32)	0.29 (-0.23, 0.47)	0.17 (-0.01, 0.21)	0.20 (-0.04, 0.17)	0.08 (-0.03, 0.18)
σ_{22}	0.87 (0.55, 1.19)	0.97 (0.18, 1.37)	0.88 (0.56, 1.22)	0.81 (0.48, 1.09)	0.85 (0.51, 1.18)
σ_{23}	0.62 (0.35, 0.89)	0.65 (0.08, 1.02)	0.65 (0.37, 0.73)	0.57 (0.33, 0.66)	0.53 (0.33, 0.72)
σ_{24}	0.46 (0.28, 0.64)	0.48 (0.05, 0.75)	0.48 (0.23, 0.55)	0.40 (0.22, 0.50)	0.39 (0.23, 0.54)
σ_{25}	0.37 (0.14, 0.59)	0.59 (0.01, 0.77)	0.42 (0.12, 0.45)	0.37 (0.13, 0.41)	0.31 (-0.24, 0.84)
σ_{26}	0.24 (0.07, 0.37)	0.37 (-0.07, 0.47)	0.27 (0.07, 0.37)	0.27 (0.07, 0.33)	0.20 (0.00, 0.41)
σ_{27}	0.30 (0.11, 0.44)	0.41 (-0.21, 0.50)	0.39 (0.06, 0.43)	0.31 (0.05, 0.37)	0.23 (0.05, 0.40)
σ_{28}	0.21 (0.05, 0.36)	0.34 (-0.20, 0.46)	0.24 (-0.02, 0.25)	0.24 (-0.02, 0.22)	0.11 (-0.02, 0.23)
σ_{33}	0.59 (0.35, 0.80)	0.61 (0.14, 0.95)	0.58 (0.31, 0.60)	0.55 (0.30, 0.57)	0.46 (0.13, 0.80)
σ_{34}	0.42 (0.25, 0.56)	0.39 (0.10, 0.75)	0.44 (0.20, 0.45)	0.37 (0.20, 0.42)	0.32 (0.20, 0.43)
σ_{35}	0.29 (0.09, 0.47)	0.45 (-0.04, 0.58)	0.31 (0.09, 0.29)	0.27 (0.11, 0.29)	0.22 (-0.16, 0.58)
σ_{36}	0.15 (0.02, 0.25)	0.23 (-0.13, 0.33)	0.16 (-0.01, 0.19)	0.17 (0.03, 0.21)	0.10 (-0.13, 0.33)
σ_{37}	0.21 (0.05, 0.33)	0.29 (-0.20, 0.41)	0.25 (0.02, 0.26)	0.21 (0.04, 0.26)	0.16 (0.03, 0.29)

Table C.12: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 10% MAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.27 (-0.17, 0.34)	0.15 (-0.01, 0.17)	0.15 (-0.01, 0.15)	0.08 (-0.00, 0.16)
σ_{44}	0.41 (0.28, 0.53)	0.37 (0.15, 0.74)	0.41 (0.23, 0.47)	0.36 (0.23, 0.46)	0.36 (0.24, 0.48)
σ_{45}	0.26 (0.08, 0.41)	0.37 (-0.02, 0.49)	0.30 (0.04, 0.24)	0.26 (0.06, 0.25)	0.17 (-0.03, 0.36)
σ_{46}	0.15 (0.02, 0.24)	0.19 (-0.10, 0.27)	0.18 (0.00, 0.17)	0.17 (0.01, 0.17)	0.09 (-0.04, 0.23)
σ_{47}	0.15 (-0.01, 0.25)	0.19 (-0.17, 0.33)	0.19 (-0.03, 0.18)	0.16 (-0.02, 0.18)	0.09 (-0.02, 0.21)
σ_{48}	0.11 (-0.00, 0.22)	0.20 (-0.12, 0.26)	0.12 (-0.06, 0.10)	0.13 (-0.04, 0.10)	0.03 (-0.05, 0.10)
σ_{55}	0.52 (0.28, 0.71)	0.65 (0.17, 0.88)	0.56 (0.29, 0.60)	0.49 (0.28, 0.56)	0.48 (-49.51, 52.12)
σ_{56}	0.31 (0.16, 0.43)	0.32 (0.04, 0.47)	0.35 (0.13, 0.38)	0.30 (0.13, 0.33)	0.25 (-0.01, 0.52)
σ_{57}	0.29 (0.10, 0.43)	0.36 (-0.00, 0.52)	0.35 (0.10, 0.34)	0.30 (0.12, 0.34)	0.27 (0.13, 0.42)
σ_{58}	0.27 (0.12, 0.40)	0.33 (0.01, 0.51)	0.30 (0.11, 0.31)	0.28 (0.13, 0.33)	0.24 (0.03, 0.45)
σ_{66}	0.32 (0.17, 0.43)	0.26 (0.02, 0.34)	0.32 (0.16, 0.37)	0.30 (0.15, 0.34)	0.27 (-2.42, 3.05)
σ_{67}	0.27 (0.15, 0.37)	0.27 (-0.02, 0.37)	0.31 (0.13, 0.35)	0.27 (0.15, 0.33)	0.27 (0.14, 0.41)
σ_{68}	0.24 (0.13, 0.33)	0.22 (-0.02, 0.32)	0.20 (0.10, 0.29)	0.25 (0.11, 0.27)	0.19 (0.10, 0.27)
σ_{77}	0.35 (0.19, 0.49)	0.38 (0.01, 0.49)	0.38 (0.23, 0.47)	0.34 (0.23, 0.45)	0.41 (0.26, 0.56)
σ_{78}	0.26 (0.13, 0.36)	0.28 (-0.03, 0.39)	0.26 (0.13, 0.33)	0.27 (0.15, 0.31)	0.25 (0.14, 0.35)
σ_{88}	0.29 (0.19, 0.37)	0.32 (-0.01, 0.41)	0.28 (0.13, 0.29)	0.31 (0.15, 0.30)	0.22 (0.10, 0.34)

Table C.13: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 20% MAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.73 (-14.39, 17.61)	0.63 (0.35, 0.66)	0.51 (0.33, 0.65)	0.51 (-0.20, 1.49)
σ_{12}	0.62 (0.37, 0.87)	0.91 (-4.81, 7.06)	0.67 (0.32, 0.81)	0.53 (0.30, 0.71)	0.57 (-0.11, 1.49)
σ_{13}	0.44 (0.23, 0.66)	0.60 (-5.72, 6.58)	0.58 (0.17, 0.47)	0.42 (0.18, 0.44)	0.33 (-0.20, 1.05)
σ_{14}	0.34 (0.20, 0.50)	0.47 (-9.60, 9.58)	0.46 (0.15, 0.40)	0.31 (0.16, 0.38)	0.28 (-0.15, 0.85)
σ_{15}	0.31 (0.14, 0.48)	0.64 (-10.27, 10.11)	0.42 (0.10, 0.36)	0.29 (0.10, 0.33)	0.21 (-0.29, 0.82)
σ_{16}	0.22 (0.08, 0.33)	0.39 (-8.72, 8.06)	0.26 (0.06, 0.34)	0.22 (0.02, 0.24)	0.14 (-0.22, 0.59)
σ_{17}	0.20 (0.06, 0.31)	0.38 (-7.64, 7.12)	0.25 (-0.03, 0.24)	0.22 (-0.03, 0.21)	0.10 (-0.36, 0.71)
σ_{18}	0.22 (0.09, 0.32)	0.34 (-14.79, 14.68)	0.21 (0.01, 0.24)	0.19 (-0.05, 0.16)	0.10 (-0.32, 0.57)
σ_{22}	0.87 (0.55, 1.19)	1.24 (-3.06, 5.55)	0.80 (0.55, 1.26)	0.69 (0.44, 1.04)	0.88 (0.16, 1.85)
σ_{23}	0.62 (0.35, 0.89)	0.84 (-2.81, 4.37)	0.60 (0.40, 0.83)	0.50 (0.30, 0.63)	0.54 (0.02, 1.25)
σ_{24}	0.46 (0.28, 0.64)	0.62 (-2.81, 3.68)	0.51 (0.24, 0.60)	0.35 (0.20, 0.48)	0.40 (-0.02, 0.94)
σ_{25}	0.37 (0.14, 0.59)	0.83 (-3.03, 3.93)	0.46 (0.08, 0.45)	0.34 (0.12, 0.41)	0.27 (-0.55, 1.10)
σ_{26}	0.24 (0.07, 0.37)	0.52 (-3.99, 4.16)	0.33 (0.07, 0.41)	0.26 (0.07, 0.32)	0.21 (-0.15, 0.67)
σ_{27}	0.30 (0.11, 0.44)	0.56 (-5.33, 5.36)	0.40 (0.04, 0.47)	0.30 (0.04, 0.33)	0.27 (-0.18, 0.81)
σ_{28}	0.21 (0.05, 0.36)	0.43 (-8.04, 7.81)	0.27 (-0.03, 0.30)	0.23 (-0.03, 0.20)	0.12 (-0.44, 0.75)
σ_{33}	0.59 (0.35, 0.80)	0.74 (-2.90, 4.42)	0.61 (0.32, 0.64)	0.52 (0.27, 0.53)	0.46 (-0.02, 1.16)
σ_{34}	0.42 (0.25, 0.56)	0.46 (-3.99, 5.18)	0.48 (0.17, 0.44)	0.32 (0.17, 0.38)	0.31 (-0.04, 0.78)
σ_{35}	0.29 (0.09, 0.47)	0.63 (-4.64, 5.76)	0.34 (0.07, 0.30)	0.26 (0.10, 0.29)	0.19 (-0.30, 0.72)
σ_{36}	0.15 (0.02, 0.25)	0.32 (-5.18, 5.84)	0.22 (0.01, 0.26)	0.18 (0.06, 0.22)	0.12 (-0.19, 0.51)
σ_{37}	0.21 (0.05, 0.33)	0.40 (-6.31, 6.78)	0.24 (0.05, 0.30)	0.21 (0.06, 0.25)	0.18 (-0.18, 0.64)

Table C.14: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 20% MAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.31 (-9.62, 9.52)	0.15 (-0.03, 0.18)	0.16 (0.00, 0.16)	0.08 (-0.32, 0.54)
σ_{44}	0.41 (0.28, 0.53)	0.39 (-6.89, 8.49)	0.42 (0.22, 0.48)	0.30 (0.22, 0.45)	0.35 (0.07, 0.76)
σ_{45}	0.26 (0.08, 0.41)	0.50 (-8.42, 10.15)	0.37 (0.05, 0.26)	0.25 (0.09, 0.26)	0.17 (-0.29, 0.66)
σ_{46}	0.15 (0.02, 0.24)	0.26 (-9.23, 10.75)	0.21 (-0.01, 0.18)	0.16 (0.03, 0.18)	0.11 (-0.15, 0.43)
σ_{47}	0.15 (-0.01, 0.25)	0.27 (-11.00, 12.20)	0.21 (-0.02, 0.16)	0.15 (0.01, 0.17)	0.13 (-0.18, 0.49)
σ_{48}	0.11 (-0.00, 0.22)	0.26 (-16.09, 16.83)	0.13 (-0.04, 0.12)	0.14 (-0.02, 0.11)	0.05 (-0.37, 0.49)
σ_{55}	0.52 (0.28, 0.71)	0.82 (-10.75, 13.93)	0.62 (0.29, 0.62)	0.46 (0.26, 0.55)	0.48 (-16.33, 20.36)
σ_{56}	0.31 (0.16, 0.43)	0.46 (-13.56, 16.29)	0.40 (0.15, 0.42)	0.27 (0.15, 0.34)	0.27 (-0.06, 0.66)
σ_{57}	0.29 (0.10, 0.43)	0.53 (-16.92, 19.57)	0.39 (0.07, 0.35)	0.29 (0.11, 0.32)	0.26 (-0.14, 0.69)
σ_{58}	0.27 (0.12, 0.40)	0.46 (-22.93, 25.45)	0.33 (0.11, 0.35)	0.27 (0.12, 0.32)	0.24 (-0.23, 0.69)
σ_{66}	0.32 (0.17, 0.43)	0.37 (-18.33, 21.34)	0.34 (0.15, 0.40)	0.28 (0.15, 0.34)	0.28 (0.06, 0.59)
σ_{67}	0.27 (0.15, 0.37)	0.39 (-23.49, 26.78)	0.33 (0.09, 0.30)	0.26 (0.14, 0.30)	0.30 (0.00, 0.64)
σ_{68}	0.24 (0.13, 0.33)	0.30 (-30.31, 33.97)	0.20 (0.10, 0.33)	0.23 (0.11, 0.27)	0.19 (-0.12, 0.52)
σ_{77}	0.35 (0.19, 0.49)	0.53 (-30.12, 34.43)	0.38 (0.19, 0.42)	0.34 (0.20, 0.40)	0.44 (0.05, 0.88)
σ_{78}	0.26 (0.13, 0.36)	0.35 (-38.27, 43.66)	0.26 (0.09, 0.26)	0.26 (0.13, 0.30)	0.25 (-0.11, 0.66)
σ_{88}	0.29 (0.19, 0.37)	0.35 (-49.27, 56.95)	0.28 (0.12, 0.29)	0.30 (0.14, 0.33)	0.22 (-73.25, 82.52)

Table C.15: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 5% MNAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.53 (0.31, 0.79)	0.59 (0.37, 0.72)	0.57 (0.34, 0.70)	0.53 (0.34, 0.69)
σ_{12}	0.62 (0.37, 0.87)	0.63 (0.33, 0.98)	0.62 (0.38, 0.84)	0.60 (0.34, 0.83)	0.58 (0.34, 0.81)
σ_{13}	0.44 (0.23, 0.66)	0.40 (0.20, 0.62)	0.47 (0.22, 0.53)	0.45 (0.21, 0.51)	0.36 (0.21, 0.50)
σ_{14}	0.34 (0.20, 0.50)	0.28 (0.15, 0.43)	0.34 (0.19, 0.43)	0.35 (0.18, 0.41)	0.30 (0.17, 0.41)
σ_{15}	0.31 (0.14, 0.48)	0.29 (0.11, 0.39)	0.32 (0.11, 0.37)	0.31 (0.10, 0.36)	0.23 (0.09, 0.36)
σ_{16}	0.22 (0.08, 0.33)	0.13 (0.04, 0.28)	0.17 (0.04, 0.27)	0.18 (0.03, 0.26)	0.14 (0.03, 0.25)
σ_{17}	0.20 (0.06, 0.31)	0.13 (-0.07, 0.31)	0.21 (-0.00, 0.27)	0.19 (-0.01, 0.27)	0.10 (-0.04, 0.24)
σ_{18}	0.22 (0.09, 0.32)	0.15 (-0.05, 0.19)	0.20 (-0.01, 0.20)	0.21 (-0.01, 0.19)	0.08 (-0.02, 0.18)
σ_{22}	0.87 (0.55, 1.19)	0.94 (0.58, 1.47)	0.87 (0.55, 1.15)	0.84 (0.57, 1.22)	0.88 (0.57, 1.19)
σ_{23}	0.62 (0.35, 0.89)	0.61 (0.38, 0.94)	0.60 (0.37, 0.75)	0.57 (0.35, 0.73)	0.54 (0.35, 0.73)
σ_{24}	0.46 (0.28, 0.64)	0.43 (0.27, 0.65)	0.48 (0.26, 0.56)	0.44 (0.26, 0.56)	0.40 (0.25, 0.54)
σ_{25}	0.37 (0.14, 0.59)	0.40 (0.15, 0.53)	0.38 (0.16, 0.47)	0.36 (0.13, 0.46)	0.30 (0.14, 0.46)
σ_{26}	0.24 (0.07, 0.37)	0.17 (0.03, 0.35)	0.20 (0.05, 0.30)	0.20 (0.04, 0.32)	0.18 (0.04, 0.31)
σ_{27}	0.30 (0.11, 0.44)	0.23 (0.00, 0.47)	0.30 (0.06, 0.37)	0.26 (0.08, 0.41)	0.24 (0.07, 0.40)
σ_{28}	0.21 (0.05, 0.36)	0.17 (-0.08, 0.23)	0.20 (-0.02, 0.21)	0.23 (-0.00, 0.24)	0.11 (-0.02, 0.22)
σ_{33}	0.59 (0.35, 0.80)	0.55 (0.30, 0.72)	0.59 (0.32, 0.63)	0.55 (0.30, 0.59)	0.47 (0.31, 0.61)
σ_{34}	0.42 (0.25, 0.56)	0.36 (0.21, 0.49)	0.42 (0.22, 0.46)	0.39 (0.21, 0.43)	0.33 (0.21, 0.44)
σ_{35}	0.29 (0.09, 0.47)	0.28 (0.11, 0.37)	0.31 (0.13, 0.32)	0.29 (0.12, 0.32)	0.22 (0.11, 0.32)
σ_{36}	0.15 (0.02, 0.25)	0.06 (0.04, 0.26)	0.10 (0.02, 0.17)	0.12 (0.02, 0.20)	0.10 (0.01, 0.19)
σ_{37}	0.21 (0.05, 0.33)	0.15 (0.04, 0.37)	0.22 (0.04, 0.26)	0.19 (0.06, 0.29)	0.17 (0.05, 0.29)

Table C.16: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 5% MNAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.12 (-0.04, 0.18)	0.14 (-0.01, 0.15)	0.17 (0.00, 0.16)	0.09 (-0.00, 0.17)
σ_{44}	0.41 (0.28, 0.53)	0.35 (0.24, 0.47)	0.41 (0.25, 0.48)	0.39 (0.25, 0.48)	0.36 (0.25, 0.47)
σ_{45}	0.26 (0.08, 0.41)	0.25 (0.09, 0.32)	0.26 (0.08, 0.29)	0.25 (0.07, 0.29)	0.18 (0.07, 0.29)
σ_{46}	0.15 (0.02, 0.24)	0.06 (0.02, 0.20)	0.09 (0.00, 0.16)	0.11 (0.00, 0.18)	0.09 (-0.00, 0.17)
σ_{47}	0.15 (-0.01, 0.25)	0.08 (0.01, 0.26)	0.16 (-0.01, 0.18)	0.14 (0.01, 0.21)	0.10 (-0.01, 0.20)
σ_{48}	0.11 (-0.00, 0.22)	0.07 (-0.05, 0.13)	0.11 (-0.05, 0.10)	0.13 (-0.04, 0.11)	0.03 (-0.04, 0.10)
σ_{55}	0.52 (0.28, 0.71)	0.49 (0.23, 0.58)	0.52 (0.32, 0.63)	0.50 (0.30, 0.61)	0.48 (0.32, 0.63)
σ_{56}	0.31 (0.16, 0.43)	0.27 (0.11, 0.34)	0.28 (0.13, 0.36)	0.28 (0.12, 0.36)	0.25 (0.13, 0.37)
σ_{57}	0.29 (0.10, 0.43)	0.28 (0.11, 0.35)	0.30 (0.13, 0.39)	0.27 (0.12, 0.37)	0.26 (0.13, 0.38)
σ_{58}	0.27 (0.12, 0.40)	0.26 (0.08, 0.31)	0.25 (0.11, 0.34)	0.27 (0.10, 0.33)	0.23 (0.12, 0.34)
σ_{66}	0.32 (0.17, 0.43)	0.27 (0.12, 0.30)	0.26 (0.16, 0.35)	0.26 (0.15, 0.35)	0.25 (0.15, 0.35)
σ_{67}	0.27 (0.15, 0.37)	0.24 (0.11, 0.33)	0.24 (0.16, 0.35)	0.25 (0.14, 0.34)	0.25 (0.14, 0.35)
σ_{68}	0.24 (0.13, 0.33)	0.21 (0.08, 0.24)	0.20 (0.09, 0.26)	0.22 (0.10, 0.26)	0.17 (0.09, 0.25)
σ_{77}	0.35 (0.19, 0.49)	0.33 (0.18, 0.51)	0.35 (0.23, 0.45)	0.34 (0.22, 0.47)	0.36 (0.23, 0.49)
σ_{78}	0.26 (0.13, 0.36)	0.24 (0.10, 0.30)	0.26 (0.14, 0.33)	0.26 (0.14, 0.31)	0.22 (0.13, 0.31)
σ_{88}	0.29 (0.19, 0.37)	0.27 (0.11, 0.28)	0.28 (0.14, 0.29)	0.29 (0.14, 0.29)	0.21 (0.13, 0.28)

Table C.17: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 10% MNAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.52 (-0.08, 1.25)	0.62 (0.37, 0.72)	0.55 (0.33, 0.70)	0.53 (0.34, 0.70)
σ_{12}	0.62 (0.37, 0.87)	0.62 (0.08, 1.41)	0.68 (0.34, 0.76)	0.59 (0.32, 0.78)	0.58 (0.33, 0.82)
σ_{13}	0.44 (0.23, 0.66)	0.38 (0.04, 1.05)	0.52 (0.22, 0.53)	0.44 (0.20, 0.51)	0.35 (0.15, 0.55)
σ_{14}	0.34 (0.20, 0.50)	0.29 (-0.02, 0.70)	0.36 (0.20, 0.44)	0.34 (0.17, 0.41)	0.30 (0.17, 0.42)
σ_{15}	0.31 (0.14, 0.48)	0.36 (0.06, 0.72)	0.33 (0.08, 0.33)	0.31 (0.09, 0.34)	0.21 (0.06, 0.36)
σ_{16}	0.22 (0.08, 0.33)	0.15 (-0.03, 0.61)	0.19 (0.04, 0.27)	0.18 (0.03, 0.27)	0.15 (0.02, 0.27)
σ_{17}	0.20 (0.06, 0.31)	0.15 (-0.03, 0.72)	0.25 (-0.02, 0.29)	0.19 (-0.01, 0.28)	0.11 (-0.05, 0.28)
σ_{18}	0.22 (0.09, 0.32)	0.16 (-0.09, 0.47)	0.22 (0.01, 0.22)	0.21 (-0.02, 0.20)	0.09 (-0.02, 0.19)
σ_{22}	0.87 (0.55, 1.19)	0.91 (0.34, 1.87)	0.87 (0.51, 1.06)	0.82 (0.53, 1.14)	0.89 (0.46, 1.32)
σ_{23}	0.62 (0.35, 0.89)	0.58 (0.19, 1.39)	0.61 (0.34, 0.72)	0.57 (0.33, 0.70)	0.54 (0.32, 0.76)
σ_{24}	0.46 (0.28, 0.64)	0.46 (0.12, 0.98)	0.46 (0.22, 0.54)	0.44 (0.23, 0.52)	0.40 (0.25, 0.55)
σ_{25}	0.37 (0.14, 0.59)	0.50 (0.15, 0.92)	0.38 (0.10, 0.41)	0.37 (0.13, 0.43)	0.30 (0.11, 0.49)
σ_{26}	0.24 (0.07, 0.37)	0.22 (-0.01, 0.71)	0.21 (0.03, 0.28)	0.21 (0.04, 0.31)	0.19 (0.04, 0.34)
σ_{27}	0.30 (0.11, 0.44)	0.29 (0.03, 0.90)	0.32 (0.04, 0.37)	0.25 (0.07, 0.40)	0.25 (0.07, 0.43)
σ_{28}	0.21 (0.05, 0.36)	0.21 (-0.07, 0.50)	0.19 (-0.03, 0.21)	0.23 (0.00, 0.24)	0.11 (-0.03, 0.25)
σ_{33}	0.59 (0.35, 0.80)	0.55 (0.15, 1.21)	0.60 (0.33, 0.64)	0.55 (0.30, 0.59)	0.46 (-5.26, 6.38)
σ_{34}	0.42 (0.25, 0.56)	0.37 (0.08, 0.84)	0.39 (0.21, 0.48)	0.38 (0.19, 0.42)	0.32 (0.19, 0.46)
σ_{35}	0.29 (0.09, 0.47)	0.35 (0.04, 0.72)	0.30 (0.14, 0.35)	0.29 (0.13, 0.32)	0.23 (0.09, 0.37)
σ_{36}	0.15 (0.02, 0.25)	0.10 (-0.02, 0.59)	0.11 (0.02, 0.18)	0.13 (0.02, 0.20)	0.10 (0.00, 0.20)
σ_{37}	0.21 (0.05, 0.33)	0.20 (0.02, 0.75)	0.22 (0.07, 0.31)	0.19 (0.06, 0.30)	0.18 (0.02, 0.35)

Table C.18: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 10% MNAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.17 (-0.09, 0.39)	0.13 (-0.02, 0.16)	0.17 (0.00, 0.18)	0.08 (-0.03, 0.20)
σ_{44}	0.41 (0.28, 0.53)	0.35 (0.11, 0.75)	0.40 (0.23, 0.48)	0.36 (0.22, 0.45)	0.35 (0.24, 0.47)
σ_{45}	0.26 (0.08, 0.41)	0.29 (-0.00, 0.55)	0.26 (0.05, 0.27)	0.25 (0.08, 0.26)	0.17 (0.05, 0.30)
σ_{46}	0.15 (0.02, 0.24)	0.06 (-0.04, 0.45)	0.09 (0.01, 0.18)	0.13 (0.01, 0.19)	0.09 (-0.00, 0.19)
σ_{47}	0.15 (-0.01, 0.25)	0.11 (-0.00, 0.54)	0.18 (0.03, 0.22)	0.14 (0.03, 0.23)	0.11 (-0.05, 0.28)
σ_{48}	0.11 (-0.00, 0.22)	0.09 (-0.09, 0.26)	0.11 (-0.03, 0.13)	0.14 (-0.02, 0.12)	0.04 (-0.05, 0.12)
σ_{55}	0.52 (0.28, 0.71)	0.47 (0.14, 0.83)	0.54 (0.28, 0.60)	0.50 (0.27, 0.55)	0.50 (-0.27, 1.31)
σ_{56}	0.31 (0.16, 0.43)	0.22 (0.04, 0.56)	0.28 (0.10, 0.32)	0.26 (0.12, 0.33)	0.26 (0.12, 0.41)
σ_{57}	0.29 (0.10, 0.43)	0.29 (0.06, 0.59)	0.32 (0.11, 0.37)	0.27 (0.12, 0.36)	0.30 (0.14, 0.46)
σ_{58}	0.27 (0.12, 0.40)	0.23 (0.00, 0.46)	0.25 (0.09, 0.34)	0.27 (0.09, 0.31)	0.25 (0.12, 0.39)
σ_{66}	0.32 (0.17, 0.43)	0.23 (0.07, 0.49)	0.25 (0.16, 0.35)	0.24 (0.15, 0.36)	0.26 (-0.76, 1.31)
σ_{67}	0.27 (0.15, 0.37)	0.27 (0.08, 0.54)	0.25 (0.15, 0.35)	0.24 (0.15, 0.35)	0.27 (0.14, 0.41)
σ_{68}	0.24 (0.13, 0.33)	0.19 (-0.00, 0.37)	0.18 (0.09, 0.27)	0.21 (0.11, 0.27)	0.17 (0.06, 0.28)
σ_{77}	0.35 (0.19, 0.49)	0.41 (0.14, 0.71)	0.37 (0.23, 0.47)	0.34 (0.22, 0.48)	0.40 (-1.72, 2.64)
σ_{78}	0.26 (0.13, 0.36)	0.27 (0.01, 0.42)	0.28 (0.12, 0.32)	0.26 (0.16, 0.34)	0.23 (0.09, 0.39)
σ_{88}	0.29 (0.19, 0.37)	0.24 (-0.03, 0.41)	0.28 (0.13, 0.28)	0.29 (0.15, 0.31)	0.21 (-0.57, 1.03)

Table C.19: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 20% MNAR was used in the analysis. (Part 1)

	GS	CCA	KB	LBS	LEM
σ_{11}	0.57 (0.36, 0.76)	0.42 (-3.95, 19.81)	0.59 (0.35, 0.73)	0.50 (0.32, 0.69)	0.56 (-0.15, 1.37)
σ_{12}	0.62 (0.37, 0.87)	0.55 (-5.12, 16.97)	0.72 (0.26, 0.73)	0.55 (0.24, 0.72)	0.58 (0.03, 1.22)
σ_{13}	0.44 (0.23, 0.66)	0.36 (-5.97, 14.27)	0.56 (0.17, 0.51)	0.42 (0.15, 0.48)	0.36 (-0.10, 0.88)
σ_{14}	0.34 (0.20, 0.50)	0.31 (-8.25, 12.61)	0.35 (0.17, 0.45)	0.33 (0.14, 0.40)	0.33 (-0.05, 0.75)
σ_{15}	0.31 (0.14, 0.48)	0.17 (-12.02, 11.28)	0.25 (0.05, 0.32)	0.28 (0.04, 0.30)	0.22 (-0.11, 0.58)
σ_{16}	0.22 (0.08, 0.33)	0.11 (-16.85, 13.21)	0.22 (-0.02, 0.20)	0.18 (-0.00, 0.22)	0.13 (-0.17, 0.47)
σ_{17}	0.20 (0.06, 0.31)	0.14 (-22.59, 16.29)	0.22 (-0.08, 0.21)	0.18 (-0.04, 0.24)	0.08 (-0.29, 0.48)
σ_{18}	0.22 (0.09, 0.32)	0.12 (-29.77, 19.72)	0.22 (-0.01, 0.23)	0.19 (-0.04, 0.21)	0.08 (-0.27, 0.46)
σ_{22}	0.87 (0.55, 1.19)	0.87 (-5.13, 15.03)	0.91 (0.44, 1.05)	0.80 (0.44, 1.02)	0.85 (0.36, 1.45)
σ_{23}	0.62 (0.35, 0.89)	0.62 (-5.61, 12.73)	0.66 (0.25, 0.73)	0.56 (0.23, 0.62)	0.50 (0.13, 0.93)
σ_{24}	0.46 (0.28, 0.64)	0.59 (-6.75, 11.49)	0.52 (0.20, 0.56)	0.46 (0.17, 0.48)	0.39 (0.09, 0.75)
σ_{25}	0.37 (0.14, 0.59)	0.43 (-9.05, 10.13)	0.36 (0.06, 0.41)	0.36 (0.06, 0.40)	0.31 (0.01, 0.66)
σ_{26}	0.24 (0.07, 0.37)	0.22 (-12.46, 11.20)	0.29 (0.02, 0.28)	0.24 (0.02, 0.28)	0.19 (-0.08, 0.51)
σ_{27}	0.30 (0.11, 0.44)	0.32 (-16.26, 13.27)	0.37 (0.01, 0.34)	0.25 (0.03, 0.35)	0.22 (-0.10, 0.59)
σ_{28}	0.21 (0.05, 0.36)	0.21 (-21.12, 15.36)	0.20 (-0.05, 0.23)	0.22 (-0.04, 0.26)	0.14 (-0.15, 0.48)
σ_{33}	0.59 (0.35, 0.80)	0.70 (-5.46, 11.34)	0.64 (0.30, 0.62)	0.55 (0.25, 0.53)	0.43 (0.13, 0.80)
σ_{34}	0.42 (0.25, 0.56)	0.52 (-5.96, 10.49)	0.41 (0.22, 0.51)	0.38 (0.16, 0.39)	0.32 (0.07, 0.62)
σ_{35}	0.29 (0.09, 0.47)	0.37 (-7.15, 9.43)	0.33 (0.12, 0.33)	0.32 (0.09, 0.29)	0.25 (0.02, 0.51)
σ_{36}	0.15 (0.02, 0.25)	0.08 (-9.20, 10.45)	0.13 (-0.01, 0.20)	0.15 (0.00, 0.18)	0.10 (-0.11, 0.35)
σ_{37}	0.21 (0.05, 0.33)	0.23 (-11.64, 12.13)	0.27 (0.03, 0.27)	0.20 (0.03, 0.25)	0.16 (-0.11, 0.45)

Table C.20: Estimates and 95% confidence intervals for variance-covariance parameters (elements of Σ). The glucose data with 20% MNAR was used in the analysis. (Part 2)

	GS	CCA	KB	LBS	LEM
σ_{38}	0.17 (0.04, 0.29)	0.18 (-14.73, 13.75)	0.15 (-0.03, 0.15)	0.19 (-0.02, 0.17)	0.09 (-0.14, 0.35)
σ_{44}	0.41 (0.28, 0.53)	0.56 (-5.96, 10.64)	0.39 (0.22, 0.48)	0.36 (0.19, 0.41)	0.34 (0.12, 0.62)
σ_{45}	0.26 (0.08, 0.41)	0.38 (-6.97, 11.15)	0.24 (0.02, 0.26)	0.25 (0.04, 0.23)	0.16 (-0.03, 0.40)
σ_{46}	0.15 (0.02, 0.24)	0.10 (-9.22, 13.44)	0.10 (-0.03, 0.13)	0.14 (-0.01, 0.15)	0.08 (-0.10, 0.32)
σ_{47}	0.15 (-0.01, 0.25)	0.17 (-12.06, 16.78)	0.18 (0.00, 0.20)	0.15 (0.00, 0.21)	0.10 (-0.13, 0.37)
σ_{48}	0.11 (-0.00, 0.22)	0.13 (-15.55, 20.34)	0.12 (-0.03, 0.15)	0.14 (-0.04, 0.14)	0.05 (-0.15, 0.28)
σ_{55}	0.52 (0.28, 0.71)	0.44 (-8.29, 14.70)	0.58 (0.27, 0.61)	0.51 (0.21, 0.51)	0.52 (0.26, 0.84)
σ_{56}	0.31 (0.16, 0.43)	0.18 (-11.85, 19.79)	0.32 (0.08, 0.34)	0.27 (0.08, 0.29)	0.25 (0.05, 0.50)
σ_{57}	0.29 (0.10, 0.43)	0.29 (-16.35, 26.26)	0.39 (0.05, 0.36)	0.28 (0.07, 0.34)	0.29 (0.04, 0.60)
σ_{58}	0.27 (0.12, 0.40)	0.16 (-21.58, 33.66)	0.29 (0.06, 0.37)	0.27 (0.05, 0.31)	0.26 (0.04, 0.53)
σ_{66}	0.32 (0.17, 0.43)	0.21 (-16.85, 28.00)	0.26 (0.15, 0.29)	0.24 (0.13, 0.29)	0.24 (0.06, 0.48)
σ_{67}	0.27 (0.15, 0.37)	0.27 (-23.25, 37.81)	0.28 (0.13, 0.34)	0.24 (0.11, 0.32)	0.26 (0.03, 0.55)
σ_{68}	0.24 (0.13, 0.33)	0.16 (-30.61, 49.27)	0.18 (0.08, 0.25)	0.21 (0.09, 0.27)	0.18 (-0.02, 0.45)
σ_{77}	0.35 (0.19, 0.49)	0.45 (-31.90, 51.65)	0.40 (0.20, 0.46)	0.33 (0.18, 0.45)	0.39 (0.08, 0.80)
σ_{78}	0.26 (0.13, 0.36)	0.27 (-41.84, 67.72)	0.30 (0.12, 0.36)	0.26 (0.12, 0.36)	0.26 (-0.03, 0.65)
σ_{88}	0.29 (0.19, 0.37)	0.22 (-54.66, 89.28)	0.28 (0.13, 0.30)	0.28 (0.13, 0.38)	0.23 (-0.06, 0.64)