Pseudo full likelihood estimation for prospective survival analysis with a general semiparametric shared frailty model:

asymptotic theory

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July 30, 2021

Running Head: Asymptotics of general frailty models

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Summary

In this work we present a simple estimation procedure for a general frailty model for analysis of prospective correlated failure times. Earlier work showed this method to perform well in a simulation study. Here we provide rigorous large-sample theory for the proposed estimators of both the regression coefficient vector and the dependence parameter, including consistent variance estimators.

*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. In this setting, 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. Frailty models express within cluster dependence through a shared unobservable 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 for 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.

We (Gorfine et al. 2006) developed a new method that can handle any parametric frailty distribution with finite moments. Nonconjugate frailty distributions can be handled by a simple univariate numerical integration over the frailty distribution. 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 method was found to perform well in a simulation study and the results are very similar to those of the EM-based method. Indeed, on a dataset-by-dataset basis, the correlation between our estimator and the EM estimator was found to be 95% for the covariate regression parameter and 98-99% for the within-cluster dependence parameter.

The purpose of the current paper is to present the theoretical justification for the method in detail. Section 2 presents the estimation procedure. Section 3 presents the consistency and asymptotic normality results, along with the covariance estimator for the parameter estimates. Section 4 presents the technical conditions required for our results and the proofs.
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 members. 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 \((\beta, \Lambda_0)\) (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

\[
L = \prod_{i=1}^n \int \Pi_{j=1}^{m_i} \{\lambda_{ij}(T_{ij})\}^{\delta_{ij}} S_{ij}(T_{ij}) f(w) dw = \prod_{i=1}^n \Pi_{j=1}^{m_i} \{\lambda_0(T_{ij}) \exp(\beta^T Z_{ij})\}^{\delta_{ij}} \Pi_{i=1}^n \int w^{N_i(.)} \exp\{-wH_i(.)\} f(w) dw,
\]

where \( N_{ij}(t) = \delta_{ij} I(T_{ij} \leq t), \ N_i(t) = \sum_{j=1}^{m_i} N_{ij}(t), \ H_{ij}(t) = \Lambda_0(T_{ij} \wedge t) \exp(\beta^T Z_{ij}), \ a \wedge b = \min\{a, b\}, \ \Lambda_0(.) \) 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

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

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

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

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

\[
U_{p+1} = \frac{1}{n} \sum_{i=1}^{n} \left[ \int w^{N_i(\tau)} \exp\{-wH_i(\tau)\} f'(w)dw \right] / \left( \int w^{N_i(\tau)} \exp\{-wH_i(\tau)\} f(w)dw \right)
\]

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

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

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 (1) 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 (3), 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

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

(4)

where \( d_k \) is the number of failures at time \( \tau_k \). Note that given the intensity model (3), 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, for estimating the cumulative hazard.

### 3 Asymptotic Properties

Let \( \gamma^o = (\beta^o^T, \theta^o)^T \) with \( \beta^o, \theta^o \) and \( \Lambda_0^o(t) \) denoting the respective true values of \( \beta, \theta \) and \( \Lambda_0(t) \), and let \( \hat{\gamma} = (\hat{\beta}^T, \hat{\theta})^T \). We assume the technical conditions listed in Section 4.1.

In Section 4.3, we establish the following results, using arguments patterned after Zucker (2005, Appendix A.3).

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

In Section 4.4, we show that \( n^{1/2}(\hat{\gamma} - \gamma^o) \) is asymptotically normally distributed. We accomplish this by analyzing in turn each of the terms in the following decomposition:

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

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

\[
+ [U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \hat{\gamma})) - U(\gamma^o, \hat{\Lambda}_0(\cdot, \gamma^o))].
\]
We show further that the covariance matrix of \( \hat{\gamma} \) can be consistently estimated by the sandwich estimator
\[
D^{-1}(\hat{\gamma})\left\{ \hat{V}(\hat{\gamma}) + \hat{G}(\hat{\gamma}) + \hat{C}(\hat{\gamma}) \right\}D^{-1}(\hat{\gamma})^T.
\]
(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 \( U(\gamma^o, \Lambda_0^o) \), \( G \) 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 Section 4.4.

4 Technical Conditions and Proofs

This section presents the technical conditions we assume for the asymptotic results and the proofs of these results.

4.1 Technical Conditions

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

1. The random vectors \( (T_{i1}^0, \ldots, T_{im_i}^0, C_{i1}, \ldots, C_{im_i}, Z_{i1}, \ldots, Z_{im_i}, W_i), i = 1, \ldots, n, \) 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 $G$ of $\mathbb{R}^{p+1}$ containing an open neighborhood of $\gamma^\circ$.

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 $\lambda^\circ_0(t)$ 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 $[(\partial/\partial \gamma)U(\gamma, \tilde{\Lambda}_0(\cdot, \gamma))]|_{\gamma = \gamma^\circ}$ is invertible with probability going to 1 as $n \to \infty$.

### 4.2 Technical Preliminaries

Since $\beta$ and $Z_{ij}$ are bounded, there exists a constant $\nu > 0$ such that
\[
\nu^{-1} \leq \exp(\beta^T Z_{ij}) \leq \nu. \tag{6}
\]

Now recall that
\[
\psi_i(\gamma, \Lambda, t) = \frac{\int w^{N_i(t) + 1} e^{-H_i(t)w} f(w)dw}{\int w^{N_i(t)} e^{-H_i(t)w} f(w)dw},
\]
with $H_i(t) = H_i(t, \gamma, \Lambda) = \sum_{j=1}^m \Lambda(T_{ij} \wedge t) \exp(\beta^T Z_{ij})$ (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 $h \geq 0$)

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

Also define $\psi_{\min}^*(h) = \min_{0 \leq r \leq m} \psi^*(r, h)$ and $\psi_{\max}^*(h) = \max_{0 \leq r \leq m} \psi^*(r, h)$. In the expression for $\psi^*(r, h)$, the numerator and denominator are bounded above since $W$ is assumed to have finite $(m + 2)$-th moment. In addition, since $W$ is nondegenerate, the numerator and denominator are strictly positive. Thus $\psi_{\max}^*(h)$ is finite and $\psi_{\min}^*(h)$ is strictly positive.

**Lemma 1:** The function $\psi^*(r, h)$ is decreasing in $h$. Hence for all $\gamma \in G$ and all $t$,

- $\psi_i(\gamma, \Lambda, t) \leq \psi_{\max}^*(0)$, (7)
- $\psi_i(\gamma, \Lambda, t) \geq \psi_{\min}^*(m\nu\Lambda(t))$. (8)

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

$$
\psi_{\min}^*(h) \geq Bh^{-1}. 
$$

**Proof:** We have

$$
\frac{\partial}{\partial h} \psi^*(r, h) = - \left[ \frac{\int w^{r+2} e^{-hw} f(w)dw}{\int w^r e^{-hw} f(w)dw} - \left( \frac{\int w^{r+1} e^{-hw} f(w)dw}{\int w^r e^{-hw} f(w)dw} \right)^2 \right].
$$

This is negative for all $h$, and so $\psi^*(r, h)$ is decreasing in $h$. Now $\psi_i(\gamma, \Lambda, t) = \psi^*(N_i(t), H_i(t))$. Since $0 \leq H_i(t) \leq m\nu\Lambda(t)$, (7) and (8) follow. As for (9), from a change of variable and Assumption 7,

$$
\lim_{h \to \infty} h\psi^*(r, h) = \frac{\int_0^\infty v^{r+b}e^{-v}dv}{\int_0^\infty v^{r+b-1}e^{-v}dv} = r + b.
$$

Now just take $\bar{h}$ large enough so that this limit is obtained up to some factor, e.g. 1.01.

**Lemma 2:** Define $\bar{\Lambda} = 1.03e^{m\sigma}\bar{h}/(m\nu)$, with $\sigma = 1.01m\nu^2/(B\gamma^*)$, with $\bar{h}$ and $B$ as above.

Then, with probability one, there exists $n'$ such that, for all $t \in [0, \tau]$ and $\gamma \in G$,

$$
\hat{\Lambda}_0(t, \gamma) \leq \bar{\Lambda} \quad \text{for} \quad n \geq n',
$$

(11)
Thus, $\hat{\Lambda}_0(t, \gamma)$ is naturally bounded, with no 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

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

where we now take $d_k = 1$ since the survival time distribution is assumed continuous.

Using Lemma 1 and (6), we have

$$\Delta \hat{\Lambda}_0(\tau_k) \leq n^{-1} \nu \psi_{min}^*(m \nu \hat{\Lambda}(\tau_{k-1}))^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} Y_{ij}(\tau) \right]^{-1}.$$

By the strong law of large numbers, there exists with probability one some $n^*$ such that

$$\frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{m_i} Y_{ij}(\tau) \geq 0.999 y^* \quad \text{for } n \geq n^*. \quad (12)$$

We thus have, for $n \geq n^*$,

$$\Delta \hat{\Lambda}_0(\tau_k) \leq n^{-1} \left( \frac{1.01 \nu y^*}{y^*} \right) \psi_{min}^*(m \nu \hat{\Lambda}(\tau_{k-1}))^{-1}. \quad (13)$$

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

$$\hat{\Lambda}_0(\tau_{k'+\ell}) \leq \left( 1 + \frac{\sigma}{n} \right) \hat{\Lambda}_0(\tau_{k'}) \leq \left( 1 + \frac{\sigma}{n} \right)^{mn} \hat{\Lambda}_0(\tau_{k'}) \leq 1.01^{\ell} m \sigma \bar{h} \hat{\Lambda}_0(\tau_{k'})$$

for $n$ large enough. But, using (13) and the fact that $\hat{\Lambda}_0(\tau_{k'-1}) \leq \bar{h}/(m \nu)$, we have

$$\hat{\Lambda}_0(\tau_{k'}) \leq \frac{\bar{h}}{m \nu} + n^{-1} \left( \frac{1.01 \nu y^*}{y^*} \right) \psi_{min}^*(\bar{h})^{-1},$$
which is less than $1.01\bar{h}/(mv)$ for $n$ large enough. The desired conclusion follows.

**Lemma 3:** We have $\sup_{s \in [0,\tau]} |\hat{\Lambda}_0(s,\gamma^0) - \hat{\Lambda}_0(s-,\gamma^0)| \to 0$ as $n \to \infty$, as an immediate consequence of Lemma 2 and (13).

### 4.3 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:** Whenever a functional norm is written below, the relevant uniform norm is intended. We define $A_{max} = \max(\bar{A},\lambda_{max} \tau)$ and $\psi^*(r,h) = \psi^*(r,h \land h_{max})$, where $h_{max} = mvA_{max}$. It is easy to see from (10) that $\psi^*(r,h)$ is Lipschitz continuous in $h$ (uniformly in $r$). Recall that $\psi_i(\gamma,\Lambda,t) = \psi^*(N_i(t),H_i(t,\gamma,\Lambda))$. Lemma 2 implies that $H_i(t,\gamma,\hat{\Lambda}_0(\cdot,\gamma)) \leq h_{max}$ for all $t \in [0,\tau]$ and $\gamma \in G$. Hence $\psi_i(\gamma,\hat{\Lambda}_0(\cdot,\gamma),t) = \psi^*(N_i(t),H_i(t,\gamma,\hat{\Lambda}_0(\cdot,\gamma)))$.

Now define, for a general function $\Lambda$,

$$\Xi_n(t,\gamma,\Lambda) = \int_0^t \frac{n^{-1}\sum_{i=1}^{m_i} dN_{ij}(s)}{n^{-1}\sum_{i=1}^{m_i} \sum_{j=1}^{m_{ij}} \psi^*(N_i(s-),H_i(s-,\gamma,\Lambda))Y_{ij}(s) \exp(\beta^TZ_{ij})}$$

and

$$\Xi(t,\gamma,\Lambda) = \int_0^t \frac{E[\sum_{i=1}^{m_i} \psi^*(N_i(s-),H_i(s-,\gamma^0,\Lambda_0^0))Y_{ij}(s) \exp(\beta^TZ_{ij})]}{E[\sum_{j=1}^{m_{ij}} \psi^*(N_i(s-),H_i(s-,\gamma,\Lambda))Y_{ij}(s-) \exp(\beta^TZ_{ij})]} \lambda_0^0(s)ds.$$

By definition, $\hat{\Lambda}_0(t,\gamma)$ satisfies the equation

$$\hat{\Lambda}_0(t,\gamma) = \Xi_n(t,\gamma,\hat{\Lambda}_0(\cdot,\gamma)). \quad (14)$$
Next, define
\[ q_\gamma(s, \Lambda) = \frac{E[\sum_{j=1}^{m_i} \psi^*(N_i(s-), H_i(s-, \gamma^\circ, \Lambda_0^\circ))Y_{ij}(s) \exp(\beta^{T}Z_{ij})] \lambda_0^\circ(s)}{E[\sum_{j=1}^{m_i} \psi^*(N_i(s-), H_i(s-, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^{T}Z_{ij})]} \]

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 a Lipschitz-like condition of the form \( |q_\gamma(s, \Lambda_1) - q_\gamma(s, \Lambda_2)| \leq K \sup_{0 \leq u \leq s} |\Lambda_1(u) - \Lambda_2(u)| \). Hence, by mimicking the argument of Hartman (1973, Theorem 1.1), we find that the equation \( \Lambda(t) = \Xi(t, \gamma, \Lambda) \) has a unique solution, which we denote by \( \Lambda_0(t, \gamma) \). The claim then is that \( \Lambda_0(t, \gamma) \) converges almost surely (uniformly in \( t \) and \( \gamma \)) to \( \Lambda_0(t, \gamma) \). Though it may be possible to prove this claim directly, we shall use a convenient indirect argument.

Define \( \tilde{\Lambda}_0^{(n)}(t, \gamma) \) to be a modified version of \( \Lambda_0(t, \gamma) \) defined by linear interpolation between the jumps. Lemma 3 implies that, with probability one,
\[ \sup_{t, \gamma} |\tilde{\Lambda}_0^{(n)}(t, \gamma) - \Lambda_0(t, \gamma)| \to 0, \]
and thus
\[ \sup_{t, \gamma} |\Xi_n(t, \gamma, \tilde{\Lambda}_0(t, \gamma)) - \Xi_n(t, \gamma, \Lambda_0(t, \gamma))| \to 0. \]

Lemma 2 shows that the family \( \mathcal{L} = \{\tilde{\Lambda}_0^{(n)}(t, \gamma), n \geq n'\} \) is uniformly bounded. We can show further that \( \mathcal{L} \) is equicontinuous. This is done 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 \( \bar{N}(t) \to E[N_i(t)] \) as \( n \to \infty \) uniformly in \( t \) with probability one, with
\[
E[N_i(t)] = \int_0^t E \left[ \sum_{j=1}^{m_i} \psi^*(N_i(s-), H_i(s-, \gamma^\circ, \Lambda_0^\circ))Y_{ij}(s) \exp(\beta^{T}Z_{ij}) \right] \lambda_0^\circ(s)ds.
\]

In view of this and \( \mathcal{L} \), there exists a probability-one set of realizations \( \Omega^* \) 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 \( B^\circ = 1.01\nu/[\psi_{\min}^*(h_{\max})y^*] \). In consequence, for all \( t \) and
$u$ with $u < t$, we find that

$$
\hat{\Lambda}_0(t, \gamma) - \hat{\Lambda}_0(u, \gamma) = \int_u^t \frac{n^{-1} \sum_i^n \sum_j^{m_i} dN_{ij}(s)}{n^{-1} \sum_i^n \sum_j^{m_i} \psi^{**}(N_i(s-), H_i(s-, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^TZ_{ij})}
$$

satisfies

$$
\hat{\Lambda}_0(t, \gamma) - \hat{\Lambda}_0(u, \gamma) \leq B^*(t-u) + \frac{\epsilon}{2} \quad \text{for all } n \geq n''(\epsilon).
$$

Moreover, it is easy to see that $\hat{\Lambda}_0(t, \gamma)$ is Lipschitz continuous in $\gamma$ with Lipschitz constant $C^*$, 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 $\hat{\Lambda}_0(t, \gamma)$ with respect to $\gamma$. As for the former, for $n \geq n''(\epsilon)$ this can be accomplished using (17), 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

$$
A(\gamma, \Lambda, s) = \frac{1}{n} \sum_i^n \sum_j^{m_i} \psi^{**}(N_i(s-), H_i(s-, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^TZ_{ij}),
$$

$$
a(\gamma, \Lambda, s) = \mathbb{E} \left[ \sum_i^{m_i} \psi^{**}(N_i(s-), H_i(s-, \gamma, \Lambda))Y_{ij}(s) \exp(\beta^TZ_{ij}) \right].
$$

For any fixed continuous $\Lambda$, the functional strong law of large numbers of Andersen & Gill (1982, Appendix III) implies that

$$
\sup_{s, \gamma} |A(\gamma, \Lambda, s) - a(\gamma, \Lambda, s)| \to 0 \quad \text{a.s.}
$$

(18)

Here we need the following more complex result:

$$
\sup_{s, \gamma} |A(\gamma, \tilde{\Lambda}^{(n)}, s) - a(\gamma, \tilde{\Lambda}^{(n)}, s)| \to 0 \quad \text{a.s.}
$$

(19)
The proof of (19) is lengthy; we give the details in Section 4.5 below. In outline form, the proof involves two steps: (1) showing that, for any given $\epsilon > 0$, we can define an appropriate finite class $L^*_\epsilon$ of functions $\Lambda$ such that $\tilde{\Lambda}^{(n)}(\cdot)$ can be suitably approximated by some member of the class; (2) applying the result (18), which will hold uniformly over the finite class.

Given (19) and the a.s. uniform convergence of $\bar{N}(t)$ to $E[N_i(t)]$, we can infer that

$$\sup_{t,\gamma} \left| \Xi_n(t, \gamma, \tilde{\Lambda}^{(n)}_0(t, \gamma)) - \Xi(t, \gamma, \tilde{\Lambda}^{(n)}_0(t, \gamma)) \right| \to 0 \quad \text{a.s.} \quad (20)$$

The result (20) is easily obtained by adapting the argument of Aalen (1976, Lemma 6.1), using the equicontinuity of $L$. It is here that we use 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 (14), (15), (16), and (20) it follows that any limit point of $\{\tilde{\Lambda}^{(n)}_0(t, \gamma)\}$ 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 $\{\tilde{\Lambda}^{(n)}_0(t, \gamma)\}$. Thus $\{\tilde{\Lambda}^{(n)}_0(t, \gamma)\}$ is a sequence in a compact set with unique limit point $\Lambda_0(t, \gamma)$. Hence $\tilde{\Lambda}^{(n)}_0(t, \gamma)$ converges a.s. uniformly in $t$ and $\gamma$ to $\Lambda_0(t, \gamma)$. In view of (15), the same holds of $\hat{\Lambda}_0(t, \gamma)$, which is the desired result. Note that $\Lambda_0(\cdot, \gamma^o) = \Lambda^*_0(\cdot)$ since $\Lambda^*_0$ trivially solves the equation $\Lambda = \Xi(t, \gamma^o, \Lambda)$.

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

**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

$$\sup_{\gamma} \| U(\gamma, \hat{\Lambda}_0(\cdot, \gamma)) - U(\gamma, \Lambda_0(\cdot, \gamma)) \| \to 0 \quad (21)$$
almost surely. The structure of $U(\gamma, \Lambda)$ reveals that there exists some constant $C^\circ$ (independent of $\gamma$) such that $\|U(\gamma, \Lambda_1) - U(\gamma, \Lambda_2)\| \leq C^\circ \|\Lambda_1 - \Lambda_2\|$. From this along with Claim A, (21) follows.

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

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

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

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

**F3.** $U(\gamma^\circ, \hat{\Lambda}_0(\cdot, \gamma^\circ)) \rightarrow 0$ as $n \rightarrow \infty$.

**F4.** The matrix $-\left[\partial U(\gamma, \hat{\Lambda}_0(\cdot, \gamma))/\partial \gamma\right]_{\gamma=\gamma^\circ}$ is invertible with probability going to 1 as $n \rightarrow \infty$. (In Foutz's paper, the matrix in question is symmetric, and so he stated the condition in terms of positive definiteness. But his proof, which is based on the inverse function theorem, shows 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 $\Lambda_0(\cdot, \gamma^\circ) = \Lambda_0(\cdot)$. Thus we need only show that $E[U(\gamma^\circ, \Lambda_0)] = 0$. 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. With Conditions F1-F4 established, the result follows.
4.4 Asymptotic Normality

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

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

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

**Step I**

We can write

\[
U(\gamma^0, \Lambda^0_0) = n^{-1} \sum_{i=1}^{n} \xi_i \text{, where } \xi_i \text{ is a } (p + 1)-\text{vector with } r\text{-th element, } r = 1, \ldots, p, \text{ given by}
\]

\[
\xi_{ir} = \sum_{j=1}^{m_i} \delta_{ij} Z_{ijr} - \frac{\sum_{j=1}^{m_i} H_{ij}(\tau) Z_{ijr} \int w^{N_i}(\tau+1) \exp\{-w\{H_i(\tau)\}f(w; \theta)dw\}}{\int w^{N_i}(\tau) \exp\{-wH_i(\tau)\}f(w; \theta)dw}
\]

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 from the central limit theorem that \( n^{\frac{1}{2}} U(\gamma^0, \Lambda^0_0) \) is asymptotically mean-zero multivariate normal. To estimate the covariance matrix, let \( \xi^*_i \) 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 \( \hat{V}(\hat{\gamma}) = n^{-1} \sum_{i=1}^{n} \xi_i \xi^{*_T} \). 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 \((\gamma^0, \hat{\Lambda}_0)\) the intent is to signify \((\gamma^0, \hat{\Lambda}_0(\cdot, \gamma^0))\)). First order Taylor
expansion of $\hat{U}_r$ about $\Lambda_0^r$, $r = 1, \ldots, p + 1$, gives

$$n^{1/2}\{U_r(\gamma^o, \hat{\Lambda}_0) - U_r(\gamma^o, \Lambda_0^o)\}$$

$$= n^{-1/2}\sum_{i=1}^{n}\sum_{j=1}^{m_i}Q_{ijr}(\gamma^o, \Lambda_0^o, T_{ij})\{\hat{\Lambda}_0(T_{ij}, \gamma^o) - \Lambda_0^o(T_{ij})\} + o_p(1), \quad (22)$$

where

$$Q_{ijr}(\gamma^o, \Lambda_0^o, T_{ij}) = \left\{ \frac{\phi_{2i}(\gamma^o, \Lambda_0^o, \tau)}{\phi_{1i}(\gamma^o, \Lambda_0^o, \tau)}R_{ij}^{*}Z_{ijr} - \frac{\phi_{3i}(\gamma^o, \Lambda_0^o, \tau)}{\phi_{1i}(\gamma^o, \Lambda_0^o, \tau)}R_{ij}^{*}\sum_{j=1}^{m_i}H_{ij}(T_{ij})Z_{ijr} \right. \\
+ \left. \frac{\phi_{2i}^2(\gamma^o, \Lambda_0^o, \tau)}{\phi_{1i}^2(\gamma^o, \Lambda_0^o, \tau)}R_{ij}^{*}\sum_{j=1}^{m_i}H_{ij}(T_{ij})Z_{ijr} \right\}$$

for $r = 1, \ldots, p$, and

$$Q_{ij(p+1)}(\gamma^o, \Lambda_0^o, T_{ij}) = R_{ij}^{*}\left\{ \frac{\phi_{2i}(\gamma^o, \Lambda_0^o, \tau)\phi_{1i}(\theta)}{\phi_{1i}^2(\gamma^o, \Lambda_0^o, \tau)} - \frac{\phi_{2i}(\gamma^o, \Lambda_0^o, \tau)}{\phi_{1i}(\gamma^o, \Lambda_0^o, \tau)} \right\},$$

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

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

The validity of the approximation (22) can be seen by an argument similar to that used in connection with (24) below.

Given the intensity process (3), the process

$$M_{ij}(t) = N_{ij}(t) - \int_0^t\lambda_0(u)\exp(\beta^T Z_{ij})Y_{ij}(u)\psi_1(\gamma^o, \Lambda_0^o, u- )du$$

is a mean zero martingale with respect to the filtration $\mathcal{F}_t$. Also, by Lemma 3, we have that $\sup_{s \in [0, \tau]}|\hat{\Lambda}_0(s, \gamma^o) - \Lambda_0(s-, \gamma^o)|$ converges to zero. Thus, replacing $s-$ by $s$ we obtain the following approximation, uniformly over $t \in [0, \tau]$:

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

$$+ \frac{1}{n}\int_0^t\left[\{\mathcal{Y}(s, \hat{\Lambda}_0)\}^{-1} - \{\mathcal{Y}(s, \Lambda_0^o)\}^{-1}\right]\sum_{i=1}^{n}\sum_{j=1}^{m_i}dN_{ij}(s), \quad (23)$$
where
\[ \mathcal{Y}(s, \Lambda) = \frac{1}{n} \sum_{i=1}^{n} \psi_i(\gamma^o, \Lambda, s) \sum_{j=1}^{m_i} Y_{ij}(s) \exp(\beta^T Z_{ij}). \]

Now let \( \mathcal{W}(s, r) = \{ \mathcal{Y}(s, \Lambda_0^r + r\Delta) \}^{-1} \) with \( \Delta = \hat{\Lambda}_0 - \Lambda_0^r \). Define \( \mathcal{W} \) and \( \dot{\mathcal{W}} \) as the first and second derivative of \( \mathcal{W} \) with respect to \( r \), respectively. Then, computing the necessary derivatives and carrying out a first order Taylor expansion of \( \mathcal{W}(s, r) \) around \( r = 0 \) evaluated at \( r = 1 \) with Lagrange remainder (Abramowitz & Stegun, 1972, p. 880),
we get
\[ \{ \mathcal{Y}(s, \hat{\Lambda}_0) \}^{-1} - \{ \mathcal{Y}(s, \Lambda_0^r) \}^{-1} = \dot{\mathcal{W}}(s, 0) + \frac{1}{2} \ddot{\mathcal{W}}(s, \hat{r}(s)) \]
\[ = -\frac{1}{n} \sum_{i=1}^{n} \frac{\sum_{j=1}^{m_i} \left[ \frac{R_i(s)\eta_{ij}(0, s)}{\{\mathcal{Y}(s, \Lambda_0^r)\}^2} - \frac{1}{2} h_i(\hat{r}(s), s) \right] \exp(\beta^T Z_{ij}) \{ \hat{\Lambda}_0(T_{ij} \land s) - \Lambda_0^r(T_{ij} \land s) \}}{\mathcal{Y}(s, \Lambda_0^r)} \]
(24)
where \( R_{ij}(u) = \exp(\beta^T Z_{ij})Y_{ij}(u) \), \( R_i(u) = \sum_{j=1}^{m_i} R_{ij}(u), \hat{r}(s) \in [0, 1] \),
\[ \eta_{ij}(r, s) = \frac{\phi_3(\gamma^o, \Lambda_0^r + r\Delta, s)}{\phi_1(\gamma^o, \Lambda_0^r + r\Delta, s)} \left( \frac{\phi_2(\gamma^o, \Lambda_0^r + r\Delta, s)}{\phi_1(\gamma^o, \Lambda_0^r + r\Delta, s)} \right)^2, \]
and \( h_i(r, s) \) is as defined in Section 4.6 below, and shown there to be \( o(1) \) uniformly in \( r \) and \( s \).

Let \( \eta_{ii}(s) = \eta_{ii}(0, s) \). Plugging (24) into (23) we get
\[ \hat{\Lambda}_0(t, \gamma^o) - \Lambda_0^r(t) \approx n^{-1} \int_0^t \{ \mathcal{Y}(s, \Lambda_0^r) \}^{-1} \sum_{i=1}^{n} \sum_{j=1}^{m_i} dM_{ij}(s) \]
\[ -n^{-2} \int_0^t \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \frac{I(T_{kl} > s)R_k(s)\eta_{kl}(s)}{\{\mathcal{Y}(s, \Lambda_0^r)\}^2} \exp(\beta^T Z_{kl}) \{ \hat{\Lambda}_0(s) - \Lambda_0^r(s) \} \sum_{i=1}^{m_i} \sum_{j=1}^{m_j} dN_{ij}(s) \]
\[ -n^{-2} \int_0^t \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \frac{I(T_{kl} \leq s)R_k(s)\eta_{kl}(s)}{\{\mathcal{Y}(s, \Lambda_0^r)\}^2} \exp(\beta^T Z_{kl}) \{ \hat{\Lambda}_0(T_{kl}) - \Lambda_0^r(T_{kl}) \} \sum_{i=1}^{m_i} \sum_{j=1}^{m_j} dN_{ij}(s) \]
\[ + n^{-2} \int_0^t \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \frac{1}{2} h_k(\hat{r}(s), s) \exp(\beta^T Z_{kl}) \{ \hat{\Lambda}_0(T_{kl}) - \Lambda_0^r(T_{kl}) \} \sum_{i=1}^{m_i} \sum_{j=1}^{m_j} dN_{ij}(s). \]
The third term of the above equation can be written, by interchanging the order of integration, as
\[ n^{-2} \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \sum_{i=1}^{m_i} \sum_{j=1}^{m_j} \int_0^t R_k(s)\eta_{kl}(s) \exp(\beta^T Z_{kl}) \left[ \int_0^s \{ \hat{\Lambda}_0(u) - \Lambda_0^r(u) \} d\bar{N}_{kl}(u) \right] dN_{ij}(s). \]
where \( \tilde{N}(t) = I(T_{ij} \leq t) \) and

\[
\Omega_{ij}(s, t) = n^{-2} \int_s^t \{ \mathcal{Y}(u, \Lambda_{ij}^0) \}^{-2} R_k(u) \eta_{ij}(u) \exp(\beta^T \mathbf{z}_{ij}) \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} dN_k(t).
\]

Hence we get

\[
\hat{\Lambda}_0(t, \gamma^0) - \Lambda_{ij}^0(t) \approx n^{-1} \int_0^t \{ \mathcal{Y}(s, \Lambda_{ij}^0) \}^{-1} \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \tilde{d}M_{ij}(s)
\]

\[
- \int_0^t \{ \hat{\Lambda}_0(s, \gamma^0) - \Lambda_{ij}^0(s) \} \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \{ \delta_{ij} \Upsilon(s) + \Omega_{ij}(s, t) + o(n^{-1}) \} d\tilde{N}_ij(s)
\]

where

\[
\Upsilon(s) = n^{-2} \{ \mathcal{Y}(s, \Lambda_{ij}^0) \}^{-2} \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} I(T_{kl} > s) R_k(s) \eta_{kl}(s) \exp(\beta^T \mathbf{z}_{kl}).
\]

The \( o(n^{-1}) \) is uniform in \( t \) (see Sec. 4.6 below) and will be dominated by \( \Omega \) and \( \Upsilon \), which are of order \( n^{-1} \). Hence the \( o(n^{-1}) \) term can be ignored.

An argument similar to that of Yang & Prentice (1999) and Zucker (2005) now yields the martingale representation

\[
\hat{\Lambda}_0(t, \gamma^0) - \Lambda_{ij}^0(t) \approx \frac{1}{n \tilde{p}(t)} \int_0^t \tilde{p}(s-) \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \tilde{d}M_{ij}(s) \frac{1}{\mathcal{Y}(s, \Lambda_{ij}^0)},
\]

where

\[
\tilde{p}(t) = \prod_{s \leq t} \left[ 1 + \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \{ \delta_{ij} \Upsilon(s) + \Omega_{ij}(s, t) \} d\tilde{N}_ij(s) \right].
\]

Based on (22), we can write

\[
U_r(\gamma^0, \hat{\Lambda}_0) - U_r(\gamma^0, \Lambda_{ij}^0) \approx n^{-1} \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \int_0^r Q_{ijkl}(\gamma^0, \Lambda_{ij}^0, s) \{ \hat{\Lambda}_0(s, \gamma^0) - \Lambda_{ij}^0(s) \} d\tilde{N}_ij(s).
\]

Plugging the martingale representation (25) into the above equation and carrying out some more algebra (again involving an interchange of integrals) gives

\[
U_r(\gamma^0, \hat{\Lambda}_0) - U_r(\gamma^0, \Lambda_{ij}^0) \approx n^{-1} \int_0^r \pi_r(s, \gamma^0, \Lambda_{ij}^0) \frac{\tilde{p}(s-) \sum_{k=1}^{m_k} \sum_{l=1}^{m_l} \tilde{d}M_{kl}(s)}{\mathcal{Y}(s, \Lambda_{ij}^0)},
\]

(26)
where
\[ \pi_r(s, \gamma, \Lambda_0) = n^{-1} \int_s^\infty \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} Q_{ijr}(\gamma, \Lambda_0, t) \tilde{N}_{ij}(t)}{\hat{p}(t)}. \]

Therefore, \( n^{1/2} \left[ \mathbf{U}(\gamma^0, \hat{\Lambda}_0(\cdot, \gamma^0)) - \mathbf{U}(\gamma^0, \Lambda_0^0(\cdot, \gamma^0)) \right] \) is asymptotically mean zero multivariate normal with covariance matrix that can be consistently estimated by
\[ G_{rl}(\hat{\gamma}) = n^{-1} \int_0^\tau \pi_{rl}(s, \hat{\gamma}, \hat{\Lambda}_0) \pi_{rl}(s, \hat{\gamma}, \hat{\Lambda}_0) \{ \hat{p}(s-) \}^2 \sum_{i=1}^n \sum_{j=1}^{m_i} dN_{ij}(s) \{ \mathcal{Y}(s, \hat{\Lambda}_0) \}^2 \]
for \( r, l = 1, \ldots, p + 1. \)

Step III

We now examine the sum of \( \mathbf{U}(\gamma^0, \Lambda_0^0) \) and \( \mathbf{U}(\gamma^0, \hat{\Lambda}_0(\cdot, \gamma^0)) - \mathbf{U}(\gamma^0, \Lambda_0^0). \) From \( \mathbf{26}, \) we have
\[ U_r(\gamma^0, \Lambda_0^0) - U_r(\gamma^0, \Lambda_0^0) \approx n^{-1} \int_0^\tau \alpha_r(s) \sum_{k=1}^{m_k} \sum_{l=1}^{dM_{kl}(s)} = \frac{1}{n} \sum_{k=1}^{m_k} \mu_{kr}, \]
where \( \alpha_r(s) \) is the limiting value of \( \pi_r(s, \gamma^0, \Lambda_0^0) \hat{p}(s-) / \mathcal{Y}(s, \Lambda_0^0) \) and \( \mu_{kr} \) is defined as
\[ \mu_{kr} = \int_0^\tau \alpha_r(s) \sum_{k=1}^{m_k} dM_{kl}(s). \]

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

We thus have
\[ U_r(\gamma^0, \Lambda_0^0) + [U_r(\gamma^0, \hat{\Lambda}_0(\cdot, \gamma^0)) - U_r(\gamma^0, \Lambda_0^0)] \approx \frac{1}{n} \sum_{i=1}^n (\xi_{ir} + \mu_{ir}), \]
which is a mean of \( n \) iid random variables. Hence \( n^{1/2} \{ U_r(\gamma^0, \Lambda_0^0) + [U_r(\gamma^0, \hat{\Lambda}_0(\cdot, \gamma^0)) - U_r(\gamma^0, \Lambda_0^0)] \} \) is asymptotically normally distributed. The covariance matrix may be estimated by \( \hat{V}(\hat{\gamma}) + \hat{G}(\hat{\gamma}) + \hat{C}(\hat{\gamma}), \) where
\[ \hat{C}_{rl}(\hat{\gamma}) = \frac{1}{n} \sum_{i=1}^n (\xi_{ir}^* \mu_{il}^* + \xi_{il}^* \mu_{ir}^*), \quad r, l = 1, \ldots, p + 1, \]
with
\[ \mu_{ir}^* = \int_0^\tau \pi_r(s, \hat{\gamma}, \hat{\Lambda}_0) \hat{p}(s-) / \mathcal{Y}(s, \Lambda_0) \sum_{j=1}^{m_j} dM_{ij}(s) \]
and

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

**Step IV**

First order Taylor expansion of \( U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \cdot)) \) about \( \gamma^0 = (\beta^0, \theta^0)^T \) gives

\[ U(\hat{\gamma}, \hat{\Lambda}_0(\cdot, \cdot)) = U(\gamma^0, \hat{\Lambda}_0(\cdot, \cdot)) + D(\gamma^0)(\hat{\gamma} - \gamma^0)^T + o_p(1), \]

where

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

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

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

\[
D_{ls}(\gamma) = -n^{-1} \sum_{i=1}^n \left\{ \frac{\phi_{2i}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}(\gamma, \hat{\Lambda}_0, \tau)} \sum_{j=1}^{m_i} Z_{ijl} \frac{\partial \hat{H}_{ij} (T_{ij})}{\partial \beta_s} \right. \\
- \left[ \frac{\phi_{3i}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}(\gamma, \hat{\Lambda}_0, \tau)} - \frac{\phi_{2i}^2(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}^2(\gamma, \hat{\Lambda}_0, \tau)} \right] \sum_{j=1}^{m_i} \hat{H}_{ij} (T_{ij}) Z_{ijl} \frac{\partial \hat{H}_{ij} (\tau)}{\partial \beta_s} \right\}, \quad (27)
\]

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

and

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

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

\[
D_{l(p+1)}(\gamma) = -n^{-1} \sum_{i=1}^n \left\{ \frac{\phi_{2i}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}(\gamma, \hat{\Lambda}_0, \tau)} \sum_{j=1}^{m_i} Z_{ijl} \frac{\partial \hat{H}_{ij} (T_{ij})}{\partial \theta} \right. \\
- \left[ \frac{\phi_{3i}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}(\gamma, \hat{\Lambda}_0, \tau)} - \frac{\phi_{2i}^2(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{1i}^2(\gamma, \hat{\Lambda}_0, \tau)} \right] \sum_{j=1}^{m_i} \hat{H}_{ij} (T_{ij}) Z_{ijl} \frac{\partial \hat{H}_{ij} (\tau)}{\partial \theta} \right\}.
\]
Finally, and where
\[\{ \phi_{n+1}(\gamma, \hat{\Lambda}_0, \tau) - \phi_{n}^{(0)}(\gamma, \hat{\Lambda}_0, \tau) \frac{\partial^2 \hat{H}_i(\tau)}{\partial \theta^2} \} \sum_{j=1}^{m} \hat{H}_{ij}(T_{ij}) Z_{ijl} \} \]

(28)

and

\[D_{(p+1)i}(\gamma) = n^{-1} \sum_{i=1}^{n} \left\{ \frac{\phi_{i}^{(0)}(\gamma, \hat{\Lambda}_0, \tau) \phi_{n}^{(0)}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{i}^{(0)}(\gamma, \Lambda_0, \tau)} - \frac{\phi_{n+1}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{i}^{(0)}(\gamma, \Lambda_0, \tau)} \right\} \frac{\partial \hat{H}_i(\tau)}{\partial \beta_i}. \]

(29)

Finally,

\[D_{(p+1)(p+1)}(\gamma) = n^{-1} \sum_{i=1}^{n} \left\{ \frac{\phi_{i}^{(0)}(\gamma, \hat{\Lambda}_0, \tau) \phi_{n}^{(0)}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{i}^{(0)}(\gamma, \Lambda_0, \tau)} - \frac{\phi_{n+1}(\gamma, \hat{\Lambda}_0, \tau)}{\phi_{i}^{(0)}(\gamma, \Lambda_0, \tau)} \right\} \frac{\partial \hat{H}_i(\tau)}{\partial \beta_i}, \]

(30)

where

\[\phi_{i}^{(0)}(\gamma, \hat{\Lambda}_0, \tau) = \int w^{N_{i}(\tau)} \exp\{-w\hat{H}_{i}(\tau)\} \frac{d^2 f(w)}{d\theta^2} dw,\]

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

and

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

\[\sum_{i=1}^{n} R_{ij}(\tau_k) \left[ \frac{\phi_{2i}(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}(\gamma, \Lambda_0, \tau_{k-1})} - \frac{\phi_{2i}(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}(\gamma, \Lambda_0, \tau_{k-1})} \right] \frac{\partial \hat{H}_i(\tau_{k-1})}{\partial \theta} \left\{ \frac{\phi_{2i}^{(0)}(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}^{(0)}(\gamma, \Lambda_0, \tau_{k-1})} - \frac{\phi_{3i}(\gamma, \hat{\Lambda}_0, \tau_{k-1})}{\phi_{1i}(\gamma, \Lambda_0, \tau_{k-1})} \right\}. \]

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

\[\hat{D}^{-1}(\hat{\gamma}) \{ \hat{V}(\hat{\gamma}) + \hat{G}(\hat{\gamma}) + \hat{C}(\hat{\gamma}) \} \hat{D}^{-1}(\hat{\gamma})^T.\]
4.5 Proof of (19)

The goal is to prove that
\[
\sup_{s, \gamma} |A(\gamma, \tilde{\Lambda}^{(n)}, s) - a(\gamma, \tilde{\Lambda}^{(n)}, s)| \to 0 \ \text{a.s.} \quad (31)
\]
This involves several steps.

First, it is easy to see that there exists a constant \( \kappa \) (independent of \( \gamma \) and \( s \)) such that
\[
\sup_{s, \gamma} |A(\gamma, \Lambda_1, s) - A(\gamma, \Lambda_2, s)| \leq \kappa \|\Lambda_1 - \Lambda_2\|, \quad (32)
\]
\[
\sup_{s, \gamma} |a(\gamma, \Lambda_1, s) - a(\gamma, \Lambda_2, s)| \leq \kappa \|\Lambda_1 - \Lambda_2\|. \quad (33)
\]
Next, for any fixed continuous \( \Lambda \), the functional strong law of large numbers of Andersen & Gill (1982, Appendix III) implies that, with probability one,
\[
\sup_{s, \gamma} |A(\gamma, \Lambda, s) - a(\gamma, \Lambda, s)| \to 0. \quad (34)
\]

Now, given \( \epsilon > 0 \), define the sets \( \{t_j^{(\epsilon)}\}, \{\gamma_k^{(\epsilon)}\}, \) and \( \{\Lambda_i^{(\epsilon)}\} \) to be finite partition grids of \([0, \tau]\), \(G\), and \([0, \Lambda_{\max}]\), respectively, with distance of no more than \( \epsilon \) between grid points. Define \( L_{\epsilon}^* \) to be the set of functions of \( t \) and \( \gamma \) defined by linear interpolation through vertices of the form \((t_j^{(\epsilon)}, \gamma_k^{(\epsilon)}, \Lambda_i^{(\epsilon)})\).

Obviously \( L_{\epsilon}^* \) is a finite set. Hence, in view of (34), there exists a probability-one set of realizations \( \Omega_\epsilon \) for which
\[
\sup_{s \in [0, \tau], \gamma \in G, \Lambda \in L_{\epsilon}^*} |A(\gamma, \Lambda, s) - a(\gamma, \Lambda, s)| \to 0. \quad (35)
\]
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 (17) and (33), we can find for any $\omega \in \Omega_0$ a suitable positive integer $\bar{n}(\epsilon, \omega)$ such that, whenever $n \geq \bar{n}(\epsilon, \omega)$,

$$|\tilde{\Lambda}_0^{(n)}(t, \gamma) - \bar{\Lambda}_0^{(n)}(u, \gamma)| \leq B^*(t - u) + \frac{\epsilon}{2} \quad \forall t, u,$$

(36)

$$\sup_{s \in [0, r], \gamma \in G, \Lambda \in L_{ij}^*} |A(\gamma, \Lambda, s) - a(\gamma, \Lambda, s)| \leq \epsilon.$$

(37)

Next, let $\tilde{\Lambda}_0^{(n)}$ denote the function defined by linear interpolation through $(t_j^{(e)}, \gamma_k^{(e)}, \tilde{\Lambda}_j^{(e)})$, where $\tilde{\Lambda}_j^{(e)}$ is the element of $\{\Lambda_i^{(e)}\}$ that is closest to $\tilde{\Lambda}_0^{(n)}(t_j^{(e)}, \gamma_k^{(e)})$. It is clear that

$$|\tilde{\Lambda}_0^{(n)}(t_j^{(e)}, \gamma_k^{(e)}) - \tilde{\Lambda}_0^{(n)}(t_j^{(e)}, \gamma_k^{(e)})| \leq \epsilon \quad \forall j, k.$$

Using (36) and the Lipschitz continuity of $\tilde{\Lambda}_0^{(n)}(t, \gamma)$ with respect to $\gamma$ (which follows from the corresponding property of $\tilde{\Lambda}_0(t, \gamma)$), we thus obtain

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

for a suitable fixed constant $B^{**}$ (depending on $B^*$ and $C^*$). Combining this with (37) and (33), we obtain

$$\sup_{s, \gamma} |A(\gamma, \tilde{\Lambda}^{(n)}, s) - a(\gamma, \tilde{\Lambda}^{(n)}, s)| \leq (2\kappa B^{**} + 1)\epsilon \quad \text{for all } n \geq \bar{n}(\epsilon, \omega).$$

Since $\epsilon$ was arbitrary, the desired conclusion (31) follows, and the proof is thus complete.

4.6 Definition and behavior of $h_i(r, s)$

The quantity $h_i(r, s)$ appearing in (24) is given by

$$h_i(r, s) = \frac{2R_i(s)\eta_{1i}(r, s)}{\{Y(s, \Lambda_0^0 + r \Delta)\}^2} \sum_{l=1}^{n} R_l(s)\eta_{l1}(r, s) \sum_{j=1}^{m_l} \exp(\beta^T \mathbf{Z}_{ij})\Delta(T_{ij} \wedge s)$$

$$- \frac{R_i(s)\eta_{2i}(r, s)}{\{Y(s, \Lambda_0^0 + r \Delta)\}^2} \sum_{j=1}^{m_i} \exp(\beta^T \mathbf{Z}_{ij})\Delta(T_{ij} \wedge s)$$

where $\Delta(T_{ij} \wedge s) = \tilde{\Lambda}_0(T_{ij} \wedge s) - \Lambda_0^0(T_{ij} \wedge s)$ 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 (6).

Moreover, for $k = 1, \ldots, 4$, we have

$$E[W_{r_{\min} + (k-1)} \exp\{-W_i m e^{\beta^T z} \Lambda_0^e(\tau)\}] \leq \phi_{ki}(\gamma^0, \Lambda_0^0, s) \leq E[W_{r_{\max} + (k-1)}]$$

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 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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