Semiparametric Regression Analysis of Interval-Censored Multi-State Data with An Absorbing State

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Acknowledgments

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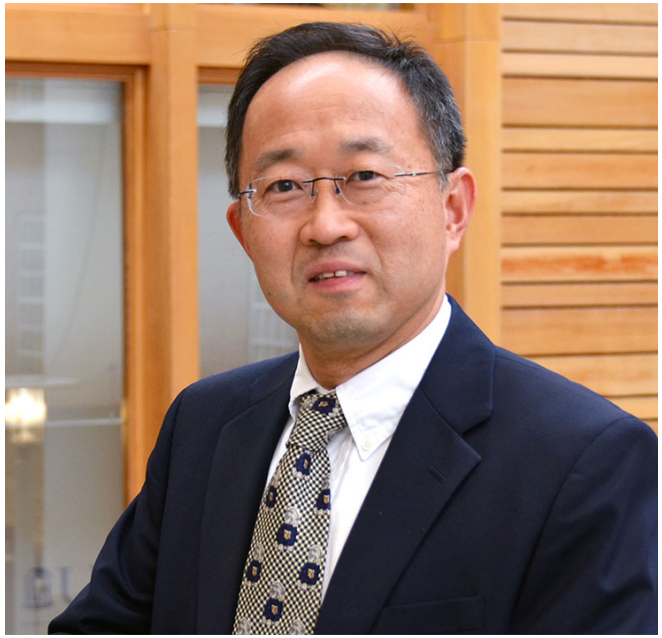

Dr. Danyu Lin

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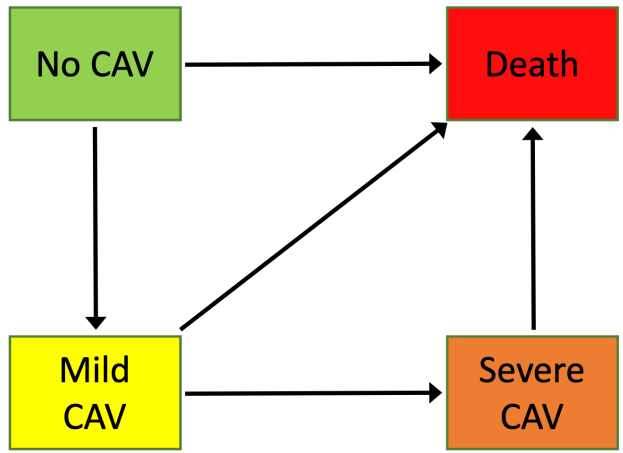
Outline

Outline

Multi-State Data

- Multi-state data arise frequently in studies of chronic diseases.
- Health status can be characterized by a finite number of disease states.
- ***Transition***: change from one state to another.



Cardiac allograft vasculopathy

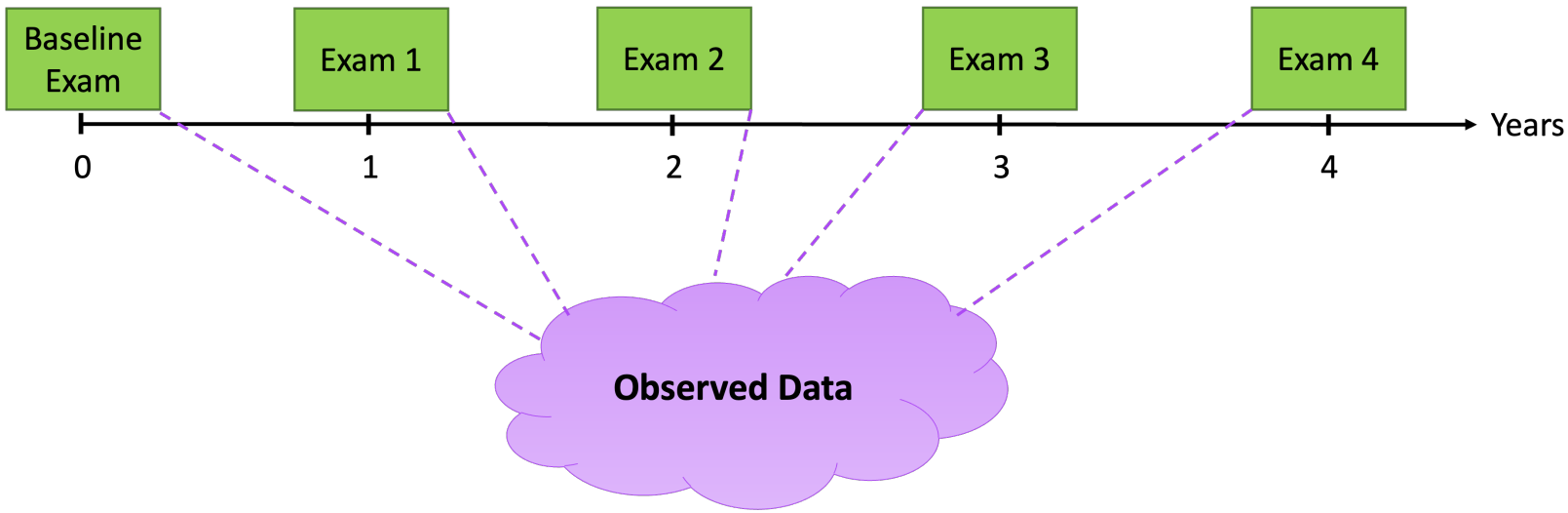
Significance

Analysis of multi-state data allows us to

- understand how a subject transitions from one state to another over time
- study the associations between risk factors and the disease process
- predict future disease progression using the disease history

Interval Censoring

- For economic and logistical reasons, subjects can only be examined periodically, such that transitions are only known to occur between two successive examinations.



- Such data are called ***interval-censored multi-state data***.

Absorbing State and Right Censoring

- In many applications, there is an ***absorbing state*** (e.g., death) which terminates the disease process.
- A common situation is that the time of entering the absorbing state is observed exactly or right-censored.
- However, the ***transient state*** from which a subject enters the absorbing state is still unknown.

Analysis Challenges

- None of the transition times among transient states are directly observed.
- Trajectory of transitions from one examination to the next is unknown.
- Dependence among transitions from the same subject.
- A mixture of interval- and right-censored transition times.
- Missing data on the transient state right before the absorbing state.

Existing Methods

Nonhomogeneous

Time-homogeneous Markov models

- Kalbfleisch & Lawless (1985); Satten (1999); Cook et al. (2002, 2004)
- simple; parametric; implemented in the msm package
- homogeneous assumption is unrealistic

Piecewise constant transition intensities

Nonparametric

- Gentleman et al. (1994); Saint-Pierre et al. (2003); Jackson (2011); Lawless & Nazeri Rad (2015)
- relatively simple; parametric
- restrictive; sensitive to the choice of change points

Spline-based intensities + penalized likelihood

- Joly & Commenges (1999); Machado & van den Hout (2018); Machado et al. (2021)
- more flexible; semiparametric
- tuning parameters (e.g., knots); inconsistent estimators

Overview of this work

- We provide a new framework to study semiparametric regression models for general interval-censored multi-state data with an absorbing state whose entry time is exactly known or right-censored.
- Our models use random effects to capture the dependence among transitions and accommodate time-dependent covariates.
- We combine ***nonparametric maximum likelihood estimation*** (NPMLE) and ***sieve estimation*** for inference.
- We devise a stable EM algorithm to compute the estimators.
- We leverage random effects to dynamically predict future process using the evolving disease history.

Outline

Notation

- We consider a random sample of n subjects and K states, with state K being absorbing and all others being transient.
- Let $N_{ijk}(t)$ denote the number of transitions $j \to k$ the ith subject has experienced by time t.
- For the ith subject, let $\boldsymbol{X}_i(t)$ denote a set of potentially time-dependent covariates and $\boldsymbol{b}_i$ denote a d-vector of random effects.

Semiparametric Regression Model

We specify that the transition intensity of $N_{ijk}(t)$ is related to $\boldsymbol{X}_i(t)$ and $\boldsymbol{b}_i$ through the proportional intensity model:

$$\lambda_{ijk}(t; \boldsymbol{X}_i, \boldsymbol{b}_i) = \lambda_{jk}(t) \exp\left\{\boldsymbol{\beta}_{jk}^{\mathsf{T}} \boldsymbol{X}_i(t) + \boldsymbol{b}_i^{\mathsf{T}} \boldsymbol{Z}_i(t)\right\} \tag{1}$$

- $\lambda_{jk}(\cdot)$: arbitrary baseline intensity function
- $\boldsymbol{\beta}_{jk}$: unknown regression parameters
- $\boldsymbol{b}_i \sim N_d(\boldsymbol{0}, \boldsymbol{\Sigma}(\gamma))$
- $\boldsymbol{Z}_i(\cdot)$: consists of 1 and covariates that are part of $\boldsymbol{X}_i(\cdot)$

Observed Data

- Examination times: $(U_{i0}, U_{i1}, \ldots, U_{iM_i})$
- Observed transient states: $(S_{i0}, S_{i1}, \ldots, S_{iM_i})$
- Time and status of entering state K: (Y_i, Δ_i)
  - $Y_i = \min(T_i, C_i)$
  - $\Delta_i = I(T_i \leqslant C_i)$
  - T_i is actual event time, C_i is censoring time
- Covariates: $\boldsymbol{X}_i(t)$

Likelihood

Under the noninformative censoring and conditional Markov assumptions, the likelihood is proportional to

$$\prod_{i=1}^{n} \int_{\boldsymbol{b}_i} \prod_{l=1}^{M_i} \boldsymbol{P}(U_{i,l-1}, U_{il}; \boldsymbol{X}_i, \boldsymbol{b}_i)^{(S_{i,l-1}, S_{il})} \times \left\{ \sum_{j \neq K} \boldsymbol{P}(U_{iM_i}, Y_i; \boldsymbol{X}_i, \boldsymbol{b}_i)^{(S_{iM_i}, j)} \right\}^{1-\Delta_i} \times \left\{ \sum_{j \in \mathcal{D}_K} \boldsymbol{P}(U_{iM_i}, Y_i; \boldsymbol{X}_i, \boldsymbol{b}_i)^{(S_{iM_i}, j)} \lambda_{ijK}(Y_i) \right\}^{\Delta_i} \phi(\boldsymbol{b}_i; \boldsymbol{\gamma}) d\boldsymbol{b}_i \tag{2}$$

- $\boldsymbol{P}(u, v; \boldsymbol{X}_i, \boldsymbol{b}_i)$ denotes the transition probability matrix between times u and v for the ith subject.
- $\phi(\boldsymbol{b}; \boldsymbol{\gamma})$ denotes the density function of $N_d(\boldsymbol{0}, \boldsymbol{\Sigma}(\boldsymbol{\gamma}))$.

Compute Transition Probability

- The transition probability matrix is given by

$$\boldsymbol{P}(u, v; \boldsymbol{X}_i, \boldsymbol{b}_i) = \prod_{u<t\leqslant v} \{\boldsymbol{I}_K + d\boldsymbol{A}(t; \boldsymbol{X}_i, \boldsymbol{b}_i)\}$$

- $\boldsymbol{A}(t; \boldsymbol{X}_i, \boldsymbol{b}_i)$ is the cumulative transition intensity matrix, with

$$\boldsymbol{A}(t; \boldsymbol{X}_i, \boldsymbol{b}_i)^{(j,k)} = \int_0^t \exp\{\beta_{jk}^{\mathsf{T}} \boldsymbol{X}_i(s) + \boldsymbol{b}_i^{\mathsf{T}} \boldsymbol{Z}_i(s)\} d\Lambda_{jk}(s).$$

- $\Lambda_{jk}(t) = \int_0^t \lambda_{jk}(s) ds$.

NPMLE + Sieve Estimation

- We adopt NPMLE approach for Λ_{jk} of
  1. all transitions among states $1, 2, \ldots, K-1$
  2. transition from state 1 to state $K \Rightarrow$ reference Λ_a
- We use B-splines to approximate the log transition intensity ratio $\psi_j = \log(\lambda_{jK}/\lambda_a)$
- Why not NPMLE for all Λ_{jk}? Inconsistent estimators!
  - unknown state right before entering state K
  - Ma & Wang (2012); Wang et al. (2012)

More on NPMLE

- We treat Λ_{jk} as step functions with nonnegative jumps at all examination times and Y_i's.
- We treat Λ_a as a step function that jumps only at those Y_i with $\Delta_i = 1$.
- Then the transition probability matrix

$$\boldsymbol{P}_i(u, v) = \prod_{u<t\leqslant v} \{\boldsymbol{I}_K + d\boldsymbol{A}_i(t)\}$$

$$\Downarrow$$

$$\widetilde{\boldsymbol{P}}_i(u, v) = \prod_{u<t_q\leqslant v} \{\boldsymbol{I}_K + \delta\boldsymbol{A}_i(t_q)\}.$$

- $\delta\boldsymbol{A}_i(t_q)$ involves the jump sizes λ_{jkq} and λ_{aq}.

Remarks

- Advantages of NPMLE:
  - uses all information told by the data
  - minimal assumption about Λ's compared to splines
  - no tuning parameters
- The combination of NPMLE and B-splines ensures estimation consistency while achieving the maximal model flexibility.
- Challenges of computing sieve NPMLE:
  - high-dimensional parameters λ_{jkq} and λ_{aq}
  - lack of analytical expressions

Poissonization

- We introduce independent latent Poisson random variables W_{ijkq} with means $\{\delta \boldsymbol{A}_i(t_q)\}^{(j,k)}$.

- The key fact is that the transition probability $\widetilde{\boldsymbol{P}}_i(u,v)^{(s_0,s_r)}$ is equal to the probability of the event

$$\bigcup_{\text{traj}(s_0,s_1,\ldots,s_r)} \Big\{ W_{ijkq} > 0 \text{ if there's a transition } j \to k \text{ at time } t_q \text{ and } W_{ijkq} = 0 \text{ otherwise} \Big\}.$$

- Thus, maximizing the original likelihood is tantamount to maximizing the likelihood arising from the events of W's.

EM Algorithm

- We can treat W_{ijkq}'s and $\boldsymbol{b}_i$'s as missing data and apply the EM algorithm for maximizing the likelihood function.

- The complete-data log-likelihood is

$$\begin{aligned}
&\sum_{i=1}^{n}\Bigg\{\sum_{(j,k)\in\mathcal{D}^*}\sum_{q=1}^{m} I(t_q \leqslant Y_i)\Big[W_{ijkq}\left\{\log\left(\lambda_{jkq}\right)+\beta_{jk}^{\mathsf{T}}\boldsymbol{X}_{iq}+\boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{Z}_{iq}\right\}\\
&\qquad -\lambda_{jkq}\exp\left\{\beta_{jk}^{\mathsf{T}}\boldsymbol{X}_{iq}+\boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{Z}_{iq}\right\}-\log(W_{ijkq}!)\Big]\\
&+\sum_{j\in\mathcal{D}_K}\sum_{q=1}^{m} I(t_q \leqslant Y_i)\Big[W_{ijKq}\left\{\log\left(\lambda_{aq}\right)+\boldsymbol{\alpha}_j^{\mathsf{T}}\boldsymbol{B}_q+\beta_{jK}^{\mathsf{T}}\boldsymbol{X}_{iq}+\boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{Z}_{iq}\right\} \qquad (3)\\
&\qquad -\lambda_{aq}\exp\left\{\boldsymbol{\alpha}_j^{\mathsf{T}}\boldsymbol{B}_q+\beta_{jK}^{\mathsf{T}}\boldsymbol{X}_{iq}+\boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{Z}_{iq}\right\}-\log(W_{ijKq}!)\Big]\\
&\qquad -\frac{d_2}{2}\log(2\pi)-\frac{1}{2}\log|\boldsymbol{\Sigma}(\gamma)|-\frac{1}{2}\boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{\Sigma}(\gamma)^{-1}\boldsymbol{b}_i\Bigg\}.
\end{aligned}$$

E-Step

- We evaluate the conditional expectations of W_{ijkq}'s and functions of $\boldsymbol{b}_i$'s given the observed data.
- All conditional expectations have explicit expressions.
- Integrals of $\boldsymbol{b}_i$ can be approximated using Gaussian-Hermite quadratures.

M-Step

- The regression and spline parameters can be updated by solving their respective score equations with the one-step Newton-Raphson approach.

- The biggest advantage of the EM algorithm is that the jump sizes can be updated explicitly:

$$\lambda_{jkq} = \frac{\sum_{i=1}^{n} I(t_q \leqslant Y_i)\widetilde{E}(W_{ijkq})}{\sum_{i=1}^{n} I(t_q \leqslant Y_i)\widetilde{E}\{\exp(\beta_{jk}^{\mathsf{T}}\boldsymbol{X}_{iq} + \boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{Z}_{iq})\}},$$

$$\lambda_{aq} = \frac{\sum_{i=1}^{n} I(t_q \leqslant Y_i)\sum_{j\in\mathcal{D}_K}\widetilde{E}(W_{ijKq})}{\sum_{i=1}^{n} I(t_q \leqslant Y_i)\sum_{j\in\mathcal{D}_K}\widetilde{E}\{\exp(\boldsymbol{\alpha}_j^{\mathsf{T}}\boldsymbol{B}_q + \beta_{jK}^{\mathsf{T}}\boldsymbol{X}_{iq} + \boldsymbol{b}_i^{\mathsf{T}}\boldsymbol{Z}_{iq})\}}.$$

- Therefore, the EM algorithm is immune to the high-dimensional parameters in NPMLE.

Asymptotic Properties

- (Mixed rates of convergence) Under some regularity conditions,

$$\|\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0\|^2 + \sum_{(j,k)\in\mathcal{D}^*} \|\widehat{\Lambda}_{jk} - \Lambda_{0jk}\|_{L_2}^2 + \|\widehat{\Lambda}_a - \Lambda_{0a}\|_{L_2}^2 + \sum_{j\in\mathcal{D}_K^*} \|\widehat{\psi}_j - \psi_{0j}\|_{L_2}^2 = o_p(n^{-1/2}).$$

- (Asymptotic normality) $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ converges in distribution to a multivariate normal vector with mean zero and a covariance matrix that attains the semiparametric efficiency bound.

- (Variance estimation) The limiting covariance matrix of $n^{1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ can be consistently estimated by the inverse of

$$n^{-1} \sum_{i=1}^{n} \left\{ \nabla pl_i(\widehat{\boldsymbol{\theta}}) \right\}^{\otimes 2}.$$

Dynamic Prediction

- The key is to update the posterior density of random effects given the disease history $\mathcal{H}(t_0)$, which is proportional to

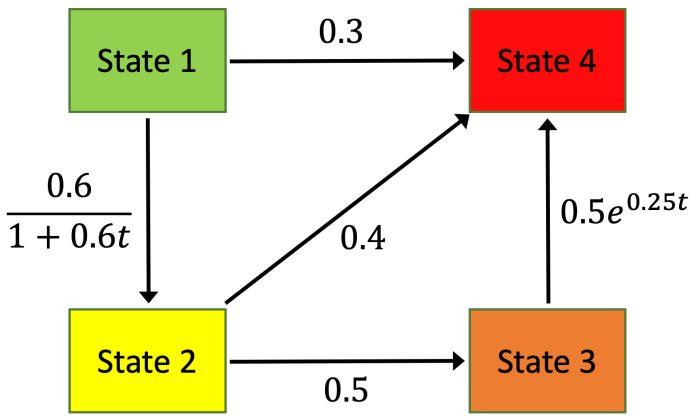
$$\prod_{l=1}^{L(t_0)} \widehat{\boldsymbol{P}}(U_{l-1}, U_l)^{(S_{l-1}, S_l)} \times \left\{ \sum_{j \neq K} \widehat{\boldsymbol{P}}(U_{L(t_0)}, t_0)^{(S_{L(t_0)}, j)} \right\} \phi(\boldsymbol{b}; \widehat{\gamma}).$$

- We then plug in this posterior density to estimate
  1. conditional probability of $S(t) = k$ given $\mathcal{H}(t_0)$, $k = 1, \ldots, K-1$
  2. conditional probability of reaching state K at time t given $\mathcal{H}(t_0)$

Outline

Simulation Setting

- $X_1 \sim \text{Bernoulli}(0.5)$ and $X_2 \sim \text{Unif}(0, 1)$
- $b \sim N(0, 0.5)$
- Six potential examination times separated by $0.05 + \text{Unif}(0, 1)$; no examinations after reaching state 4 or beyond $\tau = 3$.



Details of B-Splines

- We used cubic spline basis functions.
- We placed the boundary knots at 0 and τ, and placed two internal knots at the first and second tertiles of the observed time points.
- The estimation results are not sensitive to these choices.

Simulation Results

Table 1: Estimation of regression parameters

	$n = 500$				$n = 1000$				$n = 2000$			
	Bias	SE	SEE	CP	Bias	SE	SEE	CP	Bias	SE	SEE	CP
$\beta_{121} = 0.5$	0.026	0.272	0.254	94	0.014	0.178	0.180	96	0.003	0.134	0.127	95
$\beta_{122} = -0.5$	0.010	0.482	0.445	93	−0.005	0.322	0.312	94	−0.010	0.224	0.219	95
$\beta_{231} = 0.4$	−0.004	0.259	0.229	92	0.003	0.171	0.163	94	0.004	0.116	0.115	95
$\beta_{232} = 0.2$	0.022	0.467	0.398	91	0.016	0.296	0.283	94	0.012	0.208	0.199	94
$\beta_{141} = 0.3$	−0.007	0.309	0.256	91	0.000	0.193	0.180	94	−0.005	0.133	0.127	95
$\beta_{142} = 0.3$	−0.019	0.510	0.447	93	0.009	0.326	0.312	94	−0.002	0.219	0.220	95
$\beta_{241} = 0.3$	0.041	0.349	0.251	88	0.019	0.198	0.176	92	0.004	0.129	0.125	95
$\beta_{242} = 0.5$	0.001	0.570	0.426	86	−0.002	0.330	0.302	94	−0.006	0.226	0.214	95
$\beta_{341} = -0.2$	−0.030	0.272	0.220	90	−0.009	0.170	0.158	93	−0.003	0.114	0.113	95
$\beta_{342} = 0.5$	0.027	0.456	0.381	89	0.009	0.304	0.276	92	0.009	0.212	0.196	92
$\sigma^2 = 0.5$	−0.000	0.354	0.294	90	0.012	0.209	0.207	95	−0.002	0.130	0.141	97

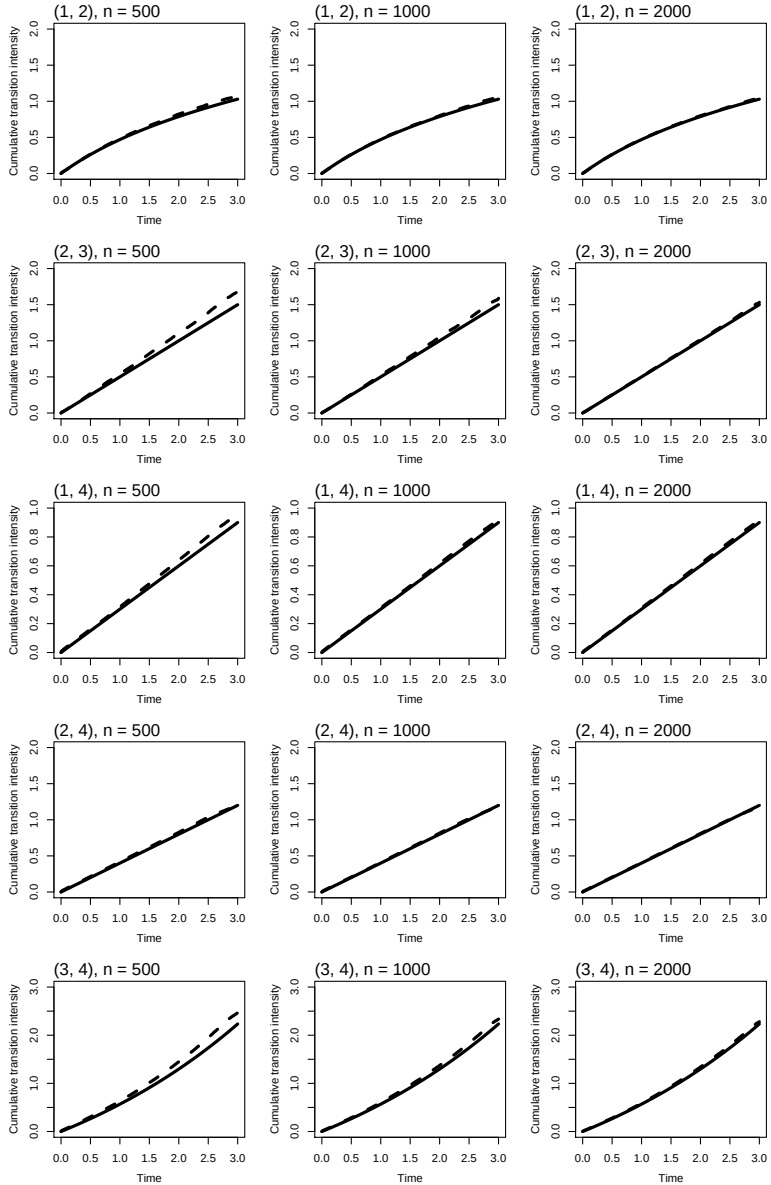


Figure 1: Estimation of cumulative baseline transition intensity functions.

Outline

CAV Study

- CAV is a deterioration of the arterial walls and is a common cause of death after heart transplantation.
- An important goal of the CAV study (Sharples et al., 2003) was to assess the effects of risk factors on CAV onset, progression, and survival.
- Starting from August 1979, a total of 622 heart transplant recipients underwent approximately yearly angiographic examinations and were classified as having no CAV, mild CAV, or severe CAV.
- Each patient was followed for up to 20 years, until death or the end of follow-up.
- The median follow-up time was 5 years; $\sim 40\%$ of the patients died during follow-up.

Analysis Specifics

- We fit a four-state random effects model.
- Tuning parameters in B-splines were determined based on AIC.
- For comparison, we also fit a homogeneous Markov model using the msm package.

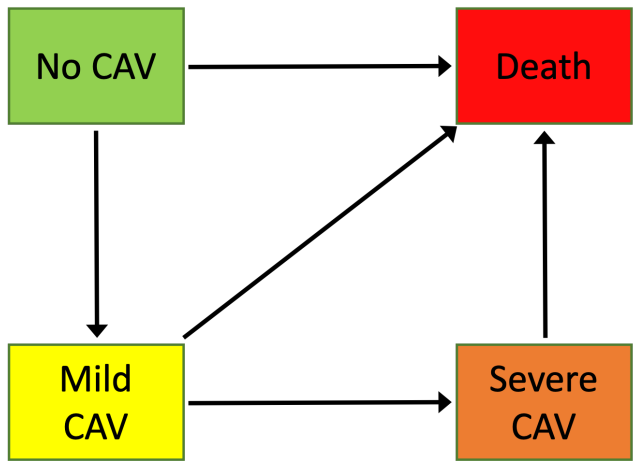


Table 2: Estimation results of regression parameters

	Proposed methods			msm package		
Covariate	Estimate	St error	p-value	Estimate	St error	p-value
No CAV to mild CAV						
Recipient age	−0.009	0.009	0.296	−0.013	0.007	0.071
Donor age	0.039	0.008	<0.001	0.027	0.006	<0.001
IHD	0.693	0.176	<0.001	0.549	0.151	<0.001
Acute rejection	0.163	0.041	<0.001	0.157	0.031	<0.001
Mild CAV to severe CAV						
Recipient age	−0.027	0.012	0.030	0.003	0.014	0.838
Donor age	−0.019	0.011	0.091	−0.009	0.011	0.378
IHD	0.335	0.269	0.213	0.081	0.227	0.722
Acute rejection	0.091	0.066	0.170	−0.015	0.055	0.783
No CAV to death						
Recipient age	0.074	0.015	<0.001	0.054	0.016	0.001
Donor age	0.032	0.010	0.002	0.020	0.009	0.032
IHD	0.144	0.255	0.573	0.085	0.223	0.703
Acute rejection	0.045	0.103	0.664	−0.058	0.085	0.498
Mild CAV to death						
Recipient age	0.074	0.031	0.017	−0.016	0.057	0.786
Donor age	0.025	0.027	0.349	−0.017	0.050	0.739
IHD	0.567	0.672	0.399	0.021	0.859	0.981
Acute rejection	0.101	0.123	0.412	0.250	0.123	0.043
Severe CAV to death						
Recipient age	−0.021	0.014	0.136	0.004	0.014	0.777
Donor age	−0.017	0.014	0.239	−0.008	0.012	0.518
IHD	−0.088	0.310	0.776	−0.232	0.225	0.303
Acute rejection	0.058	0.052	0.260	0.015	0.045	0.740

Key Findings

- Both donor age at transplant and cumulative number of acute rejection episodes are positively associated with the risk of mild CAV.
- Patients who received heart transplant due to ischemic heart disease have significantly higher risk of mild CAV.
- Older recipient and donor ages at transplant increase the risk of transition from no CAV to death.
- The variance of the random effect is estimated at 0.880 with a standard error estimator of 0.234, suggesting strong dependence among transitions.

Test Dynamic Prediction

- We randomly divide the 622 patients into training and testing sets at a 7:3 ratio.
- We fit the model using the training set to obtain the parameter estimates.
- For the testing set, we predict the RMST given the disease history up to each examination.
- For comparison, we redo the above steps using the msm package.

Prediction Error

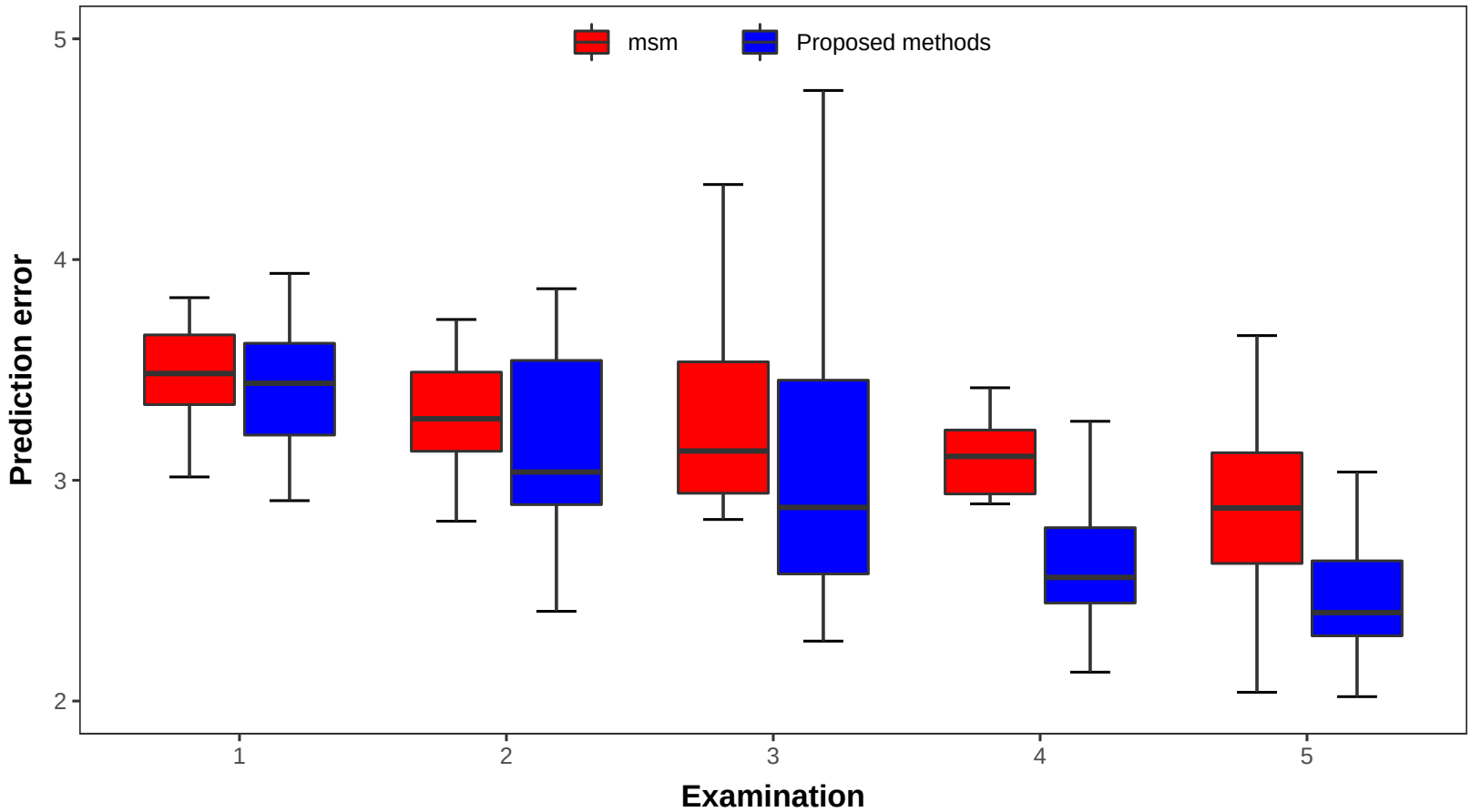


Figure 2: Boxplots of prediction error over 20 replicates at each examination.

Extension

- Our models can be extended to the competing risks set-up with more than one absorbing states, e.g., different causes of death.
- Joint modelling (with shared random effects) can be used when time-dependent covariates are measured only at a finite number of time points, or when there are more than one disease processes.
- Model diagnostics techniques, e.g., goodness-of-fit test.

Thank you!