

Semiparametric fiducial inference

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Abstract

R. A. Fisher introduced the concept of fiducial as a potential replacement for the Bayesian posterior distribution in the 1930s. During the past century, fiducial approaches have been explored in various parametric and nonparametric settings. However, to the best of our knowledge, no fiducial inference has been developed in the realm of semiparametric statistics. In this paper, we propose a novel fiducial approach for semiparametric models. To streamline our presentation, we use the Cox proportional hazards model, which is the most popular model for the analysis of survival data, as a running example.¹ Other models and extensions are also discussed. In our experiments, we find our method to perform well especially in situations when the maximum likelihood estimator fails.

keywords: Bernstein–von Mises theorem, Conic optimization, Cox model, Fiducial inference, Gibbs sampler, Semiparametric model

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¹In memory of Sir David Cox who passed away in 2022.

1 Introduction

Fiducial inference can be traced back to a series of articles by R. A. Fisher (Fisher, 1930, 1933) who introduced the concept attempts to find a middle ground between the frequentist and Bayesian perspectives. The fiducial distribution can be viewed as a potential replacement for the Bayesian posterior distribution in a data-driven sense which does not rely on a subjective prior selection.

In the past two decades, there has been a fast growing literature on fiducial methods and related approaches. For example, Wang (2000); Taraldsen and Lindqvist (2013) showed how fiducial distributions naturally arise within a decision theory framework; Hannig and Lee (2009) proposed fiducial solutions to wavelet regression and Wandler and Hannig (2012) addressed extreme value estimation from a fiducial perspective; Hannig (2009); Hannig et al. (2016) formalized the mathematical definition of generalized fiducial distribution. Their argument is based on inverting a data generating algorithm (DGA) that associates data to the parameters and a random component with a known distribution. The generalized fiducial distribution is then obtained by inverting the DGA for the parameter. A formal definition expedited the application of fiducial inference to a variety of important statistical problems such as linear mixed model (Cisewski and Hannig, 2012), ultrahigh-dimensional regression (Lai et al., 2015), censored data and survival analysis (Chen et al., 2016; Cui and Hannig, 2019; Cui et al., 2023), model selection (Williams and Hannig, 2019), empirical Bayes estimation and g -modeling (Cui and Hannig, 2023), vector autoregressive graph selection (Williams et al., 2023), etc. as well as to other fields including psychology (Liu and Hannig, 2016, 2017; Liu et al., 2019; Neupert and Hannig, 2019) and forensic science (Hannig et al., 2019). We refer to Murph et al. (2023) for a recent review of generalized fiducial inference.

Other related approaches include confidence distributions (Singh et al., 2005; Xie and Singh, 2013; Claggett et al., 2014; Schweder and Hjort, 2016; Hjort and Schweder, 2018), Dempster-

Shafer theory (Dempster, 1968; Shafer, 1976; Edlefsen et al., 2009), inferential models (Martin and Liu, 2013, 2015a,b; Liu and Martin, 2020), objective Bayesian inference (Berger et al., 2009, 2012), repro methods (Xie and Wang, 2022; Wang et al., 2022), and structural inference (Dawid et al., 1973; Fraser, 1966). We refer to Cui and Hannig (2024) for the connections between inferential model, confidence cures, and fiducial inference, and Cui and Xie (2023) for the connection between confidence distribution and fiducial inference.

While tremendous progress has been made in the area of the foundation of statistics in the past decades, there are few papers on semiparametric models. A semiparametric model is a statistical model that has parametric and nonparametric components (Bickel et al., 1993; Tsiatis, 2006; Kosorok, 2008). In this paper, we apply fiducial inference to such models and propose novel inferential tools for the finite-dimensional parameter of interest. To our knowledge, this is the first time fiducial inference has been systematically applied to semiparametric models. Specifically, we consider the celebrated Cox proportional hazards model (Cox, 1972) as a running example. We propose a novel Gibbs sampler to sample from the derived fiducial distribution using conic optimization. Upon obtaining fiducial samples, we use the samples to construct statistical inference. For example, the median of the samples is used as a point estimator, and appropriate quantiles are used to construct confidence intervals.

We establish an asymptotic theory that verifies the frequentist validity of the proposed fiducial approach. First, we prove the consistency of the proposed fiducial point estimator. Next, we establish a Bernstein–von Mises theorem for the fiducial distribution. As a consequence of the Bernstein–von Mises theorem, the proposed confidence intervals provide asymptotically correct coverage, and the proposed fiducial estimator is first-order asymptotically equivalent to the maximum partial likelihood estimator. It is noteworthy that the proposed point estimator works well in scenarios when the classic maximum partial likelihood estimator fails.

The remainder of the article is organized as follows. In Section 2, we take a new look at the Cox model from a data generating perspective and derive our generalized fiducial distribution for our parameter of interest. We then propose a novel conic optimization-based Gibbs sampler to sample from the fiducial distribution. In Section 3, we develop consistency and asymptotic normality for the proposed fiducial estimator. In Section 4, we demonstrate the superiority of our estimator compared to the maximum likelihood estimator through simulation studies. Section 5 provides several extensions of the proposed method to other semiparametric models. Section 6 describes a real data application on modern HIV trials. The article concludes with a discussion of future work in Section 7. Additional results and proofs are provided in the Appendix.

2 Methodology

2.1 The Cox proportional hazards model revisited

We consider the Cox proportional hazards model which is the most popular model (Cox, 1972) for the analysis of survival data as a running example. Suppose we observe right-censored survival data (X_i, Y_i, Δ_i) , $i \in [n] := \{1, \dots, n\}$, where $Y_i = \min\{T_i, C_i\}$, censoring indicator $\Delta_i = I\{T_i \leq C_i\}$, and T_i , C_i , X_i represent the failure time, the censoring time, and explanatory covariates for the i -th subject, respectively. We assume a noninformative censoring mechanism here, i.e., T_i and C_i are independent given X_i .

Let $S_i(\cdot)$ and $\lambda_i(\cdot)$ denote the survival function and hazard function of the i -th subject, respectively, and \mathcal{R}_i denote the at-risk index set at the time Y_i , i.e., $\mathcal{R}_i = \{j : Y_j \geq Y_i\}$. Note that the full likelihood function is

$$\prod_{i=1}^n \left[\frac{\lambda_i(Y_i)}{\sum_{j \in \mathcal{R}_i} \lambda_j(Y_i)} \right]^{\Delta_i} \left[\sum_{j \in \mathcal{R}_i} \lambda_j(Y_i) \right]^{\Delta_i} S_i(Y_i).$$

The Cox proportional hazards model posits the following form of hazard function:

$$\lambda_i(t) = \lambda_0(t)g(\beta^\top X_i),$$

where $\lambda_0(t)$ is a baseline hazard function, and $g(\beta^\top X)$ is a link function. We first consider the most prevalent case $g(\beta^\top X) = \exp(\beta^\top X)$. This leads to the following likelihood function

$$L(\beta, \lambda_0) = \prod_{i=1}^n \left[\frac{\exp(\beta^\top X_i)}{\sum_{j \in \mathcal{R}_i} \exp(\beta^\top X_j)} \right]^{\Delta_i} \left[\lambda_0(Y_i) \sum_{j \in \mathcal{R}_i} \exp(\beta^\top X_j) \right]^{\Delta_i} S_i(Y_i), \quad (1)$$

where $S_i(t) = \exp(-\Lambda_0(t) \exp(\beta^\top X_i))$ and $\Lambda_0(t) = \int_0^t \lambda_0(s) ds$.

We are interested in statistical inference on the log hazard ratio β . Under the Cox proportional hazards model, the well-known Cox's partial likelihood (Cox, 1975) is given below

$$L(\beta) = \prod_{i=1}^n \left[\frac{\exp(\beta^\top X_i)}{\sum_{j \in \mathcal{R}_i} \exp(\beta^\top X_j)} \right]^{\Delta_i}.$$

Maximizing the log partial likelihood can be achieved via Newton-Raphson algorithm, and the inverse of the Hessian matrix evaluated at the maximum likelihood estimator $\tilde{\beta}$ can be used for constructing confidence intervals. The consistency and asymptotically normality of $\tilde{\beta}$ can be established (Andersen and Gill, 1982; Lin and Wei, 1989; Fleming and Harrington, 2013). However, despite the popularity of the Cox model and partial likelihood approach, as can be seen in our simulation section, the estimation might not converge when the sample size of data is relatively small. In comparison we will see that the proposed generalized fiducial based estimation works well.

2.2 A data generating perspective for the Cox model

The generalized fiducial inference approach (Hannig et al., 2016) often has good finite sample performance especially when the sample sizes of datasets are small as long as it has a sound asymptotic property. The generalized fiducial inference usually starts with a DGA, and we now look at the Cox model from the following novel data generating perspective. In particular, we describe a DGA for which the corresponding fiducial distribution for β naturally corresponds to Cox's partial likelihood.

Without loss of generality, let c_1, \dots, c_n be the censoring times that may or may not be observed. We first model the first failure. Set $\mathcal{R}_1(t) = \{1, \dots, n\} \setminus \{i : c_i < t\}$. The hazard that any subject fails is the sum of hazards of all at-risk subjects $\bar{\lambda}_1(t) = \sum_{j \in \mathcal{R}_1(t)} \lambda_j(t) = \lambda_0(t) \sum_{j \in \mathcal{R}_1(t)} \exp(\beta^\top X_j)$. The corresponding $\bar{\Lambda}_1(t) = \int_0^t \bar{\lambda}_1(s) ds$ and $\bar{S}_1(t) = \exp(-\bar{\Lambda}_1(t))$. We generate the time of the first failure by $t_1 = \bar{S}_1^{-1}(W_1)$, where W_1 is generated from a uniform distribution on $(0, 1)$. The subject that failed first is generated as $i_1 \sim \text{Multinomial}(1, \vec{q}_1)$, where

$$\vec{q}_1 = [q_{1,1}(\beta), \dots, q_{1,n}(\beta)]^\top, \text{ and } q_{1,i}(\beta) = \begin{cases} \frac{\exp(\beta^\top X_i)}{\sum_{j \in \mathcal{R}_1(t_1)} \exp(\beta^\top X_j)} & \text{if } i \in \mathcal{R}_{i_1} = \mathcal{R}_1(t_1); \\ 0 & \text{otherwise.} \end{cases}$$

Because t_1 is the smallest failure time, any subject i with censoring time $c_i < t_1$ is a censored observation with censoring time c_i .

We continue to generate the next subjects that failed t_2, \dots, t_{k-1} repeating the above step. At the time of $(k-1)$ -th failure, we have t_{k-1} and i_1, \dots, i_{k-1} . The at-risk set after the $k-1$ -th failure is

$$\mathcal{R}_k(t) = \{1, \dots, n\} \setminus (\{i : c_i < t\} \cup \{i_1, \dots, i_{k-1}\}). \quad (2)$$

Define $\bar{\lambda}_k(t) = \sum_{j \in \mathcal{R}_k(t)} \lambda_j(t) = \lambda_0(t) \sum_{j \in \mathcal{R}_k(t)} \exp(\beta^\top X_j)$, $\bar{\Lambda}_k(t) = \int_{t_{k-1}}^{t \vee t_{k-1}} \bar{\lambda}_k(s) ds$, and $\bar{S}_k(t) = \exp(-\bar{\Lambda}_k(t))$. We generate time of k -th failure by $t_k = \bar{S}_k^{-1}(W_k)$, where W_k is generated from the Uniform(0,1) distribution. The k -th subject that failed is generated as $i_k \sim \text{Multinomial}(1, \vec{q}_k)$, where

$$\vec{q}_k = [q_{k,1}(\beta), \dots, q_{k,n}(\beta)]^\top, \text{ and } q_{k,i}(\beta) = \begin{cases} \frac{\exp(\beta^\top X_i)}{\sum_{j \in \mathcal{R}_k(t_k)} \exp(\beta^\top X_j)} & \text{if } i \in \mathcal{R}_{i_k} = \mathcal{R}_k(t_k); \\ 0 & \text{otherwise.} \end{cases} \quad (3)$$

Again subjects $i \in \mathcal{R}_k(t_{k-1}) = \mathcal{R}_{k-1} \setminus \{i_{k-1}\}$ with censoring time $c_i < t_k$ are censored observations with censoring time c_i . This is repeated until either the generated failure time $t_k = \infty$ (the last observation is censored) or $\mathcal{R}_{k+1}(t_k) = \emptyset$ (the last observation is failure).

The above procedure completes the data generation given the censoring times. As shown in the following proposition, the above data generating mechanism produces data from the Cox proportional hazards model.

Proposition 2.1. *Data generated from the above steps follows the likelihood (1).*

Remark 1. *Technically, the likelihood (1) does not allow for ties. However, ties can be introduced by allowing the cumulative hazard function $\Lambda_0(t)$ to have jumps and changing the likelihood accordingly. The details are shown in Appendix B, where we also propose an approximation to the DGA that leads to fiducial distribution which is analogous to Breslow partial likelihood (Peto, 1972; Breslow, 1974).*

Next, we will see how we utilize this DGA to conduct our fiducial inversion.

2.3 Fiducial inversion for the Cox model

In this subsection, we derive the generalized fiducial distribution to the Cox proportional hazards model by inverting the DGA from the previous section.

The GFD for β is obtained by inversion of the multinomial distributions (3). To this end, we follow Lawrence et al. (2009) as further explained in Hannig et al. (2016). Since all $m_k = 1$, i.e., all event times are distinct, the fiducial distribution for β is based on solving the inequalities,

$$U_k^* \leq \frac{\exp(\beta^\top X_{i_k})}{\sum_{j \in \mathcal{R}_{i_k}} \exp(\beta^\top X_j)} = q_{k,i_k}(\beta) := q_k(\beta), \quad k = 1, \dots, m, \quad (4)$$

where U_k^* are jointly uniform distribution on the set on which the solution to (4) exists, and i_k is the index of the subject who failed at the time of k -th failure.

Sampling (U_1^*, \dots, U_m^*) from the uniform distribution on the set on which solution to (4) exists is computationally challenging. Therefore we propose a Gibbs sampler for generating U_k^* and β_j^* . Notice that for any $k = 1, \dots, m$, the distribution of U_k^* given the rest is $\text{Uniform}(0, q_k^*)$, where the upper bound q_k^* is found by the following

constraint optimization problem:

$$\max_{\beta} \frac{\exp(\beta^{\top} X_{i_k})}{\sum_{j \in \mathcal{R}_{i_k}} \exp(\beta^{\top} X_j)} \quad (5)$$

subject to the following $(m - 1)$ constraints,

$$U_h^* \leq q_h(\beta), \quad h \in \{1, \dots, m\} \setminus \{k\}.$$

Upon obtaining q_k^* , we then update $U_k^* \sim \text{Uniform}(0, q_k^*)$.

After j -th cycle of the Gibbs sampler is finished, we want to generate a representative of the set $Q(U^*) = \{\beta : \text{satisfying (4)}\}$. To this end generate w from a standard normal distribution and then calculate β_j^* by solving

$$\max_{\beta} \beta^{\top} w \quad (6)$$

subject to the following m constraints,

$$U_h^* \leq q_h(\beta), \quad h \in \{1, \dots, m\}.$$

The complete Gibbs sampler is summarized in the following Algorithm 1.

Algorithm 1: A fiducial Gibbs sampler

Input: Dataset (X_i, Y_i, Δ_i) , n_{mcmc} , n_{burn} .

- 1 Use $q_1(\tilde{\beta}), \dots, q_m(\tilde{\beta})$ as initial values and generate U_k^* by $\text{Uniform}(0, q_k(\tilde{\beta}))$:
 - 2 **for** $j = 1$ **to** $n_{\text{burn}} + n_{\text{mcmc}}$ **do**
 - 3 **for** $k = 1$ **to** m **do**
 - 4 Solve q_k^* by (5) based on the current U_h^* , $h = 1, \dots, k - 1, k + 1, \dots, m$;
 - 5 Update U_k^* by a random sample $U_k^* \sim \text{Uniform}(0, q_k^*)$;
 - 6 **end**
 - 7 Generate β_j^* by (6) based on the current U_h^* , $h = 1, \dots, m$;
 - 8 **end**
 - 9 **return** The fiducial samples β_j^* , $j = n_{\text{burn}} + 1, \dots, n_{\text{burn}} + n_{\text{mcmc}}$.
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Once the fiducial sample is generated, we propose to use the pointwise median of β_j^* , $j = n_{\text{burn}} + 1, \dots, n_{\text{burn}} + n_{\text{mcmc}}$ as a point estimator, and empirical 0.025 quantile as a lower limit and the empirical 0.975 quantile as an upper limit.

Remark 2. *When the failure times contain ties, the approximate DGA given in Appendix B leads to a fiducial distribution for β that is the same as described above with the caveat that if some observations share failure time t_k they also share the at-risk sets \mathcal{R}_k . This is similar to the approximation of Peto-Breslow method (Peto, 1972; Breslow, 1974). In fact, the fiducial approach provides a new insight showing that Peto-Breslow approximation is achieved at the cost of Poisson approximation. This approximation works well if the jumps in Λ_0 are small, i.e., $\max_k m_k \ll m$.*

2.4 A conic optimization-based Gibbs sampler

While the optimization problems in (5) and (6) can be solved through a brute force search, the computation is usually costly when β is multivariate. In this subsection, we propose a conic optimization approach to (5) and (6).

Theorem 2.1. *The optimization problem (5) is equivalent to the following optimization problem,*

$$\begin{aligned} & \min_{\beta, s_k} -(\beta^\top X_{i_k} - s_k) \\ & \text{subject to} \quad \sum_{j \in \mathcal{R}_{i_l}} t_{j,l} \leq 1, \quad l = 1, \dots, m \\ & (t_{j,l}, 1, \beta^\top X_j - s_l) \in K_{exp}, \quad j \in \mathcal{R}_{i_l}, \quad l = 1, \dots, m \\ & \beta^\top X_{i_h} - s_h \geq \log(U_h^*), \quad h \neq k, \quad h = 1, \dots, m \end{aligned}$$

where K_{exp} is an exponential cone defined as

$$K_{exp} := \{(x_0, x_1, x_2) \in \mathbb{R}^3 : x_0 \geq x_1 \exp(x_2/x_1), x_0, x_1 \geq 0\}.$$

Theorem 2.2. *The optimization problem (6) is equivalent to the following optimization*

problem,

$$\begin{aligned}
& \min_{\beta} -\beta^{\top} w \\
& \text{subject to} \quad \sum_{j \in \mathcal{R}_l} t_{j,l} \leq 1, \quad l = 1, \dots, m \\
& (t_{j,l}, 1, \beta^{\top} X_j - s_l) \in K_{exp}, \quad j \in \mathcal{R}_l, \quad l = 1, \dots, m \\
& \beta^{\top} X_{i_h} - s_h \geq \log(U_h^*), \quad h = 1, \dots, m.
\end{aligned}$$

The proofs can be found in Appendix C. The implementation can be done through large-scale optimization software Mosek MOSEK (2015).

3 Theory

3.1 Consistency

We define for $i = 1, \dots, n$,

$$p_i(\beta) = \begin{cases} \frac{\exp(\beta^{\top} X_i)}{\sum_{j \in \mathcal{R}_i} \exp(\beta^{\top} X_j)} & \text{if failure;} \\ 1 & \text{if censored.} \end{cases} \quad (7)$$

We also define the counting process

$$N_i(t) = I\{Y_i \leq t\} \Delta_i,$$

and the at-risk process

$$Y_i(t) = I\{Y_i \geq t\}.$$

Throughout, we assume the following condition on the horizon.

Assumption 1. *There exists τ so that $P(C_i \leq \tau) = 1$ and $P(Y_i(\tau) = 1) > 0$.*

First, we show that the mode of the fiducial distribution is a maximum likelihood estimator which is consistent for the true parameter β_0 .

Theorem 3.1 (Consistency). *For a given dataset, any β maximizing fiducial probability $P^*(\beta \in Q(U^*))$ is a maximum likelihood estimator.*

3.2 A Bernstein–von Mises theorem

Note that the fiducial distribution is a data-dependent distribution which is defined for every fixed dataset. The fiducial distribution can be made into a random measure by plugging random variables (X, Y, Δ) into the observed data. We establish a Bernstein-von Mises theorem for this random measure for a one-dimensional case and a multivariate case holds similarly which is provided in the Appendix.

We first define some notation. Let $S^j(\beta, t) = \frac{1}{n} \sum_{i=1}^n Y_i(t) X_i^j \exp(\beta X_i)$, $j = 0, 1, 2$, and

$$\begin{aligned} V(\beta, t) &= \frac{S^2(\beta, t)}{S^0(\beta, t)} - \left(\frac{S^1(\beta, t)}{S^0(\beta, t)} \right)^2 \\ &= \frac{1/n \sum_{i=1}^n (X_i - \epsilon(\beta, t))^2 Y_i(t) \exp(\beta X_i)}{S^0(\beta, t)}, \end{aligned}$$

where $\epsilon(\beta, t) := \frac{S^1(\beta, t)}{S^0(\beta, t)}$. We consider the following regularity conditions:

- (1) $\int_0^\tau \lambda_0(x) dx < \infty$.
- (2) For $S^{(j)}$, $j = 0, 1, 2$, there exists a neighborhood B of β_0 such that

$$\sup_{t \in [0, \tau], \beta \in B} \|S^j(\beta, t) - s^j(\beta, t)\| \rightarrow 0,$$

in probability.

- (3) There exists $\delta > 0$ such that

$$n^{-1/2} \sup_{i \in [n], t \in [0, \tau]} |X_i| Y_i(t) I\{\beta_0 X_i > -\delta |X_i|\} \rightarrow 0,$$

in probability.

- (4) Then for all $\beta \in B$ and $t \in [0, \tau]$,

$$\frac{\partial}{\partial \beta} s^0(\beta, t) = s^1(\beta, t),$$

and

$$\frac{\partial^2}{\partial \beta^2} s^0(\beta, t) = s^2(\beta, t).$$

(5) The functions s^j are bounded for $j = 0, 1, 2$, and s^0 is bounded away from 0 on $B \times [0, \tau]$. The family of functions $s^j(\cdot, t)$, $j = 0, 1, 2$, $t \in [0, \tau]$ is an equicontinuous family at β_0 .

(6) The matrix

$$H(\beta_0) = \int_0^\tau v(\beta_0, t) s^0(\beta_0, t) \lambda_0(t) dt$$

is positive definite, where $v(\beta_0, t) := \frac{s^2}{s^0} - e^2$ and $e := s^1/s^0$.

(7) The covariate X is on a compact set.

(8) We assume that there exists a $\delta_0 > 0$ and $Q(\beta)$

$$\sup_{|\beta - \beta_0| \leq \delta_0} \left| \frac{1}{n} \frac{\partial^2 \log(L_n(\beta))}{\partial \beta^2} \Big|_{\beta = \beta} + Q(\beta) \right| \rightarrow 0,$$

in probability. Furthermore, we assume that $Q(\beta)$ is continuous.

(9) We assume that

$$\frac{1}{n} \sum_{i=1}^n \int_0^\tau \frac{|X_i S^0(\beta_0, s) - S^1(\beta_0, s)|}{S^0(\beta_0, s)} \min_{\beta} \frac{S^0(\beta, s)}{\exp(\beta X_i)} dN_i(s) \rightarrow \int_0^\tau w(\beta_0, s) ds, \quad (8)$$

in probability, and $0 < \int_0^\tau w(\beta_0, s) ds < \infty$.

(10) For any $\delta > 0$ and i , there exists an $\epsilon > 0$ such that

$$P \left(\sup_{|\beta - \beta_0| > \delta} \left(\log \frac{L_n(\beta)}{p_i(\beta)} - \log \frac{L_n(\beta_0)}{p_i(\beta_0)} \right) \leq -n\epsilon \right) \rightarrow 1.$$

Conditions (1)-(6) are typically assumed in the literature for maximum likelihood estimation of Cox model (Andersen and Gill, 1982; Fleming and Harrington, 2013). Condition (8) assumes that in a neighborhood of β the second derivative of the log likelihood has a limit $Q(\beta)$ which is continuous in β . Condition (9) assumes that the left hand side of (8) has a limit. Condition (10) is a condition for Bayesian posterior distribution to be close to the maximum likelihood estimator (Ghosh and Ramamoorthi, 2003).

Let $\eta = \sqrt{n}(\beta - \tilde{\beta})$. We define rescaled distribution $r_n(\eta) = r(\tilde{\beta} + \eta/\sqrt{n})/\sqrt{n}$, where $r(\beta)$ is the fiducial distribution implied by Algorithm 1. We have the following theorem.

Theorem 3.2 (Asymptotic normality). *Under Conditions (1)-(10), we have*

$$\int |r_n(\eta) - f_N(\eta)| d\eta \rightarrow 0,$$

in probability, where $f_N(\beta)$ is the density of a normal distribution with mean 0 and variance $H^{-1}(\beta_0)$.

To conclude, we provide the following corollary which shows that the proposed confidence intervals have asymptotically correct coverage.

Corollary 3.1 (Coverage property). *Under the assumptions in Theorem 3.2, any set $C_{n,\alpha} = \{\beta : \|\beta - \tilde{\beta}\| \leq \epsilon_{n,\alpha}\}$ with $P^*(C_{n,\alpha}) = 1 - \alpha$ is an $(1 - \alpha)$ asymptotic confidence set for β_0 .*

4 Simulation studies

In this simulation, we compare our estimator with the maximum likelihood estimator using synthetic datasets. We consider four scenarios with different combinations of $\beta_0 = (\beta_1, \beta_2)$.

The survival time follows

$$\lambda_T(t) = \lambda_0(t) \exp[\beta_1 X^{(1)} + \beta_2 X^{(2)}],$$

where the baseline hazard function $\lambda_0(t) = 1$. The censoring time is uniformly distributed on $(0, 2)$. The covariates $X^{(1)}$ and $X^{(2)}$ follow a binomial distribution with success probability $1/2$.

For each scenario, training datasets (X, Y, Δ) were generated with a sample size $n = 20$. For each training dataset, we applied our estimator as well as the maximum likelihood estimator. The fiducial estimates were based on 400 iterations of the Gibbs sampler after 40 burn-in times. The simulations were replicated 200 times for each scenario.

We compare the mean squared error (MSE) of point estimators and the coverage and average length of confidence intervals (CI). The numerical results for each scenario are presented in Table 1. For point estimators, in general, the proposed fiducial method outperforms the maximum likelihood estimator. In particular, the maximum likelihood estimator does not converge in several runs in Scenarios 1, 2, and 4. Importantly, when the maximum likelihood estimator fails, the proposed fiducial estimator provides a valid estimation. For uncertainty quantification, we see that the fiducial confidence interval is comparable to the maximum likelihood confidence interval and overall, has a shorter length.

5 Extension to other semiparametric models

5.1 Other link functions

The proposed method and Algorithm 1 naturally extend to the following model:

$$\lambda(t) = \lambda_0(t)g(\beta^\top X),$$

where g is any positive valued link. The developed large sample theory in Section 3 also applies to this generalized model.

5.2 Constrained Cox model

In certain practical problems, some prior information that restricts model parameters would result in a more interpretable conclusion. Such restrictions cannot be ignored, otherwise the statistical inference may be biased. Our fiducial method automatically solves constrained Cox models (Ding et al., 2015; Yin et al., 2021), for example, with equality constraints

$$\beta \in \{\beta : f(\beta) = 0\},$$

Table 1: Comparison of maximum likelihood estimator and the proposed fiducial estimator

($n = 20$)

Model	Estimator	MSE ($\times 10^{-2}$)	Length of CI	Coverage of CI (%)
Model 1 ($\beta_1 = -0.5, \beta_2 = 0$)	MLE $\tilde{\beta}_1$	1431*	1863.25	95
	Fiducial $\hat{\beta}_1$	84	3.10	92
	MLE $\tilde{\beta}_2$	286*	325.89	95
	Fiducial $\hat{\beta}_2$	75	3.08	94.5
Model 2 ($\beta_1 = 0, \beta_2 = 0.5$)	MLE $\tilde{\beta}_1$	300*	254.04	94
	Fiducial $\hat{\beta}_1$	57	2.64	93.5
	MLE $\tilde{\beta}_2$	261*	271.17	93
	Fiducial $\hat{\beta}_2$	60	2.68	92.5
Model 3 ($\beta_1 = 0.5, \beta_2 = 1$)	MLE $\tilde{\beta}_1$	57	2.43	92.5
	Fiducial $\hat{\beta}_1$	54	2.46	92
	MLE $\tilde{\beta}_2$	66	2.62	92.5
	Fiducial $\hat{\beta}_2$	59	2.64	91.5
Model 4 ($\beta_1 = 1, \beta_2 = 1.5$)	MLE $\tilde{\beta}_1$	49	2.47	94
	Fiducial $\hat{\beta}_1$	43	2.40	93.5
	MLE $\tilde{\beta}_2$	730*	766.87	95.5
	Fiducial $\hat{\beta}_2$	56	2.57	95

* indicates log likelihood might not converge for some runs

and inequality constraints

$$\beta \in \{\beta : g(\beta) \leq 0\}.$$

5.3 Additive hazards model

Aalen’s additive hazards model Aalen (1980); McKeague (1986); Huffer and McKeague (1991); Lin and Ying (1994)

$$\lambda(t) = \beta(t)^\top X,$$

provides an alternative to the Cox proportional hazards model. If we rewrite the model as

$$\lambda(t) = \beta_0(t)\beta(t)^\top X,$$

where $1^\top \beta(t) = 1$, the extended fiducial algorithm in Appendix B covers such scenarios if we parametrize $\beta(t)$. For example, one might impose a polynomial basis

$$\beta(t) = \alpha_0 + \alpha_1 t + \alpha_2 t^2,$$

or a spline model, e.g., a B-spline. In this case, the probability \vec{q}_k in (3) becomes

$$q_{k,l}(\vec{\alpha}) = \begin{cases} \frac{\beta^\top(t_k)X_l}{\sum_{j \in \mathcal{R}_k(t_k)} \beta^\top(t_k)X_j} & \text{if } l \in \mathcal{R}_k(t_k); \\ 0 & \text{otherwise.} \end{cases}$$

5.4 Time-varying covariates and coefficients

Our proposed method also readily extends to the Cox model with time-varying covariates (Fisher and Lin, 1999),

$$\lambda(t) = \lambda_0(t) \exp(\beta^\top X(t)).$$

For the Cox model with time-varying coefficients (Tian et al., 2005),

$$\lambda(t) = \lambda_0(t) \exp(\beta^\top(t)X(t)),$$

we can parametrize $\beta(t)$ in the same way as Section 5.3 and apply the proposed method to sample from the fiducial distribution and then conduct statistical inference.

6 Real data application

The HVTN 704/HPTN 083 and HVTN 703/HPTN 081 Antibody Mediated Prevention Phase 2b Prevention Efficacy Trials evaluated the prevention efficacy of an infused monoclonal antibody, VRC01, against the endpoint of HIV diagnosis. Participants were recruited from four continents, primarily Africa and North and South America, for random assignment 1:1:1 to treatment by a low or high dose of VRC01, or placebo. HIV diagnosis rates varied across these populations during the study in all three treatment arms, as did circulating HIV-1 strains and participant characteristics. Evaluating efficacy of a preventative intervention by Cox proportional hazards modeling is a component of the pre-planned statistical analyses of this and similar trials, however the sample sizes are limited for such models, especially when evaluating efficacy in specific sub-populations. The original study overall found that there was no significant efficacy against diagnosis of HIV-1 disease overall, however when evaluated against diagnosis of strains of HIV-1 that are susceptible to neutralization by VRC01, a pre-specified analysis, the estimated intervention efficacy, pooled across the trials, was 75.6% (95% CI 45.5% to 88.9%), supporting further research into passive immunoprophylaxis for HIV and supporting further research into the development of HIV-1 vaccines that elicit neutralizing antibodies Corey et al. (2021).

The preventative efficacy of the VRC01 infusion intervention was not reported for specific sub-populations, for example by analysis within different countries that participated in the study. Here we employed our fiducial Cox analysis methodology for evaluating efficacy within subpopulations that are too small for reliable Cox analysis by standard methodology. In this paper, we conducted a sub-population analysis to evaluate the pooled efficacy of the VRC01 infusion intervention against diagnosis of infection by susceptible HIV-1 in the subset of participants who were recruited at sites in Malawi ($n = 180$, of whom only three were diagnosed with VRC01-susceptible HIV-1) and found that by standard Cox regression analysis (employing the MLE estimator),

the estimator did not converge. Employing the fiducial estimator that we have described here, we found some evidence of a treatment effect: fiducial point estimator for efficacy 79.7%, 90% CI (39.9%, 100%), 95% CI (-4.2%, 100%), with fiducial $p = 0.053$ for efficacy departing from 0%.

7 Discussion

In this paper, we have considered fiducial inference in semiparametric models. Taking the Cox proportional hazards model as a running example, we proposed a novel Gibbs sampler to sample from fiducial distribution. We have also established the consistency and asymptotic normality of the proposed estimator. In addition, we have also discussed several extensions of our approach to other semiparametric models. Our approach was illustrated via simulation studies and a real data application. Our paper contributes to the literature on both foundations of statistics and semiparametric inference.

The proposed method may be extended in several directions. One possible extension is to consider variable selection in semiparametric models such as the Cox model (Fan and Li, 2002; He et al., 2020) following Williams and Hannig (2019). It is also possible to consider functional predictors in semiparametric models (Chen et al., 2011; Hao et al., 2021). Another important direction is to consider fiducial approaches to other semiparametric transformation models (Cheng et al., 1995; Zeng and Lin, 2006) and semiparametric models in causal inference (Robins et al., 1994; Bickel and Kwon, 2001; Laan and Robins, 2003) which also has a coarsened data structure.

Acknowledgement

The authors are thankful to Quoc Tran Dinh for helpful discussions on optimization. This research was partially supported by the National Natural Science Foundation of

China, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (UM1AI068635 and R37AI054165), and the National Science Foundation (DMS-1916115, 2113404, 2210337). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

A Proof of Proposition 2.1

Proof. Notice that based on the DGA, the likelihood that the first failure time is equal to Y_{i_1} is

$$\frac{d}{dt} \bar{S}_1(Y_{i_1}) = \bar{\lambda}_1(Y_{i_1}) \exp(-\bar{\Lambda}_1(Y_{i_1})),$$

and the probability that the subject i_1 is the first observed failure is

$$\frac{\exp(\beta^\top X_{i_1})}{\sum_{j \in \mathcal{R}_1(Y_{i_1})} \exp(\beta^\top X_j)}.$$

Similarly, given the first $k - 1$ observed failure times the conditional likelihood of $t_k = Y_{i_k}$ given $t_1 = Y_{i_1}, \dots, t_{k-1} = Y_{i_{k-1}}$ is

$$\frac{d}{dt} \bar{S}_k(Y_{i_k}) = \bar{\lambda}_k(Y_{i_k}) \exp(-\bar{\Lambda}_k(Y_{i_k})),$$

and the conditional probability that the subject i_k is the k -th observed failure is

$$\frac{\exp(\beta^\top X_{i_k})}{\sum_{j \in \mathcal{R}_k(Y_{i_k})} \exp(\beta^\top X_j)}.$$

The joint likelihood implied by our DGA is

$$\prod_{k=1}^m \frac{\exp(\beta^\top X_{i_k})}{\sum_{j \in \mathcal{R}_k(Y_{i_k})} \exp(\beta^\top X_j)} \left[\lambda_0(Y_{i_k}) \sum_{j \in \mathcal{R}_k(Y_{i_k})} \exp(\beta^\top X_j) \right] \exp(-\bar{\Lambda}_k(Y_{i_k})). \quad (9)$$

By combining integrals together and redistributing the sums over the at-risk sets we get

$$\exp\left(-\sum_{k=1}^m \bar{\Lambda}_k(Y_{i_k})\right) = \prod_{i=1}^n S_i(Y_i).$$

By rearranging terms in (9) we get (1) as desired. \square

B Data generating Algorithm

In this section, we discuss a generalization of the data extending the algorithm in Section 2.2 to more general survival models. Recall, that for each subject $i = 1, \dots, n$, the cumulative hazard is Λ_i , the subject's survival function is $S_i(t) = \exp(-\Lambda_i(t))$, and their potentially counterfactual censoring time is c_i . The subjects are assumed independent.

We proceed by iteratively generating the failure times t_k and the set of subjects that failed at that time d_k , $k = 1, \dots, K$. We will denote by $m_k = |d_k|$ the number of failures at time t_k ; notice that $m = \sum_{k=1}^K m_k$. The k -th failure removed set $\bar{\mathcal{R}}_k = \{1, \dots, n\} \setminus \bigcup_{l=1}^{k-1} d_l$, and

$$\bar{S}_k(t) = \prod_{i \in \bar{\mathcal{R}}_k} \frac{S_i((t_{k-1} \vee t) \wedge c_i)}{S_i(t_{k-1} \wedge c_i)},$$

where $t_0 = 0$. Notice that the freezing of survival function at the censoring times used together with the failure removed set has the same effect as using the usual at-risk set.

The k -th failure time is generated by $t_k = \bar{S}_k^{-1}(W_k)$, where W_k are i.i.d. $\text{Uniform}(0, 1)$. Next we need to generate which subjects d_k failed at time t_k . To this end, let $B_{k,i}^{dt}$, $i \in \bar{\mathcal{R}}_k$ be independent Bernoulli(q_k^{dt}), conditioned on the event $\{\sum_{i \in \bar{\mathcal{R}}_k} B_{k,i}^{dt} \geq 1\}$, where $q_{k,i}^{dt} = \frac{S_i((t_k - dt) \wedge c_i) - S_i(t_k \wedge c_i)}{S_i((t_k - dt) \wedge c_i)}$. Denote by $B_{k,i}$ the limiting distribution of $B_{k,i}^{dt}$ as $dt \rightarrow 0$. The set of subjects that failed at time t_k is generated by sampling $B_{k,i}$ and setting $d_k = \{i : B_{k,i} = 1\}$. This process is continued until either $\bar{\mathcal{R}}_{k+1} = \emptyset$, or the generated failure time $t_k = \infty$.

When $\bar{S}_k(t)$ is continuous at t_k , the limiting distribution has only one failure with probability one which is selected from the multinomial($1, \vec{q}_k$), where

$$q_{k,i} = \begin{cases} \frac{\frac{d}{dt} \Lambda_i(t_k)}{\sum_{j \in \mathcal{R}_k(t_k)} \frac{d}{dt} \Lambda_j(t_k)} & \text{if } i \in \mathcal{R}_k(t_k); \\ 0 & \text{otherwise,} \end{cases} \quad (10)$$

where $\mathcal{R}_k(t_k)$ is the at risk set defined in (2). Thus if $\Lambda_i(t) = \Lambda_0(t) \exp(\beta^\top X_i)$, the multinomial probability \vec{q}_k is the same as in (3). Additionally, if $\Lambda_0(t) = \int_0^t \lambda_0(s) ds$ we have exactly the same DGA as in Section 2.2.

When $\bar{S}_k(t)$ has a jump at t_k , then we can have more than one failure at that time. For any $d_k \subset \mathcal{R}_k(t_k)$, the probability of generating these failures is given by

$$P(d_k \text{ is selected}) = \frac{\bar{S}_k(t_k^-)}{\bar{S}_k(t_k^-) - \bar{S}_k(t_k)} \prod_{i \in d_k} \frac{S_i(t_k^-) - S_i(t_k)}{S_i(t_k^-)} \prod_{i \in \mathcal{R}_k(t_k) \setminus d_k} \frac{S_i(t_k)}{S_i(t_k^-)}, \quad (11)$$

where $S_i(t^-)$ denotes the left limit of the survival function.

Using an argument similar to the proof of Proposition 2.1 we can show that this DGA produces the same likelihood as generating each failure time individually. However, even if $\Lambda_i(t) = \Lambda_0(t) \exp(\beta^\top X_i)$, the probability (11) does not provide the usual nice partial likelihood. Therefore, following the usual practice of using approximate likelihood (Peto, 1972; Kalbfleisch and Prentice, 1973; Breslow, 1974; Efron, 1977), we propose an approximate DGA for this setting:

First we approximate the probability

$$\frac{S_i(t_k^-) - S_i(t_k)}{S_i(t_k^-)} \approx (\Lambda_0(t_k) - \Lambda_0(t_k^-)) \exp(\beta^\top X_i).$$

Next at each time t_k , we approximate the distribution of the number of failures $m_k = \sum_{i \in \mathcal{R}_k(t_k)} B_{k,i}$ using the Poisson(η_k) distribution conditional on the set $\{m_k \geq 1\}$, where

$$\eta_k = \sum_{i \in \mathcal{R}_k(t_k)} (\Lambda_0(t_k) - \Lambda_0(t_k^-)) \exp(\beta^\top X_i).$$

Finally, given m_k , the set d_k is generated from the multinomial(m_k, \vec{q}_k) distribution conditional on the event that each category is observed at most once, with \vec{q}_k given by (3).

C Conic optimization

In this section, we provide proofs of Theorems 2.1 and 2.2. For the problem (5), we aim to

$$\max_{\beta} \frac{\exp(\beta^\top X_{i_k})}{\sum_{j \in \mathcal{R}_{i_k}} \exp(\beta^\top X_j)}$$

subject to $U_h^* \leq q_h(\beta)$ for any $h \neq k$. It is equivalent to

$$\max_{\beta} \beta^\top X_{i_k} - \log \left(\sum_{j \in \mathcal{R}_{i_k}} \exp(\beta^\top X_j) \right)$$

subject to $\log(U_h^*) \leq \beta^\top X_{i_h} - \log(\sum_{j \in \mathcal{R}_{i_h}} \exp(\beta^\top X_j))$ for any $h \neq k$.

By introducing decision variables s_k , it is further equivalent to

$$\begin{aligned} & \min_{\beta, s_k} -(\beta^\top X_{i_k} - s_k) \\ \text{subject to} & \quad \log \left(\sum_{j \in \mathcal{R}_{i_l}} \exp(\beta^\top X_j) \right) \leq s_l, \quad l = 1, \dots, m \\ & \quad \beta^\top X_{i_h} - s_h \geq \log(U_h^*), \quad h \neq k, \quad h = 1, \dots, m. \end{aligned}$$

By introducing decision variables $t_{j,l}$, the optimization becomes

$$\begin{aligned} & \min_{\beta, s_k} -(\beta^\top X_{i_k} - s_k) \\ \text{subject to} & \quad \sum_{j \in \mathcal{R}_l} t_{j,l} \leq 1, \quad l = 1, \dots, m \\ & \quad \exp(\beta^\top X_j - s_l) \leq t_{j,l}, \quad j \in \mathcal{R}_l, \quad l = 1, \dots, m \\ & \quad \beta^\top X_h - s_h \geq \log(U_h^*), \quad h \neq k, \quad h = 1, \dots, m. \end{aligned}$$

The final optimization problem becomes

$$\begin{aligned} & \min_{\beta, s_k} -(\beta^\top X_{i_k} - s_k) \\ \text{subject to} & \quad \sum_{j \in \mathcal{R}_l} t_{j,l} \leq 1, \quad l = 1, \dots, m \\ & \quad (t_{j,l}, 1, \beta^\top X_j - s_l) \in K_{exp}, \quad j \in \mathcal{R}_l, \quad l = 1, \dots, m \\ & \quad \beta^\top X_h - s_h \geq \log(U_h^*), \quad h \neq k, \quad h = 1, \dots, m. \end{aligned}$$

For the problem (6), we aim to

$$\max_{\beta} \beta^{\top} w$$

subject to $U_h^* \leq q_h(\beta)$ for $h = 1, \dots, m$. It is equivalent to

$$\max_{\beta} \beta^{\top} w$$

subject to $\log(U_h^*) \leq \beta^{\top} X_{i_h} - \log(\sum_{j \in \mathcal{R}_{i_h}} \exp(\beta^{\top} X_j))$ for any h .

By introducing decision variables s_h , it is further equivalent to

$$\begin{aligned} & \min_{\beta} -\beta^{\top} w \\ \text{subject to} & \quad \log\left(\sum_{j \in \mathcal{R}_{i_l}} \exp(\beta^{\top} X_j)\right) \leq s_l, \quad l = 1, \dots, m \\ & \quad \beta^{\top} X_{i_h} - s_h \geq \log(U_h^*), \quad h = 1, \dots, m. \end{aligned}$$

By introducing decision variables $t_{j,l}$, the optimization becomes

$$\begin{aligned} & \min_{\beta} -\beta^{\top} w \\ \text{subject to} & \quad \sum_{j \in \mathcal{R}_{i_l}} t_{j,l} \leq 1, \quad l = 1, \dots, m \\ & \quad \exp(\beta^{\top} X_j - s_l) \leq t_{j,l}, \quad j \in \mathcal{R}_{i_l}, \quad l = 1, \dots, m \\ & \quad \beta^{\top} X_{i_h} - s_h \geq \log(U_h^*), \quad h = 1, \dots, m. \end{aligned}$$

The final optimization problem becomes

$$\begin{aligned} & \min_{\beta} -\beta^{\top} w \\ \text{subject to} & \quad \sum_{j \in \mathcal{R}_{i_l}} t_{j,l} \leq 1, \quad l = 1, \dots, m \\ & \quad (t_{j,l}, 1, \beta^{\top} X_j - s_l) \in K_{exp}, \quad j \in \mathcal{R}_{i_l}, \quad l = 1, \dots, m \\ & \quad \beta^{\top} X_{i_h} - s_h \geq \log(U_h^*), \quad h = 1, \dots, m. \end{aligned}$$

D Proofs of Consistency and Asymptotic normality

Proof of Theorem 3.1. Recall that the maximum likelihood estimator maximizes

$$\prod_{i=1}^n \left[\frac{\exp(\beta^\top X_i)}{\sum_{j \in \mathcal{R}_i} \exp(\beta^\top X_j)} \right]^{\Delta_i} = \prod_{i=1}^n p_i(\beta),$$

where p_i are defined in (7). Also recall that $Q(U^*) = \{\beta : \text{satisfying (4)}\}$. So we have that the fiducial probability

$$P^*(\beta \in Q(U^*)) \propto \prod_{i=1}^n p_i(\beta).$$

By Section 2.3 of Andersen and Gill (1982) and Theorem 8.3.1 of Fleming and Harrington (2013), the mode of fiducial distribution is consistent as $\tilde{\beta}$ is consistent.

□

Proof of Theorem 3.2. We start with one dimensional β . We omit the argument β in the expression below unless we need to specify it. Notice that the optimal solution of the problem (6) will with probability one have exactly one of its constraints active, i.e., for exactly one $k \in \{1, \dots, m\}$,

$$U_k^* = \frac{\exp(\beta X_{i_k})}{\sum_{j \in \mathcal{R}_{i_k}} \exp(\beta X_j)} = p_{i_k}(\beta),$$

and for the others $l \neq k$,

$$U_l^* < \frac{\exp(\beta X_{i_l})}{\sum_{j \in \mathcal{R}_{i_l}} \exp(\beta X_j)} = p_{i_l}(\beta).$$

We will use this observation to derive a fiducial density $r(\beta)$.

Set for $i = 1, \dots, n$,

$$\bar{r}_i(\beta) = \frac{|J_i(\beta)|}{p_i} \prod_{j=1}^n p_j,$$

where

$$|J_i(\beta)| = \left| \frac{\partial p_i(\beta)}{\partial \beta} \right| = \frac{|\exp(\beta X_i) X_i \sum_{j \in \mathcal{R}_i} \exp(\beta X_j) - \exp(\beta X_i) \sum_{j \in \mathcal{R}_i} X_j \exp(\beta X_j)|}{[\sum_{j \in \mathcal{R}_i} \exp(\beta X_j)]^2}.$$

Using the counting process we write the fiducial distribution as

$$r(\beta) \propto \sum_{i=1}^n \int_0^\tau c_i^{-1} \bar{r}_i(\beta) dN_i(s) = \prod_{j=1}^n p_j \left(\sum_{i=1}^n \int_0^\tau \frac{|J_i|}{p_i c_i} dN_i(s) \right),$$

where $c_i = \max_\beta(p_i) - \min_\beta(p_i)$ for failures and $c_i = 1$ for censored observations.

We expand $\log(L_n(\beta))$ at the maximum likelihood estimator $\tilde{\beta}$,

$$\log(L_n(\beta)) = \log L_n(\tilde{\beta}) + \frac{1}{2} \frac{\partial^2 \log(L_n(\beta))}{\partial \beta^2} \Big|_{\beta=\beta'} (\beta - \tilde{\beta})^2,$$

where β' is on the line segment between β and $\tilde{\beta}$.

We define unscaled

$$\tilde{r}(\beta) = \frac{1}{n^2} \prod_{j=1}^n p_j \left(\sum_{i=1}^n \int_0^\tau \frac{|J_i|}{p_i c_i} dN_i(s) \right),$$

and

$$\tilde{r}_n(\eta) = \tilde{r}(\tilde{\beta} + \eta/\sqrt{n}).$$

We prove our theorem by establishing the following two results:

(i) First in the following we show that

$$\log \tilde{r}_n(\eta) - \log L_n(\tilde{\beta}) \rightarrow -\frac{H(\beta_0)}{2} \eta^2 + \log \left(\int_0^\tau w(\beta_0, s) ds \right),$$

in probability.

If we parametrize $\beta_n = \tilde{\beta} + \eta/\sqrt{n}$, we have both $\tilde{\beta}$ and β' converges to β_0 . By

Theorem 3.2 of Andersen and Gill (1982), we have that

$$-\frac{1}{n} \frac{\partial^2 \log(L_n(\beta))}{\partial \beta^2} \Big|_{\beta=\beta'} \rightarrow H(\beta_0),$$

in probability. By a simple calculation, we have that

$$\begin{aligned}
& \sum_{i=1}^n \int_0^\tau \frac{|J_i|}{p_i c_i} dN_i(s) \\
&= \sum_{i=1}^n \int_0^\tau \frac{|\exp(\beta X_i) X_i \sum_j Y_j(s) \exp(\beta X_j) - \exp(\beta X_i) \sum_j Y_j(s) X_j \exp(\beta X_j)| \sum_j Y_j(s) \exp(\beta X_j)}{[\sum_j Y_j(s) \exp(\beta X_j)]^2 \exp(\beta X_i)} \\
&\quad \times \left[\frac{\max(p_i) - \min(p_i)}{\beta} \right]^{-1} dN_i(s) \\
&= \sum_{i=1}^n \int_0^\tau \frac{|X_i \sum_j Y_j(s) \exp(\beta X_j) - \sum_j Y_j(s) X_j \exp(\beta X_j)|}{[\sum_j Y_j(s) \exp(\beta X_j)]} \left[\frac{\max(p_i) - \min(p_i)}{\beta} \right]^{-1} dN_i(s) \\
&= \sum_{i=1}^n \int_0^\tau \frac{|\sum_{j \neq i} (X_i - X_j) Y_j(s) \exp(\beta X_j)|}{[\sum_j Y_j(s) \exp(\beta X_j)]} \left[\frac{\max(p_i) - \min(p_i)}{\beta} \right]^{-1} dN_i(s) \\
&= \sum_{i=1}^n \int_0^\tau \frac{|\sum_j (X_i - X_j) Y_j(s) \exp(\beta X_j)|}{[\sum_j Y_j(s) \exp(\beta X_j)]} \left[\frac{\max(p_i) - \min(p_i)}{\beta} \right]^{-1} dN_i(s).
\end{aligned}$$

Note that $\min_\beta(p_i) = 0$ for failure observations. By Conditions (5), (9), and Lemma D.1,

$$\frac{1}{n} \sum_{i=1}^n \int_0^\tau \frac{|X_i S^0(\beta_n, s) - S^1(\beta_n, s)|}{S^0(\beta_n, s)} \min_{\beta} \frac{S^0(\beta, s)}{\exp(\beta X_i)} dN_i(s) \rightarrow \int_0^\tau w(\beta_0, s) ds,$$

in probability. Therefore, we have

$$\frac{1}{n^2} \sum_{i=1}^n \int_0^\tau \frac{|J_i(\beta_n)|}{p_i(\beta_n) c_i} dN_i(s) \rightarrow \int_0^\tau w(\beta_0, s) ds,$$

in probability. So we have that

$$\log \tilde{r}_n(\eta) - \log L_n(\tilde{\beta}) \rightarrow -\frac{H(\beta_0)}{2} \eta^2 + \log \left(\int_0^\tau w(\beta_0, s) ds \right),$$

in probability, which completes the proof of (i).

(ii) Next we will show that

$$\int \tilde{r}_n(\eta) / L_n(\tilde{\beta}) d\eta \rightarrow \sqrt{\frac{2\pi}{H(\beta_0)}} \int_0^\tau w(\beta_0, s) ds,$$

in probability. We define $A = \{\beta : |\beta - \beta_0| \leq \delta\}$ and $A_n = \{\eta : |\eta + \sqrt{n}(\tilde{\beta} - \beta_0)| \leq \sqrt{n}\delta\}$.

Note that

$$\int \tilde{r}_n(\eta) / L_n(\tilde{\beta}) d\eta = \int_{A_n} \tilde{r}_n(\eta) / L_n(\tilde{\beta}) d\eta + \int_{A_n^c} \tilde{r}_n(\eta) / L_n(\tilde{\beta}) d\eta.$$

By Condition (8), for $\epsilon = H(\beta_0)/2$, there exists $\delta' > 0$ so that $|\beta - \beta_0| < \delta'$ implies $|Q(\beta) - H(\beta_0)| < \epsilon$, i.e.,

$$\sup_{|\beta - \beta_0| < \delta'} |Q(\beta) - H(\beta_0)| < \epsilon.$$

Take $\delta = \min(\delta', \delta_0)$, we have that

$$\sup_{|\beta - \beta_0| \leq \delta} \frac{1}{n} \frac{\partial^2 \log(L_n(\beta))}{\partial \beta^2} \Big|_{\beta=\beta} < -\frac{H(\beta_0)}{2}.$$

By the dominated convergence theorem, we have that

$$\int_{A_n} \tilde{r}_n(\eta)/L_n(\tilde{\beta})d\eta \rightarrow \sqrt{\frac{2\pi}{H(\beta_0)}} \int_0^\tau w(\beta_0, s)ds,$$

in probability.

For $\int_{A_n^c} \tilde{r}_n(\eta)/L_n(\tilde{\beta})d\eta$, recall that $L_n(\beta) = \prod_{i=1}^n p_i$, without loss of generality, suppose that $\min_{i \in \mathcal{R}_1} X_i < X_1 < \max_{i \in \mathcal{R}_1} X_i$. Then we have

$$p_1 = \frac{\exp(\beta X_1)}{\sum_{j \in \mathcal{R}_1} \exp(\beta X_j)} = \frac{1}{\sum_{j \in \mathcal{R}_1} \exp(\beta(X_j - X_1))},$$

is integrable. By Lemma D.1 and Condition (10),

$$\int_{A_n^c} \tilde{r}_n(\eta)/L_n(\tilde{\beta})d\eta = O\left(\int_{A_n^c} p_1 \prod_{i=2}^n p_i/p_i(\beta_0)d\beta\right) \rightarrow 0,$$

in probability. Therefore, we have that

$$\int \tilde{r}_n(\eta)/L_n(\tilde{\beta})d\eta \rightarrow \sqrt{\frac{2\pi}{H(\beta_0)}} \int_0^\tau w(\beta_0, s)ds.$$

Combining (i) and (ii), by Ferguson (1996), we have that

$$\int |r_n(\eta) - f_N(\eta)|d\eta \rightarrow 0,$$

in probability, where $f_N(\beta)$ is the density of normal with mean 0 and variance $H^{-1}(\beta_0)$. □

Remark 3. For a d -dimensional β , $v(\beta_0, t)$ in Condition (6) is replaced by $v(\beta_0, t) = \frac{\mathbf{s}^2}{s_0^2} - e^{\otimes 2}$, where \mathbf{s}^2 is the limit of

$$\frac{1}{n} \sum_{i=1}^n Y_i(t) X_i^{\otimes 2} \exp(\beta X_i),$$

and \otimes is an outer product. Moreover, for any $\mathbf{i} = (i_1, \dots, i_d)$, we replace Conditions (9) and (10) by

$$(9') \frac{1}{n} \sum_{i=1}^n \int_0^\tau \frac{|\det(J_{\mathbf{i}}(\beta))|}{\prod_{j \in \mathbf{i}} p_j c_i} dN_i(s) \rightarrow \int_0^\tau w(\beta, s) ds \text{ in probability.}$$

(10') For any $\delta > 0$ and \mathbf{i} , there exists an $\epsilon > 0$ such that

$$P \left(\sup_{\|\beta - \beta_0\| > \delta} \left(\log \frac{L_n(\beta)}{\prod_{j \in \mathbf{i}} p_j(\beta)} - \log \frac{L_n(\beta_0)}{\prod_{j \in \mathbf{i}} p_j(\beta_0)} \right) \leq -n\epsilon \right) \rightarrow 1.$$

Then we have that Theorem 3.2 holds.

Proof. Note that

$$r(\beta) \propto \sum_{\mathbf{i}=(i_1, \dots, i_d)} \prod_{l=1}^n p_l \frac{|\det(J_{\mathbf{i}}(\beta))|}{\prod_{j \in \mathbf{i}} p_j c_i},$$

where $J_{\mathbf{i}}(\beta) = \nabla_{\beta} p_{\mathbf{i}}$ is a $d \times d$ matrix. A similar result of Theorem 3.2 holds under Conditions (1)-(8), (9'), and (10'). \square

Lemma D.1. We have $0 < \frac{1}{n^2} \sum_{i=1}^n \int_0^\tau \frac{|J_i|}{p_i c_i} dN_i(s) \leq M$ almost surely for some $M > 0$.

Proof of Lemma D.1. Recall that

$$\begin{aligned} & \frac{1}{n^2} \sum_{i=1}^n \int_0^\tau \frac{|J_i|}{p_i c_i} dN_i(s) \\ &= \frac{1}{n^2} \sum_{i=1}^n \int_0^\tau \frac{|\sum_j (X_i - X_j) Y_j(s) \exp(\beta X_j)|}{[\sum_j Y_j(s) \exp(\beta X_j)]} \left[\max_{\beta} (p_i) - \min_{\beta} (p_i) \right]^{-1} dN_i(s) \\ &= \frac{1}{n} \sum_{i=1}^n \int_0^\tau \frac{|\sum_j (X_i - X_j) Y_j(s) \exp(\beta X_j)|}{[\sum_j Y_j(s) \exp(\beta X_j)]} \min_{\beta} \frac{S^0(\beta, s)}{\exp(\beta X_i)} dN_i(s). \end{aligned}$$

Note that we have

$$\left| \sum_{j \neq i} (X_i - X_j) Y_j(s) \exp(\beta X_j) \right| \neq 0$$

almost surely,

$$\frac{|\sum_j (X_i - X_j) Y_j(s) \exp(\beta X_j)|}{[\sum_j Y_j(s) \exp(\beta X_j)]} \leq \max_{i,j} |X_i - X_j| \frac{[\sum_j Y_j(s) \exp(\beta X_j)]}{[\sum_j Y_j(s) \exp(\beta X_j)]}$$

is bounded, and

$$\min_{\beta} \frac{\frac{1}{n} \sum_{i=1}^n Y_j(s) \exp(\beta X_j)}{\exp(\beta X_i)} \leq 1,$$

which completes the proof. □

Proof of Theorem 3.1. We know that $n^{1/2}(\tilde{\beta} - \beta_0) \rightarrow N(0, H^{-1}(\beta_0))$ in distribution and Theorem 3.2 implies that $n^{1/2}(\beta^* - \tilde{\beta}) \rightarrow N(0, H^{-1}(\beta_0))$ in distribution in probability.

So we have

$$1 - \alpha = P^*(\{\beta : \|\beta - \tilde{\beta}\| \leq \epsilon_{n,\alpha}\}) = P^*(\{\beta : n^{1/2}\|\beta - \tilde{\beta}\| \leq n^{1/2}\epsilon_{n,\alpha}\})$$

converges to $\Gamma(\epsilon_\infty)$, where Γ is the cumulative distribution function of the limit of $n^{1/2}\|\beta - \tilde{\beta}\|$ and ϵ_∞ is the unique limit of $n^{1/2}\epsilon_{n,\alpha}$. Therefore, we have that

$$P(\beta_0 \in \{\beta : \|\beta - \tilde{\beta}\| \leq \epsilon_{n,\alpha}\}) = P(\|\beta_0 - \tilde{\beta}\| \leq \epsilon_{n,\alpha}) \rightarrow \Gamma(\epsilon_\infty) = 1 - \alpha.$$

□

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