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SEPARATE AND JOINT ANALYSIS OF LONGITUDINAL AND
SURVIVAL DATA

by
Deepthi Rajeev

A project submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

Department of Statistics
Brigham Young University

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BRIGHAM YOUNG UNIVERSITY

GRADUATE COMMITTEE APPROVAL

of a project submitted by

Deepthi Rajeev

This project has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

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BRIGHAM YOUNG UNIVERSITY

As chair of the candidate's graduate committee, I have read the project of Deepthi Rajeev in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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ABSTRACT

SEPARATE AND JOINT ANALYSIS OF LONGITUDINAL AND SURVIVAL DATA

Deepthi Rajeev

Department of Statistics

Master of Science

Chemotherapy is a method used to treat cancer but it has a number of side-effects. Research conducted by the Department of Chemical Engineering at BYU involves a new method of administering chemotherapy using ultrasound waves and water-soluble capsules. The goal is to reduce the side-effects by localizing the delivery of the medication. As part of this research, a two-factor experiment was conducted on rats to test if the water-soluble capsules and ultrasound waves by themselves have an effect on tumor growth or patient survival.

Our project emphasizes the usage of Bayesian Hierarchical Models and WinBUGS to jointly model the survival data and the longitudinal data—mass. The results of the joint analysis indicate that the use of ultrasound and water-soluble microcapsules have no negative effect on survival. In fact, there appears to be a positive effect on the survival since the rats in the ultrasound-capsule group had higher survival rates than the rats in other treatment groups. From these results, it does appear that the new technology involving ultrasound waves and microcapsules is a promising way to reduce the side-effects of chemotherapy.

It is strongly advocated that the formulation of a joint model for any longitudi-

nal and survival data be performed. For future work for the ultrasound-microcapsule data it is recommended that joint modeling of the mass, tumor volume, and survival data be conducted to obtain additional information.

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Chapter 1

INTRODUCTION

Chemotherapy is a method used to treat cancer; unfortunately, it has many side-effects. Research conducted by the Department of Chemical Engineering at BYU involves a new method of administering chemotherapy using ultrasound waves and microcapsules (Pitt 2003) to reduce these side-effects by localizing the delivery of the medication. As part of this research, a study was carried out to test if water-soluble capsules and ultrasound waves had an effect on the growth of the tumors by themselves. The study was a two-factor experiment conducted over 12 weeks using rats that were induced with tumors in both legs. The anti-cancer drug was not a part of the experiment and hence the rats were not given any chemotherapy.

The three main questions to be answered by the experiment are:

- Does the ultrasound affect the tumor growth, mass, or survival of the rat?
- Does the microcapsule affect the tumor growth, mass, or survival of the rat?
- Do the ultrasound and the microcapsule interact to affect the tumor growth, mass, or survival of the rat?

The study was longitudinal (Verbeke and Molenberghs 2001) because mass and tumor volume were collected on each rat over a period of time. It is very likely that the measurements taken over time are not independent.

Mass, tumor volume, and the survival of the rats could be analyzed separately using appropriate longitudinal and survival analysis methods (Cox 1972; Verbeke and Molenberghs 2001). In general, this is a reasonable approach. Software packages like SAS (SAS 2006) have procedures such as `proc mixed` and `proc lifereg` to model

longitudinal data and survival data. However, if the longitudinal data are correlated with survival, joint analysis may yield more information.

Recently, the joint analysis of both longitudinal and survival data has been proposed (Tsiatis et al. 1995; Wulfsohn and Tsiatis 1997; Henderson et al. 2000; Bowman and Manatunga 2005). The analysis of the data using a joint model instead of separate models will result in unbiased and more efficient estimates. Joint modeling is accomplished using latent variables that link the longitudinal models and the survival models together. Guo and Carlin (2004) demonstrated a Bayesian approach to the joint modeling of one longitudinal model and one survival model using WinBUGS.

The purpose of this study is to conduct the separate analyses of mass, tumor volume, and survival, and in addition, the joint analysis of mass and survival for the ultrasound-microcapsule data. The work will extend that of Guo and Carlin (2004) in that the longitudinal mass model in the ultrasound-microcapsule data involves a first-order autocorrelation structure for weekly weights. Results for the separate and joint analyses will be compared.

Chapter 2

LITERATURE REVIEW

2.1 Micelles and Ultrasound in Chemotherapy

Cancer is a disease where cells multiply continuously because of mutations in the DNA. Since cells produce DNA, these affected cells also produce DNA at a faster rate than normal. Thus, drugs that hinder the production of DNA in turn affect the cancer cells. However, since it has not been possible so far to determine a unique feature that exists only in cancer cells, other cells that are healthy are also affected by the drug. For instance, certain cells in the stomach lining and hair follicles also multiply faster than the other cells and therefore, the anti-cancer drugs would disrupt the DNA production in these cells too. This results in side-effects such as hair loss or stomach problems for people under chemotherapy (DeVita 2001).

Research conducted by a group at the Department of Chemical Engineering at BYU aims to determine whether localizing the effect of the anti-cancer drug would result in a reduction of these side-effects (Pitt 2003). Water soluble plastics, called micelles, made of polyethylene oxide and polypropylene oxide, are a self-assembled collection of molecules. They possess an important property that renders them useful for the purpose of this study—when introduced into water, they spontaneously form tiny plastic spheres. Also, it has been found that an anti-cancer drug called doxorubicin is averse to water. Hence, when both micelles and the drug are mixed in water the drug seeks protection in the spheres.

Plastic spheres that act as a carrier for the drug are injected into the patient and low-frequency ultrasound waves are applied at the tumor site. This results in the bursting of the capsules and the drug is released in the affected area alone. However, it is not known whether micelles and ultrasound waves by themselves or in combination

with each other have an effect on the health and survival of the patient.

2.2 Mixed Models

A mixed model contains both fixed and random effects. For instance, the four treatments (no ultrasound and no carrier, no ultrasound with a carrier, ultrasound and no carrier, and ultrasound and carrier) in the ultrasound-microcapsule data constitute a fixed factor, but the rats under consideration were randomly selected.

In general, a mixed model is of the form:

$$Y = X\beta + Z\delta + \epsilon,$$

where X is the matrix of known values of the fixed predictors, Z is the matrix of known values of the random factors, β is the vector of unknown coefficients for the fixed effects, δ is the vector of unknown random effects, and ϵ is the vector of errors (Littell et al. 2005). In the standard mixed model, δ is distributed as a multivariate normal with mean vector 0 and covariance matrix G and ϵ is distributed as a multivariate normal with mean vector 0 and covariance matrix R . G and R are required to be positive definite matrices because they represent variance-covariance matrices. In many models, $R = \sigma^2 I$. The vectors δ and ϵ are usually assumed to be independent; thus, the covariance matrix of Y is $V = ZGZ' + R$. Hence, Y is distributed as a multivariate normal with mean vector, $X\beta$, and covariance matrix, V .

G , R , and V are functions of unknown parameters that can be estimated using either the method of Maximum Likelihood (ML) or Restricted Maximum Likelihood (REML). Once the estimate \hat{V} has been obtained, the estimate of β is given by $\hat{\beta} = (X'\hat{V}^{-1}X)^{-1}X'\hat{V}^{-1}Y$ and the approximate variance of $\hat{\beta}$ is $(X'\hat{V}^{-1}X)^{-1}$.

The SAS procedure, `proc mixed`, is useful to analyze data when there are fixed and random effects. The `repeated` statement in `proc mixed` defines the covariance matrix, R , and the `random` statement in `proc mixed` defines the covariance matrix,

G (Littell et al. 2005; SAS 2006).

2.2.1 Longitudinal Data

Some experiments involve taking multiple measurements of a variable over a period of time. These measurements are typically called longitudinal data or repeated measurements. For instance, in the ultrasound-microcapsule data, mass and tumor volume were measured weekly for each rat over a period of 12 weeks and hence are longitudinal data. The basic model for a repeated measures design involves effects for the experimental units, treatments, and time (Littell et al. 2005). The experimental units are often assigned to different levels of a factor. Such a factor is called a between-subjects factor. Similarly, since measurements are taken on an experimental unit repeatedly over time, time is called a within-subjects factor.

A repeated measures model is a special case of the general mixed model. The distinguishing feature of a repeated measures model is the specification of the covariance structure of the repeated measures. In a repeated measures model, the R matrix reflects the covariance structure, and is usually not $\sigma^2 I$. The measurements within an experimental unit are usually not equally correlated because measurements taken closer in time tend to be highly correlated compared to measurements taken further apart in time. Hence, selecting the right covariance structure for the data is very important.

There are various model-fitting criteria that can be used to ascertain a reasonable covariance structure. The information criteria make use of the log likelihood of the model and a penalty that is computed as a function of the number of parameters in the model. For instance, the Akaike Information Criterion or AIC is computed as $AIC = 2k - 2\ln(L)$, where k denotes the number of parameters in the model and $\ln(L)$ is the log likelihood (Hirotsugu 1974). The model with a smaller information criterion value is preferred to a model with a larger information criterion value.

2.3 Survival Analysis

Survival data are also called time to event data (Klein and Moeschberger 2003). Generally, the data involve the time until some event occurs. The event could be the death of the patient or the failure of the experimental unit. Time is an example of survival analysis and event is an example of reliability analysis (Meeker and Escobar 1998).

Survival data almost always involve incomplete information and hence cannot be analyzed using the basic modeling techniques. When an observation has incomplete information, it is said to be a censored observation. There are three kinds of censoring: right censoring, left censoring, and interval censoring (Klein and Moeschberger 2003). Observations that do not fail during the measurement or observation period are said to be right-censored. This could happen if a patient survives through the experiment and is still living when the experiment concludes. An observation is also right-censored if a patient leaves the experiment for some reason not connected with survival. Observations that are known to have failed before a certain time are called left-censored. Interval censoring is a more general type of censoring. When an event is known to have occurred within an interval of time, the observation is said to be interval censored.

Formally, if T represents the failure time of an experimental unit, the survivor function is defined as

$$S(t) = P(T > t),$$

where $t \in (0, \infty)$. The hazard function, defined as

$$\lambda(t) = \lim_{\Delta t \rightarrow 0^+} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t},$$

specifies the unobserved instantaneous rate at which an event occurs for units surviving at time t . Thus, $\lambda(t)\Delta t$ can be thought of as the probability that an individual at risk will experience an event in time $(t, t + \Delta t)$. Although the hazard rate is not

observed, it controls the occurrence and timing of the event. The hazard function fully specifies the survivor function because

$$\lambda(t) = \frac{-d\log S(t)}{dt}.$$

The Kaplan-Meier estimator or Product Limit Estimator provides a non-parametric maximum likelihood estimate of the survivor function (Kaplan and Meier 1958). The Kaplan-Meier estimate of $S(t)$ is given as

$$\hat{S}(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i},$$

where n_i corresponds to the number of observations at risk of failing just prior to time t_i ; d_i denotes the number of failures at time t_i .

Parametric regression models are commonly applied to survival data. The Weibull distribution, a generalization of the exponential distribution, is very flexible and widely used. Its hazard function is

$$\lambda(t) = \theta\gamma(\theta t)^{\gamma-1},$$

where $\theta > 0, \gamma > 0$. The hazard is monotonically increasing for $\gamma > 1$, monotonically decreasing for $\gamma < 1$, and constant for $\gamma = 1$.

The SAS procedure, `proc lifereg`, can be used to fit parametric models to right, left, or interval-censored data (SAS 2006). The model is assumed to be of the form

$$y = X\beta + \sigma\epsilon,$$

where y is the vector of logs of the survival times. X represents the matrix of predictor variables, β denotes the vector of unknown regression coefficients, ϵ is the vector of errors assumed to come from a known distribution, and σ is an unknown scale parameter. If survival times follow the Weibull distribution, the error distribution is the extreme value distribution. When $\sigma = 1$, the Weibull distribution reduces to the exponential distribution.

Similarly, survival times, y_i , are assumed to follow the Weibull distribution with parameters γ and $\theta_i = e^{X_i\theta}$. Klein and Moeschberger (Klein and Moeschberger 2003) specify the relationships between the two formulations of the model.

2.4 Bayesian Analysis

Bayesian statistics is considered to have evolved from a paper by Rev. Thomas Bayes published posthumously by Price in 1763 (Bayes 1763). Unaware of this paper, Laplace independently developed the Bayes Theorem and extended its results in 1774. A translated version of the paper by Laplace was published by Stigler (1986). The term Bayesian was first used by Fisher in a note attached to a paper published in 1950 (Fisher 1950).

Bayes' rule is:

$$\pi(\theta | y) = \frac{f(y | \theta)\pi(\theta)}{f(y)},$$

where $\pi(\theta | y)$ is called the posterior distribution of the vector of parameters, θ , given the data (Gelman et al. 2004). $f(y | \theta)$ is the sampling distribution or the likelihood. $\pi(\theta)$ denotes the prior distribution of the unknown parameters. $f(y)$ is the marginal distribution of y , and from the law of total probability $f(y)$ can be calculated as $f(y) = \int f(y | \theta) \pi(\theta) d\theta$. $f(y)$ is also called the normalizing constant. In his paper, Bayes demonstrated the use of a uniform prior for a binomial likelihood (Bayes 1763).

Bayesian statistics involves the use of probability as a measure of uncertainty. The unknown parameters are not considered to be fixed but rather random in nature; hence, the parameters themselves have a distribution. If the posterior distribution belongs to the same family of distributions as the prior distribution, then the prior is said to be conjugate. Since the posterior distribution incorporates information from the data, it will often be less varied and more peaked than the prior distribution. Therefore, as the sample size increases, the effect of the prior distribution on the posterior distribution decreases. In cases where the prior distribution is difficult to

obtain, vague, flat or noninformative priors can be used.

Bayesian inference can usually be carried out by taking random draws from the posterior distribution of the model parameters (Gelman et al. 2004). Before the advent of computers, this was very difficult to implement. As a result, Bayesian statistics was not very practical in the 18th and 19th centuries. With the rediscovery in the statistical literature of Markov Chain Monte Carlo (MCMC) simulation methods such as Metropolis-Hastings and Gibbs sampling in the middle of the 20th century, it became possible to draw samples from the posterior distribution. The term, Monte Carlo refers to the simulation part of the algorithm. The technique involves the drawing of samples sequentially, with the distribution of the sampled draws dependent on the previous value drawn. These draws form a Markov chain.

The Metropolis-Hastings algorithm is used to generate a sequence of samples from any probability distribution $p(x)$, requiring that the density can be calculated at x (Metropolis et al. 1953; Hastings 1970). The Gibbs sampler developed by Geman and Geman can be considered a special case of the Metropolis-Hastings algorithm (Geman and Geman 1984). The algorithm is useful when the joint distribution is not explicitly known but the conditional distribution of each parameter is known. An initial starting point for the parameters is required and the algorithm involves a set of iterative steps. At each iteration, a parameter is sampled from the conditional distribution of all other parameters at their current value. After each iteration, the value of the parameter is updated conditional on the current values of the other parameters.

A specialized software package called WinBUGS implements the Bayesian analysis of complex statistical models using MCMC methods (Spiegelhalter et al. 2003). WinBUGS uses Gibbs sampling when the priors are conjugate. When the priors are non-conjugate, WinBUGS uses Adaptive Rejection sampling. Adaptive Rejection sampling is a variation of Rejection sampling, a method that uses an envelope func-

tion when it is difficult to sample from the actual posterior distribution. Adaptive Rejection sampling makes use of a “squeezing function” and an envelope function that together form lower and upper bounds to the density function. It has been shown that as sampling proceeds, the squeezing function and the envelope function converge to the density function (Gilks and Wild 1992). This useful technique is applied to Bayesian models with non-conjugacy.

2.5 Joint modeling of Longitudinal Data and Survival Data

Experiments often generate both longitudinal data and survival data. There are many methods to analyze the data separately (Cox 1972; Verbeke and Molenberghs 2001). However, when longitudinal data are correlated with survival data, fitting separate models for each kind of data may not give complete information. Over recent years, there has been considerable interest in the joint modeling of longitudinal data and survival data.

In one approach, a two-stage modeling process was developed that dealt with survival as a function of a covariate measured repeatedly. In the first stage, the covariate is modeled using growth curve models with random effects (Laird and Ware 1982). In the second stage, the modeled value is substituted into the partial likelihood for the Cox model with time-dependent covariates and the partial likelihood is maximized. The purpose is to reduce the bias of the parameter estimates in the Cox model (Tsiatis et al. 1995). However, this procedure has a main drawback—while modeling the covariate process, survival information is not used.

To overcome this drawback, Wulfsohn and Tsiatis (Wulfsohn and Tsiatis 1997) developed a method that maximized the joint likelihood from both the covariate process and survival data simultaneously. That is, the parameters that describe the covariate process and the parameters that describe the risk of failure as a function of the covariate process are estimated at the same time. This results in the use of survival

information to get the estimates of the true covariate at any time. They use the Cox model for the hazard of failure and assume that the true covariate value is given by the growth model. The E-M algorithm is used to estimate the parameters of interest (Dempster et al. 1977). In the E-step, the expected log-likelihood of the complete data conditional on the observed data and the current estimate of the parameters is computed. In the M-step, new parameter estimates are computed by maximizing the expected log-likelihood. The algorithm involves iteration between these two steps until the parameter estimates converge.

Henderson et al. (2000) proposed the use of an unobserved or latent bivariate Gaussian process, $W(t) = [W_1(t), W_2(t)]$, to link longitudinal data and survival data in a clinical trial of schizophrenia patients. The longitudinal response variable was a measure of the psychiatric disorder and the event was drop-out due to inadequate response. They assumed that the longitudinal and event processes were conditionally independent given $W(t)$ and covariates. The correlation between $W_1(t)$ and $W_2(t)$ describes the association between the longitudinal data and survival data. It was assumed that $W_1(t)$ and $W_2(t)$ could be specified as a linear random effects model. Model adequacy was checked by comparing simulated data and observed data. The results showed good agreement, but the proposed method provided a complicated solution to the problem.

Guo and Carlin (2004) developed a Bayesian implementation of the method used by Henderson et al. (2000). They claimed that this approach was more straightforward to execute using the software WinBugs. Clinical data collected on 467 HIV-infected patients were used to demonstrate the Bayesian version of the joint modeling of longitudinal and survival data. The study was conducted to evaluate the safety and efficiency of two drugs in treating patients who were intolerant of AZT therapy. The longitudinal response variable was CD4 count and the event was death. The authors used non-informative prior distributions because they wanted to compare the

results of the joint analysis obtained using WinBugs and the SAS procedure `proc nlmixed`. As in Henderson et al. (2000), the association between the longitudinal model and the survival model was accomplished using a latent zero-mean bivariate Gaussian process. The results provide strong evidence that there is an association between the longitudinal model and the survival model. Additionally, the results of the joint model contradict the results of the two separate models. The further development and application of joint models for longitudinal and survival data is an area of much current interest (Elashoff, R. and Li, G. and Li, N. 2006; Wang, J. L. and Ding, J. 2006).

Chapter 3

METHODOLOGY

3.1 The Experiment

To determine the effects of the ultrasound and the carrier separately and in combination an experiment was conducted without the anticancer drug. The experiment consisted of four treatment groups: no ultrasound and no carrier, no ultrasound with carrier, ultrasound and no carrier, ultrasound and carrier. There were 30 rats of similar age in the study, each rat being an experimental unit. Two rats died within the first week, so they were excluded from the analysis. All the rats had a tumor in both the left leg and the right leg. One leg was randomly chosen to receive the treatment and the other leg was untreated. Sham ultrasound was applied to the chosen leg if the treatment level was “no ultrasound”. All of the rats were injected with either the carrier or saline. The rats were of both genders and were randomly assigned to the four treatment groups. Each treatment group consisted of six to eight rats. The carriers and the water soluble capsules used in the experiment were from a single batch so that the variation between the carriers would be at a minimum.

The treatments were applied once a week for six weeks. The volume of the tumors and the mass of the rats were measured for 12 consecutive weeks. Not all rats survived until the end of the experiment. The number of days until death was recorded for those rats that did not survive. Those rats that survived were euthanized at the end of the experiment.

As part of the preliminary analysis, mass, treated tumor volume, and untreated tumor volume for the four treatments were plotted against week (Figures 3.1, 3.2, and 3.3) for each rat. Kaplan-Meier survival curves were generated for each treatment for male and female rats (Figure 3.4).

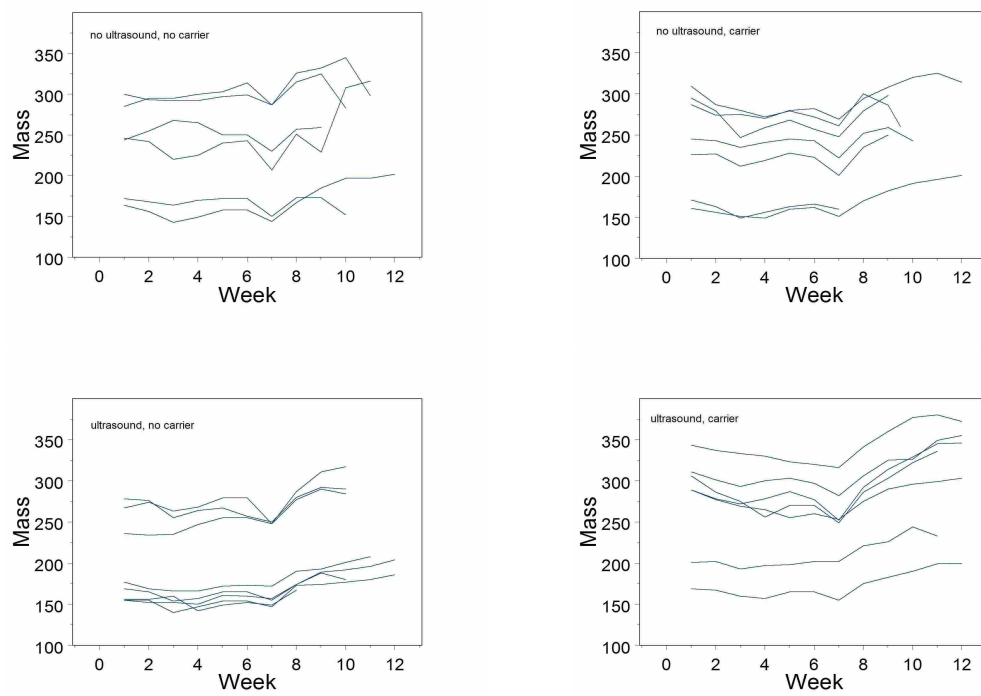


Figure 3.1: Mass profiles over time

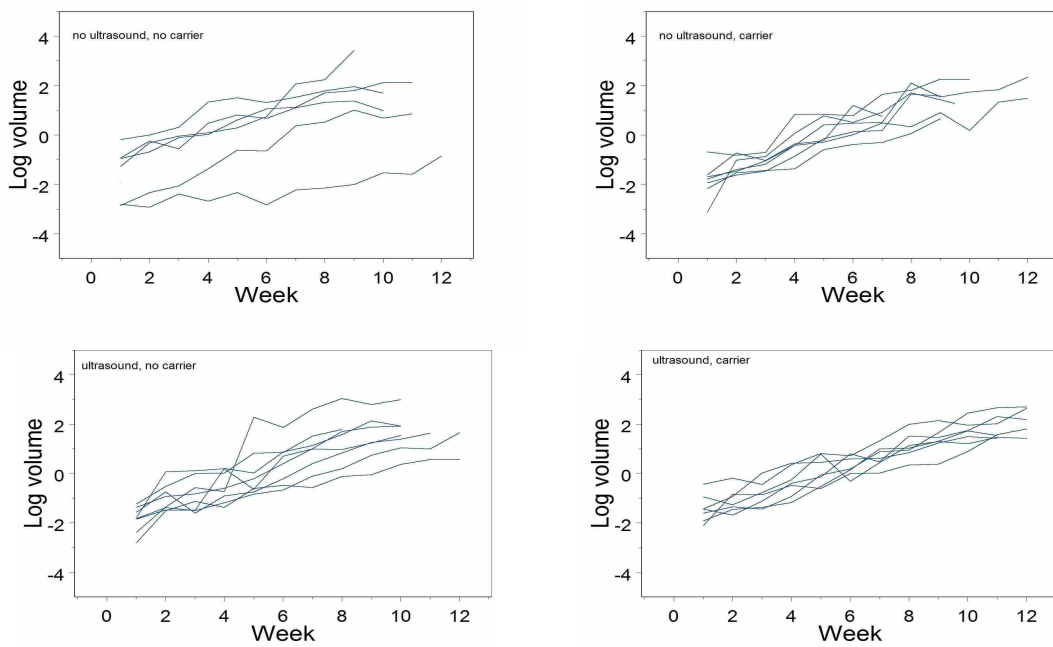


Figure 3.2: Treated tumor volume profiles over time

Individual rats have characteristic weights that vary over time (Figure 3.1). The apparent groupings in rat mass correspond exactly to gender, with female rats being significantly smaller than male rats. Also, most of the rats seem to have a tendency to lose weight shortly before death. Another obvious feature of Figure 3.1 is the apparent weight loss for every rat during week 7. This may be attributable to a student or instrument calibration effect.

There is a clear linear trend in tumor volume for both treated and untreated tumors (Figures 3.2, 3.3). Also, both treated and untreated tumor volume for most rats seem to be increasing in a roughly parallel manner for all four treatments.

It appears that survival depends on the gender of the rat and the treatment applied (Figure 3.4); female rats seem to have a better survival rate than male rats and rats in the treatment with both the ultrasound and the carrier seem to have a better survival rate than rats in the other three treatments groups.

3.2 Separate Analyses using SAS

Separate longitudinal models and survival models were fitted using the SAS procedures—`proc mixed` and `proc lifereg` (SAS 2006).

Several longitudinal models for mass were considered and compared using AIC. The final model had random intercepts for rats and a first-order autocorrelation structure for weekly weights. Fixed predictor variables included treatments, week, treatment-by-week interactions, treated leg (left or right), gender, and an indicator variable for week 7. Code for SAS procedure `proc mixed` is included in Appendix A(i).

Tumor volumes for both treated and untreated legs were analyzed jointly. Again, several longitudinal models for tumor volume were considered and compared using AIC. The final model had random intercepts and slopes among rats and between the legs of the same rat. Fixed predictor variables included treatments, week,

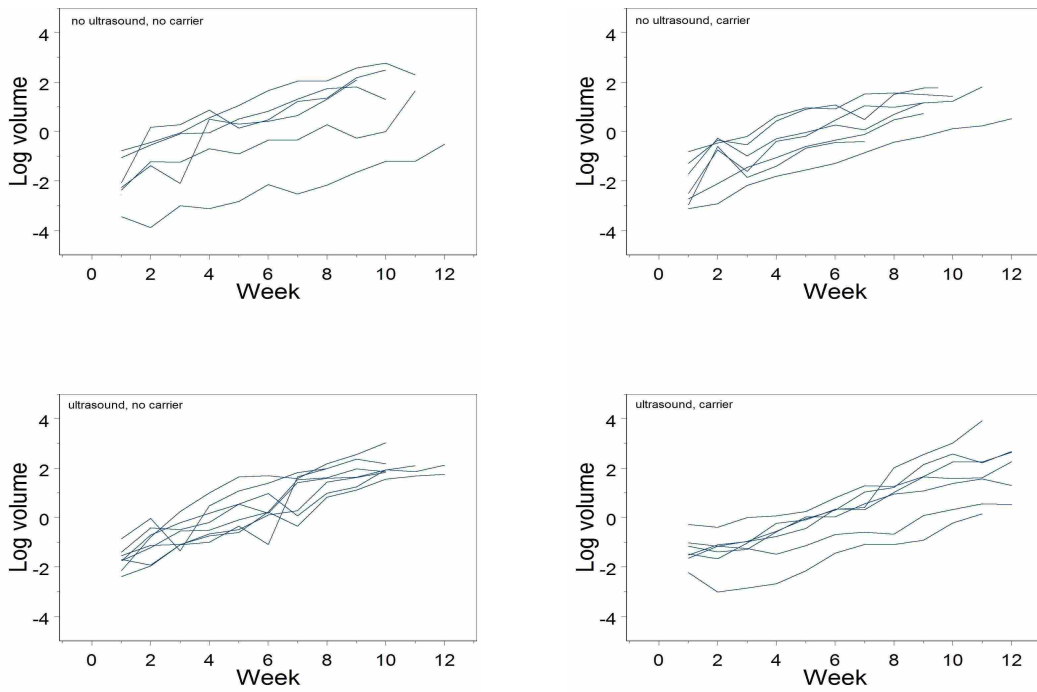


Figure 3.3: Untreated tumor volume profiles over time

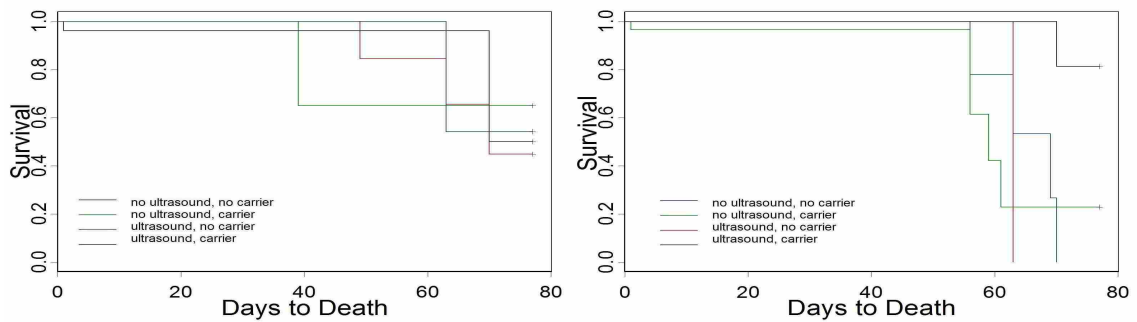


Figure 3.4: Survival profiles for female (left) and male (right) rats

treatment-by-week interactions, treated leg (indicator variable to denote if the left or right leg was treated), gender, and leg (indicator variable to denote if the leg was treated or untreated). Code for this model is included in Appendix A(ii).

The survival data was modeled using the SAS procedure proc lifereg (SAS 2006). The response variable was days to death and the explanatory variables were treatment and gender. The code is found in Appendix A(iii).

3.3 Separate Analyses using WinBUGS

WinBUGS is a software package that is used for hierarchical Bayesian analysis of statistical models (Spiegelhalter et al. 2003). Similar separate models were used for mass, tumor volume and survival as in the SAS analyses.

Modeling the first-order autocorrelation structure in WinBUGS is slightly more complicated than modeling it in SAS. WinBUGS uses the inverse of the variance-covariance matrix, called the precision matrix. To deal with this problem, we obtained τ , the inverse of the first-order auto-regressive variance-covariance matrix. τ is

$$\begin{array}{ccccccc}
 \frac{\sigma^{-2}}{1-\rho^2} & \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & 0 & \dots & \dots & \dots & 0 \\
 \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & \frac{\sigma^{-2}(1+\rho^2)}{1-\rho^2} & \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & 0 & \dots & \dots & 0 \\
 0 & \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & \frac{\sigma^{-2}(1+\rho^2)}{1-\rho^2} & \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & 0 & \dots & 0 \\
 0 & 0 & \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & \frac{\sigma^{-2}(1+\rho^2)}{1-\rho^2} & \frac{\sigma^{-2}(-\rho)}{1-\rho^2} & 0 & \dots \\
 0 & 0 & 0 & \dots & \dots & \dots & \dots \\
 \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
 0 & \vdots & \vdots & \vdots & \vdots & \ddots & \frac{\sigma^{-2}}{1-\rho^2}
 \end{array}$$

where σ^2 is the variance and ρ is the autocorrelation coefficient.

A vague normal prior for the mean of the intercepts and a vague gamma prior for the precision of the intercepts were used. All of the regression coefficients were also assigned vague normal priors. ρ was considered to be uniformly distributed with

parameters 1 and -1. σ^{-2} was assigned a vague gamma prior. The WinBUGS code for the mass model is included in Appendix B(i).

Because, the initial mass of the rats ranged from about 150 grams to 350 grams (Figure 3.1), our use of a normal prior with a standard deviation of 10000 is non-informative. Moreover, the results were similar when the model was analyzed with different priors. It can be concluded that the priors used are indeed vague.

To specify a similar model for tumor volume to that used in SAS using WinBUGS, we assumed independence among rats and independence between legs within individual rats. We specified random intercepts and slopes for rats and legs within rats. The means of the intercepts for each rat and leg within each rat were assigned vague normal priors and the precisions of the intercepts were assigned vague gamma priors. Similarly, the means of the slopes for each rat and leg within each rat were given vague normal priors and the precisions of the slopes were given vague gamma priors. The fixed predictors were the same as those included in the SAS model and their corresponding regression coefficients were assigned vague normal priors. The WinBUGS code is included in Appendix B(ii).

The survival model that was analyzed using the SAS procedure `proc lifereg` was fitted using WinBUGS. The response variable, days to death was drawn from a Weibull distribution. The predictors were treatment and gender. The regression coefficients were assigned vague normal priors. The code can be found in Appendix B(iii).

The results of the models described above and a comparison of the SAS and WinBUGS results will be discussed in the Results chapter.

3.4 Joint Analysis of Longitudinal Mass Data and Survival Data using WinBUGS

This section describes the joint modeling of the mass model and the survival model. The two models were linked together using a latent variable, U_i , that denotes

the random effects for the mass model that are specific to each rat ($i = 1$ to 28). In particular, U_i denotes the deviations of the intercept for each rat from an overall intercept. Because the mean of the deviations is zero, we specified a zero-mean normal distribution for U_i with the precision drawn from a vague gamma prior distribution. We then computed

$$W_i = \delta U_i$$

as a frailty term in the survival model. This links the mass model to the survival model. The parameter δ measures the association between the submodels. The code can be found in Appendix B(iv).

Chapter 4

RESULTS

4.1 Longitudinal Results using SAS and WinBUGS

Table 4.1 displays the SAS and WinBUGS results of the mass model. The WinBUGS results are based on a burn-in of the first 400,000 samples of a total of 1,000,000 samples drawn from the posterior distribution. A study of the trace and density plots of the posterior distributions of the coefficients indicate that the results are accurate and the MCMC algorithm converged. The plots of the coefficients of treatment-by-week interaction and gender are included in Appendix C. The time series plots based on 500 samples indicate reasonable mixing and are also included in Appendix C. The results indicate that there is no treatment effect or treatment-by-week interaction effect but there is definitely a gender effect. Week 7 is also significant. The estimate of the first-order autocorrelation in the WinBUGS model is reasonably close to the estimate obtained using SAS. As seen in Table 4.1, the coefficients of all the other parameters of the model in SAS using proc mixed and WinBUGS are also reasonably close.

The results of the tumor volume model from SAS and WinBUGS are shown in Table 4.2. The WinBUGS results are calculated after a burn-in of the first 400,000 samples from a total of 1,000,000 samples drawn from the posterior distribution. The plots of the coefficients of treatment-by-week interaction and week are included in Appendix D. The results show that there is a significant effect of week and there is also a significant difference between the left tumor and the right tumor. The WinBUGS results are extremely close to the SAS results with the exception of the estimate of week. Both the estimates indicate a significant effect of week.

Parameter	SAS		WinBUGS	
	Estimate	Standard Error	Posterior Mean	Posterior Std. Dev.
Intercept	161.95	11.23	158.30	13.48
Gender	106.58	7.73	106.60	8.36
Leg (left-right)	2.66	7.29	2.82	7.90
Treatment 2	0.46	13.42	0.46	14.97
Treatment 3	-7.90	13.16	-7.46	14.67
Treatment 4	25.68	13.36	25.98	14.89
Time	1.90	1.02	2.03	1.21
Treatment 2 * Time	-0.70	1.42	-0.86	1.68
Treatment 3 * Time	1.41	1.36	1.33	1.60
Treatment 4 * Time	1.33	1.35	1.24	1.59
Week 7	-20.41	1.21	-20.46	1.63
ρ	0.94	0.03	0.88	0.03

Table 4.1: Mass model results using SAS and WinBUGS.

Parameter	SAS		WinBUGS	
	Estimate	Standard Error	Posterior Mean	Posterior Std. Dev.
Intercept	-1.51	0.27	-1.18	0.17
Gender	0.24	0.24	0.24	0.24
Leg (left-right)	0.63	0.22	0.63	0.22
Leg (treated-untreated)	-0.14	0.14	-0.14	0.15
Treatment 2	-0.05	0.33	-0.04	0.32
Treatment 3	0.08	0.32	0.08	0.32
Treatment 4	0.12	0.33	0.11	0.32
Week	0.33	0.03	0.17	0.01
Treatment 2 * Week	0.03	0.04	0.03	0.04
Treatment 3 * Week	0.07	0.04	0.07	0.04
Treatment 4 * Week	0.01	0.04	0.01	0.04

Table 4.2: Tumor volume model results using SAS and WinBUGS.

Parameter	SAS		WinBUGS	
	Estimate	Standard Error	Posterior Mean	Posterior Std. Dev.
Intercept	4.20	0.01	4.22	0.08
Gender	0.16	0.02	0.15	0.09
Treatment 2	0.03	0.02	0.01	0.10
Treatment 3	-0.03	0.02	-0.03	0.10
Treatment 4	0.29	0.03	0.32	0.15

Table 4.3: Survival model results using SAS and WinBUGS.

4.2 Survival Results

This section describes the SAS and WinBUGS results of survival data. The model in WinBUGS is analyzed using a burn-in of 400,000 samples from a total of 1,00,0000 draws from the posterior distributions of the parameter coefficients. Table 4.3 describes the results of SAS procedure proc lifereg and WinBUGS. Table 4.4 describes the median survival time with respect to treatment and gender.

Due to different parametrization in SAS and WinBUGS, the estimates obtained in WinBUGS were converted to be consistent with the estimates obtained in SAS. This was done by multiplying the WinBUGS coefficients by the negative of the inverse of the Weibull shape parameter. The trace and density plots of the coefficients indicate that the MCMC algorithm converged (Appendix E). The results indicate that rats in the treatment with ultrasound and the carrier have a better survival rate than rats in the other three treatments groups. Also, both the SAS and WinBUGS results indicate

Median	SAS		WinBUGS	
	Female	Male	Female	Male
no ultrasound, no carrier	74.38	63.06	74.77	64.26
no ultrasound, carrier	77.10	65.37	75.63	64.97
ultrasound, no carrier	72.27	61.27	72.41	62.37
ultrasound, carrier	99.45	84.31	103.40	88.71

Table 4.4: Median Survival times using SAS and WinBUGS.

that the ultrasound and carrier treatment have a significant effect on survival.

4.3 Goodness of Fit

Goodness of fit was carried out for the non-Bayesian models. The results of the separate models in SAS and WinBUGS were very similar, so it is reasonable to assume that the goodness of fit evaluation of the SAS models would apply to the Bayesian models.

A residual plot represents the difference between the observed response variable and the predicted value. The residual plot (Figure 4.1) for the mass model was constructed and from the plot it appears that there are no odd trends. In general, the points seem to be fluctuating randomly around zero. In addition, the predicted values for mass were plotted against the observed values (Figure 4.2). For the most part, there appears to be a linear relationship between the predicted and observed values. The fit of the survival model was checked using the Cox-Snell residual plot (Klein and Moeschberger 2003) (Figure 4.3). This method involves the estimation of the cumulative hazard function for a Weibull distribution and the Cox-Snell residuals. For the most part, the plot indicates a reasonable fit.

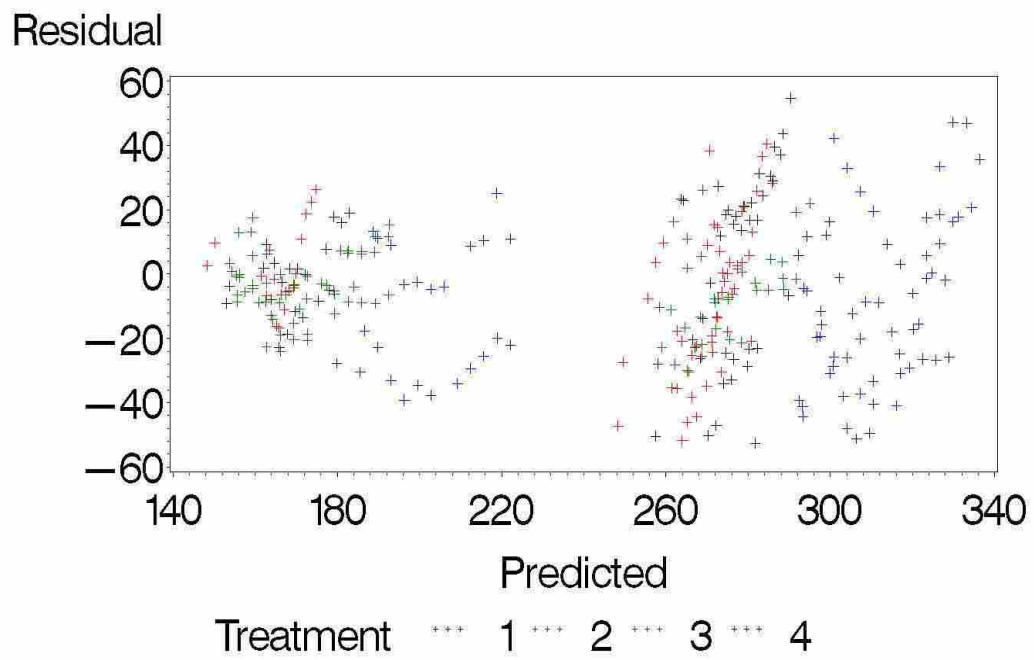


Figure 4.1: Residual plot for Mass model. Treatment 1: no ultrasound, no carrier, Treatment 2: no ultrasound, carrier, Treatment 3: ultrasound, no carrier, Treatment 4: ultrasound, carrier

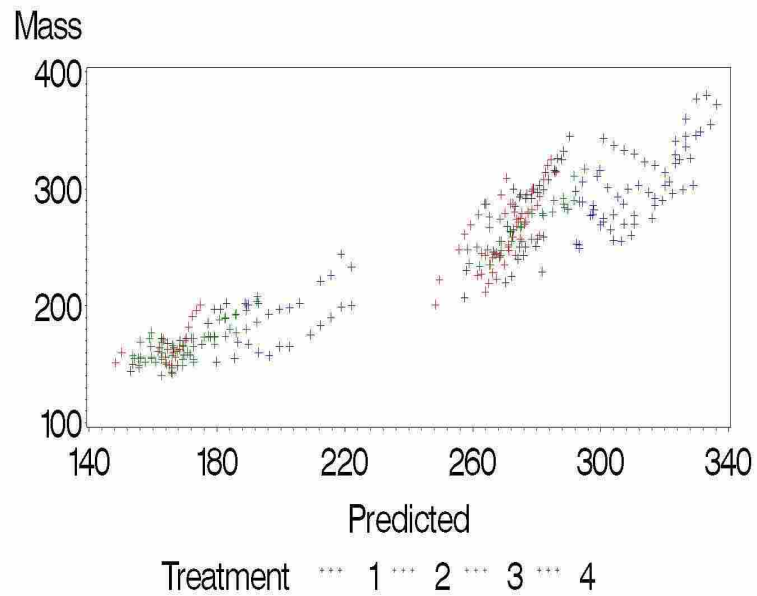


Figure 4.2: Predicted plot for Mass model. Treatment 1: no ultrasound, no carrier, Treatment 2: no ultrasound, carrier, Treatment 3: ultrasound, no carrier, Treatment 4: ultrasound, carrier

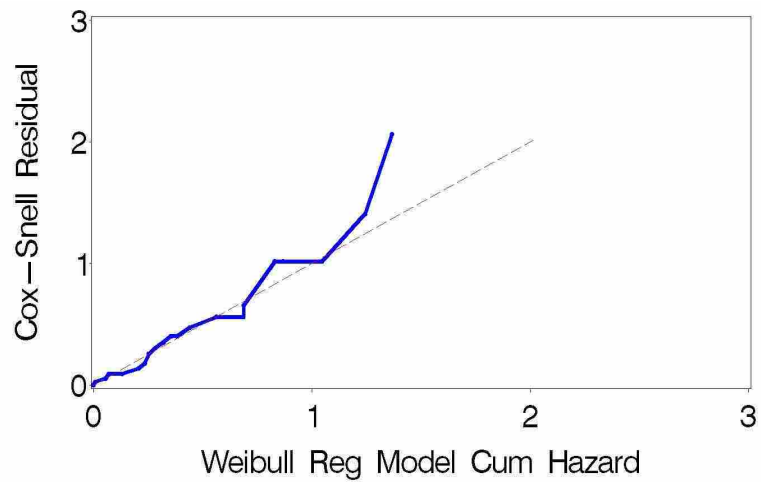


Figure 4.3: Cox-Snell Residual plot for Survival model

4.4 Joint Results

This section describes the WinBUGS results of the joint analysis of mass and survival data. The analysis is based on a burn-in of the first 100,000 samples from a total of 350,000 samples drawn from the posterior distribution. Table 4.5 displays the WinBUGS results of the joint model and the two separate models. A study of the trace and density plots of the posterior distributions of the coefficients (Appendix F) indicate that the results are accurate and MCMC algorithm converged. The time series plots based on 500 samples indicate reasonable mixing. As seen in Table 4.5, the estimates of the parameters of the separate models are similar to those of the joint model.

In the separate analysis, the median survival times for the rats in the treatment with the ultrasound and the carrier were much higher than the median survival times for the rats in the other treatments. This is possibly because the rats in this treatment group were larger than the rats in the other three treatment groups. The joint model was fitted in the hope that this difference between the treatments in the survival model would decrease once the mass of the rats was taken into account. The median survival times from both the separate and the joint models are displayed in Table 4.6. The treatment with the ultrasound and the carrier continues to have the highest median survival time.

The rats in the ultrasound, no carrier group had the lowest median survival time in the separate model. In the joint model, the rats in the no ultrasound, carrier group have the lowest median survival time. This is true for both male and female rats. The estimated coefficient δ , which measures the association between mass and the survival of the rat, is negative but not significant. Since the results of the joint model were very close to the results of the separate model, no further goodness of fit was conducted. Again, because the analyses of these models with different priors resulted in similar estimates for the parameters, we think the priors used are indeed vague.

Parameter	Separate Analysis		Joint Analysis	
	Posterior Mean	Posterior Std. Dev	Posterior Mean	Posterior Std. Dev.
	Mass Submodel		Mass Submodel	
Intercept	158.30	13.48	158.60	13.35
Gender	106.60	8.36	106.70	8.20
Leg (left-right)	2.82	7.90	2.72	7.77
Treatment 2	0.46	14.97	0.46	14.95
Treatment 3	-7.46	14.67	-7.49	14.62
Treatment 4	25.98	14.89	26.01	14.88
Time	2.03	1.21	2.01	1.23
Treatment 2 * Time	-0.86	1.68	-0.87	1.71
Treatment 3 * Time	1.33	1.60	1.35	1.63
Treatment 4 * Time	1.24	1.59	1.25	1.61
Week 7	-20.46	1.63	-20.43	1.62
ρ	0.88	0.03	0.89	0.02
	Survival Submodel		Survival Submodel	
Intercept	4.22	0.08	4.22	0.11
Gender	0.15	0.09	0.04	0.12
Treatment 2	0.01	0.10	-0.08	0.15
Treatment 3	-0.03	0.10	-0.01	0.15
Treatment 4	0.32	0.15	0.32	0.18
δ	-	-	-796.5	893.5

Table 4.5: Separate and Joint Analysis of Mass and Survival Submodels using WinBUGS.

Median	Separate Analysis		Joint Analysis	
	Female	Male	Female	Male
no ultrasound, no carrier	74.77	64.26	70.84	67.91
no ultrasound, carrier	75.63	64.97	64.67	62.14
ultrasound, no carrier	72.41	62.37	69.44	66.87
ultrasound, carrier	103.40	88.71	97.87	93.76

Table 4.6: Median Survival times for Separate and Joint Models.

Chapter 5

CONCLUSION

The results of the joint model demonstrate that the use of the ultrasound and the carrier do not have any negative effects on the survival of the rats. In fact, the rats who were in the treatment with the ultrasound and the carrier survived longer than the rats in the other three treatment groups. The joint model was conducted in the hope that the adjustment for the effect of mass on survival would account for the increased survival in the ultrasound, carrier group. It was expected that the mean survival times of all the rats would be similar in the joint model; however, this was not the case.

Once the separate models were formulated using WinBUGS, the joint modeling was accomplished fairly easily. However, formulating the separate models in WinBUGS to match the SAS results was quite a task. Accomodating the autocorrelation structure of the weekly weights was difficult in WinBUGS. Moreover, due to different parametrization of the Weibull distribution used in WinBUGS and SAS, it was necessary to convert the WinBUGS results to be more consistent with the SAS results. Nevertheless, we agree with Guo and Carlin that conducting a joint analysis for longitudinal and survival data is highly recommended and fairly easy to implement.

A method called the Bayesian χ^2 test for goodness of fit for Bayesian models was recently proposed by Johnson (2004). This method is considered better than the posterior predictive method to test the fit of a model. The diagnostic used in the Bayesian χ^2 test for goodness of fit is related to the classical χ^2 goodness of fit statistic. It requires the allocation of observations to bins according to the value of each observation's conditional distribution function, conditional on a single parameter value sampled from the posterior distribution. The implementation of this method

to the ultrasound-microcapsule data is highly recommended. It will be an extension of the work of Johnson since the ultrasound-microcapsule data is multivariate.

The results of this experiment indicate that this new technology involving ultrasound waves and microcapsules is a promising way to reduce the side-effects of chemotherapy. We recommend that the joint modeling of the mass model, tumor volume model, and the survival model should be performed to obtain a clearer picture of the effect of the ultrasound and the microcapsules.

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Appendix A

SAS CODE

```
options ls=90 formdlim="#";

/*Importing the first Excel file*/

PROC IMPORT DATAFILE="c:\deepthi\project\rats1a.xls"

OUT=rats1 REPLACE;

RANGE="A3:J332";

GETNAMES=yes;

run;

/*Sorting the dataset*/

proc sort data=rats1;

by rat_name;

run;

/*Importing the second Excel file*/

PROC IMPORT DATAFILE="c:\deepthi\project\rats2a.xls"

OUT=rats2 REPLACE;

RANGE="B2:H33";

GETNAMES=yes;

run;

/*Sorting the dataset*/

proc sort data=rats2;
```

```

by rat_name;

run;

/*Merging the two datasets by ratname*/

data mergeddata;

merge rats1 rats2;

by rat_name;

drop F6;

run;

proc sort data=mergeddata;

by treatment sex rat_name;

run;

/*Calculating volume*/

data merge2;

set mergeddata;

if leg_US = 'L' then do;

lcmt1=left1cm;

lcmt2=left2cm;

rcmu1=right1cm;

rcmu2=right2cm;

end;

if lcmt1<lcmt2 then do;

tvolume=(lcmt1*lcmt1*lcmt2)/2;

```



```

tlogv=log(tvolum);

end;

if lcmt1>lcmt2 then do;

tvolum=(lcmt2*lcmt2*lcmt1)/2;

tlogv=log(tvolum);end;

if rcmu1<rcmu2 then do;

uvolum=(rcmu1*rcmu1*rcmu2)/2;

ulogv=log(uvolum);

end;

if rcmu1>rcmu2 then do;

uvolum=(rcmu2*rcmu2*rcmu1)/2;

ulogv=log(uvolum);

end;

if leg_US = 'R' then do;

lcmu1=left1cm;

lcmu2=left2cm;

rcmt1=right1cm;

rcmt2=right2cm;

end;

if lcmu1<lcmu2 then do;

uvolum=(lcmu1*lcmu1*lcmu2)/2;

ulogv=log(uvolum);

end;

```

```

if lcmu1>lcmu2 then do;

uvolume=(lcmu2*lcmu2*lcmu1)/2;

ulogv=log(uvolume);

end;

if rcmt1<rcmt2 then do;

tvolume=(rcmt1*rcmt1*rcmt2)/2;

tlogv=log(tvolume);

end;

if rcmt1>rcmt2 then do;

tvolume=(rcmt2*rcmt2*rcmt1)/2;

tlogv=log(tvolume);

end;

run;

proc sort data=merge2;

by treatment rat_name tmtweek;

run;

data merge4;

set merge2;

leg=1;          /*treated=1*/

logv=tlogv;

output;

```

```
leg=0;          /*untreated=0*/  
  
logv=ulogv;  
  
output;  
  
  
data merge28;  
  
set merge4;  
  
if (rat_name='H02') or (rat_name='H32');  
  
then delete;  
  
run;
```

(i). Mass model

```
data merge5;

set merge28;

week7=(tmtweek=7);

run;

proc mixed data=merge5 covtest;

class treatment rat_name leg_US;

model ratmass=sex leg_US treatment week7 tmtweek
treatment*tmtweek /ddfm=kenwardroger solution;

random rat_name;

repeated/subject=rat_name type=AR(1);

run;
```

ii). Tumor Volume model

```
proc mixed data=merge28 covtest;

class sex leg_US leg treatment rat_name;

model logv=sex leg_US leg treatment tmtweek
treatment*tmtweek/ddfm=kenwardroger solution;

random intercept tmtweek/subject=rat_name type=vc;

random intercept tmtweek/subject=leg(rat_name) type=vc;

run;
```

(iii). Survival model

```
proc lifereg data=merge28;  
class treatment sex;  
model days_to_death*status(0)=treatment sex/dist=weibull;  
run;
```

Appendix B
WINBUGS CODE

(i). Mass

```
model
{
c1<-(isigmasq)/(1-pow(rho,2))
c2<-(isigmasq)*(1+pow(rho,2))/(1-pow(rho,2))
c3<-isigmasq*(-rho)/(1-pow(rho,2))
for (i in 1:M)
{
for (j in 1:M)
{
a1[i,j]<-step(1-i)*step(1-j)
b1[i,j]<-step(i-M)*step(j-M)
c1a[i,j]<-step(i-j)*step(j-i)
c1b[i,j]<-(1 - step(1-i)*step(1-j))
c1c[i,j]<-(1 - step(i-M)*step(j-M))
d1a[i,j]<-step(1-i+j)*step(1-j+i)
d1b[i,j]<-(1-step(i-j))*step(j-i)
e1a[i,j]<-step(1-j+i)*step(1-i+j)
}
```

```

e1b[i,j]<-(1-step(j-i))*step(i-j)
a[i,j]<-a1[i,j]*c1
b[i,j]<-b1[i,j]*c1
c[i,j]<-c1a[i,j]*c1b[i,j]*c1c[i,j]*c2
d[i,j]<-d1a[i,j]*d1b[i,j]*c3
e[i,j]<-e1a[i,j]*e1b[i,j]*c3
tau[i,j]<- a[i,j]+b[i,j]+c[i,j]+d[i,j]+e[i,j]
}
}
for(k in 1 : N)
{
rmass[k,1:M]~dmnorm(mu[k,1:M],tau[1:M,1:M])
for (l in 1:M)
{
mu[k, l] <- b0[k] + beta.c1*tmt2[k]+ beta.c2*tmt3[k] +
beta.c3*tmt4[k]+ 0*tmt1[k]+beta.c5*legtr[k]
+beta.c6*sex[k] +beta.c7*time1[l] +
beta.c8*tmt2[k]*time1[l] + beta.c9*tmt3[k]*time1[l]
+ beta.c10*tmt4[k]*time1[l] + beta.c11 *week7[l]
}
b0[k] ~ dnorm(beta.c0,beta.tau0)
}

```



```
beta.c0 ~ dnorm(0.0,1.0E-8)
beta.c1 ~ dnorm(0.0,1.0E-8)
beta.c2 ~ dnorm(0.0,1.0E-8)
beta.c3 ~ dnorm(0.0,1.0E-8)
beta.c5 ~ dnorm(0.0,1.0E-8)
beta.c6 ~ dnorm(0.0,1.0E-8)
beta.c7 ~ dnorm(0.0,1.0E-8)
beta.c8 ~ dnorm(0.0,1.0E-8)
beta.c9 ~ dnorm(0.0,1.0E-8)
beta.c10 ~ dnorm(0.0,1.0E-8)
beta.c11 ~ dnorm(0.0,1.0E-8)
beta.tau0 ~ dgamma(0.0001,0.0001)
sigmatau0 <- 1/beta.tau0
rho ~ dunif(-1,1)
isigmasq ~ dgamma(0.0001,0.0001)

intercept <- beta.c0
treatment2 <- beta.c1
treatment3 <- beta.c2
treatment4 <- beta.c3
leg_left_right <- beta.c5
gender <- beta.c6
time <- beta.c7
```

```

week_7 <- beta.c11

treatment2_time <- beta.c8

treatment3_time <- beta.c9

treatment4_time <- beta.c10

AR1 <- rho

}

# Data

list(time1=c(1,2,3,4,5,6,7,8,9,10,11,12), M=12, N=28,

rmas=structure(.Data=c(

.

.

.

.

.

.

.

.

.

.

),

.Dim=c(28,12)),

tmt1= c(0,0,0,0,1,0,0,0,0,0,0,1,0,0,1,0,0,

0,0,0,0,0,1,1,0,0,1,0),

tmt2= c(0,1,0,0,0,1,0,0,0,0,1,0,0,0,0,0,0,

```

```

0,0,1,1,1,0,0,0,1,0,0),
tmt3= c(1,0,0,0,0,0,1,1,1,1,0,0,1,0,0,1,0,
0,0,0,0,0,0,1,0,0,0),
tmt4= c(0,0,1,1,0,0,0,0,0,0,0,0,1,0,0,1,
1,1,0,0,0,0,0,0,0,0,1),
legtr= c(1,1,1,1,1,1,1,1,1,0,1,1,0,1,1,0,
0,0,0,0,0,0,1,0,0,0,0,0),
week7= c(0,0,0,0,0,0,1,0,0,0,0,0),
sex= c(1,1,1,1,1,1,0,0,0,0,0,0,0,0,1,1,1,
1,1,1,1,1,1,1,1,0,0,0))

# Initial values

list(
b0=c(200,200,200,200,200,200,200,200,200,200,
200,200,200,200,200,200,200,200,200,200,
200,200,200,200,200,200,200),
beta.c0=160,beta.c1=3,beta.c2=-6,beta.c3=26,
beta.c5=-4,beta.c6=107, beta.c7=1.9,beta.c8=
-0.8,beta.c9=1.3, beta.c10=1.2,beta.c11=-20,
isigmasq=1,beta.tau0=1,rho=0.9)

```

(ii). Tumor Volume

```
model
{
  mualpha ~ dnorm(0.0,1.0E-8)
  mubeta ~ dnorm(0.0,1.0E-8)
  taualpha ~ dgamma(0.0001,0.0001)
  taudel ~ dgamma(0.0001,0.0001)
  taugam ~ dgamma(0.0001,0.0001)
  tau ~ dgamma(0.0001,0.0001)
  taubeta ~ dgamma(0.0001,0.0001)
  beta.c1 ~ dnorm(0.0,1.0E-8)
  beta.c2 ~ dnorm(0.0,1.0E-8)
  beta.c3 ~ dnorm(0.0,1.0E-8)
  beta.c5 ~ dnorm(0.0,1.0E-8)
  beta.c6 ~ dnorm(0.0,1.0E-8)
  beta.c7 ~ dnorm(0.0,1.0E-8)
  beta.c8 ~ dnorm(0.0,1.0E-8)
  beta.c9 ~ dnorm(0.0,1.0E-8)
  beta.c10 ~ dnorm(0.0,1.0E-8)
  sig<-1/tau
  sigalpha<-1/taualpha
}
```

```

sigbeta<- 1/taubeta

for(i in 1 : N)
{
alpha[i]~dnorm(mualpha,taualpha)

beta[i]~dnorm(mubeta,taubeta)

for (k in 1:L)
{
del[i,k]~dnorm(alpha[i],taudel)

gam[i,k]~dnorm(beta[i],taugam)

for (j in 1:M)
{
logv[i,j,k]~dnorm(mu[i,j,k],tau)

mu[i,j,k] <- alpha[i] + del[i,k]+beta[i]*time[j]+
gam[i,k]*time[j]+ beta.c1*tmt2[i]+ beta.c2*tmt3[i]
+ beta.c3*tmt4[i]+ 0*tmt1[i]+ beta.c5*legtr[i]+
beta.c6*sex[i]+beta.c7*leg[k] +
beta.c8 * tmt2[i] * time[j] +
beta.c9 * tmt3[i] * time[j] +
beta.c10 * tmt4[i] * time[j]
}
}
}
}

```

```

treatment2 <-beta.c1

treatment3 <- beta.c2

treatment4 <- beta.c3

leg_treated_untreated <-beta.c7

leg_left_right <- beta.c5

gender <- beta.c6

treatment2_time <- beta.c8

treatment3_time <-beta.c9

treatment4_time <- beta.c10

}

# Data

list(time=c(1,2,3,4,5,6,7,8,9,10,11,12), M=12,
N=28,L=2, logv=structure(.Data=c(
.
.
.
.
.
.
.
.
.
.
.Dim=c(28,12,2)),
tmt1=c(0,0,0,0,1,0,0,0,0,0,0,1,0,0,1,0,0,0,0,0,0,
0,0,1,1,0,0,1,0),

```

```

tmt2=c(0,1,0,0,0,1,0,0,0,0,1,0,0,0,0,0,0,0,0,1,
1,1,0,0,0,1,0,0),
tmt3=c(1,0,0,0,0,0,1,1,1,1,0,0,1,0,0,1,0,0,0,0,
0,0,0,0,1,0,0,0),
tmt4=c(0,0,1,1,0,0,0,0,0,0,0,0,0,1,0,0,1,1,1,0,
0,0,0,0,0,0,0,1),
legtr= c(1,1,1,1,1,1,1,1,1,1,0,1,1,0,1,1,0,0,0,0,
0,0,0,1,0,0,0,0,0),
sex=c(1,1,1,1,1,1,0,0,0,0,0,0,0,0,1,1,1,1,1,1,
1,1,1,1,1,0,0,0),
leg=c(0,1))

# Initial Values
list(alpha=c(0.1,0.12,0.13,0.14,0.15,0.16,0.17,0.18,
0.19,0.015, 0.215,0.315,0.415,0.515,0.615,0.715,
0.815,0.151,0.152,
0.153,0.154,0.155,0.156,0.157,0.185,0.915,0.4315,0.2315),
beta=c(0.21,0.22,0.23,0.24,0.25,0.26,0.27,0.28,0.29,0.12,
0.122,0.1232,0.1342,0.132,0.142,0.152,0.162,0.172,0.182,
0.192,0.212,0.222,0.232,0.242,0.252,0.262,0.272,0.282),
del=structure(.Data=c(0.1,0.12,0.13,0.14,0.15,0.16,
0.17,0.18,0.19,0.015,0.215,0.315,0.415,0.515,
0.615,0.715,0.815,

```

```

0.151,0.152,0.153,0.154,0.155,0.156,0.157,0.185,0.915,
0.4315,0.2315,0.1215,0.6715,0.1,0.12,0.13,0.14,0.15,0.16,
0.17,0.18,0.19,0.015,0.215,0.315,0.415,0.515,0.615,0.715,
0.815,0.151,0.152,0.153,0.154,0.155,0.156,0.157,
0.185,0.915), .Dim=c(28,2)),
gam=structure(.Data=c(0.1,0.12,0.13,0.14,
0.15,0.16,0.17,0.18,
0.19,0.015,0.215,0.315,0.415,0.515,0.615,
0.715,0.815,0.151,
0.152,0.153,0.154,0.155,0.156,0.157,0.185,
0.915,0.4315,0.2315,
0.1215,0.6715,0.1,0.12,0.13,0.14,0.15,0.16,
0.17,0.18,0.19,0.015,
0.215,0.315,0.415,0.515,0.615,0.715,0.815,
0.151,0.152,0.153,
0.154,0.155,0.156,0.157,0.185,0.915),
.Dim=c(28,2)),
beta.c1=-0.05,beta.c2=0.07,beta.c3=0.11,beta.c5=-0.6,
beta.c6=-0.2,mubeta=0.33,taubeta=1,mualpha=-1.5,
taualpha=5,taugam=1,beta.c7=-0.15,beta.c8=0.02,
beta.c9=0.07,beta.c10=0.006,taubeta=262,taudel=5,
taugam=300,tau=6)

```


(iii). Survival

```
model
{
  for (i in 1:N)
  {
    surt [i] ~ dweib(p,mut [i]) I(surt.cen[i] , )
    log(mut [i] ) <- beta2.c1+
    beta2.c3 * tmt2[i] + beta2.c4 * tmt3[i] +
    beta2.c5 * tmt4[i] +
    beta2.c7*genderfem[i]
  }

  scale<- -(1/p)

  intercept<- scale * beta2.c1
  treatment2<- scale * (beta2.c3)
  treatment3<- scale * (beta2.c4)
  treatment4<- scale * (beta2.c5)
  gender<- scale * (beta2.c7)

  c2a<-beta2.c1+beta2.c3
  median2male<-pow(log(2) * exp(-c2a),1/p)
```

```

c2b<-beta2.c1+beta2.c3+beta2.c7
median2female<-pow(log(2) * exp(-c2b),1/p)
c3a<-beta2.c1+beta2.c4
median3male<-pow(log(2) * exp(-c3a),1/p)
c3b<-beta2.c1+beta2.c4+beta2.c7
median3female<-pow(log(2) * exp(-c3b),1/p)
c4a<-beta2.c1+beta2.c5
median4male<-pow(log(2) * exp(-c4a),1/p)
c4b<-beta2.c1+beta2.c5+beta2.c7
median4female<-pow(log(2) * exp(-c4b),1/p)
c100a<-beta2.c1
median100male<-pow(log(2) * exp(-c100a),1/p)
c100b<-beta2.c1+beta2.c7
median100female<-pow(log(2) * exp(-c100b),1/p)

p ~ dgamma(0.0001,0.0001)
beta2.c1 ~ dnorm(0,1.0E-8)
beta2.c3 ~ dnorm(0,1.0E-8)
beta2.c4 ~ dnorm(0,1.0E-8)
beta2.c5 ~ dnorm(0,1.0E-8)
beta2.c7 ~ dnorm(0,1.0E-8)
}

```

```

#data

list(N=28,surt=c(
.
.
.
.
),
surt.cen=c(
.
.
.
.
),
genderfem=c( 0,0,0,0,0,0,1,1,1,1,1,1,1,1,0,0,0,0,0,
0,0,0,0,0,0,1,1,1),
tmt2=c( 0,1,0,0,0,1,0,0,0,0,1,0,0,0,0,0,0,0,0,1,1,1,
0,0,0,1,0,0),
tmt3=c( 1,0,0,0,0,0,1,1,1,1,0,0,1,0,0,1,0,0,0,0,0,0,
0,0,1,0,0,0),
tmt4=c( 0,0,1,1,0,0,0,0,0,0,0,0,0,0,1,0,0,1,1,1,0,0,0,
0,0,0,0,0,1))

# initial values

```

```
list(beta2.c1=0,beta2.c3=0,beta2.c4=0,  
beta2.c5=0,p=4.8,beta2.c7=0)
```

(iv). Joint Model

```
model
{
  c1<-(isigmasq)/(1-pow(rho,2))
  c2<-(isigmasq)*(1+pow(rho,2))/(1-pow(rho,2))
  c3<-isigmasq*(-rho)/(1-pow(rho,2))
  for (i in 1:M)
  {
    for (j in 1:M)
    {
      a1[i,j]<-step(1-i)*step(1-j)
      b1[i,j]<-step(i-M)*step(j-M)
      c1a[i,j]<-step(i-j)*step(j-i)
      c1b[i,j]<-(1 - step(1-i)*step(1-j))
      c1c[i,j]<-(1 - step(i-M)*step(j-M))
      d1a[i,j]<-step(1-i+j)*step(1-j+i)
      d1b[i,j]<-(1-step(i-j))*step(j-i)
      e1a[i,j]<-step(1-j+i)*step(1-i+j)
      e1b[i,j]<-(1-step(j-i))*step(i-j)
      a[i,j]<-a1[i,j]*c1
      b[i,j]<-b1[i,j]*c1
    }
  }
}
```

```

c[i,j]<-c1a[i,j]*c1b[i,j]*c1c[i,j]*c2
d[i,j]<-d1a[i,j]*d1b[i,j]*c3
e[i,j]<-e1a[i,j]*e1b[i,j]*c3
tau[i,j]<- a[i,j]+b[i,j]+c[i,j]+d[i,j]+e[i,j]
}
}
for(k in 1 : N)
{
rmass[k,1:M]~dmnorm(mu[k,1:M],tau[1:M,1:M])
for (q in 1:M)
{
mu[k, q] <- b0 + beta.c1*tmt2[k]+ beta.c2*tmt3[k] +
beta.c3*tmt4[k]+ 0*tmt1[k]+beta.c5*legtr[k]
+beta.c6*sex[k] +beta.c7*time1[q] +
beta.c8*tmt2[k]*time1[q] + beta.c9*tmt3[k]*time1[q]
+ beta.c10*tmt4[k]*time1[q] + beta.c11 *week7[q] +U[k]
}

surt[k] ~ dweib(p,mut [k]) I(surt.cen[k] , )
log(mut [k] ) <- beta2.c1+ 0*tmt1[k]+
beta2.c3 * tmt2[k] + beta2.c4 * tmt3[k] +
beta2.c5 * tmt4[k] +
beta2.c7*genderfem[k] + r1*U[k]

```

```

U[k] ~ dnorm(0,tauU0)
}
b0 ~ dnorm(0.0,1.0E-8)
tauU0 ~ dgamma(0.0001,0.0001)
r1 ~ dnorm(0.0,1.0E-8)
beta.c1 ~ dnorm(0.0,1.0E-8)
beta.c2 ~ dnorm(0.0,1.0E-8)
beta.c3 ~ dnorm(0.0,1.0E-8)
beta.c5 ~ dnorm(0.0,1.0E-8)
beta.c6 ~ dnorm(0.0,1.0E-8)
beta.c7 ~ dnorm(0.0,1.0E-8)
beta.c8 ~ dnorm(0.0,1.0E-8)
beta.c9 ~ dnorm(0.0,1.0E-8)
beta.c10 ~ dnorm(0.0,1.0E-8)
beta.c11 ~ dnorm(0.0,1.0E-8)
rho~dunif(-1,1)
isigmasq~dgamma(0.0001,0.0001)

intercept_mass<- b0
treatment2_mass<- beta.c1
treatment3_mass<- beta.c2
treatment4_mass<- beta.c3

```

```

leg_left_right <- beta.c5

gender_mass <- beta.c6

time<- beta.c7

week_7 <- beta.c11

treatment2_time<- beta.c8

treatment3_time<- beta.c9

treatment4_time<- beta.c10

AR1<- rho

scale<- -(1/p)

intercept_survival<- scale * beta2.c1

treatment2_survival<- scale * (beta2.c3)

treatment3_survival<- scale * (beta2.c4)

treatment4_survival<- scale * (beta2.c5)

gender_survival<- scale * (beta2.c7)

c2a<-beta2.c1+beta2.c3

median2male<-pow(log(2) * exp(-c2a),1/p)

c2b<-beta2.c1+beta2.c3+beta2.c7

median2female<-pow(log(2) * exp(-c2b),1/p)

c3a<-beta2.c1+beta2.c4

median3male<-pow(log(2) * exp(-c3a),1/p)

c3b<-beta2.c1+beta2.c4+beta2.c7

median3female<-pow(log(2) * exp(-c3b),1/p)

```



```

c4a<-beta2.c1+beta2.c5
median4male<-pow(log(2) * exp(-c4a),1/p)
c4b<-beta2.c1+beta2.c5+beta2.c7
median4female<-pow(log(2) * exp(-c4b),1/p)
c100a<-beta2.c1
median100male<-pow(log(2) * exp(-c100a),1/p)
c100b<-beta2.c1+beta2.c7
median100female<-pow(log(2) * exp(-c100b),1/p)

p ~ dgamma(0.0001,0.0001)
beta2.c1 ~ dnorm(0,1.0E-8)
beta2.c3 ~ dnorm(0,1.0E-8)
beta2.c4 ~ dnorm(0,1.0E-8)
beta2.c5 ~ dnorm(0,1.0E-8)
beta2.c7 ~ dnorm(0,1.0E-8)
}

# data
list(time1=c(1,2,3,4,5,6,7,8,9,10,11,12), M=12, N=28,
rmass=structure(.Data=c(
.
.
.
.

```

```

.Dim=c(28,12)),
tmt1= c( 0,0,0,0,1,0,0,0,0,0,0,1,0,0,1,0,0,0,0,0,
0,0,1,1,0,0,1,0),
tmt2= c( 0,1,0,0,0,1,0,0,0,0,1,0,0,0,0,0,0,0,0,1,
1,1,0,0,0,1,0,0),
tmt3= c( 1,0,0,0,0,0,1,1,1,1,0,0,1,0,0,1,0,0,0,0,
0,0,0,0,1,0,0,0),
tmt4= c( 0,0,1,1,0,0,0,0,0,0,0,0,0,1,0,0,1,1,1,0,
0,0,0,0,0,0,0,1),
legtr= c( 1,1,1,1,1,1,1,1,1,0,1,1,0,1,1,0,0,0,0,
0,0,0,1,0,0,0,0),
week7= c(0,0,0,0,0,0,1,0,0,0,0,0),
sex= c( 1,1,1,1,1,1,0,0,0,0,0,0,0,0,1,1,1,1,1,1,
1,1,1,1,1,0,0,0),
surt=c(
.
.
.
.
),
surt.cen=c(
.
.

```

```

.
.
),
genderfem=c( 0,0,0,0,0,0,1,1,1,1,1,1,1,1,0,0,0,0,
0,0,0,0,0,0,0,1,1,1))

# Initial Values

list(
b0=160,beta.c1=0.43,beta.c2=-8,beta.c3=26,beta.c5=3,
beta.c6=107, beta.c7=1.9,beta.c8=-0.7,beta.c9=1.4,
beta.c10=1.3,beta.c11=-20,
isigmasq=1,rho=0.9,
beta2.c1=22,beta2.c3=0,beta2.c4=0,
beta2.c5=0,p=4.8,beta2.c7=0,
tauU0=1, r1=0)

```

Appendix C

MASS GRAPHS

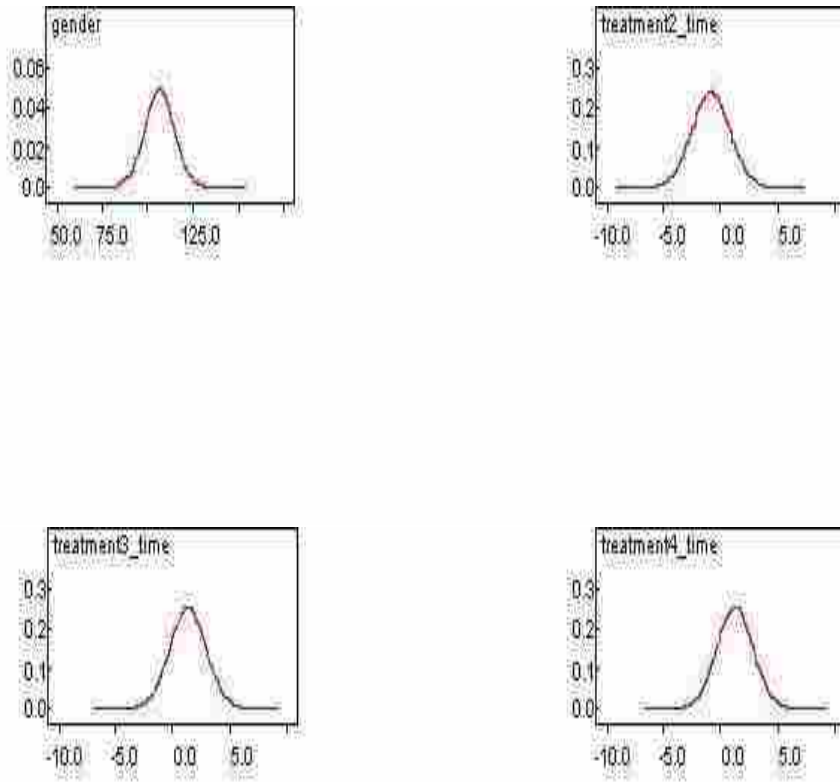


Figure C.1: Posterior Distributions for selected coefficients in Mass model

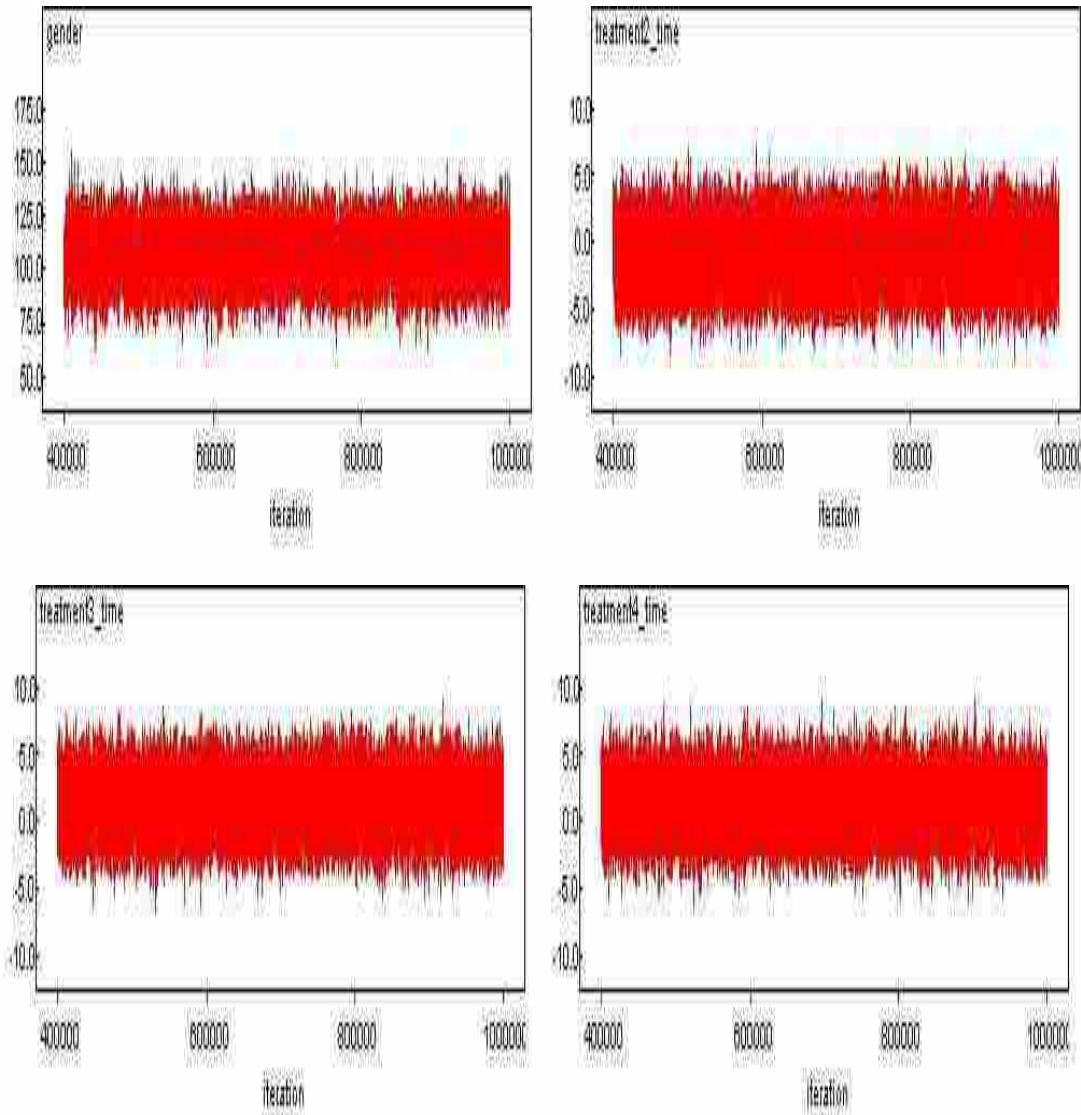


Figure C.2: Time series plots for selected coefficients in Mass model

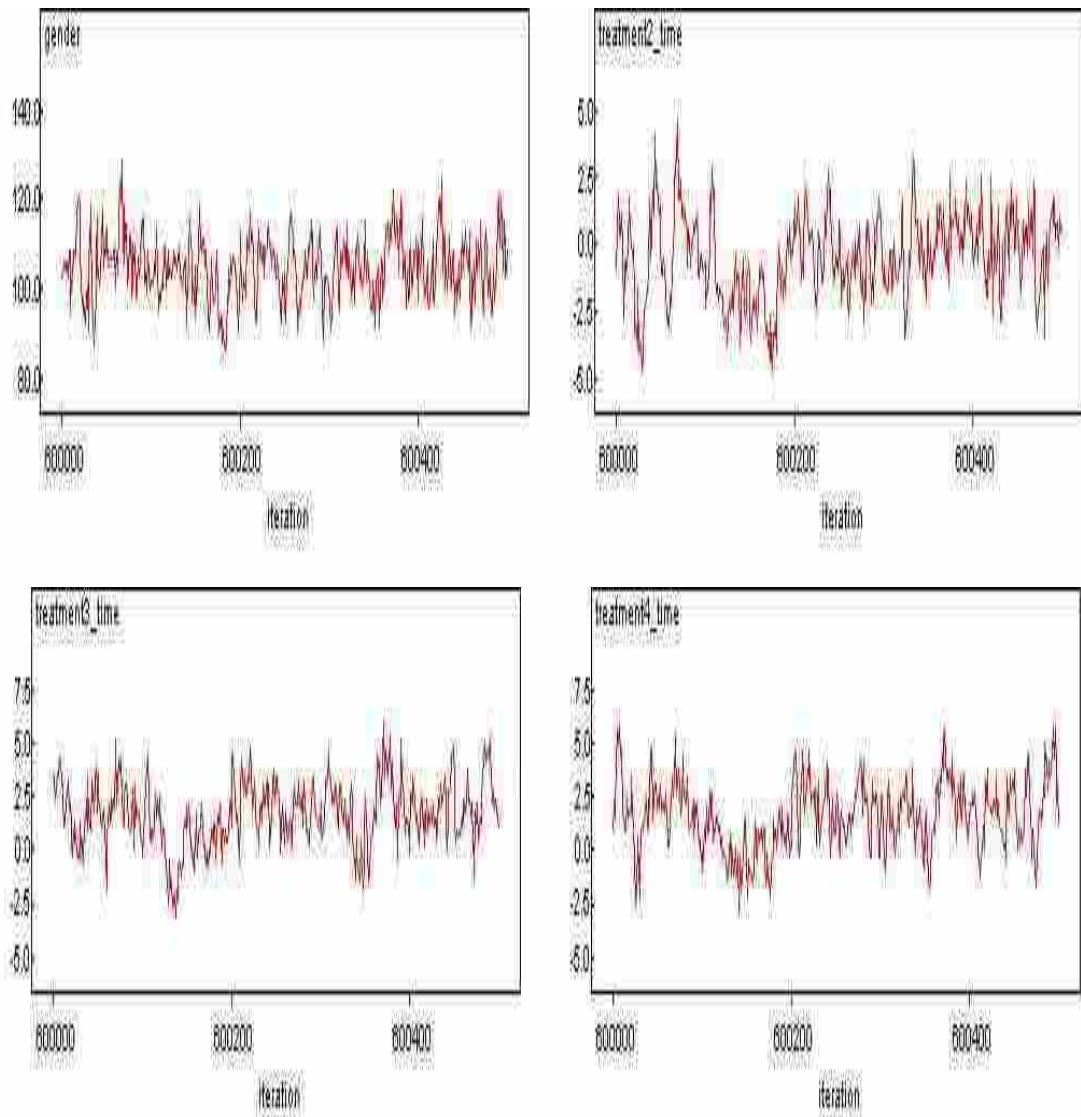


Figure C.3: Plots to demonstrate mixing for selected coefficients in Mass model

Appendix D

TUMOR VOLUME GRAPHS

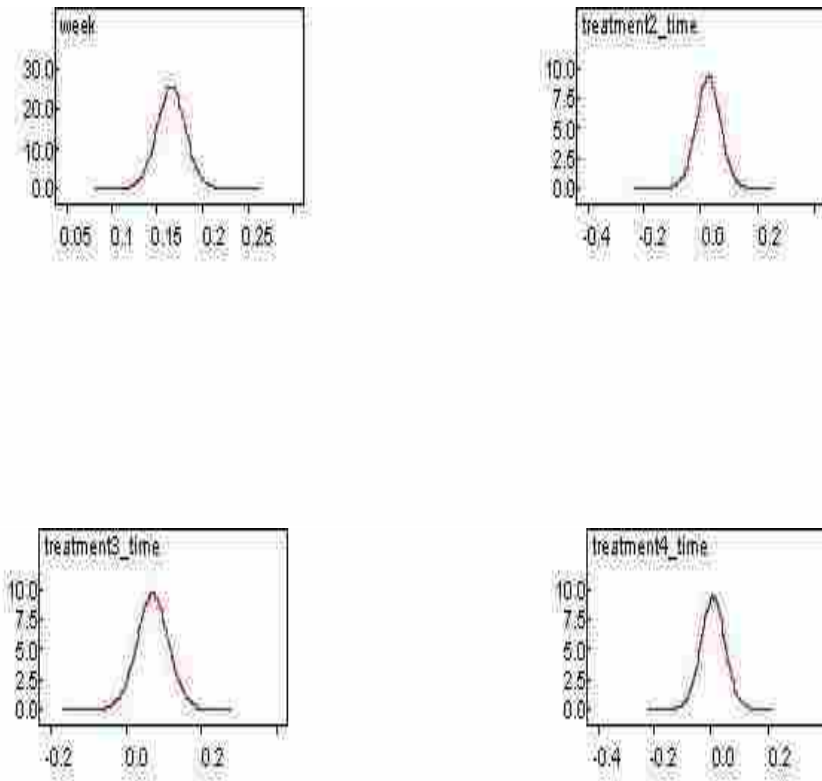


Figure D.1: Posterior Distributions for selected coefficients in Tumor volume model

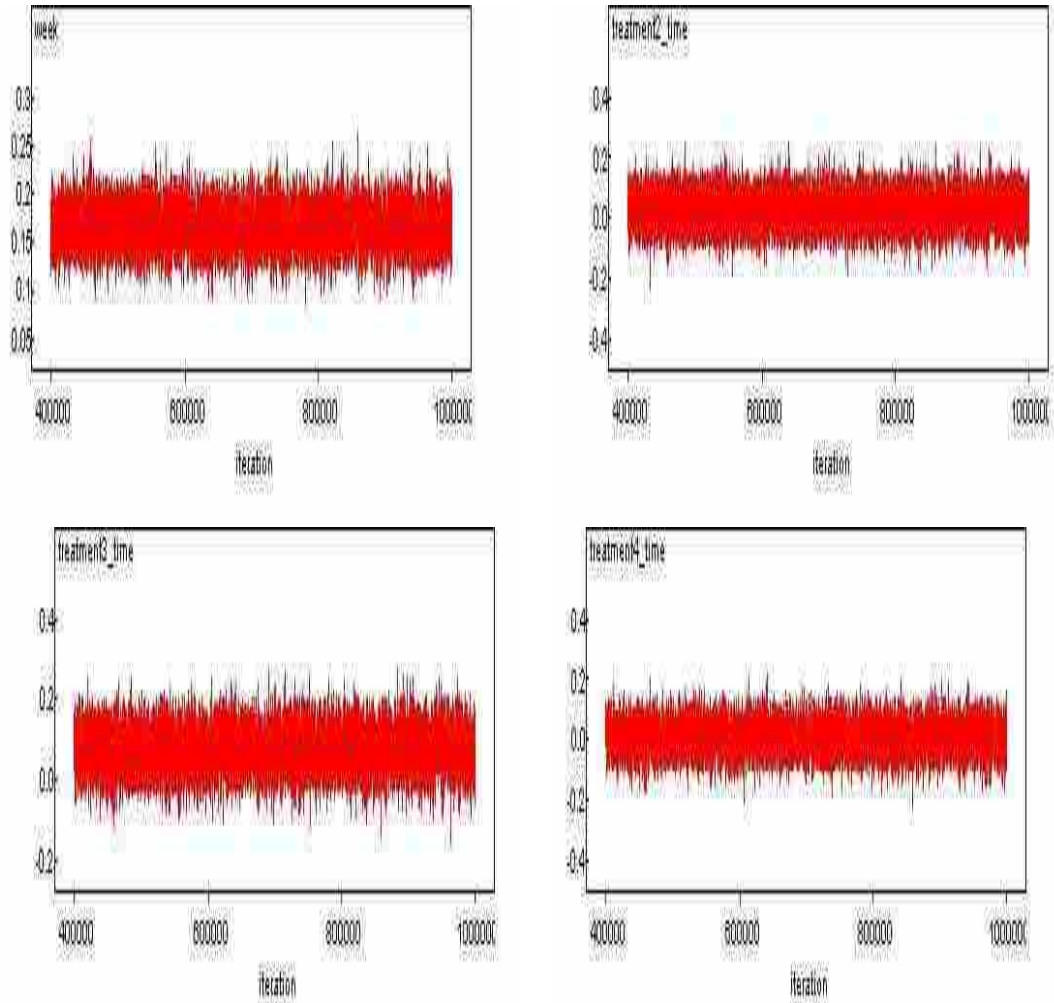


Figure D.2: Time Series plots for selected coefficients in Tumor volume model

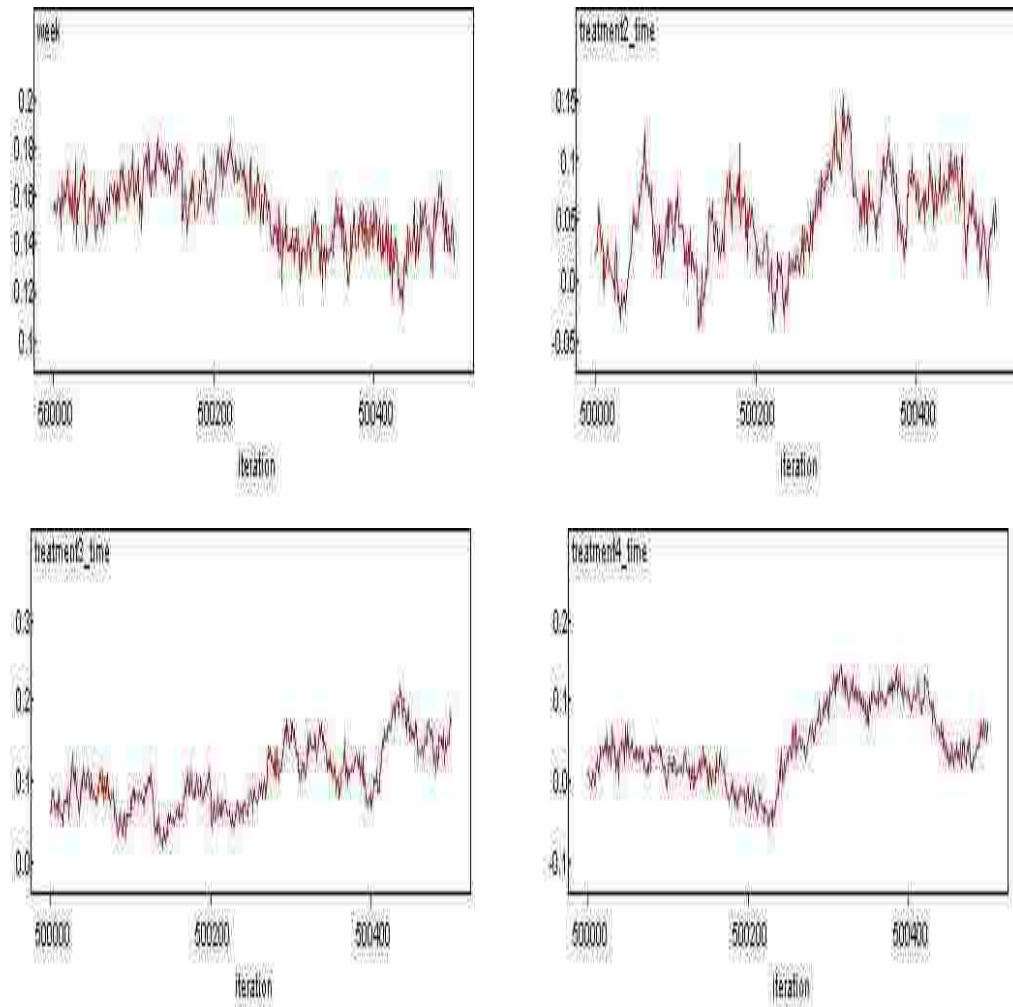


Figure D.3: Plots to demonstrate mixing for selected coefficients in Tumor volume model

Appendix E

SURVIVAL GRAPHS

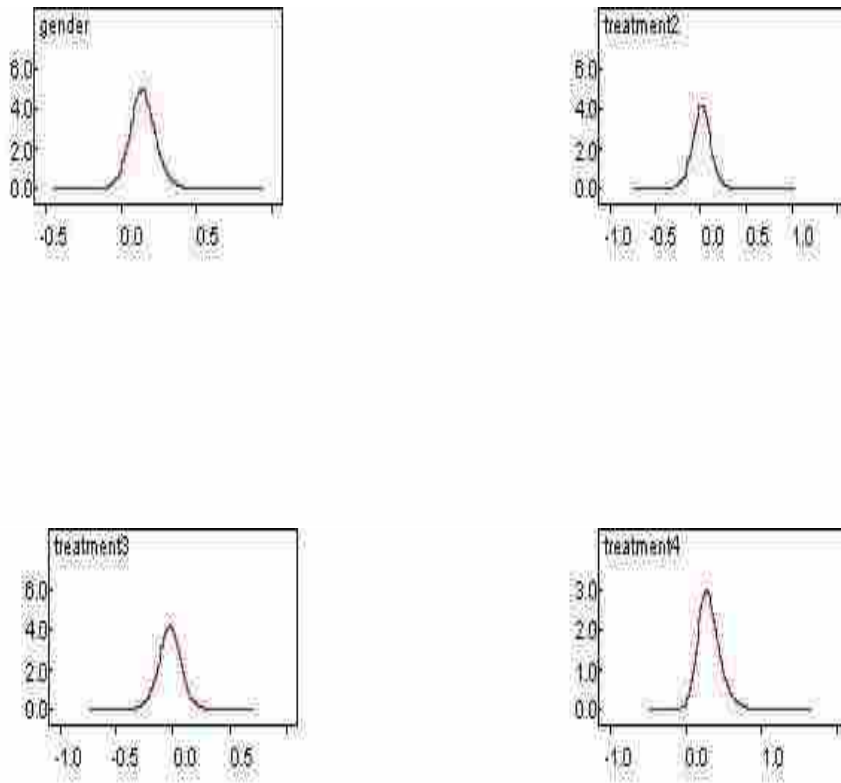


Figure E.1: Posterior Distributions for selected coefficients in Survival model

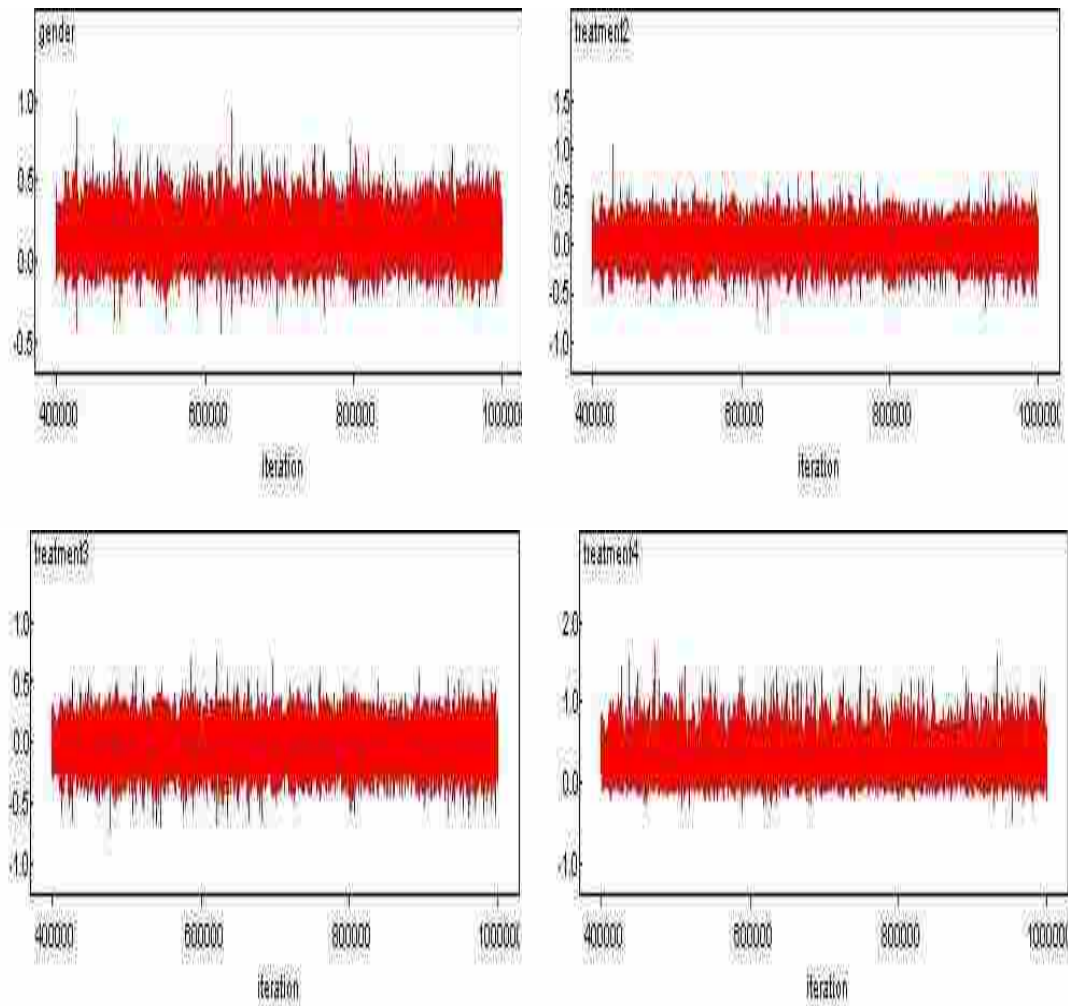


Figure E.2: Time Series plots for selected coefficients in Survival model

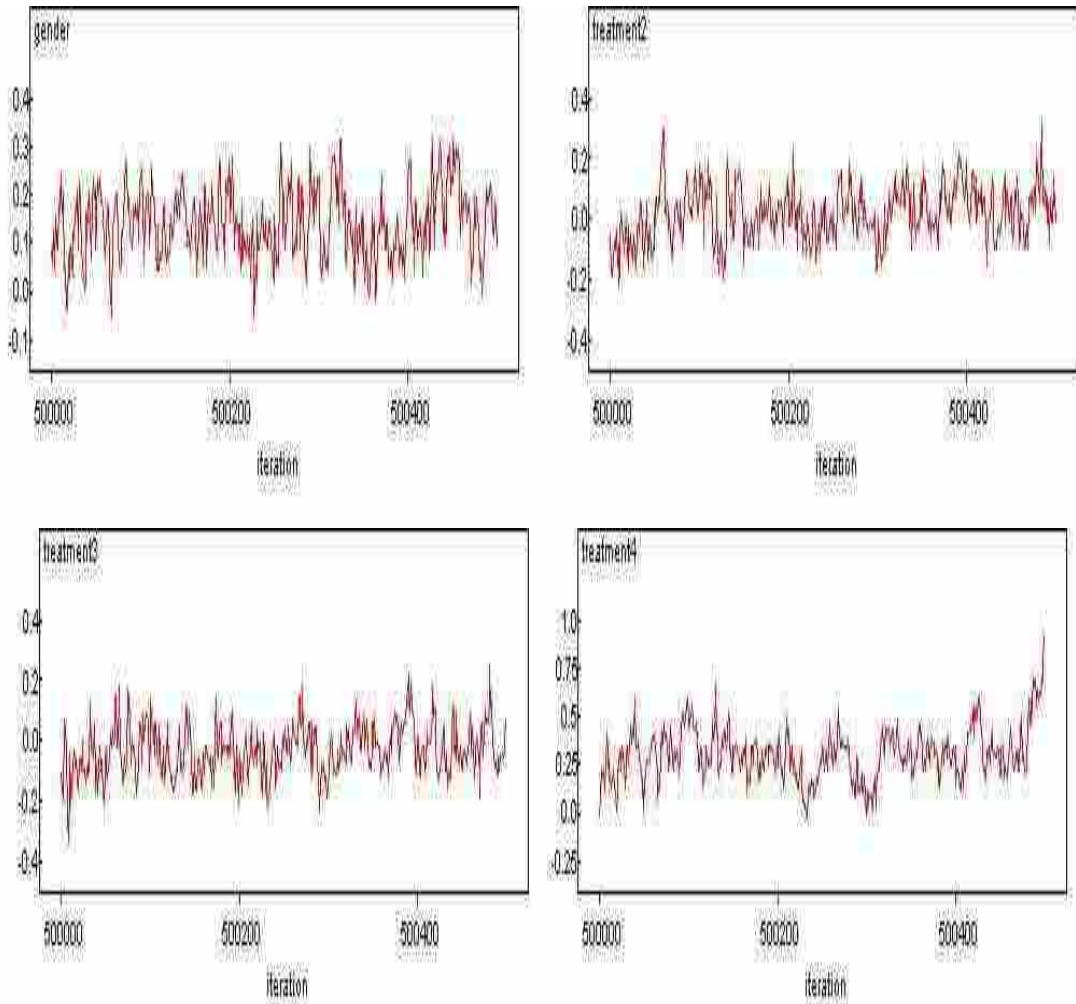


Figure E.3: Plots to demonstrate mixing for selected coefficients in Survival model

Appendix F

JOINT MODEL GRAPHS

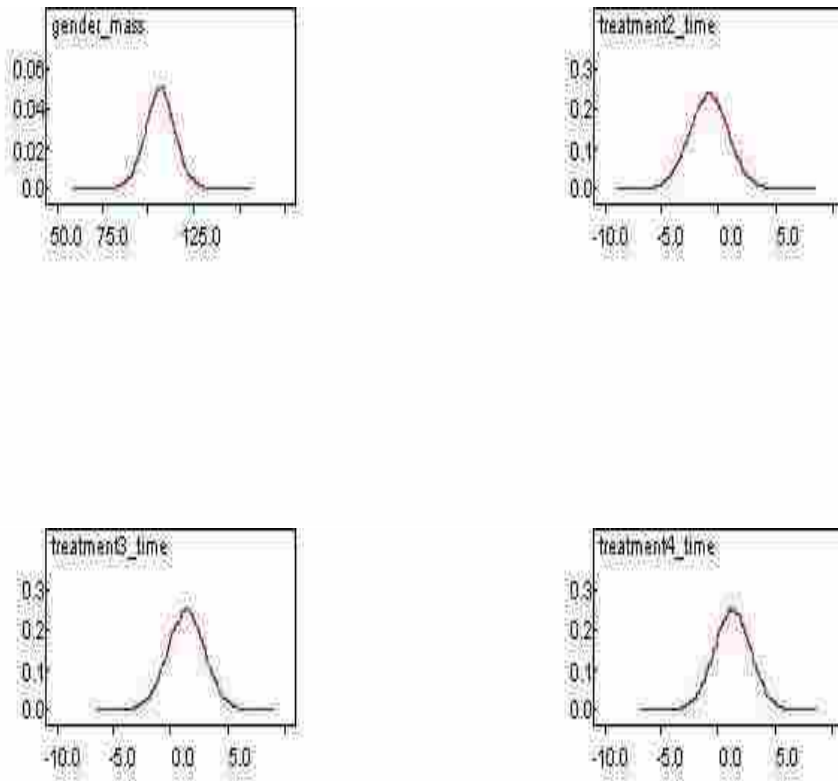


Figure F.1: Posterior Distributions for selected coefficients of the Mass Submodel in the Joint Model

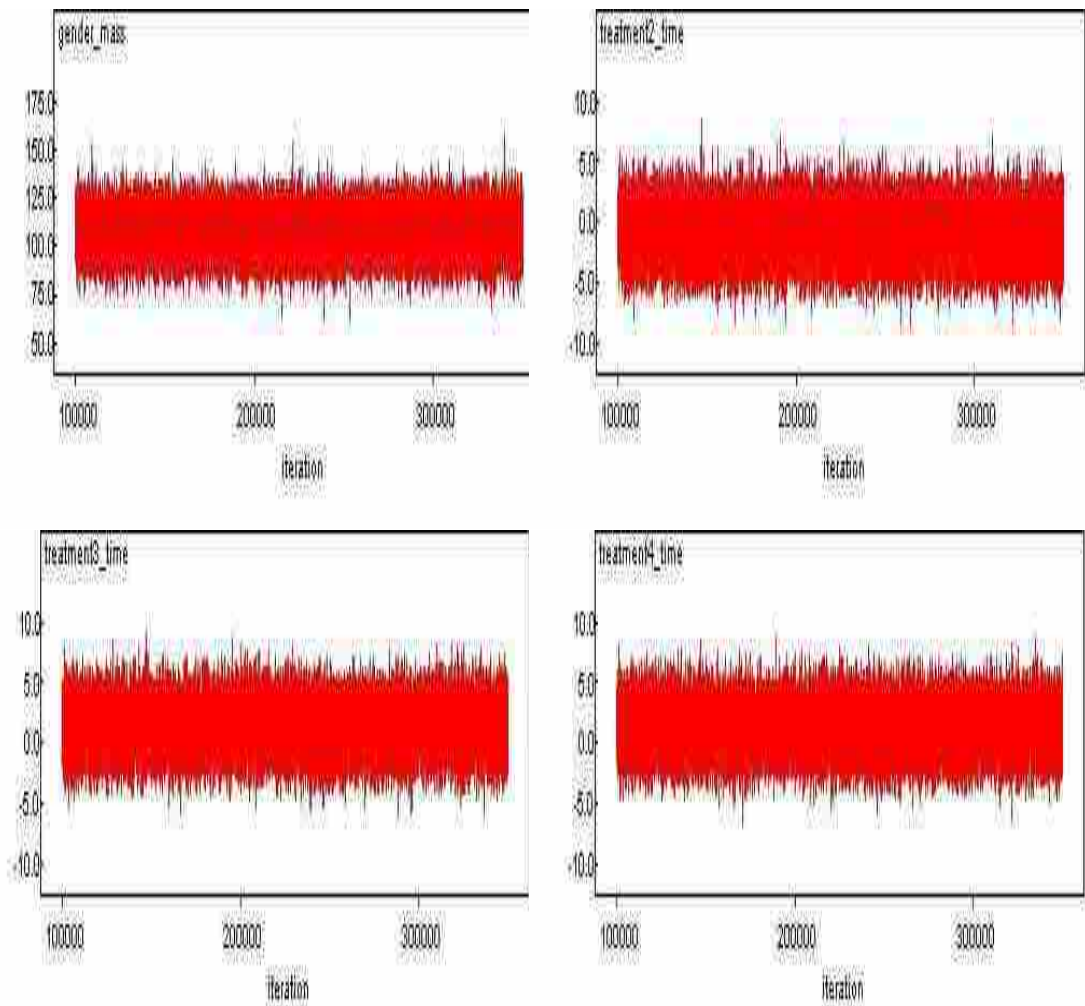


Figure F.2: Time Series plots for selected coefficients of the Mass Submodel in the Joint Model

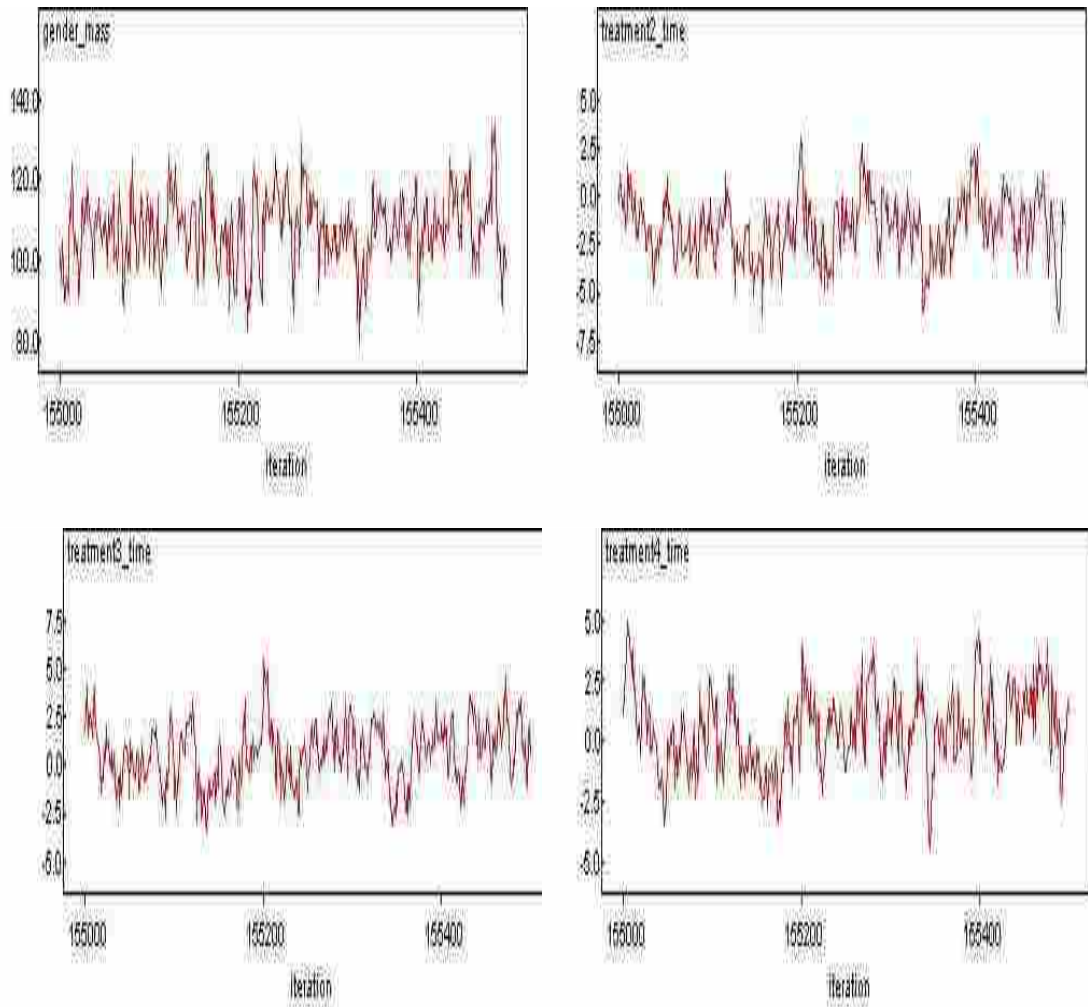


Figure F.3: Plots to demonstrate mixing for selected coefficients of the Mass Submodel in the Joint Model

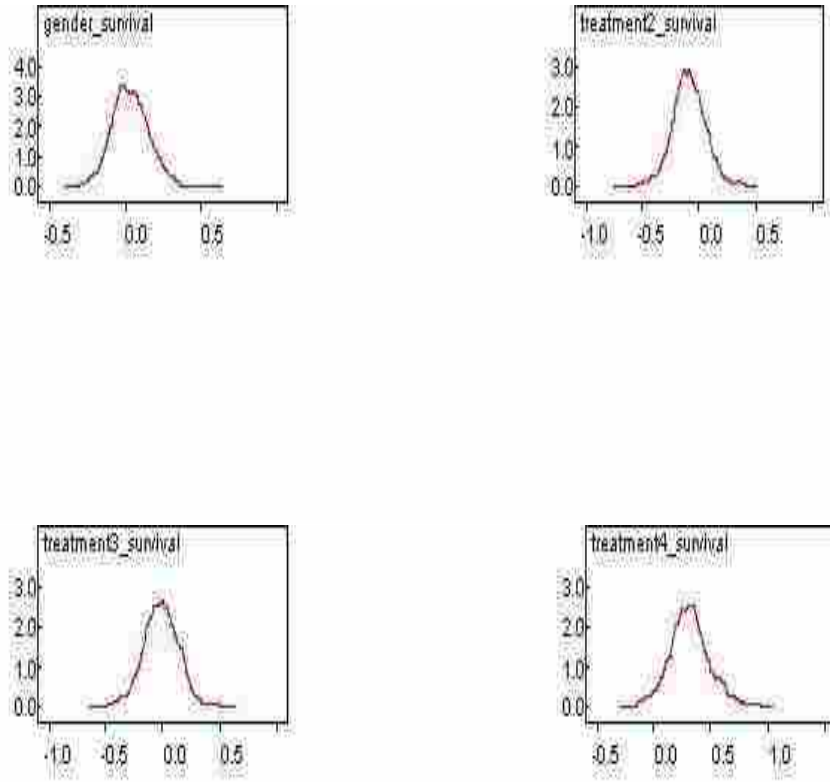


Figure F.4: Posterior Distributions for selected coefficients of the Survival Submodel in the Joint Model

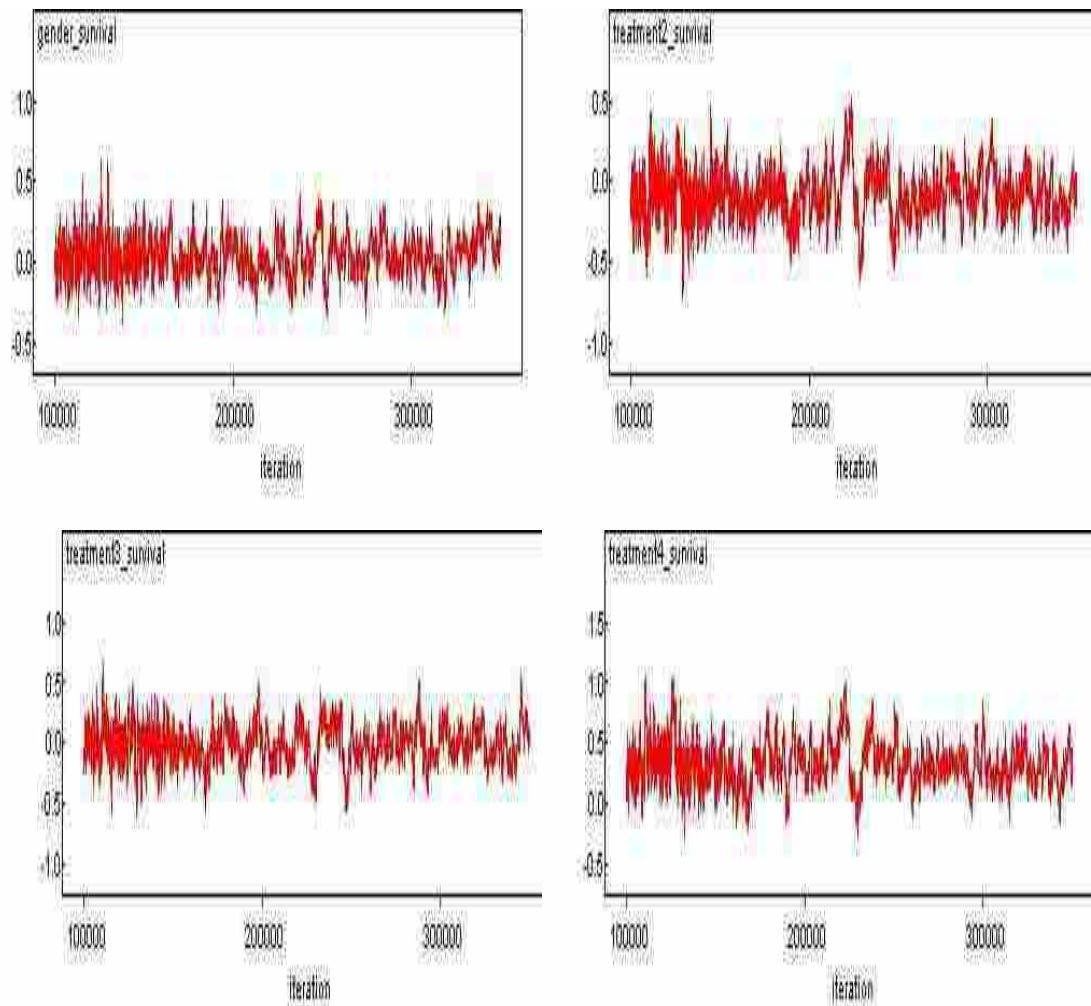


Figure F.5: Time Series plots for selected coefficients of the Survival Submodel in the Joint Model

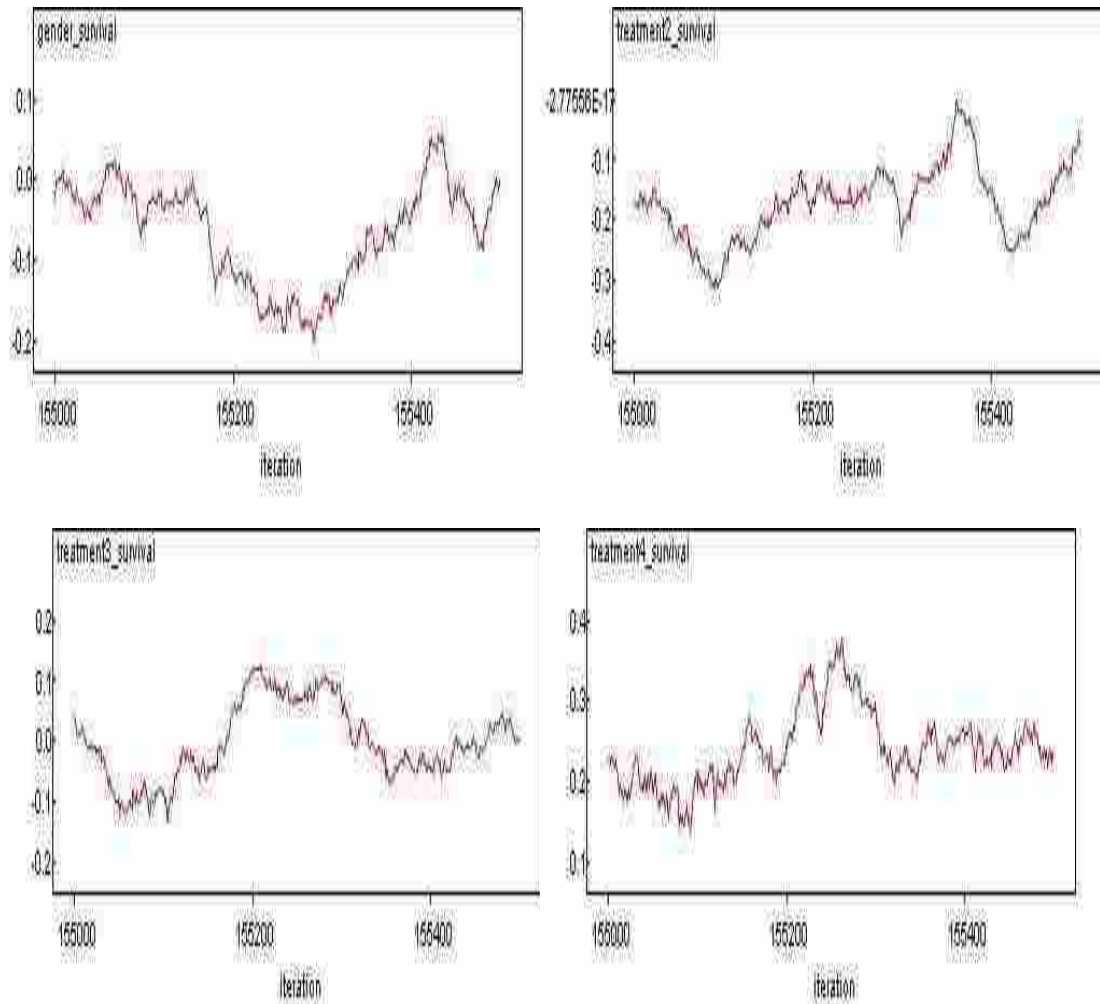


Figure F.6: Plots to demonstrate mixing for selected coefficients of the Survival Sub-model in the Joint Model