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A Joint Longitudinal-Survival Model with Possible Cure: An Analysis of Patient Outcomes on the Liver Transplant Waiting List

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Abstract
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ABSTRACT

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Data from transplant patients has many unique characteristics that can cause problems with statistical modeling. The patient's underlying disease / health trajectory is known to affect both longitudinal biomarker values and the probability of both death and transplant. In liver transplant patients, biomarker values show a sharp exponential increase in the days preceding death or transplant. Patients who receive transplants show an immediate drop in biomarker values post-transplant, followed by an exponential decrease. Patients' survival probabilities also change post-transplant, with dependencies on pre-transplant biomarker values. To properly incorporate these clinical features, we developed a joint longitudinal-survival model that links an exponential growth-decay longitudinal model to a modified cure survival model. This allows us to evaluate patient biomarker trajectories and survival times both pre- and post-transplant. The models are linked by patient-level shared random effects that appear in the biomarker trajectories and the frailties of the survival functions. Estimates are obtained via the EM algorithm, with random effects integrated out of the complete data likelihood function using adaptive quadrature techniques. Simulations show our model performs reasonably well under a variety of conditions. We demonstrate our methods using liver transplant data from the United Network of Organ

Sharing (UNOS). We use total serum bilirubin as our longitudinal outcome, with age at waitlisting and gender as linear covariates. Gender is used as a covariate in the survival model both pre- and post-transplant.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

CHAPTER 1

Introduction

Transplant waiting list data is a relatively new resource to researchers. National transplant registry data was not collected until 1987. (Contrast this with other studies, such as the United States census, the Framingham Heart Study, and the Nurses' Health Study, which began in 1790, 1948, and 1976, respectively.) In 1984, Congress passed the National Organ Transplant Act (NOTA). NOTA created the national transplant registry, which is now called the Organ Procurement and Transplantation Network (OPTN). The United Network of Organ Sharing (UNOS) was given a federal contract in 1986 to manage OPTN. More detailed information can be found on the OPTN website (http://optn.transplant.frsa.gov).

This registry (henceforth known as the UNOS registry) contains data about all patients who are waitlisted for an organ transplant. This data includes both demographic and medical information. Each organ has its own set of relevant biomarker values which can be used to measure organ function and can serve as surrogates to indicate underlying illness and overall health status. For example, on the liver transplant waiting list, patients' bilirubin levels are collected to measure liver function. In contrast, forced vital capacity (FEV) is used to assess the lung function of patients on the lung transplant waiting list.

Transplant data have many interesting features that can present challenges with statistical methods typically used to analyze transplant data. It is reasonable to hypothesize that patients' longitudinal biomarker values are related to survival times in complex ways. Sicker patients may be more likely to die or be removed from the

waiting list. Healthier patients may be passed over for transplants in favor of giving organs to others in a more critical situation. This relationship is not necessarily acknowledged in simple statistical analyses. A more complex model is often required to properly analyze this data. Joint statistical models that incorporate "informative dropout" are more appropriate for analyzing this type of data (Little and Rubin, 1987).

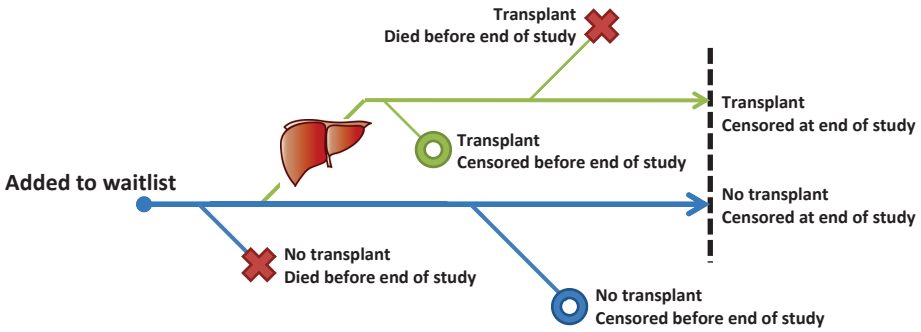
Transplant data has additional complications that cause issues even when joint models are used to account for informative dropout. For example, some (but not all) of the patients on the waiting list for an organ will receive a transplant. Transplant is expected to change a patient's survival time (i.e. transplant changes a patient's relative hazard of death). This violates the key assumption of constant relative hazards in the Cox proportional hazard model, commonly used to model patient survival times (e.g. Wulfsohn and Tsiatis, 1997; Hsieh et al., 2006).

In this dissertation, we develop a joint longitudinal-survival model that addresses these challenges of modeling transplant data. This new model allows for non-linear biomarker trajectories, as well as the possibility of patient health improvement via transplant. Use of a two-part survival model avoids the assumption of non-constant relative hazards in patients who receive transplants.

1.1. Modeling transplant data

Transplant data has many characteristics that make it somewhat difficult to model. Researchers must consider the impact of inclusion/exclusion criteria, censoring processes, possible cure via medical intervention, and missing longitudinal data. Though these issues do show up in other types of studies, they do not often appear simultaneously.

Figure 1.1: Survival outcomes



After patients are placed on the transplant waiting list, they can experience a variety of different outcomes (illustrated in Figure 1.1). Patients may or may not receive a transplant, and patients can either die or be censored from the study. This gives us four different outcome possibilities: died before receiving transplant, censored before receiving transplant, died after receiving transplant, or censored after receiving transplant.

Patients can leave the study for "random" or "non-random" reasons. For example, a patient may move far away and have to switch care providers. This would be considered a random dropout, since the patient's decision to move is likely unrelated to his disease process. In contrast, a patient could stop participating in the study because he is too sick to make it to his follow-up appointments. This would be considered non-random since the patient's reasons for dropout are directly related to his disease process. A more in-depth discussion of the implications of patient dropout

can be found in Chapter 2.

In studies of transplant data, researchers often focus primarily on pre- or post-transplant data, but not both (Merion et al., 2003; Crowley and Hu, 1977). This is not necessarily the best study design. It is possible that healthier patients or patients with other desirable characteristics (e.g. a common blood type) are more likely to be selected for transplant (Crowley and Hu, 1977). These patients are therefore more likely to be censored in a pre-transplant study, and are more likely to enroll in a post-transplant study. Assuming random patient dropout is clearly not appropriate here. Care must be taken when setting up study assumptions, as incorrect assumptions about patients' dropout processes could change inference results (Heitjan, 1993).

Another potential pitfall arises in the fact that pre-transplant risk factors can affect post-transplant outcomes. Baliga et al. (1992) showed that pre-transplant factors, such as the need for pre-transplant dialysis, are associated with poor post-transplant outcomes, such as a higher risk of post-transplant sepsis and death. A common method of incorporating pre-transplant data into post-transplant analysis is to include summary measures of pre-transplant activity. For example, Hariharan et al. (2002) and Chertow et al. (1996) considered pre-transplant interventions (e.g. blood transfusions and dialysis) and panel reactive antibody (PRA) levels in the recipient (a measure of immune response) as potential factors affecting post-transplant outcomes. Although proper in intent, this strategy does not capture the changes in patient biomarker values. These changes may be of interest in pre-transplant studies as well as post-transplant studies. Merion et al. (2003) showed that the rate of change in a patient's liver function is an important predictor of mortality on the waiting list. Wu et al. (2010) demonstrated that the slope of changes in post-transplant renal function is predictive of graft survival. It is reasonable to suspect that pre-transplant

biomarker trajectories could be related to post-transplant outcomes. At this time, models that incorporate these trajectory features have not been developed.

Additional complications arise when the goal of a study is to compare pre- and post-transplant outcomes. A commonly-used method is to model the data as two separate cohorts. Bloom et al. (2005) demonstrated this process. Analysis of pre-transplant mortality is assessed using all patients' pre-transplant data. Patients in this group are censored at the time of transplant. Post-transplant mortality is then analyzed using post-transplant data from any patient who received a transplant. Though this method allows for the comparison of pre- and post-transplant survival outcomes, it ignores the fact that the two analysis groups overlap. Since they contain some of the same patients, they are likely not completely independent.

To properly analyze patient survival times, we must acknowledge two issues. First, patients who receive transplants can still die, but they are presumably less likely to die post-transplant than those patients who do not receive transplants. Second, not all patients will receive transplants. Law et al. (2002) and Li et al. (2010) assumed that each patient had some probability of being cured by treatment. The survival times for patients who were not cured were modeled using a Cox proportional hazards model. These cure models allow for the potential difference in survival probabilities for patients who are cured. Unfortunately, cure models make some assumptions that are inappropriate for transplant data. First, cure models assume that all patients receive the treatment. Second, these models assume that patients who are "cured" cannot die from the disease being treated (Baker, 1978). Therefore, standard cure models do not allow for us to draw conclusions about pre- *and* post-transplant survival, nor will they allow us to compare treated and untreated patients.

Like most longitudinal analyses, studies using transplant data have to overcome the

problem of missing data. Authors use a variety of approaches to deal with the problem of patient dropout in longitudinal studies of transplant data. Fann et al. (2002) and Felder-Puig et al. (2006) used multiple imputation (MI) to analyze data from adult and pediatric bone marrow transplant patients, respectively. MI relies on relationships between the variables in the dataset. For example, suppose we have a simple dataset that contains a patient's weight, height, and age. For patients with missing values for height, we could use MI to predict the missing height values using patients' weights and/or ages. MI methods are useful tools when neither the dropout mechanism nor the actual missing values are of interest (Little and Rubin, 1987). In the case of transplant data, however, we are interested in both the dropout process (death) and the missing data (potential future biomarker values).

Another method used to deal with missing data is last observation carried forward (LOCF) (Pocock, 1984). LOCF imputes a subject's missing observations with the last observed value for that subject. Clearly, this method has a high potential for improper inference. Biased parameter estimates and underestimated variance are particular problems. (Saha and Jones (2009) discussed these issues in depth.) Furthermore, like MI, LOCF does not allow for inference about the dropout process or the missing data values.

Joint models, which allow for inference about both submodels, are needed. These models are discussed in detail in Chapter 2.

1.2. Liver transplant data

UNOS is a widely-used source of transplant data. When subjects are initially wait-listed for an organ transplant, they are entered into the UNOS database. Patient records are updated occasionally, with the frequency of updates depending on the

type of organ. For liver transplant patients, UNOS requires updates with varying frequency, based upon patients' Model for End-Stage Liver Disease (MELD) scores. MELD scores are used to predict 90-day mortality for patients on the liver transplant waiting list, with higher scores indicating a higher probability of death (Wiesner et al., 2003). UNOS uses this information to rank patients and determine liver distribution policies (Kamath et al., 2001).

The MELD score combines three different biomarker values: serum creatinine (Cr), serum total bilirubin (TBIL), and the international normalized ratio of prothrombin time (commonly referred to as INR). MELD scores are calculated using the following formula:

$$MELD = 3.78 \cdot \log[TBIL] + 11.2 \cdot \log[INR] + 9.57 \cdot \log[Cr] + 6.43$$

Any MELD component with a value of less than 1 is replaced with 1, to prevent negative scores. Adjustments are also made for patients who have been on dialysis in the past week. For those patients, 4.0 is used as the value for serum creatinine. MELD scores are rounded to the nearest whole integer, and are capped at a value of 40.

MELD scores are used to predict pre-transplant survival times of patients and are unfortunately not validated for use post-transplant. Since we are interested in both pre- and post-transplant data, we have chosen to use a single component of the MELD score, bilirubin, for our analysis. INR, serum creatinine, or another continuous biomarker could also be a valid longitudinal outcome.

A potential source of bias in the data comes from the fact that MELD scores (and therefore bilirubin, INR, and creatinine values) are, by law, updated more often for

sicker patients (UNOS, 2002). To avoid this bias, we limited the analysis to patients for whom we could augment the UNOS data with data from the Hospital of the University of Pennsylvania (HUP). This gives us more observations per subject, regardless of health status. We collected data from all patients waitlisted at HUP between February 27, 2002, and May 13, 2011. The start date was chosen because that is the day on which UNOS began using MELD scores to rank all patients on the waitlist. Data are collected more consistently after that point. Our initial dataset consisted of 1,387 patients, each with a minimum of four observations. Patients who did not receive transplants were followed for a maximum of five years. Patients who received transplants were followed either for five years post-waitlisting, or from time of waitlisting until three years post transplant, whichever came first.

Samples of this data were used to demonstrate the methods in Chapters 3 and 4. Demographic and baseline summaries of these samples are given in Tables 3.4 and 4.4.

1.3. Discussion

The unique characteristics of transplant data clearly require the use of advanced statistical techniques that allow for a link between longitudinal and survival outcomes. In this dissertation, we develop a method for combining longitudinal and survival data in the presence of possible patient cure. Using a shared parameter model, we link the longitudinal and survival submodels via random effects that appear in both the subject-specific longitudinal trajectories and survival frailties.

In this chapter, we have outlined the unique issues associated with transplant data, as well as some authors' attempts to analyze it. We have also provided a discussion of the need for joint modeling of data with informative dropout.

In the remainder of this dissertation, we develop a joint longitudinal-survival model to analyze liver transplant data. Chapter 2 gives a thorough background of the issue of informative dropout and what statistical models can be used to compensate for it. Chapter 3 develops an initial joint model, where patients are assumed to be cured post-transplant. Chapter 4 extends the model in Chapter 3 to include the possibility of post-transplant death. We demonstrate our methods using liver transplant data from the United Network of Organ Sharing and the Hospital of the University of Pennsylvania. Chapter 5 summarizes the methods developed and the implications for the analysis of transplant data.

CHAPTER 2

Informative Dropout

Missing data is a challenge that exists in almost every kind of study. The validity of many standard longitudinal analysis methods depends on the randomness of the dropout process (Diggle et al., 2002). In real data, this may or may not be the case. Missingness can occur due to several different processes, each of which has different implications for the statistical analysis of the data.

2.1. Missingness patterns

Missingness can be classified as missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR). These patterns are defined by what portions (if any) of the observed data are dependent on the missing data (Rubin, 1976). Let $\boldsymbol{Y}$ be the complete data. We can then divide $\boldsymbol{Y}$ into two subsets: the observed data $\boldsymbol{Y_{obs}}$ and the unobserved data $\boldsymbol{Y_{miss}}$. $\boldsymbol{R}$ is a vector of indicator variables describing the missingness pattern of the data. Let $f_Y\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right)$ be the probability density function (PDF) of $\boldsymbol{Y}$ and $f_R\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right)$ be the missingness process.

We can write the joint PDF of $\boldsymbol{Y}$ and $\boldsymbol{R}$ as

$$f_{Y,R}\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}, \boldsymbol{R}\right) = f_Y\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) f_R\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) \tag{2.1.1}$$

We integrate the missing data out of the full PDF.

$$\begin{aligned} f_{Y_{obs},R}\left(\boldsymbol{Y_{obs}}, \boldsymbol{R}\right) &= \int f_{Y,R}\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}, \boldsymbol{R}\right) d\boldsymbol{Y_{miss}} \\ &= \int f_{Y}\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) f_{R}\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) d\boldsymbol{Y_{miss}} \end{aligned} \tag{2.1.2}$$

This gives us the PDF for the observed data.

2.1.1. Missing completely at random

If the data are MCAR, the missingness process depends on neither the observed nor the missing data. This gives us the following simplification for (2.1.2).

$$\begin{aligned} f_{Y_{obs},R}\left(\boldsymbol{Y_{obs}}, \boldsymbol{R}\right) &= \int f_{Y}\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) f_{R}\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) d\boldsymbol{Y_{miss}} \\ &= \int f_{Y}\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) f_{R}\left(\boldsymbol{R}\right) d\boldsymbol{Y_{miss}} \\ &= f_{R}\left(\boldsymbol{R}\right) \int f_{Y}\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) d\boldsymbol{Y_{miss}} \\ &= f_{R}\left(\boldsymbol{R}\right) f_{Y}\left(\boldsymbol{Y_{obs}}\right) \end{aligned} \tag{2.1.3}$$

Maximum likelihood theory seeks to maximize the likelihood with respect to our data, so maximizing (2.1.3) with respect to $\boldsymbol{Y_{obs}}$ is equivalent to maximizing

$$f^{*}_{Y_{obs},R} = C \cdot f_{Y}\left(\boldsymbol{Y_{obs}}\right) \tag{2.1.4}$$

where C is a constant. This is true because $f_{R}\left(\boldsymbol{R}\right)$ does not depend on $\boldsymbol{Y_{obs}}$. Therefore, if the data are MCAR, all standard longitudinal methods can be used. This kind of missingness is considered "ignorable".

2.1.2. Missing at random

For MAR data, the missingness process can depend on $\boldsymbol{Y_{obs}}$, but not on $\boldsymbol{Y_{miss}}$. This more relaxed assumption still allows us to simplify (2.1.2), though not quite as much as with MCAR data.

$$\begin{aligned} f_{Y_{obs},R}\left(\boldsymbol{Y_{obs}}, \boldsymbol{R}\right) &= \int f_Y\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) f_R\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) d\boldsymbol{Y_{miss}} \\ &= \int f_Y\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) f_R\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}\right) d\boldsymbol{Y_{miss}} \\ &= f_R\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}\right) \int f_Y\left(\boldsymbol{Y_{obs}}, \boldsymbol{Y_{miss}}\right) d\boldsymbol{Y_{miss}} \\ &= f_R\left(\boldsymbol{R} \mid \boldsymbol{Y_{obs}}\right) f_Y\left(\boldsymbol{Y_{obs}}\right) \end{aligned} \tag{2.1.5}$$

Missingness in MAR data is still considered to be "ignorable". Diggle et al. (2002) noted that standard likelihood-based longitudinal analyses, such as generalized linear mixed models, can still be used with MAR data, though there is a potential for a loss in efficiency. Analyses that rely on other methods of estimation, such as generalized estimating equations (GEE), cannot be used. Using GEE with MAR data can lead to parameter estimates with a bias as high as 50% (Touloumi et al., 2001).

2.1.3. Not missing at random

If data are NMAR, the missingness process depends on both $\boldsymbol{Y_{obs}}$ and $\boldsymbol{Y_{miss}}$. No simplification can be made to (2.1.2). This missingness is considered "non-ignorable" or "informative". NMAR data requires the use of a joint longitudinal-missingness model in order to obtain proper parameter estimates.

2.2. Analysis methods

Little and Rubin (1987) defined four broad (somewhat overlapping) classes of procedures used to compensate for missing data.

1. Complete-case analysis

   Complete-case analysis is a very straightforward method of dealing with missing data. Subjects with any missing data are simply excluded from analysis. This simplicity comes at a cost, however. Little and Rubin (1987) noted that the loss of information from excluded subjects can result in less precise estimates, or, even worse, severe bias in parameter estimates.

2. Probability weighting

   Probability weighting treats the missing data patterns as if they were part of the sampling design. The data are then analyzed using methods similar to standard stratified analysis. Chand and Rothwell (1977) give an example of a standard stratified data analysis. Slight changes must be made to "true" stratified analysis methods to account for increased variance (since the sampling weights are not actually fixed by design). There is also still a potential for estimate bias, if the data are NMAR (Little and Rubin, 1987).

3. Missing-value imputation

   Imputation methods "fill in" missing data values using fully-observed data. Last observation carried forward (LOCF) and multiple imputation (MI), discussed in Section 1.1, are two examples of imputation procedures. Imputation methods have many of the same pitfalls as complete-case methods. If the data are NMAR, parameter estimates are subject to bias (Lavori et al., 1995; Sterne et al., 2009) and incorrect standard errors (Lavori et al., 1995).

4. Model-based procedures

   Model-based missing data analysis requires the specification of a model for both the outcome and the missingness process (Little and Rubin, 1987). A variety of model-based procedures are discussed in the remainder of this chapter.

Methods for dealing with NMAR data arose out of the need for proper study design and data analysis in longitudinal trials. In many of these trials, it is reasonable to suspect that patient dropout could depend on patients' longitudinal outcomes. For example, the outcome for the Intermittent Positive Pressure Breathing (IPPB) trial was patients' longitudinal measurements of forced expiratory volume (FEV). Wu and Carroll (1988) showed that dropout from the IPPB trial was not random. Patients with low initial FEVs or rapid rates of decline in FEV were more likely to die. Similar issues were encountered in the Modification of Diet in Renal Disease (MDRD) trial. The outcome for the MDRD trial was patient kidney function, as measured by glomerular filtration rate (GFR). Patients with very low GFRs were more likely to be removed from the study due to death, beginning dialysis, or kidney transplant (Beck et al., 1991). Similar challenges are encountered when analyzing data from many different areas of study, including AIDS (De Gruttola and Tu, 1994), opiate addiction (Follmann and Wu, 1995), pain relief (Pulkstenis et al., 1998), and prostate cancer (Law et al., 2002).

There are two standard classes of joint models: selection and pattern-mixture models. The types of models differ with respect to which parts of the complete-data likelihood are conditional and which are marginal. For the following discussion, we assume that we have data with repeated longitudinal observations, $\boldsymbol{Y_{obs}}$, and dropout time information, t. Dropout is governed by some random process $\boldsymbol{R}$.

2.2.1. Pattern-mixture models

Pattern-mixture models assume that patient longitudinal outcomes are conditional on the drop-out process (Little, 1993). Analysis is done by stratifying subjects on dropout time and combining the within-stratum models to form an overall marginal longitudinal model.

$$f_{Y_{obs},t}\left(\boldsymbol{Y_{obs}}, t\right) = \int f_Y\left(\boldsymbol{Y_{obs}} \mid t, \boldsymbol{R}\right) f_R\left(\boldsymbol{R} \mid t\right) f_t\left(t\right) d\boldsymbol{R} \tag{2.2.1}$$

This model is robust to misspecification, though it has the consequence of modeling the longitudinal data as conditional on the dropout process. This is a reasonable strategy in some cases, in particular when dealing with survey non-response. With non-response, we generally assume that patients with similar patterns of responses to some survey questions will have similar responses to other survey questions. Therefore, we can use the information from subjects with fully-observed responses to "fill in" the subjects with missing data. This is the justification for the method of multiple imputation, where the fully-observed data is used to predict the values for the missing data (Little and Rubin, 1987).

Conditioning the longitudinal model on future dropout is not always reasonable, though, particularly if the end goal of analysis is to develop a predictive model. In a predictive model, the subject's dropout time would be some unknown future event. A pattern-mixture model would clearly be unreasonable in a predictive model, since we would be attempting to predict an unknown outcome based on an unknown predictor (future dropout time). This model also prevents us from explicitly modeling the dropout process. The dropout process may be of interest if, for example, subject dropout is related to subject survival times.

2.2.2. Selection models

Selection models assume the drop-out process is conditional on patient longitudinal outcomes. Results are obtained by modeling the available data and adding on a conditional missingness model (Laird and Ware, 1982).

$$f_{Y_{obs},t}\left(\boldsymbol{Y_{obs}}, t\right) = \int f_Y\left(\boldsymbol{Y_{obs}}\right) f_t\left(t \mid \boldsymbol{Y_{obs}}, \boldsymbol{R}\right) f_R\left(\boldsymbol{R}\right) d\boldsymbol{R} \tag{2.2.2}$$

Selection models have the advantage of not conditioning analysis on future, unknown dropout times. However, they are not robust to violations of the assumption of normal longitudinal errors, or to misspecification of the dropout process (Little and Rubin, 1987).

2.2.3. Shared-parameter models

Shared-parameter models are a specific case of selection models. They have become a very popular method of dealing with informative dropout. Shared-parameter models treat the longitudinal and survival submodels as conditionally independent given underlying shared random effects. These random effects contribute to both the longitudinal and survival portions of the model (Ratcliffe et al., 2004).

$$f_{Y_{obs},t}\left(\boldsymbol{Y_{obs}}, t\right) = \int f_Y\left(\boldsymbol{Y_{obs}} \mid \boldsymbol{R}\right) f_t\left(t \mid \boldsymbol{R}\right) f_R\left(\boldsymbol{R}\right) d\boldsymbol{R} \tag{2.2.3}$$

The conditional independence assumption means that shared-parameter models are fairly straightforward to understand and explain. Both the longitudinal trajectories and dropout processes can be modeled explicitly. The longitudinal trajectories and dropout processes can, in theory, be modeled using any type of statistical submodel.

Several specific combinations have been proposed.

Early work with shared-parameter models focused on joint models with tractable, closed-form parameter estimates. Schluchter (1992) and De Gruttola and Tu (1994) employed multivariate normal models for patient biomarker trajectories and a one-to-one normalizing transformation of patient survival times. Both authors assumed that the shared random effects are normally distributed. This allowed for straightforward calculation of parameter estimates thought the use of the EM algorithm (Dempster et al., 1977).

Both authors modeled patient biomarker values using a standard linear mixed effects model:

$$\boldsymbol{Y}_i = \boldsymbol{X}_i\boldsymbol{\alpha} + \boldsymbol{Z}_i\boldsymbol{r}_i + \boldsymbol{\epsilon}_i \tag{2.2.4}$$

where $\boldsymbol{\epsilon}_i \sim N(\mathbf{0}, \sigma_\epsilon^2 \boldsymbol{I}_i)$, $\boldsymbol{X}_i$ and $\boldsymbol{Z}_i$ are both known, subject-specific design matrices, and $\boldsymbol{\alpha}$ and $\boldsymbol{r}_i$ are vectors of unknown fixed and random parameters, respectively.

Transformed patient survival times were also modeled using a random effects model:

$$T_i = \boldsymbol{w}_i^T\boldsymbol{\zeta} + \boldsymbol{\lambda}\boldsymbol{r}_i + \tau_i \tag{2.2.5}$$

where $\tau_i \sim N(0, s^2)$, $\boldsymbol{w}_i$ is a known design vector, $\boldsymbol{\zeta}$ and $\boldsymbol{\lambda}$ are unknown fixed parameters, and $\boldsymbol{r}_i$ is the shared link between this survival time model and (2.2.4) above.

These models give the following observed-data likelihood:

$$L_{obs} = \prod_{i=1}^{n} \Bigg[\int_{\boldsymbol{r}_i} \phi\left(\boldsymbol{Y}_i \mid \boldsymbol{r}_i, \boldsymbol{\alpha}, \sigma_\epsilon^2\right) \left(\phi\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{\zeta}, \boldsymbol{\lambda}, s^2\right)\right)^{\delta_i=1} \times \left(1 - \Phi\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{\zeta}, \boldsymbol{\lambda}, s^2\right)\right)^{\delta_i=0} \phi\left(\boldsymbol{r}_i\right) d\boldsymbol{r}_i \Bigg] \tag{2.2.6}$$

where t_i is the minimum of a patient's death (T_i) and censoring (C_i) time, δ_i is an indicator for death (1) or censoring (0), and n is the total number of subjects. $\phi(\cdot)$ and $\Phi(\cdot)$ are the PDF and cumulative density function (CDF) of the normal distribution, respectively.

Other authors have extended the methods proposed by Schluchter (1992) and De Gruttola and Tu (1994) to include non-linear longitudinal trajectories. For example, Chen et al. (2004) modeled patient immune response using either a linear or quadratic trajectory. Linear and quadratic models are not appropriate for transplant data, as neither model can capture a rapid growth or decay in biomarker values. Biomarker trajectories should be modeled using a more flexible trajectory. Specifically, exponential trajectories are often a reasonable representation of disease progress (Law et al., 2002). This exponential growth-decay model can capture the quick increases and decreases in biomarker values experienced by transplant patients. Non-parametric models have also been used. Elmi et al. (2011) proposed a B-spline for modeling longitudinal trajectories. B-splines are particularly useful when all patients are observed at regular intervals. Unfortunately, transplant patients are observed at many different times which vary from patient to patient. Furthermore, patients tend to have more observations clustered around the time of transplant. Use of a B-spline in this situation would therefore require patient-level knots to be used. The model would be very complex, both computationally and intuitively.

A popular choice for modeling non-normal patient dropout is a Cox proportional hazards model (Wu and Carroll, 1988; Law et al., 2002; Yu et al., 2004; Liu et al., 2004; Tsiatis and Davidian, 2004). Cox models allow the researcher to estimate hazard ratios, relative risks, and odds ratios without requiring assumptions to be made about patients' baseline hazards (Cox, 1972). Wulfsohn and Tsiatis (1997) proposed a linear process with subject-specific random slopes and intercepts for the longitudinal trajectories, and a Cox model for survival times. As with the methods discussed above, the authors assumed that the random effects were normally distributed. The proposed longitudinal model is

$$\boldsymbol{Y}_i = \alpha_{0i} + \alpha_{1i}\boldsymbol{u}_i + \boldsymbol{e}_i \tag{2.2.7}$$

where $\boldsymbol{e}_i \sim N(\boldsymbol{0}, \sigma_\epsilon^2 \boldsymbol{I}_i)$, $\boldsymbol{u}_i$ is the vector of observation times for subject i, and α_{0i} and α_{1i} follow a subject-specific bivariate normal distribution. Thus,

$$\begin{pmatrix} \alpha_{0i} \\ \alpha_{1i} \end{pmatrix} \sim N\left[\begin{pmatrix} \alpha_0 \\ \alpha_1 \end{pmatrix}, s_\alpha^2 \boldsymbol{I}_2 \right] \tag{2.2.8}$$

This is a slight extension of the longitudinal models proposed by Schluchter (1992) and De Gruttola and Tu (1994). Wulfsohn and Tsiatis (1997) modeled the longitudinal trajectories as fixed values measured with error. Patient survival times are analyzed using a Cox proportional hazard model.

$$\lambda(t) = \lambda_0(t) \exp\left(\zeta\left(\alpha_{0i} + \alpha_{1i} t\right)\right) \tag{2.2.9}$$

The two models above lead to the following observed data likelihood:

$$L_{obs} = \prod_{i=1}^{n} \Bigg[\int_{-\infty}^{\infty} \left(\prod_{j=1}^{m_i} \phi\left(y_{ij} \mid \boldsymbol{\alpha}_i\right) \right) \times \left[\lambda_0\left(t_i\right) \exp\left(\zeta\left(\alpha_{0i} + \alpha_{1i} t_i\right)\right)\right]^{\delta_i = 1} \exp\left(- \int_0^{t_i} \lambda_0\left(u\right) \exp\left(\beta\left(\alpha_{0i} + \alpha_{1i} u\right)\right) du \right) \times \phi\left(\boldsymbol{\alpha}_i\right) \Bigg] \tag{2.2.10}$$

where t_i is the minimum of survival and censoring time, δ_i is an indicator of death or censoring, and $\phi\left(\cdot\right)$ is the normal PDF. n and m_i are the number of subjects and observations per subject, respectively.

Simple Cox regression models do not adequately model the survival processes of transplant patients, however. Cox models assume that the likelihood of death increases as the study progresses, which is clearly not the case with patients who receive some sort of treatment intervention (Cox, 1972). It is reasonable to suspect that the probability of death for a patient who receives a treatment would be lower than that of a patient who does not receive a treatment. We must allow for this change in survival probabilities in our analysis. One method of doing this would be to use a cure model (Baker, 1978). Cure models assume that there are latent "cured" and "susceptible" groups. Given a treatment, patients in the cured group experience a quick improvement in health and are classified as "long-term survivors". Susceptible patients may or may not die over the course of the study. Though cure models do accommodate the possibility of a change in death risk post-transplant, they ignore two key features of transplant data. First, patients who receive transplants can indeed die post-transplant. Second, not every patient in the study will receive a transplant.

Other proposed models for patient dropout include discrete dropout times (Wu and

Carroll, 1988) and a logistic dropout process (Elmi, 2009). These models are not appropriate for transplant data, as the data contains continuous survival times.

2.3. Conclusion

In this chapter, we have discussed the issue of informative dropout in longitudinal studies. We have presented two classes of methods for dealing with informative dropout: pattern mixture models and selection models. We also discussed the history and evolution of the shared parameter model (a special case of a selection model).

The methods discussed in this chapter do not allow for all of the issues associated with transplant data. A valid model for transplant data would need to incorporate non-linear longitudinal trajectories which could differ pre- and post-transplant, survival probabilities which differ pre- and post-transplant, and a link that connects the pre- and post-transplant models. No such model currently exists.

In the following chapters, we will develop a model that compensates for the particular issues presented by transplant data.

CHAPTER 3

A Joint Longitudinal-Survival Model with Post-Transplant Cure

3.1. Introduction

Data from transplant patients have many interesting and unique characteristics. The data often contain both repeated longitudinal measurements as well as patient survival information. Unfortunately, studies using this kind of data often focus on either the longitudinal measurements (e.g., Karam et al., 2003) or patient survival (e.g. Gonwa et al., 1995). However, it has been shown that longitudinal and survival information are not independent (Kim et al., 2008). Ignoring the informative link between the two types of data can lead to biased parameter estimates, or, in extreme cases, incorrect inference (Diggle et al., 2002). Joint modeling should be used to analyze transplant data. Linking longitudinal and survival information allows for better inference. In this chapter, we develop a joint longitudinal-survival model that incorporates both patient survival information and longitudinal health trajectories. We use liver transplant data (discussed in Section 1.2) from the United Network of Organ Sharing (UNOS) and the Hospital of the University of Pennsylvania (HUP) to demonstrate this model.

Many authors have acknowledged the need for joint modeling. For example, Schluchter (1992); De Gruttola and Tu (1994); Yu et al. (2004); Chen et al. (2004), and Law et al. (2002) all proposed models for simultaneously analyzing longitudinal and survival information. These models all incorporated the idea of informative dropout into their analysis (Tsiatis and Davidian, 2004). There are three factors that must be considered in developing a joint model: the longitudinal submodel, the survival

submodel, and the link between the two submodels.

The model link is important, as it determines how the longitudinal and survival submodels interact. Authors have proposed a variety of different links. One straightforward approach is to include the longitudinal biomarker values as a time-varying covariate in the survival model (Yu et al., 2004). Unfortunately, this does not allow for inference to be made about the longitudinal biomarker values (since a covariate cannot be an outcome). Another approach is to assume that the patients can be divided into latent classes, with each class having its own survival and longitudinal models (Chen et al., 2004). This approach groups patients based on some future, unknown dropout time. This is undesirable if we wish to develop a dynamic prediction model. Therefore, both of these approaches are inappropriate for transplant data.

We believe that there are random effects that contribute to both the survival and longitudinal models. We include shared patient-level random effects in both the longitudinal and survival submodels. Law et al. (2002) used a somewhat similar approach. The authors assumed that patient longitudinal trajectories follow a trajectory governed by patient-specific, normally-distributed random effects. The patient-specific biomarker trajectories and the population-averaged expected value of the random effects were included as covariates in the survival model. Unlike Law et al. (2002), we assume a mixed-effects model for the longitudinal trajectories. We also do not assume normality of the random effects. Further, we assume that patients who receive treatment are certainly cured (i.e. for patients who receive transplants, the probability of survival is 1). (Note that this is not a clinically reasonable assumption. We relax this assumption in Chapter 4.)

As with standard longitudinal modeling, the options for which longitudinal model to use depend heavily on the type of data being examined. Ten Have et al. (2000) chose

an ordinal logistic model to analyze functional status data, while Chen et al. (2004) used a linear or quadratic model for melanoma data. Based on exploratory data analysis, we believe that our biomarker data follows a U-shaped (but not quadratic) trajectory. One option is to model this data non-parametrically using a B-spline as proposed by Elmi et al. (2011). However, B-splines are computationally intensive and difficult to interpret. Therefore, we will focus on a mixture of exponentials, similar to the model proposed by Law et al. (2002). This will allow us to have an interpretable parametric model.

A variety of survival submodels are also available, though not all are appropriate for transplant data. Many authors advocate the use of a Cox proportional hazards model (Cox, 1972; Liu et al., 2004; Law et al., 2002). A Cox model is reasonable for survival data where each subject has an increasing risk of death as the study progresses. These models also assume that, were the study to last for an infinite amount of time, all subjects would die. This assumption is invalid in the case of transplant data. Subjects have the possibility of receiving a transplant, and likely have a very different survival mechanism post-transplant than they did pre-transplant. Li et al. (2010); Law et al. (2002) and Chen et al. (2004) used cure models in their analysis. Cure models assume that, after receiving a treatment, some patients will be "cured" and cannot experience death. A simple cure model is still inadequate for transplant data, however. Cure models assume that all patients receive an intervention, which is not true of transplant candidates. Therefore, we must develop a modified cure model, which allows some patient to receive treatment and experience disease cure, while other patients continue the study untreated and potentially die.

In this chapter, we develop a shared-parameter longitudinal-survival model. Patient dropout and survival are modeled using a modified cure model. Longitudinal

biomarker trajectories are modeled using a mixture of exponentials. The two submodels are linked by shared random effects that are present in both the longitudinal trajectory model and the frailty term in the survival model.

We present our model and estimation procedures in Section 3.2. We then demonstrate our methods in Section 3.4 using data from the combined UNOS/HUP dataset. Finally, we present a simulation study in Section 3.3.

3.2. Model

Let $\boldsymbol{Y}_i$ be the $(m_i \times 1)$ vector denoting the observed longitudinal outcomes for patient $i = 1, \ldots, n$, and $\boldsymbol{u}_i$ be the corresponding observation times. Let t_i be the observed failure time for patient i, where t_i is the minimum of T_i, the true survival time, and C_i, the censoring time. As is standard practice, we define an event indicator $\delta_i = I\left(T_i \leq C_i\right)$.

A second indicator, τ_i, represents whether or not a patient receives a transplant. It is defined as 1 (for patients who receive transplants) and 0 otherwise. t_{TX_i} is the time of transplant for patient i, where applicable. For patients who received transplants, t_i and t_{TX_i} are equivalent.

3.2.1. Submodels

We assume that each patient has a biomarker trajectory represented by a non-linear random-effects exponential decay-growth process similar to the one originally proposed by Law et al. (2002). We modify the model slightly by including both random

and fixed effects, rather than just random effects, in the longitudinal model.

$$\begin{aligned}\boldsymbol{Y}_i(\boldsymbol{u}_i) = (\boldsymbol{X}_i\boldsymbol{\alpha})^T + \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\right)\exp\left(-(\beta_2 + r_{2i})\,\boldsymbol{u}_i\right) \\ + I(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i})(\beta_3 + r_{3i})\exp\left((\beta_4 + r_{4i})(\boldsymbol{u}_i - t_{TX_i})\right) + \boldsymbol{\epsilon}_i \quad (3.2.1)\end{aligned}$$

where $\boldsymbol{\epsilon}_i \sim N(\boldsymbol{0}, \sigma_\epsilon^2 \boldsymbol{I})$ and $\exp(r_{ji})$ follows a gamma distribution that will depend on the linking process used. $\boldsymbol{\alpha}$ is a $(p \times 1)$ vector of fixed effects. r_{ji} is the $j = 1, \ldots, 4$ random effect for patient i.

The pre-transplant amplitude parameter, β_1, is interpreted as the average baseline starting value for the biomarker measurements. The parameters $\boldsymbol{\alpha}$ and r_{1i} are additional fixed effects and random effects, respectively, that determine a subject's deviation from the overall population average. Similarly, β_3 and r_{3i} are the fixed and random components of the instantaneous change in biomarker values brought on by a patient receiving a transplant. The parameters β_2 and β_4 are population-averaged growth/decay terms. Random effects r_{2i} and r_{4i} that are of the same signs as β_2 and β_4 indicate that a patient's biomarker values are changing at a faster rate than the expected population average. Conversely, random effects of opposite signs as the population parameters indicate that a patient's biomarker values are changing at a slower rate than the overall population's.

For the survival portion of our model, we use a cure model similar to the one proposed by Li et al. (2010):

$$S_i(u_{ik}) = \begin{cases} \pi_i, & \tau_i = 1, u_{ik} \geq t_{TX_i} \\ (1 - \pi_i)\exp\left(-u_{ik} b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right)\right), & \text{otherwise} \end{cases} \quad (3.2.2)$$

Unlike Li et al. (2010), we assume that patients who received transplants are cer-

tainly cured and cannot experience a decline in health. Therefore, patients receiving transplants have a cure probability of 1 (i.e. $\pi_i = 1$.)

We define

$$b_i = \gamma_1 \exp(r_{1i}) + \gamma_2 \exp(r_{2i}) \tag{3.2.3}$$

as a subject-specific frailty which links the longitudinal and survival submodels. This frailty is influenced by both the amplitude and growth rate of a patient's biomarker trajectory. We assume $\gamma_1 + \gamma_2 = 1$ so that we can interpret γ_1 and γ_2 as weighting factors. These weights represent the relative influence of pre-transplant longitudinal amplitude and growth rate on patient frailty. This also ensures that $b_i = 1$ when $r_{1i} = r_{2i} = 0$ (meaning the frailty has no influence on the survival probability). The survival parameter, $\boldsymbol{\zeta}_\omega$, is a set of linear predictors that affects a patient's likelihood of death prior to transplant. Larger values of $\boldsymbol{\zeta}_\omega$ indicate a higher probability of death.

Similarly to Li et al. (2010), we require $b_i \sim \Gamma(\theta^{-1}, \theta^{-1})$. By the properties of the gamma distribution, it follows that $\exp(r_{ji}) \sim \Gamma\left(\frac{\gamma_j}{\theta}, \frac{\theta}{\gamma_j}\right)$. We can then derive the distribution of r_{ji} using a change of variables. Let $\exp(r_{ji}) = R_{ji}$, so $r_{ji} = \log(R_{ji}) = g(R_{ji})$. Let $f_R(R_{ji})$ be the distribution of R_{ji}. The derivation of the distribution of

r_{ji}, $h\left(r_{ji}\right)$ follows.

$$\begin{aligned} h\left(r_{ji}\right) &= \left|\frac{d}{dr_{ji}}\left(g^{-1}\left(R_{ji}\right)\right)\right| \cdot f_R\left(g^{-1}\left(R_{ji}\right)\right) \\ &= \left|\frac{d}{dr_{ji}}\left(\exp\left(r_{ji}\right)\right)\right| \cdot f_R\left(\exp\left(r_{ji}\right)\right) \\ &= \exp\left(r_{ji}\right) \cdot \frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{\gamma_j}{\theta}-1} \exp\left(-\exp\left(r_{ji}\right)\frac{\gamma_j}{\theta}\right)}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{\gamma_j}{\theta}} \Gamma\left(\frac{\gamma_j}{\theta}\right)} \\ &= \frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{\gamma_j}{\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{\gamma_j}{\theta}} \exp\left(\frac{\gamma_j}{\theta}\exp\left(r_{ji}\right)\right) \Gamma\left(\frac{\gamma_j}{\theta}\right)} \end{aligned} \tag{3.2.4}$$

Recall that γ_3 and γ_4 are present in our longitudinal submodel. These parameters have a similar interpretation as γ_1 and γ_2. However, they are related to post-transplant outcomes (of interest in Chapter 4). This model does not investigate post-transplant survival. Thus, γ_3 and γ_4 are not estimated here and will be arbitrarily set to 0.4 and 0.6, respectively. Since these parameters are ultimately integrated out of the model during estimation, the arbitrary values do not appreciably affect the estimated values of the other model parameters.

3.2.2. Estimation

Parameter estimates are obtained using an EM-based algorithm. The EM algorithm uses the complete-data likelihood to find the maximum likelihood estimates in the M-step and the expectations of the sufficient statistics in the E-step.

For simplicity's sake, we divide our likelihood into three portions, each corresponding to a different set of patient outcomes.

1. Patient receives a transplant ($\tau_i = 1, \delta_i = 0$)

$$L_{\tau_i=1,\delta_i=0} = S^{\star}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{3.2.5}$$

2. Patient does not receive a transplant, but death is not observed ($\tau_i = 0, \delta_i = 0$)

$$L_{\tau_i=0,\delta_i=0} = S^{*}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{3.2.6}$$

3. Patient does not receive a transplant, and death is observed ($\tau_i = 0, \delta_i = 1$)

$$L_{\tau_i=0,\delta_i=1} = \lambda^{*}\left(t_i \mid \boldsymbol{r}_i\right) S^{*}\left(t_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{3.2.7}$$

where

$$S^{\star}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) = \exp\left(-t_i b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right)$$

$$\begin{aligned} g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) = \frac{1}{\left(2\pi\right)^{m/2}\left(\sigma_{\epsilon}^2\right)^{1/2}} \exp\Bigg[& -\frac{1}{2\sigma_{\epsilon}^2}\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\ & - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ & - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)^T \\ & \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ & - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg] \end{aligned}$$

$$h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) = \left(\prod_{j=1}^{2} \frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{\gamma_j}{\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{\gamma_j}{\theta}} \exp\left(\frac{\gamma_j}{\theta}\exp\left(r_{ji}\right)\right)\Gamma\left(\frac{\gamma_j}{\theta}\right)} \right) \times \left(\prod_{j=3}^{4} \frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{\gamma_j}{\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{\gamma_j}{\theta}} \exp\left(\frac{\gamma_j}{\theta}\exp\left(r_{ji}\right)\right)\Gamma\left(\frac{\gamma_j}{\theta}\right)} \right)^{I(\tau_i=1)}$$

$$\lambda^*\left(t_i \mid \boldsymbol{r}_i\right) = b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right)$$

Combining (3.2.5), (3.2.6), and (3.2.7) gives us our full complete-data likelihood.

$$
\begin{aligned}
L &= \prod_{i=1}^{n}\Big[{L_{\tau_i=1,\delta_i=0}}^{I(\tau_i=1)I(\delta_i=0)}{L_{\tau_i=0,\delta_i=0}}^{I(\tau_i=0)I(\delta_i=0)}{L_{\tau_i=0,\delta_i=1}}^{I(\tau_i=0)I(\delta_i=1)}\Big] \\
&= \prod_{i=1}^{n}\Bigg[\exp\left(-t_i b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right) \\
&\quad \times \left[b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right]^{\delta_i=1} \\
&\quad \times \frac{1}{(2\pi)^{m/2}\left(\sigma_{\epsilon}^{2}\right)^{1/2}} \exp\Bigg[-\frac{1}{2\sigma_{\epsilon}^{2}}\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T} \\
&\quad - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T}\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
&\quad - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)^{T} \\
&\quad \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T} - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T}\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
&\quad - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg] \\
&\quad \times \left(\prod_{j=1}^{2}\frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{\gamma_j}{\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{\gamma_j}{\theta}}\exp\left(\frac{\gamma_j}{\theta}\exp\left(r_{ji}\right)\right)\Gamma\left(\frac{\gamma_j}{\theta}\right)}\right) \\
&\quad \times \left(\prod_{j=3}^{4}\frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{\gamma_j}{\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{\gamma_j}{\theta}}\exp\left(\frac{\gamma_j}{\theta}\exp\left(r_{ji}\right)\right)\Gamma\left(\frac{\gamma_j}{\theta}\right)}\right)^{I(\tau_i=1)}\Bigg]
\end{aligned}
\tag{3.2.8}
$$

This gives us the following complete-data log-likelihood:

$$
\begin{aligned}
l = \sum_{i=1}^{n} \Bigg\{ & -t_i b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right) \\
& + I\left(\delta_i = 1\right)\left(\log b_i + \boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right) \\
& - \quad \frac{m}{2}\log\left(2\pi\right) - \frac{1}{2}\log\sigma_{\epsilon}^{2} - \frac{1}{2\sigma_{\epsilon}^{2}}\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\
& - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - \quad \left(I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Big)^T \\
& \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - \left(I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Big) \\
& + \sum_{j=1}^{2}\left[\frac{\gamma_j}{\theta}r_{ji} - \frac{\gamma_j}{\theta}\exp\left(r_{ji}\right) - \frac{\gamma_j}{\theta}\log\left(\frac{\theta}{\gamma_j}\right) - \log\Gamma\left(\frac{\gamma_j}{\theta}\right)\right] \\
& + I\left(\tau_i = 1\right)\sum_{j=3}^{4}\left[\frac{\gamma_j}{\theta}r_{ji} - \frac{\gamma_j}{\theta}\exp\left(r_{ji}\right) - \frac{\gamma_j}{\theta}\log\left(\frac{\theta}{\gamma_j}\right) - \log\Gamma\left(\frac{\gamma_j}{\theta}\right)\right]\Bigg\} \qquad (3.2.9)
\end{aligned}
$$

For the M-step of the algorithm, we can use the principles of maximum likelihood to determine closed-form estimates for $\boldsymbol{\alpha}$, $\boldsymbol{\beta}$, and σ_{ϵ}^{2}.

The most straightforward way to derive the estimate for $\boldsymbol{\alpha}$ is to note that our model can be re-parameterized with respect to $\boldsymbol{\alpha}$. Let

$$
\begin{aligned}
\boldsymbol{Y}_i^{*} = \boldsymbol{Y}_i & - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)
\end{aligned}
$$

and

$$
\boldsymbol{X}_i^{*} = 1 - \exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right)
$$

Then

$$\boldsymbol{Y}_i^* = \left(\boldsymbol{X}_i^* \boldsymbol{\alpha}\right)^T + \boldsymbol{\epsilon}_i \tag{3.2.10}$$

We apply standard formulas for ordinary least squares regression to (3.2.10) and obtain the following parameter estimate for $\boldsymbol{\alpha}$.

$$\begin{aligned}
\hat{\boldsymbol{\alpha}} &= \frac{1}{n}\sum_{i=1}^{n} E\left[\left(\left(\boldsymbol{X}_i^*\right)^T \boldsymbol{X}_i^*\right)^{-1} \boldsymbol{X}_i^* \boldsymbol{Y}_i^*\right] \\
&= \frac{1}{n}\sum_{i=1}^{n} E\Bigg[\Big[\left(\left(1-\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right)\right)\boldsymbol{X}_i\right)^T \left(\left(1-\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right)\right)\boldsymbol{X}_i\right)\Big]^{-1} \\
&\qquad \times \left(\left(1-\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right)\right)\boldsymbol{X}_i\right)^T \\
&\qquad \times \Big(\boldsymbol{Y}_i - \left(\beta_1+r_{1i}\right)\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right) \\
&\qquad - I\left(\tau_i=1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3+r_{3i}\right)\exp\left(\left(\beta_4+r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg]
\end{aligned} \tag{3.2.11}$$

Solving for β_1 is also very simple. First, we simplify the complete-data log-likelihood.

$$\begin{aligned}
l_{\alpha,\beta} = -\frac{1}{2\sigma_\epsilon^2}\cdot\frac{1}{n}\sum_{i=1}^{n}\Bigg[\frac{1}{m_i}\sum_{k=1}^{m_i}\Big[&\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\
&- \left(\beta_1+r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right)\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right) \\
&- \left(I\left(\tau_i=1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3+r_{3i}\right)\exp\left(\left(\beta_4+r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Big]^2\Bigg] + C_{\alpha.\beta}
\end{aligned} \tag{3.2.12}$$

where $C_{\alpha,\beta}$ represents all the parts of the log-likelihood that do not contain $\boldsymbol{\alpha}$ or $\boldsymbol{\beta}$.

We then calculate the partial derivative of (3.2.12) with respect to β_1.

$$\begin{aligned}\frac{\partial l_{\alpha,\beta}}{\partial \beta_1} \propto \frac{1}{n}\sum_{i=1}^{n}\Bigg[\frac{1}{m_i}\sum_{k=1}^{m_i}\Bigg[&\boldsymbol{Y}_i - (\boldsymbol{X}_i\boldsymbol{\alpha})^T \\ &- \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\right)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ &- \left(I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Bigg] \\ &\circ \exp\left(\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right)\Bigg] \end{aligned} \tag{3.2.13}$$

where $\boldsymbol{a} \circ \boldsymbol{b}$ is the Hadamard product of vectors $\boldsymbol{a}$ and $\boldsymbol{b}$. Setting (3.2.13) equal to zero and solving for β_1, we find the parameter estimate for β_1.

$$\begin{aligned}\hat{\beta}_1 = \frac{1}{n}\sum_{i=1}^{n} E\Bigg[\frac{1}{m_i}\sum_{k=1}^{m_i}\Bigg[&\left[\boldsymbol{Y}_i - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\right. \\ &\left. - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right] \\ &\circ \exp\left(\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) - r_{1i} + (\boldsymbol{X}_i\boldsymbol{\alpha})^T\Bigg]\Bigg] \end{aligned} \tag{3.2.14}$$

The parameter estimate for β_2 is slightly more complicated to calculate, but can still be done rather easily. We first take the partial derivative of (3.2.12) with respect to β_2.

$$\begin{aligned}\frac{\partial l_{\alpha,\beta}}{\partial \beta_2} \propto \frac{1}{n}\sum_{i=1}^{n}\Bigg[\frac{1}{m_i}\sum_{k=1}^{m_i}\Bigg[&\boldsymbol{Y}_i - (\boldsymbol{X}_i\boldsymbol{\alpha})^T \\ &- \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\right)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ &- \left(I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Bigg] \\ &\circ \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\right)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right)\Bigg] \end{aligned} \tag{3.2.15}$$

Setting (3.2.15) equal to zero and solving for β_2 gives us

$$\hat{\beta}_2 = \frac{1}{n}\sum_{i=1}^{n} E\left[\frac{1}{m_i}\sum_{k=1}^{m_i}\log\left[\frac{1}{\boldsymbol{u}_i \circ \left(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right)\exp\left(-r_{2i}\boldsymbol{u}_i\right)}\left(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \right.\right.\right.$$
$$\left.\left.\left. - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\right]\right] \tag{3.2.16}$$

Similar approaches are used to solve for β_3 and β_4 estimates.

$$\hat{\beta}_3 = \begin{cases} \frac{1}{\sum I\left(\tau_i = 1\right)}\sum_{i=1}^{n} E\left[\frac{1}{\sum I\left(\boldsymbol{u}_i \geq t_{TX_i}\right)}\sum_{k=1}^{m_i}\left[\left(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \right.\right.\right. \\ \quad \left. - \left(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right)\right) \\ \quad \left.\left. \times \exp\left(-\left(\beta_4 + r_{4i}\right)\boldsymbol{u}_i\right) - r_{3i}\right]\right], & \tau_i = 1 \\ 0, & \text{otherwise} \end{cases} \tag{3.2.17}$$

$$\hat{\beta}_4 = \begin{cases} \frac{1}{\sum I\left(\tau_i = 1\right)}\sum_{i=1}^{n} E\left[\frac{1}{\sum I\left(\boldsymbol{u}_i \geq t_{TX_i}\right)}\right. \\ \quad \times \sum_{k=1}^{m_i}\log\left[\frac{1}{\boldsymbol{u}_i \circ \left(\beta_3 + r_{3i}\right)\exp\left(r_{4i}\boldsymbol{u}_i\right)}\right. \\ \quad \times\left(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right. \\ \quad \left.\left.\left. - \left(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right)\right)\right]\right], & \tau_i = 1 \\ 0, & \text{otherwise} \end{cases} \tag{3.2.18}$$

Although we have closed-form estimates for all of the longitudinal submodel parameters, estimates for $\boldsymbol{\alpha}$, β_2, and β_4 are calculated via the `fminsearch` function in MATLAB. The `fminsearch` algorithm finds the minimum of a multivariable function using unconstrained nonlinear optimization. It is more computationally stable than using the closed-form estimates directly, due to the relationship between the closed-form estimates and observation times. We use `fminsearch` to solve

$$\left[\hat{\boldsymbol{\alpha}},\ \hat{\beta}_2,\ \hat{\beta}_4\right]^T = \arg\min\ E\left[l_{\alpha,\beta}\left(\boldsymbol{\alpha}, \beta_2, \beta_4\right)\right] \tag{3.2.19}$$

Calculating all parameter estimates via `fminsearch` would be overly time-consuming. Therefore, estimates for β_1 and β_3 will be calculated using (3.2.14) and (3.2.17).

We estimate variance by subtracting subject-level expected values from subject observed values.

$$\hat{\sigma_\epsilon^2} = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{m_i}\left(\boldsymbol{Y}_i - E\left[\boldsymbol{Y}_i\right]\right)\left(\boldsymbol{Y}_i - E\left[\boldsymbol{Y}_i\right]\right)^T \tag{3.2.20}$$

where

$$\begin{aligned} E\left[\boldsymbol{Y}_i\right] = E\big[&\left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T + \left(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ &+ I\left(\tau_i = 1,\ \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\big] \end{aligned}$$

Estimates for $\boldsymbol{\gamma}$, $\boldsymbol{\zeta}_\omega$, and θ cannot be derived in a closed form. We will approximate them using the MATLAB `fmincon` function (which uses constrained nonlinear

optimization) to solve

$$\left[\hat{\gamma_1},\ \hat{\gamma_2},\ \hat{\boldsymbol{\zeta}_\omega},\ \hat{\theta}\right]^T = \arg\min\ E\left[l_{\gamma,\zeta_\omega,\theta}\left(\gamma_1, \gamma_2, \boldsymbol{\zeta}_\omega, \theta\right)\right] \tag{3.2.21}$$

where

$$\begin{aligned} l_{\gamma,\zeta_\omega,\theta} = \sum_{i=1}^{n} \Bigg\{ & -t_i b_i \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right) \\ & + I\left(\delta_i = 1\right)\left(\log b_i + \boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right) \\ & + \sum_{j=1}^{2}\left[\frac{\gamma_j}{\theta} r_{ji} - \frac{\gamma_j}{\theta}\exp\left(r_{ji}\right) - \frac{\gamma_j}{\theta}\log\left(\frac{\theta}{\gamma_j}\right) - \log\Gamma\left(\frac{\gamma_j}{\theta}\right)\right] \\ & + I\left(\tau_i = 1\right)\sum_{j=3}^{4}\left[\frac{\gamma_j}{\theta} r_{ji} - \frac{\gamma_j}{\theta}\exp\left(r_{ji}\right) - \frac{\gamma_j}{\theta}\log\left(\frac{\theta}{\gamma_j}\right) - \log\Gamma\left(\frac{\gamma_j}{\theta}\right)\right] \Bigg\} \end{aligned} \tag{3.2.22}$$

The E-step will evaluate the following integral:

$$E\left[f\left(\boldsymbol{r}_i\right)\right] = \int_0^\infty \int_0^\infty \int_0^\infty \int_0^\infty f\left(\boldsymbol{r}_i\right)\ h\left(\boldsymbol{r}_i\right)\ dr_{1i} dr_{2i} dr_{3i} dr_{4i} \tag{3.2.23}$$

where $f\left(\boldsymbol{r}_i\right)$ is any sufficient statistic. Expanding equations (3.2.14) and (3.2.17) gives us the following sufficient statistics:

r_{1i}	r_{3i}
$\exp\left(r_{2i}\boldsymbol{u}_i\right)$	$\exp\left(-r_{4i}\boldsymbol{u}_i\right)$
$\exp\left(r_{2i}\boldsymbol{u}_i\right)\exp\left(r_{4i}\boldsymbol{u}_i\right)$	$\exp\left(-r_{2i}\boldsymbol{u}_i\right)\exp\left(-r_{4i}\boldsymbol{u}_i\right)$
$r_{3i}\exp\left(r_{2i}\boldsymbol{u}_i\right)\exp\left(r_{4i}\boldsymbol{u}_i\right)$	$r_{1i}\exp\left(-r_{2i}\boldsymbol{u}_i\right)\exp\left(-r_{4i}\boldsymbol{u}_i\right)$

We will use adaptive Gaussian quadrature (AGQ) to determine the numerical value of (3.2.23) (Pinheiro and Chao, 2006). This method requires integration over a normal distribution. Since our random effects are not normally distributed, we the standardization methods proposed in Liu and Yu (2008). The resulting integral is

$$E\left[f\left(\boldsymbol{r}_i\right)\right] = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\left(f\left(\boldsymbol{r}_i\right)\ \frac{h\left(\boldsymbol{r}_i\right)}{\phi\left(\boldsymbol{r}_i\right)}\right)\phi\left(\boldsymbol{r}_i\right)\ dr_{1i}dr_{2i}dr_{3i}dr_{4i} \tag{3.2.24}$$

where $\phi\left(\boldsymbol{r}_i\right)$ is a standard multivariate normal distribution for $\boldsymbol{r}_i$.

It is clearly not tractable to solve (3.2.24) analytically, so we will approximate it with the following sum:

$$E\left[f\left(\boldsymbol{r}_i\right)\right] \approx \sum_k\sum_k\sum_k\sum_k\left[f\left(\boldsymbol{r}_{i,k}\right)\ h^*\left(\boldsymbol{r}_{i,k}\right)\ w_{1k}w_{2k}w_{3k}w_{4k}\right] \tag{3.2.25}$$

where w_{jk} is the k^{th} weight for the $j = 1, \ldots, 4$ random effect and $h^*\left(\boldsymbol{r}_{i,k}\right) = \frac{h\left(\boldsymbol{r}_{i,k}\right)}{\phi\left(\boldsymbol{r}_{i,k}\right)}$.

3.3. Simulations

Simulations were done to evaluate model performance under a variety of conditions. These conditions varied the percentage of patients who received transplants. Datasets were simulated under each condition, with each containing 500 patients. Data were simulated in the following manner:

1. Exponentiated subject-specific random effects were calculated using a gamma distribution, where

$$\exp\left(r_{ji}\right) \sim \Gamma\left(\frac{\gamma_j}{\theta}, \frac{\theta}{\gamma_j}\right) \qquad\qquad j = 1, \ldots, 4$$

   Subject-specific random effects were calculated by taking the natural log of the

exponentiated random effects, i.e. $r_{ji} = \log(\exp(r_{ji}))$.

2. Patient-specific pre-transplant frailties were calculated

$$b_i = \gamma_1 \exp(r_{1i}) + \gamma_2 \exp(r_{2i})$$

3. Pre-transplant survival times were simulated using the methods proposed by Bender et al. (2005)

$$T_i = -\frac{\log U}{b_i \exp(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega)}$$

where U is a standard uniform random variable

4. A random sample of patients who would be "offered" transplants was determined.

$$\tau_i \sim Binomial(n, p_{Tx})$$

where p_{Tx} is the percentage of patients who will be offered transplants. Subject-specific transplant times were calculated, so that $t_{TX_i} = 0.99 \times T_i$

5. Patient survival/censoring status was determined

$$[t_i, \delta_i] = \begin{cases} [\min(T_i, C_{\text{end}}),\ T_i \leq C_{\text{end}}], & \tau_i = 0 \\ [t_{TX_i},\ 0], & \tau_i = 1 \end{cases}$$

where C_{end} is the end time of the study

6. Longitudinal data was simulated for all subjects

$$y_{ik} = \begin{cases} \Big[(\boldsymbol{X}_i\boldsymbol{\alpha})^T + \Big(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right) u_{ik}\right) \\ \quad + I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \\ \qquad \times \exp\left(\left(\beta_4 + r_{4i}\right)\left(u_{ik} - t_{TX_i}\right)\right) + \sigma_\epsilon^2\Big], & \tau_i = 1 \\ (\boldsymbol{X}_i\boldsymbol{\alpha})^T + \Big(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right) u_{ik}\right), & \tau_i = 0,\, u_{ik} \leq t_i \\ \text{missing}, & \text{otherwise} \end{cases}$$

Some simulations also utilized "independent" data. Longitudinal data were simulated using an independent mixed-effects exponential growth-decay model. Survival data were simulated using a Cox model that was unlinked to the longitudinal model.

Using the data simulated under a joint model, we compared the results of our joint model to the results of a fully-independent model. We assumed a transplant rate of 20%. The fully-independent model separately fitted a mixed-effects exponential growth-decay model to all of the longitudinal data, and a Cox proportional hazard model to the pre-transplant survival data. Results of the simulations are shown in Table 3.1. Longitudinal parameter estimates are relatively unbiased, regardless of whether a joint or independent model is used. This is to be expected. Liu (2011) show that fixed (i.e. not time-varying) estimates will be fairly unbiased even when analysis is done using a correctly-specified mixed-effects independent model. Survival estimates are similar on average in both models.

Using data simulated under an independent model, we compare our joint model to an independent model. Data were simulated assuming that 50% of patients received transplants. Results are shown in Table 3.2. Again, estimates for the longitudinal

Table 3.1: Simulation results for joint vs. indep. model, when joint model is true

		Joint model	Independent model
Parameter	Truth	Est. (SE)	Est. (SE)
α_1	0.1	0.10 (0.0001)	0.10 (0.0001)
α_2	2	2.03 (0.007)	2.03 (0.007)
β_1	6	6.00 (0.0007)	6.00 (0.0007)
β_2	0.5	0.49 (0.001)	0.49 (0.001)
β_3	-2	-2.00 (0.003)	-2.00 (0.003)
β_4	0.2	0.21 (0.003)	0.21 (0.003)
γ_1	0.2	0.19 (0.001)	0.19 (0.001)
γ_2	0.8	0.81 (0.001)	0.81 (0.001)
θ	0.03	0.03 (0.0002)	0.03 (0.0002)
$\boldsymbol{\zeta}_\omega$	-2	-2.15 (0.02)	-2.01 (0.02)
σ^2_ϵ	1	1.00 (0.001)	1.00 (0.001)

trajectory parameters are relatively unbiased for both models. Our new joint model over-estimated the fixed-effect survival parameters. This is to be expected, since the model is misspecified.

The results of a comparison of model performance under a variety of conditions are shown in Table 3.3. Simulation results show that the longitudinal submodel does reasonably well across all conditions. The quality of the pre-transplant survival estimates deteriorates as the percentage of patients receiving transplants increases. This is understandable, since we have assumed that patients who receive transplants cannot die. Therefore, a high proportion of patients receiving transplants implies that only a small amount of pre-transplant survival information is available.

A more complicated model does not make much of a difference in the quality of parameter estimation when we are only interested in pre-transplant survival. The end goal of this dissertation, however, is to draw conclusions about both pre- and post-transplant survival times, while incorporating information from longitudinal biomarker values. Therefore, proper estimation of survival parameters is very important. In this chap-

Table 3.2: Simulation results for joint vs. indep. model, when indep. model is true

		Joint model	Independent model
Parameter	Truth	Est. (SE)	Est. (SE)
α_1	0.1	0.10 (0.0001)	0.10 (0.0001)
α_2	2	2.04 (0.007)	2.04 (0.007)
β_1	6	6.00 (0.0007)	6.00 (0.0007)
β_2	0.5	0.49 (0.001)	0.49 (0.001)
β_3	-2	-2.00 (0.002)	-2.00 (0.002)
β_4	0.2	0.21 (0.002)	0.21 (0.002)
γ_1	0.2	0.19 (0.001)	0.19 (0.001)
γ_2	0.8	0.81 (0.001)	0.81 (0.001)
θ	0.03	0.03 (0.0002)	0.03 (0.0002)
$\boldsymbol{\zeta}_\omega$	-2	-2.54 (0.05)	-1.76 (0.03)
σ^2_ϵ	1	1.00 (0.001)	1.00 (0.001)

Table 3.3: Simulation results for model performance across varying conditions

		20% Tx	50% Tx	90% Tx
Parameter	Truth	Est. (SE)	Est. (SE)	Est. (SE)
α_1	0.1	0.10 (0.0001)	0.10 (0.0001)	0.10 (0.0001)
α_2	2	2.03 (0.007)	2.04 (0.006)	2.05 (0.008)
β_1	6	6.00 (0.0007)	6.00 (0.0008)	6.00 (0.0007)
β_2	0.5	0.49 (0.001)	0.49 (0.001)	0.49 (0.002)
β_3	-2	-2.00 (0.003)	-2.00 (0.002)	-2.00 (0.002)
β_4	0.2	0.21 (0.003)	0.21 (0.002)	0.21 (0.002)
γ_1	0.2	0.19 (0.001)	0.19 (0.001)	0.19 (0.003)
γ_2	0.8	0.81 (0.001)	0.81 (0.001)	0.81 (0.003)
θ	0.03	0.03 (0.0002)	0.03 (0.0002)	0.03 (0.0004)
$\boldsymbol{\zeta}_\omega$	-2	-2.15 (0.02)	-2.54 (0.04)	-4.49 (0.33)
σ^2_ϵ	0.25	1.00 (0.001)	1.00 (0.002)	1.00 (0.001)

ter, we demonstrate that our model performs equally as well as an independent model. In Chapter 4, we will examine the implications of ignoring pre-transplant survival and biomarker information when making inferences about post-transplant survival.

3.4. Application

The United Network of Organ Sharing (UNOS) registry collects data on every patient who is on the waiting list for an organ transplant. Patient history, baseline, and demographic variables are recorded at the time of waitlisting. Updates to the registry occur with varying frequency (based on organ, illness severity, and other factors). Patients who receive a transplant will also have an entry in the UNOS registry.

Liver transplant patients have their records updated every time they receive an update to their Model for End-stage Liver Disease (MELD) score. MELD scores have been used to rank waitlisted patients since February 27, 2002. Law requires that MELD scores are updated more often for sicker patients (UNOS, 2002), which could cause bias in statistical inference. In an attempt to avoid this potential bias, we merged UNOS data with data from the Hospital of the University of Pennsylvania (HUP). The resulting dataset had more observations per subject, regardless of disease severity. An in-depth discussion of the motivations and creation of the UNOS/HUP dataset can be found in Section 1.2.

In this chapter, we assume that patients who receive transplants are definitely cured and therefore cannot die. Table 3.4 shows the percentage of death and censoring, as well as average follow-up and survival times. Patients were followed for a maximum of five years (1826 days) post-waitlisting. Our analytic dataset (referred to as Subset 1) consisted of 500 patients waitlisted for a liver transplant at HUP between February, 27, 2002, and May, 13, 2011. Approximately 30% of our patients received transplants

Table 3.4: Descriptive statistics for UNOS/HUP Subset 1

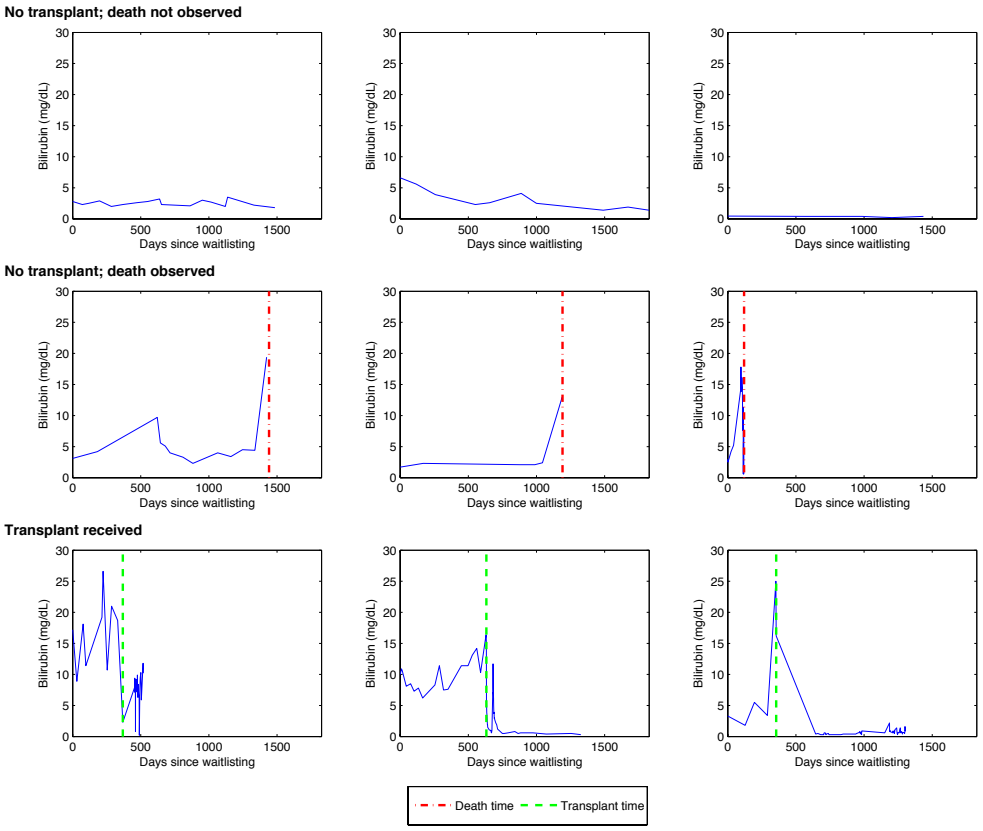
	Tx group	No Tx group	Total
n (%)	171 (34)	329 (66)	500
Number censored (%)	171 (100)	231 (70)	402 (80)
Number dead (%)	-	98 (30)	-
Mean follow-up time	3.1 years	2.5 years	2.7 years
Median time to Tx	5.9 months	-	-
Median observable survival time[🚲]	-	5.0 years	-
Male gender (%)	114 (67)	248 (75)	362 (72)
Mean age at WLing (years)	53.7	52.6	53.0

[🚲] - Due to censoring, the median observed survival time is equal to the maximum survival time

during this timeframe, with a median waiting time of 6.5 months. Of the patients who did not receive transplants, approximately 30% were observed to have died by the end of the study. Average follow-up time for all subjects was 2.7 years, with transplanted patients having longer follow-up times than those who did not have a transplant (3.1 vs. 2.5 years). Demographics (gender and age at waitlisting) were similar for both groups.

Transplant data has unique characteristics that must be considered when forming a statistical model (see Section 1.1). Figure 3.1 illustrates some of these characteristics. Sicker patients (indicated by higher bilirubin levels) may be more likely to be removed from the waitlist or die. In addition, we expect that patients who receive a transplant will see an improvement in health and a lower likelihood of death. Visual comparison between patients who did and did not die show that survivors who did not receive transplants tend to have lower, steadier bilirubin levels. Patients with drastic increases in their bilirubin levels (or those who are waitlisted with higher levels initially) are more likely to either die or receive a transplant. This highlights the possibility of informative dropout. Patients who receive transplants also have a noticeable improvement in liver function (as indicated by a drop in bilirubin levels)

Figure 3.1: Bilirubin trajectories (UNOS/HUP Subset 1)



post-transplant.

We model this data using the methods developed in Section 3.2. For this analysis, we include age at waitlisting and gender as linear terms in the longitudinal submodel and gender as the explanatory variable in the survival submodel. A set of 100 bootstraps were run to determine standard errors for the estimates (Efron, 1982). Results from 15 of the bootstraps were excluded from the calculations in Table 3.5 due to outliers in the parameter estimates. Results indicate that age at waitlisting does not significantly affect bilirubin levels (0.53 mg/dL increase in bilirubin level for each additional year; 95% CI = [-1.55,2.61]). Male gender has a small, but significant, effect on bilirubin values (0.16 mg/dL higher than women; 95% CI = [0.10,0.22]).

Table 3.5: Data analysis results for UNOS/HUP Subset 1

	Joint model	Independent model
Parameter	Est. (Bootstrap SE)	Est. (Bootstrap SE)
α_1 (age at WLing)	0.53 (1.06)	0.56 (1.04)
α_2 (male gender)	0.16 (0.03)	0.16 (0.03)
β_1	3.42 (0.02)	3.42 (0.02)
β_2	-0.79 (0.05)	-0.79 (0.05)
β_3	54.11 (102.33)	46.33 (99.18)
β_4	-9.89 (9.70)	-9.91 (9.37)
γ_1	0.20 (0.001)	0.20 (0.009)
γ_2	0.80 (0.001)	0.80 (0.009)
θ	0.08 (0.005)	0.07 (0.005)
$\boldsymbol{\zeta}_\omega$ (male gender)	-0.70 (0.007)	-0.07 (0.02)
σ^2_ϵ	13.09 (0.25)	13.09 (0.24)

The remaining longitudinal parameter estimates show an overall average bilirubin level of 3.42 mg/dL at waitlisting (95% CI = [3.38,3.46]). Patients who do not receive transplants have increasing bilirubin levels, as indicated by the negative value of β_2. This is reasonable, since patients are expected to become more ill as their time on the waiting list increases. For this data, post-transplant trajectories are not significantly different from pre-transplant trajectories. The estimates for β_3 and β_4 are both non-significant. Our results show that male transplant recipients are less likely to die on the waiting list (hazard ratio = $\exp(-0.70) = 0.50$). This agrees with the findings of Moylan et al. (2008). (Mindikoglu et al. (2010) note that this disparity may actually be due to differences in kidney function. Though this warrants further investigation, our data do not allow for proper consideration of the effect of kidney function.)

We also fitted independent longitudinal and survival models to the data in order to assess the sensitivity of the results to the model link. The independent model gives a highly attenuated estimate for pre-transplant survival. This indicates that, under "real world" conditions, the implications of using a joint model versus an independent model are even more pronounced than in idealized simulations.

3.5. Discussion

In this chapter, we have developed a joint longitudinal-survival model that incorporates patient cure post-transplant. This model combines a non-linear exponential growth-decay model with a modified cure model in order to investigate the relationship between longitudinal trajectories (both pre- and post-transplant) and survival times pre-transplant. We assume that all patients who receive transplants are cured. This model does well under a variety of circumstances. We also show that the model performs as well as an independent model. This result is key to the extensions that will be presented in Chapter 4.

CHAPTER 4

A Joint Longitudinal-Survival Model with Possible Post-Transplant Death

4.1. Introduction

Data from transplant patients has many characteristics that can make it difficult to model properly. To investigate both patient survival and longitudinal health trajectories, we must overcome the "standard" issues with both kinds of models: non-random dropout in longitudinal and survival studies, proportional hazards or distributional assumptions about survival times, etc. (Diggle et al., 2002; Cox, 1972). In addition, it is reasonable to suspect that there is some sort of link between patients' longitudinal trajectories and survival processes. It is not sufficient to model the longitudinal trajectories and survival times with independent models. Failing to acknowledge the potential link could lead to biased parameter estimates and possibly incorrect inference (Diggle et al., 2002). We must incorporate the presence of non-random dropout (or "informative missingness") into our analysis (Little and Rubin, 1987). To do this, we need to use a joint longitudinal-survival model (discussed in detail in Chapter 2).

The need for joint modeling has been acknowledged by researchers in fields other than transplantation. Yu et al. (2004); Chen et al. (2004) and Law et al. (2002) developed joint models for dealing with informative dropout. These authors propose models with a variety of different submodels and model links. The choice of longitudinal and survival submodels, as well as the choice of model link, depends on the type of study data.

Many different longitudinal models have been considered. Methods have been developed for both continuous and non-continuous data. Ten Have et al. (2000) used an ordinal logistic model to analyze ordinal functional status data. For continuous data, parametric and non-parametric models have been proposed (Chen et al., 2004; Elmi et al., 2011; Law et al., 2002). The model developed by Chen et al. (2004) can be used for linear or quadratic data. A more complex parametric exponential growth-decay model was proposed by Law et al. (2002). Elmi et al. (2011) used a non-parametric B-spline to model labor and delivery data. None of these models fully address the features of transplant data. Non-continunous models are clearly not appropriate for continunous biomarkers. Linear and quadratic models do not capture the quick increases and decreases that occur in transplant patients' biomarker values. B-splines can capture these dynamic features. However, B-splines can be computationally intensive and difficult to interpret. A useful model for longitudinal biomarkers in transplant data is the exponential growth-decay process proposed by Law et al. (2002). This model can incorporate exponential increases and decreases in biomarker values, as well as an immediate drop in values post-transplant. Law et al. (2002)'s model is not entirely appropriate, however, so we will modify Law et al. (2002)'s model slightly. We remove the assumption of normally-distributed random effects. We also include both fixed and random effects in our longitudinal model. ((Law et al., 2002) treats patient longitudinal trajectory effects as random.)

The informative dropout process is often assumed to be a survival process (Liu et al., 2004; Law et al., 2002; Chen et al., 2004), though it can be any dichotomous outcome. Elmi (2009) proposed a logistic model for the dropout process. Most often, though, authors use a Cox proportional hazards model to analyze patient survival times. Law et al. (2002) and Chen et al. (2004) modified the Cox model to incorporate the

possibility of patient cure. Standard Cox models assume a decreasing probability of death (Cox, 1972). This assumption is not appropriate in the case of transplant data, since we expect patients to have a change in health post-transplant. Cure models allow for this change in hazard of death (Baker, 1978). Cure models are not entirely adequate for transplant data, however. These models assume that all patients receive a treatment, and that those who are "cured" cannot die from the disease being treated. Not all waitlisted patients will receive transplants, and not all patients who receive transplant will survive long-term. Therefore, we take the "spirit" of a cure model and adapt it to include two different Cox models – one for pre-transplant survival and one for post-transplant survival. The two Cox models are related via a frailty term that appears in both models.

The link between the longitudinal and survival models determines how the survival process and longitudinal trajectories affect one another. A simple way to link the two models is to include the longitudinal trajectories as a time-varying covariate in the survival model (Yu et al., 2004). Though this is straightforward, it does not allow us to explicitly model the longitudinal process as an outcome. If the longitudinal outcome is of interest, patients can be divided into latent classes with class-specific longitudinal and survival models (Chen et al., 2004). However, it is not possible to determine a patient's class ahead of time. Therefore, it is more appropriate to model transplant data using a shared parameter model, where patient-level random effects are present in both the longitudinal and survival models. (Shared parameter models are discussed in detail in Section 2.2.)

In this chapter, we extend the joint model proposed in Chapter 3. We link an exponential growth-decay longitudinal submodel to a modified cure submodel using patient-level random effects. We then demonstrate our model using liver transplant

data from the United Network of Organ Sharing (UNOS) and the Hospital of the University of Pennsylvania (HUP) in Section 4.4. (This dataset is discussed in detail in Section 1.2.)

4.2. Model

For this model, we use the same variables described in Section 3.2, with some small additions. We add in another patient-level design matrix, $\boldsymbol{X}_{\pi i}$, which is associated with a patient's post-transplant survival. We also modify our assumptions regarding the distribution of the random effects.

4.2.1. Submodels

As in Chapter 3, we assume that each patient has a biomarker trajectory represented by a non-linear exponential decay-growth process similar to the model proposed by Law et al. (2002).

$$\begin{aligned}\boldsymbol{Y}_i(\boldsymbol{u}_i) = (\boldsymbol{X}_i\boldsymbol{\alpha})^T + \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i\boldsymbol{\alpha})^T\right)\exp\left(-(\beta_2 + r_{2i})\,\boldsymbol{u}_i\right) \\ + I(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i})\,(\beta_3 + r_{3i})\exp\left((\beta_4 + r_{4i})\,(\boldsymbol{u}_i - t_{TX_i})\right) + \boldsymbol{\epsilon}_i \quad (4.2.1)\end{aligned}$$

where $\boldsymbol{\epsilon}_i \sim N(\boldsymbol{0}, \sigma_\epsilon^2 \boldsymbol{I})$. $\boldsymbol{\alpha}$ is a $(p \times 1)$ vector of fixed effects. r_{ji}, the $j = 1, \ldots, 4$ random effect for patient i, is assumed to be log-gamma distributed.

The interpretation of the longitudinal submodel parameters is discussed in Section 3.2. The first amplitude parameter, β_1, is the overall population average bilirubin level at time of waitlisting. The linear term, $\boldsymbol{\alpha}$, represents how an individual's covariate values affect his initial bilirubin level. The second amplitude parameter, β_3, is the average change in bilirubin levels post-transplant. The exponential rate terms, β_2 and β_4, are the growth rates pre- and post-transplant, respectively.

We change our proposed survival model by incorporating the possibility of patient death post-transplant. Thus,

$$S_i(u_{ik}) = \begin{cases} \exp\left(-\left(u_{ik} - t_{TX_i}\right) b_{2i} \exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_\pi\right)\right), & \tau_i = 1, u_{ik} \geq t_{TX_i} \\ \exp\left(-u_{ik} b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right)\right), & \text{otherwise} \end{cases} \tag{4.2.2}$$

where

$$b_{1i} = \gamma_1 \exp(r_{1i}) + \gamma_2 \exp(r_{2i})$$
$$b_{2i} = c b_{1i} + (1-c)\left(\gamma_3 \exp(r_{3i}) + \gamma_4 \exp(r_{4i})\right)$$

As in Section 3.2, $\boldsymbol{\zeta}_\omega$ is a set of parameters that affect pre-transplant survival. Similarly, $\boldsymbol{\zeta}_\pi$ is a set of linear predictors that are related to patients' post-transplant survival probabilities. The frailties b_{1i} and b_{2i} influence pre- and post-transplant survival functions, respectively. The post-transplant frailty, b_{2i}, incorporates b_{1i} in the post-transplant survival function. The weighting parameter, c, determines the relative effect of pre- and post-transplant random effects on post-transplant survival.

The change in the survival model gives us a more clinically-relevant model, as it allows for the possibility of post-transplant death. For patients who do not receive a transplant, a single Cox model represents their survival times. Patients who receive transplants have a survival function that changes at the time of transplant. The frailty in the second survival model, b_{2i}, links pre- and post-transplant survival by combining the pre-transplant frailty with post-transplant random effects.

As in Chapter 3, we place distributional restrictions on b_{1i} and b_{2i}. We assume $b_{1i} \sim \Gamma(\theta^{-1}, \theta)$ and $b_{2i} \sim \Gamma\left((c\theta)^{-1}, c\theta\right)$. By the properties of the gamma distribution,

it follows that

$$\exp\left(r_{1i}\right) \sim \Gamma\left(\frac{1}{2\theta}, \frac{\theta}{\gamma_1}\right)$$

$$\exp\left(r_{2i}\right) \sim \Gamma\left(\frac{1}{2\theta}, \frac{\theta}{\gamma_2}\right)$$

$$\exp\left(r_{3i}\right) \sim \Gamma\left(\frac{1-c}{2c\theta}, \frac{c\theta}{(1-c)\,\gamma_3}\right)$$

$$\exp\left(r_{4i}\right) \sim \Gamma\left(\frac{1-c}{2c\theta}, \frac{c\theta}{(1-c)\,\gamma_4}\right)$$

Therefore,

$$h\left(r_{ji}\right) = \begin{cases} \dfrac{(\exp(r_{ji}))^{\frac{1}{2\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{1}{2\theta}} \exp\left(\frac{\gamma_j}{\theta}\exp(r_{ji})\right)\Gamma\left(\frac{1}{2\theta}\right)}, & j = 1, 2 \\ \dfrac{(\exp(r_{ji}))^{\frac{1-c}{2c\theta}}}{\left(\frac{c\theta}{(1-c)\gamma_j}\right)^{\frac{1-c}{2c\theta}} \exp\left(\frac{(1-c)\gamma_j}{c\theta}\exp(r_{ji})\right)\Gamma\left(\frac{1-c}{2c\theta}\right)}, & j = 3, 4 \end{cases} \tag{4.2.3}$$

4.2.2. Estimation

Parameter estimates are obtained using an EM-based algorithm. The EM algorithm uses the complete-data likelihood to find the maximum likelihood estimates in the M-step and the expectations of the sufficient statistics in the E-step.

For simplicity's sake, we divide our likelihood into four portions, each corresponding to a different set of patient outcomes.

1. Patient receives a transplant, and death is not observed $(\tau_i = 1, \delta_i = 0)$

$$L_{\tau_i=1,\delta_i=0} = S^{\star}_{Tx}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) h_{Tx}\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{4.2.4}$$

2. Patient receives a transplant, and death is observed $(\tau_i = 1, \delta_i = 1)$

$$L_{\tau_i=1,\delta_i=1} = \lambda^{*}_{Tx}\left(t_i \mid \boldsymbol{r}_i\right) S^{*}_{Tx}\left(t_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) h_{Tx}\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{4.2.5}$$

3. Patient does not receive a transplant, and death is not observed $(\tau_i = 0, \delta_i = 0)$

$$L_{\tau_i=0,\delta_i=0} = S^{*}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{4.2.6}$$

4. Patient does not receive a transplant, and death is observed $(\tau_i = 0, \delta_i = 1)$

$$L_{\tau_i=0,\delta_i=1} = \lambda^{*}\left(t_i \mid \boldsymbol{r}_i\right) S^{*}\left(t_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) \tag{4.2.7}$$

where

$$S^{\star}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) = \exp\left(-t_i b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right)$$

$$\lambda^{*}\left(t_i \mid \boldsymbol{r}_i\right) = b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)$$

$$S^{\star}_{Tx}\left(t_i \mid \boldsymbol{r}_i, \boldsymbol{X}_i\right) = \exp\left(-\left(t_i - t_{TX_i}\right) b_{2i} \exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_{\pi}\right)\right) \exp\left(-t_{TX_i} b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right)$$

$$\lambda^{*}_{Tx}\left(t_i \mid \boldsymbol{r}_i\right) = b_{2i}\exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_{\pi}\right)$$

$$\begin{aligned} g\left(\boldsymbol{Y}_i \mid \boldsymbol{X}_i, \boldsymbol{r}_i\right) = \frac{1}{\left(2\pi\right)^{m/2}\left(\sigma^2_{\epsilon}\right)^{1/2}}\exp\Bigg[-\frac{1}{2\sigma^2_{\epsilon}}\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\ - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)^T \\ \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\ - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg] \end{aligned}$$

$$h\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) = h\left(r_{1i}\right)h\left(r_{2i}\right)$$

$$h_{Tx}\left(\boldsymbol{r}_i \mid \boldsymbol{X}_i\right) = h\left(r_{3i}\right)h\left(r_{4i}\right)$$

Combining (4.2.4), (4.2.5), (4.2.6), and (4.2.7) gives us our full complete-data likelihood.

$$
\begin{aligned}
L = \prod_{i=1}^{n} \Big[& L_{\tau_i=1,\delta_i=0}{}^{I(\tau_i=1)I(\delta_i=0)} L_{\tau_i=1,\delta_i=1}{}^{I(\tau_i=1)I(\delta_i=1)} L_{\tau_i=0,\delta_i=0}{}^{I(\tau_i=0)I(\delta_i=0)} \\
& \times L_{\tau_i=0,\delta_i=1}{}^{I(\tau_i=0)I(\delta_i=1)} \Big] \\
= \prod_{i=1}^{n} \Bigg[& \left(\exp\left(-t_i b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right)\right)^{I(\tau_i=0)} \\
& \times \left[\exp\left(-t_{TX_i} b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right) \exp\left(-\left(t_i - t_{TX_i}\right) b_{2i} \exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_{\pi}\right)\right)\right]^{I(\tau_i=1)} \\
& \times \left[b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\right]^{\tau_i=0,\delta_i=1} \\
& \times \left[b_{2i} \exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_{\pi}\right)\right]^{\tau_i=1,\delta_i=1} \\
& \times \frac{1}{(2\pi)^{m/2}\left(\sigma_{\epsilon}^2\right)^{1/2}} \exp\Bigg[-\frac{1}{2\sigma_{\epsilon}^2}\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\
& - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)^T \\
& \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg] \\
& \times \left(\prod_{j=1}^{2} \frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{1}{2\theta}}}{\left(\frac{\theta}{\gamma_j}\right)^{\frac{1}{2\theta}} \exp\left(\frac{\gamma_j}{\theta}\exp\left(r_{ji}\right)\right)\Gamma\left(\frac{1}{2\theta}\right)}\right) \\
& \times \left(\prod_{j=3}^{4} \frac{\left(\exp\left(r_{ji}\right)\right)^{\frac{1-c}{2c\theta}}}{\left(\frac{c\theta}{(1-c)\gamma_j}\right)^{\frac{1-c}{2c\theta}} \exp\left(\frac{(1-c)\gamma_j}{c\theta}\exp\left(r_{ji}\right)\right)\Gamma\left(\frac{1-c}{2c\theta}\right)}\right)^{I(\tau_i=1)} \Bigg]
\end{aligned}
\tag{4.2.8}
$$

This gives us the following complete-data log-likelihood:

$$
\begin{aligned}
l = \sum_{i=1}^{n} \Bigg\{ & -I\left(\tau_i = 0\right) t_i b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right) \\
& - I\left(\tau_i = 1\right)\left[t_{TX_i} b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right)\left(t_i - t_{TX_i}\right) b_{2i} \exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_{\pi}\right)\right] \\
& + I\left(\tau_i = 0, \delta_i = 1\right)\left[\log b_{1i} + \boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_{\omega}\right] \\
& + I\left(\tau_i = 1, \delta_i = 1\right)\left[\log b_{2i} + \boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_{\pi}\right] \\
& - \quad \frac{m}{2}\log\left(2\pi\right) - \frac{1}{2}\log\sigma_{\epsilon}^{2} - \frac{1}{2\sigma_{\epsilon}^{2}}\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T} \\
& - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T}\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - \quad \left(I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Big)^{T} \\
& \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T} - \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^{T}\Big)\exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) \\
& - \left(I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right)\exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right)\Big) \\
& + \sum_{j=1}^{2}\left[\frac{1}{2\theta}r_{ji} - \frac{\gamma_j}{\theta}\exp\left(r_{ji}\right) - \frac{1}{2\theta}\log\left(\frac{\theta}{\gamma_j}\right) - \log\Gamma\left(\frac{1}{2\theta}\right)\right] \\
& + I\left(\tau_i = 1\right)\sum_{j=3}^{4}\left[\frac{1-c}{2c\theta}r_{ji} - \frac{\left(1-c\right)\gamma_j}{c\theta}\exp\left(r_{ji}\right) - \frac{1-c}{2c\theta}\log\left(\frac{c\theta}{\left(1-c\right)\gamma_j}\right)\right. \\
& \left. - \log\Gamma\left(\frac{1-c}{2c\theta}\right)\right]\Bigg\} \qquad (4.2.9)
\end{aligned}
$$

Parameter estimates are calculated in the same way as (3.2.11), (3.2.14), (3.2.16), (3.2.17), and (3.2.18) in Section 3.2. Therefore, the longitudinal parameter estimates are

$$\begin{aligned}\hat{\boldsymbol{\alpha}} &= \frac{1}{n}\sum_{i=1}^{n} E\left[\left(\left(\boldsymbol{X}_i^*\right)^T \boldsymbol{X}_i^*\right)^{-1} \boldsymbol{X}_i^* \boldsymbol{Y}_i^*\right] \\ &= \frac{1}{n}\sum_{i=1}^{n} E\Bigg[\Big[\left(\left(1-\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right)\right)\boldsymbol{X}_i\right)^T \left(\left(1-\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right)\right)\boldsymbol{X}_i\right)\Big]^{-1} \\ &\quad \times \left(\left(1-\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right)\right)\boldsymbol{X}_i\right)^T \\ &\quad \times \Big(\boldsymbol{Y}_i - \left(\beta_1+r_{1i}\right)\exp\left(-\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right) \\ &\quad - I\left(\tau_i=1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3+r_{3i}\right)\exp\left(\left(\beta_4+r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg] \end{aligned} \tag{4.2.10}$$

$$\begin{aligned}\hat{\beta}_1 &= \frac{1}{n}\sum_{i=1}^{n} E\Bigg[\frac{1}{m_i}\sum_{k=1}^{m_i}\Big[\Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\ &\quad - I\left(\tau_i=1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3+r_{3i}\right)\exp\left(\left(\beta_4+r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big) \\ &\quad \times \exp\left(\left(\beta_2+r_{2i}\right)\boldsymbol{u}_i\right) - r_{1i} + \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big]\Bigg] \end{aligned} \tag{4.2.11}$$

$$\begin{aligned}\hat{\beta}_2 &= \frac{1}{n}\sum_{i=1}^{n} E\Bigg[\frac{1}{m_i}\sum_{k=1}^{m_i}\log\Bigg[\frac{1}{\boldsymbol{u}_i \circ \left(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\right)\exp\left(-r_{2i}\boldsymbol{u}_i\right)} \\ &\quad \times \Big(\boldsymbol{Y}_i - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T \\ &\quad - I\left(\tau_i=1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3+r_{3i}\right)\exp\left(\left(\beta_4+r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big)\Bigg]\Bigg] \end{aligned} \tag{4.2.12}$$

$$\hat{\beta}_3 = \begin{cases} \frac{1}{\sum I(\tau_i = 1)} \sum_{i=1}^{n} E\Bigg[\frac{1}{\sum I(\boldsymbol{u}_i \geq t_{TX_i})} \sum_{k=1}^{m_i} \Big[\big(\boldsymbol{Y}_i - (\boldsymbol{X}_i \boldsymbol{\alpha})^T \\ \quad - \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i \boldsymbol{\alpha})^T \right) \exp\left(- \left(\beta_2 + r_{2i} \right) \boldsymbol{u}_i \right) \big) \\ \quad \times \exp\left(- \left(\beta_4 + r_{4i} \right) \boldsymbol{u}_i \right) - r_{3i} \Big] \Bigg], & \tau_i = 1 \\ 0, & \text{otherwise} \end{cases} \tag{4.2.13}$$

$$\hat{\beta}_4 = \begin{cases} \frac{1}{\sum I(\tau_i = 1)} \sum_{i=1}^{n} E\Bigg[\frac{1}{\sum I(\boldsymbol{u}_i \geq t_{TX_i})} \\ \quad \times \sum_{k=1}^{m_i} \log \Bigg[\frac{1}{\boldsymbol{u}_i \circ (\beta_3 + r_{3i}) \exp(r_{4i} \boldsymbol{u}_i)} \\ \quad \times \Big(\boldsymbol{Y}_i - (\boldsymbol{X}_i \boldsymbol{\alpha})^T \\ \quad - \left(\beta_1 + r_{1i} - (\boldsymbol{X}_i \boldsymbol{\alpha})^T \right) \exp\left(- \left(\beta_2 + r_{2i} \right) \boldsymbol{u}_i \right) \Big) \Bigg] \Bigg], & \tau_i = 1 \\ 0, & \text{otherwise} \end{cases} \tag{4.2.14}$$

Estimates for α, β_2, and β_3 are calculated using numerical approximation techniques, due to the relationship between the closed-form estimates and observation times. We use MATLAB's `fminsearch` function (an unconstrained nonlinear optimization

routine) to solve

$$\left[\hat{\boldsymbol{\alpha}},\ \hat{\beta}_2,\ \hat{\beta}_4\right]^T = \arg\min\ E\left[l_{\alpha,\beta}\left(\boldsymbol{\alpha}, \beta_2, \beta_4\right)\right] \tag{4.2.15}$$

where

$$\begin{aligned} l_{\alpha,\beta} = -\frac{1}{2\sigma_\epsilon^2} \cdot \frac{1}{n} \sum_{i=1}^{n} \Bigg[\frac{1}{m_i} \sum_{k=1}^{m_i} \Big[& \boldsymbol{Y}_i - \left(\boldsymbol{X}_i \boldsymbol{\alpha}\right)^T \\ & - \left(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i \boldsymbol{\alpha}\right)^T\right) \exp\left(-\left(\beta_2 + r_{2i}\right) \boldsymbol{u}_i\right) \\ & - \left(I\left(\tau_i = 1,\ \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\right) \Big]^2 \Bigg] + C_{\alpha.\beta} \end{aligned} \tag{4.2.16}$$

and $C_{\alpha,\beta}$ represents all the parts of the log-likelihood that do not contain $\boldsymbol{\alpha}$ or $\boldsymbol{\beta}$. (Note that this is the same equation as (3.2.12).)

Calculating all parameter estimates via `fminsearch` would be overly time-consuming. Therefore, as in Chapter 3, estimates for β_1 and β_3 will be calculated using (4.2.11) and (4.2.13).

We estimate variance by subtracting subject-level expected values from subject observed values.

$$\hat{\sigma_\epsilon^2} = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{m_i} \left(\boldsymbol{Y}_i - E\left[\boldsymbol{Y}_i\right]\right)\left(\boldsymbol{Y}_i - E\left[\boldsymbol{Y}_i\right]\right)^T \tag{4.2.17}$$

where

$$E\left[\boldsymbol{Y}_i\right] = E\Big[\left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T + \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i\boldsymbol{\alpha}\right)^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right)\boldsymbol{u}_i\right) + I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \exp\left(\left(\beta_4 + r_{4i}\right)\left(\boldsymbol{u}_i - t_{TX_i}\right)\right)\Big]$$

Estimates for $\boldsymbol{\gamma}$, $\boldsymbol{\zeta}_\omega$, $\boldsymbol{\zeta}_\pi$, and θ cannot be derived in a closed form. We will approximate them using the `fmincon` function in MATLAB to solve

$$\left[\hat{\boldsymbol{\gamma}},\, \hat{\boldsymbol{\zeta}_\omega},\, \hat{\boldsymbol{\zeta}_\pi},\, \hat{\theta},\, \hat{c}\right]^T = \arg\min\; E\left[l_{\gamma,\zeta_\omega,\zeta_\pi,\theta,c}\left(\boldsymbol{\gamma}, \boldsymbol{\zeta}_\omega, \boldsymbol{\zeta}_\pi, \theta, c\right)\right] \tag{4.2.18}$$

where

$$\begin{aligned} l_{\gamma,\zeta_\omega,\zeta_\pi,\theta,c} = \sum_{i=1}^{n} \Bigg\{ & -I\left(\tau_i = 0\right) t_i b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right) \\ & - I\left(\tau_i = 1\right)\left(t_{TX_i} b_{1i} \exp\left(\boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right)\left(t_i - t_{TX_i}\right) b_{2i} \exp\left(\boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_\pi\right)\right) \\ & + I\left(\tau_i = 0, \delta_i = 1\right)\left(\log b_{1i} + \boldsymbol{X}_{\omega i}\boldsymbol{\zeta}_\omega\right) \\ & + I\left(\tau_i = 1, \delta_i = 1\right)\left(\log b_{2i} + \boldsymbol{X}_{\pi i}\boldsymbol{\zeta}_\pi\right) \\ & + \sum_{j=1}^{2}\left[\frac{1}{2\theta} r_{ji} - \frac{\gamma_j}{\theta}\exp\left(r_{ji}\right) - \frac{1}{2\theta}\log\left(\frac{\theta}{\gamma_j}\right) - \log\Gamma\left(\frac{1}{2\theta}\right)\right] \\ & + I\left(\tau_i = 1\right)\sum_{j=3}^{4}\Bigg[\frac{1-c}{2c\theta} r_{ji} - \frac{\left(1-c\right)\gamma_j}{c\theta}\exp\left(r_{ji}\right) \\ & - \frac{1-c}{2c\theta}\log\left(\frac{c\theta}{\left(1-c\right)\gamma_j}\right) - \log\Gamma\left(\frac{1-c}{2c\theta}\right)\Bigg]\Bigg\} \end{aligned} \tag{4.2.19}$$

`fmincon` is similar to `fminsearch`, except that it uses *constrained* nonlinear optimization to solve a scalar function.

As in Chapter 3, the E-step will evaluate the following integral:

$$E\left[f\left(\boldsymbol{r}_i\right)\right] = \int_0^\infty \int_0^\infty \int_0^\infty \int_0^\infty f\left(\boldsymbol{r}_i\right)\ h\left(\boldsymbol{r}_i\right)\ dr_{1i}dr_{2i}dr_{3i}dr_{4i} \tag{4.2.20}$$

where $f\left(\boldsymbol{r}_i\right)$ is any sufficient statistic. Expanding (4.2.11) and (4.2.13) gives us the following sufficient statistics:

r_{1i}	r_{3i}
$\exp\left(r_{2i}\boldsymbol{u}_i\right)$	$\exp\left(-r_{4i}\boldsymbol{u}_i\right)$
$\exp\left(r_{2i}\boldsymbol{u}_i\right)\exp\left(r_{4i}\boldsymbol{u}_i\right)$	$\exp\left(-r_{2i}\boldsymbol{u}_i\right)\exp\left(-r_{4i}\boldsymbol{u}_i\right)$
$r_{3i}\exp\left(r_{2i}\boldsymbol{u}_i\right)\exp\left(r_{4i}\boldsymbol{u}_i\right)$	$r_{1i}\exp\left(-r_{2i}\boldsymbol{u}_i\right)\exp\left(-r_{4i}\boldsymbol{u}_i\right)$

We will use adaptive Gaussian quadrature (AGQ) to determine the numerical value of (4.2.20) (Pinheiro and Chao, 2006). This method requires integration over a normal distribution. Since our random effects are not normally distributed, we the standardization methods proposed in Liu and Yu (2008). The resulting integral is:

$$E\left[f\left(\boldsymbol{r}_i\right)\right] = \int_{-\infty}^\infty \int_{-\infty}^\infty \int_{-\infty}^\infty \int_{-\infty}^\infty \left(f\left(\boldsymbol{r}_i\right)\ \frac{h\left(\boldsymbol{r}_i\right)}{\phi\left(\boldsymbol{r}_i\right)}\right)\phi\left(\boldsymbol{r}_i\right)\ dr_{1i}dr_{2i}dr_{3i}dr_{4i} \tag{4.2.21}$$

where $\phi\left(\boldsymbol{r}_i\right)$ is a standard multivariate normal distribution for $\boldsymbol{r}_i$.

It is clearly not tractable to solve (4.2.21) analytically, so we will approximate it with the following sum:

$$E\left[f\left(\boldsymbol{r}_i\right)\right] \approx \sum_k \sum_k \sum_k \sum_k \left[f\left(\boldsymbol{r}_{i,k}\right)\ h^*\left(\boldsymbol{r}_{i,k}\right)\ w_{1k}w_{2k}w_{3k}w_{4k}\right] \tag{4.2.22}$$

where w_{jk} is the k^{th} weight for the $j = 1, \ldots, 4$ random effect and $h^*\left(\boldsymbol{r}_{i,k}\right) = \frac{h\left(\boldsymbol{r}_{i,k}\right)}{\phi\left(\boldsymbol{r}_{i,k}\right)}$.

4.3. Simulations

To investigate the performance of our model, we analyzed 100 simulated datasets, with a sample size of $n = 500$ each. The model was tested under three different conditions, and compared to an independent model (where longitudinal, pre-transplant survival, and post-transplant survival were all considered independent of one another). Subjects were followed for five years after waitlisting and were required to have at least two observations pre- and post-transplant (with a minimum of four observations total).

Data simulations involved several steps:

1. Exponentiated subject-specific random effects were calculated using a gamma distribution, where

$$\begin{aligned} \exp(r_{ji}) &\sim \Gamma\left(\frac{1}{2\theta}, \frac{\theta}{\gamma_j}\right) && j = 1, 2 \\ \exp(r_{ji}) &\sim \Gamma\left(\frac{1-c}{2c\theta}, \frac{c\theta}{(1-c)\gamma_j}\right) && j = 3.4 \end{aligned}$$

   Subject specific random effects were calculated by taking the natural log of the exponentiated random effects, i.e. $r_{ji} = \log(\exp(r_{ji}))$.

2. Patient-specific pre-transplant frailties were calculated

$$b_{1i} = \gamma_1 \exp(r_{1i}) + \gamma_2 \exp(r_{2i})$$

3. Pre-transplant survival times were simulated using the methods proposed by

Bender et al. (2005)

$$T_i = -\frac{\log U}{b_{1i} \exp\left(\boldsymbol{X}_{\omega i} \boldsymbol{\zeta}_{\omega}\right)}$$

where U is a standard uniform random variable

4. A random sample of patients who would be "offered" transplants was determined.

$$\tau_i \sim Binomial\left(n, p_{Tx}\right)$$

where p_{Tx} is the percentage of patients who will be offered transplants. Subject-specific transplant times were calculated, so that $t_{TX_i} = 0.99 \times T_i$

5. Patient pre-transplant survival/censoring status was determined for patients who did not receive transplants

$$[t_i, \delta_i] = \left[\min\left(T_i, C_{\text{end}}\right),\ T_i \leq C_{\text{end}}\right]$$

where C_{end} is the end time of the study

6. Post-transplant survival/censoring times were determined for patients who received transplants using a similar process as described above

   (a) Patient-specific post-transplant frailties were calculated

$$b_{2i} = c b_{1i} + (1 - c)\left(\gamma_3 \exp\left(r_{3i}\right) + \gamma_4 \exp\left(r_{4i}\right)\right)$$

(b) Post-transplant survival times were simulated

$$T_i^{Tx} = -\frac{\log U}{b_{2i} \exp\left(\boldsymbol{X}_{\pi i} \boldsymbol{\zeta}_{\pi}\right)} + t_{TX_i}$$

(c) Patient post-transplant survival/censoring status was determined

$$[t_i, \delta_i] = \left[\min\left(T_i^{Tx}, C_{\text{end}}\right),\ T_i^{Tx} \leq C_{\text{end}}\right]$$

7. Longitudinal data was simulated for all subjects

$$y_{ik} = \begin{cases} \Big[\left(\boldsymbol{X}_i \boldsymbol{\alpha}\right)^T + \Big(\beta_1 + r_{1i} - \left(\boldsymbol{X}_i \boldsymbol{\alpha}\right)^T\Big) \exp\left(-\left(\beta_2 + r_{2i}\right) u_{ik}\right) \\ \quad + I\left(\tau_i = 1,\, \boldsymbol{u}_i \geq t_{TX_i}\right)\left(\beta_3 + r_{3i}\right) \\ \quad\quad \times \exp\left(\left(\beta_4 + r_{4i}\right)\left(u_{ik} - t_{TX_i}\right)\right) + \sigma_\epsilon^2\Big], & u_{ik} \leq t_i \\ \text{missing}, & \text{otherwise} \end{cases}$$

Data simulated from a joint model were used to compare the joint model results with that of an independent model, as in Chapter 3. Results of the simulations are shown in Table 4.1. As in Chapter 3, we see that the model generally does well estimating the longitudinal trajectory parameters, and again is not very different from the independent model. This is to be expected in models with no time-varying covariates (Liu, 2011). On average, the joint model performs better when estimating post-transplant survival, while the independent model performs better when estimating pre-transplant survival. The mean bias difference in pre-transplant survival estimates is small, though. On average, the independent model pre-transplant estimates have a 0.76% lower bias than the joint model estimates. The joint model has advantages

Table 4.1: Simulation results for joint vs. indep. model, when joint model is true

		Joint model	Independent model
Parameter	Truth	Est. (SE)	Est. (SE)
α_1	0.3	0.29 (0.0004)	0.29 (0.0004)
α_2	3.5	3.40 (0.03)	3.42 (0.03)
β_1	4	4.02 (0.01)	4.00 (0.01)
β_2	-0.1	-0.10 (0.0003)	-0.10 (0.0003)
β_3	-4	-3.83 (0.05)	-3.87 (0.05)
β_4	-1	-0.98 (0.005)	-0.99 (0.004)
γ_1	0.55	0.56 (0.0008)	0.56 (0.0007)
γ_2	0.4	0.38 (0.0004)	0.39 (0.0004)
γ_3	0.25	0.26 (0.002)	0.26 (0.002)
γ_4	0.2	0.21 (0.001)	0.21 (0.001)
θ	0.03	0.02 (0.0003)	0.02 (0.0004)
c	0.75	0.79 (0.003)	0.78 (0.003)
$\boldsymbol{\zeta}_\omega$	-2	-2.14 (0.009)	-1.92 (0.01)
$\boldsymbol{\zeta}_\pi$	-3	-3.16 (0.16)	-3.24 (0.17)
σ^2_ϵ	1	1.13 (0.02)	1.17 (0.02)

over the independent model when estimating post-transplant survival parameters. For post-transplant survival, the joint model estimates have about 3% less bias than the independent model estimates. Sharing information across the submodels clearly improves our estimation abilities.

Data were also simulated assuming independent submodels. These data were used to compare the joint model results with that of an independent model. It is important to note that it is impossible to simulate fully-independent data. Patients who receive transplants must always survive to transplant. Therefore, pre- and post-transplant survival are inevitably linked. This implies that both the joint model and the fully-independent model are misspecified. We present the fully-independent results in order to compare our model against "standard practice."

Results of the simulations are shown in Table 4.2. Results from one of the simulations were excluded from the calculations in Table 4.2 due to outliers in the parameter

Table 4.2: Simulation results for joint vs. indep. model, when indep. model is true

		Joint model	Independent model
Parameter	Truth	Est. (SE)	Est. (SE)
α_1	0.3	0.29 (0.0005)	0.29 (0.0005)
α_2	3.5	3.36 (0.02)	3.35 (0.02)
β_1	4	4.12 (0.01)	4.09 (0.02)
β_2	-0.1	-0.10 (0.0005)	-0.10 (0.0005)
β_3	-4	-3.82 (0.10)	-3.90 (0.10)
β_4	-1	-0.99 (0.003)	-0.99 (0.003)
γ_1	0.55	0.56 (0.001)	0.57 (0.001)
γ_2	0.4	0.37 (0.0005)	0.38 (0.0005)
γ_3	0.25	0.26 (0.001)	0.26 (0.001)
γ_4	0.2	0.21 (0.0006)	0.21 (0.0006)
θ	0.03	0.02 (0.0002)	0.02 (0.0003)
c	0.75	0.77 (0.002)	0.78 (0.002)
$\boldsymbol{\zeta}_\omega$	-2	-2.83 (0.02)	-1.33 (0.02)
$\boldsymbol{\zeta}_\pi$	-3	-2.99 (0.03)	-2.30 (0.03)
σ^2_ϵ	1	1.19 (0.03)	1.24 (0.03)

estimates. We see that the longitudinal parameter estimates are generally unbiased for both the joint and independent models. Pre-transplant survival estimates are biased for both the independent and joint models, which is to be expected, since both models are misspecified. Bias is also present in the independent model post-transplant survival estimates. In contrast, the joint model produces unbiased post-transplant survival estimates, even under a misspecified model.

Another simulation was done to compare the performance of the model under various conditions, as defined by the number of patients who receive transplants. Results of that simulation are shown in Table 4.3. Longitudinal parameter values are estimated well in all simulated situations. Some differences in the pre-transplant survival parameter estimates appear as the percentage of transplanted patients increase. This is due to the relative lack of pre-transplant information under those conditions. It is also important to note that a transplant percentage of 90% is unreasonable clinically.

Table 4.3: Simulation results for model performance across varying conditions

		20% Tx	50% Tx	90% Tx
Parameter	Truth	Est. (SE)	Est. (SE)	Est. (SE)
α_1	0.3	0.29 (0.0004)	0.29 (0.0004)	0.29 (0.0006)
α_2	3.5	3.40 (0.03)	3.37 (0.03)	3.33 (0.02)
β_1	4	4.02 (0.009)	4.04 (0.008)	4.08 (0.017)
β_2	-0.1	-0.10 (0.0003)	-0.10 (0.0003)	-0.10 (0.0005)
β_3	-4	-3.83 (0.05)	-3.76 (0.04)	-3.82 (0.06)
β_4	-1	-0.98 (0.005)	-0.98 (0.001)	-0.99 (0.003)
γ_1	0.55	0.56 (0.0008)	0.56 (0.0009)	0.56 (0.0012)
γ_2	0.4	0.38 (0.0004)	0.38 (0.0006)	0.37 (0.0008)
γ_3	0.25	0.26 (0.002)	0.26 (0.001)	0.26 (0.001)
γ_4	0.2	0.20 (0.0010)	0.21 (0.0007)	0.21 (0.0005)
θ	0.03	0.02 (0.0003)	0.02 (0.0003)	0.02 (0.0003)
c	0.75	0.79 (0.003)	0.79 (0.002)	0.79 (0.002)
$\boldsymbol{\zeta}_\omega$	-2	-2.14 (0.009)	-2.59 (0.02)	-4.18 (0.04)
$\boldsymbol{\zeta}_\pi$	-3	-3.16 (0.16)	-2.93 (0.03)	-2.84 (0.02)
σ^2_ϵ	1	1.13 (0.02)	1.10 (0.01)	1.16 (0.03)

Percentages ranging from 20-50% are much more reasonable.

4.4. Application

In this chapter, we modify the assumptions made in Chapter 3 to include the possibility of post-transplant death. Descriptive statistics for this dataset (referred to as Subset 2) are found in Table 4.4. Patients were followed for a maximum of five years (1826 days) post-waitlisting, or three years (1096 days) post-transplant, whichever was shorter. The analysis dataset contained 500 patients who were waitlisted for a liver transplant at HUP between February, 27, 2002, and May, 13, 2011. Approximately 30% of our patients received transplants during this timeframe. Of the patients who did not receive transplants, approximately 30% were observed to have died by the end of the study. Of the patients who did receive transplants, approximately 13% were observed to have died within three years of transplant. Average follow-up time for all subjects was 2.2 years, with transplanted patients having longer follow-up

Table 4.4: Descriptive statistics for UNOS/HUP Subset 2

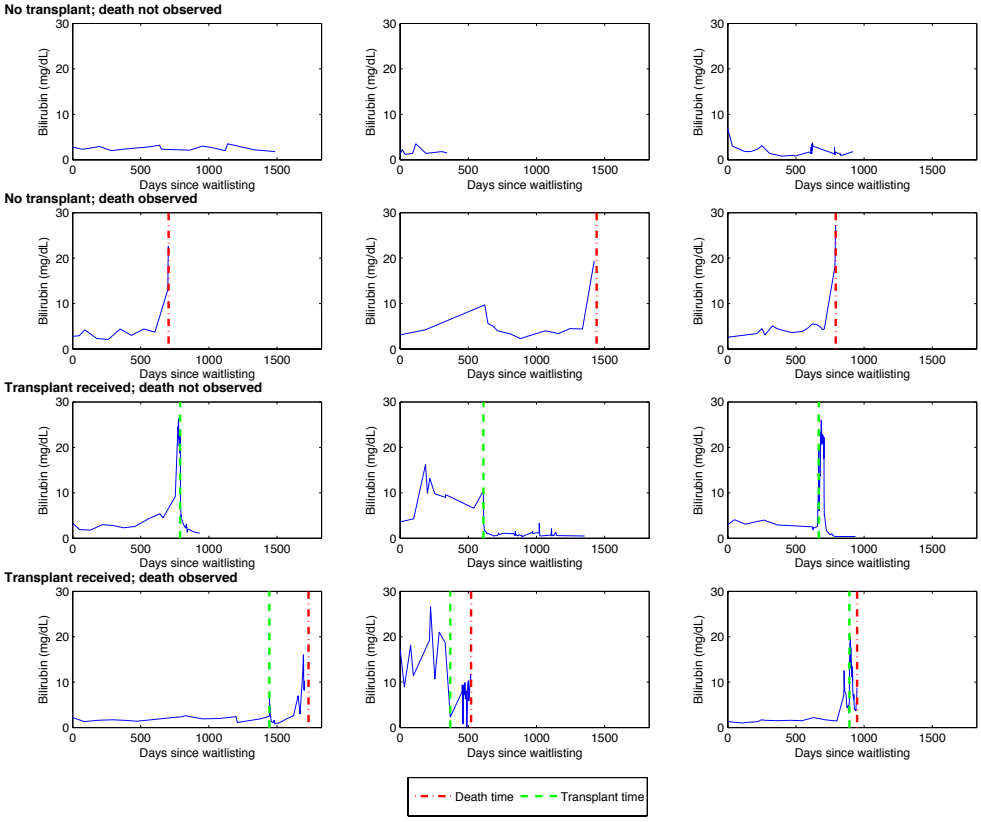
	Tx group	No Tx group	Total
n (%)	166 (33)	334 (67)	500
Number censored (%)	144 (87)	244 (73)	388 (78)
Number dead (%)	22 (13)	90 (27)	112 (22)
Mean follow-up time	2.6 years	2.0 years	2.2 years
Median time to Tx	5.6 months	-	-
Median observable survival time[🚲]	4.7 years	5 years	5 years
Male gender (%)	117 (71)	223 (67)	340 (68)
Mean age at WLing (years)	51.6	53.2	52.7

[🚲] - Due to censoring, the median observed survival time is equal to the maximum survival time

times than those who did not receive a transplant (2.6 vs. 2.0 years). Median time to transplant was 5.6 months. Median survival times could not be accurately calculated due to censoring. Demographics (gender and age at waitlisting) were similar for both groups.

As discussed in Section 1.1, transplant data has many characteristics that pose challenges with statistical modeling. Figure 4.1 highlights some of these characteristics. Prior to transplant, patients who have a spike in bilirubin levels (indicating a worsening of disease), are more likely to die or receive a transplant. Post-transplant, a similar pattern holds. Patients who experience a large spike in bilirubin levels post-transplant are more likely to die. These spikes prior to either transplant or death indicate that patients are not dying or being offered transplanted in a random fashion. Sicker patients appear to be more likely to receive transplants or die. The exponential growth-decay model lets us capture this increase in bilirubin values pre-transplant, as well as the immediate drop and exponential decrease post-transplant. Modifying a standard cure model to include both a pre- and post-transplant Cox survival model allows us to analyze survival times pre- as well as post-transplant. The shared random effects in the model link the longitudinal biomarker values to pre- and

Figure 4.1: Bilirubin trajectories (UNOS/HUP Subset 2)



post-transplant survival.

Results for our data analysis are shown in Table 4.5. Standard errors were calculated via 100 bootstrap iterations (Efron, 1982). Results from one of the bootstraps were excluded from the calculations in Table 4.5 due to outliers in the parameter estimates.

As in Section 3.4, we include both gender and age at waitlisting as covariates in the longitudinal model. Gender alone is a covariate in both the pre- and post-transplant survival models. Our results show that male gender and age at waitlisting are significantly related to patient bilirubin values. Males and older individuals have higher bilirubin values (3.97 mg/dL, 95% CI = [3.32,4.62]; and 0.26 mg/dL/year, 95% CI

Table 4.5: Data analysis results for UNOS/HUP Subset 2

	Joint model	Independent model
Parameter	Est. (Bootstrap SE)	Est. (Bootstrap SE)
α_1 (male gender)	3.97 (0.33)	3.99 (0.32)
α_2 (age at WLing)	0.26 (0.006)	0.26 (0.006)
β_1	4.08 (0.04)	4.09 (0.04)
β_2	-0.13 (0.001)	-0.13 (0.001)
β_3	-4.37 (0.11)	-4.34 (0.12)
β_4	-1.01 (0.02)	-1.01 (0.02)
γ_1	0.55 (0.0001)	0.55 (0.0001)
γ_2	0.43 (0.0003)	0.43 (0.0003)
γ_3	0.24 (0.0007)	0.24 (0.0007)
γ_4	0.21 (0.0004)	0.21 (0.0004)
θ	0.005 (0.0001)	0.005 (0.0001)
c	0.96 (0.0008)	0.96 (0.0008)
$\boldsymbol{\zeta}_\omega$ (male gender)	-2.25 (0.01)	-0.10 (0.02)
$\boldsymbol{\zeta}_\pi$ (male gender)	-2.96 (0.03)	-0.34 (0.18)
σ^2_ϵ	16.69 (0.36)	16.70 (0.35)

= [0.25,0.27], respectively). Estimates for β_1 and β_2 indicate that patients have an average bilirubin level of 4.08 mg/dL at waitlisting, and that patients experience an average gradual increase in bilirubin levels pre-transplant (growth rate = 0.13 mg/dL). Estimates of post-transplant parameters β_3 and β_4 indicate that patients experience a drop in bilirubin levels of 4.37 mg/dL post-transplant, followed by a decrease over time (growth rate = -1.01 mg/dL).

Survival parameter estimates indicate that males are significantly less likely than females to die both pre- and post-transplant (hazard ratio = 0.11 and 0.05, respectively.) This confirms analyses done by Mindikoglu et al. (2010) and Hariharan et al. (2002), where the authors found higher survival rates for males on the waiting list and post-transplant.

A comparison of the joint model results with those from a fully-independent "standard practice" analysis reveals an interesting result. Estimates for both pre- and

post-transplant survival are drastically attenuated. Futhermore, the independent model gives non-significant results for post-transplant survival. This highlights the importance of carefully choosing an inference method, as conclusions can differ across methods.

4.5. Discussion

In this chapter, we modified the model proposed in Chapter 3 to include the possibility of post-transplant death. We again use an exponential growth-decay curve to represent patient longitudinal trajectories. We change the survival function by adding in a second Cox model for patient survival post-transplant. We have shown that this model does reasonably well under varying conditions defined by different transplant percentages. Post-transplant survival estimates are improved in our model as compared with the independent model.

CHAPTER 5

Conclusion

In this dissertation, we introduce a joint longitudinal-survival model. This model is developed to address the complex and underappreciated statistical issues presented by data from transplant patients. We review the history and issues associated with transplant data in Chapter 1. In Chapter 2, we discuss the problem of informative dropout and the models used to compensate for it.

In Chapter 3, we propose an exponential growth-decay longitudinal submodel and a modified cure submodel to investigate pre-treatment survival times. These submodels are linked by shared random effects that appear in both patients' longitudinal trajectories and their pre-transplant survival frailties. Patients who receive transplants are assumed to be "cured" and cannot die during the study. We demonstrate our model using liver transplant data from the United Network of Organ Sharing (UNOS) and the Hospital of the University of Pennsylvania (HUP). Serum total bilirubin is our longitudinal outcome, with age at waitlisting and gender being considered as covariates in the submodels. Simulations show that our model is more efficient than a Cox model for estimating parameters related to patient survival.

In Chapter 4, we extend our model to include the possibility of post-transplant patient death. To do this, we modify the cure submodel to contain two Cox models, one for pre-transplant survival and another for post-transplant survival. We continue to model the longitudinal trajectories using an exponential growth-decay curve. The longitudinal and survival submodels are linked by shared random effects, which are present in patient-specific longitudinal trajectories as well as in the frailties of the two

Cox models. We again apply our methods to liver transplant data from UNOS and HUP. We consider patients' serum total bilirubin values as the longitudinal outcome of interest. Pre- and post-transplant survival times are investigated as well. Our model shows an improvement in the estimation of the survival parameters, as compared with an independent model. An important future goal of this work is to predict patient survival times; therefore, it is critical that our proposed joint model performs better than an independent model when determining estimates for survival parameters.

Many opportunities exist for extending this model. Future directions are primarily aimed at developing a model that is more clinically relevant and useful to patients. Proposed extensions include:

1. Multivariate outcomes

   Multivariate outcomes are of interest since one biomarker alone may not adequately capture a patient's health status. Specifically, we know that liver transplant patients' MELD scores are made up of three different biomarkers: serum total bilirubin, serum creatinine, and INR. Though the MELD score is not validated post-transplant, these biomarkers are likely still relevant post-transplant (e.g. Wu et al., 2010).

2. Repeated events

   Liu et al. (2004) developed a joint model that considers the effect of a recurrent event (hospitalization) on a terminal event (death). This is of obvious value in a transplant setting, where patients may experience a variety of repeated events of interest (e.g. hospitalization, acute rejection, infection). Terminal events to consider could be death or re-transplant.

3. Value censoring

Value censoring happens when observations are missing due to exceeding some threshold. This can happen when biomarker values are above or below some detectable limit (Wu, 2004). For example, MELD scores are value-censored by UNOS, as they are capped at 40. Statistically, this problem is dealt with via a Tobit model (Tobin, 1958).

4. Multiple types of transplant

   Different types of transplants are available to patients. Organs can come from "standard criteria" donors (SCD) or from "expanded criteria" donors (ECD). ECD organs have characteristics that may make them associated with poorer outcomes than SCD organs (Metzger et al., 2003). Patients can also receive organs from donors with an increased risk of viral infection (called CDC organs). There is debate as to whether or not the extra risk associated with ECD and CDC organs is of practical significance, considering the long wait times for transplants(Amin et al., 2004; Reese et al., 2009).

5. Predictive model / Point-and-click software

   A predictive model would be of most use for clinicians. Rizopoulos (2011) proposed a model for dynamic prediction relating longitudinal CD4 counts to a patient's probability of death. A similar model (that incorporates any or all of the above extensions) could be developed and could be of great use clinically, particularly if point-and-click software were made available (de Leeuw and Zeileis).

The models presented in this dissertation are a decided improvement on standard independent and joint analysis methods. The methods we propose allow for more accurate and precise estimation of factors that affect patient survival times after being placed on the liver transplant waiting list. These models provide us with the

tools needed to properly analyze patient data from the time of waitlisting, past the time of transplant, and on to possible post-transplant death. Extensions of these models could be used to create effective clinical tools that would be used to counsel patients on their healthcare options.

APPENDIX

Abbreviations

NOTA	National Organ Transplant Act
OPTN	Organ Procurement and Transplantation Network
UNOS	United Network of Organ Sharing
HUP	Hospital of the University of Pennsylvania
MELD	Model for End-Stage Liver Disease
Cr	Serum creatinine
TBIL	Total serum bilirubin
INR	International normalized ratio (of prothrombin time)
Tx	Transplant
WL	Waitlisting

Table of Notation

Variable	Dimension	Description
$\boldsymbol{Y}_i$	$m_i \times 1$	Subject-specific longitudinal measures
$\boldsymbol{u}_i$	$m_i \times 1$	Subject-specific observation times
$\boldsymbol{\alpha}$	$p \times 1$	Fixed effects for longitudinal model
$\boldsymbol{\Sigma} = \sigma_\epsilon^2 \boldsymbol{I}$	$m_i \times m_i$	Covariance matrix for longitudinal measures
$\boldsymbol{X}_i$	$m \times p$	Covariates for fixed effects
$\boldsymbol{\zeta}_\pi$	$p_\pi \times 1$	Fixed effects for subject-specific probability of death post-transplant (Chapter 4)
$\boldsymbol{X}_{\pi i}$	$p_\pi \times 1$	Covariates for probability of death post-transplant (Chapter 4)
$\boldsymbol{\zeta}_\omega$	$p_\omega \times 1$	Fixed effects for subject-specific probability of death pre-transplant
$\boldsymbol{X}_{\omega i}$	$p_\omega \times 1$	Covariates for probability of death pre-transplant
$\boldsymbol{r}_i$	4×1	Subject-specific random effects
$\boldsymbol{\gamma}$	4×1	Fixed effects relating subject-specific random effects to subject-specific frailty
t_i	1×1	Subject survival time
b_i	1×1	Subject-specific pre-transplant frailty (Chapter 3)
b_{2i}	1×1	Subject-specific pre-transplant frailty (Chapter 4)
b_{1i}	1×1	Subject-specific post-transplant frailty (Chapter 4)
c	1×1	Weighting factor that relates pre- and post-transplant survival (Chapter 4)

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