Prospective survival analysis with a general semiparametric shared frailty model - a pseudo full likelihood approach

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Summary

In this work we provide a simple estimation procedure for a general frailty model for analysis of prospective correlated failure times. Rigorous large-sample theory for the proposed estimators of both the regression coefficient vector and the dependence parameter is given, including consistent variance estimators. In a simulation study under the widely used gamma frailty model, our proposed approach was found to have essentially the same efficiency as the EM-based estimator considered by other authors, with negligible difference between the standard errors of the two estimators. The proposed approach, however, provides a framework capable of handling general frailty distributions with finite moments and yields an explicit consistent variance estimator.

Key words: Correlated failure times; EM algorithm; Frailty model; Prospective family study; Survival analysis.
1 Introduction

Many epidemiological studies involve failure times that are clustered into groups, such as families or schools, where some unobserved characteristics shared by the members of the same cluster (e.g. genetic information or unmeasured shared environmental exposures) could influence time to the studied event. In frailty models within cluster dependence is represented through a shared unobservable variable as a random effect. Estimation in the frailty model has received much attention under various frailty distributions, including gamma (Gill, 1985, 1989; Nielsen et al., 1992; Klein 1992, among others), positive stable (Hougaard, 1986; Fine et al., 2003), inverse Gaussian, compound Poisson (Henderson and Oman, 1999) and log-normal (McGilchrist, 1993; Ripatti and Palmgren, 2000; Vaida and Xu, 2000, among others). Hougaard (2000) provides a comprehensive review of the properties of the various frailty distributions. In a frailty model, the parameters of interest typically are the regression coefficients, the cumulative baseline hazard function, and the dependence parameters in the random effect distribution.

Since the frailties are latent covariates, the Expectation-Maximization (EM) algorithm is a natural estimation tool, with the latent covariates estimated in the E-step and the likelihood maximized in the M-step by substituting the estimated latent quantities. Gill (1985), Nielsen et al. (1992) and Klein (1992) discussed EM-based maximum likelihood estimation for the semiparametric gamma frailty model. One problem with the EM algorithm is that variance estimates of the estimated parameters are not readily available (Louis, 1982; Gill, 1989; Nielsen et al., 1992; Andersen et al., 1997). It was suggested (Gill, 1989; Nielsen et al, 1992) that a nonparametric information calculation could yield consistent variance estimators. Parner (1998), building on Murphy (1994, 1995), proved the consistency and asymptotic normality of the maximum likelihood estimator in the gamma frailty model. Parner also presented a consistent estimator of the limiting covari-
ance matrix of the estimator based on inverting a discrete observed information matrix. He noted that since the dimension of the observed information matrix is the dimension of the regression coefficient vector plus the number of observed survival times, inverting the matrix is practically infeasible for a large data set with many distinct failure times. Thus, he proposed another covariance estimator based on solving a discrete version of a second order Sturm-Liouville equation. This covariance estimator requires substantially less computational effort, but still is not so simple to implement.

The purpose of our work here is to develop a new inference technique that can handle any parametric frailty distribution with finite moments. Our new method possesses a number of desirable properties: a non-iterative procedure for estimating the cumulative hazard function; consistency and asymptotic normality of parameter estimates; a direct consistent covariance estimator; and easy computation and implementation. The rest of the paper is organized as follows. In Section 2 we present the estimation procedure. Consistency and asymptotic results for the estimators are given in Section 3. As the frailty model is often applied using a gamma frailty distribution, Section 4 compares the finite sample performance of our approach and the EM-based approach under the gamma distribution. Section 5 provides an example using a diabetic retinopathy data set. Section 6 presents concluding remarks.

2 The Proposed Approach

Consider $n$ families, with family $i$ containing $m_i$ members, $i = 1, \ldots, n$. Let $\delta_{ij} = I(T_{ij}^0 \leq C_{ij})$ be a failure indicator where $T_{ij}^0$ and $C_{ij}$ are the failure and censoring times, respectively, for individual $ij$. Also let $T_{ij} = \min(T_{ij}^0, C_{ij})$ be the observed follow-up time and $Z_{ij}$ be a $p \times 1$ vector of covariates. In addition, we associate with family $i$ an unobservable family-level covariate $W_i$, the “frailty”, which induces dependence among family mem-
The conditional hazard function for individual \(ij\) conditional on the family frailty \(W_i\), is assumed to take the form

\[
\lambda_{ij}(t) = W_i \lambda_0(t) \exp(\beta^T Z_{ij}) \quad i = 1, \ldots, n \quad j = 1, \ldots, m_i
\]

where \(\lambda_0\) is an unspecified conditional baseline hazard and \(\beta\) is a \(p \times 1\) vector of unknown regression coefficients. This is an extension of the Cox (1972) proportional hazards model, with the hazard function for an individual in family \(i\) multiplied by \(W_i\). We assume that, given \(Z_{ij}\) and \(W_i\), the censoring is independent and noninformative for \(W_i\) and \((\beta, \Lambda_0)\) (in the sense of Andersen et al., 1993, Sec. III.2.3). We assume further that the frailty \(W_i\) is independent of \(Z_{ij}\) and has a density \(f(w; \theta)\), where \(\theta\) is an unknown parameter. For simplicity we assume that \(\theta\) is a scalar, but the development extends readily to the case where \(\theta\) is a vector. Let \(\tau\) be the end of the observation period. The full likelihood of the data then can be written as

\[
L = \prod_{i=1}^{n} \int \lambda_0(T_{ij}) \delta_{ij} S_{ij}(T_{ij}) f(w) dw
\]

where \(N_{ij}(t) = \delta_{ij} I(T_{ij} \leq t), N_i(t) = \sum_{j=1}^{m_i} N_{ij}(t), H_{ij}(t) = \Lambda_0(T_{ij} \wedge t) \exp(\beta^T Z_{ij}), a \wedge b = \min\{a, b\}\), \(\Lambda_0(\cdot)\) is the baseline cumulative hazard function, \(S_{ij}(\cdot)\) is the conditional survival function of subject \(ij\), and \(H_i(t) = \sum_{j=1}^{m_i} H_{ij}(t)\). The log-likelihood is given by

\[
l = \sum_{i=1}^{n} \sum_{j=1}^{m_i} \delta_{ij} \log(\lambda_0(T_{ij}) \exp(\beta^T Z_{ij})) + \sum_{i=1}^{n} \log \left\{ \int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f(w) dw \right\}.
\]

The normalized scores (log-likelihood derivatives) for \((\beta_1, \ldots, \beta_p)\) are given by

\[
U_r = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \delta_{ij} Z_{ijr} - \frac{1}{n} \sum_{i=1}^{n} \left[ \sum_{j=1}^{m_i} H_{ij}(T_{ij}) Z_{ijr} \right] \int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f(w) dw \frac{\int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f(w) dw}{\int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f(w) dw}
\]

for \(r = 1, \ldots, p\). The normalized score for \(\theta\) is

\[
U_{p+1} = \frac{1}{n} \sum_{i=1}^{n} \int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f'(w) dw \frac{\int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f(w) dw}{\int w^{N_i(\tau)} \exp\{-w H_i(\tau)\} f(w) dw}
\]
where $f'(w) = \frac{d}{d\theta} f(w)$. Let $\gamma = (\beta^T, \theta)$ and $U(\gamma, \Lambda_0) = (U_1, \ldots, U_p, U_{p+1})^T$. To obtain estimators $\hat{\beta}$ and $\hat{\theta}$, we propose to substitute an estimator of $\Lambda_0$, denoted by $\hat{\Lambda}_0$, into the equations $U(\gamma, \Lambda_0) = 0$.

Let $Y_{ij}(t) = I(T_{ij} \geq t)$ and let $\mathcal{F}_t$ denote the entire observed history up to time $t$, that is

$$\mathcal{F}_t = \sigma\{N_{ij}(u), Y_{ij}(u), Z_{ij}, i = 1, \ldots, n; j = 1, \ldots, m_i; 0 \leq u \leq t\}.$$ 

Then, as discussed by Gill (1992) and Parner (1998), the stochastic intensity process for $N_{ij}(t)$ with respect to $\mathcal{F}_t$ is given by

$$\lambda_0(t) \exp(\beta^T Z_{ij}) Y_{ij}(t) \psi_i(\gamma, \Lambda_0, t\!-\!),$$

where

$$\psi_i(\gamma, \Lambda_0, t) = E(W_i|\mathcal{F}_t).$$

Using a Bayes theorem argument and the joint density with observation time restricted to $[0, t)$, we obtain

$$\psi_i(\gamma, \Lambda, t) = \phi_{2i}(\gamma, \Lambda, t)/\phi_{1i}(\gamma, \Lambda, t),$$

where

$$\phi_{ki}(\gamma, \Lambda_0, t) = \int w^{N_i(t)+(k-1)} \exp\{-wH_i(t)\} f(w)dw, \quad k = 1, \ldots, 4.$$

Given the intensity model, in which $\exp(\beta^T Z)\psi_i(\gamma, \Lambda_0, t\!-\!)$ may be regarded as a time dependent covariate effect, a natural estimator of $\Lambda_0$ is a Breslow (1974) type estimator along the lines of Zucker (2005). For given values of $\beta$ and $\theta$ we estimate $\Lambda_0$ as a step function with jumps at the observed failure times $\tau_k, k = 1, \ldots, K$, with

$$\Delta \hat{\Lambda}_0(\tau_k) = \frac{d_k}{\sum_{i=1}^n \psi_i(\gamma, \hat{\Lambda}_0, \tau_{k-1}) \sum_{j=1}^{m_i} Y_{ij}(\tau_k) \exp(\beta^T Z_{ij})}$$

where $d_k$ is the number of failures at time $\tau_k$. Note that given the intensity model, the estimator of the $k$th jump depends on $\hat{\Lambda}_0$ up to and including time $\tau_{k-1}$. By this approach,
we avoid complicating the iterative optimization process with a further iterative scheme, like that of Shih and Chatterjee (2002), for estimating the cumulative hazard.

3 Large-Sample Study

Let $\gamma^o = (\beta^o, \theta^o)^T$ with $\beta^o, \theta^o$ and $\Lambda^0_0(t)$ denoting the respective true values of $\beta, \theta$ and $\Lambda_0(t)$, and let $\hat{\gamma} = (\hat{\beta}^T, \hat{\theta})^T$. In Appendix A, the conditions assumed in establishing the asymptotic properties of $\hat{\gamma}$ are listed and discussed.

Using arguments similar to those of Zucker (2005, Appendix A.3), the following can be shown (see, Appendix A):

A. $\hat{\Lambda}_0(t, \gamma)$ converges almost surely to $\Lambda_0(t, \gamma)$ uniformly in $t$ and $\gamma$.

B. $U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))$ converges almost surely uniformly in $t$ and $\gamma$ to a limit $u(\gamma, \Lambda_0(\cdot, \gamma))$.

C. There exists a unique consistent root to $U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) = 0$.

To show that $\hat{\gamma}$ is asymptotically normally distributed, we write

$$0 = U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma}))$$

$$= U(\gamma^o, \Lambda^0_0) + [U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U(\gamma^o, \Lambda^0_0)]$$

$$+ [U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) - U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o))].$$

In Appendix B we analyze each of the above three terms and prove that $n^{1/2}(\hat{\gamma} - \gamma^o)$ is asymptotically mean-zero normally distributed, with a covariance matrix that can be consistently estimated by the sandwich estimator

$$D^{-1}(\gamma)\{\hat{V}(\gamma) + \hat{G}(\gamma) + \hat{C}(\gamma)\}D^{-1}(\gamma)^T. \quad (5)$$

The matrix $D$ consists of the derivatives of the $U_r$’s with respect to the parameters $\gamma$. $V$ is the asymptotic covariance matrix of $U(\gamma^o, \Lambda^0_0)$, $G$ is the asymptotic covariance matrix
of \[ U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U(\gamma^o, \Lambda_0^o) \], and \( C \) is the asymptotic covariance matrix between \( U(\gamma^o, \Lambda_0^o) \) and \[ U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U(\gamma^o, \Lambda_0^o) \]. The term \( G + C \) reflects the added variance resulting from the need to estimate the cumulative hazard function. All the above matrices are defined explicitly in the Appendix.

4 Simulation Study for the Gamma Frailty Case

Gill (1985), Klein et al. (1992), and Nielsen et al. (1992) dealt with the gamma frailty model by applying the EM algorithm to the Cox partial likelihood. This method may be interpreted as a semi-parametric full maximum likelihood method. Murphy (1994, 1995) showed consistency and asymptotic normality for the model without covariates, where the unknown parameters are the integrated hazard function and the gamma frailty parameters. Parner (1998) extended the consistency and asymptotic normality results to the correlated gamma frailty model with covariates. In what follows we compare our proposed method to the EM method under the gamma frailty distribution with expectation 1 and variance \( \theta \).

The following is the EM-based estimation algorithm as given in Nielsen et al. (1992).

**Step I:** Using standard Cox regression software, obtain initial estimates of \( \beta \) and \( \Lambda_0 \), taking \( W_i = 1, i = 1, \ldots, n \) (i.e. \( \theta = 0 \)).

**Step II (E step):** Using the current values of \( \beta \), \( \Lambda_0 \) and \( \theta \), estimate the frailty value \( W_i \) by

\[
\hat{W}_i = \frac{N_i(\tau) + \theta^{-1}}{\hat{H}_i(\tau) + \theta^{-1}}.
\]  

(6)

**Step III (M step):** Update the estimate of \( \beta \) by fitting a Cox proportional hazard model with covariates \( Z \) and offset term \( \log(\hat{W}) \). Update the estimate of \( \Lambda_0 \) by
the traditional Breslow type estimator associated with the Cox model. Update the estimate of $\theta$ by the maximum likelihood estimator based on (II).

**Step IV:** Iterate between Steps II and III until convergence.

Our estimation technique can be summarized by the following algorithm.

**Step I:** Using standard Cox regression software, obtain initial estimates of $\beta$ and as initial value for $\hat{\theta}$, let $\hat{\theta} = 0$.

**Step II:** Using the current values of $\beta$ and $\theta$, estimate $\Lambda_0$ using the non-iterative estimate presented by Equation (4).

**Step III:** Using the current estimate $\hat{\Lambda}_0$, estimate $\beta$ and $\theta$ by solving $U(\gamma, \hat{\Lambda}) = 0$.

**Step IV:** Iterate between Steps II and III until convergence.

It is easy to see that under the gamma distribution for $W_i$,

$$\psi_i(\gamma, \Lambda_0, t-) = E(W_i|F_{t-}) = \frac{N_i(t-) + \theta^{-1}}{H_i(t-) + \theta^{-1}}.$$  

(7)

Murphy (1994) showed that for the model without covariates, an estimator of the cumulative hazard function based on the EM algorithm with (7) instead of (6) converges to the true value of the cumulative hazard function. This result can be extended to the case where covariates are included in the model.

Note that in Murphy (1994), the cumulative hazard function at $\tau_k$ includes the cumulative information up through time $\tau_k$, whereas in the EM algorithm the accumulated information is up through time $\tau$, the entire study period. In contrast, in our approach the cumulative hazard function at $\tau_k$ only includes the information up through the previous failure time point $\tau_{k-1}$. Hence, one might suspect our estimators are somewhat less efficient than the EM-based estimators. Part of the goal of our simulation study was to assess the extent of this potential efficiency loss.
The setup for the simulation study is similar to that of Hsu et al. (2004) for investigating a semiparametric estimation of marginal hazard function from case-control family study, with the required modifications for the current prospective setting. For each family we generated a common frailty value \( W \) from the gamma distribution with scale and shape parameters both equal \( \theta^{-1} \). We consider 300 families, each of size 2. A single covariate from the standard normal distribution was incorporated. Conditional on \( W \), the survivor function is

\[
S(t|Z, W) = \exp\{-W \exp(\beta Z)(0.01t)^{4.6}\}
\]

Thus, with \( \beta = \ln(2) \) or \( \ln(3) \) and a normal distribution for the censoring, with mean 60 years and standard deviation of 15 years, the censoring level is approximately 85% and 80%, respectively. The censoring distribution was chosen in order to generate appropriate mean age at onset and distribution, similar to what is often observed for late onset diseases. With censoring distributed according to \( N(130, 15^2) \) the respective censoring levels are approximately 35% and 30%. Table 1 summarizes the results for the two estimation techniques, for \( \beta^o = \ln(2) \) or \( \ln(3) \) and \( \theta^o = 2 \). For our method, we compare the mean estimated standard error based on our theoretical formula with the empirical standard error, and provide the empirical coverage rate of 95% Wald-type confidence interval. For the EM-based method, we report only the empirical standard error. In addition, the empirical correlation between the EM-based estimators and our estimators is presented. It is evident that both estimation techniques perform very well in term of bias. Also, for our method, good agreement was observed between the estimated and the empirical standard error. The high values of the correlations implies similarity between the two estimation techniques not only on an average basis, but actually on a data set by data set basis.
5 Example

We now apply our method under the gamma frailty distribution to a diabetic retinopathy data set. The Diabetic Retinopathy Study (DRS) was begun in 1971 to study the effectiveness of laser photocoagulation in delaying the onset of blindness in patients with diabetic retinopathy. Patients with diabetic retinopathy and visual acuity of 20/100 or better in both eyes were eligible for the study. For each study subject, one eye was randomly selected for treatment laser photocoagulation and the other eye was observed without treatment. The outcome variable is time to blindness of each eye. For illustrative purposes the following analysis involves 197 high-risk patients as defined by DRS criteria. Of the 394 measurements, 239 (61%) are censored. The regression coefficient estimate of the treatment effect was $-0.890$ and $-0.910$ according to our proposed estimator and the EM algorithm, respectively. The respective estimated standard errors, 0.175 and 0.174, are based on 50 bootstrap samples. The estimate of $\theta$ was 0.865 with our approach, and 0.857 with the EM approach. The respective estimated standard errors are 0.367 and 0.365. As one can see, both method yield extremely similar results. Both indicated that the treatment appeared effective in delaying the time to blindness, and that the times to blindness for both eyes are highly dependent. The hazard rate of one eye becoming blind given the other eye is blind is almost twice $(1+\theta)$ as high as that given the other eye is not blind.

6 Discussion

We have presented a method for estimating the regression coefficient vector and frailty parameter in a prospective frailty survival model. The procedure is applicable to any frailty distribution with finite moments. We have shown that our estimators of the regression
coefficients and frailty parameter are consistent and asymptotically normally distributed, and given an explicit consistent estimator for the variances of the parameter estimates. For the popular gamma frailty model, we have presented simulation results showing that our estimator is essentially as efficient as the estimator based on the EM algorithm. For our procedure, a consistent covariance estimator is available which is much easier to compute than its counterpart for the EM method as given by Parner (1998). Nonconjugate frailty distributions can be handled by a simple univariate numerical integration over the frailty distribution.

The estimation approach used here for estimating the cumulative hazard function can be applied in some other important settings, such as the case-control family study. Our approach avoids an iterative procedure for the \( \hat{\Lambda}_0 \), enabling the asymptotic properties of the estimator to be derived in a relatively straightforward fashion. Shih and Chatterjee (2002) proposed a semi-parametric quasi-partial-likelihood approach for estimating the regression coefficients in survival data from a case-control family study. Their cumulative hazard estimator requires an iterative solution, and thus the properties of their estimates could only be investigated so far by a simulation study. If their method is modified by using our approach to estimating \( \Lambda_0(u) \), the proof presented in Appendix B can serve as a basis for the asymptotic properties of the resulting procedure, with appropriate modifications. The extension to this case will be presented in a separate paper.

7 Appendix: Asymptotic Theory

7.1 Assumptions and Background

In deriving the asymptotic properties of \( \hat{\gamma} \) we make the following assumptions:

1. The random vectors \( (T_{i1}, \ldots, T_{im_i}, C_{i1}, \ldots, C_{im_i}, Z_{i1}, \ldots, Z_{im_i}, W_i), \ i = 1, \ldots, n, \) are
independent and identically distributed.

2. There is a finite maximum follow-up time $\tau > 0$, with $E[\sum_{j=1}^{m_i} Y_{ij}(\tau)] = y^* > 0$ for all $i$.

3. (a) Conditional on $Z_{ij}$ and $W_i$, the censoring is independent and noninformative of $W_i$ and $(\beta, \Lambda_0)$.

(b) $W_i$ is independent of $Z_{ij}$ and of $m_i$.

4. The frailty random variable $W_i$ has finite moments up to order $(m + 2)$, where $m$ is a fixed upper bound on $m_i$.

5. $Z_{ij}$ is bounded.

6. The parameter $\gamma$ lies in a compact subset $\mathcal{G}$ of $\mathbb{R}^{p+1}$ containing an open neighborhood of $\gamma^o$.

7. There exist $b > 0$ and $C > 0$ such that
   \[ \lim_{w \to 0} w^{-(b-1)} f(w) = C. \]

8. The baseline hazard function $\lambda_0^o(t)$ is bounded over $[0, \tau]$ by some constant $\lambda_{\text{max}}$.

9. The function $f'(w; \theta) = (d/d\theta) f(w; \theta)$ is absolutely integrable.

10. The censoring distribution has at most finitely many jumps on $[0, \tau]$.

11. The matrix $[(\partial/\partial \gamma) U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))]_{\gamma = \gamma^o}$ is invertible with probability going to 1 as $n \to \infty$.

The matrix $(\partial/\partial \gamma) U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))$ is presented explicitly in Section 7.3, Step IV. From \[335-337\], it is seen that a general proof of invertibility is intractable, but given the data, one can easily check that numerically the matrix is invertible.
7.2 Technical Preliminaries

Here we present some technical results that are needed for the asymptotic theory. First note that, by the boundedness of $\beta$ and $Z_{ij}$, there exists a constant $\nu > 0$ such that

$$\nu^{-1} \leq \exp(\beta^T Z_{ij}) \leq \nu.$$  \hspace{1cm} (8)

Next, recall that

$$\psi_i(\gamma, \Lambda, t) = \int w^N_i(t) + 1 e^{-H_i(t)w} f(w) dw$$

with $H_i(t) = H_i(t, \gamma, \Lambda) = \sum_{j=1}^{m_i} \Lambda(T_{ij} \wedge t) \exp(\beta^T Z_{ij})$ (here we define $H_i$ so as to allow dependence on a general $\gamma$ and $\Lambda$, which will often not be explicitly indicated in the notation). Define (for $0 \leq r \leq m$ and $h \geq 0$)

$$\psi^*(r, h) = \frac{\int w^{r+1} e^{-hw} f(w) dw}{\int w^r e^{-hw} f(w) dw}.$$  \hspace{1cm} (9)

Also define $\psi^*_{\text{min}}(h) = \min_{0 \leq r \leq m} \psi^*(r, h)$ and $\psi^*_{\text{max}}(h) = \max_{0 \leq r \leq m} \psi^*(r, h)$. Note that, in the expression for $\psi^*(r, h)$, the numerator and denominator are bounded from above by the assumption that $W$ has finite $(m + 2)$-th moment. In addition, the numerator and denominator are by necessity strictly positive, for otherwise $W$ would have a degenerate distribution concentrated at 0. Thus $\psi^*_{\text{max}}(h)$ is finite and $\psi^*_{\text{min}}(h)$ is strictly positive.

**Lemma 1:** The function $\psi^*(r, h)$ is decreasing in $h$. In consequence, we have, for all $\gamma \in \mathcal{G}$ and all $t$,

$$\psi_i(\gamma, \Lambda, t) \leq \psi^*_{\text{max}}(0),$$  \hspace{1cm} (9)

$$\psi_i(\gamma, \Lambda, t) \geq \psi^*_{\text{min}}(m \nu \Lambda(t)).$$  \hspace{1cm} (10)

In addition, there exist $B > 0$ and $\bar{h} > 0$ such that, for all $h \geq \bar{h}$,

$$\psi^*_{\text{min}}(h) \geq B \bar{h}^{-1}.$$  \hspace{1cm} (11)
Proof: We have
\[
\frac{\partial}{\partial h} \psi^*(r, h) = -\left[ \frac{\int w^{r+2} e^{-hw} f(w) dw}{\int w^{r} e^{-hw} f(w) dw} - \left( \frac{\int w^{r+1} e^{-hw} f(w) dw}{\int w^{r} e^{-hw} f(w) dw} \right)^2 \right].
\] (12)

This quantity is negative for all \( h \), which establishes that \( \psi^*(r, h) \) is a decreasing function of \( h \). Now, by definition, \( \psi_i(\gamma, \Lambda, t) = \psi^*(N_i(t), H_i(t)) \). We have \( 0 \leq H_i(t) \leq m\nu \Lambda(t) \).

The inequalities (9) and (10) follow immediately.

As for (11), using a change of variable and Assumption 7, we find that
\[
\lim_{h \to \infty} h \psi^*(r, h) = \frac{\int_0^\infty v^r b e^{-v} dv}{\int_0^\infty v^{r+1} e^{-v} dv} = r + b.
\]

Choosing \( \bar{h} \) large enough so that the above limit is obtained up to a factor of, say, 1.01, the result follows.

We define
\[
\bar{\Lambda} = 1.03e^{m\sigma} \left( \frac{\bar{h}}{m\nu} \right),
\]
with \( \sigma = 1.01m\nu^2 / (By^*) \), where \( \bar{h} \) and \( B \) are as in Lemma 1.

Lemma 2: With probability one, there exists \( n' \) such that, for all \( t \in [0, \tau] \) and \( \gamma \in \mathcal{G} \),
\[
\hat{\Lambda}_0(t, \gamma) \leq \bar{\Lambda} \text{ for } n \geq n'.
\] (13)

Remark: The point of this lemma is that \( \hat{\Lambda}_0(t, \gamma) \) is automatically bounded above, without any need to impose an upper bound artificially.

Proof: To simplify the writing below, we will suppress the argument \( \gamma \) in \( \hat{\Lambda}_0(t, \gamma) \). Recall
\[
\Delta \hat{\Lambda}_0(\tau_k) = \frac{1}{\sum_{i=1}^n \psi_i(\gamma, \hat{\Lambda}_0(\tau_{k-1})) \sum_{j=1}^{m_i} Y_{ij}(\tau_k) \exp(\beta^T Z_{ij})},
\]
where we now take \( d_k = 1 \) since the survival time distribution is assumed continuous.

Using Lemma 1 and (8), we have
\[
\Delta \hat{\Lambda}_0(\tau_k) \leq n^{-1} \nu_{\psi*_{min}}(m\nu \bar{\Lambda}(\tau_{k-1}))^{-1} \left[ \frac{1}{n} \sum_{i=1}^n \sum_{j=1}^{m_i} Y_{ij}(\tau) \right]^{-1}.
\]
Now, since $\sum_{j=1}^{m_i} Y_{ij}(\tau)$ are iid random variables with expectation $y^*$, by the strong law of large numbers we have
\[
\frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} Y_{ij}(\tau) \to y^*
\]
almost surely. Hence, with probability one, there exists $n^*$ such that
\[
\frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} Y_{ij}(\tau) \geq 0.999y^* \quad \text{for } n \geq n^*.
\]
(14)

We thus have, for $n \geq n^*$,
\[
\Delta \hat{\Lambda}_0(\tau_k) \leq n^{-1} \left( \frac{1.01\nu}{y^*} \right) \psi_{\min}(m\nu\hat{\Lambda}(\tau_{k-1}))^{-1}.
\]
(15)

Now, if $\hat{\Lambda}_0(t) \leq \bar{h}/(m\nu)$ for all $t$ then we are done. Otherwise, there exists $k'$ such that $\hat{\Lambda}_0(\tau_k) \leq \bar{h}/(m\nu)$ for $k < k'$ and $\hat{\Lambda}_0(\tau_k) \geq \bar{h}/(m\nu)$ for $k \geq k'$. Using the last inequality of Lemma 1, we obtain, for $k > k'$,
\[
\Delta \hat{\Lambda}_0(\tau_k) \leq n^{-1} \sigma \hat{\Lambda}_0(\tau_{k-1}),
\]
or, in other words,
\[
\hat{\Lambda}_0(\tau_k) \leq \left( 1 + \frac{\sigma}{n} \right) \hat{\Lambda}_0(\tau_{k-1}).
\]

Iterating the above inequality we get
\[
\hat{\Lambda}_0(\tau_{k'+\ell}) \leq \left( 1 + \frac{\sigma}{n} \right)^\ell \hat{\Lambda}_0(\tau_{k'}) \leq \left( 1 + \frac{\sigma}{n} \right)^{mn} \hat{\Lambda}_0(\tau_{k'}) \leq 1.01\epsilon^{m\sigma} \hat{\Lambda}_0(\tau_{k'})
\]
for $n$ large enough. But, using (15) and the fact that $\hat{\Lambda}_0(\tau_{k'-1}) \leq \bar{h}/(m\nu)$, we have
\[
\hat{\Lambda}_0(\tau_{k'}) \leq \frac{\bar{h}}{m\nu} + n^{-1} \left( \frac{1.01\nu}{y^*} \right) \psi_{\min}(\bar{h})^{-1},
\]
which is less than $1.01\bar{h}/(m\nu)$ for $n$ large enough. The desired conclusion follows.

**Lemma 3**: $\sup_{s \in [0,\tau]} |\hat{\Lambda}_0(s, \gamma^\circ) - \hat{\Lambda}_0(s-, \gamma^\circ)| \to 0$ as $n \to \infty$. 

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Proof: Since \( \hat{\Lambda}_0(s, \gamma) - \hat{\Lambda}_0(s, \gamma) \) equals \( \Delta \hat{\Lambda}_0(\tau_k) \) for \( s = \tau_k \) and zero otherwise, it is enough to show that \( \sup_k \Delta \hat{\Lambda}_0(\tau_k, \gamma^o) \to 0 \) as \( n \to \infty \). But from Lemma 2 and (15) we have
\[
\Delta \hat{\Lambda}_0(\tau_k) \leq n^{-1} \left( \frac{1.01}{y^*} \right) \psi_{\min}^*(m\nu) - 1.
\]
for \( n \) sufficiently large. The conclusion follows immediately.

7.3 Consistency

We now show the almost sure consistency of \( \hat{\beta} \) and \( \hat{\Lambda}_0 \). The argument is built on Claims A-C of Section 3, which we prove below. Our argument follows Zucker (2005, Appendix A.3).

Claim A: \( \hat{\Lambda}_0(t, \gamma) \) converges a.s. to some function \( \Lambda_0(t, \gamma) \) uniformly in \( t \) and \( \gamma \).

Proof: In the proof below, whenever a functional norm is written, the relevant uniform norm is intended.

Define \( \Lambda_{\text{max}} = \max(\bar{\Lambda}, \lambda_{\text{max}} \tau) \) and \( \psi^{**}(r, h) = \psi^*(r, h \wedge h_{\text{max}}) \), where \( h_{\text{max}} = m\nu\Lambda_{\text{max}} \).

It is easy to see from (12) that \( \psi^{**}(r, h) \) is Lipschitz continuous in \( h \) (uniformly in \( r \)). Recall that \( \psi_i(\gamma, \Lambda, t) = \psi^*(N_i(t), H_i(t, \gamma, \Lambda)) \). But Lemma 2 implies that \( H_i(t, \gamma, \hat{\Lambda}_0(\cdot, \gamma)) \leq h_{\text{max}} \) for all \( t \in [0, \tau] \) and \( \gamma \in \mathcal{G} \). Hence we see that \( \psi_i(\gamma, \hat{\Lambda}_0(\cdot, \gamma), t) = \psi^{**}(N_i(t), H_i(t, \gamma, \hat{\Lambda}_0(\cdot, \gamma))) \).

Now define, for a general function \( \Lambda \),
\[
\Xi_n(t, \gamma, \Lambda) = \int_0^t \frac{n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} \psi^{**}(N_i(s), H_i(s, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^T Z_{ij})}{n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} \psi^{**}(N_i(s), H_i(s, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^T Z_{ij})} ds
\]
and
\[
\Xi(t, \gamma, \Lambda) = \int_0^t \frac{E[ \sum_{i=1}^{m_i} \psi^{**}(N_i(s), H_i(s, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^T Z_{ij})] \lambda_0(s) ds}{E[ \sum_{i=1}^{m_i} \psi^{**}(N_i(s), H_i(s, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^T Z_{ij})] \lambda_0(s) ds}.
\]

By definition, \( \hat{\Lambda}_0(t, \gamma) \) satisfies the equation
\[
\hat{\Lambda}_0(t, \gamma) = \Xi_n(t, \gamma, \hat{\Lambda}_0(\cdot, \gamma)).
\]
Next, define
\[
q_\gamma(s, \Lambda) = \frac{\mathbb{E}[\sum_{j=1}^{m_i} \psi^*(N_i(s-), H_i(s-, \gamma^0, \Lambda_0^0))Y_{ij}(s)\exp(\beta^T z_{ij})]}{\mathbb{E}[\sum_{j=1}^{m_i} \psi^{**}(N_i(s-), H_i(s-, \gamma, \Lambda))Y_{ij}(s)\exp(\beta^T z_{ij})]}\lambda_0^0(s).
\]
This function is uniformly bounded by \(B^* = [\psi^{max}(0)/\psi^{min}(h_{max})] \lambda_{max}\). Moreover, by the Lipschitz continuity of \(\psi^{**}(r, h)\) with respect to \(h\), it satisfies the Lipschitz-like condition (for some constant \(K\))
\[
|q_\gamma(s, \Lambda_1) - q_\gamma(s, \Lambda_2)| \leq K \sup_{0 \leq u \leq s} |\Lambda_1(u) - \Lambda_2(u)|.
\]
Hence, by mimicking step by step the argument of Hartman (1973, Theorem 1.1), we find that the equation \(\Lambda(t) = \Xi(t, \gamma, \Lambda)\) has a unique solution. We denote this solution by \(\Lambda_0(t, \gamma)\). The claim then is that \(\hat{\Lambda}_0(t, \gamma)\) converges almost surely (uniformly in \(t\) and \(\gamma\)) to this function \(\Lambda_0(t, \gamma)\). Though it may be possible to prove this claim directly, we shall use a convenient indirect argument.

Define \(\bar{\Lambda}_0^{(n)}(t, \gamma)\) to be a modified version of \(\hat{\Lambda}_0(t, \gamma)\) defined by linear interpolation between the jumps, where we have added the superscript \(n\) for emphasis. Lemma 3 implies that, with probability one,
\[
\sup_{t, \gamma} |\bar{\Lambda}_0^{(n)}(t, \gamma) - \hat{\Lambda}_0(t, \gamma)| \to 0,
\]
and thus
\[
\sup_{t, \gamma} |\Xi_n(t, \gamma, \hat{\Lambda}_0(t, \gamma)) - \Xi_n(t, \gamma, \hat{\Lambda}_0(t, \gamma))| \to 0.
\]
Lemma 2 shows that the family \(\mathcal{L} = \{\bar{\Lambda}_0^{(n)}(t, \gamma), n \geq n'\}\) is uniformly bounded. We will establish in a moment that \(\mathcal{L}\) is also equicontinuous. It then follows, by the Arzela-Ascoli theorem, that the closure of \(\mathcal{L}\) in \(C([0, \tau] \times \mathcal{G})\) is compact.

The equicontinuity of \(\mathcal{L}\) is shown as follows. Recall that \(N_i(t) = \sum_{j=1}^{m_i} N_{ij}(t)\). Write \(\bar{N}(t) = n^{-1} \sum_{i=1}^{n} \sum_{j=1}^{m_i} N_{ij}(t)\). We have \(\bar{N}(t) \to \mathbb{E}[N_i(t)]\) as \(n \to \infty\) uniformly in \(t\) with
probability one, with
\[
E[N_i(t)] = \int_0^t E \left[ \sum_{j=1}^{m_i} \psi^*(N_i(s^-), H_i(s^-, \gamma, \Lambda^0_j)) Y_{ij}(s) \exp(\beta^T Z_{ij}) \right] \lambda_0(s) ds.
\]

In view of this and (14) there exists a probability-one set of realizat ions \( \Omega^* \) on which the following holds: for any given \( \epsilon > 0 \), we can find \( n''(\epsilon) \) such that \( \sup_t |\bar{N}(t) - E[N_i(t)]| \leq \epsilon/(4B^\circ) \) for all \( n \geq n''(\epsilon) \), where \( B^\circ = 1.01\nu/[\psi^*_\text{min}(h_{\text{max}})y^*] \). In consequence, for all \( t \) and \( u \) with \( u < t \), we find that
\[
\hat{A}_0(t, \gamma) - \hat{A}_0(u, \gamma) = \int_u^t \frac{n^{-1} \sum_{i=1}^{m_n} \sum_{j=1}^{m_i} dN_{ij}(s)}{n^{-1} \sum_{i=1}^{m_n} \sum_{j=1}^{m_i} \psi^*(N_i(s^-), H_i(s^-, \gamma, \Lambda)) Y_{ij}(s) \exp(\beta^T Z_{ij})}
\]
satisfies
\[
\hat{A}_0(t, \gamma) - \hat{A}_0(u, \gamma) \leq B^\bullet(t - u) + \frac{\epsilon}{2} \quad \text{for all } n \geq n''(\epsilon).
\]

Moreover, it is easy to see that \( \hat{A}_0(t, \gamma) \) is Lipschitz continuous in \( \gamma \) with Lipschitz constant \( C^\ast \), say, that is independent of \( t \).

These two results imply that \( \mathcal{L} \) is equicontinuous. This is seen as follows. For given \( \epsilon \), we need to find \( \delta^*_1 \) and \( \delta^*_2 \) such that \( |\tilde{\Lambda}_0^{(n)}(t, \gamma) - \tilde{\Lambda}_0^{(n)}(u, \gamma)| \leq \epsilon \) whenever \( |t - u| \leq \delta^*_1 \) and \( |\tilde{\Lambda}_0^{(n)}(t, \gamma) - \tilde{\Lambda}_0^{(n)}(t, \gamma')| \leq \epsilon \) whenever \( ||\gamma - \gamma'|| \leq \delta^*_2 \). The latter is easily obtained using the Lipschitz continuity of \( \hat{A}_0(t, \gamma) \) with respect to \( \gamma \). As for the former, for \( n \geq n''(\epsilon) \) this can be accomplished using (14), while for \( n \) in the finite set \( n' \leq n < n''(\epsilon) \) this can be accomplished using the fact that the function \( \tilde{\Lambda}_0^{(n)}(t, \gamma) \) is uniformly continuous on \([0, \tau]\) for every given \( n \).

We have thus shown that \( \mathcal{L} \) is (almost surely) a relatively compact set in the space \( C([0, \tau] \times \mathcal{G}) \).

Next, define
\[
A(\gamma, \Lambda, s) = \frac{1}{n} \sum_{i=1}^{m_n} \sum_{j=1}^{m_i} \psi^*(N_i(s^-), H_i(s^-, \gamma, \Lambda)) Y_{ij}(s) \exp(\beta^T Z_{ij}),
\]
\[
a(\gamma, \Lambda, s) = E \left[ \sum_{j=1}^{m_i} \psi^*(N_i(s^-), H_i(s^-, \gamma, \Lambda)) Y_{ij}(s) \exp(\beta^T Z_{ij}) \right].
\]
We show below that, with probability one,
\[
\sup_{s, \gamma} |A(\gamma, \Lambda^{(n)}(s)) - a(\gamma, \Lambda^{(n)}(s))| \to 0.
\]  
(20)

Given this and the a.s. uniform convergence of \( \bar{N}(t) \) to \( \mathbb{E}[N_i(t)] \), we can infer that
\[
\sup_{t, \gamma} |\bar{\Xi}(t, \gamma, \Lambda^{(n)}_0(t, \gamma)) - \Xi(t, \gamma, \Lambda^{(n)}_0(t, \gamma))| \to 0.
\]  
(21)

The result (21) is easily obtained by adapting the argument of Aalen (1976, Lemma 6.1), making use of the equicontinuity of \( \mathcal{L} \). It is here that we make use of Assumption 10, for the adaptation of Aalen’s argument requires \( a(\gamma, \Lambda, s) \) to be piecewise continuous with finite left and right limits at each point of discontinuity.

From (16), (17), (18), and (21) it follows that any limit point of \( \{\Lambda^{(n)}_0(t, \gamma)\} \) must satisfy the equation \( \Lambda = \Xi(t, \gamma, \Lambda) \). Since \( \Lambda_0(t, \gamma) \) is the unique solution of this equation, it is the unique limit point of \( \{\Lambda^{(n)}_0(t, \gamma)\} \). Thus \( \{\Lambda^{(n)}_0(t, \gamma)\} \) is a sequence in a compact set with unique limit point \( \Lambda_0(t, \gamma) \). Hence \( \Lambda^{(n)}_0(t, \gamma) \) converges a.s. uniformly in \( t \) and \( \gamma \) to \( \Lambda_0(t, \gamma) \). In view of (17), the same holds of \( \tilde{\Lambda}_0(t, \gamma) \), which is the desired result.

To complete the proof, we must establish (20). This involves several steps. First, it is easy to see that there exists a constant \( \kappa \) (independent of \( \gamma \) and \( s \)) such that
\[
\sup_{s, \gamma} |A(\gamma, \Lambda_1(s)) - A(\gamma, \Lambda_2(s))| \leq \kappa \|\Lambda_1 - \Lambda_2\|,
\]  
(22)

\[
\sup_{s, \gamma} |a(\gamma, \Lambda_1(s)) - a(\gamma, \Lambda_2(s))| \leq \kappa \|\Lambda_1 - \Lambda_2\|.
\]  
(23)

Next, for any fixed continuous \( \Lambda \), the functional strong law of large numbers of Andersen & Gill (1982, Appendix III) implies that, with probability one,
\[
\sup_{s, \gamma} |A(\gamma, \Lambda(s)) - a(\gamma, \Lambda(s))| \to 0.
\]  
(24)

Now, given \( \epsilon > 0 \), define the sets \( \{t^{(\epsilon)}_j\}, \{\gamma^{(\epsilon)}_k\}, \) and \( \{\Lambda^{(\epsilon)}_l\} \) to be finite partition grids of \([0, \tau], \mathcal{G}, \) and \([0, \Lambda_{\text{max}}]\), respectively, with distance of no more than \( \epsilon \) between grid points.
Define $\mathcal{L}_\epsilon^*$ to be the set of functions of $t$ and $\gamma$ defined by linear interpolation through vertices of the form $(t^{(c)}_j, \gamma^{(c)}_k, \Lambda^{(c)}_l)$.

Obviously $\mathcal{L}_\epsilon^*$ is a finite set. Hence, in view of (24), there exists a probability-one set of realizations $\Omega_\epsilon$ for which

$$\sup_{s \in [0, \tau], \gamma \in \mathcal{G}, \Lambda \in \mathcal{L}_\epsilon^*} |A(\gamma, \Lambda, s) - a(\gamma, \Lambda, s)| \to 0. \quad (25)$$

Define

$$\Omega^{**} = \bigcap_{\ell=1}^{\infty} \Omega_{1/\ell}$$

and $\Omega_0 = \Omega^* \cap \Omega^{**}$, with $\Omega^*$ as defined earlier. Clearly $\Pr(\Omega_0) = 1$. From now on, we restrict attention to $\Omega_0$.

Now let $\epsilon > 0$ be given. Choose $\ell > \epsilon^{-1}$. In view of (19) and (25), we can find for any $\omega \in \Omega_0$ a suitable positive integer $\bar{n}(\epsilon, \omega)$ such that, whenever $n \geq \bar{n}(\epsilon, \omega)$,

$$|\bar{\Lambda}^{(n)}(t, \gamma) - \bar{\Lambda}^{(n)}(u, \gamma)| \leq B^*(t - u) + \frac{\epsilon}{2} \quad \forall t, u, \quad (26)$$

and

$$\sup_{s \in [0, \tau], \gamma \in \mathcal{G}, \Lambda \in \mathcal{L}_1^{1/\ell}} |A(\gamma, \Lambda, s) - a(\gamma, \Lambda, s)| \leq \epsilon. \quad (27)$$

Next, let $\tilde{\Lambda}^{(n)}_0$ denote the function defined by linear interpolation through $(t^{(c)}_j, \gamma^{(c)}_k, \bar{\Lambda}^{(c)}_{jk})$, where $\bar{\Lambda}^{(c)}_{jk}$ is the element of $\{\Lambda^{(c)}_l\}$ that is closest to $\bar{\Lambda}^{(n)}_0(t^{(c)}_j, \gamma^{(c)}_k)$. It is clear that

$$|\tilde{\Lambda}^{(n)}_0(t^{(c)}_j, \gamma^{(c)}_k) - \bar{\Lambda}^{(n)}_0(t^{(c)}_j, \gamma^{(c)}_k)| \leq \epsilon \quad \forall j, k.$$  

Using (26) and the Lipschitz continuity of $\tilde{\Lambda}^{(n)}_0(t, \gamma)$ with respect to $\gamma$ (which follows from the corresponding property of $\hat{\Lambda}_0(t, \gamma)$), we thus obtain

$$\sup_{t, \gamma} |\bar{\Lambda}^{(n)}_0(t, \gamma) - \bar{\Lambda}^{(n)}_0(t, \gamma)| \leq B^{**} \epsilon$$

for a suitable fixed constant $B^{**}$ (depending on $B^*$ and $C^*$). Combining this with (27) and (25), we obtain

$$\sup_{s, \gamma} |A(\gamma, \bar{\Lambda}^{(n)}_0, s) - a(\gamma, \bar{\Lambda}^{(n)}_0, s)| \leq (2\kappa B^{**} + 1)\epsilon \quad \text{for all } n \geq \bar{n}(\epsilon, \omega).$$
Since $\epsilon$ was arbitrary, the desired conclusion (20) follows, and the proof is thus complete.

**Remark:** Note that $\Lambda_0(\cdot, \gamma^o) = \Lambda_0^o(\cdot)$ since $\Lambda_0^o$ trivially solves the equation $\Lambda = \Xi(t, \gamma^o, \Lambda)$.

**Claim B:** With probability one, $U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))$ converges to $u(\gamma, \Lambda_0(\cdot, \gamma)) = E[U(\gamma, \Lambda_0(\cdot, \gamma))]$ uniformly in $\gamma$ over $G$.

**Proof:** Since $U(\gamma, \Lambda_0(\cdot, \gamma))$ is the mean of iid terms, the functional strong law of numbers of Andersen & Gill (1982, Appendix III) implies that $U(\gamma, \Lambda_0(\cdot, \gamma))$ converges uniformly in $\gamma$ almost surely to $u(\gamma, \Lambda_0(\cdot, \gamma))$. It remains only to show that

$$\sup_{\gamma} |U(\gamma, \hat{\Lambda}_0(\cdot, \gamma)) - U(\gamma, \Lambda_0(\cdot, \gamma))| \rightarrow 0 \quad (28)$$

almost surely. Now it may be seen easily from the structure of $U(\gamma, \Lambda)$ that there exists some constant $C^o$ (independent of $\gamma$) such that

$$|U(\gamma, \Lambda_1) - U(\gamma, \Lambda_2)| \leq C^o ||\Lambda_1 - \Lambda_2||.$$

Given this result along with the result of Claim A, the result (28) follows immediately.

**Claim C:** There exists a unique consistent root to $U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \gamma)) = 0$.

**Proof:** We apply Foutz’s (1977) theorem on consistency of maximum likelihood type estimators. The following conditions must be verified:

**F1.** $\partial U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))/\partial \gamma$ exists and is continuous in an open neighborhood about $\gamma^o$.

**F2.** The convergence of $\partial U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))/\partial \gamma$ to its limit is uniform in open neighborhood of $\gamma^o$.

**F3.** $U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) \rightarrow 0$ as $n \rightarrow \infty$. 
**F4.** The matrix $-\left[ \partial U(\gamma, \Lambda_0(\cdot, \gamma))/\partial \gamma \right]_{\gamma=\gamma^0}$ is invertible with probability going to 1 as $n \to \infty$. (In Foutz’s paper, the matrix in question is symmetric, and so he stated the condition in terms of positive definiteness. But it is clear from his proof, which is based on the inverse function theorem, that the basic condition needed is invertibility.)

It is easily seen that Condition F1 holds. Given Assumptions 2, 4, and 5, Condition F2 follows from the previously-cited functional law of large numbers. As for Condition F3, in Claim B we showed that $U(\gamma, \Lambda_0(\cdot, \gamma))$ converges a.s. uniformly to $u(\gamma, \Lambda_0(\cdot, \gamma)) = E[U(\gamma, \Lambda_0(\cdot, \gamma))]$. We noted already that $\Lambda_0(\cdot, \gamma^0) = \Lambda_0(\cdot)$. Thus all we need is to show that $E[U(\gamma^0, \Lambda_0)] = 0$. Since $U$ is a score function derived from a classical iid likelihood, this result follows from classical likelihood theory. Condition F4 has been assumed in Assumption 11; we noted previously that, given the data, it can be checked numerically. With Conditions F1-F4 thus verified, it follows from Foutz’s theorem that $\hat{\gamma} \to \gamma^0$ as $n \to \infty$ with probability one.

### 7.4 Asymptotic Normality

To show that $\hat{\gamma}$ is asymptotically normally distributed, we write

$$0 = U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma}))$$

$$= U(\gamma^0, \Lambda_0^0) + [U(\gamma^0, \Lambda_0^0(\cdot, \gamma^0)) - U(\gamma^0, \Lambda_0^0)]$$

$$+ [U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \gamma)) - U(\gamma^0, \Lambda_0(\cdot, \gamma^0))]$$

In the following we consider each of the above terms of the right-hand side of the equation.

**Step I**

We can write $U(\gamma^0, \Lambda_0^0)$ as

$$U(\gamma^0, \Lambda_0^0) = \frac{1}{n} \sum_{i=1}^{n} \xi_i,$$
where $\xi_i$ is a $(p+1)$-vector with $r$-th element, $r = 1, \ldots, p$, given by
\[ \xi_{ir} = \sum_{j=1}^{m_i} \delta_{ij} Z_{ijr} - \frac{\sum_{j=1}^{m_i} H_{ij}(\tau) Z_{ijr}}{\int w^{N_i(\tau)} \exp\{-wH_i(\tau)\} f(w; \theta)dw} \]
and $(p+1)$-th element given by
\[ \xi_{i(p+1)} = \frac{\int w^{N_i(\tau)} \exp\{-wH_i(\tau)\} f'(w; \theta)dw}{\int w^{N_i(\tau)} \exp\{-wH_i(\tau)\} f(w; \theta)dw}. \]

Thus $U(\gamma^0, \Lambda_0^0)$ is the mean of the iid mean-zero random vectors $\xi_i$. It hence follows immediately from the classical central limit theorem that $n^{1/2} U(\gamma^0, \Lambda_0^0)$ is asymptotically mean-zero multivariate normal. To estimate the covariance matrix, let $\hat{\gamma}^*$ be the counterpart of $\xi_i$ with estimates of $\gamma$ and $\Lambda_0$ substituted for the true values. Then an empirical estimator of the covariance matrix is given by
\[ \hat{V}(\hat{\gamma}) = \frac{1}{n} \sum_{i=1}^{n} \xi_i^* \xi_i^{*T}. \]

This is a consistent estimator of the covariance matrix since $\hat{\Lambda}_0(t, \gamma)$ converges to $\Lambda_0(t, \gamma)$ a.s. uniformly in $t$ and $\gamma$ (Claim A), and $\hat{\gamma}$ is a consistent estimator of $\gamma^0$ (Claim C).

**Step II**

Let $\hat{U}_r = U_r(\gamma^0, \hat{\Lambda}_0), r = 1, \ldots, p$, and $\hat{U}_{p+1} = U_{p+1}(\gamma^0, \hat{\Lambda}_0)$ (in this segment of the proof, when we write $(\gamma^0, \Lambda_0)$ the intent is to signify $(\gamma^0, \hat{\Lambda}_0(\cdot, \gamma^0))$. First order Taylor expansion of $\hat{U}_r$ about $\Lambda_0^0, r = 1, \ldots, p+1$, gives
\[ n^{1/2} \{U_r(\gamma^0, \hat{\Lambda}_0) - U_r(\gamma^0, \Lambda_0^0)\} = n^{-1/2} \sum_{i=1}^{n} \sum_{j=1}^{m_i} Q_{ijr}(\gamma^0, \Lambda_0^0, T_{ij}) \{\hat{\Lambda}_0(T_{ij}, \gamma^0) - \Lambda_0^0(T_{ij})\} + o_p(1), \quad (29) \]
where
\[ Q_{ijr}(\gamma^0, \Lambda_0^0, T_{ij}) = - \left\{ \frac{\phi_{2i}(\gamma^0, \Lambda_0^0, \tau)}{\phi_{1i}(\gamma^0, \Lambda_0^0, \tau)} R_{ij}^* Z_{ijr} - \frac{\phi_{3i}(\gamma^0, \Lambda_0^0, \tau)}{\phi_{1i}(\gamma^0, \Lambda_0^0, \tau)} R_{ij}^* \sum_{j=1}^{m_i} H_{ij}(T_{ij}) Z_{ijr} \right\} \]
\[ + \frac{\phi_{2i}(\gamma^0, \Lambda_0^0, \tau)}{\phi_{1i}^2(\gamma^0, \Lambda_0^0, \tau)} R_{ij}^* \sum_{j=1}^{m_i} H_{ij}(T_{ij}) Z_{ijr} \]
for \( r = 1, \ldots, p \), and

\[
Q_{ij(p+1)}(\gamma^\circ, \Lambda^\circ, T_{ij}) = R_{ij}^* \left\{ \frac{\phi_2\left(\gamma^\circ, \Lambda^\circ, \tau\right)\phi_i^{(\theta)}(\gamma^\circ, \Lambda^\circ, \tau)}{\phi_1^2(\gamma^\circ, \Lambda^\circ, \tau)} - \frac{\phi_2^{(\theta)}(\gamma^\circ, \Lambda^\circ, \tau)}{\phi_1(\gamma^\circ, \Lambda^\circ, \tau)} \right\},
\]

where \( R_{ij}^* = \exp(\beta^T Z_{ij}) \) and

\[
\phi_{ki}^{(\theta)}(\gamma, \Lambda_0, t) = \int w^{N_i \{t\} + (k-1)} \exp\{-w H_i \{t\}\} f'(w) dw, \quad k = 1, 2.
\]

The validity of the approximation \(^{29}\) can be seen by an argument similar to that used in connection with \(^{31}\) below.

Based on the intensity process \(^{3}\), the process

\[
M_{ij}(t) = N_{ij}(t) - \int_0^t \lambda_0(u) \exp(\beta^T Z_{ij}) Y_{ij}(u) \psi_i(\gamma^\circ, \Lambda^\circ, u-) du
\]

is a mean zero martingale with respect to the filtration \( \mathcal{F}_t \). Also, by Lemma 3, we have that \( \sup_{s \in [0, \tau]} |\hat{\Lambda}_0(s, \gamma^\circ) - \hat{\Lambda}_0(s-, \gamma^\circ)| \) converges to zero. Thus, replacing \( s- \) by \( s \) we obtain the following approximation, uniformly over \( t \in [0, \tau] \):

\[
\hat{\Lambda}_0(t, \gamma^\circ) - \Lambda_0^\circ(t) \approx \frac{1}{n} \int_0^t \left\{ \mathcal{Y}(s, \Lambda^\circ) \right\}^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} dM_{ij}(s) + \frac{1}{n^2} \int_0^t \left[ \left\{ \mathcal{Y}(s, \hat{\Lambda}_0) \right\}^{-1} - \left\{ \mathcal{Y}(s, \Lambda^\circ) \right\}^{-1} \right] \sum_{i=1}^n \sum_{j=1}^{m_i} dN_{ij}(s), \tag{30}
\]

where

\[
\mathcal{Y}(s, \Lambda) = \frac{1}{n} \sum_{i=1}^n \sum_{j=1}^{m_i} \psi_i(\gamma^\circ, \Lambda, s) Y_{ij}(s) \exp(\beta^T Z_{ij}).
\]

Now let

\[
\mathcal{W}(s, r) = \left\{ \mathcal{Y}(s, \Lambda^\circ + r \Delta) \right\}^{-1}
\]

with \( \Delta = \hat{\Lambda}_0 - \Lambda_0^\circ \). Define \( \tilde{\mathcal{W}} \) and \( \tilde{\mathcal{W}} \) as the first and second derivative of \( \mathcal{W} \) with respect to \( r \), respectively. Then, by a first order Taylor expansion of \( \mathcal{W}(s, r) \) around \( r = 0 \) evaluated at \( r = 1 \) with Lagrange remainder (Abramowitz and Stegun, 1972, p. 880) we get (after
computing the necessary derivatives)

\[
\{\mathcal{Y}(s, \hat{\Lambda}_0)\}^{-1} - \{\mathcal{Y}(s, \Lambda_0^\circ)\}^{-1} = \hat{\mathcal{W}}(s, 0) + \frac{1}{2} \hat{\mathcal{W}}(s, \tilde{r}(s)) \]

\[
= -\frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \left[ R_{ij}(s) \eta_{1i}(0, s) \{\mathcal{Y}(s, \Lambda_0^\circ)\}^2 - \frac{1}{2} h_i(\tilde{r}(s), s) \right] \exp(\beta^T \mathbf{Z}_{ij}) \{\hat{\Lambda}_0(T_{ij} \wedge s) - \Lambda_0^\circ(T_{ij} \wedge s)\}, \tag{31}
\]

where \( R_{ij}(u) = \exp(\beta^T \mathbf{Z}_{ij})Y_{ij}(u), \) \( R_i(u) = \sum_{j=1}^{m_i} R_{ij}(u), \) \( \tilde{r}(s) \in [0, 1], \)

\[
\eta_{1i}(r, s) = \frac{\phi_{2i}(\gamma^0, \Lambda_0^\circ + r \Delta, s)}{\phi_{1i}(\gamma^0, \Lambda_0^\circ + r \Delta, s)} \left\{ \frac{\phi_{2i}(\gamma^0, \Lambda_0^\circ + r \Delta, s)}{\phi_{1i}(\gamma^0, \Lambda_0^\circ + r \Delta, s)} \right\}^2,
\]

and \( h_i(r, s) \) is as defined §7.5 below. We show there that \( h_i(r, s) \) is \( o(1) \) uniformly in \( r \) and \( s. \)

Let \( \eta_{1i}(s) = \eta_{1i}(0, s). \) Plugging (31) into (30) we get

\[
\hat{\Lambda}_0(t, \gamma^0) - \Lambda_0^\circ(t) \approx n^{-1} \int_0^t \{\mathcal{Y}(s, \Lambda_0^\circ)\}^{-1} \sum_{i=1}^{m_i} \sum_{j=1}^{m_i} dM_{ij}(s)
\]

\[
- n^{-2} \int_0^t \sum_{k=1}^{n} \sum_{l=1}^{n} \frac{I(T_{kl} > s) R_{kl}(s) \eta_{1k}(s)}{\{\mathcal{Y}(s, \Lambda_0^\circ)\}^2} \exp(\beta^T \mathbf{Z}_{kl}) \{\hat{\Lambda}_0(s) - \Lambda_0^\circ(s)\} \sum_{i=1}^{m_i} \sum_{j=1}^{m_i} dN_{ij}(s)
\]

\[
- n^{-2} \int_0^t \sum_{k=1}^{n} \sum_{l=1}^{n} \frac{I(T_{kl} \leq s) R_{kl}(s) \eta_{1k}(s)}{\{\mathcal{Y}(s, \Lambda_0^\circ)\}^2} \exp(\beta^T \mathbf{Z}_{kl}) \{\hat{\Lambda}_0(T_{kl}) - \Lambda_0^\circ(T_{kl})\} \sum_{i=1}^{m_i} \sum_{j=1}^{m_i} dN_{ij}(s)
\]

\[
+ n^{-2} \int_0^t \sum_{k=1}^{n} \sum_{l=1}^{n} \frac{1}{2} h_k(\tilde{r}(s), s) \exp(\beta^T \mathbf{Z}_{kl}) \{\hat{\Lambda}_0(T_{kl}) - \Lambda_0^\circ(T_{kl})\} \sum_{i=1}^{m_i} \sum_{j=1}^{m_i} dN_{ij}(s).
\]

The third term of the above equation can be written, by interchanging the order of integration, as

\[
n^{-2} \sum_{k=1}^{n} \sum_{l=1}^{n} \sum_{i=1}^{m_i} \int_0^t \frac{R_{kl}(s) \eta_{1k}(s)}{\{\mathcal{Y}(s, \Lambda_0^\circ)\}^2} \exp(\beta^T \mathbf{Z}_{kl}) \left[ \int_0^s \{\hat{\Lambda}_0(u) - \Lambda_0^\circ(u)\} d\tilde{N}_{kl}(u) \right] dN_{ij}(s)
\]

\[
= \int_0^t \{\hat{\Lambda}_0(s) - \Lambda_0^\circ(s)\} \sum_{i=1}^{m_i} \sum_{j=1}^{m_i} \Omega_{ij}(s, t) d\tilde{N}_{ij}(s),
\]

where \( \tilde{N}_{ij}(t) = I(T_{ij} \leq t) \) and

\[
\Omega_{ij}(s, t) = n^{-2} \int_s^t \{\mathcal{Y}(u, \Lambda_0^\circ)\}^{-2} R_{ij}(u) \eta_{1i}(u) \exp(\beta^T \mathbf{Z}_{ij}) \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} dN_{kl}(u).
\]

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Hence we get
\[ \hat{\Lambda}_0(t, \gamma^o) - \Lambda_0^o(t) \approx n^{-1} \int_0^t \{ \mathcal{Y}(s, \Lambda_0^o) \}^{-1} \sum_{i=1}^{n} \sum_{j=1}^{m_i} dM_{ij}(s) \]
\[- \int_0^t \{ \hat{\Lambda}_0(s, \gamma^o) - \Lambda_0^o(s) \} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \{ \delta_{ij} \mathcal{Y}(s) + \Omega_{ij}(s, t) + o(n^{-1}) \} d\tilde{N}_{ij}(s) \]
where
\[ \mathcal{Y}(s) = n^{-2} \{ \mathcal{Y}(s, \Lambda_0^o) \}^{-2} \sum_{k=1}^{n} \sum_{l=1}^{m_k} I(T_{kl} > s) R_{kl}(s) \eta_{lk}(s) \exp(\beta^T z_{kl}). \]
The $o(n^{-1})$ is uniform in $t$ (see §7.5) and will be dominated by $\Omega$ and $\mathcal{Y}$, which are of order $n^{-1}$. Hence the $o(n^{-1})$ term can be ignored.

Given the all the above, an argument similar to that of Yang & Prentice (1999) and Zucker (2005) yields following martingale representation
\[ \hat{\Lambda}_0(t, \gamma^o) - \Lambda_0^o(t) \approx \frac{1}{n\hat{p}(t)} \int_0^t \hat{p}(s-) \frac{\sum_{i=1}^{n} \sum_{j=1}^{m_i} dM_{ij}(s)}{\mathcal{Y}(s, \Lambda_0^o)}, \tag{32} \]
where
\[ \hat{p}(t) = \prod_{s \leq t} \left[ 1 + \sum_{i=1}^{n} \sum_{j=1}^{m_i} \{ \delta_{ij} \mathcal{Y}(s) + \Omega_{ij}(s, t) \} d\tilde{N}_{ij}(s) \right]. \]

Based on (29), we can write
\[ U_r(\gamma^o, \hat{\Lambda}_0) - U_r(\gamma^o, \Lambda_0^o) \approx n^{-1} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \int_0^\tau Q_{ijr}(\gamma^o, \Lambda_0^o, s) \{ \hat{\Lambda}_0(s, \gamma^o) - \Lambda_0^o(s) \} d\tilde{N}_{ij}(s). \]

Plugging the martingale representation (32) into the above equation and interchanging the order of integration gives
\[ U_r(\gamma^o, \hat{\Lambda}_0) - U_r(\gamma^o, \Lambda_0^o) \]
\[ \approx n^{-2} \sum_{i=1}^{n} \sum_{j=1}^{m_i} \int_0^\tau Q_{ijr}(\gamma^o, \Lambda_0^o, t) \int_0^t \hat{p}(s-) \frac{\sum_{k=1}^{n} \sum_{l=1}^{m_k} dM_{kl}(s)}{\mathcal{Y}(s, \Lambda_0^o)} d\tilde{N}_{ij}(t) \]
\[ = n^{-1} \int_0^\tau \pi_r(s, \gamma^o, \Lambda_0^o) \hat{p}(s-) \frac{\sum_{k=1}^{n} \sum_{l=1}^{m_k} dM_{kl}(s)}{\mathcal{Y}(s, \Lambda_0^o)}, \tag{33} \]
where
\[ \pi_r(s, \gamma, \Lambda_0) = n^{-1} \int_s^\tau \frac{\sum_{i=1}^{n} \sum_{j=1}^{m_i} Q_{ijr}(\gamma, \Lambda_0, t) d\tilde{N}_{ij}(t)}{\hat{p}(t)}. \]
Therefore, \( n^{1/2}[\mathbf{U}(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - \mathbf{U}(\gamma^o, \Lambda_0^o(\cdot, \gamma^o))] \) is asymptotically mean zero multivariate normal with covariance matrix that can be consistently estimated by

\[
G_{rl}(\hat{\gamma}) = n^{-1} \int_0^\tau \pi_r(s, \hat{\gamma}, \hat{\Lambda}_0) \pi_l(s, \hat{\gamma}, \hat{\Lambda}_0) \{\hat{p}(s-)\}^2 \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} dN_{ij}(s)}{\mathcal{Y}(s, \Lambda_0)} \}
\]

for \( r, l = 1, \ldots, p + 1 \).

**Step III**

We now examine the sum of \( \mathbf{U}(\gamma^o, \Lambda_0^o) \) and \( \mathbf{U}(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - \mathbf{U}(\gamma^o, \Lambda_0^o) \). From (33),

\[
U_r(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U_r(\gamma^o, \Lambda_0^o) \approx n^{-1} \int_0^\tau \alpha_r(s) \sum_{k=1}^{m_k} \sum_{l=1}^{d} dM_{kl}(s) = \frac{1}{n} \sum_{k=1}^{m_k} \mu_{kr},
\]

where \( \alpha_r(s) \) is the limiting value of \( \pi_r(s, \gamma^o, \Lambda_0^o) \hat{p}(s-) / \mathcal{Y}(s, \Lambda_0^o) \) and \( \mu_{kr} \) is defined as

\[
\mu_{kr} = \int_0^\tau \alpha_r(s) \sum_{l=1}^{d} dM_{kl}(s).
\]

Arguments in Yang and Prentice (1999, Appendix A) can be used to show that \( \hat{p}(s-) \) has a limit. Also, clearly \( \mathbb{E}[\mu_{kr}] = 0 \).

We thus have

\[
U_r(\gamma^o, \Lambda_0^o) + [U_r(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U_r(\gamma^o, \Lambda_0^o)] \approx \frac{1}{n} \sum_{i=1}^n (\xi_{ir} + \mu_{ir}),
\]

which is a mean of \( n \) iid random variables. Hence \( n^{1/2}\{U_r(\gamma^o, \Lambda_0^o) + [U_r(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o)) - U_r(\gamma^o, \Lambda_0^o)]\} \) is asymptotically normally distributed. The covariance matrix may be estimated by \( \hat{\mathbf{V}}(\hat{\gamma}) + \hat{\mathbf{G}}(\hat{\gamma}) + \hat{\mathbf{C}}(\hat{\gamma}) \), where

\[
\hat{\mathbf{C}}_{rl}(\hat{\gamma}) = n^{-1} \sum_{i=1}^n (\xi_{ir}^* \mu_{rl}^* + \xi_{il}^* \mu_{lr}^*), \quad r, l = 1, \ldots, p + 1,
\]

with

\[
\mu_{ir}^* = \int_0^\tau \frac{\pi_r(s, \gamma^o, \hat{\Lambda}_0) \hat{p}(s-) \sum_{j=1}^{m_i} dM_{ij}(s)}{\mathcal{Y}(s, \Lambda_0)} \]
and

\[
\dot{M}_{ij}(t) = N_{ij}(t) - \int_0^t \exp(\beta^T Z_{ij}) Y_{ij}(u) \psi_t(\gamma, \dot{\Lambda}_0, u-) d\dot{\Lambda}_0(u).
\]

**Step IV**

First order Taylor expansion of \(U(\gamma, \dot{\Lambda}_0, \cdot, \gamma))\) about \(\gamma^o = (\beta^o, \theta^o)^T\) gives

\[
U(\gamma, \dot{\Lambda}_0, \cdot, \gamma)) = U(\gamma^o, \dot{\Lambda}_0, \cdot, \gamma^o)) + D(\gamma^o)(\gamma - \gamma^o)^T + o_p(1),
\]

where

\[
D_{ls}(\gamma) = \partial U_l(\gamma, \dot{\Lambda}_0, \cdot, \gamma))/\partial \gamma_s
\]

for \(l, s = 1, \ldots, p + 1\), with \(\gamma_{p+1} = \theta\).

For \(l, s = 1, \ldots, p\) we have

\[
D_{ls}(\gamma) = -n^{-1} \sum_{i=1}^n \left\{ \phi_{2i}(\gamma, \dot{\Lambda}_0, \tau) \sum_{j=1}^{m_i} \frac{\partial H_{ij}(T_{ij})}{\partial \beta_s} \right. \\
- \left[ \phi_{3i}(\gamma, \dot{\Lambda}_0, \tau) \frac{\partial^2 H_{ij}(\gamma, \dot{\Lambda}_0, \tau)}{\partial \beta_s} \right] \right. \\
- \left. \left. \sum_{j=1}^{m_i} \frac{\partial H_{ij}(T_{ij})}{\partial \beta_s} \right) \gamma_{ijl} \right\}, \quad (34)
\]

\[
\frac{\partial \dot{H}_{ij}(\tau_k)}{\partial \beta_s} = \frac{\partial \dot{\Lambda}_0(T_{ij} \wedge \tau_k)}{\partial \beta_s} \exp(\beta^T Z_{ij}) + \dot{\Lambda}_0(T_{ij} \wedge \tau_k) \exp(\beta^T Z_{ij}) Z_{ij}
\]

and

\[
\frac{\partial \Delta \dot{\Lambda}_0(\tau_k)}{\partial \beta_s} = -d_k \left\{ \sum_{i=1}^n \phi_{2i}(\gamma, \dot{\Lambda}_0, \tau_{k-1}) R_i(\tau_k) \right\}^{-2} \\
\sum_{i=1}^n \left[ \phi_{3i}(\gamma, \dot{\Lambda}_0, \tau_{k-1}) \frac{\partial H_{ij}(\tau_{k-1})}{\partial \beta_s} \right] R_i(\tau_k) \\
+ \phi_{2i}(\gamma, \dot{\Lambda}_0, \tau_{k-1}) \sum_{j=1}^{m_i} R_{ij}(\tau_k) Z_{ij}.
\]

For \(l = 1, \ldots, p\) we have

\[
D_{l(p+1)}(\gamma) = -n^{-1} \sum_{i=1}^n \left\{ \phi_{2i}(\gamma, \dot{\Lambda}_0, \tau) \sum_{j=1}^{m_i} \frac{\partial H_{ij}(T_{ij})}{\partial \theta} \right\}
\]
Finally, and where

\[ \begin{bmatrix} \phi_{2i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau) - \phi_{2i}(\gamma, \hat{\Lambda}_0, \tau) \phi_{1i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau) \\ \phi_{1i}(\gamma, \Lambda_0, \tau) \phi_{1i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau) \end{bmatrix} + \left\{ \frac{\phi_{2i}^2(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}(\gamma, \Lambda_0, \tau)} - \frac{\phi_{3i}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}(\gamma, \Lambda_0, \tau)} \right\} \frac{\partial \hat{H}_i(\tau)}{\partial \theta} \right\} \]

(35)

and

\[ D_{(p+1)l}(\gamma) = n^{-1} \sum_{i=1}^{n} \left\{ \frac{\phi_{1i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau_0) \phi_{2i}(\gamma, \hat{\Lambda}_0, \tau_0)}{\phi_{1i}(\gamma, \Lambda_0, \tau_0)} - \frac{\phi_{2i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau_0)}{\phi_{1i}(\gamma, \Lambda_0, \tau_0)} \right\} \frac{\partial \hat{H}_i(\tau)}{\partial \beta_l} \] (36)

Finally,

\[ D_{(p+1)(p+1)}(\gamma) = n^{-1} \sum_{i=1}^{n} \left\{ \phi_{1i}^{(\theta,\theta)}(\gamma, \hat{\Lambda}_0, \tau_0) - \left[ \phi_{1i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau_0) \right]^2 \phi_{1i}^{(\theta)}(\gamma, \Lambda_0, \tau_0) \right\} \frac{\partial \hat{H}_i(\tau)}{\partial \theta} \]

(37)

where

\[ \phi_{1i}^{(\theta,\theta)}(\gamma, \hat{\Lambda}_0, \tau_0) = \int w^{N_i(\tau)} \exp\{-w\hat{H}_i(\tau)\} \frac{d^2f(w)}{d\theta^2} dw, \]

\[ \frac{\partial \hat{H}_{ij}(\tau_k)}{\partial \theta} = \frac{\partial \hat{\Lambda}_0(T_{ij} \wedge \tau_k)}{\partial \theta} \exp(\beta^T Z_{ij}), \]

and

\[ \frac{\partial \Delta \hat{\Lambda}_0(\tau_k)}{\partial \theta} = -d_k \left\{ \sum_{i=1}^{n} \phi_{2i}(\gamma, \hat{\Lambda}_0, \tau_{k-1}) \right\}^{-2} \frac{\sum_{i=1}^{n} R_i(\tau_k)}{\phi_{1i}(\gamma, \Lambda_0, \tau_{k-1})} \left[ \frac{\phi_{2i}^{(\theta)}(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}^{(\theta)}(\gamma, \Lambda_0, \tau_{k-1})} - \frac{\phi_{2i}(\gamma, \hat{\Lambda}_0, \tau_{k-1}) \phi_{1i}^{(\theta)}(\gamma, \Lambda_0, \tau_{k-1})}{\phi_{1i}^{(\theta)}(\gamma, \Lambda_0, \tau_{k-1})} \right] + \frac{\partial \hat{H}_i(\tau_{k-1})}{\partial \theta} \left\{ \frac{\phi_{2i}^2(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}^2(\gamma, \Lambda_0, \tau_{k-1})} - \frac{\phi_{3i}(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}(\gamma, \Lambda_0, \tau_{k-1})} \right\}. \]

Step V

Combining the results above we get that \( n^{1/2}(\hat{\gamma} - \gamma_0) \) is asymptotically zero-mean normally distributed with a covariance matrix that can be consistently estimated by

\[ \hat{D}^{-1}(\hat{\gamma})(\hat{V}(\hat{\gamma}) + \hat{G}(\hat{\gamma}) + \hat{C}(\hat{\gamma})) \hat{D}^{-1}(\hat{\gamma})^T. \]
7.5 Definition and behavior of \( h_i(r, s) \)

The quantity \( h_i(r, s) \) appearing in (31) is given by

\[
\begin{align*}
    h_i(r, s) &= \frac{2R_i(s)\eta_{1i}(r, s)}{\{\mathcal{Y}(s, \Lambda^0_0 + r\Delta)\}^3} \sum_{i=1}^n R_i(s)\eta_{1i}(r, s) \sum_{j=1}^{m_i} \exp(\beta^T \mathbf{Z}_{ij}) \Delta(T_{ij} \wedge s) \\
        &- \frac{R_i(s)\eta_{2i}(r, s)}{\{\mathcal{Y}(s, \Lambda^0_0 + r\Delta)\}^2} \sum_{j=1}^{m_i} \exp(\beta^T \mathbf{Z}_{ij}) \Delta(T_{ij} \wedge s)
\end{align*}
\]

where \( \Delta(T_{ij} \wedge s) = \hat{\Lambda}_0(T_{ij} \wedge s) - \Lambda^0_0(T_{ij} \wedge s) \) and

\[
\eta_{2i}(r, s) = 2 \left\{ \frac{\phi_{2i}(\gamma^0, \Lambda^0_0 + r\Delta, s)}{\phi_{1i}(\gamma^0, \Lambda^0_0 + r\Delta, s)} \right\}^3 + \frac{\phi_{4i}(\gamma^0, \Lambda^0_0 + r\Delta, s)}{\phi_{1i}(\gamma^0, \Lambda^0_0 + r\Delta, s)} - 3 \frac{\phi_{2i}(\gamma^0, \Lambda^0_0 + r\Delta, s)\phi_{3i}(\gamma^0, \Lambda^0_0 + r\Delta, s)}{\phi_{1i}(\gamma^0, \Lambda^0_0 + r\Delta, s)} \}^2.
\]

For all \( i = 1, \ldots, n \) and \( s \in [0, \tau] \), we have \( 0 \leq R_i(s) \leq m\nu \), where \( \nu \) is as in (8).

Moreover, for \( k = 1, \ldots, 4 \), we have

\[
E[W_i^{r_{\min} + (k-1)} \exp \{-W_i \nu e^{\beta^T \mathbf{Z} \Lambda^0_0(\tau)}\}] \leq \phi_{ki}(\gamma^0, \Lambda^0_0, s) \leq E[W_i^{r_{\max} + (k-1)}]
\]

where \( r_{\max} = \arg\max_{1 \leq r \leq m} E(W_i^r) \), \( r_{\min} = \arg\min_{1 \leq r \leq m} E(W_i^r) \). Hence, \( \eta_{1i} \) and \( \eta_{2i} \) are bounded. In addition, the proof of Lemma 2 show that \( \mathcal{Y}(s, \Lambda^0 + r\Delta) \) is uniformly bounded away from zero for \( n \) sufficiently large. Finally, in the consistency proof we obtained \( \|\Delta\| = o(1) \). Therefore \( h_i(r, s) \) is \( o(1) \) uniformly in \( r \) and \( s \).

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Table 1: Simulation results for the gamma frailty model with single normal covariate; \( n = 300 \) and family size equals 2. \( Z \sim N(0, 1); \beta^o = \log(2) \) or \( \log(3) \); \( \theta^o = 2 \)

| \( \beta \) | \( \beta = \ln(2); 35\% \) censoring | \( \beta = \ln(2); 85\% \) censoring | \( \beta = \ln(3); 30\% \) censoring | \( \beta = \ln(3); 80\% \) censoring |
|---|---|---|---|---|
| \( \beta \) | 0.692 | 0.689 | 1.978 | 1.969 |
| Empirical mean | 0.248 | 0.253 | 0.268 | 0.308 |
| Empirical SD | 0.242 | - | 0.242 | - |
| Mean estimated SD | 95.6 | - | 96.3 | - |
| 95% Wald-type CI | 0.952 | 0.989 | 0.952 | 0.989 |
| Correlation | | | | |
| \( \theta \) | 1.102 | 1.078 | 1.985 | 1.961 |
| Empirical mean | 0.255 | 0.266 | 0.265 | 0.259 |
| Empirical SD | 0.231 | - | 0.279 | - |
| Mean estimated SD | 96.9 | - | 96.1 | - |
| 95% Wald-type CI | 0.951 | 0.982 | 0.957 | 0.993 |
| Correlation | | | | |