Regression modelling of overall survival and progression-free survival

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ABSTRACT

REGRESSION MODELLING OF OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

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There are three endpoints commonly used in oncology clinical trials, which are known as overall survival (OS), time to progression (TTP) and progression-free survival (PFS). Recently, PFS has become an important alternative endpoint to OS. In this thesis, both exponential and Weibull distributions are used to investigate the joint model of OS and PFS. Regression modelling will be introduced to investigate the effect of a treatment indicator on the distribution parameters for OS, TTP, and PFS. Both simulated data and real data will be used to investigate and demonstrate methods. The parameters of the models will be estimated by the maximum likelihood estimation. Furthermore, Wald tests will be performed to investigate covariate effects.

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Chapter 1

Introduction

In oncology clinic trials, overall survival (OS) is a primary endpoint to test new anti-cancer drugs or therapies (Brody, 2016). OS is an unambiguous, unbiased and reliable cancer endpoint, which is defined as the time from randomization until death from any cause or censoring at the end (Driscoll and Rixe, 2009). However, due to cost effectiveness and ease of measurement, some surrogate endpoints such as time to progression (TTP) and progression-free survival (PFS) are being used instead of OS (Brody, 2016). PFS represents the time from randomization until disease progression or death, whichever occurs first. TTP represents the time from randomization to disease progression only, and treats death before progression as censoring (Fleischer et al., 2009; Rathwell, 2017). Both TTP and PFS are more widely accepted and used to improve clinical benefits (e.g., earlier phases of drug development or treatments) (Li and Zhang, 2015). In recent years, Fleischer et al. (2009) and Li and Zhang (2015) proposed parametric statistical models to describe the dependency between OS and PFS based on the assumption of exponential and Weibull distributions, respectively. The motivation of this thesis is to extend their models in terms of a regression approach to investigate the joint model of OS and PFS.

The models and the method of estimation will be introduced in Chapters 2 and 3, respectively. A simulation study will be described in Chapter 4. In Chapter 5, a real data set based

on a study of hepatocellular carcinoma (HCC) will be used to demonstrate the application of methods introduced in this thesis. Conclusions and suggestions for future research will be included in Chapter 6.

1.1 Background

OS is the most common endpoint in oncology clinical trials, followed by PFS and TTP. Research has mainly focused on the dependence structure between OS and PFS and the investigation of statistical models was neglected. To fill this gap, Fleischer et al. (2009) first introduced an exponential model for describing the dependence between PFS and OS. Based on his approach, Fleischer et al. (2009) applied two different methods for estimating the parameters of the model. They were known as the plug-in approach and maximum likelihood estimation. Both estimators were investigated using a simulation study. The correlation coefficient between OS and disease progression has been discussed as well. Furthermore, the model was applied to three examples from non-small cell lung cancer studies.

On the basis of the work from Fleischer et al. (2009), Li and Zhang (2015) extended the exponential to the more flexible Weibull distribution. They concluded that the use of the Weibull distribution was more robust to describe the dependence between PFS and OS, compared to the exponential model. In their research, the maximum likelihood method was applied for the estimation of model parameters. Both a simulation study and real data application from the Radiation Therapy Oncology Group (RTOG) were conducted. In addition, they plotted both Kaplan-Meier curves and model estimated curves to assess the goodness of fit.

Other papers have followed the framework of Fleischer et al. (2009) or Li and Zhang (2015). For example, Belkacemi et al. (2014) proposed a statistical model for OS to test the existence of an association between PFS and post-progression survival (PPS) by using

a conditional exponential distribution. Maximum likelihood estimation was used again to estimate the model parameters. The correlation coefficient was found between PFS and PPS, as well as between PFS and OS. In their clinical trial data analysis, they concluded that there is a significant association between PFS and PPS (Belkacemi et al., 2014). More recently, Weber and Titman (2019) proposed several methods for quantifying the association between PFS and OS such as copula-based, nonparametric, and illness-death model-based methods. The simulation study showed that the illness-death model-based approach was the most appropriate method which provided good estimates by using Kendall's τ. The copula-based method sometimes also performed well but depended on the selection of copula, especially the Clayton copula.

In this thesis, the aim is to extend the approaches of Fleischer et al. (2009) and Li and Zhang (2015) by adding regression modelling. The regression model allows one to investigate the effects of covariates (i.e., different treatment groups). Two groups will be compared in both a simulation study and real data application.

1.2 Hepatocellular Carcinoma Study

Hepatocellular carcinoma (HCC), a cancer that starts in the liver, has now become the third leading cause of cancer deaths worldwide (Cicalease, 2019). Most HCCs occur in Asia and Africa, especially for those who had chronic liver diseases and cirrhosis caused by hepatitis B and hepatitis C. Both hepatitis B and hepatitis C are serious virus infections that will lead to liver damage (Mayo Clinilc (c), 2019). HCC incidence has grown rapidly in recent years (Martin, 2019). Other factors such as large amounts of drinking alcohol, iron storage disease, obesity, and diabetes may also increase HCC risk (Martin, 2019). Several tests (blood tests and imaging tests) and procedures (liver biopsy) can be used to diagnose HCC (Mayo Clinic (b), 2019). Various treatments such as surgery, destroying cancer cells

with heat or cold, radiation therapy, and immunotherapy, can be used to treat HCC (Mayo Clinic (a), 2019). Treatment for each individual will be different. It will depend on the size and location of their HCC and how healthy their liver is (Mayo Clinic (a), 2019).

The HCC dataset can be found in R (R Core Team, 2019), known as hepatoCellular under the package asaur (Moore, 2016). In the study, there are 227 HCC patients who have been investigated. A total of 48 clinical variables were measured (e.g., age, gender, hepatitis B surface antigen, cirrhosis, tumour size). All HCC patients had the treatment called curative resection of the liver between 2007 and 2010. The curative resection of the liver was defined as a complete removal of all tumour nodules, with a cutting margin of at least 1 cm (Li et al., 2014). The patients were all followed up after their surgery between 2007 and 2014, with a range from 2 to 83 months. Four different conditions occurred after follow up. Specifically, 20.3% of patients experienced progression without death; 31.3% of patients had progression first and then died; 11.4% of patients died before progression occurred; and 37% of patients remained alive without progression or death at the end of follow up (Rathwell, 2017).

CXC chemokine ligand 17 (CXCL17) is often expressed in some aggressive types of cancer cells such as breast, lung, and liver (Matsui et al., 2012). The expression of CXCL17 in tumour cells may play an important role in tumour progression (Matsui et al., 2012). In the HCC study, the variable of interest among all of 48 variables is CXCL17 level. The samples were collected before treatment (i.e., during the surgery). This variable was analyzed by Li et al. (2014) and Rathwell (2017). CXCL17 is a categorical variable with two levels: 0 represents the low level and 1 represents the high level. Since the original variable from the HCC dataset is a quantitative variable, the median of the variable will be calculated to define the levels of CXCL17. The median of CXCL17 is 46.440. Values smaller than the median, are considered low level and values greater than the median, are considered high level. Figure 1.1 shows the histogram of the original CXCL17 variable in the HCC dataset. The distribution of CXCL17 indicates positive skewness. Since the median of 46.440 is close

to the edge of the first category, the highest frequency of the histogram, the cutoff in this case may be reasonable. In addition, in order to compare the results from Rathwell (2017), the same cutoff will be applied in this study. However, to make such cutoff in a clinical setting, an ideal cut point should be defined in advance based on a medical criterion. The purpose of their studies was to determine whether there is any significant difference between the level of CXCL17 with respect to OS and PFS based on different methods. Kaplan-Meier estimation and the log-rank test have been used by Li et al. (2014) and maximum likelihood estimation and a Wald test have been used by Rathwell (2017). In this thesis, a Wald test will be applied as well but within a regression approach. The HCC data analysis results are reported in Chapter 5.

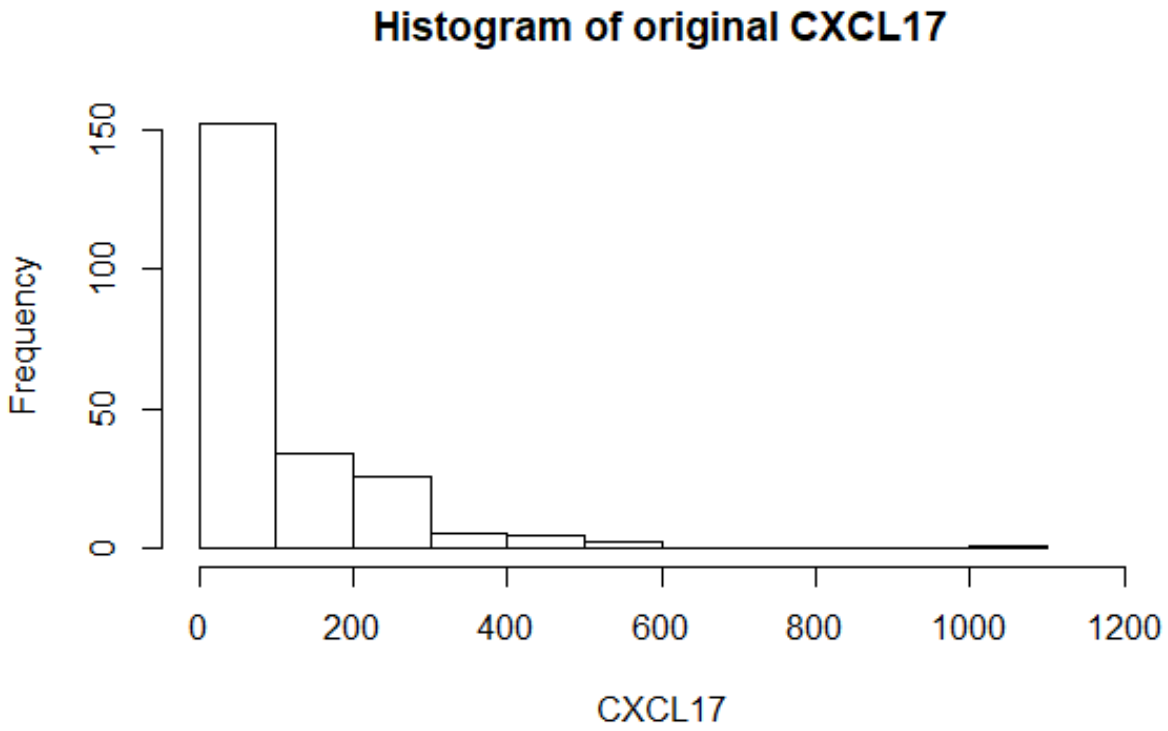

Figure 1.1: Histogram of the original CXCL17 variable in the HCC data set.

Chapter 2

Statistical Models

Two different models will be introduced in this chapter, known as the Weibull and exponential models. The models are based on failure-time distributions that describe time to disease progression or death. On the basis of the framework of Fleischer et al. (2009), and also Li and Zhang (2015), an extension to the regression approach will be applied to the parameters: the Weibull distribution with shape parameter τ and rate parameter λ; and the exponential which is a special case of the Weibull with $\tau = 1$. The Weibull distribution is given as follows (Rathwell, 2017):

$$f(t) = \lambda\tau t^{(\tau-1)} \exp(-\lambda t^{\tau}), \tag{2.1}$$

where $\lambda > 0$, $\tau > 0$, and $t \geq 0$. Similarly, the parametrization of the exponential distribution is:

$$f(t) = \lambda \exp(-\lambda t), \tag{2.2}$$

where $\lambda > 0$ and $t \geq 0$. Note that the mean of the exponential distribution is $1/\lambda$.

2.1 Joint Exponential Model

A general joint exponential model was proposed by Fleischer et al. (2009). This model uses TTP and PFS, and splits OS into two parts: OS_{orig} and OS'. OS_{orig} is defined as pre-progression survival and OS' is defined as post-progression survival. Li and Zhang (2015) set OS_{orig} as the hypothetical original OS. Therefore, PFS is given by the minimum of TTP and OS_{orig}. If the time to death without progression occurs, then OS and PFS are the same. If the progression occurs first during the time from progression to death, then OS' will be applied to represent the time to death after progression. In this case, OS equals to the sum of TTP and OS' (Li and Zhang, 2015). The general model is assumed with an exponential distribution for TTP, PFS, OS_{orig}, and OS' such that

$$\begin{aligned} TTP &\sim Exp(\lambda_1) \\ OS_{orig} &\sim Exp(\lambda_2) \\ PFS = min(TTP, OS_{orig}) &\sim Exp(\lambda_1 + \lambda_2) \\ OS' &\sim Exp(\lambda_3) \end{aligned} \tag{2.3}$$

where $\lambda_1, \lambda_2, \lambda_3 > 0$.

To extend the exponential distribution assumption into a regression approach, the rate parameters will be defined such that $\lambda_1 = \exp(\alpha_0 + \alpha_1 X), \lambda_2 = \exp(\beta_0 + \beta_1 X)$, and $\lambda_3 = \exp(\gamma_0 + \gamma_1 X)$ where X is the indicator of the treatment groups, with $X = 0$ if control, and $X = 1$ if treatment. Therefore, the assumptions of joint exponential model in our case are:

$$TTP \sim Exp(\exp(\alpha_0 + \alpha_1 X)) \tag{2.4}$$

$$OS_{orig} \sim Exp(\exp(\beta_0 + \beta_1 X)) \tag{2.5}$$

$$PFS = min(TTP, OS_{orig}) \sim Exp(\exp(\alpha_0 + \alpha_1 X) + \exp(\beta_0 + \beta_1 X)) \tag{2.6}$$

$$OS' \sim Exp(\exp(\gamma_0 + \gamma_1 X)) \tag{2.7}$$

$$OS = \begin{cases} PFS, \text{if } PFS \neq TTP \\ TTP + OS', \text{if } PFS = TTP \end{cases} \tag{2.8}$$

where $X = 0$ if control, 1 if treatment. Note that OS_{orig}, OS' and TTP are assumed all independent.

2.2 Joint Weibull Model

Based on the construction of the exponential model from Fleischer et al. (2009), the joint Weibull model was developed by Li and Zhang (2015). The assumptions of the Weibull model is similar to the exponential, but with a shape parameter τ being added (i.e., $Weibull(\tau, \lambda)$). When $\tau = 1$, the Weibull model will become a special case which is the exponential model. For mathematical convenience, we will assume a common shape parameter τ but different regression coefficient parameters $\alpha_0, \alpha_1, \beta_0, \beta_1, \gamma_0$ and γ_1. Therefore, the assumptions of the joint Weibull model is shown as follows:

$$TTP \sim Weibull(\tau, \exp(\alpha_0 + \alpha_1 X)) \tag{2.9}$$

$$OS_{orig} \sim Weibull(\tau, \exp(\beta_0 + \beta_1 X)) \tag{2.10}$$

$$PFS = min(TTP, OS_{orig}) \sim Weibull(\tau, \exp(\alpha_0 + \alpha_1 X) + \exp(\beta_0 + \beta_1 X)) \tag{2.11}$$

$$OS' \sim Weibull(\tau, \exp(\gamma_0 + \gamma_1 X)) \tag{2.12}$$

$$OS = \begin{cases} PFS, \text{if } PFS \neq TTP \\ TTP + OS', \text{if } PFS = TTP \end{cases} \tag{2.13}$$

where $X = 0$ if control, 1 if treatment. Moreover, OS_{orig}, OS', and TTP are assumed all independent.

Chapter 3

Model Estimation

3.1 Estimation

Maximum likelihood estimation was used by Fleischer et al. (2009) to estimate the parameters. In this thesis, maximum likelihood estimation will be used as well for both exponential and Weibull models. First, define f_1, f_2, and f_3 as the density functions for TTP, OS_{orig}, and OS', respectively; S_1, S_2, and S_3 are the survival functions for TTP, OS_{orig}, and OS', respectively. Both f_1 and S_1 follow the distribution of $Exp(\lambda_1)$ or $Weibull(\tau, \lambda_1)$; f_2 and S_2 follow the distribution of $Exp(\lambda_2)$ or $Weibull(\tau, \lambda_2)$; and f_3 and S_3 follow the distribution of $Exp(\lambda_3)$ or $Weibull(\tau, \lambda_3)$. To allow the λ parameters to depend on a single covariate X, regression models will be used such that $\lambda_1 = exp(\alpha_0 + \alpha_1 X), \lambda_2 = exp(\beta_0 + \beta_1 X)$, and $\lambda_3 = exp(\gamma_0 + \gamma_1 X)$. Note that, in general, the covariate can be a treatment indicator, condition (e.g. CXCL17 levels), demographic information on the patients (e.g. age).

Now, let θ be a vector of parameters that will be estimated, such as $\theta = (\tau, \alpha_0, \alpha_1, \beta_0, \beta_1, \gamma_0, \gamma_1)$, and the corresponding maximum likelihood estimates will be $\hat{\theta} = (\hat{\tau}, \hat{\alpha}_0, \hat{\alpha}_1, \hat{\beta}_0, \hat{\beta}_1, \hat{\gamma}_0, \hat{\gamma}_1)$. Furthermore, four types of patients will be defined from the observed datasets (Li and Zhang, 2015):

1. Patients who have disease progression then censor without death

2. Patients who have disease progression then die

3. Patients who die first before any disease progression occurs

4. Patients who censor with neither progression nor death.

Let k index the type of patients where $k = 1, ..., 4$, and let z_i be an indicator vector where $z_i = (z_{i1}, ..., z_{i4})$ with $z_{ik} = 1$ if patient is type of k and 0 otherwise ($i = 1, ..., n$). Thus, $\sum_{k=1}^{4} z_{ik} = 1$. There are two different times, t_{i1} and t_{i2}, that are observed for type 1 or 2 patients. The time t_{i1} represents time to disease progression and time t_{i2} represents time after disease progression occurs until death or censoring. For type 3 and 4 patients, only the time t_{i1} is observed, which is time to death or censoring. Note that t_{i2} is missing for these two cases (Li and Zhang, 2015; Rathwell, 2017).

The likelihood contribution for a patient of type k is $L_i^{(k)}(\theta)$ (Li and Zhang, 2015) where if $k = 1$, then for type 1 patients

$$L_i^{(1)}(\theta) = f_1(t_{i1})S_2(t_{i1})S_3(t_{i2})$$

if $k = 2$, then for type 2 patients

$$L_i^{(2)}(\theta) = f_1(t_{i1})S_2(t_{i1})f_3(t_{i2})$$

if $k = 3$, then for type 3 patients

$$L_i^{(3)}(\theta) = S_1(t_{i1})f_2(t_{i1})$$

if $k = 4$, then for type 4 patients

$$L_i^{(4)}(\theta) = S_1(t_{i1})S_2(t_{i1}).$$

Now, the likelihood contribution for the Weibull model can be shown as follows:

$$L_i^k(\cdot) = \begin{cases} \lambda_1\tau t_{i1}^{(\tau-1)} \exp(-\lambda_1 t_{i1}^\tau) \exp(-\lambda_2 t_{i1}^\tau) \exp(-\lambda_3 t_{i2}^\tau), \text{if } k = 1 \\ \lambda_1\tau t_{i1}^{(\tau-1)} \exp(-\lambda_1 t_{i1}^\tau) \exp(-\lambda_2 t_{i1}^\tau)\lambda_3\tau t_{i2}^{(\tau-1)} \exp(-\lambda_3 t_{i2}^\tau), \text{if } k = 2 \\ \exp(-\lambda_1 t_{i1}^\tau)\lambda_2\tau t_{i1}^{(\tau-1)} \exp(-\lambda_2 t_{i1}^\tau), \text{if } k = 3 \\ \exp(-\lambda_1 t_{i1}^\tau) \exp(-\lambda_2 t_{i1}^\tau), \text{if } k = 4. \end{cases} \tag{3.1}$$

The corresponding log-likelihood contribution is:

$$\log L_i^k(\cdot) = \begin{cases} \log\lambda_1 + \log\tau + (\tau-1)\log t_{i1} - (\lambda_1+\lambda_2)t_{i1}^\tau - \lambda_3 t_{i2}^\tau, \text{if } k = 1 \\ \log\lambda_1 + \log\lambda_3 + 2\log\tau + 2(\tau-1)\log t_{i1} - (\lambda_1+\lambda_2)t_{i1}^\tau - \lambda_3 t_{i2}^\tau, \text{if } k = 2 \\ \log\lambda_2 + \log\tau + (\tau-1)\log t_{i1} - (\lambda_1+\lambda_2)t_{i1}^\tau, \text{if } k = 3 \\ -(\lambda_1+\lambda_2)t_{i1}^\tau, \text{if } k = 4. \end{cases} \tag{3.2}$$

The overall log-likelihood will be the summation for all individuals of their likelihood contributions and can be written as

$$\log L(\hat{\tau}, \hat{\alpha}_0, \hat{\alpha}_1, \hat{\beta}_0, \hat{\beta}_1, \hat{\gamma}_0, \hat{\gamma}_1) = \sum_{i=1}^{n}\sum_{k=1}^{4} z_{ik} \log L_i^k(\cdot). \tag{3.3}$$

When $\tau = 1$, the above likelihood function for the joint Weibull model becomes the

likelihood function for the joint exponential model. The R function *optim()* (R Core Team, 2019) will be used to obtain the maximum likelihood estimates for the exponential and Weibull models. A method called Broyden-Fletcher-Goldfarb-Shanno (BFGS) will be applied in the function to return the gradient (R Core Team, 2019). The function to be optimized is provided to *optim* as an argument. The *optim* function performs minimization. Therefore, to maximize the log-likelihood, the function supplied to *optim* must be multiplied by -1. The estimated standard errors were found by using the Hessian approach. A $p \times p$ Hessian matrix which here is the matrix of the second derivatives of the negative log-likelihood function was obtained by the function of *optim* in R (R Core Team, 2019). Thus, here the Hessian $H(\theta)$ with respect to the parameters based on the *optim* function is given as by (Faraway, 2016):

$$H(\theta) = -\frac{\partial^2 \log L(\theta)}{\partial\theta\partial\theta'}.$$

The Fisher information matrix, $I(\theta)$, is the negative of the expected value of the matrix of second derivatives of the log likelihood function such that here we have:

$$I(\theta) = E(H(\theta)).$$

Therefore, the variance-covariance matrix of $\hat{\theta}$ is:

$$Var(\hat{\theta}) = (I(\theta))^{-1}. \tag{3.4}$$

Thus, the estimated standard errors can be found by computing the square roots of the diagonal terms in the variance-covariance matrix in Equation 3.4 (Faraway, 2016; Rathwell, 2017).

3.2 Wald Test

The Wald test will be used to determine whether the treatment groups differ significantly. The vector of parameter estimates $\hat{\theta}$ in both joint exponential and joint Weibull models were found by maximum likelihood estimation. In this study, the Wald test will be applied to test the slope parameters α_1, β_1, and γ_1. The hypotheses at $\alpha = 0.05$ are

$$H_0 : \alpha_1 = 0 \text{ vs. } H_1 : \alpha_1 \neq 0;$$

$$H_0 : \beta_1 = 0 \text{ vs. } H_1 : \beta_1 \neq 0;$$

and

$$H_0 : \gamma_1 = 0 \text{ vs. } H_1 : \gamma_1 \neq 0.$$

For example, denote the value of the parameter under the null hypothesis as α_1, then the Wald statistic is defined as (Wasserman, 2006):

$$W = \frac{(\hat{\alpha}_1 - \alpha_1)}{se(\hat{\alpha}_1)} \sim N(0, 1). \tag{3.5}$$

To test whether the coefficient differs from 0 or not (i.e., $\alpha_1 = 0$), the Wald statistic simplifies to

$$W = \frac{\hat{\alpha}_1}{se(\hat{\alpha}_1)} \sim N(0, 1). \tag{3.6}$$

Note that if $\alpha_1 = 0$, $\beta_1 = 0$, and $\gamma_1 = 0$, then there will be no effect of CXCL17 levels in the HCC dataset with respect to TTP, OS, and PFS.

Chapter 4

Simulation

Li and Zhang (2015) conducted a simulation study to evaluate the fit of both joint exponential and joint Weibull models. They generated data (i.e. event times) from various distributions such as exponential, Weibull with both same shape and different shape parameters, log-logistic, and log-normal. Based on the Kaplan-Meier plots, they found that the Weibull model generally provided a better fit than the exponential model. In this chapter, simulations will be conducted as well to investigate covariate effects with different parameter settings. The related R code is shown in Appendix B.

Both joint exponential and joint Weibull models will be applied to the simulated data. Li and Zhang (2015) set the parameters as $\tau = 3, \lambda_1 = 2, \lambda_2 = 1$, and $\lambda_3 = 2$ when they generated event times from a Weibull distribution. These values will form a basis for the simulations conducted for this thesis. TTP, OS_{orig}, and OS' will be generated from the assumed distributions and a fixed censoring time of 1 year will be used. As mentioned in Chapter 3, a regression approach is introduced here such that $\lambda_1 = \exp(\alpha_0 + \alpha_1 X), \lambda_2 = \exp(\beta_0 + \beta_1 X)$, and $\lambda_3 = \exp(\gamma_0 + \gamma_1 X)$, where $X = 0$ if control, 1 if treatment. Here, the parameters for the joint exponential model are: $\alpha_0 = \log(2), \beta_0 = \log(1)$, and $\gamma_0 = \log(2)$, stating with all the slope parameters set to $\alpha_1 = \beta_1 = \gamma_1 = 0$. Note that if $\alpha_1 =$

$\beta_1 = \gamma_1 = 0$, then there are no treatment effects. In the simulation study, a total of three different combination sets of the slope parameters $(\alpha_1, \beta_1, \gamma_1)$ have been used for each different sample size within each model, one null case and two alternative cases. The intercept parameters $(\alpha_0, \beta_0, \gamma_0)$ will maintain the same all the time. In addition, the parameters for the joint Weibull models will have the same settings, but with a shape parameter $\tau = 3$. Two treatment groups will be developed through all of the simulations and the number of individuals in each group will be equal for different sample sizes. Sample sizes of 200, 500, and 1000 will be considered in the simulations, which means a size of 100, 250, and 500 will be generated for each group, respectively. Furthermore, the number of replications for each parameter set is 500.

For example, for patient i,

i. Generate $TTP_i \sim Exp(\exp(\alpha_0 + \alpha_1 X))$ or $Weibull(\tau, \exp(\alpha_0 + \alpha_1 X))$.

ii. Next, generate $OS_{orig} \sim Exp(\exp(\beta_0 + \beta_1 X))$ or $Weibull(\tau, \exp(\beta_0 + \beta_1 X))$.

iii. If $TTP_i < OS_{orig}$, then generate $OS' \sim Exp(\exp(\gamma_0 + \gamma_1 X))$ or $Weibull(\tau, \exp(\gamma_0 + \gamma_1 X))$ so that $OS_{orig} = TTP_i + OS'$. Otherwise, $TTP_i > OS_{orig}$.

In the simulation study, the mean of the parameter estimates, the mean of their estimated standard errors, standard deviation of the parameter estimates and the bias of the parameter estimates will be computed and shown in the table. As mentioned above, 500 replications were used, which means 500 estimates were obtained for each parameter by maximum likelihood estimation and also 500 standard error estimates. Therefore, the mean of the estimates and the mean of the estimated standard errors for each parameter were calculated by averaging the values of 500 estimates and estimated standard errors, respectively. For example, the mean of the parameter estimate for α_0 can be calculated as follows:

$$\bar{\hat{\alpha}}_0 = \frac{\sum_{i=1}^{500} \hat{\alpha}_{0i}}{500}.$$

The standard errors for estimates were found by using the Hessian approach as discussed in Section 3.1. Then, the mean of the standard errors was calculated as:

$$\text{The mean of } SE(\hat{\alpha}_0) = \frac{\sum_{i=1}^{500} SE(\hat{\alpha}_{0i})}{500}.$$

The standard deviations were obtained directly by applying the *sd()* function in R to the 500 parameter estimates (R Core Team, 2019). For instance, the standard deviation of $\hat{\alpha}_0$ can be computed by the following equation:

$$\text{sd of } \hat{\alpha}_0 = \sqrt{\frac{\sum_{i=1}^{500} \hat{\alpha}_{0i} - \bar{\hat{\alpha}}_0}{500 - 1}}.$$

The bias of the estimator was calculated as the mean of the 500 parameter estimates minus the true parameter value (e.g., $\bar{\hat{\alpha}}_0 - \alpha_0$).

Table 4.1: Percent censoring for the exponential and Weibull models, when $n = 100,000$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, $\alpha_1 = \beta_1 = \gamma_1 = 0$, and $\tau = 3$ for Weibull.

		Percent	Censoring
		OS	PFS
Exponential	control	11.084%	2.440%
	treatment	10.916%	2.465%
Weibull	control	28.493%	2.440%
	treatment	28.259%	2.465%

Table 4.2: Percent censoring for the exponential and Weibull models, when $n = 100,000$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, $\alpha_1 = \beta_1 = \gamma_1 = 0.5$, and $\tau = 3$ for Weibull.

		Percent Censoring	
		OS	PFS
Exponential	control	11.084%	2.440%
	treatment	3.408%	0.363%
Weibull	control	28.493%	2.440%
	treatment	21.847%	0.363%

Table 4.3: Percent censoring for the exponential and Weibull models, when $n = 100,000$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, $\alpha_1 = 0.8, \beta_1 = 0.7$, $\gamma_1 = 0.2$, and $\tau = 0.8$ for Weibull.

		Percent Censoring	
		OS	PFS
Exponential	control	11.084%	2.440%
	treatment	4.864%	0.078%
Weibull	control	28.493%	2.440%
	treatment	23.093%	0.078%

The censoring for large sample sizes are generated. Tables 4.1 – 4.3 give an overview of the percent censoring for the joint exponential and Weibull models when $n = 100,000$ with different sets of parameters. The percent censoring of control group for OS in exponential and Weibull models are 11.084% and 28.493%, respectively. The range of percent censoring of treatment group for OS in both models is $(3.408\%, 28.259\%)$. Moreover, the percent censoring of control group for PFS in both models is 2.440%, and the range of percent censoring of treatment group for PFS in both models is $(0.078\%, 2.465\%)$.

Table 4.4 – 4.6 shows the percentage of each type patients for both joint and Weibull models when $n = 100,000$ with different sets of parameters. For example, for the exponential model with the null case slope parameters, 46.253% of patients experienced progression first and then died; 17.095% had progression without death; 31.747% of patients died before the

progression occurred; and 4.905% of patients experienced neither progression nor death.

Table 4.4: Percentage of each type patient for the exponential and Weibull models, when $n = 100,000$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, $\alpha_1 = \beta_1 = \gamma_1 = 0$, and $\tau = 3$ for Weibull.

	Exponential	Weibull
Progression first then died	46.253%	11.571%
Progression occurred without death	17.095%	51.775%
Died before progression occurred	31.747%	31.722%
Neither progression nor death	4.905%	4.932%

Table 4.5: Percentage of each type patient for the exponential and Weibull models, when $n = 100,000$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, $\alpha_1 = \beta_1 = \gamma_1 = 0.5$, and $\tau = 3$ for Weibull.

	Exponential	Weibull
Progression first then died	53.053%	17.083%
Progression occurred without death	11.689%	47.577%
Died before progression occurred	32.455%	32.428%
Neither progression nor death	2.803%	2.912%

Table 4.6: Percentage of each type patient for the exponential and Weibull models, when $n = 100,000$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, $\alpha_1 = 0.8, \beta_1 = 0.7$, $\gamma_1 = 0.2$, and $\tau = 3$ for Weibull.

	Exponential	Weibull
Progression first then died	52.609%	17.009%
Progression occurred without death	13.430%	49.150%
Died before progression occurred	31.443%	31.208%
Neither progression nor death	2.518%	2.633%

The first simulated event times data were generated from exponential distributions with null cases for the slope parameters. More specially, TTP was generated from $Exp(2)$ (i.e., $\alpha_0 = \log(2)$, $\alpha_1 = 0$), OS_{orig} was generated from $Exp(1)$ (i.e., $\beta_0 = \log(1)$, $\beta_1 = 0$), and OS' was generated from $Exp(2)$ (i.e., $\gamma_0 = \log(2)$, $\gamma_1 = 0$).

Table 4.7: Simulation results of exponential with $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

(a) $n = 200$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\alpha}_0$	0.697	0.126	0.127	0.004
$\hat{\alpha}_1$	-0.013	0.179	0.176	-0.013
$\hat{\beta}_0$	0.008	0.178	0.179	0.008
$\hat{\beta}_1$	-0.014	0.253	0.267	-0.014
$\hat{\gamma}_0$	0.692	0.148	0.148	-0.002
$\hat{\gamma}_1$	-0.010	0.210	0.213	-0.010

(b) $n = 500$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\alpha}_0$	0.699	0.080	0.081	0.006
$\hat{\alpha}_1$	-0.003	0.112	0.115	-0.003
$\hat{\beta}_0$	0.004	0.113	0.114	0.004
$\hat{\beta}_1$	-0.017	0.160	0.157	-0.017
$\hat{\gamma}_0$	0.696	0.093	0.088	0.003
$\hat{\gamma}_1$	-0.002	0.132	0.133	-0.002

(c) $n = 1000$

Estimates	Mean	Mean of SE	SD	Bias
α_0	0.698	0.056	0.057	0.005
α_1	-0.007	0.079	0.081	-0.007
β_0	-0.003	0.080	0.082	-0.003
β_1	0.002	0.113	0.112	0.002
γ_0	0.698	0.066	0.064	0.005
γ_1	-0.003	0.093	0.092	-0.002

Table 4.7 shows results from the simulation of exponential data with previous setting at sample sizes of 200, 500, and 1000. As shown in Table 4.7, the mean of standard error estimates and the standard deviation for all the parameter estimates were decreasing as the sample sizes were increasing. Moreover, these two values for each estimate are very close to each other. In addition, the mean of the estimates was very close to their true parameters in all the cases so that bias is small, even with the small sample size of 200.

Next, the simulated data were generated from Weibull distributions with the same setting as the exponential, but now with a shape parameter $\tau = 3$. (i.e., TTP was generated from $Weibull(3, 2)$ (i.e., $\tau = 3, \alpha_0 = \log(2)$, $\alpha_1 = 0$), OS_{orig} was generated from $Weibull(3, 1)$ (i.e., $\tau = 3, \beta_0 = \log(1)$, $\beta_1 = 0$), and OS' was generated from $Weibull(3, 2)$ ($\tau = 3, \gamma_0 = \log(2)$, $\gamma_1 = 0$)). Table 4.8 shows the results of parameter estimates from the simulation of Weibull with different sample sizes. The results are quite similar to the exponential model. The mean of the estimates was close to the true parameter values for all three cases. Results of the mean of standard error and the standard deviation for all estimates showed a decreasing pattern when the sample sizes increased and they are very close to each other for each estimate. Unlike the exponential case, the result of bias gave a more clear trend in Weibull. Bias tended to be closer to zero (i.e. unbiased) when sample sizes were getting larger.

Table 4.9 shows the results of empirical Type I error for both joint exponential and joint Weibull models under the Wald test. The hypotheses at $\alpha = 0.05$ are

$$H_0 : \alpha_1 = 0 \text{ vs. } H_1 : \alpha_1 \neq 0;$$

$$H_0 : \beta_1 = 0 \text{ vs. } H_1 : \beta_1 \neq 0;$$

and

$$H_0 : \gamma_1 = 0 \text{ vs. } H_1 : \gamma_1 \neq 0.$$

Table 4.8: Simulation results of Weibull with $\tau = 3$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

(a) $n = 200$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\tau}$	3.021	0.166	0.167	0.021
$\hat{\alpha}_0$	0.703	0.133	0.137	0.010
$\hat{\alpha}_1$	-0.013	0.179	0.177	-0.013
$\hat{\beta}_0$	0.014	0.184	0.187	0.014
$\hat{\beta}_1$	-0.014	0.253	0.268	-0.014
$\hat{\gamma}_0$	0.670	0.323	0.328	-0.023
$\hat{\gamma}_1$	0.012	0.435	0.456	0.012

(b) $n = 500$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\tau}$	3.011	0.105	0.102	0.011
$\hat{\alpha}_0$	0.702	0.084	0.086	0.008
$\hat{\alpha}_1$	-0.003	0.112	0.116	-0.003
$\hat{\beta}_0$	0.007	0.116	0.117	0.007
$\hat{\beta}_1$	-0.017	0.160	0.157	-0.017
$\hat{\gamma}_0$	0.698	0.198	0.207	0.005
$\hat{\gamma}_1$	-0.006	0.267	0.289	-0.006

(c) $n = 1000$

Estimates	Mean	Mean of SE	SD	Bias
τ	3.005	0.074	0.073	0.005
α_0	0.699	0.059	0.059	0.006
α_1	-0.007	0.079	0.081	-0.007
β_0	-0.002	0.082	0.083	0.002
β_1	0.002	0.113	0.112	0.002
γ_0	0.670	0.139	0.147	0.006
γ_1	-0.002	0.187	0.191	-0.002

Table 4.9: Empirical type one error for exponential and Weibull with $H_0 : \alpha_1 = 0$ vs. $H_1 : \alpha_1 \neq 0$; $H_0 : \beta_1 = 0$ vs. $H_1 : \beta_1 \neq 0$; and $H_0 : \gamma_1 = 0$ vs. $H_1 : \gamma_1 \neq 0$.

	Joint Exponential			Joint Weibull		
Parameters	$n = 200$	$n = 500$	$n = 1000$	$n = 200$	$n = 500$	$n = 1000$
α_1	0.062	0.050	0.054	0.064	0.050	0.054
β_1	0.076	0.046	0.050	0.080	0.046	0.048
γ_1	0.060	0.048	0.044	0.052	0.062	0.056

The purpose of computing empirical Type I error probability is to check whether it is approximately equal to the nominal value of $\alpha = 0.05$. To check the results from the table, an interval of (0.031, 0.069) will be calculated based on the following equation:

$$0.05 \pm 1.96 \times \sqrt{\frac{0.05(0.95)}{500}}.$$

Therefore, Table 4.9 shows that the results of the empirical Type I error for all the parameters are inside the interval for both joint exponential and Weibull models, except β_1 in sample size of 200, where both exponential and Weibull fall outside the interval. From the table, both β_1 and γ_1 obtained empirical Type I error close to 0.05 when n=500 and 1000 in joint exponential model. In joint Weibull model, β_1 obtained the empirical Type I error close to 0.05 when $n = 500$ and 1000. Also, the empirical Type I error for α_1 is exactly 0.05 at $n = 500$ in both models. Therefore, in general, the empirical Type I error approaches 0.05 as the sample size increases.

The above two simulations in exponential and Weibull models were both dealing with the null case of slope parameters with different sample sizes. In the following scenarios, all the slope parameters will be changed to the value of 0.5 instead. For example, TTP was generated from $Exp(\exp(\log(2) + 0.5X))$, OS_{orig} was generated from $Exp(\exp(0.5X))$, and OS' was generated from $Exp(\exp(\log(2) + 0.5X))$ (i.e., $\alpha_0 = \gamma_0 = \log(2), \beta_0 = \log(1), \alpha_1 = \beta_1 = \gamma_1 = 0.5$); or TTP was generated from $Weibull(3, \exp(\log(2) + 0.5X))$, OS_{orig} was generated from

$Weibull(3,\ \exp(0.5X))$, and OS' was generated from $Weibull(3,\ \exp(\log(2) + 0.5X))$ (i.e., $\tau = 3, \alpha_0 = \gamma_0 = \log(2), \beta_0 = \log(1), \alpha_1 = \beta_1 = \gamma_1 = 0.5$))

Tables 4.10 and 4.11 show the results of parameter estimates from the simulation of exponential and Weibull with $n = 200, 500$, and 1000, respectively. Similar to the previous results, the mean of standard error and the standard deviation for all the parameter estimates were close to each other and decreasing as the sample sizes were increasing in both models. The means of the estimates were still close to their true parameter values in all the cases. No obvious differences could be found when the slope parameters have been changed, compared to the null cases.

Table 4.12 gives the results of empirical power for both joint exponential and joint Weibull models with different sample sizes. The hypotheses at $\alpha = 0.05$ are:

$$H_0 : \alpha_1 = 0 \text{ vs. } H_1 : \alpha_1 \neq 0;$$

$$H_0 : \beta_1 = 0 \text{ vs. } H_1 : \beta_1 \neq 0;$$

and

$$H_0 : \gamma_1 = 0 \text{ vs. } H_1 : \gamma_1 \neq 0.$$

The power of a test represents the probability of rejecting the null hypothesis H_0 given that H_1 is true. Table 4.12 shows the power of the test when the true values of the parameters are $\alpha_1 = \beta_1 = \gamma_1 = 0.5$. As seen in the table, power increases as the sample size increases for tests of all the parameters, although the increase is slower for γ_1 in the Weibull model. Power of 0.80 is usually considered adequate. The power of the tests are greater than 0.8 for the sample sizes of 500 and 1000 in both joint exponential and Weibull models for all parameters except γ_1 in Weibull when $n = 500$. In addition, a sample size of 200 is unavailable to obtain power for β_1 in both models since their type I errors are not inside the interval. For γ_1,

Table 4.10: Simulation results of exponential with $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

(a) $n = 200$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\alpha}_0$	0.697	0.126	0.127	0.004
$\hat{\alpha}_1$	0.489	0.177	0.173	-0.011
$\hat{\beta}_0$	0.008	0.178	0.179	0.008
$\hat{\beta}_1$	0.487	0.250	0.267	-0.012
$\hat{\gamma}_0$	0.692	0.148	0.148	-0.002
$\hat{\gamma}_1$	0.498	0.197	0.200	-0.002

(b) $n = 500$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\alpha}_0$	0.699	0.080	0.081	0.006
$\hat{\alpha}_1$	0.497	0.111	0.114	-0.003
$\hat{\beta}_0$	0.004	0.113	0.114	0.004
$\hat{\beta}_1$	0.486	0.158	0.155	-0.014
$\hat{\gamma}_0$	0.696	0.093	0.088	0.003
$\hat{\gamma}_1$	0.500	0.124	0.121	0

(c) $n = 1000$

Estimates	Mean	Mean of SE	SD	Bias
α_0	0.698	0.056	0.057	0.005
α_1	0.494	0.079	0.080	-0.006
β_0	-0.003	0.080	0.082	-0.003
β_1	0.502	0.111	0.110	0.002
γ_0	0.698	0.066	0.064	0.005
γ_1	0.497	0.087	0.086	-0.003

Table 4.11: Simulation results of Weibull with $\tau = 3$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

(a) $n = 200$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\tau}$	3.022	0.159	0.158	0.022
$\hat{\alpha}_0$	0.703	0.133	0.137	0.010
$\hat{\alpha}_1$	0.493	0.178	0.175	-0.007
$\hat{\beta}_0$	0.014	0.183	0.186	0.014
$\hat{\beta}_1$	0.491	0.251	0.270	-0.009
$\hat{\gamma}_0$	0.671	0.321	0.327	-0.022
$\hat{\gamma}_1$	0.521	0.375	0.393	0.021

(b) $n = 500$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\tau}$	3.012	0.100	0.098	0.012
$\hat{\alpha}_0$	0.702	0.084	0.086	0.009
$\hat{\alpha}_1$	0.499	0.112	0.114	-0.001
$\hat{\beta}_0$	0.007	0.116	0.117	0.007
$\hat{\beta}_1$	0.487	0.159	0.155	-0.013
$\hat{\gamma}_0$	0.699	0.197	0.208	0.006
$\hat{\gamma}_1$	0.502	0.230	0.238	0.002

(c) $n = 1000$

Estimates	Mean	Mean of SE	SD	Bias
τ	3.006	0.071	0.068	0.006
α_0	0.699	0.059	0.059	0.006
α_1	0.494	0.079	0.080	-0.005
β_0	-0.002	0.082	0.083	-0.002
β_1	0.503	0.112	0.111	0.003
γ_0	0.700	0.139	0.147	0.006
γ_1	0.495	0.162	0.167	-0.005

Table 4.12: Empirical power for exponential and Weibull with $H_0 : \alpha_1 = 0$ vs. $H_1 : \alpha_1 \neq 0$; $H_0 : \beta_1 = 0$ vs. $H_1 : \beta_1 \neq 0$; and $H_0 : \gamma_1 = 0$ vs. $H_1 : \gamma_1 \neq 0$. (when true values are $\alpha_1 = 0.5$, $\beta_1 = 0.5$, and $\gamma_1 = 0.5$).

	Joint Exponential			Joint Weibull		
Parameters	$n = 200$	$n = 500$	$n = 1000$	$n = 200$	$n = 500$	$n = 1000$
α_1	0.816	0.998	1	0.818	0.998	1
β_1	–	0.874	0.996	–	0.876	0.996
γ_1	0.712	0.982	1	0.260	0.586	0.874

a sample size of 200 is adequate for the exponential model, but not adequate for Weibull model.

Other simulations are performed as well. All the parameters are the same as those described above, except the values of slope parameters and the shape parameter in Weibull. The slope parameters will be modified to $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$, based on the results of HCC dataset (see Table 5.1). The shape parameter will be changed to $\tau = 0.8$ in joint Weibull model. Tables 4.13 and 4.14 give the results of parameter estimates from the simulation of exponential and Weibull with n = 200, 500, and 1000, respectively. As seen in the tables, the means of the estimates were close to their true parameter values in all the cases. In addition, the mean of standard error and the standard deviation for all the parameter estimates were close to each other and decreasing when the sample sizes were increasing in both models.

Table 4.15 gives the results of empirical power for both joint exponential and joint Weibull models with different sample sizes when true values of the slope parameters are $\alpha_1 = 0.8$, $\beta_1 = 0.7$, and $\gamma_1 = 0.2$. The hypothesis tests at $\alpha = 0.05$ are still the same. As seen in the table, the power of the test for α_1 equals 1 in all cases. Power of the test for β_1 and γ_1 increases as the sample size increases, but the increase for γ_1 is much slower in both exponential and Weibull models. Moreover, a sample size of 200 is still not adequate to obtain power of .80 for β_1 in both models. The power of the tests for γ_1 are not adequate

Table 4.13: Simulation results of exponential with $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0, \alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

(a) $n = 200$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\alpha}_0$	0.697	0.126	0.127	0.004
$\hat{\alpha}_1$	0.790	0.175	0.170	-0.010
$\hat{\beta}_0$	0.008	0.178	0.179	0.008
$\hat{\beta}_1$	0.685	0.254	0.266	-0.015
$\hat{\gamma}_0$	0.692	0.148	0.148	-0.002
$\hat{\gamma}_1$	0.197	0.197	0.200	-0.003

(b) $n = 500$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\alpha}_0$	0.699	0.080	0.081	0.006
$\hat{\alpha}_1$	0.798	0.110	0.113	-0.002
$\hat{\beta}_0$	0.004	0.113	0.114	0.004
$\hat{\beta}_1$	0.684	0.161	0.157	-0.016
$\hat{\gamma}_0$	0.696	0.093	0.088	0.003
$\hat{\gamma}_1$	0.198	0.124	0.123	-0.002

(c) $n = 1000$

Estimates	Mean	Mean of SE	SD	Bias
α_0	0.698	0.056	0.057	0.005
α_1	0.794	0.078	0.080	-0.006
β_0	-0.003	0.080	0.082	-0.003
β_1	0.701	0.113	0.113	0.001
γ_0	0.698	0.066	0.064	0.005
γ_1	0.195	0.088	0.086	-0.005

Table 4.14: Simulation results of Weibull with $\tau = 0.8$, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_0 = \log(1) = 0, \alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

(a) $n = 200$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\tau}$	0.806	0.037	0.036	0.006
$\hat{\alpha}_0$	0.703	0.131	0.134	0.010
$\hat{\alpha}_1$	0.795	0.178	0.173	-0.005
$\hat{\beta}_0$	0.014	0.182	0.184	0.014
$\hat{\beta}_1$	0.690	0.256	0.270	-0.010
$\hat{\gamma}_0$	0.696	0.147	0.146	0.003
$\hat{\gamma}_1$	0.198	0.193	0.195	-0.002

(b) $n = 500$

Estimates	Mean	Mean of SE	SD	Bias
$\hat{\tau}$	0.802	0.024	0.023	0.002
$\hat{\alpha}_0$	0.701	0.083	0.085	0.007
$\hat{\alpha}_1$	0.799	0.111	0.114	-0.001
$\hat{\beta}_0$	0.006	0.115	0.116	0.006
$\hat{\beta}_1$	0.686	0.162	0.159	-0.014
$\hat{\gamma}_0$	0.699	0.092	0.091	0.006
$\hat{\gamma}_1$	0.197	0.121	0.121	-0.003

(c) $n = 1000$

Estimates	Mean	Mean of SE	SD	Bias
τ	0.801	0.017	0.017	0.001
α_0	0.699	0.058	0.058	0.006
α_1	0.795	0.079	0.081	-0.005
β_0	-0.002	0.081	0.084	-0.002
β_1	0.702	0.114	0.114	0.002
γ_0	0.700	0.065	0.066	0.007
γ_1	0.195	0.086	0.086	-0.005

Table 4.15: Empirical power for exponential and Weibull with $H_0 : \alpha_1 = 0$ vs. $H_1 : \alpha_1 \neq 0$; $H_0 : \beta_1 = 0$ vs. $H_1 : \beta_1 \neq 0$; and $H_0 : \gamma_1 = 0$ vs. $H_1 : \gamma_1 \neq 0$. (when true values are $\alpha_1 = 0.8$, $\beta_1 = 0.7$, and $\gamma_1 = 0.2$).

	Joint Exponential			Joint Weibull		
Parameters	$n = 200$	$n = 500$	$n = 1000$	$n = 200$	$n = 500$	$n = 1000$
α_1	1	1	1	1	1	1
β_1	0.77	0.996	1	0.774	0.994	1
γ_1	0.186	0.35	0.606	0.18	0.362	0.63

for all cases.

Figures 1-18 in Appendix A show the normal quantile plots of the slope parameter estimates for both exponential and Weibull models in different simulation scenarios. In general, all the estimates follow the normal distribution, even for the small sample size.

Chapter 5

Application to Real Data

5.1 Hepatocellular Carcinoma Dataset

Li et al. (2014) and Rathwell (2017) conducted an analysis on the study of HCC. Li et al. (2014) applied Kaplan-Meier estimation and log-rank test and showed statistically significant results of CXCL17 levels with respect to OS and TTP, based on an unadjusted model. Rathwell (2017) applied a Wald test to check whether there is any significant difference between the levels of CXCL17 based on three different models: joint exponential, joint Weibull and naïve Weibull models. A naïve Weibull model is an intercept-only model that can be directly fitted using the function *survreg()* in R (Therneau, 2019). She found out that there was no strong evidence to support the difference between the levels of CXCL17 for any of the parameters in all the models.

In this chapter, the HCC dataset will be used to demonstrate the use of the regression model for the distributions of Weibull and exponential and also to test for a difference between the CXCL17 levels using Wald tests. As mentioned earlier, CXCL17 is a categorical variable with two levels: 0 represents the low level and 1 represents the high level. The median of the original variable had been computed to define the levels of CXCL17. The

numbers below the median were considered as low level; and those above the median were considered as high level.

Table 5.1: Parameter estimates based on CXCL17 level within HCC dataset, for joint exponential and joint Weibull models.

	Parameter Estimates						
Model	$\hat{\tau}$	$\hat{\alpha}_0$	$\hat{\alpha}_1$	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\gamma}_0$	$\hat{\gamma}_1$
	$SE(\hat{\tau})$	$SE(\hat{\alpha}_0)$	$SE(\hat{\alpha}_1)$	$SE(\hat{\beta}_0)$	$SE(\hat{\beta}_1)$	$SE(\hat{\gamma}_0)$	$SE(\hat{\gamma}_1)$
Joint Exponential	N/A	-4.335	0.787	-5.767	0.665	-3.614	0.216
		0.147	0.189	0.302	0.397	0.196	0.246
Joint Weibull	0.760	-3.445	0.730	-4.876	0.606	-2.836	0.217
	0.044	0.218	0.190	0.342	0.397	0.241	0.246

Table 5.1 gives the parameter estimates for both joint exponential and joint Weibull models with respect to CXCL17. As seen in Table 5.2, Wald tests have been used to test the slope parameters, α_1, β_1, and γ_1, for both models to examine if there is any significant difference between the levels of CXCL17 with respect to OS, TTP, and PFS. For TTP, both joint exponential and Weibull models indicate evidence against the null hypothesis that parameter $\alpha_1 = 0$ (p-value = 0.00003127 and 0.000122, respectively), which means there is a significant difference between the CXCL17 levels with respect to TTP. Furthermore, both models show that there are no evidences for differences between the levels of CXCL17 with respect to OS and PFS. In addition, a Wald test show a significant result and give a p-value of < 0.0001 against the null hypothesis that $\tau = 1$. Therefore, the joint Weibull model is more preferable to apply in the HCC study.

Table 5.2: Wald test results for both joint exponential and joint Weibull models.

	p-value for joint exponential model	p-value for joint Weibull model
τ	N/A	< 0.0001
α_1	0.00003127	0.000122
β_1	0.094	0.127
γ_1	0.380	0.378

Chapter 6

Conclusion And Further Work

In this study, both joint exponential and joint Weibull models have been proposed to describe the dependence structure between OS and PFS, based on the extension of Fleischer et al. (2009) and Li and Zhang (2015). The regression approach is introduced to investigate the covariate effect on the distribution parameters for OS, TTP, and PFS. The simulations have been conducted with various slope parameters at sample sizes of 200, 500, and 1000. In each scenario, the mean of the parameter estimates, the mean of their estimated standard errors, standard deviation of the parameter estimates and the bias of the parameter estimates were computed. The results in both exponential and Weibull models are quite similar. The mean of standard error estimates and the standard deviation for all the parameter estimates were very close to each other and showed decreasing trends as the sample sizes increase in both models. The mean of the estimates was very close to the true parameters in all cases which lead to a small bias.

In addition, the empirical type I error and empirical power for each parameter were computed as well. There are some problems when the sample size is small (e.g., $n = 200$). The empirical Type I error for all the parameters are inside the interval (0.031, 0.069) except β_1 in sample size of 200. In the case of obtaining the power of the test when the true values

of the slope parameters are all equal to 0.5, power increases as the sample size increases for tests of all the parameters, but the increase is slower for γ_1 in the Weibull model. The power of the test is adequate in all cases except γ_1 with a sample size of 200 for Weibull model. For another case to obtain the power of the test when the true values of the slope parameters were modified to $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$, power of the test for β_1 and γ_1 increased as the sample size increased, but the increase for γ_1 is much slower in both exponential and Weibull models. The power of the test for α_1 all equal to 1 in this scenario. And for γ_1, the power of the tests are not adequate in all cases.

Furthermore, the HCC dataset is used to investigate and demonstrate both models. The Wald tests have been performed to investigate a difference between the CXCL17 levels based on the slope parameters. For both joint exponential and Weibull models, there is a significant difference between the levels of CXCL17 with respect to TTP. However, no evidence can be found for differences between the CXCL17 levels with respect to OS and PFS.

This thesis is mainly focused on one categorical variable with only two levels. In the future work, the method of the regression model can be also be used for more variables with various levels. For example, Rathwell (2017) analyzed a study on a nasopharyngeal carcinoma dataset. There are three treatment levels in this dataset. Thus, the regression approach can be extended to one or more categorical variables with more levels, and one or more continuous variables. In addition, the slope parameters are tested individually in the study. Therefore, the likelihood ratio test (LRT) can be applied to perform an overall test (i.e., $H_0 : \alpha_1 = \beta_1 = \gamma_1 = 0$) in future work.

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Appendix A

Normal Quantile Plots For Slope Parameter Estimates

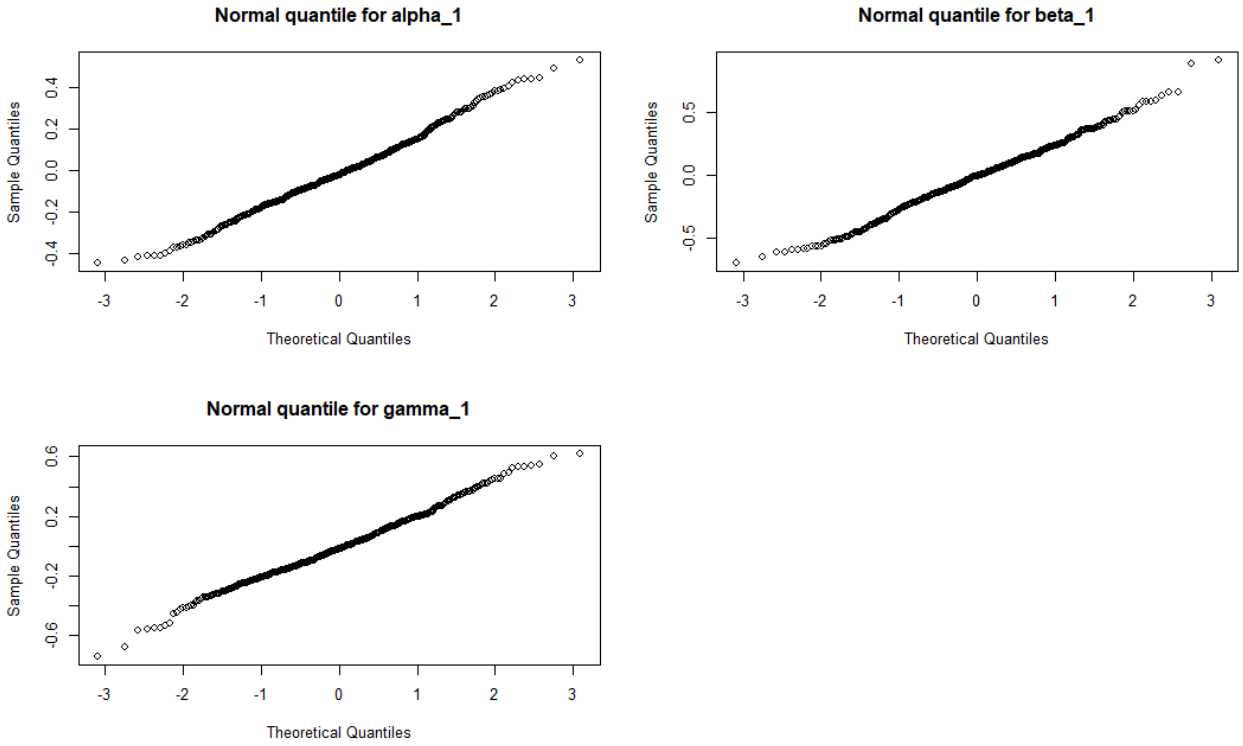

Figure A.1: Normal quantile for exponential with n=200, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

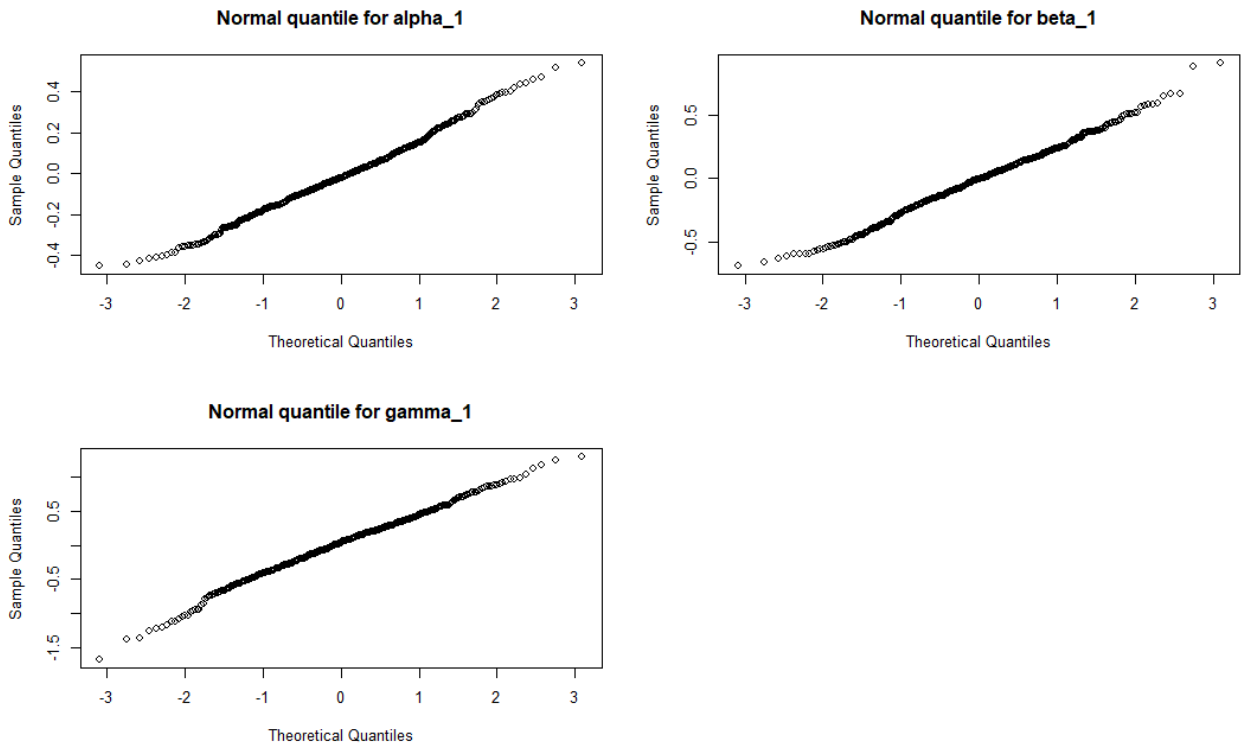

Figure A.2: Normal quantile for Weibull with n=200, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

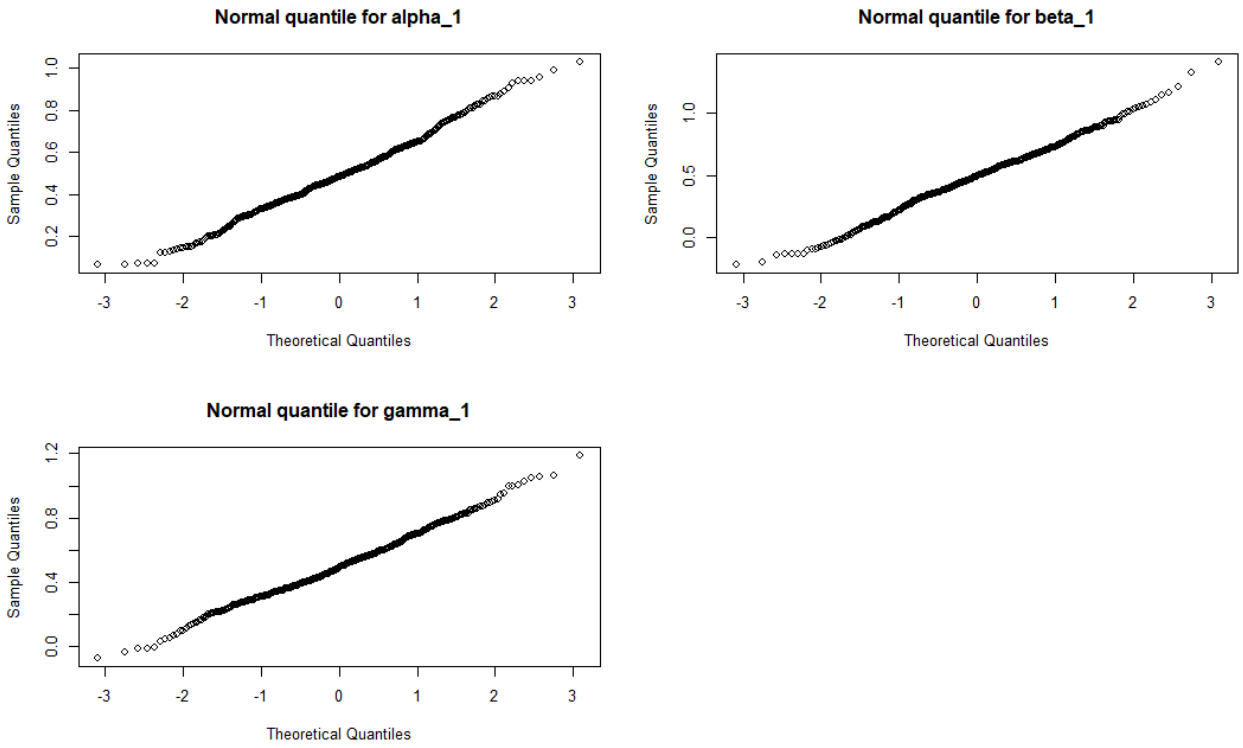

Figure A.3: Normal quantile for exponential with n=200, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

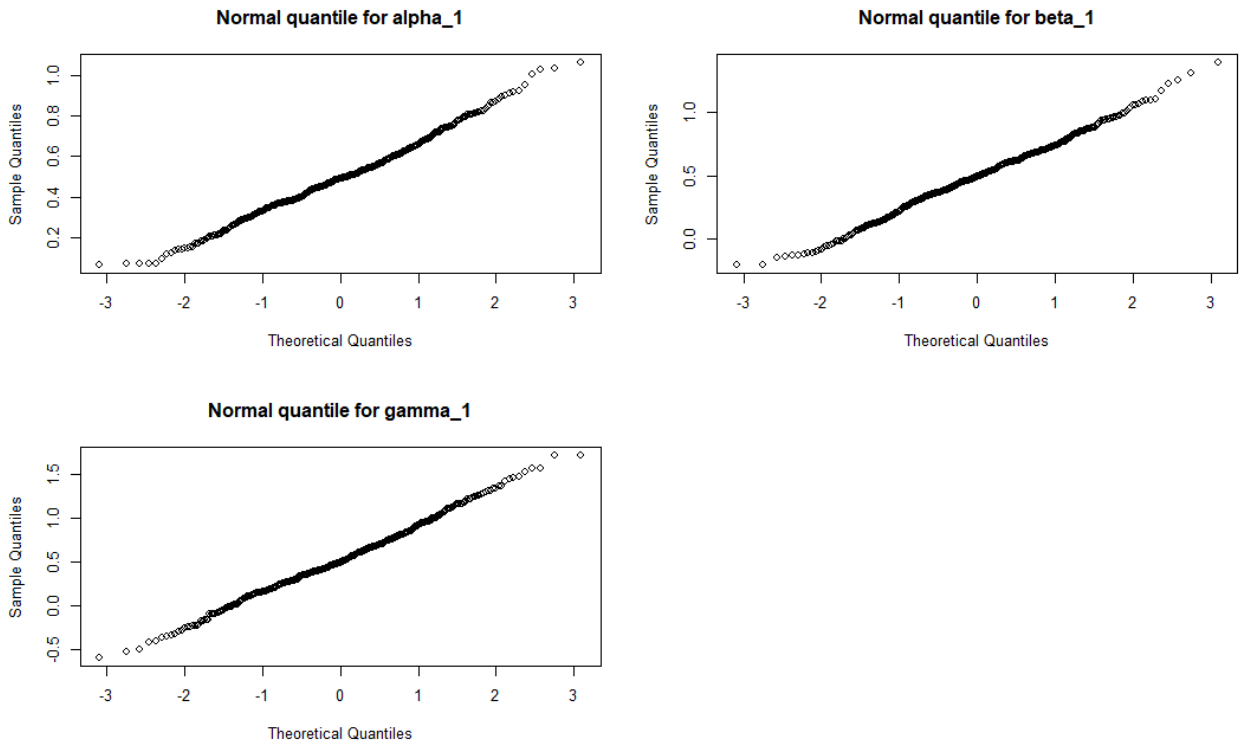

Figure A.4: Normal quantile for Weibull with n=200, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

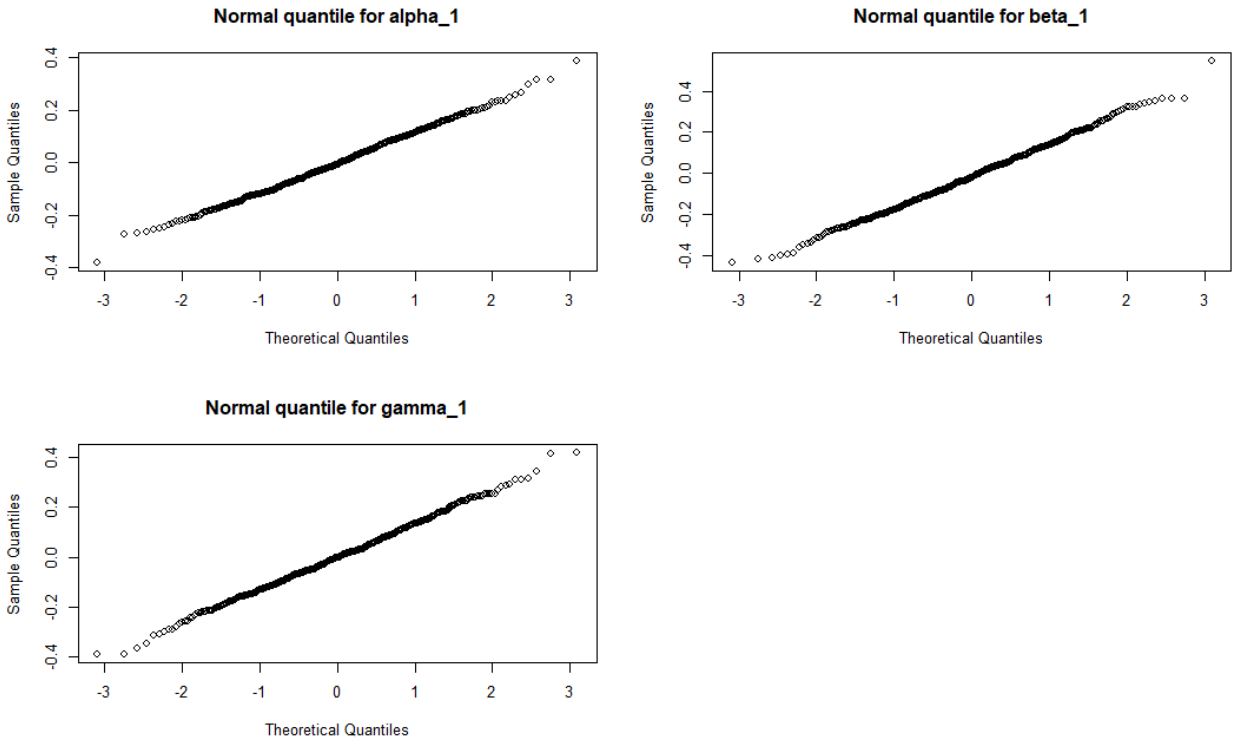

Figure A.5: Normal quantile for exponential with n=500, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

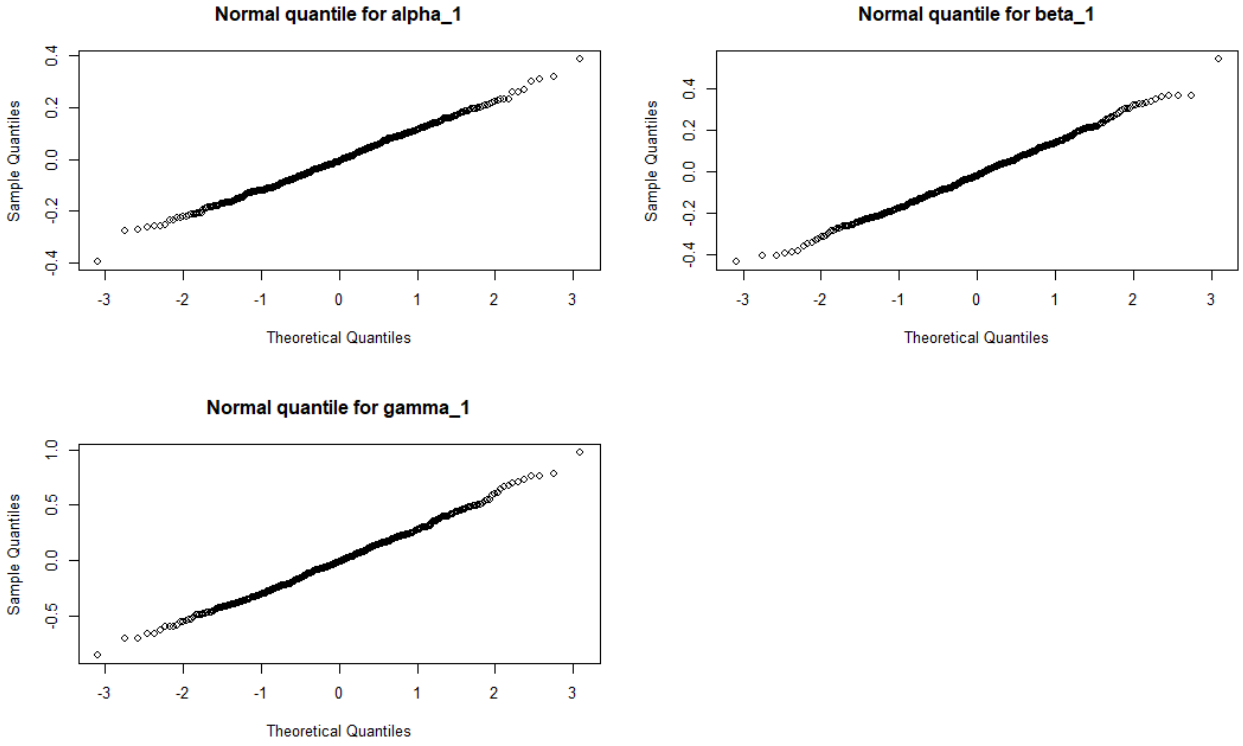

Figure A.6: Normal quantile for Weibull with n=500, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

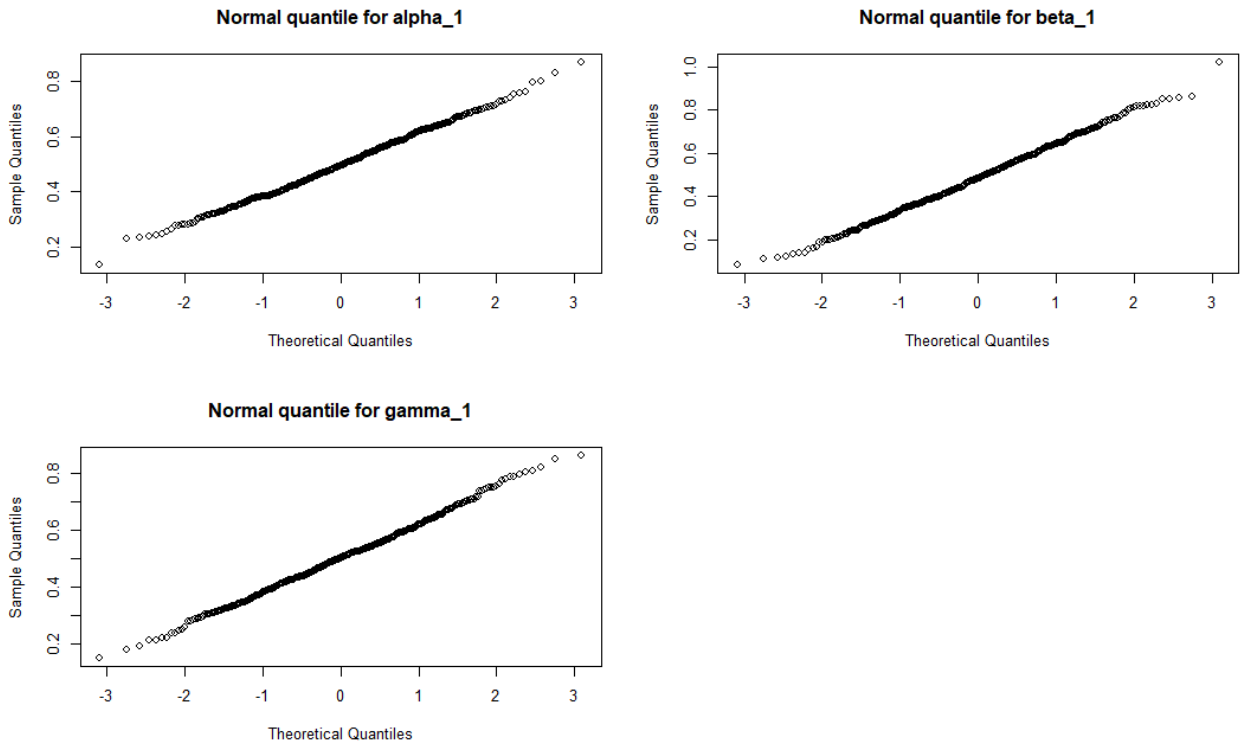

Figure A.7: Normal quantile for exponential with n=500, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

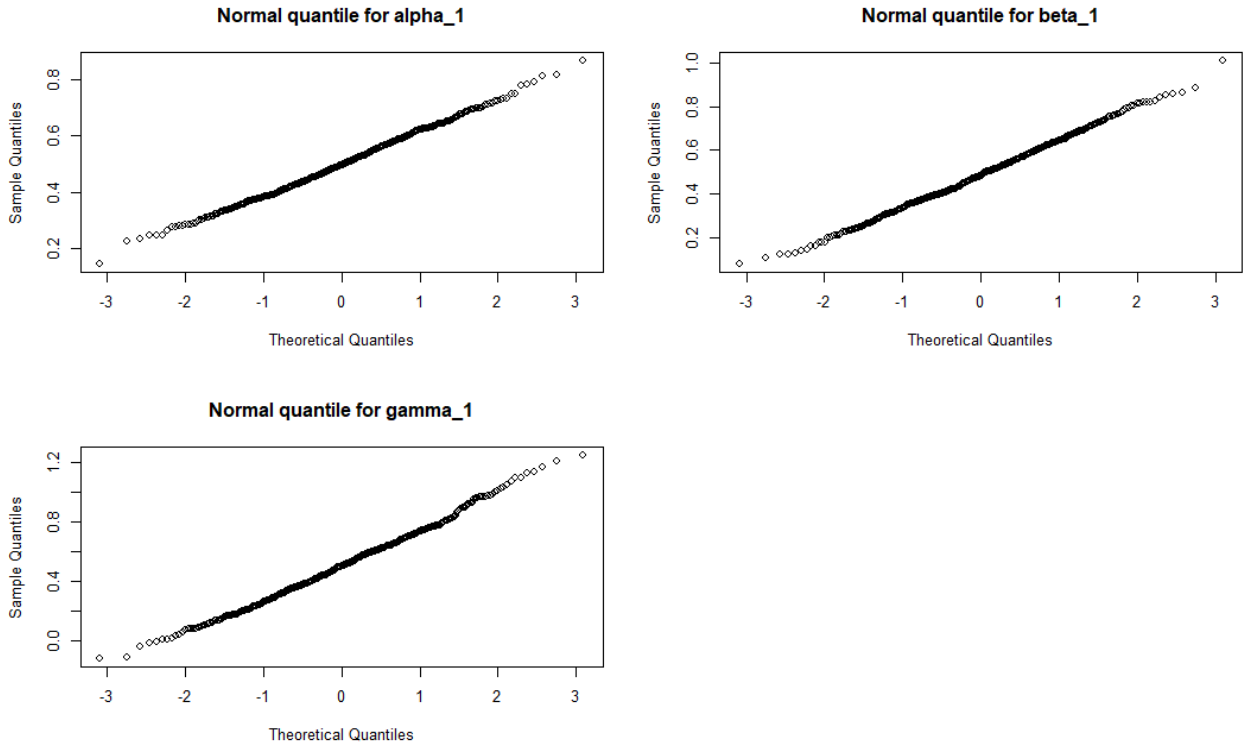

Figure A.8: Normal quantile for Weibull with n=500, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

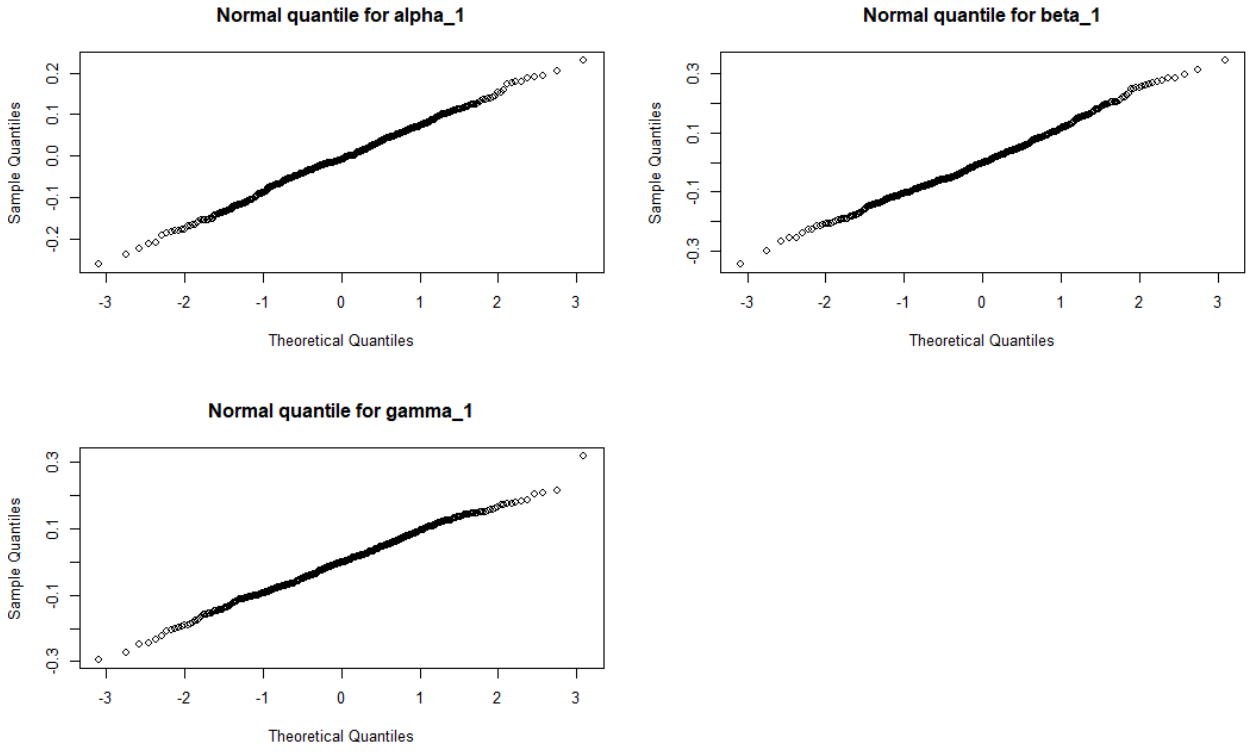

Figure A.9: Normal quantile for exponential with n=1000, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

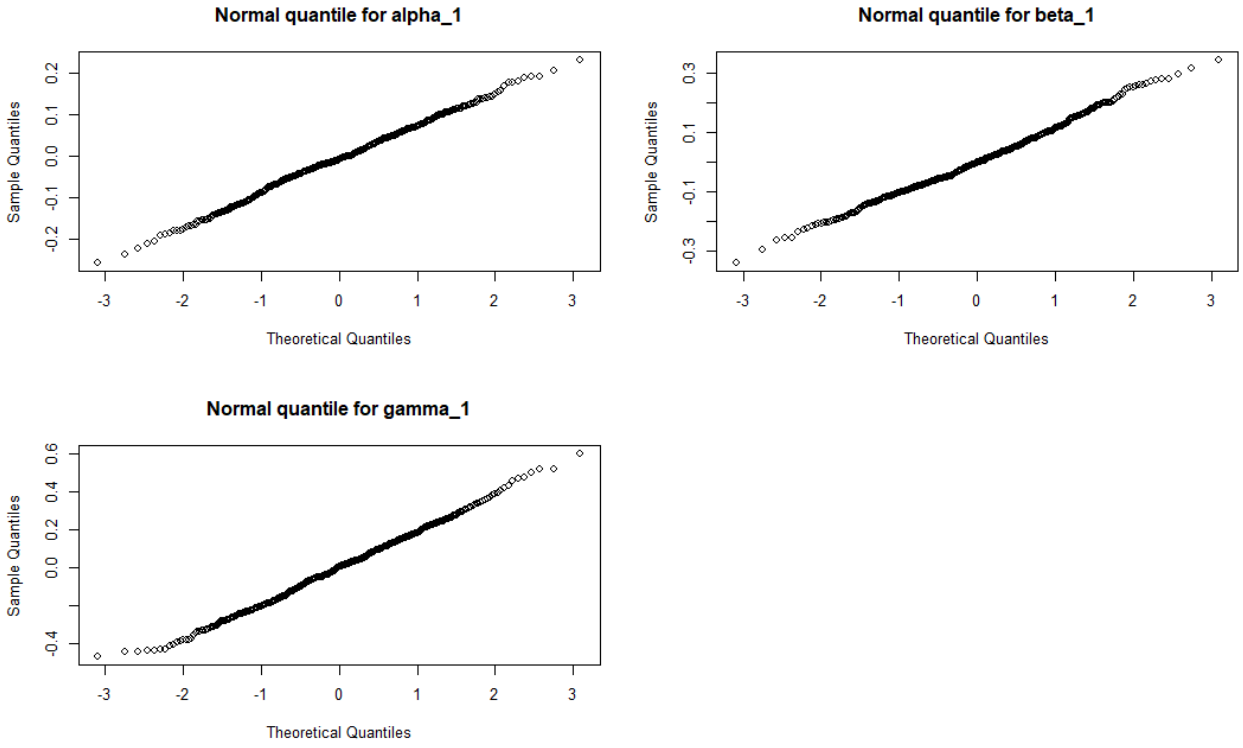

Figure A.10: Normal quantile for Weibull with n=1000, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0$.

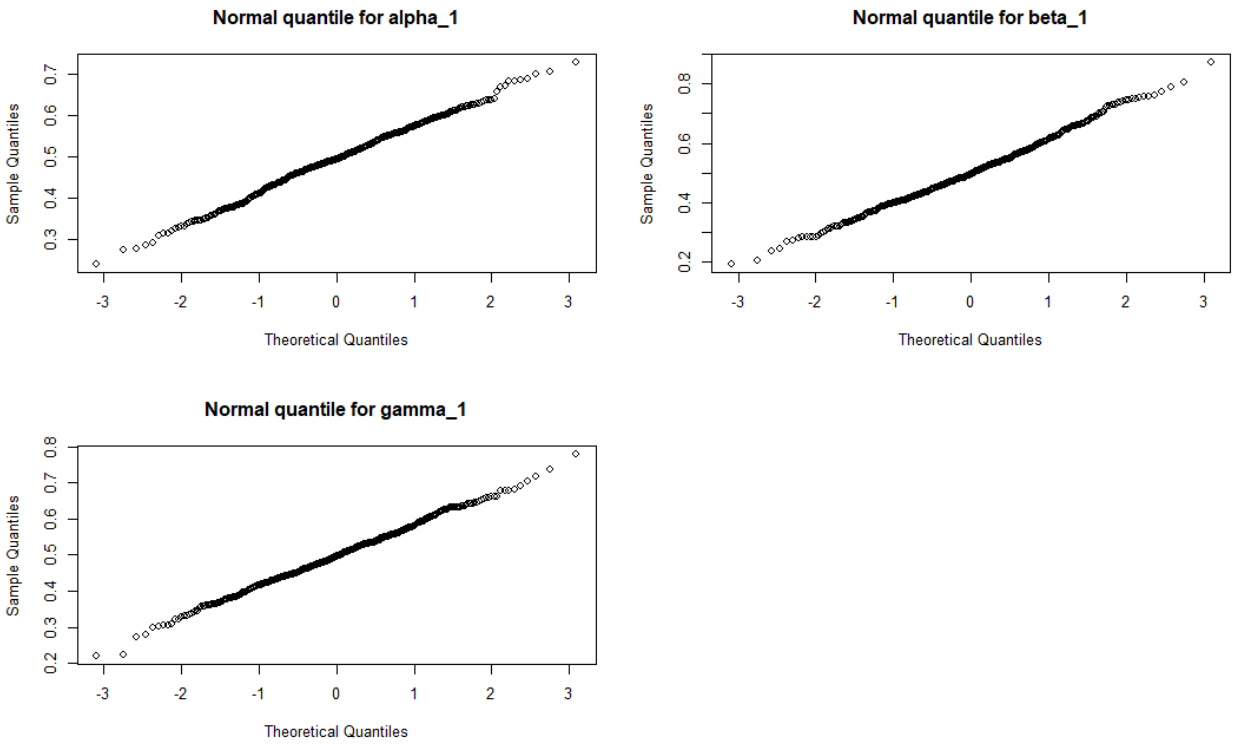

Figure A.11: Normal quantile for exponential with n=1000, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

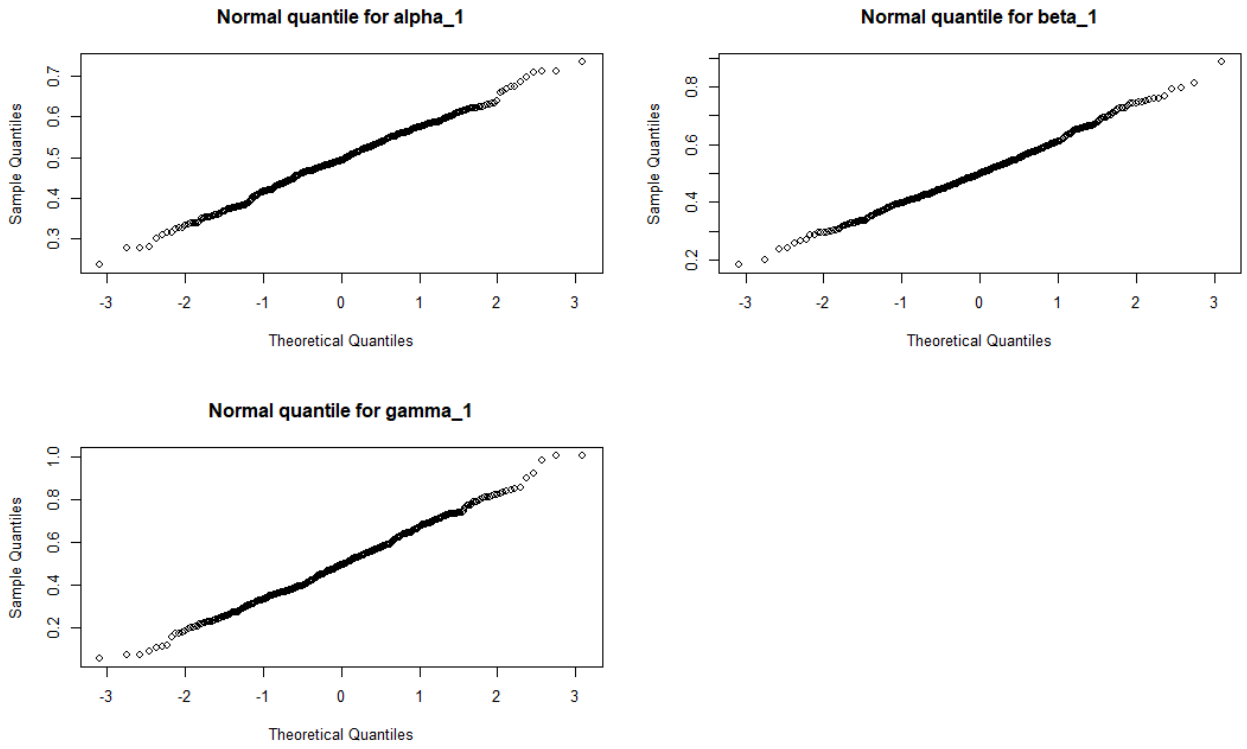

Figure A.12: Normal quantile for Weibull with n=1000, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\beta_1 = \log(1) = 0$, and $\alpha_1 = \beta_1 = \gamma_1 = 0.5$.

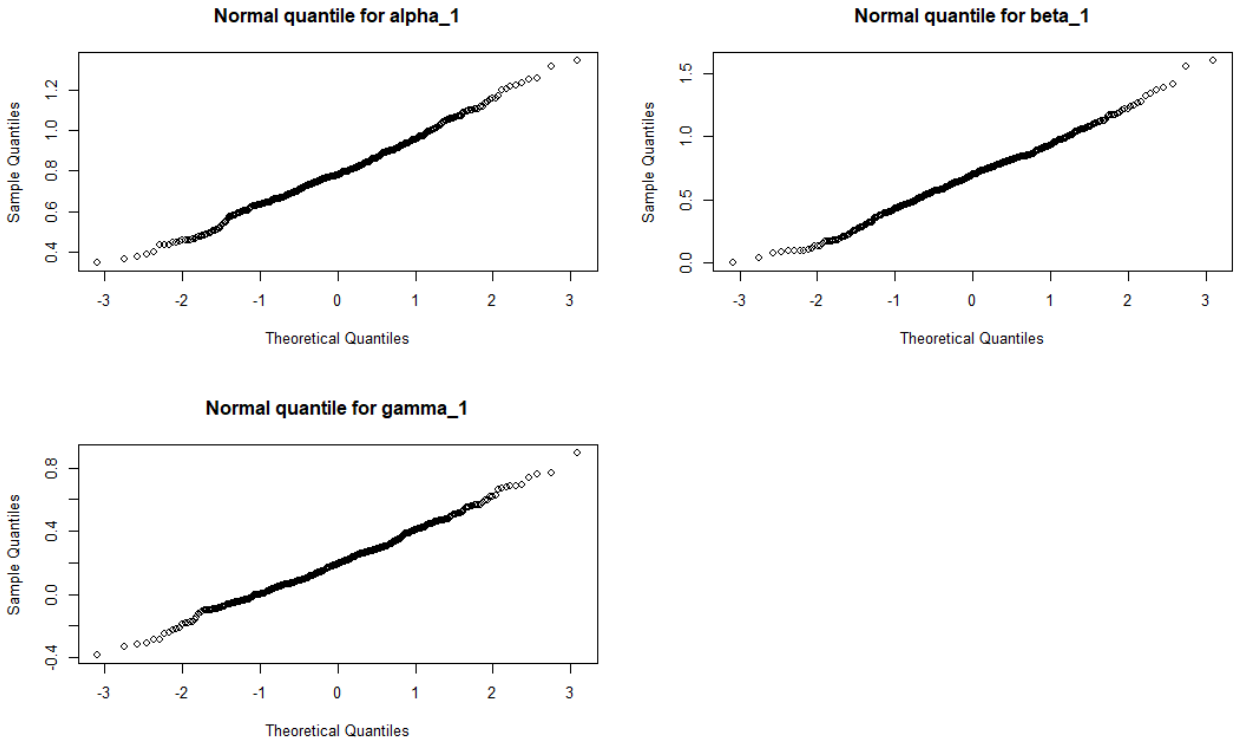

Figure A.13: Normal quantile for exponential based on HCC results with n=200, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

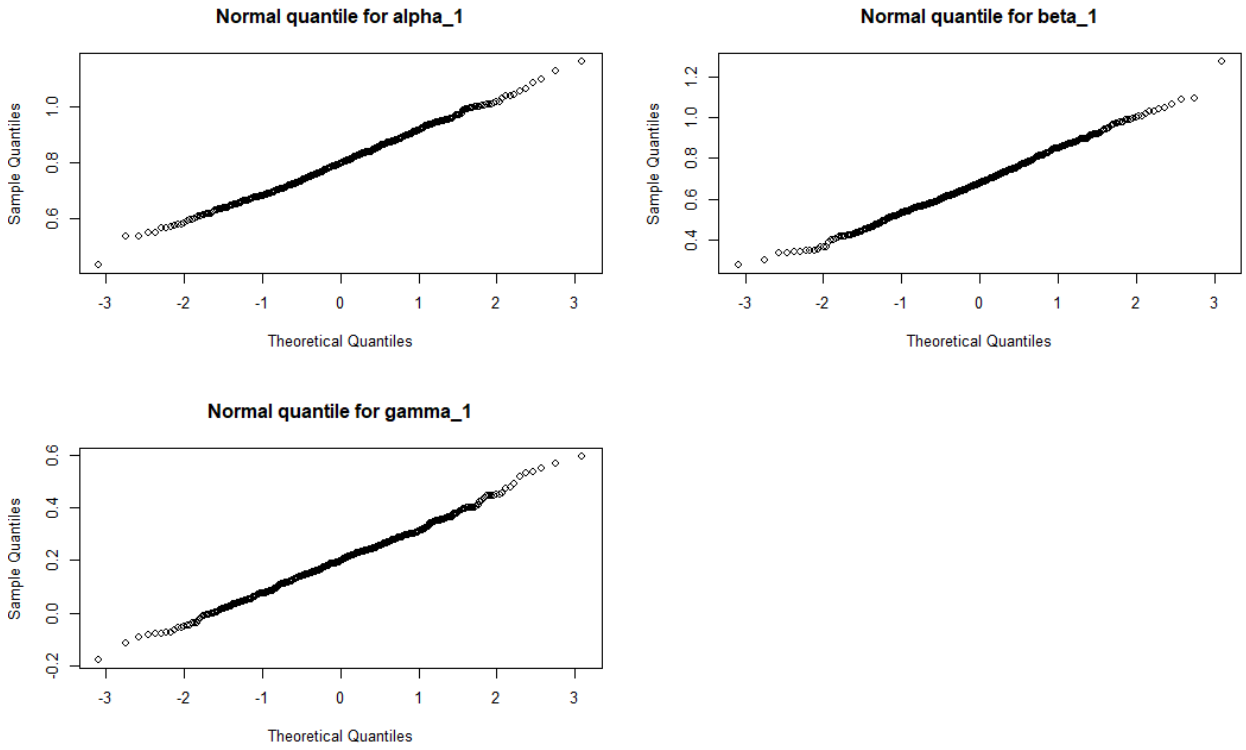

Figure A.14: Normal quantile for exponential based on HCC results with n=500, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

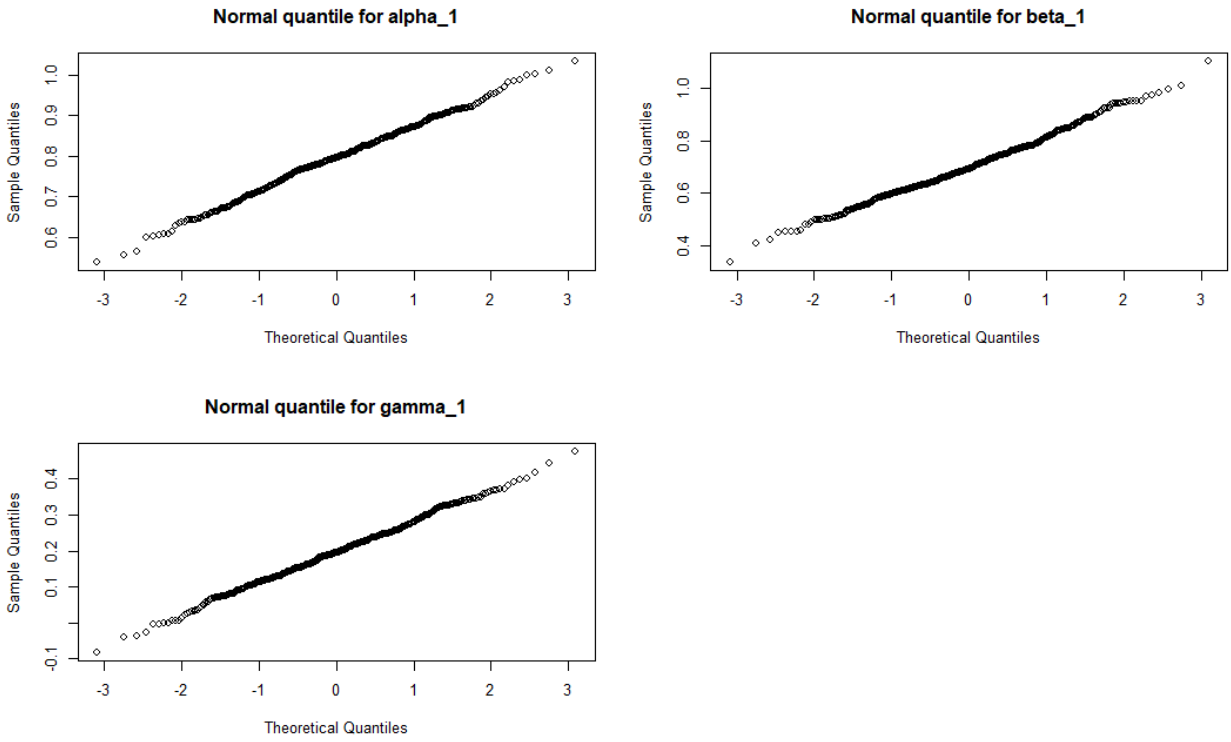

Figure A.15: Normal quantile for exponential based on HCC results with n=1000, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

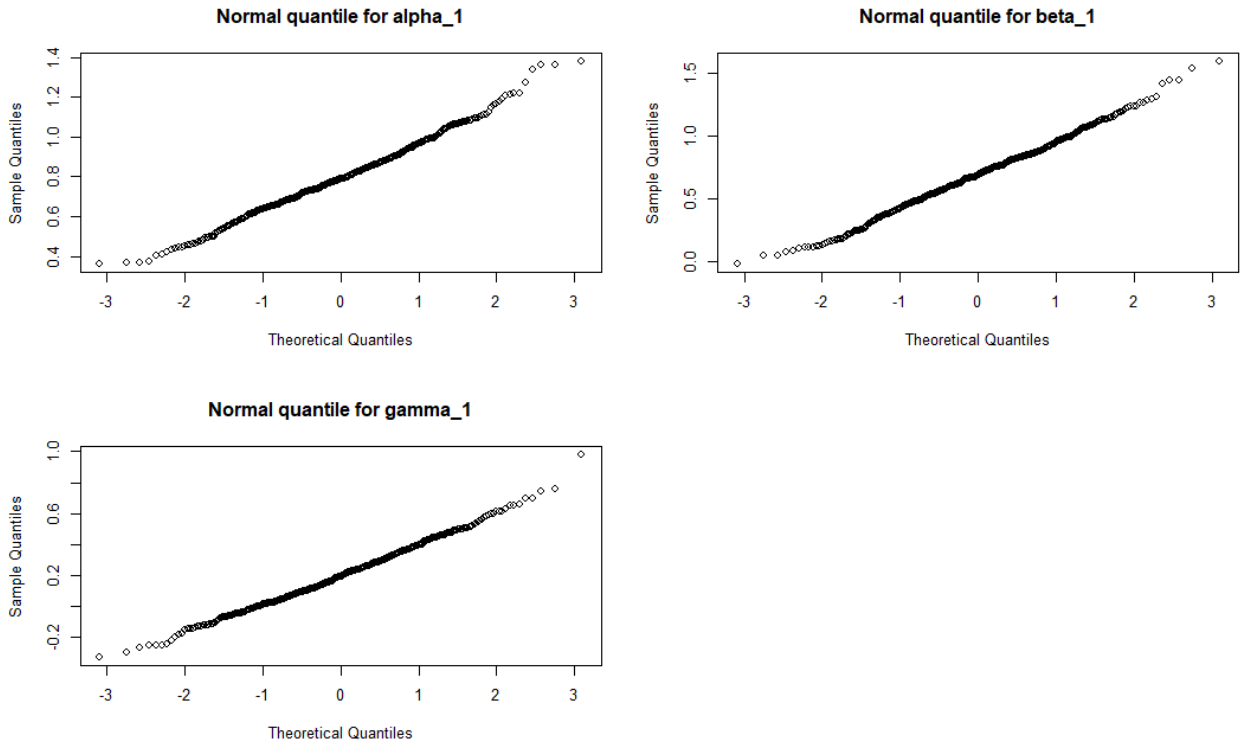

Figure A.16: Normal quantile for Weibull based on HCC results with n=200, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

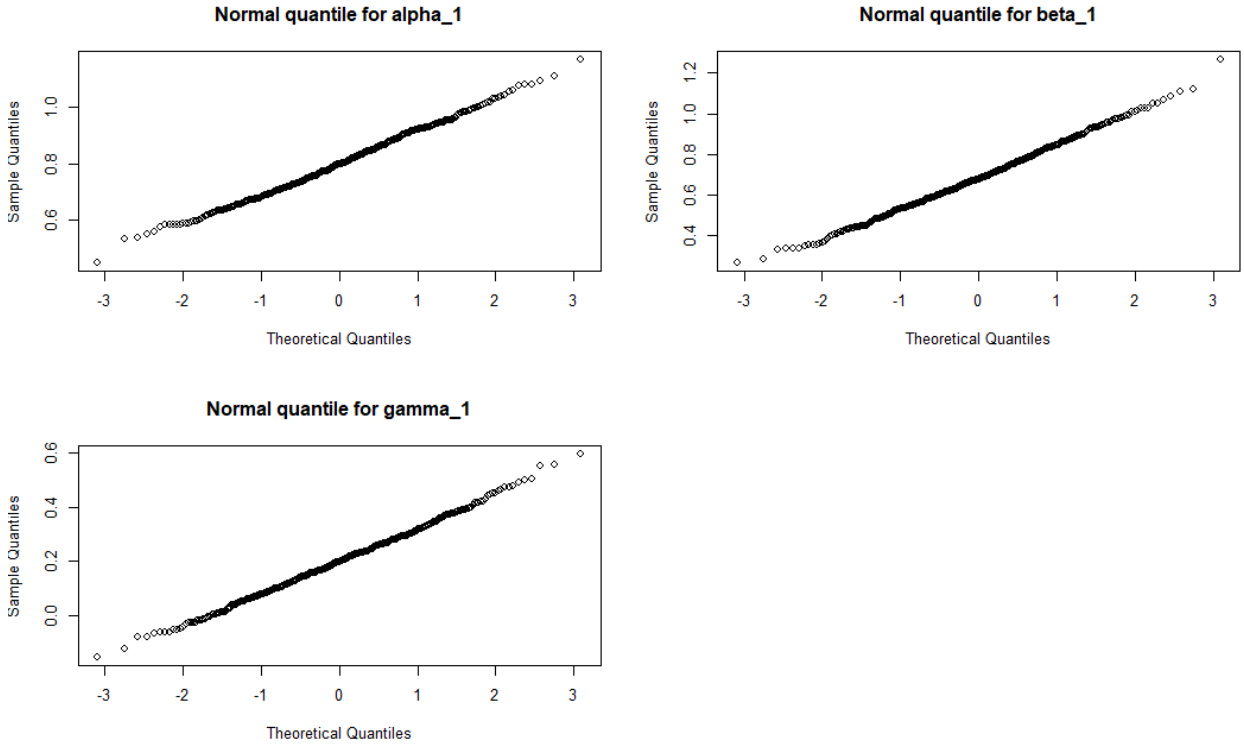

Figure A.17: Normal quantile for Weibull based on HCC results with n=500, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

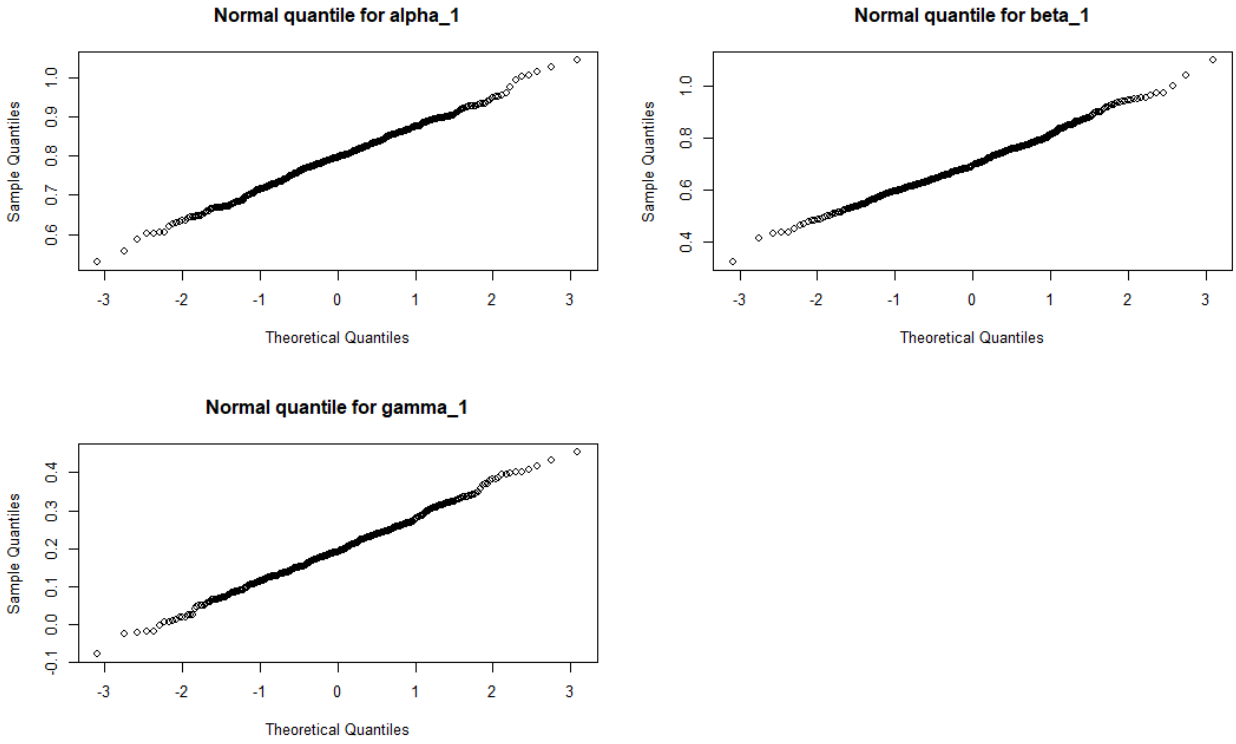

Figure A.18: Normal quantile for Weibull based on HCC results with n=1000, iter=500, $\alpha_0 = \gamma_0 = \log(2) = 0.693$, $\alpha_1 = 0.8, \beta_1 = 0.7$, and $\gamma_1 = 0.2$.

Appendix B

Source Code

The R code is mainly derived from Rathwell (2017).

```
# Likelihood algorithm
# for density function
lf.weib = function (a0, a1, k, t, x){

  (a0 + a1*x) + log(k) + (k-1)*log(t) + (-exp(a0+a1*x) * t^(k))

}

# for survival function
ls.weib = function (a0, a1, k, t, x){

  -exp(a0+a1*x) * t^(k)

}

# Likelihood algorithm for EXPONENTIAL
loglik.exp = function (theta){
  ll = rep(0, length(mydata[,1]))
  for ( i in 1: length(ll)){
    if (mydata$Prog[i] == 1 & mydata$Death[i] == 0){
      ll[i] = lf.weib(theta[1], theta[2], 1, t1[i], x[i]) +
```

```
        ls.weib(theta[3], theta[4], 1, t1[i], x[i]) +
        ls.weib(theta[5], theta[6], 1, t2[i], x[i])
    }

    if (mydata$Prog[i] == 1 & mydata$Death[i] == 1){
      ll[i] = lf.weib(theta[1], theta[2], 1, t1[i], x[i]) +
        ls.weib(theta[3], theta[4], 1, t1[i], x[i]) +
        lf.weib(theta[5], theta[6], 1, t2[i], x[i])
    }

    if (mydata$Prog[i] == 0 & mydata$Death[i] == 1){
      ll[i] = ls.weib(theta[1], theta[2], 1, t1[i], x[i]) +
        lf.weib(theta[3], theta[4], 1, t1[i], x[i])
    }

    if (mydata$Prog[i] == 0 & mydata$Death [i] == 0){
      ll[i] = ls.weib(theta[1], theta[2], 1, t1[i], x[i]) +
        ls.weib(theta[3], theta[4], 1, t1[i], x[i])
    }
  }
  sum(ll)/(-1)
}



# Likelihood algorithm for WEIBULL
loglik.weib = function (theta){
  ll = rep(0, length(mydata[,1]))
  for (i in 1:length(ll)){
    if (mydata$Prog[i] == 1 & mydata$Death[i]==0){
      ll[i] = lf.weib(theta[1], theta[2], theta[7], t1[i], x[i]) +
        ls.weib(theta[3], theta[4], theta[7], t1[i], x[i]) +
        ls.weib(theta[5], theta[6], theta[7], t2[i], x[i])
    }
```

```
    if (mydata$Prog[i] == 1 & mydata$Death[i]==1){
      ll[i] = lf.weib(theta[1], theta[2], theta[7], t1[i], x[i]) +
        ls.weib(theta[3], theta[4], theta[7], t1[i], x[i]) +
        lf.weib(theta[5], theta[6], theta[7], t2[i], x[i])
    }

    if (mydata$Prog[i] == 0 & mydata$Death[i]==1){
      ll[i] = ls.weib(theta[1], theta[2], theta[7], t1[i], x[i]) +
        lf.weib(theta[3], theta[4], theta[7], t1[i], x[i])
    }

    if (mydata$Prog[i] == 0 & mydata$Death[i]==0){
      ll[i] = ls.weib(theta[1], theta[2], theta[7], t1[i], x[i]) +
        ls.weib(theta[3], theta[4], theta[7], t1[i], x[i])
    }
  }
  sum(ll)/(-1)
}

# wald tests
# slope = 0
wald.test <- function(k, s){
  z.stat <- abs(k)/s
  p.val <- 2*pnorm(z.stat, lower.tail=F)
  return(c(z.stat, p.val))
}


# Simulation for exponential

library(dplyr)
# alpha1 = log(2) alpha2 = 0 (TTP)
# beta1 = log(1) beta2 = 0 (OSorig)
```

```
# gamma1 = log(2) gamma2 = 0 (OSprime)

# Using set.seed() allows us to reproduce the same random sample
set.seed(123)

weibf <- function(n, theta0, theta1, x, k){
  u.rv <- runif(n)
  w.rv <- (-(1/exp(theta0 + theta1*x))*log(1-u.rv))^(1/k)
}

n=1000
alpha0=log(2); alpha1=0.8;
beta0=log(1); beta1=0.7;
gamma0=log(2); gamma1=0.2;
k=1

x1 <-rep(0, 500)
x2 <-rep(1, 500)
x <- combine(x1,x2)

iter=500

betamatexp=matrix(0, nrow=iter, ncol=6)
sematexp=matrix(0, nrow=iter, ncol=6)

for (i in 1:iter){

  # generate data
  sim.ttp <- weibf(n, alpha0, alpha1, x, k)
  sim.os <- weibf(n, beta0, beta1, x, k)
  sim.osp <- weibf(n, gamma0, gamma1, x, k)
  mydata <- as.data.frame(cbind(sim.os, sim.ttp, sim.osp))

  # applied a fixed censoring time at 1 year
```

```
  mydata$sim.os <- ifelse(mydata$sim.os < 1, mydata$sim.os, 1)
  mydata$sim.ttp <- ifelse(mydata$sim.ttp < 1, mydata$sim.ttp, 1)
  mydata$Prog <- ifelse((mydata$sim.ttp < mydata$sim.os) & (mydata$sim.ttp
                        < 1), 1, 0)
  mydata$Death <- ifelse(mydata$Prog==1,
                        ifelse((mydata$sim.ttp + mydata$sim.osp < 1), 1, 0),
                        ifelse(mydata$sim.os < 1, 1, 0))

  t1 <- pmin(mydata$sim.ttp, mydata$sim.os)
  t2 <- pmin(mydata$sim.osp, (1 - mydata$sim.ttp))

  options(warn=-1)

  # parameter estimates and se for exp
  mle.sim.exp <- optim(theta <- c(1, 1, 1, 1, 1, 1), loglik.exp, method="BFGS",
                       hessian=T)
  mle.sim.exp$par

  se.sim.exp <- sqrt(diag(solve(optim(theta <- c(1, 1, 1, 1, 1, 1), loglik.exp,
                                      method="BFGS", hessian=T)$hessian)))


  betamatexp[i,]=mle.sim.exp$par
  sematexp[i,]=se.sim.exp

}

colMeans(betamatexp)
colMeans(sematexp)

# standard deviation
sd(betamatexp[,1])
sd(betamatexp[,2])
sd(betamatexp[,3])
```

```
sd(betamatexp[,4])
sd(betamatexp[,5])
sd(betamatexp[,6])

#histograms for each parameter
par(mfrow = c(3,2))
hist(betamatexp[,1], main = "histogram of alpha_0", xlab = "alpha_0")
hist(betamatexp[,2], main = "histogram of alpha_1", xlab = "alpha_1")
hist(betamatexp[,3], main = "histogram of beta_0", xlab = "beta_0")
hist(betamatexp[,4], main = "histogram of beta_1", xlab = "beta_1")
hist(betamatexp[,5], main = "histogram of gamma_0", xlab = "gamma_0")
hist(betamatexp[,6], main = "histogram of gamma_1", xlab = "gamma_1")

# normal quantile for slope parameters
par(mfrow = c(2,2))
qqnorm(betamatexp[,2], main = "Normal quantile for alpha_1")
qqnorm(betamatexp[,4], main = "Normal quantile for beta_1")
qqnorm(betamatexp[,6], main = "Normal quantile for gamma_1")

# Empirical type one error
est=betamatexp[,6] # [,2]-alpha1, [,4]-beta1, [,6]-gamma1
se=sematexp[,6]
p=numeric(iter)

for(j in 1:iter){
  z.stat <- abs(est[j])/se[j] #do test
  p[j]=2*pnorm(z.stat, lower.tail=F) #save p-value
}
phat=mean(p<.05) #Proportion of trials that reject
phat



#Case 1: empirical power under the case of all slope parameters equal to 0.5
#Case 2: empirical power under the case of alpha_1=0.8, beta_1=0.7, gamma_1=0.2
```

```
for(j in 1:iter){
  z.stat <- abs(est[j])/se[j] #do test
  p[j]=2*pnorm(z.stat, lower.tail=F) #calculate p-value
}
phat=mean(p<.05) #Proportion of trials that reject
phat


# Simulation for Weibull
library(dplyr)
# a = 3
# alpha1 = log(2) alpha2 = 0 (TTP)
# beta1 = log(1) beta2 = 0 (OSorig)
# gamma1 = log(2) gamma2 = 0 (OSprime)

# Using set.seed() allows us to reproduce the same random sample
set.seed(123)

weibf <- function(n, theta0, theta1, x, k){
  u.rv <- runif(n)
  w.rv <- (-(1/exp(theta0 + theta1*x))*log(1-u.rv))^(1/k)
}

n=500
alpha0=log(2); alpha1=0; # TTP
beta0=log(1); beta1=0; # OSorig
gamma0=log(2); gamma1=0; # OSprime
k=0.8

x1 <-rep(0, 250)
x2 <-rep(1, 250)
x <- combine(x1,x2)

iter=500
```

```
betamatweib=matrix(0, nrow=iter, ncol=7)
sematweib=matrix(0, nrow=iter, ncol=7)

for (i in 1:iter){

  # generate data
  sim.ttp <- weibf(n, alpha0, alpha1, x, k)
  sim.os <- weibf(n, beta0, beta1, x, k)
  sim.osp <- weibf(n, gamma0, gamma1, x, k)
  mydata <- as.data.frame(cbind(sim.os, sim.ttp, sim.osp))

  # applied a fixed censoring time at 1 year
  mydata$sim.os <- ifelse(mydata$sim.os < 1, mydata$sim.os, 1)
  mydata$sim.ttp <- ifelse(mydata$sim.ttp < 1, mydata$sim.ttp, 1)
  mydata$Prog <- ifelse((mydata$sim.ttp < mydata$sim.os) & (mydata$sim.ttp
                        < 1), 1, 0)
  mydata$Death <- ifelse(mydata$Prog==1,
                         ifelse((mydata$sim.ttp + mydata$sim.osp < 1), 1, 0),
                         ifelse(mydata$sim.os < 1, 1, 0))

  t1 <- pmin(mydata$sim.ttp, mydata$sim.os)
  t2 <- pmin(mydata$sim.osp, (1 - mydata$sim.ttp))

  options(warn=-1)

  # parameter estimates and se for weibull
  mle.sim.weib <- optim(theta <- c(1,1,1,1,1,1,1), loglik.weib, method="BFGS",
                        hessian=T)
  mle.sim.weib$par

  se.sim.weib <- sqrt(diag(solve(optim(theta <- c(1,1,1,1,1,1,1), loglik.weib,
                                 method="BFGS", hessian=T)$hessian)))
```

```
  betamatweib[i,]=mle.sim.weib$par
  sematweib[i,]=se.sim.weib

}

colMeans(betamatweib)
colMeans(sematweib)

# Standard deviation
sd(betamatweib[,1])
sd(betamatweib[,2])
sd(betamatweib[,3])
sd(betamatweib[,4])
sd(betamatweib[,5])
sd(betamatweib[,6])
sd(betamatweib[,7])

# histograms for each parameter
par(mfrow = c(4,2))
hist(betamatweib[,7], main = "histogram of tau", xlab = "tau")
hist(betamatweib[,1], main = "histogram of alpha_0", xlab = "alpha_0")
hist(betamatweib[,2], main = "histogram of alpha_1", xlab = "alpha_1")
hist(betamatweib[,3], main = "histogram of beta_0", xlab = "beta_0")
hist(betamatweib[,4], main = "histogram of beta_1", xlab = "beta_1")
hist(betamatweib[,5], main = "histogram of gamma_0", xlab = "gamma_0")
hist(betamatweib[,6], main = "histogram of gamma_1", xlab = "gamma_1")

# normal quantile for slope parameters
par(mfrow = c(2,2))
qqnorm(betamatweib[,2], main = "Normal quantile for alpha_1")
qqnorm(betamatweib[,4], main = "Normal quantile for beta_1")
qqnorm(betamatweib[,6], main = "Normal quantile for gamma_1")

est=betamatweib[,2]
```

```
se=sematweib[,2]
p=numeric(iter)

# empirical type one error
for(j in 1:iter){
  z.stat <- abs(est[j])/se[j] #do test
  p[j]=2*pnorm(z.stat, lower.tail=F) #save p-value
}
phat=mean(p<.05) #Proportion of trials that reject
phat



#Case 1: empirical power under the case of all true values of slope parameters
         equal to 0.5
#Case 2: empirical power under the case of alpha_1=0.8, beta_1=0.7, gamma_1=0.2

for(j in 1:iter){
  z.stat <- abs(est[j])/se[j] #do test
  p[j]=2*pnorm(z.stat, lower.tail=F) #Calculate pvalue
}
phat=mean(p<.05) #Proportion of trials that reject
phat



# hepatoCellular data
data("hepatoCellular")
summary(hepatoCellular)

hc.dat <- hepatoCellular[, c(16:19, 21)]
hc.dat$P.h <- ifelse(hc.dat$CXCL17P <= median(hc.dat$CXCL17P), 0, 1)
hc.dat$P.l <- ifelse(hc.dat$CXCL17P <= median(hc.dat$CXCL17P), 1, 0)
hc.dat$P <- ifelse(hc.dat$CXCL17P <= median(hc.dat$CXCL17P), "low", "high")
hc.dat$Prog <- ifelse(hc.dat$Recurrence==1 & (hc.dat$OS-hc.dat$RFS) != 0, 1, 0)
hc.dat$TTP <- ifelse(hc.dat$Prog == 1, hc.dat$RFS, hc.dat$OS)
```

```
hc.dat$OS.prime <- ifelse(hc.dat$Prog == 1 & hc.dat$Death == 1, 1, 0)
hc.dat$Post.prog <- (hc.dat$OS - hc.dat$TTP)


################################################
# for all individuals
mydata = hc.dat
mydata$Death = hc.dat$Death
mydata$Prog = hc.dat$Prog

# Prog occurred first and then died => 71 patients
sum(mydata$Prog==1&mydata$Death==1)

# Neither prog nor death => 84 patients
sum(mydata$Prog==0&mydata$Death==0)

# Prog occurred only => 46 patients
sum(mydata$Prog==1&mydata$Death==0)

# Death without prog occurred => 26 patients
sum(mydata$Prog==0&mydata$Death==1)

t1 = hc.dat$TTP
t2 = hc.dat$Post.prog

# high level = 1, low level = 0
x <- ifelse(hc.dat$CXCL17P <= median(hc.dat$CXCL17P), 0, 1)
options(warn=-1)

# parameter estimates and se for exp
mle.exp <- optim(theta <- c(1,1,1,1,1,1), loglik.exp, method="BFGS",
                 hessian=T)
mle.exp$par
```

```
sqrt(diag(solve(optim(theta <- c(1,1,1,1,1,1), loglik.exp, method="BFGS",
                                hessian=T)$hessian)))

# parameter estimates and se for weibull
mle.weib <- optim(theta <- c(1,1,1,1,1,1,1), loglik.weib, method="BFGS",
                  hessian=T)
mle.weib$par

sqrt(diag(solve(optim(theta <- c(1,1,1,1,1,1,1), loglik.weib, method="BFGS",
                                 hessian=T)$hessian)))
```