Maximum Likelihood Estimation for Semiparametric Regression Models with Interval-Censored Multi-State Data

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Abstract

Interval-censored multi-state data arise in many studies of chronic diseases, where the health status of a subject can be characterized by a finite number of disease states and the transition between any two states is only known to occur over a broad time interval. We formulate the effects of potentially time-dependent covariates on multi-state processes through semiparametric proportional intensity models with random effects. We adopt nonparametric maximum likelihood estimation (NPMLE) under general interval censoring and develop a stable expectation-maximization (EM) algorithm. We show that the resulting parameter estimators are consistent and that the finite-dimensional components are asymptotically normal with a covariance matrix that attains the semiparametric efficiency bound and can be consistently estimated through profile likelihood. In addition, we demonstrate through extensive simulation studies that the proposed numerical and inferential procedures perform well in realistic settings. Finally, we provide an application to a major epidemiologic cohort study.

Keywords: EM algorithm; Nonparametric likelihood; Proportional intensity; Random effects; Semiparametric efficiency; Time-dependent covariates

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1 Introduction

In many studies of chronic diseases, the health status of a subject can be characterized using a finite number of disease states, and the disease history of that subject can be viewed as a multi-state stochastic process. For example, an old person may first develop mild cognitive impairment (MCI) and then progress to dementia (Flicker et al., 1991); a patient with chronic obstructive pulmonary disease may progress through four stages of the disease (Pauwels et al., 2001). It is important to understand how a subject transitions from one state to another over time and to incorporate the disease history into medical decision-making. It is also of interest to study the associations between risk factors and disease processes. For economic and logistical reasons, subjects can only be examined periodically, such that the state transitions are only known to occur between two successive examinations. Such data are called interval-censored multi-state data. The fact that none of the transition times are directly observed makes semiparametric regression analysis of such data extremely challenging, both theoretically and computationally.

Most of the literature on interval-censored multi-state data adopts parametric models for transitions and imposes the time-homogeneous Markov assumption (Kalbfleisch and Lawless, 1985; Satten, 1999; Cook, 1999; Cook et al., 2002, 2004). Parametric models are restrictive, and the homogeneity assumption is violated in many applications. Several authors used piecewise constant approximations of transition intensities to allow for time nonhomogeneity (Gentleman et al., 1994; Saint-Pierre et al., 2003; Ocañ-Riola, 2005; Jackson, 2011). Others specified spline functions for transition intensities and then applied piecewise constant approximations for the likelihood construction (Machado and van den Hout, 2018; Machado et al., 2021). However, the choices for the number of spline pieces and the change points are arbitrary, and the results may be sensitive to these choices. When
the Markov assumption fails, random effects can be used to accommodate the dependence of transitions. Satten (1999) and Cook et al. (2004) considered random effects in modeling the transitions. Their methods make strong assumptions about the distribution of the random effects and are only applicable to progressive processes.

In this article, we provide a new framework based on semiparametric proportional intensity models with random effects to study general interval-censored multi-state data. Our formulation allows the baseline intensity functions for the transitions between any two states to be completely arbitrary and accommodates time-dependent covariates. In addition, we introduce random effects and their possible interactions with covariates to further capture the dependence among the transitions of the same subject. We adopt the NPMLE approach and develop a stable EM algorithm that involves maximization over only a small number of parameters and performs well even with complex transition patterns. We establish the asymptotic properties of the parameter estimators through novel use of modern empirical process theory. We compare the performance of the proposed and existing methods through extensive simulation studies. Finally, we apply the proposed methods to data on MCI and dementia from the Atherosclerosis Risk in Communities (ARIC) study (Knopman et al., 2016; Wright et al., 2021).

2 Theory and Methods

2.1 Models, Data, and Likelihood

We consider a multi-state process with $K$ states in a study of $n$ subjects. Let $\mathcal{D}$ denote the set of all state pairs $(j, k)$ such that $j \neq k$ and transition from $j$ to $k$ is feasible. We assume that it is impossible for a subject to return to a prior state through other states; otherwise,
there would be infinite many loops between two states within any time interval, which
would cause non-identifiability issues. For \( i = 1, \ldots, n \), let \( X_i(\cdot) \) denote a \( d_1 \)-vector of
potentially time-dependent covariates for the \( i \)th subject, and \( b_i \) denote the corresponding
\( d_2 \)-vector of random effects that is normal with mean zero and covariance matrix \( \Sigma(\gamma) \)
indexed by \( d_3 \)-dimensional parameters \( \gamma \). For \( (j, k) \in D \), let \( N_{ijk}(t) \) denote the number of
times that the \( i \)th subject transitions from state \( j \) to state \( k \) by time \( t \). Under proportional
intensity models, the transition intensities of \( N_{ijk}(t) \) conditional on \( X_i \) and \( b_i \) take the
form
\[
\lambda_{ijk}(t; X_i, b_i) = \lambda_{jk}(t) \exp\{\beta_{jk}^T X_i(t) + b_i^T Z_i(t)\},
\]
where \( Z_i(\cdot) \) consists of 1 and covariates that may be part of \( X_i(\cdot) \), \( \beta_{jk} \) is a vector of
unknown regression parameters, and \( \lambda_{jk}(\cdot) \) is an arbitrary baseline intensity function.

We define the \( K \times K \) cumulative transition intensity matrix \( A_i(t; X_i, Z_i, b_i) \), whose
off-diagonal elements are
\[
A_i(t; X_i, Z_i, b_i)^{(j,k)} = \begin{cases} 
\int_0^t \exp\{\beta_{jk}^T X_i(s) + b_i^T Z_i(s)\} d\Lambda_{jk}(s) & \text{if } (j, k) \in D, \\
0 & \text{otherwise},
\end{cases}
\]
and whose diagonal elements are
\[
A_i(t; X_i, Z_i, b_i)^{(j,j)} = -\sum_{k \neq j} A_i(t; X_i, Z_i, b_i)^{(j,k)},
\]
where \( \Lambda_{jk}(t) = \int_0^t \lambda_{jk}(s)ds \), and we use superscript \( (j, k) \) to denote the \( (j, k) \)th element
of a matrix. For any \( 0 \leq t_1 \leq t_2 \), let \( P_i(t_1, t_2; X_i, Z_i, b_i) \) denote the \( K \times K \) transition
probability matrix over the time interval \( (t_1, t_2] \). According to Theorem II.6.7 of Andersen
et al. (1993), the relationship between the two matrices \( P_i \) and \( A_i \) can be characterized
via product integration:
\[
P_i(t_1, t_2; X_i, Z_i, b_i) = \prod_{t_1 < t \leq t_2} \{I_K + dA_i(t; X_i, Z_i, b_i)\},
\]
where $I_K$ is the $K \times K$ identity matrix, and $dA(\cdot)$ is the element-wise differential for a matrix-valued function $A(\cdot)$. Here,

$$
\mathcal{P}_{s \in [t_1, t_2]} \{ I + dA(s) \} = \lim_{\max |s_l - s_{l-1}| \to 0} \prod_{l=1}^{L} \{ I + A(s_l) - A(s_{l-1}) \},
$$

where $t_1 = s_0 < s_1 < \cdots < s_L = t_2$ is a partition of $[t_1, t_2]$, and the matrix product is taken in its natural order from left to right (Gill and Johansen, 1990).

We consider a very general interval-censoring scheme, where every subject can be examined an arbitrary number of times. For $i = 1, \ldots, n$, let $n_i$ denote the number of examinations after the baseline examination for the $i$th subject, and let $0 = \tau_{i0} < \tau_{i1} < \cdots < \tau_{im_i}$ denote the corresponding examination times. The state occupied at each examination is denoted by $S_{il}$, $l = 0, \ldots, n_i$. Then the observed data consist of $\{ (\tau_{i0}, \tau_{i1}, \ldots, \tau_{im_i}), (S_{i0}, S_{i1}, \ldots, S_{im_i}), X_i, Z_i \}$, $i = 1, \ldots, n$. Write $\theta = (\beta^T, \gamma^T)^T = (\{ \beta_{jk}^T \}_{(j,k) \in D}, \gamma^T)^T$ and $\Omega = \{ \Lambda_{jk} \}_{(j,k) \in D}$. Under the conditional Markov assumption, the observed-data likelihood conditional on the initial states is given by

$$
L_n(\theta, \Omega) = \prod_{i=1}^{n} \int b_i \prod_{l=1}^{n_i} P_i(\tau_{il-1}, \tau_{il}; X_i, Z_i, b_i)(S_{il-1}, S_{il}) \phi(b_i; \Sigma(\gamma)) db_i,
$$

where $\phi(b; \Sigma) = (2\pi)^{-d_2/2} |\Sigma|^{-1/2} \exp(-b^T \Sigma^{-1} b/2)$.

### 2.2 Nonparametric Maximum Likelihood Estimation

We adopt the NPMLE approach to estimate the parameters $\theta$ and $\Omega$. Specifically, for each $(j, k) \in D$, we treat $\Lambda_{jk}(\cdot)$ as a step function with nonnegative jumps at $0 < u_1 < u_2 < \cdots < u_m$, which are the unique values of $\tau_{il}$ ($i = 1, \ldots, n; l = 1, \ldots, n_i$). For $(j, k) \in D$ and $s = 1, \ldots, m$, let $\lambda_{jks}$ denote the jump size of $\Lambda_{jk}$ at $u_s$. Then the transition probability matrix $P_i(t_1, t_2; X_i, Z_i, b_i)$ is equal to

$$
\tilde{P}_i(t_1, t_2; X_i, Z_i, b_i) = \prod_{t_1 < u_s \leq t_2} \{ I_K + \Delta A_i(u_s; X_i, Z_i, b_i) \},
$$
where the elements of the matrix $\Delta A_i(u_s; X_i, Z_i, b_i)$ are given by

$$
\Delta A_i(u_s; X_i, Z_i, b_i)_{(j,k)} =
\begin{cases} 
\lambda_{jk} \exp(\beta_{jk}^T X_{is} + b_i^T Z_{is}) & \text{if } (j,k) \in D, \\
- \sum_{k'=(j,k') \in D} \lambda_{jk'} \exp(\beta_{j'k'}^T X_{is} + b_i^T Z_{is}) & \text{if } j = k, \\
0 & \text{otherwise,}
\end{cases}
$$

with $X_{is} = X_i(u_s)$ and $Z_{is} = Z_i(u_s)$. We maximize

$$
\prod_{i=1}^n \prod_{l=1}^{n_i} \mathcal{P}(\tau_{i,l-1}, \tau_{i,l}; X_i, Z_i, b_i)^{(S_{i,l-1}, S_{i,l})} \phi(b_i; \Sigma(\gamma)) db_i.
$$

Direct maximization of (1) is very difficult, since it involves matrix multiplication and there are no analytical expressions for $\lambda_{jk}$'s. Thus, we introduce latent Poisson random variables whose observed-data likelihood is equal to (1) but can be maximized through an EM algorithm.

For $i = 1, \ldots, n$, $(j,k) \in D$, and $s = 1, \ldots, m$, we introduce independent latent Poisson random variables $W_{ijks}$ with means $\lambda_{ijks} = \lambda_{jk} \exp(\beta_{jk}^T X_{is} + b_i^T Z_{is})$. For the $i$th subject, let $(\tau_1, \tau_2)$ be any of the time intervals $(\tau_{i,l-1}, \tau_{i,l})$, $l = 1, \ldots, n_i$. The unique time points within $[\tau_1, \tau_2]$ are labeled as $u_{s_0} = \tau_1 < u_{s_1} < u_{s_2} \cdots < u_{s_q} < \tau_2 = u_{s_{q+1}}$. A transition from state $S_1$ at $\tau_1$ to state $S_2$ at $\tau_2$ consists of all possible transition paths of the form $(k_0 = S_1, k_1, k_2, \ldots, k_q, S_2 = k_{q+1})$, where $k_1, \ldots, k_q$ are the unknown states occupied at $u_{s_1}, \ldots, u_{s_q}$. Given a feasible path $(S_1, k_1, \ldots, k_q, S_2)$, we define the event $V_i(k_1, \ldots, k_q; \tau_1, \tau_2, S_1, S_2)$ as follows: for $l = 1, \ldots, q + 1$, if $k_{l-1} \neq k_l$, then $W_{ik_{l-1}k_l} > 0$ and $W_{ik_{l-1}k_l'} = 0$ for all $k' \neq k_{l-1}, k_l$; otherwise $W_{ik_{l-1}k_l'} = 0$ for all $k' \neq k_{l-1}$. We claim that the transition probability from state $S_1$ at $\tau_1$ to state $S_2$ at $\tau_2$ is equal to the probability of observing the following event:

$$
Y_i(\tau_1, \tau_2, S_1, S_2) = \bigcup_{(k_1, \ldots, k_q) \in \mathcal{A}_q} V_i(k_1, \ldots, k_q; \tau_1, \tau_2, S_1, S_2),
$$
where $A_q$ is the set of all possible combinations of $k_1, \ldots, k_q$ that connect $S_1$ to $S_2$.

To see this, we consider a sequence of time points $t_0 = \tau_1 < t_1 < \cdots < t_r < \tau_2 = t_{r+1}$ such that there is at most one transition within each time interval $(t_{l-1}, t_l]$, $l = 1, \ldots, r + 1$, and the transition time is not necessarily $t_l$. Let $j_0, \ldots, j_{r+1}$ denote the state occupied at $t_0, \ldots, t_{r+1}$. The transition probability can be written as

$$P_i(t_1, t_2; X_i, Z_i, b_i)(S_1, S_2) = \sum_{(j_1, \ldots, j_{r+1}) \in A_r} \prod_{l=1}^{r+1} \left[ \exp \left\{ - \sum_{k \neq j_{l-1}} \int_{t_{l-1}}^{t_l} dA_i(t; X_i, Z_i, b_i)^{(j_{l-1}, k)} \right\} \right] I(j_{l-1} = j_l) \times \left\{ 1 - \exp \left\{ - \int_{t_{l-1}}^{t_l} dA_i(t; X_i, Z_i, b_i)^{(j_{l-1}, j_l)} \right\} \right\} \times \exp \left\{ - \sum_{k \neq j_{l-1}, j_l} \int_{t_{l-1}}^{t_l} dA_i(t; X_i, Z_i, b_i)^{(j_{l-1}, k)} \right\} I(j_{l-1} \neq j_l)$$

(2)

In the NPMLE approach, transitions within $(\tau_1, \tau_2]$ can only occur at $u_{s_1}, u_{s_2}, \ldots, u_{s_{q+1}}$, which ensures at most one transition within each interval $(u_{s_{l-1}}, u_{s_l}]$, $l = 1, \ldots, q + 1$. Thus, we can replace $\{(t_0, \ldots, t_{r+1}), (j_0, \ldots, j_{r+1})\}$ in (2) with $\{(u_{s_0}, \ldots, u_{s_{q+1}}), (k_0, \ldots, k_{q+1})\}$ and plug in the discretized $A_i$ to obtain

$$\tilde{P}_i(t_1, t_2; X_i, Z_i, b_i)(S_1, S_2) = \sum_{(k_1, \ldots, k_q) \in A_q} \prod_{l=1}^{q+1} \left[ \exp \left\{ - \sum_{k' \neq k_{l-1}} \Delta A_i(u_{s_l}; X_i, Z_i, b_i)^{(k_{l-1}, k')} \right\} \right] I(k_{l-1} = k_l) \times \left\{ 1 - \exp \left\{ -\Delta A_i(u_{s_l}; X_i, Z_i, b_i)^{(k_{l-1}, k_l)} \right\} \right\} \times \exp \left\{ - \sum_{k' \neq k_{l-1}, k_l} \Delta A_i(u_{s_l}; X_i, Z_i, b_i)^{(k_{l-1}, k')} \right\} I(k_{l-1} \neq k_l) = \sum_{(k_1, \ldots, k_q) \in A_q} \prod_{l=1}^{q+1} \left[ \exp \left\{ - \sum_{k' \neq k_{l-1}} \lambda_{k_{l-1} k'} \right\} \right] I(k_{l-1} = k_l) \times \left\{ 1 - \exp(\lambda_{k_{l-1} k_l}) \right\} \times \exp \left\{ - \sum_{k' \neq k_{l-1}, k_l} \lambda_{k_{l-1} k'} \right\} I(k_{l-1} \neq k_l) \right] \cdot
We can verify that all the events \( V_i(k_1, \ldots, k_q; \tau_1, \tau_2, S_1, S_2) \) are mutually exclusive. Thus,

\[
\Pr\{Y_i(\tau_1, \tau_2, S_1, S_2)\} = \sum_{(k_1, \ldots, k_q) \in A_q} \prod_{t=1}^{q+1} \left[ \exp\left(- \sum_{k' \neq k_t} \lambda_{ik_{t-1}k's_t}\right) \right]^{I(k_{t-1} = k_t)} \times \left[ 1 - \exp(-\lambda_{ik_{t-1}k's_t}) \right] \left[ - \sum_{k' \neq k_{t-1}, k_t} \lambda_{ik_{t-1}k's_t} \right]^{I(k_{t-1} \neq k_t)},
\]

which equals \( \tilde{P}_i(\tau_1, \tau_2; X_i, Z_i, b_i)(S_1, S_2) \). Hence, maximizing (1) is tantamount to maximizing the likelihood based on the observations \( O_i = \bigcap_{l=1}^{n_i} Y_i(\tau_{i,l-1}, \tau_{i,l}, S_{i,l-1}, S_{i,l}), \ i = 1, \ldots, n \).

To maximize the latter likelihood, we develop an EM algorithm by treating \( W_{ijks} \ (i = 1, \ldots, n; (j, k) \in D; s = 1, \ldots, m) \) and \( b_i \ (i = 1, \ldots, n) \) as missing data. The complete-data log-likelihood is

\[
\sum_{i=1}^{n} \left\{ \sum_{(j,k) \in D} \sum_{s=1}^{m} I(t_s \leq \tau_{i,n_i}) \left\{ W_{ijks} \log \left[ \lambda_{jks} \exp(\beta_{jk}^T X_{is} + b_i^T Z_{is}) \right] - \lambda_{jks} \exp(\beta_{jk}^T X_{is} + b_i^T Z_{is}) - \log(W_{ijks}) \right\} - \frac{1}{2} \log(2\pi) - \frac{1}{2} \log|\Sigma| - \frac{1}{2} b_i^T \Sigma^{-1} b_i \right\}.
\]

In the E-step, we calculate the conditional expectations of \( W_{ijks}, \exp(\beta_{jk}^T X_{is} + b_i^T Z_{is}) \) and \( b_i^{\otimes 2} \) given \( O_i \), where \( a^{\otimes 2} = aa^T \) for any vector or matrix \( a \). The last two conditional expectations can be derived from the fact that the conditional distribution of \( b_i \) given \( O_i \) is proportional to

\[
\prod_{l=1}^{n_i} \tilde{P}_i(\tau_{i,l-1}, \tau_{i,l}; X_i, Z_i, b_i)(S_{i,l-1}, S_{i,l}) \phi(b_i; \Sigma(\gamma)).
\]

In addition, the first conditional expectation follows from the conditional expectation of \( W_{ijks} \) given \( O_i \) and \( b_i \). Assume that \( u_s \) falls within the time interval \( (\tau_{i,l-1}, \tau_{i,l}) \). As before, we denote all the unique time points within the closed interval \([\tau_{i,l-1}, \tau_{i,l}]\) as \( \tau_{i,l-1} = \)
Suppose that \( u_s = u_{s_l} \) for some \( l \). Only those paths with \( k_{l-1} \neq j \) or \( (k_{l-1}, k_l) = (j, k) \) will contribute to the above equation. Thus, the above conditional expectation becomes

\[
\begin{align*}
\sum_{j' \neq j} & \frac{\tilde{P}_i(\tau_{l,1}, u_{s-1})(S_{l-1,j'}) \tilde{P}_i(u_{s-1}, \tau_{il})}{\tilde{P}_i(\tau_{l,1}, S_{l-1,S_{il}})} \times \left\{ \sum_{w=1}^{\infty} w \times \Pr(W_{ijks} = w) \right\} \\
+ & \frac{\tilde{P}_i(\tau_{l,1}, u_{s-1})(S_{l-1,j}) \tilde{P}_i(u_{s}, \tau_{il})}{\tilde{P}_i(\tau_{l,1}, S_{il,S_{il}})} \times \left\{ \sum_{w=1}^{\infty} w \times \Pr(W_{ijks} = w, W_{ij'k's} = 0, k' \neq j, k) \right\} \\
= & \frac{\sum_{j' \neq j} \tilde{P}_i(\tau_{l,1}, u_{s-1})(S_{l-1,j'}) \tilde{P}_i(u_{s-1}, \tau_{il})}{\tilde{P}_i(\tau_{l,1}, S_{il,S_{il}})} \lambda_{ijks} \\
+ & \frac{\tilde{P}_i(\tau_{l,1}, u_{s-1})(S_{l-1,j}) \tilde{P}_i(u_{s}, \tau_{il})}{\tilde{P}_i(\tau_{l,1}, S_{il,S_{il}})} \lambda_{ijks} \exp\left( -\sum_{k' \neq j,k} \lambda_{ij'k's} \right).
\end{align*}
\]

Finally, we approximate the integrals over \( b_i \) using Gaussian-Hermite quadratures.

In the M-step, we update \( \lambda_{ijks} \) by

\[
\frac{\sum_{i=1}^{n} I(u_s \leq \tau_{i,n_i}) \tilde{E}(W_{ijks})}{\sum_{i=1}^{n} I(u_s \leq \tau_{i,n_i}) \tilde{E}\{\exp(\beta^T_{jk}X_{is} + b^T_{is}Z_{is})\}},
\]

for \( (j, k) \in \mathcal{D} \) and \( s = 1, \ldots, m \), where \( \tilde{E}(\cdot) \) denotes the conditional expectation given \( \mathcal{O}_i \).

After plugging in the new \( \lambda_{ijks} \) values into (3), we solve the following score equation for \( \beta_{jk} \ ((j, k) \in \mathcal{D}) \) using the one-step Newton-Raphson method:

\[
\sum_{i=1}^{n} \sum_{s=1}^{m} I(u_s \leq \tau_{i,n_i}) \tilde{E}(W_{ijks}) \left[ X_{is} - \frac{\sum_{i'=1}^{n} I(u_s \leq \tau_{i',n_{i'}}) X_{i'is} \tilde{E}\{\exp(\beta^T_{jk}X_{i'is} + b^T_{i'is}Z_{i'is})\}}{\sum_{i'=1}^{n} I(u_s \leq \tau_{i',n_{i'}}) \tilde{E}\{\exp(\beta^T_{jk}X_{i'is} + b^T_{i'is}Z_{i'is})\}} \right] = 0.
\]
Finally, we update \( \Sigma \) by \( \frac{n}{n-1} \sum_{i=1}^{n} \tilde{E}(b_i \otimes 2) \).

We iterate between the E-step and the M-step until convergence. Denote the resulting estimators of \( \theta \) and \( \Omega \) by \( \hat{\theta} = (\hat{\beta}^T, \hat{\gamma}^T)^T = (\{\hat{\beta}^T_{jk}\}_{(j,k)\in \mathcal{D}}, \hat{\gamma}^T)^T \) and \( \hat{\Omega} = \{\hat{\Lambda}_{jk}\}_{(j,k)\in \mathcal{D}} \).

In the M-step, the jump sizes \( \lambda_{jks} \)'s are updated through explicit expressions, so optimization over a large number of parameters is avoided. When \( n \) and \( m \) are very large, the EM algorithm can be demanding, since it needs to perform matrix multiplication many times. Thus, we provide some strategies to speed up the computation. First, we estimate the jump sizes using Turnbull (1976)'s method and remove those time points with estimates smaller than a threshold of the order \( 1/m \). Second, we set the initial parameter estimates to be the convergent values from the EM algorithm without random effects. Finally, we remove the time points where the jump sizes are smaller than a threshold of the order \( 1/m \). Our experiences showed that all these strategies can significantly reduce the computation time without impairing estimation accuracy.

3 Asymptotic Theory

Let \(|\mathcal{D}|\) denote the cardinality of \( \mathcal{D} \). We establish the asymptotic properties of \( (\hat{\theta}, \hat{\Omega}) \) under the following regularity conditions. We consider a generic subject and omit the subscript \( i \) in all random quantities.

**Condition 1.** The true value of \( \theta \), denoted by \( \theta_0 = (\beta_0^T, \gamma_0^T)^T = (\{\beta_{0,jk}\}_{(j,k)\in \mathcal{D}}, \gamma_0^T)^T \), lies in the interior of a known compact set \( \Theta = \{(\beta^T, \gamma^T)^T : \beta \in \mathcal{B}, \gamma \in \mathcal{C}\} \), where \( \mathcal{B} \) is a compact set in \( \mathbb{R}^{|\mathcal{D}| \times d_1} \), and \( \mathcal{C} \) is a compact set in the domain of \( \gamma \), such that \( \Sigma(\gamma) \) is a positive-definite matrix with eigenvalues bounded away from 0 and \( \infty \). The true value of \( \Omega \), denoted by \( \Omega_0 = \{\Lambda_{0,jk}\}_{(j,k)\in \mathcal{D}} \), is continuously differentiable with positive derivatives in \([0, \tau]\).
Condition 2. With probability one, $X(t)$ and $Z(t)$ are continuously differentiable in $[0, \tau]$. If there exist a deterministic function $a_1(t)$ and a constant vector $a_2$ such that $a_1(t) + a_2^T X(t) = 0$ with probability one, then $a_1(t) = 0$ for $t \in [0, \tau]$ and $a_2 = 0$.

Condition 3. The support of $S_0$ covers all the non-absorbing states among $1, \ldots, K$, where an absorbing state is a state that cannot transition to any other state.

Condition 4. The number of examination times $N$ is positive with $E(N) < \infty$. The conditional probability $\Pr(\tau_N = \tau | N, X, Z)$ is greater than some positive constant $\eta_1$. In addition, with $[0, \tau]$ being the union of the supports of $(\tau_1, \ldots, \tau_N)$, the conditional densities of $(\tau_{l-1}, \tau_l)$ given $(N, X, Z)$, denoted by $f_l(t_1, t_2)$ ($l = 1, \ldots, N$), have continuous second-order partial derivatives with respect to $t_1$ and $t_2$ when $t_2 - t_1 \geq \eta_2$ for some positive constant $\eta_2$, and are continuously differentiable functionals with respect to $X$ and $Z$. Finally, $\Pr\{\min_{1 \leq l \leq N}(\tau_l - \tau_{l-1}) \geq \eta_2 | N, X, Z\} = 1$.

Condition 5. For a pair of parameters $(\theta_1, \Omega_1)$ and $(\theta_2, \Omega_2)$, if

$$
\int_b P(0, t; X, Z, b, \beta_1, \Omega_1) \phi(b; \Sigma(\gamma_1)) db = \int_b P(0, t; X, Z, b, \beta_2, \Omega_2) \phi(b; \Sigma(\gamma_2)) db
$$

with probability one for any $t \in [0, \tau]$, then $\beta_1 = \beta_2$, $\gamma_1 = \gamma_2$, and $\Omega_1(t) = \Omega_2(t)$ for $t \in [0, \tau]$.

Condition 6. If there exist a $K \times K$ matrix-valued function $a_3(t; b)$ and a $d_3$-vector $a_4$ such that

$$
\int_b \left[ \int_0^t P(0, s; X, Z, b, \beta_0, \Omega_0) da_3(s; b) P(s, t; X, Z, b, \beta_0, \Omega_0) 
+ P(0, t; X, Z, b, \beta_0, \Omega_0) a_3^T \frac{\phi'(b; \Sigma(\gamma_0))}{\phi(b; \Sigma(\gamma_0))} \right] \phi(b; \Sigma(\gamma_0)) db = 0
$$

with probability one for any $t \in [0, \tau]$, where $\phi'_{\gamma}$ is the derivative of $\phi(b; \Sigma(\gamma))$ with respect to $\gamma$, then $a_3(t; b) = 0$ for $t \in [0, \tau]$ and $a_4 = 0$. 
Remark 1. Conditions 1 and 2 are standard for regression analysis with time-dependent covariates. Condition 3 assumes that the initial state can be any non-absorbing state, which ensures that all possible transitions can occur during the study. Condition 4 pertains to the joint distribution of the examination times. First, it requires that the largest examination time reaches $\tau$ with positive probability. Second, it requires smoothness of the joint density of the examination times, which is used to prove the Donsker property of some function classes and the smoothness of the least favorable direction. Finally, this condition requires any two successive examination times to be separated by a positive gap; otherwise, transition times may be exactly observed, which calls for a different theoretical treatment. Conditions 5 and 6 ensure the identifiability of the proposed model and the invertibility of the information operator along any submodel under true parameter values. If $X$ and $Z$ are both time-independent, then Conditions 5 and 6 can be replaced by conditions (1) $Z$ is linearly independent, that is, any symmetric matrix $C$ satisfying $Z^T CZ = 0$ with probability one must be a zero matrix. (2) $\Sigma(\gamma_1) = \Sigma(\gamma_2)$ implies $\gamma_1 = \gamma_2$.

We state the strong consistency of $(\hat{\theta}, \hat{\Omega})$ and the limiting distribution of $n^{1/2}(\hat{\theta} - \theta_0)$.

Theorem 1. Under Conditions 1-5, $\|\hat{\theta} - \theta_0\| + \sum_{(j,k) \in D} \|\hat{\Lambda}_{jk} - \Lambda_{0jk}\|_{\infty} \to 0$ almost surely, where $\| \cdot \|$ is the Euclidean norm and $\| \cdot \|_{\infty}$ is the supremum norm over $[0, \tau]$.

Theorem 2. Under Conditions 1-6, $n^{1/2}(\hat{\theta} - \theta_0)$ converges in distribution to a multivariate normal vector with mean zero and covariance matrix that attains the semiparametric efficiency bound.

The proofs of the theorems are provided in the Appendix. The limiting covariance matrix of $\hat{\theta}$ can be consistently estimated through profile likelihood (Murphy and Van der Vaart, 2000). Denote the profile log-likelihood for $\theta$ by $pl_n(\theta) = \max_{\Omega} \log L_n(\theta, \Omega)$, which can be obtained from the above EM algorithm with $\theta$ fixed. Let $pl_{ni}$ denote the $i$th subject’s
contribution to \( p_l \) and \( e_j \) denote the \( j \)th canonical vector of the same dimension as \( \theta \). Then the covariance matrix of \( \hat{\theta} \) can be estimated by the inverse of the matrix whose \((j, k)\)th element is 
\[
\sum_{i=1}^{n} \{ p_{nl}(\hat{\theta} + h_n e_j) - p_{nl}(\hat{\theta}) \} \{ p_{nl}(\hat{\theta} + h_n e_k) - p_{nl}(\hat{\theta}) \} / h_n^2,
\]
where \( h_n \) is some constant of order \( n^{-1/2} \).

## 4 Simulation Studies

We conducted a series of simulation studies with three states, which are numbered 1, 2, and 3. Possible transitions include 1 to 2 and 2 to 3. We generated two time-independent covariates, \( X_1 \sim \text{Ber}(0.5) \) and \( X_2 \sim \text{Unif}(0, 1) \), and random effect \( b \sim N(0, \sigma^2) \) with \( \sigma^2 = 0.8 \). We set \( \Lambda_{12}(t) = \log(1 + 0.3t) \), \( \Lambda_{23}(t) = 0.3t \), \( (\beta_{121}, \beta_{122}) = (0.5, -0.5) \), \( (\beta_{231}, \beta_{232}) = (0.4, 0.2) \), where \( \Lambda_{jk} \) pertains to the transition from \( j \) to \( k \), and \( \beta_{jkl} \) pertains to the transition from \( j \) to \( k \) and the \( l \)th covariate. The initial state of each subject was 1 or 2 with equal probabilities. We generated six potential examination times for each subject, with the first being \( \text{Unif}(0, 1) \), and the gap between any two successive examination times being \( 0.05 + \text{Unif}(0, 1) \). We set the study end time \( \tau = 3 \) and excluded all the examinations beyond \( \tau \). We simulated 10,000 replicates with \( n = 400, 800, \) or \( 1600 \).

We applied all three computational strategies described in Section 2.2. We removed all the time points whose jump sizes were smaller than 0.0001. We set the initial values of \( \beta_{jk} \)'s to 0 and the initial values of \( \lambda_{jks} \)'s to \( 1/m \). In addition, we set the initial value of \( \sigma^2 \) to 1. The convergence criterion was that the maximal change in the parameter estimates at two successive iterations is smaller than 0.0001. For the variance estimation, we set \( h_n = 5n^{-1/2} \), although the results differed only in the third decimal place when \( h_n \) ranged from \( n^{-1/2} \) to \( 10n^{-1/2} \).

For comparisons, we included the \texttt{ msm } package (Jackson, 2011), which fits time-
homogeneous or piecewise homogeneous Markov models. The implementation is via the 
`msm()` function, and the change points are specified in the `pci` argument when piecewise constant transition intensities are assumed. We let the function automatically generate the initial parameter values and used the default settings for maximum likelihood estimation. We placed the change points of the intensities at 0.5, 1, 1.5, 2, and 2.5.

Table 1 summarizes the estimation results on the regression parameters. The EM algorithm converged in all replicates. The biases of the parameter estimators are small and decrease as $n$ increases. The variance estimators are accurate, and the confidence intervals have proper coverage probabilities. The parameter estimators in the `msm` package are severely biased. When $n = 400$, nearly 5% of the replicates failed due to sparse data within some of the pieces.

Figure 1 shows the estimation results on the cumulative transition intensity functions. The median of the proposed estimates is almost identical to the truth, whereas the median of the estimates from `msm` deviates substantially from the truth.

Section S.2 of the supplementary materials reports simulation studies with more complex disease processes. The proposed methods continued to perform well.

5 Application

The ARIC study recruited 15,792 participants aged 45–64 years in 1987–1989 from four communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. All participants received a baseline examination upon enrollment, followed by three examinations conducted approximately every three years between 1990 and 1998, and three further examinations in 2011–2013, 2016–2017, and 2018–2019. At each of the last three examinations, MCI and dementia were
Table 1: Estimation of the regression parameters in the simulation studies with three states.

| Parameter     | Proposed methods | msm package |
|---------------|------------------|-------------|
|               | Bias  SE  SEE CP | Bias  SE  SEE CP |
| \(n = 400\)  |                  |             |
| \(\beta_{121} = 0.5\) | 0.014 0.265 0.259 95.0 | -0.091 0.209 0.207 92.4 |
| \(\beta_{122} = -0.5\) | -0.021 0.458 0.448 94.7 | 0.087 0.363 0.356 94.0 |
| \(\beta_{231} = 0.4\) | 0.013 0.206 0.198 94.5 | -0.078 0.156 0.147 90.4 |
| \(\beta_{232} = 0.2\) | 0.005 0.350 0.339 94.5 | -0.053 0.268 0.254 92.8 |
| \(\sigma^2 = 0.8\) | 0.060 0.422 0.396 95.1 |             |
| \(n = 800\)  |                  |             |
| \(\beta_{121} = 0.5\) | 0.010 0.181 0.181 95.4 | -0.092 0.145 0.146 90.4 |
| \(\beta_{122} = -0.5\) | -0.008 0.315 0.311 95.1 | 0.095 0.253 0.251 93.1 |
| \(\beta_{231} = 0.4\) | 0.007 0.139 0.138 95.3 | -0.079 0.107 0.104 87.4 |
| \(\beta_{232} = 0.2\) | 0.006 0.240 0.236 94.6 | -0.053 0.187 0.179 92.8 |
| \(\sigma^2 = 0.8\) | 0.024 0.270 0.263 95.5 |             |
| \(n = 1600\) |                  |             |
| \(\beta_{121} = 0.5\) | 0.002 0.127 0.126 94.8 | -0.096 0.103 0.103 84.8 |
| \(\beta_{122} = -0.5\) | -0.000 0.217 0.216 95.0 | 0.100 0.176 0.177 91.2 |
| \(\beta_{231} = 0.4\) | 0.000 0.098 0.096 94.9 | -0.080 0.076 0.073 79.7 |
| \(\beta_{232} = 0.2\) | -0.002 0.168 0.164 94.7 | -0.057 0.132 0.126 91.3 |
| \(\sigma^2 = 0.8\) | -0.004 0.181 0.178 95.6 |             |

Note: Bias and SE denote the median bias and empirical standard error, respectively. SEE denotes the median of the standard error estimator, and CP denotes the empirical coverage percentage of the 95% confidence interval. The log transformation was used to construct the confidence interval for \(\sigma^2\). For msm with \(n = 400\), each entry is based on 9,490 replicates. All other entries are based on 10,000 replicates.
Figure 1: Estimation of the cumulative transition intensities in the simulation studies with three states. The solid, dashed, and dotted curves show the true values, the median estimates based on 10,000 replicates using the proposed methods, and the median estimates based on 10,000 replicates (9,490 replicates for $n = 400$) using the \texttt{msm} package, respectively.
assessed from current and longitudinal cognitive tests by a panel of reviewers (4 physicians and 4 neuropsychologists), yielding a syndromic diagnosis such that one of three states: normal, MCI, or dementia was determined at each examination (Knopman et al., 2016). It is unlikely for an individual to return to a less severe state from a more severe cognitive impairment state (e.g., MCI to normal, dementia to MCI).

We considered a three-state progressive model (i.e., normal to MCI to dementia). The transitions between the three states were interval-censored. The time scale for the analysis was years since the baseline examination. We evaluated the effects of the following baseline risk factors on the transitions between the states: age (years), gender (female vs. male), race-center (Forsyth County; Black, Jackson; White, Minneapolis; and White, Washington County), education level (basic or intermediate vs. advanced), diabetes (no vs. yes), cigarette smoking status (non-smoker vs. smoker), body mass index (kg/m$^2$), and systolic blood pressure (mmHg). We included a random intercept to capture the potential dependence between transitions. After removing participants with unknown states at the fifth examination or missing data on risk factors, a total of 6,407 participants remained. The mean follow-up time was 27.5 years and the median was 28.8 years. Table 2 summarizes the frequency that each pair of states was observed over successive examinations. The second, third, and fourth examinations are omitted, because no information about MCI or dementia was collected at those three examinations.

We used the same estimation procedure as in the simulation studies, except that the threshold for jump sizes was set to $10^{-6}$. The number of unique time points was 3,155 in the beginning of the analysis and 147 at the end. The computation time was about two hours on a computer with Windows 10 (2.1 GHz processor, 32 GB RAM, 64-bit). The estimation results on the regression parameters are presented in Table 3. Older people have...
Table 2: Frequency for each pair of states over successive examinations among 6,407 participants in the ARIC study.

| From       | Normal | MCI  | Dementia |
|------------|--------|------|----------|
| Normal     | 8,936  | 2,052| 459      |
| MCI        | 0      | 332  | 136      |
| Dementia   | 0      | 0    | 214      |

significantly higher risk of developing both MCI and dementia, males are more likely to develop MCI, advanced education can significantly reduce the risk of progression from MCI to dementia, people with diabetes have significantly higher risk of MCI, and baseline body mass index and systolic blood pressure are both positively associated with the risk of MCI. The variance of the random intercept was estimated at 0.9282, with estimated standard error of 0.1461, suggesting strong dependence between the transition from normal to MCI and the transition from MCI to dementia.

Figure 2 shows the estimated cumulative transition intensities for subjects with different combinations of education level and diabetes status and with all other covariates set to be the sample medians. The left panel shows that having diabetes considerably increases the risk of MCI. The right panel shows that subjects with an advanced education have much lower risk of dementia than those without advanced education.

Figure 3 shows the estimated transition probabilities from normal and MCI to different states over five-year time intervals, with the covariates equal to the sample medians. Unsurprisingly, the probabilities of progression toward more severe states generally increase...
Table 3: Estimation results on the regression parameters in the ARIC study.

| Covariate                          | Normal to MCI                      | MCI to dementia                  |
|-----------------------------------|------------------------------------|----------------------------------|
|                                   | Estimate  | St error | p-value | Estimate  | St error | p-value |
| Age (years)                       | 0.0892    | 0.0031   | <0.0001 | 0.1110    | 0.0057   | <0.0001 |
| Male                              | 0.3188    | 0.0520   | <0.0001 | 0.1636    | 0.1018   | 0.1080  |
| Advanced education                | −0.1003   | 0.0525   | 0.0561  | −0.6164   | 0.1097   | <0.0001 |
| Diabetes                          | 0.5587    | 0.0994   | <0.0001 | 0.3962    | 0.1651   | 0.0164  |
| Smoker                            | 0.1549    | 0.0661   | 0.0191  | 0.2009    | 0.1355   | 0.1382  |
| Body mass index (kg/m²)           | 0.0213    | 0.0049   | <0.0001 | 0.0164    | 0.0090   | 0.0684  |
| Systolic blood pressure (mmHg)    | 0.0051    | 0.0015   | 0.0007  | 0.0058    | 0.0028   | 0.0383  |
| Black, Jackson                    | −0.0008   | 0.0792   | 0.9919  | 1.4692    | 0.1614   | <0.0001 |
| White, Minneapolis               | −0.2052   | 0.0721   | 0.0044  | 0.4848    | 0.1621   | 0.0028  |
| White, Washington County          | −0.0828   | 0.0722   | 0.2515  | 0.5218    | 0.1593   | 0.0011  |

Note: For each categorical variable, the group not shown is the reference group.
Figure 2: Estimated cumulative transition intensities for subjects with different combinations of education level and diabetes status at baseline in the ARIC study. The black curves pertain to subjects without advanced education, and the red curves pertain to subjects with advanced education. The solid curves pertain to subjects with diabetes, and the dashed curves pertain to subjects without diabetes. The other covariates are set to be the sample medians.
Figure 3: Estimated transition probabilities over five-year time intervals for subjects with median covariate values in the ARIC study.

6 Discussion

We have developed powerful methods for analyzing very general interval-censored multi-state data. Unlike spline-based methods, we estimate the baseline transition intensity functions in a completely nonparametric manner and avoid any tuning parameters. We have established for the first time a rigorous asymptotic theory for the semiparametric estimation of multi-state models under interval censorship. We have shown through extensive simulation studies that the proposed methods outperform the existing methods implemented in the \texttt{msm} package.

Our work contains major innovations. First, the proposed EM algorithm is much more sophisticated and computationally challenging than that of Zeng et al. (2017) because it is necessary to consider all possible transition paths when estimating conditional expec-
tations. No such calculations were required in the case of multivariate interval-censored data. We also provide several strategies to significantly speed up the computation. Second, the presence of product integration poses substantial theoretical challenges, especially in proving the Donsker property of the relevant function classes and in handling the score and information operators. We have addressed these new challenges by using the results on product integration from Andersen et al. (1993).

Our formulation allows for an absorbing state and assumes that the transition time to the absorbing state is interval-censored. Sometimes the absorbing state can be exactly observed (e.g., death). Therefore, an interesting extension of our work is to study a mixture of interval- and right-censored data, where the transition times among the non-absorbing states are interval-censored, and the transition time to the absorbing state is right-censored.

We have only considered routinely scheduled examinations and noninformative loss to follow-up. Inspired by the recent work of Lawless and Cook (2019) and Cook and Lawless (2021), we may extend our work to allow for disease-driven examinations and informative loss to follow-up by jointly modeling the disease process, the recurrent examination process, and the loss to follow-up process. Specifically, we may add loss to follow-up as a new state to the original state space, and we may consider a two-dimensional state space with one component characterizing the disease state and the other component counting the number of examinations. The former is relatively easy, while the latter can be very challenging unless strong assumptions about the transition intensities are made.

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Supplementary Materials

The supplementary materials contain three lemmas and additional simulation results.

Appendix. Proofs of Theorems

The proofs of Theorems 1 and 2 make use of three lemmas, which are stated and proved in Section S.1 of the supplementary materials. We use the notation: \( \mathbb{P}_n \) denotes the empirical measure for \( n \) independent subjects, \( \mathbb{P} \) denotes the true probability measure, and \( G_n = n^{1/2} (\mathbb{P}_n - \mathbb{P}) \) is the corresponding empirical process. Let \( L(\theta, \Omega) \) denote the likelihood function for a single subject

\[
L(\theta, \Omega) = \int_b \prod_{l=1}^N P(\tau_{t-1}, \tau_{t}; b, \beta, \Omega)^{(S_{l-1}, S_l)} \phi(b; \Sigma(\gamma))db,
\]

and let \( \ell(\theta, \Omega) \) denote the corresponding log-likelihood function. For simplicity, we suppress the arguments \( X \) and \( Z \) in any transition probability matrix of the form \( P(t_1, t_2; X, Z, b, \beta, \Omega) \).

Proof of Theorem 1. We first show that \( \lim \sup_n \hat{\Lambda}_{jk}(\tau) < \infty \) with probability one for any \((j, k) \in \mathcal{D}\). By the strong law of large numbers, \((\mathbb{P}_n - \mathbb{P}) \ell(\theta_0, \Omega_0) \to 0 \) almost surely. Then by the definition of the parameter estimators,

\[
\lim_{n} \inf \mathbb{P}_n \ell(\hat{\theta}, \hat{\Omega}) \geq \lim_{n} \inf \mathbb{P}_n \ell(\theta_0, \Omega_0) = \mathbb{P} \ell(\theta_0, \Omega_0)
\]
with probability one. In addition,

\[
\liminf_n \mathbb{P}_n \ell(\hat{\theta}, \hat{\Omega}) = \liminf_n \mathbb{P}_n \log \left[ \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \hat{\beta}, \hat{\Omega})^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\hat{\gamma})) \, db \right] \\
\leq \liminf_n \mathbb{P}_n I(S_0 = S_N) \log \left[ \int_b P(0, \tau_N; b, \hat{\beta}, \hat{\Omega})^{(S_0, S_0)} \phi(b; \Sigma(\hat{\gamma})) \, db \right]
\]

\[
= \liminf_n \mathbb{P}_n I(S_0 = S_N)
\times \log \left[ \int_b \exp \left\{ - \sum_{k: (S_0, k) \in D} \int_0^{\tau_N} \exp \left\{ \beta_{S_0 k}^T X(s) + b^T Z(s) \right\} d\hat{\Lambda}_{S_0 k}(s) \right\} \times \phi(b; \Sigma(\hat{\gamma})) \, db \right]
\]

\[
\leq \liminf_n \mathbb{P}_n I(S_0 = S_N, \tau_N = \tau)
\times \log \left[ \int_b \exp \left\{ - \sum_{(S_0, k) \in D} \exp (-M - M\|b\|) \hat{\Lambda}_{S_0 k}(\tau) \right\} \times \phi(b; \Sigma(\hat{\gamma})) \, db \right],
\]

where \( M = \sup_{t \in [0, t]} \left\{ \sup_{X, \beta, \gamma} |\beta_{j k}^T X(t)| + \sup_{Z} |Z(t)| \right\} \) and is finite under Condition 2.

Since for any \( x > 0, e^{-x} \leq x^{-1} \), \( \liminf_n \mathbb{P}_n \ell(\hat{\theta}, \hat{\Omega}) \) can be further bounded from above by

\[
\liminf_n \mathbb{P}_n I(S_0 = S_N, \tau_N = \tau)
\times \log \left[ \int_b \exp \left\{ -M - M\|b\| \right\} \times \sum_{(S_0, k) \in D} \hat{\Lambda}_{S_0 k}(\tau) \right]^{-1} \times \phi(b; \Sigma(\hat{\gamma})) \, db
\]

\[
\leq \liminf_n \mathbb{P}_n I(S_0 = S_N, \tau_N = \tau) \left[ C(M) - \log \left\{ \sum_{(S_0, k) \in D} \hat{\Lambda}_{S_0 k}(\tau) \right\} \right],
\]

where \( C(M) \) is a deterministic function of \( M \). Under Condition 4, \( \lim_n \mathbb{P}_n I(S_0 = S_N, \tau_N = \tau) = \text{Pr}(S_0 = S_N, \tau_N = \tau) > 0 \), such that

\[
\limsup_n \log \left\{ \sum_{(S_0, k) \in D} \hat{\Lambda}_{S_0 k}(\tau) \right\} \leq C(M) - O(1) \times \mathbb{P}(\theta_0, \Omega_0) < \infty
\]

with probability one. Since \( S_0 \) can take an arbitrary value in \( \{1, \ldots, K \} \) under Condition 3,
the above inequality implies that \( \limsup_n \Lambda_{jk}(\tau) \leq w < \infty \) with probability one for some positive finite constant \( w \) and any \((j, k) \in D \).

We have shown that each component of \( \hat{\Omega} \) has bounded total variation in \([0, \tau]\). By Helly’s selection lemma, for any subsequence of \((\hat{\theta}, \hat{\Omega})\), we can choose a further subsequence such that \( \hat{\Omega} \) converges to \( \Omega^* \) pointwise in \([0, \tau]\), and that \( \hat{\theta} = (\hat{\beta}, \hat{\gamma}) \) converges to \( \theta^* = (\beta^*, \gamma^*) \). Next, we will show that \((\theta^*, \Omega^*) = (\theta_0, \Omega_0)\). Define the function

\[
m(\theta, \Omega) = \log \left\{ \frac{L(\theta, \Omega) + L(\theta_0, \Omega_0)}{2} \right\}
\]

and class

\[
\mathcal{M} = \{m(\theta, \Omega) : \theta \in \Theta, \Omega \in \mathcal{L}_w\},
\]

where \( \mathcal{L}_w \) is the set of \(|D|\)-dimensional non-decreasing functions \( \{\Lambda_{jk}\}_{(j, k) \in D} \) whose total variations in \([0, \tau]\) are bounded by \( w \), with \( \Lambda_{jk}(0) = 0 \). By the concavity of the log function,

\[
\mathbb{P}_n m(\hat{\theta}, \hat{\Omega}) \geq \mathbb{P}_n \frac{\ell(\hat{\theta}, \hat{\Omega}) + \ell(\theta_0, \Omega_0)}{2} \geq \mathbb{P}_n \ell(\theta_0, \Omega_0) = \mathbb{P}_n m(\theta_0, \Omega_0),
\]

which implies

\[
(\mathbb{P}_n - \mathbb{P})m(\hat{\theta}, \hat{\Omega}) + \mathbb{P}m(\hat{\theta}, \hat{\Omega}) \geq (\mathbb{P}_n - \mathbb{P})m(\theta_0, \Omega_0) + \mathbb{P}m(\theta_0, \Omega_0).
\]

We show in Lemma S.1 that \( \mathcal{M} \) is a Donsker class, and we have verified that \( m(\hat{\theta}, \hat{\Omega}) \in \mathcal{M} \).

Thus, \((\mathbb{P}_n - \mathbb{P})m(\hat{\theta}, \hat{\Omega}) \rightarrow 0 \) almost surely. In addition, \((\mathbb{P}_n - \mathbb{P})m(\theta_0, \Omega_0) = (\mathbb{P}_n - \mathbb{P})\ell(\theta_0, \Omega_0) \rightarrow 0 \) almost surely. Because \( \left| \prod_{l=1}^{N} P(\tau_{l-1}, \tau_l; b, \beta, \Omega)^{(S_{l-1}, S_l)} \right| < 1 \) for any \( \beta \in \mathcal{B} \) and \( \Omega \in \mathcal{L}_w \) with probability one, we conclude that with respect to the probability measure for \((\tau_1, \ldots, \tau_N)\),

\[
\int_{\mathcal{B}} \left\{ \prod_{l=1}^{N} P(\tau_{l-1}, \tau_l; b, \beta^*, \hat{\Omega})^{(S_{l-1}, S_l)} - \prod_{l=1}^{N} P(\tau_{l-1}, \tau_l; b, \beta^*, \Omega^*)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma^*))db \rightarrow 0.
\]

By the dominated convergence theorem and the fact that \( L(\theta, \Omega) + L(\theta_0, \Omega_0) \) is bounded away from zero for any \( \theta \in \Theta \) and \( \Omega \in \mathcal{L}_w \),

\[
\left| \mathbb{P}m(\hat{\theta}, \hat{\Omega}) - \mathbb{P}m(\theta^*, \Omega^*) \right|
\]
\[
P_m(\hat{\theta}, \hat{\Omega}) - P_m(\theta^*, \hat{\Omega}) + P_m(\theta^*, \hat{\Omega}) - P_m(\theta^*, \Omega^*)
\leq O(\|\hat{\theta} - \theta^*\|) + P \log \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta, \hat{\Omega})^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma^*)) db + L(\theta_0, \Omega_0)
\]
\[
= \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta^*, \Omega^*)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma^*)) db + L(\theta_0, \Omega_0)
\]
\[
\rightarrow 0.
\]

Thus, \(P_m(\hat{\theta}, \hat{\Omega}) \rightarrow P_m(\theta^*, \Omega^*)\) almost surely. Now we can take the limits on both sides of (4) and finally obtain \(P_m(\theta^*, \Omega^*) \geq P_m(\theta_0, \Omega_0)\). By the properties of the Kullback-Leibler information, \(L(\theta^*, \Omega^*) = L(\theta_0, \Omega_0)\) with probability one. Therefore,

\[
\int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta^*, \Omega^*)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma^*)) db
\]
\[
= \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma_0)) db.
\]

For any fixed sequence of monitoring times \(0 = \tau_0 < \tau_1 < \cdots < \tau_N \leq \tau\), and any feasible start and end states \((S_0, S_N)\), we let \((S_1, S_2, \ldots, S_{N-1})\) go over all possible combinations.

Then the summation of the resulting equations yields

\[
\int_b \left\{ \sum_{(S_1, \ldots, S_{N-1})} \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta^*, \Omega^*)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma^*)) db
\]
\[
= \int_b \left\{ \sum_{(S_1, \ldots, S_{N-1})} \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma_0)) db,
\]

which implies

\[
\int_b P(0, \tau_N; b, \beta^*, \Omega^*)^{(S_0, S_N)} \phi(b; \Sigma(\gamma^*)) db = \int_b P(0, \tau_N; b, \beta_0, \Omega_0)^{(S_0, S_N)} \phi(b; \Sigma(\gamma_0)) db.
\]

The above equation holds for any \(\tau_N \in [0, \tau]\) and any feasible \((S_0, S_N)\), which covers the whole set \(D\) under Condition 3. Thus, for any \(t \in [0, \tau]\),

\[
\int_b P(0, t; b, \beta^*, \Omega^*) \phi(b; \Sigma(\gamma^*)) db = \int_b P(0, t; b, \beta_0, \Omega_0) \phi(b; \Sigma(\gamma_0)) db.
\]
with probability one. By the identifiability in Condition 5, \( \beta^* = \beta_0, \gamma^* = \gamma_0 \), and \( \Omega^*(t) = \Omega_0(t) \) for \( t \in [0, \tau] \). The continuity of \( \Omega_0(t) \) further implies \( \|\hat{\theta} - \theta_0\| + \sum_{(j,k) \in D} \|\hat{\Lambda}_{jk} - \Lambda_{0jk}\|_\infty \to 0 \) almost surely.

\[ \mathbb{P}_n\{\ell_\theta(\hat{\theta}, \hat{\Omega}) = 0\} = 1 \text{ and } \mathbb{P}_n\{\ell_\Omega(\hat{\theta}, \hat{\Omega}) = 0\} = 1.\]
In addition, $\mathbb{P}\{\ell_\theta(\theta_0, \Omega_0)\} = 0$ and $\mathbb{P}\{\ell_\Omega(\theta_0, \Omega_0)(h)\} = 0$. Hence,

$$
\mathbb{G}_n\{\ell_\theta(\hat{\theta}, \hat{\Omega})\} = -n^{1/2} \left[ \mathbb{P}\{\ell_\theta(\hat{\theta}, \hat{\Omega})\} - \mathbb{P}\{\ell_\theta(\theta_0, \Omega_0)\} \right],
$$

$$
\mathbb{G}_n\{\ell_\Omega(\hat{\theta}, \hat{\Omega})(h)\} = -n^{1/2} \left[ \mathbb{P}\{\ell_\Omega(\hat{\theta}, \hat{\Omega})(h)\} - \mathbb{P}\{\ell_\Omega(\theta_0, \Omega_0)(h)\} \right].
$$

We apply Taylor expansion at $(\theta_0, \Omega_0)$ to the right-hand sides of the above two equations.

By Lemma S.2, the second-order terms are bounded by

$$
n^{1/2} \left\{ O(1) E \left[ \sum_{(j,k) \in \mathcal{D}} \sum_{l=1}^N \left\{ \hat{\Lambda}_{jk}(\tau_l) - \Lambda_{0jk}(\tau_l) \right\}^2 \right] + O(1) \| \hat{\beta} - \beta_0 \|^2 + O(1) \| \hat{\gamma} - \gamma_0 \|^2 \right\}
$$

$$
\leq n^{1/2} \left\{ O_p \left( n^{-2/3} \right) + O_p \left( \| \hat{\beta} - \beta_0 \|^2 + \| \hat{\gamma} - \gamma_0 \|^2 \right) \right\}
$$

$$
= O_p \left( n^{1/2} \| \hat{\beta} - \beta_0 \|^2 + n^{1/2} \| \hat{\gamma} - \gamma_0 \|^2 + n^{-1/6} \right).
$$

Therefore,

$$
\mathbb{G}_n\{\ell_\theta(\hat{\theta}, \hat{\Omega})\} = -n^{1/2} \mathbb{P}\{\ell_\theta(\hat{\theta} - \theta_0) + \ell_\theta(\hat{\Omega} - \Omega_0)\}
$$

$$
+ O_p \left( n^{1/2} \| \hat{\beta} - \beta_0 \|^2 + n^{1/2} \| \hat{\gamma} - \gamma_0 \|^2 + n^{-1/6} \right),
$$

$$
\mathbb{G}_n\{\ell_\Omega(\hat{\theta}, \hat{\Omega})(h)\} = -n^{1/2} \mathbb{P}\{\ell_\Omega(h)(\hat{\theta} - \theta_0) + \ell_\Omega(\hat{\Omega} - \Omega_0)\}
$$

$$
+ O_p \left( n^{1/2} \| \hat{\beta} - \beta_0 \|^2 + n^{1/2} \| \hat{\gamma} - \gamma_0 \|^2 + n^{-1/6} \right),
$$

where $\ell_\theta$ is the second derivative of $\ell(\theta, \Omega)$ with respect to $\theta$, $\ell_\theta(\theta, \Omega)$ is the derivative of $\ell_\theta$ along the submodel $d\Omega_{\epsilon, h}$, $\ell_\Omega(\theta)$ is the derivative of $\ell_\Omega(h)$ with respect to $\theta$, and $\ell_\Omega(h, \hat{\Omega} - \Omega_0)$ is the derivative of $\ell_\Omega(h)$ along the submodel $d\Omega_0 + \epsilon d(\hat{\Omega} - \Omega_0) = \{d\Lambda_{0jk} + \epsilon d(\hat{\Lambda}_{jk} - \Lambda_{0jk})\}_{(j,k) \in \mathcal{D}}$. All the derivatives are evaluated at $(\theta_0, \Omega_0)$.

Let $\ell_\Omega^\star : L_2(\mathbb{P}) \to \mathcal{H}$ be the adjoint operator of $\ell_\Omega$. We define $h^\star$ to be the least favorable direction such that $\ell_\Omega^\star \ell_\Omega(h^\star) = \ell_\Omega^\star \ell_\theta$. Lemma S.3 establishes the existence of $h^\star$. Note that $h^\star$ is a $(|\mathcal{D}| \times d_1 + d_3)$-dimensional vector of functions in $\mathcal{H}$. Thus,

$$
E\{\ell_\Omega(h^\star, \hat{\Omega} - \Omega_0)\} = -E \left\{ \ell_\Omega(h^\star) \ell_\Omega(\hat{\Omega} - \Omega_0) \right\}
$$
\[\begin{align*}
= - \int \ell_\Omega \ell_\Omega(h^*)(d\hat{\Omega} - d\Omega_0) = - \int \ell_\Omega \ell_\theta(d\hat{\Omega} - d\Omega_0)\\
= - E \left\{ \ell_\theta \ell_\Omega(\hat{\Omega} - \Omega_0) \right\} = E \left\{ \ell_\theta \ell_\Omega(\hat{\Omega} - \Omega_0) \right\},
\end{align*}\]

so the difference between (5) and (6) yields

\[\mathbb{G}_n \left\{ \ell_\theta(\hat{\theta}, \hat{\Omega}) - \ell_\Omega(\hat{\theta}, \hat{\Omega})(h^*) \right\} = n^{1/2} E \left[ \{\ell_\theta - \ell_\Omega(h^*)\}^\otimes 2 \right] (\hat{\theta} - \theta_0) + O_p \left( n^{1/2} \|\hat{\beta}_0 - \beta_0\|^2 + n^{1/2} \|\hat{\gamma}_0 - \gamma_0\|^2 + n^{-1/6} \right).\]

By Lemma S.3, the above equation entails that \(n^{1/2}(\hat{\theta} - \theta_0) = O_p(1)\) and yields

\[n^{1/2}(\hat{\theta} - \theta_0) = \left( E \left[ \{\ell_\theta - \ell_\Omega(h^*)\}^\otimes 2 \right] \right)^{-1} \mathbb{G}_n \left\{ \ell_\theta - \ell_\Omega(h^*) \right\} + o_p(1).\]

This implies that the influence function for \(\hat{\theta}\) is exactly the efficient influence function, such that \(n^{1/2}(\hat{\theta} - \theta_0)\) converges weakly to a zero-mean multivariate normal vector whose covariance matrix attains the semiparametric efficiency bound (Bickel et al., 1993).

\[\square\]

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Supplementary Materials for “Maximum Likelihood Estimation for Semiparametric Regression Models with Multi-State Interval-Censored Data”

Yu Gu, Donglin Zeng, Gerardo Heiss, and D. Y. Lin

S.1 Some Useful Lemmas

Lemma S.1. Under Conditions 1-5, the class $\mathcal{M}$ is Donsker.

Proof. Let

$$M = \sup_{t \in [0, \tau]} \left\{ \sup_{X, \beta_{jk}} |\beta_{jk}^T X(t)| + \sup_{Z} |Z(t)| \right\},$$

$$M' = \sup_{t \in [0, \tau]} \left\{ \sup_{X, \beta_{jk}} |\beta_{jk}^T X'(t)| + \sup_{Z} |Z'(t)| \right\},$$

both of which are finite under Condition 2. Again, we suppress the arguments $X$ and $Z$ in any cumulative transition intensity matrix of the form $A(t; X, Z, b, \beta, \Omega)$. For any $\theta_1, \theta_2 \in \Theta$, $\Omega_1, \Omega_2 \in \mathcal{L}_w$, and $(t_1, t_2] \subset [0, \tau]$, we denote $A(t; b, \beta_i, \Omega_i)$ by $A_i(t; b)$, and denote $P(t_1, t_2; b, \beta_i, \Omega_i)$ by $P_i(t_1, t_2; b)$, $i = 1, 2$. For any $m \times n$ matrix $B$ with elements $B_{ij}$, we define its norm as $\|B\|_1 = \sum_{i=1}^m \sum_{j=1}^n |B_{ij}|$. Since $A(t; b, \beta, \Omega)$ has zero row sums by
\[ \| A_1(t; b) - A_2(t; b) \|_1 \leq 2 \sum_{(j,k) \in D} \int_0^t \left| \exp \{ \beta_{1jk}^T X(s) + b^T Z(s) \} - \exp \{ \beta_{2jk}^T X(s) + b^T Z(s) \} \right| d\Lambda_{1jk}(s) \]

\[ = 2 \sum_{(j,k) \in D} \int_0^t \exp \{ \beta_{1jk}^T X(s) + b^T Z(s) \} d\Lambda_{1jk}(s) \]
\[ + \exp \{ \beta_{2jk}^T X(t) + b^T Z(t) \} \times | \Lambda_{1jk}(t) - \Lambda_{2jk}(t) | \]
\[ + \int_0^t | \Lambda_{1jk}(s) - \Lambda_{2jk}(s) | \times \left| \frac{d}{ds} \exp \{ \beta_{2jk}^T X(s) + b^T Z(s) \} \right| ds \]
\[ \leq 2 \sum_{(j,k) \in D} \left\{ e^{M\|b\|} \times C_0 \| \beta_{1jk} - \beta_{2jk} \| + e^{M+M\|b\|} \times | \Lambda_{1jk}(t) - \Lambda_{2jk}(t) | \right\} \]
\[ + e^{M+M\|b\|} (M' + M'\|b\|) \times \| \Lambda_{1jk} - \Lambda_{2jk} \|_{L_1} \]
\[ \leq e^{C_1+C_2\|b\|} \sum_{(j,k) \in D} \left\{ \| \beta_{1jk} - \beta_{2jk} \| + | \Lambda_{1jk}(t) - \Lambda_{2jk}(t) | + \| \Lambda_{1jk} - \Lambda_{2jk} \|_{L_1} \right\}, \]

where \( C_0, C_1, \) and \( C_2 \) are some positive constants, and \( \| \cdot \|_{L_r} \) denotes the \( L_r \)-norm with respect to the Lebesgue measure in \([0, \tau]\) for any \( r \geq 1 \).

For any \((j, k) \in D\), by applying Duhamel's equation in Theorem II.6.2 of Andersen et al. (1993) and the integration by parts formula,

\[ \left| P_1(t_1, t_2; b)^{\langle j, k \rangle} - P_2(t_1, t_2; b)^{\langle j, k \rangle} \right| \]
\[ = \left| \left\{ \int_{t_1}^{t_2} P_1(t_1, t; b) \left[ dA_1(t; b) - dA_2(t; b) \right] P_2(t, t_2; b) \right\}^{\langle j, k \rangle} \right| \]
\[ \leq \left| \left\{ P_1(t_1, t_2; b) [A_1(t_2; b) - A_2(t_2; b)] - [A_1(t_1; b) - A_2(t_1; b)] P_2(t_1, t_2; b) \right\}^{\langle j, k \rangle} \right| \]
\[ + \left| \left\{ \int_{t_1}^{t_2} P_1(t_1, dt; b) \left[ A_1(t; b) - A_2(t; b) \right] P_2(t, t_2; b) \right\}^{\langle j, k \rangle} \right| \]
\[ + \left| \left\{ \int_{t_1}^{t_2} P_1(t_1, t; b) \left[ A_1(t; b) - A_2(t; b) \right] P_2(dt, t_2; b) \right\}^{\langle j, k \rangle} \right|, \]
where the differentials of the transition probability matrices are calculated by

\[
P_1(t_1, dt; b) = P_1(t_1, t + dt; b) - P_1(t_1, t; b)
= P_1(t_1, t; b) \times [P_1(t, t + dt; b) - I]
= P_1(t_1, t; b)dA_1(t; b),
\]

\[
P_2(dt, t_2; b) = P_2(t + dt, t_2; b) - P_2(t, t_2; b)
= [I - P_2(t, t + dt; b)] \times P_2(t + dt, t_2; b)
= - dA_2(t; b)P_2(t+, t_2; b).
\]

Since any transition probability matrix has all elements no larger than 1,

\[
|P_1(t_1, t_2; b)^{(j,k)} - P_2(t_1, t_2; b)^{(j,k)}| \\
\leq \|A_1(t_2; b) - A_2(t_2; b)\|_1 + \|A_1(t_1; b) - A_2(t_1; b)\|_1 \\
+ \int_{t_1}^{t_2} \|dA_1(t; b)\|_1 \times \|A_1(t; b) - A_2(t; b)\|_1 \\
+ \int_{t_1}^{t_2} \|A_1(t; b) - A_2(t; b)\|_1 \times \|dA_2(t; b)\|_1.
\]

We use \(Q_{ijk}\) to denote the probability measure generated by \(\Lambda_{ijk}(t)\), for \(i = 1, 2\) and \((j, k) \in D\), and use \(\|\cdot\|_{L_r(Q)}\) to denote the \(L_r(Q)\)-norm \(\|f\|_{L_r(Q)} = (\int |f|^r dQ)^{1/r}\), for any probability measure \(Q\) and \(r \geq 1\). By plugging in the upper bound for \(\|A_1(t; b) - A_2(t; b)\|_1\) in (S1) into the last two integrals in the above inequality, we obtain

\[
\int_{t_1}^{t_2} \|dA_1(t; b)\|_1 \times \|A_1(t; b) - A_2(t; b)\|_1 \\
= 2 \sum_{(j, k) \in D} \int_{t_1}^{t_2} \|A_1(t; b) - A_2(t; b)\|_1 \times \exp\left\{\beta_{1jk}^T X(t) + b^T Z(t)\right\} d\Lambda_{ijk}(t) \\
\leq 2e^{M+M\|b\|} \sum_{(j, k) \in D} \int_{t_1}^{t_2} \|A_1(t; b) - A_2(t; b)\|_1 d\Lambda_{ijk}(t) \\
\leq e^{C_3+C_4\|b\|} \sum_{(j, k), (l, r) \in D} \left\{\|\beta_{1lr} - \beta_{2lr}\|_1 + \int_{t_1}^{t_2} |\Lambda_{1lr}(t) - \Lambda_{2lr}(t)| d\Lambda_{ijk}(t) + \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1}\right\}
\]
\[
\leq e^{C_5+C_6\|b\|} \sum_{(j,k), (l,r) \in D} \left\{ \|\beta_{1lr} - \beta_{2lr}\| + \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1(Q_{1jk})} + \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1} \right\}.
\]

Likewise,
\[
\int_{t_1}^{t_2} \|A_1(t; b) - A_2(t; b)\|_1 \times \|dA_2(t; b)\|_1 \\
\leq e^{C_7+C_6\|b\|} \sum_{(l,r) \in D} \left\{ \|\beta_{1lr} - \beta_{2lr}\| + \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1(Q_{2lr})} + \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1} \right\}.
\]

where \(C_3, C_4, C_5,\) and \(C_6\) are some positive constants. Therefore, there exist some positive constants \(C_7\) and \(C_8,\) such that
\[
|P_1(t_1, t_2; b)^{(j,k)} - P_2(t_1, t_2; b)^{(j,k)}| \\
\leq e^{C_7+C_6\|b\|} \sum_{(l,r) \in D} \left\{ \|\beta_{1lr} - \beta_{2lr}\| + \|\Lambda_{1lr}(t_1) - \Lambda_{2lr}(t_1)\| + \|\Lambda_{1lr}(t_2) - \Lambda_{2lr}(t_2)\| \\
+ \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1} + \sum_{(l',r') \in D} \left\{ \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1(Q_{1l'r'})} + \|\Lambda_{1lr} - \Lambda_{2lr}\|_{L_1(Q_{2l'r'})} \right\} \right\}.
\]

It then follows from the mean-value theorem that
\[
\left| \prod_{l=1}^N P_1(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} - \prod_{l=1}^N P_2(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} \right| \\
\leq \sum_{l=1}^N \left| P_1(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} - P_2(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} \right| \\
\leq e^{C_9+C_{10}\|b\|} \sum_{(j,k) \in D} \left\{ \|\beta_{1jk} - \beta_{2jk}\| + \|\Lambda_{1jk} - \Lambda_{2jk}\|_{L_1(\mu_1)} \right\}
\]

for some positive constants \(C_9\) and \(C_{10}\) and some finite positive measure \(\mu_1.\) Thus, the difference between two likelihood functions is
\[
|L(\theta_1, \Omega_1) - L(\theta_2, \Omega_2)| \\
\leq \int_b \left| \prod_{l=1}^N P_1(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} - \prod_{l=1}^N P_2(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} \right| \phi(b; \Sigma(\gamma_1)) db \\
+ \int_b \left| \prod_{l=1}^N P_2(\tau_{l-1}, \tau_l; b)^{(S_{l-1}, S_l)} \times |\phi(b; \Sigma(\gamma_1)) - \phi(b; \Sigma(\gamma_2))| \right| db
\]
\[
\leq O(1) \left[ \sum_{(j,k) \in D} \left\{ \| \beta_{1jk} - \beta_{2jk} \| + \| \Lambda_{1jk} - \Lambda_{2jk} \|_{L_1(\mu_1)} \right\} + \| \gamma_1 - \gamma_2 \| \right]
\]
\[
\leq O(1) \left\{ \| \theta_1 - \theta_2 \| + \sum_{(j,k) \in D} \| \Lambda_{1jk} - \Lambda_{2jk} \|_{L_1(\mu_1)} \right\},
\]
so
\[
\| L(\theta_1, \Omega_1) - L(\theta_2, \Omega_2) \|_{L_2(P)}^2 \leq O(1) \left\{ \| \theta_1 - \theta_2 \|^2 + \sum_{(j,k) \in D} \| \Lambda_{1jk} - \Lambda_{2jk} \|^2_{L_2(\mu_2)} \right\},
\]
for some finite positive measure \( \mu_2 \).

Let \( d \) be the dimension of \( \Theta \), which is equal to \( |D| \times d_1 + d_3 \). There are at most \( O(\epsilon^{-d}) \) \( \epsilon \)-brackets covering \( \Theta \), with respect to the Euclidean norm. Since each component of \( L_w \) consists of functions with bounded total variations in \( [0, \tau] \), Lemma 2.2 of van de Geer (2000) entails that the bracketing entropy of \( L_w \) satisfies \( \log N[\epsilon,L_w,L_2(\mu_2)] \lesssim \epsilon^{-1} \), where \( x \lesssim y \) means that \( x \leq cy \) for a positive constant \( c \). Thus, there are a total of \( \exp\{O(\epsilon^{-1})\} \times O(\epsilon^{-d}) \) brackets \( [\theta_1, \theta_2] \times [\Omega_1, \Omega_2] \) covering \( \Theta \times L_w \), such that
\[
\| L(\theta_1, \Omega_1) - L(\theta_2, \Omega_2) \|_{L_2(P)}^2 < O(\epsilon).
\]
Hence, the class of functions \( \{ L(\theta, \Omega) : (\theta, \Omega) \in \Theta \times L_w \} \) is Donsker. Since \( L(\theta_0, \Omega_0) \) is bounded away from zero, the preservation of the Donsker property under Lipschitz transformations implies that the class \( \mathcal{M} \) is also Donsker. \( \square \)

**Lemma S.2.** Under Conditions 1-6,
\[
E \left[ \sum_{(j,k) \in D} \sum_{l=1}^N \left\{ \hat{\Lambda}_{jk}(\tau_l) - \Lambda_{0jk}(\tau_l) \right\}^2 \right] = O_p(n^{-2/3}) + O \left( \| \hat{\beta} - \beta_0 \|^2 + \| \hat{\gamma} - \gamma_0 \|^2 \right).
\]

**Proof.** We have shown in Theorem 1 that \( \hat{\Omega} \in L_w \) and \( m(\hat{\theta}, \hat{\Omega}) \in \mathcal{M} \). Define
\[
J(\delta) = \int_0^\delta \sqrt{1 + \log N[\epsilon, \mathcal{M}, L_2(P)]} \, d\epsilon.
\]
It is easy to show that $J(\delta) \leq O(\sqrt{\delta})$. By Lemma 1.3 of van de Geer (2000) and the mean value theorem,

$$
\mathbb{P}\{m(\theta, \Omega) - m(\theta_0, \Omega_0)\} \lesssim -H^2 \{(\theta, \Omega), (\theta_0, \Omega_0)\},
$$

where $H \{(\theta, \Omega), (\theta_0, \Omega_0)\}$ is the Hellinger distance

$$
H \{(\theta, \Omega), (\theta_0, \Omega_0)\} = \left\{ \int \left[ \sqrt{L(\theta, \Omega)} - \sqrt{L(\theta_0, \Omega_0)} \right]^2 d\mu \right\}^{1/2}
$$

with respect to the dominating measure $\mu$.

The above results, together with the fact that $\widehat{(\theta, \Omega)}$ maximizes $\mathbb{P}_n m(\theta, \Omega)$ and the consistency result in Theorem 1, imply that all conditions in Theorem 3.4.1 of van der Vaart and Wellner (1996) hold. Therefore, $H \{(\widehat{\theta}, \widehat{\Omega}), (\theta_0, \Omega_0)\} = O_p(r_n^{-1})$, where $r_n$ satisfies $r_n^2 J(r_n^{-1}) \lesssim \sqrt{n}$. In particular, we choose $r_n$ in the order of $n^{1/3}$ such that

$$
H \{(\widehat{\theta}, \widehat{\Omega}), (\theta_0, \Omega_0)\} = O_p(n^{-1/3}).
$$

By the mean value theorem,

$$
E \left[ \left( \int b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \widehat{\beta}, \widehat{\Omega})^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\widehat{\gamma})) \right] db
- \int b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma(\gamma_0)) \right] db
\right)^2
= O_p(n^{-2/3}).
$$

Let $\Sigma_0 = \Sigma(\gamma_0)$. By the mean value theorem and Proposition II.8.7 in Andersen et al. (1993),

$$
O_p(n^{-2/3}) + O(1)\|\widehat{\beta} - \beta_0\|^2 + O(1)\|\widehat{\gamma} - \gamma_0\|^2
\geq E \left[ \left( \int b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \widehat{\Omega})^{(S_{l-1}, S_l)} \right\} - \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma_0) \right] db
\right)^2
$$

$$
\geq C_1 E \left[ \sum_{l=1}^N \int b \left\{ \prod_{l' \neq l} P(\tau_{l'-1}, \tau_{l'}; b, \beta_0, \Omega_0)^{(S_{l'-1}, S_{l'})} \right\}
\times \left\{ \int_{\tau_{l-1}}^{\tau_l} P(\tau_{l-1}, t; b, \beta_0, \Omega_0) dA(t; b, \beta_0, \widehat{\Omega} - \Omega_0) P(t, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \phi(b; \Sigma_0) \right\} \right] db
\right)^2
$$
for some positive constant $C_1$. Define the metric space

$$\mathcal{V} = \{ g = \{ g_{jk} \}_{(j,k) \in \mathcal{D}} : \| g_{jk} \|_{L_2(P)} < \infty, g_{jk}(0) = 0 \}$$

and the norm

$$\| g \|_1 = \left\{ E \left[ \sum_{(j,k) \in \mathcal{D}} \sum_{l=1}^{N} g_{jk}(\tau_l)^2 \right] \right\}^{1/2}.$$ 

The space $(\mathcal{V}, \| \cdot \|_1)$ is a Banach space. In addition, we define the seminorm

$$\| g \|_2 = \left\{ E \left[ \left( \sum_{(j,k) \in \mathcal{D}} \left\{ R_{ijk}(\tau_l) g_{jk}(\tau_l) - \int_0^{\tau_l} g_{jk}(t) dR_{ijk}(t) \right\}^2 \right) \right] \right\}^{1/2},$$

where

$$R_{ijk}(t) = \int_b \left\{ \prod_{l' \neq l} P(\tau_{l-1}, \tau_{l'}; b, \beta_0, \Omega_0)^{(S_{l'-1}, S_{l'})} \right\}$$

$$\times P(\tau_{l-1}, t; b, \beta_0, \Omega_0)^{(S_{l-1}, j)} \exp \{ \beta_{0jk}^T X(t) + b^T Z(t) \}$$

$$\times \left[ P(t, \tau_l; b, \beta_0, \Omega_0)^{(k, S_l)} - P(t, \tau_l; b, \beta_0, \Omega_0)^{(j, S_l)} \right]$$

$$\times I(\tau_{l-1} < t \leq \tau_l) \phi(b; \Sigma_0) db$$

for any $l \in \{1, \ldots, N\}$, $(j, k) \in \mathcal{D}$, and $t \in [0, \tau]$. If $\| g \|_2 = 0$ for some $g \in \mathcal{V}$, then with probability one,

$$\sum_{l=1}^{N} \sum_{(j,k) \in \mathcal{D}} \left\{ R_{ijk}(\tau_l) g_{jk}(\tau_l) - \int_0^{\tau_l} g_{jk}(t) dR_{ijk}(t) \right\} = 0,$$

which implies that $g_{jk}$ has bounded total variation over $[0, \tau]$. Thus, the above equation can be written as

$$0 = \sum_{l=1}^{N} \sum_{(j,k) \in \mathcal{D}} \int_{\tau_{l-1}}^{\tau_l} R_{ijk}(t) dg_{jk}(t)$$

$$= \sum_{l=1}^{N} \int_b \left\{ \prod_{l' \neq l} P(\tau_{l-1}, \tau_{l'}; b, \beta_0, \Omega_0)^{(S_{l'-1}, S_{l'})} \right\}$$

$$\times \left\{ \int_{\tau_{l-1}}^{\tau_l} P(\tau_{l-1}, t; b, \beta_0, \Omega_0) dA(t; b, \beta_0, g) P(t, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \phi(b; \Sigma_0) db \right\}^{(S_{l-1}, S_l)} \phi(b; \Sigma_0) db$$
\[\lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0 + \epsilon g)^{(S_{l-1}, S_l)} - \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma_0) db.\]

We evaluate the above equation at all possible \((S_1, S_2, \ldots, S_{N-1})\) given the start and end states \((S_0, S_N)\). Taking the sum of the resulting equations yields

\[\lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left\{ P(0, \tau_N; b, \beta_0, \Omega_0 + \epsilon g)^{(S_0, S_N)} - P(0, \tau_N; b, \beta_0, \Omega_0)^{(S_0, S_N)} \right\} \phi(b; \Sigma_0) db = 0.\]

The above equation holds for any arbitrary \(\tau_N\) and feasible \((S_0, S_N)\), which covers the whole set \(D\) under Condition 3. Thus, for any \(t \in [0, \tau]\),

\[0 = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left[ P(0, t; b, \beta_0, \Omega_0 + \epsilon g) - P(0, t; b, \beta_0, \Omega_0) \right] \phi(b; \Sigma_0) db\]

\[= \int_b \int_0^t P(0, s; b, \beta_0, \Omega_0) dA(s; b, \beta_0, g) P(s, t; b, \beta_0, \Omega_0) \phi(b; \Sigma_0) db\]

By Condition 6, for any \(t \in [0, \tau]\) and any \((j, k) \in D\),

\[A(t; b, \beta_0, g)^{(j,k)} = \int_0^t \exp \left\{ \beta_{0jk}^T X(s) + b^T Z(s) \right\} dg_{jk}(s) = 0.\]

Therefore, \(g_{jk}(t) = 0\) for any \(t \in [0, \tau]\) and \((j, k) \in D\). Hence, \(\| \cdot \|_2\) is a norm in \(V\).

Next we show that the space \((V, \| \cdot \|_2)\) is also a Banach space. We only need to show the completeness of the space. Consider any arbitrary Cauchy sequence \(\{g_n = \{g_{njk}\}_{(j,k) \in D}\}\) in the space \((V, \| \cdot \|_2)\). We have

\[\|g_n - g_m\|_2^2 = E \left[ \left( \sum_{l=1}^N \sum_{(j,k) \in D} \left\{ R_{ljk}(\tau_l) [g_{njk}(\tau_l) - g_{mjk}(\tau_l)] - \int_0^{\tau_l} [g_{njk}(t) - g_{mjk}(t)] dR_{ljk}(t) \right\} \right)^2 \right]\]

converges to zero almost surely. Thus,

\[\sum_{l=1}^N \sum_{(j,k) \in D} \left\{ R_{ljk}(\tau_l) [g_{njk}(\tau_l) - g_{mjk}(\tau_l)] - \int_0^{\tau_l} [g_{njk}(t) - g_{mjk}(t)] dR_{ljk}(t) \right\}\]

converges to zero almost surely. Suppose that \(N = 1\). Since \(\tau_1\) can take any value within \([0, \tau]\), the above convergence implies that

\[\sum_{(j,k) \in D} \left\{ R_{1jk}(\tau_l) [g_{njk}(\tau_l) - g_{mjk}(\tau_l)] - \int_0^{\tau_l} [g_{njk}(t) - g_{mjk}(t)] dR_{1jk}(t) \right\} \to 0\]
almost surely for any \( t \in [0, \tau] \). For any given \((j, k) \in D\), consider two subjects with the same observations except that the state pair \((S_0, j)\) is feasible for one of them and is unfeasible for the other. Subtracting the above equations for these two subjects yields

\[
\sum_{k': (j, k') \in D} \left\{ R_{jk'}(t)[g_{njk'}(t) - g_{mjk'}(t)] - \int_0^t [g_{njk'}(s) - g_{mjk'}(s)]dR_{jk'}(s) \right\} \to 0
\]

almost surely. Similarly, we consider two subjects with the same observations except that the state pair \((k, S_1)\) is feasible for one of them and is unfeasible for the other. Subtracting the above equations for these two subjects yields

\[
R_{jk}(t)[g_{njk}(t) - g_{mjk}(t)] - \int_0^t [g_{njk}(s) - g_{mjk}(s)]dR_{jk}(s) \to 0
\]

almost surely. Let \( G_{njk}(t) = R_{jk}(t)g_{njk}(t) - \int_0^t g_{njk}(s)dR_{jk}(s) \). Then \( G_{njk}(t) \) converges to some function \( G_{jk}(t) \in \mathcal{V} \). In addition, we can easily verify that

\[
G_{njk}(t) = \frac{R_{jk}(t)}{R'_{jk}(t)} \times \left\{ \frac{\int_0^t g_{njk}(s)dR_{jk}(s)}{R_{jk}(t)} \right\}.
\]

Since \( R_{jk}(t) \) and \( R'_{jk}(t) \) are both uniformly bounded over \([0, \tau]\) under Condition 2, we conclude that \( g_n \) converges in \( \mathcal{V} \). Hence, the space \((\mathcal{V}, \| \cdot \|_2)\) is a Banach space.

By the Cauchy–Schwarz inequality, for any \( g \in \mathcal{V} \),

\[
\|g\|_2^2 = E \left[ \left( \sum_{l=1}^N \sum_{(j,k) \in D} \left\{ R_{ijk}(\tau_l)g_{jk}(\tau_l) - \int_0^{\tau_l} g_{jk}(t)dR_{ijk}(t) \right\} \right)^2 \right]
\]

\[
\leq 2E \left[ \left( \sum_{l=1}^N \sum_{(j,k) \in D} R_{ijk}(\tau_l)g_{jk}(\tau_l) \right)^2 \right] + 2E \left[ \left( \sum_{l=1}^N \sum_{(j,k) \in D} \int_0^{\tau_l} g_{jk}(t)dR_{ijk}(t) \right)^2 \right]
\]

\[
\leq C_2 E \left[ \sum_{l=1}^N \sum_{(j,k) \in D} g_{jk}(\tau_l)^2 \right]
\]

\[
= C_2 \|g\|_1^2,
\]

where \( C_2 \) is a positive constant. Then it follows from the open mapping theorem in Banach spaces that the norms \( \| \cdot \|_1 \) and \( \| \cdot \|_2 \) are equivalent, so \( \|g\|_2 \geq C_3 \|g\|_1 \) for some constant
\[ O_p(n^{-2/3}) + O(1)\|\beta - \beta_0\|^2 + O(1)\|\gamma - \gamma_0\|^2 \geq C_1 C_3 E \left[ \sum_{(j,k) \in D} \sum_{l=1}^N \left( \tilde{\Lambda}_{jk}(\tau_l) - \Lambda_{0jk}(\tau_l) \right)^2 \right] \]

The desired result thus follows. \[\square\]

**Lemma S.3.** Under Conditions 1-6, the following are true:

(i) The solution \( h^* \) to the equation system \( \ell_{\Theta}^* \ell_{\Omega}(h) = \ell_{\Theta}^* \ell_{\theta} \) exists;

(ii) \( \ell_{\Theta}(\tilde{\Theta}, \tilde{\Omega}) - \ell_{\Theta}(\hat{\Theta}, \hat{\Omega})(h^*) \) belongs to a Donsker class and converges in \( L^2(\mathbb{P}) \) norm to \( \ell_{\Theta} - \ell_{\Theta}(h^*) \);

(iii) The matrix \( E \left[ \{\ell_{\Theta} - \ell_{\Theta}(h^*)\} \otimes^2 \right] \) is invertible.

**Proof.** Throughout the proof, a function is evaluated at \((\theta_0, \Omega_0)\) if the arguments \((\theta, \Omega)\) are missing. We first verify (i). We equip \( \mathcal{H} \) with an inner product defined by

\[
\langle h^{(1)}, h^{(2)} \rangle = \sum_{(j,k) \in D} \int_0^\tau h^{(1)}_{jk}(t) h^{(2)}_{jk}(t) d\Lambda_{0jk}(t).
\]

By the definition of the adjoint operator, for any \( h^{(1)}, h^{(2)} \in \mathcal{H} \),

\[
\langle \ell_{\Theta}^* \ell_{\Omega}(h^{(1)}), h^{(2)} \rangle = \mathbb{P} \left\{ \ell_{\Omega}(h^{(1)}) \ell_{\Omega}(h^{(2)}) \right\} = \sum_{(j,k) \in D} \int_0^\tau \Gamma_{jk}(h^{(1)})(t) h^{(2)}_{jk}(t) d\Lambda_{0jk}(t) = \langle \Gamma(h^{(1)}), h^{(2)} \rangle,
\]

where \( \Gamma(h) = \{\Gamma_{jk}(h)\}_{(j,k) \in D} \), and

\[
\Gamma_{jk}(h)(t) = \sum_{(j', k') \in D} \int_0^\tau E \left[ \sum_{l, l' = 1}^N B_{ijk}(t) B_{ljk'}(s) \right] h_{jk}(s) d\Lambda_{0jk}(s).
\]

Thus, \( \ell_{\Theta}^* \ell_{\Omega}(h) = \Gamma(h) \) for \( h \in \mathcal{H} \). Likewise,

\[
\mathbb{P} \{ \ell_{\Theta} \ell_{\Omega}(h) \} = \sum_{(j,k) \in D} \int_0^\tau E \left[ \sum_{l=1}^N B_{ijk}(t) \ell_{\theta} \right] h_{jk}(t) d\Lambda_{0jk}(t)
\]
implies that \( \ell^*_\Theta (t) = \Psi \), where \( \Psi = \{ \psi_{jk}(t) \}_{(j,k) \in D} \) with \( \psi_{jk}(t) = E[\sum_{l=1}^{N} B_{lj}(t) \ell_{\theta}] \). Therefore, solving the equation system in (i) is equivalent to solving the integral equation system

\[
\Gamma(h^*) = \Psi. \tag{S2}
\]

Let \( H_{jkj\prime k\prime}(t, s) = \sum_{l,l^\prime=1}^{N} B_{lj}(t) B_{lj\prime}(s) \). We examine \( E[H_{jkj\prime k\prime}(t, s)] \) by considering \( t \geq s \) and \( t < s \). If \( t \geq s \),

\[
E[H_{jkj\prime k\prime}(t, s)]
= E \left[ \sum_{l \leq l^\prime} \sum_{\tau_{\prime-1}=0}^{s} \int_{\tau_{l-1}=\tau_{\prime-1}+\eta_2}^{\tau_{l}=\tau_{l-1}+\eta_2} B_{lj}(t) B_{lj\prime}(s) \right. \times f_l(\tau_{l-1}, \tau_l) f_{l\prime}(\tau_{l\prime-1}, \tau_{l\prime}) \, d\tau_l \, d\tau_{l-1} \, d\tau_{l\prime} \, d\tau_{l\prime-1}
+ \sum_{l=1}^{N} \int_{\tau_{l-1}=s}^{\tau_{l-1}=0} B_{lj}(t) B_{lj\prime}(s) f_l(\tau_{l-1}, \tau_l) \, d\tau_l \, d\tau_{l-1}. \tag{S3}
\]

If \( t < s \),

\[
E[H_{jkj\prime k\prime}(t, s)]
= E \left[ \sum_{l \leq l^\prime} \sum_{\tau_{\prime-1}=0}^{s} \int_{\tau_{l-1}=\tau_{\prime-1}+\eta_2}^{\tau_{l}=\tau_{l-1}+\eta_2} B_{lj}(t) B_{lj\prime}(s) \right. \times f_l(\tau_{l-1}, \tau_l) f_{l\prime}(\tau_{l\prime-1}, \tau_{l\prime}) \, d\tau_l \, d\tau_{l-1} \, d\tau_{l\prime} \, d\tau_{l\prime-1}
+ \sum_{l=1}^{N} \int_{\tau_{l-1}=s}^{\tau_{l-1}=0} B_{lj}(t) B_{lj\prime}(s) f_l(\tau_{l-1}, \tau_l) \, d\tau_l \, d\tau_{l-1},
\]

where \( x \wedge y = \min(x, y) \) and \( x \vee y = \max(x, y) \), and where \( \eta_2 \), the minimum gap between any two successive examination times, and \( f_l(\cdot, \cdot) \), the conditional density function of \((\tau_{l-1}, \tau_l)\) given \((N, X, Z)\), are both as defined in Condition 4. We split the integral on the left side of (S2) into two parts accordingly. Then differentiation of (S2) twice with respect to \( t \) yields the following integral equation system:

\[
\sum_{(j', k') \in D} \left\{ r_{1jkj\prime k\prime}(t) h_{j'k'}^{*}(t) + \int_{0}^{t} r_{2jkj\prime k\prime}(t, s) h_{j'k'}^{*}(s) \, ds + \int_{t}^{\tau} r_{3jkj\prime k\prime}(t, s) h_{j'k'}^{*}(s) \, ds \right\} = \psi_{jk}(t), \tag{S3}
\]
where
\[ r_{1jk'k'}(t) = \left[ \frac{\partial}{\partial t} E[H_{jk'k'}(t, s)] \right]_{s=t-} - \left[ \frac{\partial}{\partial t} E[H_{jk'k'}(t, s)] \right]_{s=t+} \Lambda_{0jk'}(t) \]
\[ r_{2jk'k'}(t, s) = \frac{\partial^2}{\partial t^2} E[H_{jk'k'}(t, s)] \Lambda_{0jk'}(s) \]
\[ r_{3jk'k'}(t, s) = \frac{\partial^2}{\partial t^2} E[H_{jk'k'}(t, s)] \Lambda_{0jk'}(s). \]

By simple calculations,
\[ r_{1jk'k'}(t) = - \left\{ E \left[ \sum_{l=1}^{N} B_{ljk}(t) B_{lj'k'}(t) \mid \tau_l = t \right] + E \left[ \sum_{l=1}^{N} B_{ljk}(t) B_{lj'k'}(t) \mid \tau_{l-1} = t \right] \right\} \Lambda_{0jk'}(t). \]

For \( l = 1, \ldots, N \), let \( B_l(t) = \{ B_{ljk}(t) \}_{(j,k) \in \mathcal{D}} \). We also define \( G(t) \) to be a \( |\mathcal{D}| \times |\mathcal{D}| \) diagonal matrix with elements \( \{ \Lambda_{0jk}'(t) \}_{(j,k) \in \mathcal{D}} \). Then the \( |\mathcal{D}| \times |\mathcal{D}| \) matrix with the \( \{(j,k), (j',k')\} \)th element being \( r_{1jk'k'} \) can be expressed as
\[ - \left\{ E \left[ \sum_{l=1}^{N} B_l(t)^{\otimes 2} \mid \tau_{l-1} = t \right] + E \left[ \sum_{l=1}^{N} B_l(t)^{\otimes 2} \mid \tau_l = t \right] \right\} \times G(t), \]
which is negative definite. Thus, the linear operator of \( h^* \) on the left side of (S3) is the sum of an invertible operator and two compact operators. By Theorem 4.25 of Rudin (1973), showing the invertibility of this operator is equivalent to showing that it is one to one.

Since it is the second derivative of \( \Gamma \), it suffices to show that \( \Gamma \) is one to one. If \( \Gamma(h) = 0 \), then \( \langle \Gamma(h), h \rangle = \mathbb{P}\{ \ell_{\Omega}(h) \ell_{\Omega}(h) \} = 0 \). Thus, with probability one,
\[ 0 = \ell_{\Omega}(h) = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left\{ \prod_{l=1}^{N} P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0, h)^{(S_{l-1}, S_l)} - \prod_{l=1}^{N} P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \phi(b; \Sigma_0) db, \]
where \( \Sigma_0 = \Sigma(\gamma_0) \). We evaluate the above equation at all possible \( (S_1, S_2, \ldots, S_{N-1}) \) given the start and end states \( (S_0, S_N) \). By taking the sum of the resulting equations, we obtain
\[ \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left\{ P(0, \tau_N; b, \beta_0, \Omega_0)^{(S_0, S_N)} - P(0, \tau_N; b, \beta_0, \Omega_0)^{(S_0, S_N)} \right\} \phi(b; \Sigma_0) db = 0. \]
The above equation holds for any \( \tau_N \in [0, \tau] \) and any feasible \((S_0, S_N)\), which covers the whole set \( D \) under Condition 3. Thus, for any \( t \in [0, \tau] \),
\[
0 = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left[ P(0, t; b, \beta_0, \Omega_{0e,h}) - P(0, t; b, \beta_0, \Omega_0) \right] \phi(b; \Sigma_0) db \\
= \int_0^t \int_0^t P(0, s; b, \beta_0, \Omega_0) dA(s; b, \beta_0, \int h d\Omega_0) P(s, t; b, \beta_0, \Omega_0) \phi(b; \Sigma_0) db.
\]
By Condition 6, for \((j, k) \in D\),
\[
\int_0^t \exp \left\{ \beta_{0jk}^T X(s) + b^T Z(s) \right\} h_{jk}(s) d\Lambda_{0jk}(s) = 0.
\]
Differentiating the two sides with respect to \( t \) yields \( h_{jk} \equiv 0 \), which implies \( h \equiv 0 \). Hence, the linear operator of (S3) is invertible and thus the solution \( h^* \) exists.

Next we verify (ii). Under Conditions 1, 2 and 4, \( r_{ij,k',k} \) \((i = 1, 2, 3, (j, k), (j', k') \in D\) and \( \psi''_{jk} \) \((j, k) \in D\) in (S3) are all continuously differentiable functions. Therefore, for \((j, k) \in D\), \( h_{jk}^* \) is continuously differentiable on \([0, \tau]\), which implies bounded variation. By the arguments in the proof of Lemma 1, \( \ell_\theta(\hat{\Theta}, \hat{\Omega}) - \ell_\Omega(\hat{\Theta}, {\hat{\Omega}})(h^*) \) belongs to a Donsker class and converges in \( L_2(\mathbb{P}) \) norm to \( \ell_\theta - \ell_\Omega(h^*) \), as stated in (ii).

Finally, we verify (iii). If the matrix \( E[\{\ell_\theta - \ell_\Omega(h^*)\} \otimes 2] \) is singular, then there exist vectors \( v = (v_1, v_2) \) with \( v_1 = \{v_{1jk}\}_{(j, k) \in D} \in \mathbb{R}^{|D| \times d_1} \) and \( v_2 \in \mathbb{R}^{d_3} \), such that \( v^T E[\{\ell_\theta - \ell_\Omega(h^*)\} \otimes 2] v = 0 \). It follows that, with probability one, the score function along the submodel \( \{\theta_0 + \epsilon v, d\Omega_{0e}(v^T h^*)\} \) is zero, where \( d\Omega_{0e}(v^T h^*) = \{(1 - \epsilon v^T h_{jk}^*) d\Lambda_{0jk}\}_{(j, k) \in D} \).

Therefore,
\[
\lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0 + \epsilon v_1, \Omega_{0e}(v^T h^*))^{(S_{l-1}, S_l)} - \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} \\
\times \phi(b; \Sigma_0) db + \int_b \left\{ \prod_{l=1}^N P(\tau_{l-1}, \tau_l; b, \beta_0, \Omega_0)^{(S_{l-1}, S_l)} \right\} v_2 \phi_{\gamma}^T(b; \Sigma_0) db = 0
\]
with probability one, where \( \Sigma_0 = \Sigma(\gamma_0) \). We evaluate the above equation at all possible \((S_1, S_2, \ldots, S_{N-1})\) given the start and end states \((S_0, S_N)\). Then taking the sum of the
resulting equations yields
\[
\lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left\{ P(0, \tau_N; b, \beta_0 + \epsilon v_1, \Omega_0, (v^T h^*))^{(S_0, S_N)} - P(0, \tau_N; b, \beta_0, \Omega_0)^{(S_0, S_N)} \right\} \phi(b; \Sigma_0) db \\
+ \int_b \left\{ P(0, \tau_N; b, \beta_0, \Omega_0)^{(S_0, S_N)} \right\} v_2^T \phi'_\gamma(b; \Sigma_0) db = 0.
\]

The above equation holds for any arbitrary \( \tau_N \) and feasible \((S_0, S_N)\). Thus, for any \( t \in [0, \tau] \),

\[
0 = \lim_{\epsilon \to 0} \frac{1}{\epsilon} \int_b \left[ P(0, t; b, \beta_0 + \epsilon v_1, \Omega_0, (v^T h^*)) - P(0, t; b, \beta_0, \Omega_0) \right] \phi(b; \Sigma_0) db \\
+ \int_b P(0, t; b, \beta_0, \Omega_0) v_2^T \phi'_\gamma(b; \Sigma_0) db
\]

where the off-diagonal elements of the matrix \( d\tilde{A}(s; b, \beta_0, \Omega_0) \) are

\[
d\tilde{A}(s; b, \beta_0, \Omega_0)^{jk} = \left[ v_{1jk}^T X(s) - v^T h^*_{jk}(s) \right] \exp \left\{ \beta_{0jk}^T X(s) + b^T Z(s) \right\} d\Lambda_{0jk}(s)
\]

if \((j, k) \in D\) and 0 otherwise, and the diagonal elements are

\[
d\tilde{A}(s; b, \beta_0, \Omega_0)^{jj} = -\sum_{k \neq j} d\tilde{A}(s; b, \beta_0, \Omega_0)^{jk}.
\]

By Condition 6, \( v_2 = 0 \) and

\[
\int_0^t \left[ v_{1jk}^T X(s) - v^T h^*_{jk}(s) \right] \exp \left\{ \beta_{0jk}^T X(s) + b^T Z(s) \right\} d\Lambda_{0jk}(s) = 0
\]

for \((j, k) \in D\). Differentiating the two sides with respect to \( t \) yields \( v_{1jk}^T X(t) - v^T h^*_{jk}(t) = 0 \).

By Condition 2, \( v_{1jk} = 0 \). Hence, the matrix \( E[\{ \ell_\theta - \ell_\Omega(h^*) \} \otimes 2] \) is invertible.

\[\Box\]

### S.2 Additional Simulation Studies

We conducted a series of simulation studies with more complex disease processes. We considered a four-state model with possible transitions including 1 to 2, 2 to 3, 2 to 4, and
3 to 4. For each subject, we generated two time-independent covariates, $X_1 \sim \text{Ber}(0.5)$ and $X_2 \sim \text{Unif}(0,1)$, and random effect $b \sim N(0, \sigma^2)$ with $\sigma^2 = 0.8$. We set $(\beta_{121}, \beta_{122}) = (0.5, -0.5)$, $\Lambda_{12}(t) = \log(1 + 0.5t)$, $(\beta_{231}, \beta_{232}) = (0.4, 0.2)$, $\Lambda_{23}(t) = 0.5t$, $(\beta_{241}, \beta_{242}) = (0.3, 0.5)$, $\Lambda_{24}(t) = 0.4t$, $(\beta_{341}, \beta_{342}) = (-0.3, 0.7)$, and $\Lambda_{34}(t) = 0.6t$. The initial state of each subject belonged to 1, 2, or 3, with probabilities 0.25, 0.5, or 0.25, respectively. We generated six potential examination times for each subject, with the first being $\text{Unif}(0,1)$, and the gap between any two successive examination times being $0.05 + \text{Unif}(0,1)$. We set the study end time to be 3, beyond which no examinations occurred. As is shown in Table S1 and Figure S1, the proposed methods continue to perform well.

References

Andersen, P. K., Borgan, O., Gill, R. D. and Keiding, N. (1993), *Statistical Models Based on Counting Processes*, New York: Springer.

Rudin, W. (1973), *Functional Analysis*, New York: McGraw-Hill.

van de Geer, S. (2000), *Empirical Processes in M-estimation*, Cambridge: Cambridge University Press.

van der Vaart, A. W. and Wellner, J. A. (1996), *Weak Convergence and Empirical Processes*, New York: Springer.
Table S1: Estimation of the regression parameters in the simulation studies with four states.

|       | \( n = 400 \) |       | \( n = 800 \) |       | \( n = 1600 \) |
|-------|---------------|-------|---------------|-------|---------------|
|       | Bias | SE   | SEE  | CP  | Bias | SE   | SEE  | CP  | Bias | SE   | SEE  | CP  |
| \( \beta_{121} = 0.5 \) | 0.028 | 0.367 | 0.352 | 94.6 | 0.011 | 0.247 | 0.241 | 94.7 | 0.003 | 0.171 | 0.167 | 94.6 |
| \( \beta_{122} = -0.5 \) | -0.049 | 0.642 | 0.612 | 94.3 | -0.018 | 0.432 | 0.417 | 94.7 | -0.010 | 0.296 | 0.287 | 94.6 |
| \( \beta_{231} = 0.4 \)  | 0.031 | 0.308 | 0.273 | 92.1 | 0.022 | 0.203 | 0.190 | 93.1 | 0.009 | 0.138 | 0.133 | 94.0 |
| \( \beta_{232} = 0.2 \)  | 0.016 | 0.534 | 0.474 | 92.1 | 0.002 | 0.354 | 0.329 | 93.3 | -0.008 | 0.242 | 0.229 | 93.7 |
| \( \beta_{241} = 0.3 \)  | 0.017 | 0.542 | 0.289 | 91.0 | 0.001 | 0.229 | 0.201 | 92.8 | -0.002 | 0.150 | 0.142 | 93.9 |
| \( \beta_{242} = 0.5 \)  | 0.041 | 0.646 | 0.499 | 90.8 | 0.015 | 0.390 | 0.346 | 92.9 | 0.008 | 0.256 | 0.242 | 94.1 |
| \( \beta_{341} = -0.3 \) | -0.015 | 0.283 | 0.246 | 91.7 | -0.005 | 0.187 | 0.172 | 93.5 | -0.001 | 0.126 | 0.121 | 94.1 |
| \( \beta_{342} = 0.7 \)  | 0.045 | 0.498 | 0.431 | 91.5 | 0.020 | 0.325 | 0.300 | 93.0 | 0.002 | 0.220 | 0.209 | 93.9 |
| \( \sigma^2 = 0.8 \)    | 0.123 | 0.417 | 0.358 | 90.5 | 0.043 | 0.239 | 0.233 | 94.2 | -0.004 | 0.155 | 0.156 | 95.7 |

Note: Bias and SE denote the median bias and empirical standard error, respectively. SEE denotes the median of the standard error estimator, and CP denotes the empirical coverage percentage of the 95% confidence interval. The log transformation is used to construct the confidence interval for \( \sigma^2 \). Each entry is based on 10,000 replicates.
Figure S1: Estimation of the cumulative transition intensities in the simulation studies with four states. The solid and dashed curves show the true values and median estimates based on 10,000 replicates, respectively.