Predicting disease Risk by Transformation Models in the Presence of Unspecified Subgroup Membership

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Abstract

Some biomedical studies lead to mixture data. When a discrete covariate defining subgroup membership is missing for some of the subjects in a study, the distribution of the outcome follows a mixture distribution of the subgroup-specific distributions. Taking into account the uncertain distribution of the group membership and the covariates, we model the relation between the disease onset time and the covariates through transformation models in each sub-population, and develop a nonparametric maximum likelihood based estimation implemented through EM algorithm along with its inference procedure. We further propose methods to identify the covariates that have different effects or common effects in distinct populations, which enables parsimonious modeling and better understanding of the difference across populations. The methods are illustrated through extensive simulation studies and a real data example.

Key words: Censored data, EM algorithm, Laplace transformation, mixed populations, uncertain population identifier, semiparametric models, transformation models

1 Introduction

Some biomedical studies lead to mixture data. When a discrete covariate defining subgroup membership is missing for some of the subjects in a study, the distribution of the outcome follows a mixture distribution of the subgroup-specific distributions. One example is kin-cohort study (Wacholder et al. 1998) with the goal of estimating penetrance function of a deleterious mutation (Khoury et al. 1993), i.e., the cumulative risk of disease for mutation
carriers. However, the mutation status is only collected in an initial sample of participants referred as probands, but not in their relatives. For example, genetic mutation status is not available for relatives who have deceased or have not undergone genetic testing due to resource constraints from collecting blood samples in all family members. The disease phenotype information for these relatives is often available from other sources such as interviewing the proband in a family (Marder et al. 2003). Consider late-onset disease such as Parkinson’s disease (PD), parents of study participants are often deceased. Therefore even though age-at-onset of PD is provided by a family member, no genotyping can be performed on deceased parents. When estimating disease risk distribution for mutation carriers and non-carriers using these relatives’ disease onset information, the unknown mutation status needs to be accounted for by using distribution of mutation status in these relatives estimated from living relatives who provide blood sample (Wang et al. 2012, Ma & Wang 2014).

We consider estimating subgroup-specific distribution for outcomes that are subject to censoring and with missing subgroup identifiers. The nonparametric models in Wacholder et al. (1998), Wang et al. (2012) and Ma & Wang (2014) do not include any covariates other than the mutation status. In this work, we consider how to include covariates which can have identical or different effects across subgroups. Popular semiparametric models for censored outcomes such as Cox proportional hazards model, accelerated failure time model, and transformation model have been studied extensively in the literature. However, they have been less explored in mixture data setting. Recently, Altstein & Li (2013) proposed a latent subgroup analysis for semiparametric accelerated failure time model in clinical trials setting. Our work here differs from Altstein & Li (2013) in that the distribution of the subgroup identifiers is available in our problem, and we assume a semiparametric transformation model in each subgroup. Transformation model is applied to analyze neurological disorder data (e.g., Huntington’s disease [HD] as in our motivating study) due to its useful biological and clinical interpretations; see for example Zhang et al. (2012).
We propose a semiparametric transformation model for mixture data. Compared to the parametric transformation model in the literature (Zhang et al. 2012), we allow for greater flexibility to account for subgroup heterogeneity. This is achieved in our model through characterizing the outcome in each subpopulation using different distribution indexed by both parameters and error distributions. Specifically, each subpopulation can have distinct scale or shape parameter and distribution function. They can also have both shared covariate effect and/or subgroup-specific covariate effect. In addition, we assume an unknown transformation to avoid the difficulty in specifying a parametric transformation. When assuming homogeneous covariate effect, we account for missing population identifier by taking advantage of the distribution of the mixing proportion and using a weighted least-square type estimator which greatly simplifies the procedure. When we assume a subgroup-specific covariate effect, the weighted least-square estimator no longer applies, and we use the EM algorithm. We perform extensive simulation studies to examine performance of the proposed approach and apply to estimating the survival function for HD mutation carriers in a large genetic epidemiology study (Dorsey & The Huntington Study Group COHORT Investigators 2012).

2 Modeling, Estimation, and Asymptotic Properties

Assume there are \( n \) observations from \( p \) populations. Here \( p \) is usually determined by the research purpose as of which populations are to be examined. For genetic studies that we consider, populations are defined by mutation carrier status. Throughout the article, we assume \( p \) is pre-determined. Denote the data from the \( i \)th relative as \( O_i = (q_i, x_i, z_i, y_i, \delta_i) \), where \( q_i \) is a length \( p \) vector, with the \( j \)th entry \( q_{ij} \) being the probability that the \( i \)th observation is a random sample of the \( j \)th population. We also allow a subject’s population membership to be known by allowing \( q_i \) to be a vector with 1 in one component and zero in all others. Let \( t_i \) be the time to event and \( c_i \) be the censoring time. Let \( y_i = \min(t_i, c_i) \) and \( \delta_i = I(t_i \leq c_i) \). Let \( x_i \) denote the covariate vector that has a common effect on the event
time across different populations, while $z_i$ denote the covariate vector that has a different effect in different populations. For simplicity, we sort the data so that $y_i \leq y_k$ for all $i < k$.

2.1 Model

For the $j$th population, the linear transformation model we propose has the form

$$H(T) = -X^T \beta - Z^T \alpha_j + \epsilon_j.$$  \hspace{1cm} (1)

Here $H$ is an unknown, monotonically increasing function. Without loss of generality, we assume $H(0) = -\infty$. Also, we assume $\epsilon_j$ is independent of $X$, $Z$, and has a known population-specific distribution $f_j(\epsilon_j)$. There are a few features of the model that accommodate population heterogeneity worth noting. First, in each population, the model is a classical linear transformation model, and hence it retains the usual generality and flexibility of this class. Second, the baseline population distribution can be heterogeneous due to the different choice of $f_j$. For example, the first population may satisfy Cox proportional hazard assumption if $f_1$ is the extreme value distribution, and the second population may satisfy a proportional odds model if $f_2$ is a logistic distribution. Selection of $f_j$ for each population can be based on scientific or biological knowledge of a particular population. Third, the covariate effect is also allowed to vary, reflected in the population-specific $\alpha_j$. Thus, a same covariate can have positive, none or even negative effect in different populations. By including the term $x^T \beta$, we also allow the possibility that some covariates have homogeneous effect across populations. We will develop a test to assess whether a covariate exhibits evidence of deviation from a homogeneous effect model.

Let $\theta = (\beta^T, \alpha_1^T, \ldots, \alpha_p^T)^T$, $\Phi(t) = \exp\{H(t)\}$, $\phi(t) = \exp\{H(t)\}h(t)$. The conditional distribution function of the $i$th relative from (1) is then

$$f(y_i, \delta_i \mid x_i, z_i; \theta, \Phi, \phi) = \left[ h(y_i) \sum_{j=1}^p q_{ij} f_j \{H(y_i) + x_i^T \beta + z_i^T \alpha_j\} \right]^{\delta_i} \left[ 1 - \sum_{j=1}^p q_{ij} F_j \{H(y_i) + x_i^T \beta + z_i^T \alpha_j\} \right]^{1-\delta_i} = \phi(y_i)^{\delta_i} \Psi(O_i; \theta, \Phi),$$
where $\Phi$ is a function that depends only on $\theta$ and $\Phi$, but not $\phi$. Clearly this model can no longer be viewed as a transformation model, hence the existing estimation procedures for transformation models do not apply. To ensure that the model is still identifiable, in addition to requiring $H(0) = -\infty$, we further require that the $q_i$ variable takes $m$ different vector values, denoted $u_1, \ldots, u_m$, so that the matrix $(u_1, \ldots, u_m)$ has rank $p$. Under this assumption, if the problem is not identifiable, then there will be $u_k^T(f_1, \ldots, f_p)^T = u_k^T(f_1^*, \ldots, f_p^*)^T$ for $k = 1, \ldots, m$, where $f_1^*, \ldots, f_p^*$ denote alternative transformation models to $f_1, \ldots, f_p$. This directly leads to $(u_1, \ldots, u_m)^T(f_1, \ldots, f_p)^T = (u_1, \ldots, u_m)^T(f_1^*, \ldots, f_p^*)^T$, hence $f_i = f_i^*$ for $i = 1, \ldots, p$. Thus, the identifiability of the classical transformation model under our parameterization leads to the overall identifiability of the problem. We point out that the identifiability here excludes any permutation. That is, it is stronger than the identifiability up to a permutation in most classical mixture models (Holzmann et al. 2006). We can achieve the stronger form of identifiability because the mixture probabilities, while different for different observations, are known.

2.2 Estimation

We propose a nonparametric maximum likelihood estimator (NPMLE) to estimate $\theta$ and $\Phi(\cdot)$. Specifically, we obtain $\hat{\theta}$ and $\hat{H} = \log(\hat{\Phi})$ through maximizing

$$l(\theta, \Phi) = \sum_{i=1}^n \delta_i \log\{\phi(y_i)\} + \sum_{i=1}^n \log\{\Psi(O_i; \theta, \Phi)\}$$

with respect to $\theta$ and $\Phi$, where we restrict $\Phi$, hence $H$, to be a piecewise constant non-decreasing function with non-negative jumps only at the observed event times. Following the existing literature (Wacholder et al. 1998, Wang et al. 2012), we exclude the probands from the analysis sample and the likelihood to protect against potential ascertainment bias from unknown sources which may be difficult to adjust (e.g., convenience sample of patients visiting a clinic). Given the mutation carrier status, we also assume the relatives’ phenotypes are conditionally independent of probands’ phenotypes, which is an assumption satisfied by
any monogenic disorder with a known genetic cause controlled in the model (e.g., HD in our application).

Although conceptually simple, the computation of NPMLE is not straightforward because the maximization is with respect to not only $\gamma$, but also $\Phi(\cdot)$ at all the $y_i$’s that are not censored. As sample size increases, the potential number of parameters increases as well, hence the computational problem does not simplify in the asymptotic sense. To overcome the computational difficulty, we use an EM algorithm. To this end, we first use Laplace transformation in each population to obtain

$$1 - F_j(x) = \int_0^\infty \exp(-r_j e^x) \psi_j(r_j) dr_j,$$

where $\psi_j(\cdot)$ is the inverse Laplace transformation of $1 - F_j(x)$ as a function of $e^x$, consequently

$$1 - \sum_{j=1}^p q_{ij} F_j\{H(y_i) + x_i^T \beta + z_i^T \alpha_j\} = \sum_{j=1}^p q_{ij} \int_0^\infty \exp\{-r_{ij} e^{H(y_i) + x_i^T \beta + z_i^T \alpha}\} \psi_j(r_{ij}) dr_{ij}$$

and

$$h(y_i) \sum_{j=1}^p q_{ij} f_j\{H(y_i) + x_i^T \beta + z_i^T \alpha_j\} = \sum_{j=1}^p q_{ij} \int_0^\infty \exp\{-r_{ij} \Phi(y_i) e^{x_i^T \beta + z_i^T \alpha}\} \phi(y_i) \exp(x_i^T \beta + z_i^T \alpha) r_{ij} \psi_j(r_{ij}) dr_{ij}.$$

Recall that the $i$th observation is $O_i$, and let $D = (O_1, \ldots, O_n)$. Let $0 < t_1 < \cdots < t_K < \tau$ be the distinct event times, and write the quantities to be estimated $\gamma = \{\theta^T, H(t_1), \ldots, H(t_K)\}^T$. The log-likelihood is then $l(\gamma; D) = \sum_{i=1}^n l_i(\gamma; O_i)$, where

$$l_i(\gamma; O_i) = \log \sum_{j=1}^p \int_0^\infty \{\phi(y_i) r_{ij} \exp(x_i^T \beta + z_i^T \alpha_j)\} \delta_i \exp\{-r_{ij} \Phi(y_i) e^{x_i^T \beta + z_i^T \alpha}\} q_{ij} \psi_j(r_{ij}) dr_{ij}.$$

We take advantage of the special data structure above and view the population identifiers $G = (G_1, \ldots, G_n)$ and $r = (r_1, \ldots, r_n)$ as the missing variable, where $G_i = I_j$ represents that
the $i$th observation is a random sample from the $j$th population, and $r_i \equiv (r_{i1}, \ldots, r_{ip})^T$ is the introduced random effects to facilitate computation. Then the complete data loglikelihood is $l(\gamma | D, G, r) = \sum_{i=1}^{n} l_i(\gamma | O_i, G_i, r_i)$, where

$$l_i(\gamma | O_i, G_i = I_j, r_{ij}) = \log \left\{ \{\phi(y_i) r_{ij} \exp(x_i^T \beta + z_i^T \alpha_j)\}^{\delta_i} \exp\{ -r_{ij} \Phi(y_i)e^{x_i^T \beta + z_i^T \alpha_j} \} \right\} = \delta_i \log \{\phi(y_i) r_{ij}\} + \delta_i (x_i^T \beta + z_i^T \alpha_j) - r_{ij} \Phi(y_i)e^{x_i^T \beta + z_i^T \alpha_j}.$$

Recognizing that this is a Cox model log-likelihood. Thus, in the E-step, we calculate

$$Q(\gamma, \gamma^{(u)}, D) \equiv E_{\gamma^{(u)}} \{ l(\gamma | D, G, r | D) \} = \frac{\sum_{i=1}^{n} \int \sum_{j=1}^{p} l_i(\gamma | O_i, G_i = I_j, r_{ij}) a_{ij}^{(u)} dr_{ij}}{\sum_{i=1}^{n} \int a_{ij}^{(u)} dr_{ij}},$$

where

$$a_{ij}^{(u)} = \{\phi^{(u)}(y_i) r_{ij} \exp(x_i^T \beta^{(u)} + z_i^T \alpha_j^{(u)})\}^{\delta_i} \exp\{ -r_{ij} \Phi^{(u)}(y_i)e^{x_i^T \beta^{(u)} + z_i^T \alpha_j^{(u)}} \} q_{ij} \psi_j(r_{ij}).$$

In the M-step, we maximize $Q(\gamma, \gamma^{(u)}, D)$ with respect to $\gamma$ subject to the constraints $0 < H(t_1) < \cdots < H(t_K) \leq 1$ to obtain $\gamma^{(u+1)}$. Specifically, taking derivative with respect to $\gamma$, we obtain estimating equations

$$0 = \sum_{i=1}^{n} \int \sum_{j=1}^{p} \left\{ \delta_i x_i - x_i r_{ij} \Phi(y_i)e^{x_i^T \beta + z_i^T \alpha_j} \right\} a_{ij}^{(u)} dr_{ij}$$

$$= \sum_{i=1}^{n} \delta_i x_i - x_i \Phi(y_i)e^{x_i^T \beta} \sum_{j=1}^{p} e^{z_i^T \alpha_j} \int r_{ij} a_{ij}^{(u)} dr_{ij} / \sum_{j=1}^{p} a_{ij}^{(u)} dr_{ij}.$$

For $j = 1, \ldots, p,$

$$0 = \sum_{i=1}^{n} \int (\delta_i z_i - z_i r_{ij} e^{H(y_i)+x_i^T \beta + z_i^T \alpha_j}) a_{ij}^{(u)} dr_{ij}$$

$$= \sum_{i=1}^{n} \delta_i z_i \int a_{ij}^{(u)} dr_{ij} - z_i \Phi(y_i)e^{x_i^T \beta + z_i^T \alpha_j} \int r_{ij} a_{ij}^{(u)} dr_{ij} / \sum_{j=1}^{p} a_{ij}^{(u)} dr_{ij}.$$

For $k = 1, \ldots, K,$

$$0 = \sum_{y_i \geq t_k} \int \sum_{j=1}^{p} \left\{ \frac{l(y_i,t_k)}{\phi_k} - r_{ij} e^{x_i^T \beta + z_i^T \alpha_j} \right\} a_{ij}^{(u)} dr_{ij}$$

$$= \frac{1}{\phi_k} \sum_{y_i \geq t_k} e^{x_i^T \beta} \sum_{j=1}^{p} e^{z_i^T \alpha_j} \int r_{ij} a_{ij}^{(u)} dr_{ij} / \sum_{j=1}^{p} a_{ij}^{(u)} dr_{ij}.$$
This yields
\[
\phi_k = \left( \sum_{y_i \geq t_k} e^{x_i^T \beta} \sum_{j=1}^p e^{x_j^T \alpha_j} f_t r_{ij} a_{ij}^u \, dr_{ij} \right)^{-1},
\]
or in general
\[
\phi(y_k; \beta, \alpha) = \delta_k \left( \sum_{i=1}^n I(y_i \geq y_k) e^{x_i^T \beta} \sum_{j=1}^p e^{x_j^T \alpha_j} f_t r_{ij} a_{ij}^u \, dr_{ij} \right)^{-1}
\]
Plugging into the estimating equation for \( \beta, \alpha \), we obtain
\[
\sum_{i=1}^n \delta_i \mathbf{x}_i - \mathbf{x}_i \Phi(y_i; \beta, \alpha) e^{x_i^T \beta} \sum_{j=1}^p e^{x_j^T \alpha_j} f_t r_{ij} a_{ij}^u \, dr_{ij} = 0 \tag{3}
\]
and
\[
\sum_{i=1}^n \delta_i \mathbf{z}_i f_t r_{ij} a_{ij}^u \, dr_{ij} = 0
\]
at \( j = 1, \ldots, p \).

We solve the estimating equations (3) to obtain \( \hat{\beta}^{(u+1)}, \hat{\alpha}^{(u+1)}, j = 1, \ldots, p \), and then substitute into (2) to obtain \( \Phi^{(u+1)}(t) \) and hence also \( H^{(u+1)}(t) = \log \{ \Phi^{(u+1)}(t) \} \). The procedure iterates between the E-step and the M-step until convergence.

We point out that although the functions \( \psi_j(r) \)'s are left as unknown, we can still calculate \( \int a_{ij}^u \, dr_{ij} \) and \( \int r_{ij} a_{ij}^u \, dr_{ij} \) in the M-step. Specifically,
\[
\int a_{ij}^u \, dr_{ij} = q_{ij} \left\{ 1 - F_j(t) \right\}^{1-\delta_i} \left\{ h_j^{(u)}(y_i) f_j(t) \right\}^{\delta_i} \left|_{t=H_j^{(u)}(y_i)+x_i^T \beta^{(u)}+z_i^T \alpha_j^{(u)}} \right. \right.
\]
and
\[
\int r_{ij} a_{ij}^u \, dr_{ij} = \left\{ e^{-t} q_{ij} f_j(t) \right\}^{1-\delta} \left\{ e^{-t} q_{ij} h_j^{(u)}(y_i) \left\{ f_j(t) - f_j'(t) \right\} \right\}^{\delta} \left|_{t=H_j^{(u)}(y_i)+x_i^T \beta^{(u)}+z_i^T \alpha_j^{(u)}} \right. \right.
\]
as shown in Appendix A.1, by taking advantage of the Laplace/inverse Laplace transform relation. In fact, even if an explicit form of \( \psi_j(r) \) can be obtained, it is not necessary to go through the calculation because \( \psi_j(r) \) itself is not needed. Finally, because \( \psi_j \) is defined as the inverse Laplace transform of a bounded function, it always exists for any \( \epsilon \) distribution.
2.3 Theoretical properties

Although (1) is not a transformation model, under the list of conditions imposed in Appendix A.2, (1) can be cast into the general framework by Zeng & Lin (2007). To this end, we can verify that our Conditions (a), (b), (c) lead to their conditions (C1), (C2), (C3) respectively. Our Conditions (d) and (e) jointly ensure their conditions (C4) and (C8). Our Condition (f) leads to their condition (C6) and our Condition (g) leads to their conditions (C5), (C7). These are mild conditions mainly imposing identifiability, sufficient smoothness and boundedness of various functions, and is usually satisfied in practice. Having verified the regularity conditions C1-C7 of Zeng & Lin (2007), we can readily use their results to obtain the asymptotic properties of the NPMLE in the linear transformation model in the mixture data setting. We state the results in Theorem 1 and provide the proof in Appendix A.3.

Theorem 1. Let \( \theta_0, \Phi_0 \) denote the true value of \( \theta, \Phi \), write \( \Phi = \{\Phi(t_1), \ldots, \Phi(t_K)\}^T \). Under conditions (a)-(g) listed in Appendix A.2, \( \hat{\theta}, \hat{\Phi} \) are consistent, and have the asymptotic property that \( \sqrt{n}(\hat{\theta} - \theta, \hat{\Phi} - \Phi) \) converges weakly to a zero mean Gaussian process. Specifically, for any function \( a_1(s) \) with bounded total variation and any vector \( a_2 \), \( \sqrt{n} \int a_1(s)d\{\hat{\Phi}(s) - \Phi(s)\} + \sqrt{n}a_2^\top(\hat{\theta} - \theta) \) converges to a zero mean normal distribution whose variance can be approximated with

\[
\nu\{a_1(\cdot), a_2\} \equiv - (a_1^\top, a_2^\top) \left\{ \frac{\partial^2 l(\hat{\Phi}, \hat{\theta})}{\partial(\hat{\Phi}^\top, \hat{\theta}^\top)\partial(\Phi^\top, \theta^\top)^\top} \right\}^{-1} (a_1^\top, a_2^\top)^\top,
\]

where \( a_1 = \{a_1(t_1), \ldots, a_1(t_K)\}^T \).

2.4 Inference

In practice, often the main interest is in the covariate effects described by \( \theta \). In such cases, we can perform inference using the results of profiling procedure. Specifically, at any \( \theta \), we use the same EM algorithm to calculate \( \hat{H}(T, \theta) \) except that we held \( \theta \) fixed, and then calculate the information matrix using numerical derivative. This procedure provides a
simplification because it bypasses the need to invert a potentially high dimensional matrix. For example, the $\alpha$-100% confidence interval for the $j$th component of $\theta$, $\theta_j$ is

$$\hat{\theta}_j \pm Z_{(1+\alpha)/2} \left[ -\sum_{i=1}^{n} \frac{\partial^2 l_i(\theta, \hat{H}(t_1, \theta), \ldots, \hat{H}(t_{K}, \theta))}{\partial \theta_j^2} \bigg|_{\theta=\hat{\theta}} \right]^{-1/2} \approx \hat{\theta}_j \pm Z_{(1+\alpha)/2} \left[ \sum_{i=1}^{n} -\frac{l_i(\theta + be_j, \hat{H}(t_1, \hat{\theta} + be_j), \ldots, \hat{H}(t_{K}, \hat{\theta} + be_j))}{b^2} + \frac{2l_i(\theta, \hat{H}(t_1, \hat{\theta}), \ldots, \hat{H}(t_{K}, \hat{\theta})) - l_i(\theta - be_j, \hat{H}(t_1, \hat{\theta} - be_j), \ldots, \hat{H}(t_{K}, \hat{\theta} - be_j))}{b^2} \right]^{-1/2},$$

where $Z_{(1+\alpha)/2}$ is the $(1+\alpha)/2$ quantile of the standard normal distribution, $l_i$ is the likelihood evaluated at the $i$th observation, $e_j$ is the vector with zero components everywhere except the $j$th component being 1, and $b$ is a small number that facilitates numerical derivative.

Likewise, for hypothesis testing of the form $H_0 : \theta = c$, we can construct the test statistic

$$Z = \left[ -\sum_{i=1}^{n} \frac{\partial^2 l_i(\theta, \hat{H}(t_1, \theta), \ldots, \hat{H}(t_{K}, \theta))}{\partial \theta \partial \theta^T} \bigg|_{\theta=\hat{\theta}} \right]^{1/2} (\theta - c) \approx \left[ \sum_{i=1}^{n} -\frac{l_i(\theta + be_j + be_k, \hat{H}(t_1, \hat{\theta} + be_j + be_k), \ldots, \hat{H}(t_{K}, \hat{\theta} + be_j + be_k))}{4b^2} + \frac{l_i(\theta + be_j - be_k, \hat{H}(t_1, \hat{\theta} + be_j - be_k), \ldots, \hat{H}(t_{K}, \hat{\theta} + be_j - be_k))}{4b^2} + \frac{l_i(\theta - be_j + be_k, \hat{H}(t_1, \hat{\theta} - be_j + be_k), \ldots, \hat{H}(t_{K}, \hat{\theta} - be_j + be_k))}{4b^2} - \frac{l_i(\theta - be_j - be_k, \hat{H}(t_1, \hat{\theta} - be_j - be_k), \ldots, \hat{H}(t_{K}, \hat{\theta} - be_j - be_k))}{4b^2} \right]^{1/2}_{jk} \times (\theta - c),$$

and note that $Z$ is approximately a standard multivariate normal random variable under $H_0$. Here, we use the notation $(A_{jk})$ to denote the square matrix $A$ of size the length of $\theta$ with its $(j,k)$ entry given as $A_{jk}$. 
3 Homogeneous and no covariate effect model

When either $\beta$ or $\alpha_j$ does not appear in (1), the model becomes more restrictive while the computation simplifies. If $\beta$ does not appear, then there is no homogeneous covariate effect in the transformation model. In terms of estimation, the procedures follows the same line with some minor simplifications. However, if $\alpha_j$ does not appear, model (1) greatly simplifies and can be treated quite differently, as we now explain.

The common-effect covariate effect model for the $j$th population is

$$H(T) = -X^T \beta + \epsilon_j,$$

where all the components in the model retain the same interpretation as in (1). The implication of the model is that the heterogeneity between subpopulations is due to differential distribution of random measurement errors $\epsilon_j$ (i.e., different variability of measurement errors), but not the heterogeneous effect of covariates. The conditional distribution is then simplified to

$$f(Y, \Delta | X) = \left[ h(y) \sum_{j=1}^{p} q_j f_j \{ H(y) + x^T \beta \} \right]^\delta \left[ 1 - \sum_{j=1}^{p} q_j F_j \{ H(y) + x^T \beta \} \right]^{1-\delta}$$

$$= [h(y)q^T f \{ H(y) + x^T \beta \}]^\delta [1 - q^T F \{ H(y) + x^T \beta \}]^{1-\delta},$$

where $f = (f_1, \ldots, f_p)^T$, $F = (F_1, \ldots, F_p)^T$, and $h(y) \equiv H'(y)$, because the same transformation $H$ and the same parameter $\beta$ are assumed across all $p$ populations. The population difference is only reflected in the distribution of $\epsilon_j$, which is assumed to be $f_j$. We can however still use the different $f_j$’s of the model to account for unexplained residual population heterogeneity, for example, to account that subjects from different populations will have different variances.

As before, estimating the distribution in each population is equivalent to estimating $H$ and $\beta$. Recall that $q_j$’s can have $m \geq p$ different vector values $u_1, \ldots, u_m$. Assign the $n$ observations to these $m$ groups according to their $q$ values. Assume there are respectively $r_1, \ldots, r_m$ observations in each group. In group $k$, we can view the model as a transformation
model with the same transformation $H$, the same parameter $\beta$, but a new distribution for $\epsilon$, which has the mixture form $u_k^Tf(\epsilon)$. Thus, we can use the existing estimation method for transformation models to obtain the estimators of $H$ and $\beta$, using exclusively the $k$th group data. Denote the resulting estimator $\hat{H}_k$ and $\hat{\beta}_k$. We can then take the weighted average to obtain the final estimator $\hat{H}(t) = \sum_{k=1}^m w_k(t)\hat{H}_k(t)$ and $\hat{\beta} = \sum_{k=1}^m w_k\hat{\beta}_k$. To be consistent with the estimation in the general model (1), we use the NPMLE proposed by Zeng & Lin (2006) here. Thus, we obtain $\hat{\beta}_k$, $\hat{H}_k$ via maximizing

$$l_k(H, \beta) = n^{-1}\sum_{i=1}^n I(q_i = u_k) \left( \delta_i \log [h(y_i)u_k^Tf\{H(y_i) + x_i^T\beta]\right) + (1 - \delta_i) \log [1 - u_k^TF\{H(y_i) + x_i^T\beta]\}$$

with respect to $\beta$ and $H$. Here, we restrict $H(y)$ to be a piecewise constant nondecreasing function with nonnegative jumps only at $y_i$’s where $q_i = u_k$ and $\delta_i = 1$. We write these jump points $t_1, \ldots, t_K$, and write $H_k = \{H(t_1), \ldots, H(t_K)\}^T$. Zeng & Lin (2006) showed that the resulting $\hat{\beta}_k$, $\hat{H}_k$ are consistent, and have the asymptotic property that $\sqrt{n}(\hat{\beta}_k - \beta, \hat{H}_k - H)$ converges weakly to a zero mean Gaussian process. Specifically, for any function $a_1(s)$ with bounded total variation and any vector $a_2$, $\sqrt{n}\int a_1(s)d\{\hat{H}_k(s) - H(s)\} + \sqrt{n}a_2^T(\hat{\beta}_k - \beta)$ converges to a zero mean normal distribution whose variance can be approximated with

$$v_k\{a_1(\cdot), a_2\} \equiv -(a_1^T, a_2^T) \left\{ \frac{\partial^2 l_k(\hat{H}_k, \hat{\beta}_k)}{\partial (H_k^T, \beta^T)\partial (H_k^T, \beta^T)^T} \right\}^{-1}(a_1^T, a_2^T)^T,$$

where $a_1 = \{a_1(t_1), \ldots, a_1(t_K)\}^T$.

It remains to determine the choice of weights $w_k$. Because the estimation in different group is based on different subjects, they are independent. Hence the optimal weights are proportional to the inverse of the variance of the estimators. To be specific, the optimal weights for $\hat{H}(t)$ are $w_k(t) = v_k\{I(s \leq t), 0\}^{-1}/[\sum_{k=1}^m v_k\{I(s \leq t), 0\}]^{-1}$ and $w_k$ is a diagonal matrix with the $j$th diagonal element $w_{kj} = v_k(0, e_j)^{-1}/[\sum_{k=1}^m v_k(0, e_j)^{-1}]$. In practice, this may not work well since it relies on the asymptotic results. Based on prior work in Ma & Wang (2014), a simple choice of $w_k(t) = w_k = r_k^{-1}$ has satisfactory performance.
Because the within group NPMLE already guarantees the monotonicity of each $\hat{H}_k$, the final weighted average estimator for $\hat{H}$ is automatically monotone. Asymptotic property of $\hat{H}$ and $\beta$ is standard. Specifically, $\sqrt{n} (\beta - \hat{\beta}, \hat{H} - H)$ converges weakly to a zero mean Gaussian process. For any function $a_1(t)$ with bounded total variation and any vector $a_2$,

\[
\sqrt{n} \int a_1(s) d\{\hat{H}(s) - H(s)\} + \sqrt{n} a_2^T (\hat{\beta} - \beta)
\]

converges to a zero mean normal distribution whose variance can be approximated with

\[
v\{a_1(\cdot), a_2\} \equiv \sum_{k=1}^m v_k \{a_1(\cdot) w_k(\cdot), w_k a_2\}
\]

where $t_1, \ldots, t_K$ are the observed event times, i.e. the $y_i$ values where the corresponding $\delta_i = 1$, $a_1 = \{a_1(t_1), \ldots, a_1(t_K)\}^T$.

It is of interest to test whether population heterogeneity in the covariate effects is present in (1). This is equivalent to testing $\alpha_1 = \alpha_2 = \cdots = \alpha_p$, and can be written as testing $A\theta = 0$, where $A$ is a $(p-1)d_z \times (d_x + pd_z)$ block matrix where the $(j, j)$ block is $I$ and the $(2, j)$ block is $-I$ for $j = 3, \ldots, p + 1$. All other blocks are zero. Based on the asymptotic results in Section 2, we can conveniently use a Wald test, where under $\Phi_0$, $n(A\theta)^T V^{-1} A\theta$ has $\chi^2$ distribution with $(p-1)d_z$ degrees of freedom, where

\[
V = -(0_{(p-1)d_z \times K}, A) \left\{ \frac{\partial^2 l(\hat{\Phi}, \hat{\theta})}{\partial (\hat{\Phi}^T, \hat{\theta}^T) \partial (\hat{\Phi}^T, \hat{\theta}^T)^T} \right\}^{-1} (0_{(p-1)d_z \times K}, A)^T.
\]

Our final note in this section is to point out the special case where no covariate is included in the model, hence $\beta$ does not appear. The procedure derived above in this section can be directly applied with the simplification of deleting all the steps concerning estimating $\beta$. In other words, we would estimate $H(\cdot)$ from each of the $m$ groups, and then combine these results via a weighted average. This is very similar to the approaches in Wacholder et al. (1998) and in Ma & Wang (2014), except that the estimation of $H(\cdot)$ in each group is carried out via MLE here instead of least squares in these works, and the weight selection is further different from that in Wacholder et al. (1998).
4 Simulation Studies

We performed six sets of simulation studies to demonstrate the performance of the proposed method for the transformation model in the mixture data context. We present three of the simulation studies here and relegate the remaining three to Appendix A.4. Our first set of simulations contain homogeneous covariate effect. We generate data using $p = 2$, without $\alpha_j$, and $X$ is a bivariate random vector. The first component of $X$ is a binary variable, taking values 1 or 0 each with probability 0.5. The second component of $X$ is a uniform random variable between -1 and 1. The transformation $H$ is a logarithm function. We set $f_1$ to be the extreme value distribution, thus the first population has a Cox proportional hazard model. We set $f_2$ to be the logistic distribution, hence the second population has a proportional odds model. The censoring distribution is exponential, resulting an overall censoring rate about 25%. The results are in the first block of Table 1 and upper-left plot of Figure 1. For comparison, we also experimented the estimation by treating the homogeneous effect as heterogeneous, and estimated $\beta_1, \beta_2$ as $\alpha_{11}, \alpha_{21}, \alpha_{12}, \alpha_{22}$ instead. The results are in the second block of Table 1 and upper-right plot of Figure 1. It can be seen that the estimations are still consistent, yet the estimation variability roughly doubled, because we are using about half of the effective information.

The second set of simulations study the heterogeneous covariate effect. It includes $\alpha_j$, but not $\beta$. We generated data using $p = 2$. $Z$ contains the same structure as $X$ as in the first simulation for the first two terms and an intercept term for the third term. We keep $H$ the same as in the first simulation. Note that usually, in the transformation models, the intercept term is not identifiable. However, in our case, the difference of the intercepts in different populations is identifiable, and hence will be estimated. In this setting, we used two slightly different models for $f_1, f_2$. Specifically, we set $f_1$ to be standard normal and $f_2$ to be a $t$ distribution with 5 degrees of freedom. The censoring distribution is still exponential to achieve a 20% overall censoring rate. Results are in the second block of Table 1 and lower-left plot of Figure 1.
Our third simulation considers a more complex simulation including both \( \beta \) and \( \alpha_j \). We generated data using \( p = 2 \). \( X \) is bivariate. The first component of \( X \) is either 1 or 0 with equal probability, and the second component of \( X \) is a standard normal random variable. \( Z \) contains a uniform covariate on \([-1, 1]\) and a constant 1 to capture intercept. The true \( H \) is still the log transformation. This time, we will use two similar models for \( f_1, f_2 \). Specifically, we set both \( f_1, f_2 \) to be normal with mean zero, but with different variances, where the second population has four times the variance as the first one. The censoring distribution is exponential yielding a 20% overall censoring rate. The results are in the third block of Table 1 and the lower-right plot of Figure 1.

The simulation studies suggest that the proposed method has satisfactory finite sample performance. Specifically, the parameter estimation yields small biases in all three simulations measured by the mean and median of the 1000 estimates. In addition, inference results are precise, in that the sample standard deviation from the 1000 simulations are closely matched by both the average and the median of the 1000 estimated standard deviations calculated from the asymptotic results. The overall distribution of the estimated parameters are also close to normal, as indicated by the empirical coverage of the 95% confidence intervals, which are close to their nominal levels. The estimation of the transformation function \( H \), as shown in Figure 1, is within the expectation. Overall, the average of the curve estimation approximately overlays the true \( H \) curve, while the 95% confidence bands have performance better than the typical nonparametric curve estimation. This is due to the fact that \( H \) is estimated with the root-\( n \) rate, instead of the usual nonparametric rate. We also experimented different transformation function form for \( H \), and the overall performance is similar. The details of these simulations are in Appendix A.4.

5 Application to Huntington’s Disease Study

HD is the most prevalent monogenic neurodegenerative disorder caused by expansion of C-A-G repeats at the HD gene on chromosome 4 (MacDonald et al. 1993). Typically neurological,
cognitive and physical symptoms begin to exhibit around 30-50 years of age for affected individuals, and eventually they die from pneumonia, heart failure, or other complications 15-20 years after the diagnosis of HD (Foroud et al. 1999). The subjects analyzed here were recruited in the Cooperative Huntington’s Observational Research Trial (COHORT, Dorsey & The Huntington Study Group COHORT Investigators 2012), an epidemiological study of the natural history of HD. The probands were recruited primarily at academic research centers from 50 sites in the United States, Canada, and Australia. Probands were either clinically diagnosed with HD or the individuals who pursued HD genetic testing and carry a mutation but who were not clinically diagnosed. The initial probands underwent clinical examination and genotyping for HD mutation, and reported family history information on their first-degree relatives. The relatives were not genotyped because there was no resource for in-person collection of blood samples. Thus the relatives’ HD mutation status is unknown, while the distribution of their mutation status can be estimated from the pedigree structure and the probands’ carrier status. The full details of the COHORT study design are described in Dorsey & The Huntington Study Group COHORT Investigators (2012) and Wang et al. (2012).

Wang et al. (2012) proposed nonparametric methods to estimate survival functions in HD mutation carriers and non-carriers using first-degree relatives in COHORT study. The COHORT recruitment criteria are to include individuals from age 15 to age 89 who have none zero probabilities to be genetically at-risk and not at-risk for HD. Family history of the disease was not part of recruitment design. Therefore, the data of the first-degree relatives are free of sampling bias. Wang et al. (2012) has shown that the survival function in non-carriers estimated from the relative data matches adequately with the US population mortality rates, while the survival function in carriers estimated from the same relative data is very different. However, the nonparametric estimator in Wang et al. (2012) does not allow adjustment for covariate effect, thus it cannot be used for predicting survival function in relatives based on various covariates, such as the relative’s gender and the relative’s
There were 4105 subjects included in the COHORT analysis, and they were either mutation carriers or not, hence $p = 2$. The heterogeneous covariate effect model (1) was used to study the effect of several covariates on mortality in HD mutation carriers, where the model of the carriers, $f_1$ is normal with mean zero standard deviation 0.2, and for the non-carriers, $f_2$ is the distribution of $0.2T_5$, where $T_5$ stands for a student t random variable with degrees-of-freedom 5. The main research interest is to predict age at death based on CAG repeats length, adjusting for gender, proband’s HD clinical diagnosis status and a relative’s relationship to the probands. We assume all covariates to have differential effect in each mutation group to allow for maximal flexibility, i.e. all covariates are included in $Z$ and $X$ does not appear in (1). The covariates included in the model are: CAG repeats length at the HD gene, gender, and proband’s HD diagnosis status. As expected, the effects of CAG repeats length has a significant effect on age-at-death with an estimated effect of $-0.76$ (SE: 0.09, $p$-value $< 0.001$). The results suggest that if all covariates are the same, the subjects with one unit CAG repeat longer are expected to have a 2.38 years shorter lifespan. Here 2.38 is calculated as the average of $\hat{H}^{-1}(U) - \hat{H}^{-1}(U - 0.76)$ for a random $U$, where $\hat{H}$ is the estimated transformation function and is close to a linear function (See Figure 2). This finding is consistent with the clinical literature which indicated an inverse association between CAG repeats length and HD age at diagnosis and death Foroud et al. (1999), Langbehn et al. (2004). Further, proband’s HD diagnosis also has a significant effect after adjusting for CAG repeats and other covariates. Thus having a positive HD diagnosis in a family member is associated with an earlier mean age-at-death in carrier potentially due to other shared familial risk factors.

The estimated transformation $H(\cdot)$ and its bootstrap confidence interval are presented in Figure 2. The nonparametric function suggests that a linear transformation may fit the data adequately, and under a parametric approximation, prediction formula for the age-at-death in a mutation carrier subject can be obtained. The approximated linear function is
\( \hat{H}(t) = -24.35 + 0.32t \). We show this linear transformation in Figure 3.

A limitation of our analysis is that probands data were not included to protect against potential bias resulting from unknown sources in COHORT study which does not use a population-based ascertainment scheme for probands. When the proband ascertainment is population-based, for example, probands are randomly selected from diseased population (case-family design), their data may be included through a retrospective likelihood. It will be interesting to replicate our analysis in an independent study using such a design and include probands data in the analyses.

6 Discussion

In this work, we proposed a semiparametric transformation model to estimate distribution function and covariate effect for censored mixed population data. We assume that it is not known from which population an observation is drawn from, while the probability of an observation belonging to each population is known. This implies that as a mixed sample, the distribution of the mixture, although it may be different for different observation, is known. A potential interesting extension of our method is to further parametrize the mixing distributions and estimate the parameters from data. Specifically, this implies that \( q_{ij} \)'s are not completely known, but are modeled parametrically, semiparametrically or nonparametrically and then estimated as \( \hat{q}_{ij} \). It will be interesting and challenging to develop methods that can account for the additional discrepancy between \( \hat{q}_{ij} \) and \( q_{ij} \) and deliver appropriate estimation of the survival function and covariate effect using \( \hat{q}_{ij} \).

Our method has the flexibility to account for cross-population heterogeneity by characterizing the outcome in each population using different distributions specified by covariate parameters and error distributions (e.g., distinct scale or shape parameter; population-specific covariate effect), while simultaneously allow for common components across populations (e.g., shared covariate effect). In practice, whether or not to adopt population specific effect or shared effect is often determined by the purpose of the analysis and prior
knowledge. In many cases, covariates whose effects are of particular research interest should be modeled carefully and preferably assumed to be population-specific as a precaution, while covariates that are not of interest while their effect should be controlled to avoid bias can be modeled across population.

Finally, we have assumed that the relative observations are independent and excluded probands from the analyses. In proband-relative studies, multiple relatives from a same family may be collected and thus could have residual familial correlation (arising from other unknown causal genes or shared environmental familial factors) unexplained by our model. While our current approach is still consistent if the probands are representative samples of the probands population, the inference developed above will no longer be valid. Furthermore, when probands are not representative samples and there is residual familial aggregation, ascertainment scheme may need to be modeled and probands and relative data need to be analyzed jointly. How to best accommodate familial correlation and adjust for probands ascertainment scheme will be highly challenging and interesting.

Acknowledgements

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Transformation models with mixed populations

Figure 1: True function (solid line), median estimation (dashed line), mean estimation (dotted line) and 95\% confidence band (dash-dotted line) of $H(T)$ in simulations 1.1 (upper-left), 1.2 (upper-right), 2 (lower-left), and 3 (lower-right).
Figure 2: Estimated $H$ function (solid line), median estimation (dashed line), mean estimation (dash-dotted line) and 95% confidence band (dashed line) of $H(T)$ in real data analysis. Median, mean and 95% confidence band are based on 1000 bootstrapped samples. The mean, median and estimated functions almost overlap one another.

Figure 3: Fitted linear function $\hat{H}(t)$ versus age $t$ for HD data analysis.
Table 1: Simulation results based on 1000 repetitions.

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<th>true</th>
<th>mean</th>
<th>median</th>
<th>sd</th>
<th>mean(\hat{sd})</th>
<th>median(\hat{sd})</th>
<th>95% CI</th>
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Table 2: COHORT analysis results: estimated covariate effects (age, gender, proband’s diagnosis of HD), their standard errors, and p-values.

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<td>se</td>
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</tr>
<tr>
<td>p-value</td>
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<td>&lt; 0.001</td>
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Appendix

A.1 Derivation of $\int a_{ij}^{(u)} dr_{ij}$ and $\int r_{ij} a_{ij}^{(u)} dr_{ij}$

Here we show the derivation of the relationships

\[
\int a_{ij}^{(u)} dr_{ij} = q_{ij} \left\{ 1 - F_j(t) \right\} \int_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}}^{t+\delta_i} \frac{\partial h^{(u)}(y_i)}{\partial t} f_j(t) \, dt
\]
\[
\int r_{ij} a_{ij}^{(u)} dr_{ij} = e^{t} q_{ij} f_j(t) \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}} \right. \quad \text{if } \delta_i = 0
\]
\[
\int r_{ij} a_{ij}^{(u)} dr_{ij} = -e^{t} q_{ij} h^{(u)}(y_i) \left. \left\{ f'_j(t) - f_j(t) \right\} \right|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}} \quad \text{if } \delta_i = 1.
\]

Let $t = H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}$. Then

\[
a_{ij}^{(u)} = \left\{ h^{(u)}(y_i) r_{ij} \exp(t) \right\} \delta_i \exp(-r_{ij} e^{t}) q_{ij} \psi_j(r_{ij}) \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}} \right.
\]

When $\delta_i = 0$,

\[
\frac{da_{ij}^{(u)}}{dt} = -r_{ij} e^{t} \exp(-r_{ij} e^{t}) q_{ij} \psi_j(r_{ij}) \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}} \right.
\]
\[
\frac{da_{ij}^{(u)}}{dt^2} = -r_{ij} e^{t} \exp(-r_{ij} e^{t}) q_{ij} \psi_j(r_{ij}) + r_{ij}^{2} e^{2t} \exp(-r_{ij} e^{t}) q_{ij} \psi_j(r_{ij}) \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}} \right.
\]

When $\delta_i = 1$,

\[
\frac{da_{ij}^{(u)}}{dt} = -h^{(u)}(y_i) r_{ij}^{2} e^{2t} \exp(-r_{ij} e^{t}) q_{ij} \psi_j(r_{ij})
\]
\[
+ h^{(u)}(y_i) r_{ij} e^{t} \exp(-r_{ij} e^{t}) q_{ij} \psi_j(r_{ij}) \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}} \right.
\]

Thus, when $\delta_i = 0$,

\[
r_{ij} a_{ij}^{(u)} = -e^{-t} \frac{da_{ij}^{(u)}}{dt} \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}, \delta_i=0} \right.
\]

when $\delta_i = 1$,

\[
r_{ij} a_{ij}^{(u)} = h^{(u)}(y_i) e^{-t} \left( \frac{d^2 a_{ij}^{(u)}}{dt^2} - \frac{da_{ij}^{(u)}}{dt} \right) \left|_{t=H^{(u)}(y_i) + x_{i}^{T} \beta^{(u)} + z_{i}^{T} \alpha^{(u)}, \delta_i=0} \right.
\]
A.2 List of regularity conditions

We impose the following list of regularity conditions to achieve this purpose.

(a) The parameter value $\theta_0$ belongs to the interior of a compact set $\Theta \in \mathbb{R}^d$, and $\phi_0(t) > 0$ for all $t \in [0, \tau]$. (C1).

(b) With probability 1, $\Pr(Y_i \geq \tau | X_i, Z_i) > \delta_0 > 0$ for some constant $\delta_0 > 0$. (C2).

(c) $f_j(s)$ is bounded away from zero and infinity on its support for $j = 1, \ldots, p$. (C3).

(d) $f_j(s)$ is three times continuously differentiable and $f_j^{(v)}(s)/\exp(ks), v = 0, \ldots, 3, k = 2, \ldots, 4$, are square integrable on $(-\infty, \log(\tau)]$ for $j = 1, \ldots, p$. (C4), (C8).

(e) The covariates $X, Z$ have finite $k$th moments for $k = 1, \ldots, 6$. (C4), (C8).

(f) The first moment of $\log f_j(s)$ exists for $j = 1, \ldots, p$. (C6).

(g) $m \geq p$ and the matrix $(u_1, \ldots, u_m)$ has rank $p$. (C5), (C7).

A.3 Proof of Theorem 1

Because NPMLE for the linear transformation model in the mixture model setting we consider here can be cast into the general framework established in Zeng & Lin (2007), we prove Theorem 1 through verifying the conditions (C1)-(C8) required by Zeng & Lin (2007).

First, our Condition (a) ensures that the true parameter value is in the interior of a compact set of the parameter space, with Conditions (c) and (d), we further guarantee the differentiability and positivity of the hazard function. This leads to condition (C1) of Zeng & Lin (2007).

Next, our Condition (b) requires a positive probability to survive or be uncensored at the end of the time interval under consideration, which is equivalent to condition (C2) of Zeng & Lin (2007).
Further, our Condition (c) directly excludes the pathological situation that the moments or total variation involving the survival process becomes unbounded by requiring each \( f_j \) to be bounded and bounded away from zero. This guarantees that condition (C3) of Zeng & Lin (2007) is satisfied.

Condition (C4) of Zeng & Lin (2007) is a type of Lipschitz condition, with respect to both parameter and function. This is guaranteed by the stronger differentiability conditions in our Condition (d) and and the moment conditions in Condition (e).

Our Condition (g) ensures the identifiability of the problem, which is stated in condition (C5) of Zeng & Lin (2007).

Condition (C6) of Zeng & Lin (2007) requires sufficient smoothness and boundedness of the hazard functions and some functions derived from them. This is achieved here by our Conditions (c), (d) and (f).

Condition (C7) of Zeng & Lin (2007) is an identifiability condition that arises due to the generality of the framework they consider. In our problem it is guaranteed to hold under Condition (g) and the parameterization of requiring \( H(0) = -\infty \).

Finally, condition (C8) of Zeng & Lin (2007) is similar to their (C4) but is strengthened to hold along each path in a neighborhood of the true parameter value. Our Conditions (d) and (e) are imposed for all the parameter values in a compact set hence they jointly ensure this condition to hold.

\( \square \)

### A.4 Additional simulations

The fourth simulation resembles the first simulation, with everything the same as in the first simulation except that the true transformation \( H \) is \( \log\{t/(1-t)\} \). In this case, the overall censoring rate is about 25%. The results are in Table 3 and Figure 4.

Similarly, the fifth simulation resembles the second simulation but with a different \( H \) function. In this case, the true transformation \( H \) is \( \log\{t/(1-t)\} \). and the overall censoring
rate is about 20%. The results are in Table 3 and Figure 4.

Finally, the sixth simulation resembles the third simulation except in terms of the function $H$. The true transformation $H$ is $\log\{t/(1 - t)\}$, and the overall censoring rate about 25%. The results are in Table 3 and Figure 4.

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<th>$\beta_1$</th>
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<th>0.9776</th>
<th>0.4393</th>
<th>0.4605</th>
<th>0.4601</th>
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**References**


Figure 4: True function (solid line), median estimation (dashed line), mean estimation (dotted line) and 95% confidence band (dash-dotted line) of $H(T)$ in simulations 1 (upper-left), 2 (upper-right) and 3 (lower).


