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Efficient empirical likelihood inference for recovery rate of COVID19 under double-censoring

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ABSTRACT

Doubly censored data are very common in epidemiology studies. Ignoring censorship in the analysis may lead to biased parameter estimation. In this paper, we highlight that the publicly available COVID19 data may involve high percentage of double-censoring and point out the importance of dealing with such missing information in order to achieve better forecasting results. Existing statistical methods for doubly censored data may suffer from the convergence problems of the EM algorithms or may not be good enough for small sample sizes. This paper develops a new empirical likelihood method to analyze the recovery rate of COVID19 based on a doubly censored dataset. The efficient influence function of the parameter of interest is used to define the empirical likelihood (EL) ratio. We prove that $-2\log(EL\text{-ratio})$ asymptotically follows a standard $\chi^2$ distribution. This new method does not require any scale parameter adjustment for the log-likelihood ratio and thus does not suffer from the convergence problems involved in traditional EM-type algorithms. Finite sample simulation results show that this method provides much less biased estimate than existing methods, when censoring percentage is large. The application to COVID19 data will help researchers in other field to achieve better estimates and forecasting results.

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1. Introduction

Doubly censored data, with both right and left censoring, occur when time-to-event data are censored either from above or below. Doubly-censored data are very common in studies of infectious disease with incubation period. The left censoring happens when the originating date of the incubation period is not fully observed due to practical sampling factors beyond experimental control. The date of the failure event is often right-censored. A particular doubly censored data on AIDS study can be found in De Gruttola and Lagakos (1989). Another example is time from symptom onset to recovery for people who get COVID19. For COVID19 studies (Verity et al., 2020), the incubation rate and recovery rate are the key factors for us to understand the epidemiology. In particular, in the current COVID19 outbreak, better understanding of the recovery rate will help governments to take the right intervention strategy at the right time. However, many existing research for COVID19 are based on published information from government or ministry of health websites and media reports (Verity et al., 2020). Such data have high percentage of missing information, such as high percentage of left or right censoring. This may distort the estimation of recovery rate, which could further distort the epidemiology model.

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Fig. 1. $\delta = 2$, right censoring and observing $R$ only.

Fig. 2. $\delta = 3$, left censoring and observing $L$ only; exposure date observed and symptom date missing.

Fig. 3. $\delta = 1$, $X$ observed; exposure date means the ending date of exposure period.

forecasting, as we can see from Ferguson et al. (2020) that different model parameters will give very different forecasting results.

The dataset used in Verity et al. (2020) is from

https://github.com/mrc-ide/COVID19_CFR_submission

which has a large number of missing information on the symptom onset and on the date of recovery. Our main research interests here are to employ survival analysis techniques (Kenah, 2013; KhudaBukhsh et al., 2020) to study the recovery time, e.g. the time from symptom onset to recovery $X$, and to study the sensitivity of recovery rate on the epidemiology forecasting. The recovery times are clearly observed under right censoring because when the data were reported, recovery may not have happened to many patients. Therefore the right censoring time $R$ is the time from the symptom onset date to the reporting date. See Fig. 1 for scenarios when right censoring happens. Under right censoring, we will have no information about the left-censoring time $L$, the recorded exposure ending time to recovery. On the other hand, as we know that the symptom usually occur after exposure to the virus, when symptom onset date is missing and also reporting date is missing but the date of exposure to virus is available, we can imitate the reasonable condition of $X < L$ on $X$, which gives the left censoring time $L$. So when left-censoring occurs the time $L$ is from the date of exposure to the date of recovery. See Fig. 2 for details of left-censoring. Under left censoring, we will have no information about $R$. When $X \in [L, R]$, we will observe $X$ but cannot observe $L$ and $R$. This is shown in Fig. 3. In such cases we usually have that, $X = L$ (symptoms immediately occur after exposure; events recorded on the same day) or $L < X$ (the recorded exposure date means the ending time of an exposure period). We also have $X \leq R$ which means that recovery occurs before reporting.

In summary, under doubly censoring, the event time $X$ is observed if $L \leq X \leq R$. We observe $L$ in the case of left censoring with $X < L$, or observe $R$ in the case of right censoring with $X > R$. Let $(X_i, L_i, R_i), i = 1, \ldots, n$, be $n$ independent copies of $(X, L, R)$, then observations under doubly censorship can be summarized as $n$ independent pairs $(W_i, \delta_i), i = 1, \ldots, n$, where

$$W_i = \max(\min(X_i, R_i), L_i), \quad \text{and} \quad \delta_i = \begin{cases} 1, & \text{if } L_i \leq X_i \leq R_i, \\ 2, & \text{if } X_i > R_i, \\ 3, & \text{if } X_i < L_i. \end{cases}$$

Usually, we assumed that the event time $X$ is independent of the censoring vector $(L, R)$.

Denote $F$ as the cumulative distribution function of $X$. Suppose that we are interested in a parameter $\theta$, defined by a functional $\theta = \theta(F)$. Many important parameters can be represented as this form, or sometimes we obtain $\theta$ via the
corresponding estimating equation \( g(X, \theta) \). For example, if we are interested in the expectation of a known function \( m(X) \), then \( \hat{\theta} = \int m(x) dF(x) \), and the corresponding estimating equation is \( g(X, \theta) = m(X) - \hat{\theta} \). Other examples include:

1. \( \theta \) is the cumulative hazard function at given time \( t_0 \), i.e. \( \theta = -\ln(1 - F(t_0)) \), then the estimating equation is \( g(X, \theta) = I_{X \geq t_0} - e^{-\theta} \).
2. \( \theta \) is the mean residual life time at given time \( t_0 \), i.e.

\[
\theta = E(X - t_0 | X > t_0) = \tilde{F}^{-1}(t_0) \int_{t_0}^{\infty} (s - t_0) \, dF(s),
\]

where \( \tilde{F} = 1 - F \), then the estimating equation is \( g(X, \theta) = (X - t_0 - \theta) I_{X \geq t_0} \).

To draw inference on the unknown parameter \( \theta \), a straightforward approach is to implement a distribution function estimation for \( F \) (Turnbull, 1974; Tsai and Crowley, 1985; Chang and Yang, 1987; Chang, 1990). Using the distribution function estimation, the asymptotic-normality based confidence interval for the parameter of interest \( \theta \) can be constructed via the asymptotic variance estimator of the parameter estimate. But there are two main drawbacks associated with this method. First, the asymptotic variance usually takes a complicated form. Secondly, these confidence intervals based on asymptotic normal distribution do not always perform well for small samples. Other existing research about doubly-censored data may depend on specific model assumptions, such as (quantile) regression analysis (Zhang and Li, 1996; Ren and Gu, 1997; Ji et al., 2012) and two-sample tests (Shen et al., 2016). In this paper, we will solve these estimation problems via empirical likelihood method (Owen, 1988), which is a very useful tool for constructing confidence interval for \( \theta \) in nonparametric settings. Based on estimating equation \( g(X, \theta) \), the original Empirical Likelihood (OEL) in Owen (1988) is defined as

\[
R^O(\theta) = \sup \left\{ \frac{1}{n} \sum_{i=1}^{n} p_i g(X_i, \theta) = 0, \sum_{i=1}^{n} p_i = 1, p_i \geq 0, i = 1, 2, \ldots, n \right\}.
\]

It can be proved that

\[
L^O(\theta_0) = -2 \log R^O(\theta_0) \rightarrow \chi^2(1), \text{ in dist.}
\]

A very important work by Qin and Lawless (1994) generalized the EL method to make inference for parameter defined by a general estimating equation. In general, the empirical likelihood approach has a number of advantages, such as the shape of the confidence region is determined automatically by the data. In many cases, the log empirical likelihood ratio statistics has asymptotic \( \chi^2 \) distribution, therefore the confidence interval for \( \theta \) can be constructed without estimating asymptotic variance.

However, applying OEL methods to incomplete data will lead to a scaled \( \chi^2 \) result. When the data is right censored, Wang and Jing (2001) utilized the Buckley–James estimator to define the estimating equation, and proved that the asymptotic distribution of the corresponding log-likelihood is a scaled \( \chi^2 \) distribution. This limiting distribution can be used to construct the confidence interval for \( \theta \), if the scaled parameter is estimated. To avoid estimating the scaled parameter, He et al. (2016) used the efficient influence function of the parameter under right censorship to define the log-likelihood ratio statistics and proved its asymptotic distribution is a \( \chi^2 \) distribution. The confidence interval for \( \theta \) based on this method is much more accurate. Under doubly censoring, Ren (2001) proposed Leveraged Bootstrap Empirical Likelihood (LBEL) by combining the EL method with the bootstrap. Since the asymptotic distribution of the log-likelihood based on LBEL method is a scaled \( \chi^2 \) distribution, the scaled parameter as an adjustment coefficient needs to be estimated in practice. Besides, the LBEL method demands that the parameter of interest should be the linear functional of \( F \).

Notice that the EL likelihood function \( \prod_{i=1}^{n} p_i \) is not the real likelihood function for doubly censored data, Murphy and van der Vaart (1997) defined the likelihood function based on observations \((W_i, \delta_i)\) as

\[
L^{DC}(F) = \prod_{i=1}^{n} \Delta F(W_i)^{[\delta_i=1]}(\tilde{F}(W_i))^{[\delta_i=2]} F(W_i)^{[\delta_i=3]},
\]

where DC is the abbreviation for Double Censoring, \( \Delta F(t) = F(t) - F(t-) \) and \( \tilde{F} = 1 - F \) is the survival function. Using (1), Murphy and van der Vaart (1997) showed that this log-likelihood ratio subject to nonparametric moment constraints obeys the Wilks’ phenomenon under some assumptions. This method avoids the scaled parameter, but is computationally difficult to find the nonparametric maximum likelihood. To solve this problem, Shen et al. (2016) proposed an EM algorithm to calculate this log-likelihood ratio statistics. However, EM algorithm may suffer from the problem of convergence to a local maximum point. Different from Shen et al. (2016), we investigate another approach in this paper. Inspired by He et al. (2016), we develop the likelihood statistics defined by efficient score function for the parameter of interest \( \theta \). This method is called Efficient-EL method in our paper. Under this new approach, we demonstrate that the log empirical likelihood ratio converges to the standard \( \chi^2 \) distribution without using any scale parameter adjustment, which means the confidence interval for different kinds of parameters \( \theta \) can be obtained by a unified algorithm. In the mean time, it is computationally much more efficient than existing EL methods under doubly censoring.
The rest of the paper is organized as follows. The Efficient-EL inference for the differential functional parameter $\theta$ under doubly-censored data is given in Section 2, including the large sample properties and the computing algorithm. Simulation studies of the Efficient-EL and the EM-EL method proposed by Shen et al. (2016) are provided in Section 3. We find that our approach performs much better for longer tail distributions, which usually lead to higher censoring proportions. In the mean time, the new method still performs as good as existing methods for lighter tail distributions which lead to lower censoring proportions. An application on COVID-19 study based on our proposed methodology is presented in Section 4. The paper concludes with a discussion in Section 5.

2. Efficient empirical likelihood inference

Denote $G_L(t) = P(L \leq t)$ and $G_R(t) = P(R \leq t)$ as the distribution of $L$ and $R$ respectively. Suppose we are interested in the estimation problem for a parameter $\theta = \theta(F)$, and the corresponding estimating equation for $\theta$ is $g(X, \theta) = 0$. Since $X$ cannot be observed unless it falls in $[L, R]$, we define $g^{DC}(W, \delta; \theta) = I_{\{\delta = 1\}} \frac{g(W, \theta)}{G_R(W) - G_L(W)} + I_{\{\delta = 2\}} \frac{g(W, \theta)}{1 - G_R(W)} + I_{\{\delta = 3\}} \frac{g(W, \theta)}{G_L(W)}$. It is easy to see that, given the distribution $F$, $G_L$, $G_R$, we have $E g^{DC}(W, \delta; \theta) = 0$ which gives an estimating equation for $\theta$. Then, the EL ratio can be defined by

$$R^{DC}(\theta) = \sup \left\{ \prod_{i=1}^{n} n p_i \left| \sum_{i=1}^{n} p_i g^{DC}(W_i, \delta_i; \theta) = 0 \right. , \sum_{i=1}^{n} p_i = 1 , p_i \geq 0 , i = 1 , \ldots , n \right\} .$$

Substituting the unknown $G_L$, $G_R$ with its consistent estimators will lead to a scaled asymptotic $\chi^2$ distribution. Murphy and van der Vaart (1997) used the likelihood function (1) to solve the problem. Different from their idea, we will try to reconsider the estimating equation to overcome the scaled $\chi^2$ asymptotic distribution problem.

2.1. The main theorems

Assume $[\alpha, \beta] \subset [0, \infty)$ be the support of $F$, and the following assumptions hold.

$$G_L(x) - G_R(x-) > 0 \text{ on } x \in [\alpha, \beta], \quad (A1)$$

$$F, G_L \text{ and } G_R \text{ are continuous with } G_L(\beta) = 1, G_R(\alpha) = 0. \quad (A2)$$

Define $BV[\alpha, \beta] = \{h : [\alpha, \beta] \rightarrow \mathbb{R}, h \text{ is bounded and of bounded variation} \}$ and $H_F = \{h \in BV[\alpha, \beta] : \int h dF = 0\}$. The following Lemma provides the efficient influence function for $\theta$.

Lemma 2.1. Let $dF(x) = (1 + t h(x)) dF(x)$ be a submodel of $F(x)$, which approaches $F$ at direction $h \in H_F$. Assume (A1) and (A2) hold and the Hadamard derivative of $\theta(F_t)$ exists, denoted by $\hat{\theta}_0$. Then the efficient influence function for $\theta$ is

$$\psi(w, \delta; \theta) = \ell^\ast \ell_F^{-1} \hat{\theta}_0,$$

where $\ell_F$ is the score operator

$$(\ell_F h)(w, \delta) = I_{\{\delta = 1\}} h(w) + I_{\{\delta = 2\}} \int_{[0, w]} h dF + I_{\{\delta = 3\}} \frac{\int_{[0, w]} h dF}{F(w)},$$

and $\ell^\ast$ is its corresponding adjoint operator

$$(\ell^\ast g)(s) = g(s, 1) (G_L(s) - G_R(s-)) + \int_{[0, s]} g(u, 2) dG_R(u) + \int_{[s, \infty]} g(u, 3) dG_L(u).$$

Proof. See Appendix. □

The assumptions (A1) and (A2) guarantee the operator $\ell^\ast \ell_F : BV[\alpha, \beta] \rightarrow BV[\alpha, \beta]$ is invertible. The following are some examples of derivatives $\hat{\theta}_0$ (in all of the examples we let $t_0$ be fixed).

[1.] For mean $\theta = EX$, we have $\hat{\theta}_0 = x - \theta$.

[2.] For the $k$th moments $\theta = EX^k$, we have $\hat{\theta}_0 = x^k - \theta$.

[3.] For cumulative distribution function $\theta = F(t_0)$, we have $\hat{\theta}_0 = I_{[x \leq t_0]} - \theta$.

[4.] For cumulative hazard function $\theta = -\ln(1 - F(t_0))$, we have $\hat{\theta}_0 = 1 - e^\theta I_{[x > t_0]}$.

Since the operators $\ell^\ast$ and $\ell_F$ depend on $(F, G_L, G_R)$, we should write $\psi = \psi(w, \delta; \theta, F, G_L, G_R)$ more precisely. Let $\xi = (F, G_L, G_R)$, the efficient influence function can be denoted as $\psi(W, \delta; \theta, \xi)$, hence $E \psi(W, \delta; \theta, \xi) = 0$. 

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Notice that the nuisance parameter $\xi$ is unknown, we need to estimate it firstly.

For $j = 1, 2, 3$, define

$$
\hat{H}_k(t) = \frac{1}{n} \sum_{i=1}^{n} 1_{[W_i \leq t, \delta_i = k]} \quad \text{and} \quad \hat{H}(t) = \sum_{k=1}^{3} \hat{H}_k(t).
$$

Chang and Yang (1987) gave the self-consistent estimators $\hat{F}, \hat{G}_L, \hat{G}_R$ of $F, G_L, G_R$ by solving the following equations:

$$
\hat{H}(t) = (1 - \hat{F}(t))\hat{G}_R(t) + \hat{F}(t)\hat{G}_L(t), \quad (2)
$$

$$
\hat{G}_R(t) = \int_0^t \frac{d\hat{H}_2(u)}{1 - \hat{F}(u)}, \quad (3)
$$

$$
\hat{G}_L(t) = 1 - \int_t^\infty \frac{d\hat{H}_3(u)}{\hat{F}(u)}. \quad (4)
$$

Based on Eq. (2), a naive and simple iterative algorithm can be used to get $\hat{F}$, and then $\hat{G}_L, \hat{G}_R$ can be calculated by Eqs. (3) and (4). In order to guarantee the asymptotic consistency and normality of $\hat{F}, \hat{G}_L$ and $\hat{G}_R$, we assume $F, G_L$ and $G_R$ satisfy conditions (A1)-(A6) in Chang (1990) throughout this paper.

Define $\hat{\xi} = (\hat{F}, \hat{G}_L, \hat{G}_R)$, then the efficient influence function $\psi(W_i, \delta_i; \theta, \xi)$ for $\theta$ can be estimated by $\psi(W_i, \delta_i; \theta, \hat{\xi})$. For simplicity of notations, denote $\psi_i(\theta) = \psi(W_i, \delta_i; \theta, \xi)$ and $\hat{\psi}_i(\theta) = \psi(W_i, \delta_i; \theta, \hat{\xi})$, then the corresponding Efficient EL ratio is defined as $\hat{R}^{Elastic}(\theta) \equiv \hat{R}^{DC}(\theta, \hat{\xi}) = \sup \left\{ \prod_{i=1}^{n} n \prod_{i=1}^{n} p_i \hat{\psi}_i(\theta) = 0, \prod_{i=1}^{n} p_i = 1, p_i \geq 0, i = 1, 2, \ldots, n \right\}$.

Using Lagrangian multipliers, $p_i = n^{-1}(1 + \hat{\psi}_i(\theta))^{-1}$, we further have

$$
\hat{R}^{Elastic}(\theta) = \prod_{i=1}^{n} \frac{1}{1 + \hat{\psi}_i(\theta)},
$$

where $\lambda$ is the solution of the following equation

$$
\frac{1}{n} \sum_{i=1}^{n} \frac{\hat{\psi}_i(\theta)}{1 + \hat{\psi}_i(\theta)} = 0
$$

and the following asymptotic results.

**Theorem 2.1.** Suppose the assumptions in Lemma 2.1 hold, $\theta_0$ is the true value of the parameter of interest, and $E \psi^2(W; \delta; \theta_0)$ exists, then we have

$$
\hat{R}^{Elastic}(\theta_0) \equiv -2 \log \hat{R}^{Elastic}(\theta_0) \rightarrow \chi^2(1), \quad \text{in dist.}
$$

**Proof.** Under Lemmas B.1 and B.2 in Appendix, this proof is similar to the proof of Original EL and therefore it is omitted. $\square$

**Theorem 2.1** shows that the estimated log empirical likelihood ratio converges to the standard $\chi^2$ distribution without adjustment, which means the confidence interval for different kinds of parameters $\theta$ can be obtained by an unified algorithm. Hence, a confidence region for the parameter $\theta$ with asymptotic coverage probability $1 - \alpha$ can be defined as

$$
CI = \left\{ \theta : 2 \sum_{i=1}^{n} \log \left( 1 + \hat{\psi}_i(\theta) \right) \leq \chi^2_\alpha(1) \right\}. \quad (6)
$$

By recalling the definition of the efficient influence function for $\theta$

$$
\psi_w(W, \delta; \theta) = \ell_F(\ell_F^* \ell_F)^{-1} \hat{\theta}_0,
$$

in the following subsection we present an algorithm for the calculation of the numerical solution of $\hat{\psi}_i$ and the confidence region $CI$.  

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2.2. Algorithm for efficient-EL method

Before presenting the algorithm, we need to introduce the following notations.

\[
\hat{K}_1(t) = \begin{cases} 
    \frac{1}{n-1} \sum_{i=1}^{n} \left(1 - \hat{F}(W_i)\right)^{-2} I_{[\hat{F}(W_i) < t]}, & \text{if } t < B_n, \\
    \hat{K}_1(B_n -), & \text{if } t \geq B_n,
\end{cases}
\]

\[
\hat{K}_2(t) = \begin{cases} 
    \frac{1}{n-1} \sum_{i=1}^{n} \hat{F}^{-2}(W_i) I_{[\hat{F}(W_i) \geq t]}, & \text{if } t \geq A_n, \\
    \hat{K}_2(A_n), & \text{if } t < A_n,
\end{cases}
\]

where \(A_n = \min\{W_i : \hat{F}(W_i) > 0\}\), \(B_n = \max\{W_i : \hat{F}(W_i) < 1\}\), and

\[
K_{ij} = \frac{1}{n} \left(\hat{K}_1(W_i \wedge W_j) + \hat{K}_2(W_i \vee W_j) - I_{[\hat{F}(W_i) = 1]} - I_{[\hat{F}(W_j) = 1]}\right).
\]

For a given \(\theta\), define the least favorable direction \(h_0(x) = (\ell^* \epsilon_x)^{-1} \hat{\theta}_0(x; \theta)\), then the efficient influence function is \(\psi(w, \delta; \theta, \xi) = \ell^* \epsilon_x h_0(x)\). Notice that only the values of \(\psi(w, \delta; \theta, \xi)\) at the sample points \((W_i, \delta_i)\) are needed, therefore we can just calculate \(\hat{h}_0(W_1), \hat{h}_0(W_2), \ldots, \hat{h}_0(W_n)\). The following Corollary 2.1 shows a key equation for \(\hat{h}_0(W_i)\) which will be used in the Efficient-EL algorithm.

**Corollary 2.1.** The estimator \(\hat{h}_0(W_i)\) satisfies the equation

\[
\begin{pmatrix}
\hat{h}_0(W_1; \theta) \\
\vdots \\
\hat{h}_0(W_n; \theta)
\end{pmatrix} = \begin{pmatrix}
\Delta G_1 + K_11 & K_{12} & \cdots & K_{1n} \\
K_{21} & \Delta G_2 + K_{22} & \cdots & K_{2n} \\
\vdots & \vdots & \ddots & \vdots \\
K_{n1} & K_{n2} & \cdots & \Delta G_n + K_{nn}
\end{pmatrix} \begin{pmatrix}
\hat{h}_0(W_1) \\
\vdots \\
\hat{h}_0(W_n)
\end{pmatrix},
\]

where \(\Delta G_i := \hat{C}_L(W_i) - \hat{C}_R(W_i -)\).

The Efficient-EL ratio \(\hat{K}^{duc}(\theta)\) can then be calculated by the following algorithm. Hence, the confidence interval for \(\theta, CI\) in (6), can be constructed using the output \(\hat{\psi}(\theta)\) by this algorithm.

**Algorithm 1 Efficient-EL Algorithm**

1: Solving (2)-(4) to get the self-consistent estimators \(\hat{F}, \hat{C}_L\) and \(\hat{C}_R\) of \(F, G_L\) and \(G_R\).
2: for \(i = 1\) to \(n\), do
3: Calculate \(\hat{h}_0(W_i; \theta)\) and \(\Delta G_i = \hat{C}_L(W_i) - \hat{C}_R(W_i -)\),
4: for \(j = 1\) to \(n\), do
5: Calculate \(K_{ij}\),
6: end for
7: end for
8: Solve the equation (7) and get \(\hat{h}_0(W_1), \hat{h}_0(W_2), \ldots, \hat{h}_0(W_n)\).
9: for \(i = 1\) to \(n\), do
10: Calculate \(\hat{\psi}(\theta) = \psi(W_i, \delta_i; \theta, \xi)\),
11: if \(A_n \leq W_i < B_n\) then
12: \(\hat{\psi}(\theta) = I_{[\hat{F}(W_i) = 1]} \hat{h}_0(W_i) + \frac{I_{[\hat{F}(W_i) = 1]} \sum_{k=1}^{n} I_{[\hat{F}(W_k) > W_i]} \hat{h}_0(W_k)}{n(1 - \hat{F}(W_i))} \Delta G_k + \frac{I_{[\hat{F}(W_i) = 1]} \sum_{k=1}^{n} I_{[\hat{F}(W_k) < W_i]} \hat{h}_0(W_k)}{n\hat{F}(W_i)} \Delta G_k\),
13: else if \(W_i < A_n\) then
14: \(\psi(W_i, \delta_i; \theta, \xi)\),
15: else
16: \(\hat{\psi}(\theta) = \psi(B_n -, \delta_i; \theta, \xi)\),
17: end if
18: end for
19: Output \(\hat{\psi}(\theta)\).

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3. Simulation studies

In this section, we will implement simulation studies to study recovery time distribution, which is very important for the analysis of Susceptible–Exposed–Infectious–Resistant (SEIR) epidemiology model. SEIR model in epidemic disease studies involves four states: susceptible (S), exposed (E), infected (I), and resistant (R) via

\[
\begin{align*}
\frac{dS}{dt} &= -\frac{\beta}{N} SI, \\
\frac{dE}{dt} &= \frac{\beta}{\sigma} SI - \sigma E, \\
\frac{dI}{dt} &= \sigma E - \gamma I, \\
\frac{dR}{dt} &= \gamma I.
\end{align*}
\]

In this SEIR model, the infectious rate \(\beta\) controls the rate of spread which represents the probability of transmitting disease between a susceptible and an infectious individual. The incubation rate \(\sigma\) is the rate of latent individuals becoming infectious (average duration of incubation is \(1/\sigma\)). Recovery rate \(\gamma\) is determined by the average duration of infection. \(N = S + E + I + R\) is the total population. The basic reproductive number, \(R_0 = \beta/\gamma\), does not change in this model.

Here we focus on using the proposed double censoring model to estimate the recovery time, because the infection time only involves right censoring in the data and therefore they can be estimated using standard right censoring techniques (Kenah, 2013). Therefore, our simulation focus will be on the mean recovery time and model forecasting to illustrate the importance of recovery time estimation on the forecasting accuracy. We will also study the mean residual recovery time, which is also very important to forecast the expected additional recovery time given that the patient has not recovered at a certain time.

3.1. Simulation studies for recovery time

In this subsection, we will illustrate the performance of our method via different simulation scenarios. We denote \(\text{Uniform}(a, b)\) as the uniform distribution on \([a, b]\), \(\text{Exp}(\lambda)\) as the exponential distribution with mean \(\lambda\), and \(\text{LogNormal}(\mu, \sigma^2)\) as the Log-Normal distribution with parameters \(\mu\) and \(\sigma^2\).

There are two parameters of our interests. The first is the mean of \(X\), denoted by \(\theta_1\), and its corresponding estimating equation is \(g_1(X, \theta_1) = X - \theta_1\). Note that \(\theta_1\) is the inverse of the mean recovery rate parameter \(\gamma\). The second is the Mean Residual Lifetime (MRL) of \(X\) given \(t_0\), denoted by \(\theta_2(t_0)\) or \(MRL(t_0)\), and its corresponding estimating equation is \(g_2(X, \theta_2) = (X - t_0 - \theta_2)_{[X<t_0]}\). MRL stands for the remaining mean time needed for an infected patient to recover.

Based on the simulated data, we use all complete data \(X_i\) to construct the benchmark confidence interval, named as complete data EL (or complete-EL) result. We will compare the Efficient-EL confidence interval proposed in the previous section and EM-EL confidence interval given in Shen et al. (2016), with the benchmark complete-EL results.

3.1.1. Simulation results for mean and mean residual lifetime

\(\text{Uniform}(0, 3)\) is considered as the underlying lifetime distribution \(F\) in this subsection. The left censoring time \(L\) and censoring interval length \(R - L\) are uniformly distributed on interval \([c_1, c_2]\) and \([c_3, c_4]\). We set \(c_1\) and \(\mu_i\) to be different values to achieve 10%, 20%, 30% left censoring proportions and 10%, 20%, 30% right censoring proportions respectively. Based on 5000 simulated data sets, we construct Efficient-EL confidence intervals, EM-EL confidence intervals and Complete-EL confidence intervals. The coverage probabilities for mean and MRL are summarized in Table 1.

From these results, we notice that as the sample size \(n\) increases, all coverage probabilities converge to the nominal levels. When \(n\) is fixed, coverage probabilities of Efficient-EL confidence intervals and EM-EL confidence intervals decrease as the censoring proportion increases. The coverage probabilities of the confidence intervals for parameter \(MRL(t_0)\) decrease when \(t_0\) increases. In all cases, the performance of Efficient-EL and EM-EL methods are close to that of Complete-EL method when censoring proportion is not large.

In the top half of the Table 1, Efficient-EL and EM-EL methods perform similarly. The difference among these two methods and Complete-EL method is small, especially for small censoring proportion or large sample size. However, the performance of these methods for the parameter MRL is different (see the bottom half of Table 1). The coverage probabilities of Efficient-EL confidence intervals perform better than that of EM-EL for almost all scenarios when \(t_0 = 10\%\) quantile of \(F\). Meanwhile, Efficient-EL method performs as good as EM-EL when \(t_0 = 50\%\) quantile of \(F\), for most cases.

We also plot the results of Table 1 and draw the coverage probability curves of different methods in Fig. 4. Comparing to EM-EL method, Efficient-EL method shows a much better convergence pattern, converging faster to the Complete-EL results.

3.1.2. The impact of different censoring proportions and different distributions

In this section, we investigate the impact of different censoring proportions. Here we use Exponential distribution and Log-Normal distribution as the underlying distributions and consider the complicated parameter \(MRL(t_0)\), where \(t_0\) is the 30% quantile of the underlying distributions. For exponential distribution, we set the left censoring time \(L\) as \(\text{Exp}(c_1)\) and censoring interval length \(R - L\) as \(\text{Exp}(c_2)\). For \(\text{LogNorm}(0, 0.64)\), the left censoring time \(L\) follows \(\text{Exp}(c_1)\), and censoring interval length \(R - L\) follows \(\text{LogNorm}(c_2, 0.25)\). Let \(c_1\) to be different values to achieve 20% left censoring and 40% right...
Table 1
Coverage probabilities for Mean and MRL with 10%, 50% quantile under Uniform(0, 3) distribution. Two percentages in each column stand for left censoring proportion and right censoring proportion. Efficient-EL results with better performances than EM-EL highlighted in bold.

|       | Nominal Level = 0.90 |       | Nominal Level = 0.95 |
|-------|----------------------|-------|----------------------|
|       | 10% + 10% | 20% + 20% | 30% + 30% | 10% + 10% | 20% + 20% | 30% + 30% |
| n = 50 | Complete-EL | 0.898 | 0.894 | 0.896 | 0.944 | 0.943 | 0.945 |
|        | Efficient-EL | **0.897** | **0.888** | **0.877** | **0.944** | **0.935** | **0.932** |
|        | EM-EL | 0.896 | 0.878 | 0.873 | 0.944 | 0.932 | 0.930 |
| n = 80 | Complete-EL | 0.906 | 0.899 | 0.897 | 0.955 | 0.949 | 0.948 |
|        | Efficient-EL | **0.903** | **0.892** | **0.887** | **0.950** | **0.942** | **0.940** |
|        | EM-EL | 0.904 | 0.891 | 0.882 | 0.951 | 0.943 | 0.940 |
| n = 100 | Complete-EL | 0.909 | 0.896 | 0.903 | 0.953 | 0.948 | 0.954 |
|        | Efficient-EL | **0.906** | **0.898** | **0.899** | **0.951** | **0.946** | **0.944** |
|        | EM-EL | 0.905 | 0.888 | 0.891 | 0.952 | 0.944 | 0.942 |
| MRL(t₀ = 10% quantile) |       |       |       |       |       |       |
|       | 10% + 10% | 20% + 20% | 30% + 30% | 10% + 10% | 20% + 20% | 30% + 30% |
| n = 50 | Complete-EL | 0.907 | 0.898 | 0.906 | 0.954 | 0.943 | 0.953 |
|        | Efficient-EL | **0.904** | **0.874** | **0.854** | **0.949** | **0.929** | **0.910** |
|        | EM-EL | 0.898 | 0.851 | 0.831 | 0.947 | 0.914 | 0.894 |
| n = 80 | Complete-EL | 0.895 | 0.894 | 0.892 | 0.949 | 0.948 | 0.945 |
|        | Efficient-EL | **0.892** | **0.880** | **0.866** | **0.941** | **0.931** | **0.921** |
|        | EM-EL | 0.886 | 0.859 | 0.835 | 0.936 | 0.921 | 0.907 |
| n = 100 | Complete-EL | 0.896 | 0.889 | 0.897 | 0.949 | 0.948 | 0.947 |
|        | Efficient-EL | **0.896** | **0.884** | **0.868** | **0.949** | **0.936** | **0.923** |
|        | EM-EL | 0.898 | 0.859 | 0.838 | 0.946 | 0.925 | 0.907 |
| MRL(t₀ = 50% quantile) |       |       |       |       |       |       |
|       | 10% + 10% | 20% + 20% | 30% + 30% | 10% + 10% | 20% + 20% | 30% + 30% |
| n = 50 | Complete-EL | 0.897 | 0.891 | 0.896 | 0.945 | 0.943 | 0.950 |
|        | Efficient-EL | **0.871** | **0.838** | 0.819 | 0.928 | 0.896 | 0.877 |
|        | EM-EL | 0.888 | 0.833 | 0.831 | 0.938 | 0.897 | 0.895 |
| n = 80 | Complete-EL | 0.895 | 0.901 | 0.891 | 0.949 | 0.950 | 0.841 |
|        | Efficient-EL | **0.885** | **0.856** | **0.844** | **0.935** | **0.912** | **0.909** |
|        | EM-EL | 0.889 | 0.848 | 0.846 | 0.941 | 0.909 | 0.915 |
| n = 100 | Complete-EL | 0.893 | 0.901 | 0.897 | 0.949 | 0.948 | 0.947 |
|        | Efficient-EL | **0.892** | **0.873** | 0.871 | 0.942 | **0.928** | **0.923** |
|        | EM-EL | 0.894 | 0.857 | 0.864 | 0.945 | 0.921 | 0.929 |

Fig. 4. The coverage probabilities for MRL(t₀ = 0.5) under Uniform(0, 3) distribution when nominal level is 90%. The figures from left to right show the results for different censoring percentages: left plot 10% left-censoring and 10% right-censoring; middle plot 20% left-censoring and 20% right-censoring; right plot: 30% left-censoring and 30% right-censoring.

censoring, and 40% left censoring and 20% right censoring, respectively. Based on 5000 simulated data sets, the coverage probabilities are summarized in Figs. 5 and 6.

We can see that higher right censoring proportion leads to lower coverage probabilities. The coverage probabilities of confidence intervals constructed by the proposed Efficient-EL approach is much better than EM-EL methods under Exponential distribution. In Fig. 5, the left plot with 20% left censoring and 40% right censoring shows that Efficient-EL has coverage probability 0.80 which is much closer to the benchmark (about 0.90), while EM-EL only has coverage probability less than 0.60. The right plot with 40% left censoring and 20% right censoring also shows Efficient-EL is better. In particular, EM-EL seems to have the problem not converging to the benchmark 0.90 as sample size increases.
Fig. 5. The coverage probabilities for MRL($t_0 = 0.3$) under Exp(1) distribution when nominal level is 90%. The left figure shows the results for 20% left and 40% right censoring proportion, while the right figure shows the result for 40% left and 20% right censoring proportion.

Fig. 6. The coverage probabilities for MRL($t_0 = 0.3$) under LogNorm(0, 0.64) distribution when nominal level is 90%. The left figure is the coverage probability curve under 20% left and 40% right censoring proportion setting, while the right figure shows the result under 40% left and 20% right censoring proportion setting.

Under the Log-Normal distribution, EM-EL appears to perform similarly as Efficient-EL, but EM-EL does not show a clear pattern of convergence (see Fig. 6). In other words, as sample size increases the coverage probabilities of Efficient-EL based confidence intervals steadily increase, while the coverage probabilities of EM-EL seem not to have a clear increasing pattern (coverage probabilities of EM-EL may not converge to the nominal level as sample size becomes larger). Taking censoring proportion 40%+20% as a specific example, as the sample size increase from 50 to 150, the coverage probabilities of Efficient-EL increase from 0.784 to 0.815, while EM-EL decrease from 0.845 to 0.820. See Fig. 6 for details.

In summary, under both exponential distribution and log-normal distribution, the new Efficient-EL approach is more reliable for highly-censored data.

3.2. SEIR model forecasting

In this subsection, we will present how the SEIR forecasting results are affected by choosing different recovery rate parameter $\gamma$, i.e. the sensitivity of $\gamma$. In our simulation we set population $N = 10^6$ and discrete time steps of size 0.1 of a simulated day. We consider the reproduction number $R_0 = 2$ and 3, then let the average duration of infection be 10, 20 and 30 days (the corresponding recovery rate $\gamma$ is 1/10, 1/20, 1/30, respectively). These values are chosen according to the data analysis result in Section 4. The incubation period($= 1/\sigma$) is chosen between 2 and 10 days, which mimic the real COVID data analysis results (World Health Organization, 2020-01-27). From the summarized results presented in Fig. 7, we can see that under different $R_0$ and $\sigma$ values, the total number of infections will be highly affected by the recovery rate $\gamma$. The maximum number of infection can be different in the scale of 20,000 to 100,000 in a population of 1,000,000. Therefore, even if the confidence interval of recovery rate was estimated wrongly at a very small scale, the final forecasting results will be very different.
Fig. 7. Maximum number of infections curves under different quarantine protocols. Three different sets of curves represent different recovery period.

### Table 2

The analysis of COVID19 data for different groups.

| Group       | Proportion | Sample size | Efficient-EL Mean | EM-EL Mean |
|-------------|------------|-------------|-------------------|------------|
|             | Left       | Observed    | Right             | CI lower   | CI upper   |
| Male        | 0.052      | 0.185       | 0.763             | 218        | 18.171     | 25.567     | 18.541     | 22.186     | 20.243     | 19.842     |
| Female      | 0.063      | 0.184       | 0.753             | 218        | 18.171     | 25.567     | 18.541     | 22.186     | 20.243     | 17.759     |
| Age under 30| 0.140      | 0.215       | 0.645             | 85         | 9.527      | 22.411     | 15.596     | 22.186     | 20.243     | 19.605     |
| Age 30–50   | 0.082      | 0.212       | 0.707             | 186        | 17.651     | 21.172     | 17.853     | 21.528     | 20.243     | 17.759     |
| Age 50–60  | 0.066      | 0.168       | 0.766             | 115        | 18.947     | 23.813     | 19.856     | 23.955     | 21.731     | 19.605     |
| Age 60–70  | 0.076      | 0.124       | 0.800             | 83         | 17.902     | 24.627     | 19.680     | 24.786     | 22.041     | 21.731     |
| Age over 70| 0.089      | 0.089       | 0.822             | 68         | 18.951     | 25.614     | 19.935     | 23.970     | 22.173     | 21.731     |
| Overall     | 0.059      | 0.170       | 0.771             | 547        | 18.784     | 20.928     | 18.804     | 20.837     | 20.013     | 19.605     |

4. Analysis of COVID19 data

4.1. Recovery time analysis

There has already been a vast literature on COVID19 research about Susceptible–Exposed–Infectious–Resistant (SEIR) epidemiology model, based on which the UK government’s lock-down strategy were made (Ferguson et al., 2020). Recovery time is a very important factor in such SEIR model. However publicly available data could have a large proportion of missing information, to stop us achieving a proper analysis for it. For example, the dataset from

https://github.com/mrc-ide/COVID19_CFR_submission

has a large number of missing information on the symptom onset and on the date of recovery. It actually gave a double censoring dataset for the recovery time. The event time $X$ of interest is time length from symptom onset to recovery. The right censoring variable $R$ is from symptom onset to the reporting date. The left censoring variable $L$ is from the date of exposure (or the ending date of exposure period) to recovery. The total number of observations used in our analysis is $n = 547$ and the data are collected from 20th January 2020 to 28th February 2020.

Firstly, we list the censoring proportions of this dataset under different groups in Table 2. Using the Efficient-EL and EM-EL methods, the confidence intervals of recovery time for different groups can be calculated, respectively. These results are listed in Table 2. From Table 2, we can see that the elder groups have longer average recovery period, but there is no significant different between male and female. The confidence intervals based on EM-EL method seem to be shorter than that of Efficient-EL. This corresponds to the simulation results where EM-EL has worse coverage probability in most cases.

4.2. SEIR model forecasting

We also carry out a simulation study similar to Ferguson et al. (2020) to compare the forecasting results based on different model parameter values, in order to address the importance of parameter estimation for such forecasting analysis. We set $\sigma = 1/5.1$, according to Ferguson et al. (2020). Since SEIR model dose not include mortality, we classify death and recovered as one group, re-estimate the recovery time and get the 95% confidence interval [18.784, 20.928] and mean 20.013. Hence, three different recovery periods: short duration 15 days ($\gamma = 1/15$, corresponding to results without using double censoring analysis, no right censoring, over estimation of recovery rate), medium duration 20 days ($\gamma = 1/20$, corresponding to our result based on double censoring) and long duration 25 days ($\gamma = 1/25$, corresponding
to results without using double censoring analysis, no left censoring, under estimation of recovery rate) are considered in our simulation.

We also consider two different quarantine protocols: no government interventions $R_0 = 2.4$ following (Ferguson et al., 2020) and with mild government interventions $R_0 = 1.5$, which lead to the parameter value $\beta = R_0 \gamma$ in our simulation. All of our simulation are carried out via the R package deSolve of SEIR model. The daily new cases are plotted in Fig. 8, where for the curves from left to right, the dashed line means 15-day recovery period, the solid line means 20-day recovery period and the dotted line means 25-day recovery period. For both $R_0 = 2.4$ and $R_0 = 1.5$ we can see that with a shorter recovery time, the COVID19 outbreak will end much quicker. Also the mode of daily infected cases will be much smaller under the scenario of shorter recovery time.

To achieve the herd immunity proposed by the UK government requires a proportion of the UK population being immune to the virus to stop it from spreading. It is well-known that such herd immunity can be stimulated by vaccination or recovery following infection. Based our result using a sophisticated double censoring statistical model, we can see clearly that the recovery period should be much shorter than the estimated figures proposed by other existing works. With $R_0 = 1.5$, the peak of the curve with recovery rate 1/20 is will occur on day 592 (95% confidence interval [527, 761]), the peak with recovery rate 1/15 will occur on day 479 (95% confidence interval [422, 609]) and the peak with recovery rate 1/25 will occur on day 705 (95% confidence interval [621, 883]). Therefore, with a slight over or under estimation for the recovery rate, the forecasting peak date will be different at a scale of about 110 days. This would imply that the outbreak could end about four months earlier than people expected.

5. Conclusions

Through our COVID19 forecasting analysis and Ferguson et al. (2020), we can see that correct estimation of SEIR model parameters may change the final forecasting results significantly, for example the peak date estimation may be different at the scale of months. For such a rapid spread disease, it will be extremely challenging to carry out a real-time monitoring task for the pandemic (Birrell et al., 2020). The data collected in real-time will certainly involve different
kind of censoring. This paper highlighted the importance of dealing with the censored data and presented an efficient new statistical estimation approach. By utilizing the efficient influence function of the parameter of interest as an estimating equation, a new method of constructing EL confidence interval for doubly censored data is proposed in this paper. This new Efficient-EL method is easy to calculate since it does not need to estimate scale parameter. Simulation studies show that the new method performances better than the EM-EL method in terms of coverage probabilities.

Comparing model predictions with our estimated recovery rate parameter and existing parameter values used in other research works, we found that the peak of the epidemic predicted could be months different from each other. This could lead to wrong health policy decisions, for example taking or removing lock-down decisions at the wrong time points, which may lead to a second peak of outbreak or making the lock-down period too long to cause severe economic damage and mental health problems for more people. Our analysis highlights the importance of doing such sophisticated survival analysis will provide better estimation for the parameters in the SEIR models.

To our knowledge, this is the first work which considered using censoring techniques in survival analysis to carry out parameter estimation for COVID19 data. Most existing COVID19 research such as Kucharski et al. (2020) and Ferguson et al. (2020) did not address the issues of highly contaminated data due to censoring or simply use prespecified model parameters. Although only a relatively small dataset is used, the methodology can be used by other researcher who have the access to larger COVID19 dataset with individual information. It will help interdisciplinary collaboration between statisticians and epidemiologists and help policy makers on public health policy making.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Proof of Lemma 2.1

**Proof.** For any \( h \in H_F \), define \( dF_t = (1 + th) \, dF \), then the likelihood of doubly censored random variable is

\[
L_t(w, \delta) = \Delta F_t(w)^{\delta_{(1,0)}}(\tilde{F}_t(w))^{\delta_{(2,0)}}F_t(w)^{\delta_{(3,0)}}.
\]

Let \( P_F \) be the distribution of doubly censored random variable \((W, \delta)\), then the score operator \( \ell_F : H_F \to L^2(P_F) \) is

\[
(\ell_F h)(w, \delta) = \frac{d}{dt} \bigg|_{t = 0} \ln L_t(w, \delta) = I_{\delta_{(1,0)}} h(w) + I_{\delta_{(2,0)}} \int_{(w, \infty)} h \, dF - \frac{h}{1 - F(w)} + I_{\delta_{(3,0)}} \int_{[0, w)} h \, dF - \frac{h}{F(w)}.
\]

By the definition of the adjoint operator \( \ell^* : L^2(P_F) \to H_F \), for any \( h_1, h_2 \in H_F \),

\[
(\ell_F h_1, \ell_F h_2)_{P_F} = (h_1, \ell^* \ell_F h_2)_{F}.
\]

Using Fubini’s theorem,

\[
(\ell_F h_1, \ell_F h_2)_{P_F} = \int (\ell_F h_1, \ell_F h_2) \, dP_F
\]

\[
= \int h_1(x)h_2(x) \left( G_t(x) - G_t(x^-) \right) \, dF + \int \frac{h_1(u)h_2(u)}{1 - F(u)} \, dG_t(u) + \int \frac{h_1(u)h_2(u)}{F(l)} \, dG_t(l)
\]

\[
= \int h_1(x) \left( h_2(x) \left( G_t(x) - G_t(x^-) \right) + \int \frac{h_2(u)}{1 - F(u)} \, dG_t(u) + \int \frac{h_2(u)}{F(l)} \, dG_t(l) \right)
\]

we get

\[
(\ell^* \ell_F h)(x) = \left( G_t(x) - G_t(x^-) \right) h(x) + \int \left( \int_{(x, \infty)} \frac{dG_t}{F} + \int_{[0, x \cap \delta]} \frac{dG_t}{1 - F} \right) h(s) \, dF(s).
\]
According to Lemma A.2 (i) in Murphy and van der Vaart (1997), under the assumptions, the operator $\ell^*\ell_F$ is one to one, onto and continuously invertible. By the definition of $\hat{\theta}_0$, for any $h \in H$,

$$\frac{\partial}{\partial t} \bigg|_{t=0} \theta(F_t) = \int \hat{\theta}_0 \ h \ \text{d}F = (\hat{\theta}_0, \ h)_F = (\ell^*\ell_F(\ell^*\ell_F)^{-1}\hat{\theta}_0, \ h)_F = (\ell_F(\ell^*\ell_F)^{-1}\hat{\theta}_0, \ \ell_F h)_F.$$

According to the definition in Tsiatis (2007), $\psi(w, \delta; \theta) = \ell_F(\ell^*\ell_F)^{-1}\hat{\theta}_0$ is the efficient influence function. □

**Appendix B. Lemma for Theorem 2.1**

To prove Theorem 2.1, we need the following two Lemmas. Define

$$h_0 = (\ell^*\ell_F)^{-1}\hat{\theta}_0(x; \theta_0), \quad \hat{h}_0 = (\ell^*\ell_F)^{-1}\hat{\theta}_0(x; \theta_0).$$

**Lemma B.1.** Under the assumptions of Theorem 2.1, we have

$$\left\| \hat{h}_0 - h_0 \right\|_{\infty} \to 0.$$

**Proof.** From

$$\left\| \hat{h}_0 - h_0 \right\|_{\infty} \leq \left\| (\ell^*\ell_F)^{-1}(\ell^*\ell_F)h_0 - (\ell^*\ell_F)h_0 \right\|_{\infty},$$

we just need to prove

$$\left\| \ell^*\ell_F - \ell_F, \ell_F \right\|_{\infty} = \sup_{h \in BV[\alpha, \beta]} \left\| \ell^*\ell_F h(x) - \ell_F^*\ell_F h(x) \right\|_{\infty} \to 0,$$

and to prove the result $\left\| (\ell^*\ell_F)^{-1} \right\|_{\infty}$ is bounded.

[1] Since

$$\ell_F h(w, \delta) = I_{[\delta=1]} h(w) + I_{[\delta=2]} \frac{\int_{[w, \infty)} h \ \text{d}F}{1 - F(w)} + I_{[\delta=3]} \frac{\int_{[0, w]} h \ \text{d}F}{F(w)},$$

so

$$\ell_F h(w, 2) = \frac{\int_{[w, \infty)} h \ \text{d}F}{1 - F(w)}, \quad \ell_F h(w, 3) = \frac{\int_{[0, w]} h \ \text{d}F}{F(w)}.$$

Hence

$$\ell^*\ell_F h(x) = h(x)\left( G_t(x) - G_R(x) \right) + \int_{[0, x]} \ell^*\ell_F h(r, 2) \ \text{d}G_R(r) + \int_{[x, \infty)} \ell^*\ell_F h(l, 3) \ \text{d}G_R(l),$$

and

$$\left\| \ell^*\ell_F h(x) - \ell_F^*\ell_F h(x) \right\|_{\infty} = \Delta_1 + \Delta_2 + \Delta_3,$$

$$\Delta_1 = \sup_{x \in [\alpha, \beta]} \left\| \left( G_t(x) - G_R(x) \right) - \left( \hat{G}_t(x) - \hat{G}_R(x) \right) \right\| \text{h}(x),$$

$$\Delta_2 = \sup_{x \in [\alpha, \beta]} \left\| \int_{[0, x]} \ell^*\ell_F h(r, 2) \ \text{d}G_R(r) - \int_{[0, x]} \ell^*\ell_F h(r, 2) \ \text{d}\hat{G}_R(r) \right\|,$$

$$\Delta_3 = \sup_{x \in [\alpha, \beta]} \left\| \int_{[x, \infty)} \ell^*\ell_F h(l, 3) \ \text{d}G_R(l) - \int_{[x, \infty)} \ell^*\ell_F h(l, 3) \ \text{d}\hat{G}_R(l) \right\|.$$
Lemma 3.1 in Chang (1990) shows that the first part of above equation is $o(1)$, and the proof of Lemma A.2(ii) in Murphy and van der Vaart (1997) shows that the second part is also $o(1)$. Therefore $\Delta_2 \to 0$. Similarly, we get $\Delta_3 \to 0$. Hence, for any $h \in \text{BV}[\alpha, \beta]$, 

$$ \| \ell^* \ell_F h(x) - \ell^* \ell_F h(x) \|_\infty \to 0. $$

[2.] Now we will prove that $\| (\ell^* \ell_F)^{-1} \|_\infty$ is bounded. For the convenience of proof, we denote $S = \ell^* \ell_F$ and $\hat{S} = \ell^* \ell_{\hat{F}}$. Next, we define

$$ \hat{T} = S^{-1}(S - \hat{S}), \quad \hat{u} = \sum_{k=0}^{\infty} \hat{t}^k. $$

It is easy to verify that

$$ \hat{S}^{-1} = \hat{u} S^{-1} \quad \text{and} \quad \hat{u}^{-1} = I - \hat{T}. $$

Since $\| \hat{T} \|_\infty = \| S^{-1}(S - \hat{S}) \|_\infty \leq \| S^{-1} \|_\infty \| S - \hat{S} \|_\infty \to 0$, we have

$$ \| \hat{u} \|_\infty = \left\| \sum_{k=0}^{\infty} \hat{t}^k \right\|_\infty \leq \sum_{k=0}^{\infty} \| \hat{t}^k \|_\infty = \frac{1}{1 - \| \hat{T} \|_\infty} \to 1. $$

Therefore

$$ \| \hat{S}^{-1} \|_\infty = \| \hat{u} S^{-1} \|_\infty \leq \| \hat{u} \|_\infty \| S^{-1} \|_\infty $$

is bounded. □

Lemma B.2. Define $\psi_0 = \psi_i(\theta_0)$, $\hat{\psi}_0 = \hat{\psi}_i(\theta_0)$ and $\sigma^2 = E \psi^2(W, \delta; \theta_0)$. Under the assumptions of Theorem 2.1, we have

$$ \max_{1 \leq i \leq n} \left| \hat{\psi}_0 \right| = o_p(n^{1/2}), \quad (B.2) $$

$$ \sqrt{n} \left( \frac{1}{n} \sum_{i=1}^{n} \hat{\psi}_0 \right) \to N(0, \sigma^2), \quad (B.3) $$

$$ \frac{1}{n} \sum_{i=1}^{n} \hat{\psi}_0^2 = \sigma^2 + o_p(1). \quad (B.4) $$

Proof. [1.] Since

$$ \max_{1 \leq i \leq n} \left| \hat{\psi}_0 \right| \leq \max_{1 \leq i \leq n} \left| \hat{\psi}_0 - \psi_0 \right| + \max_{1 \leq i \leq n} |\psi_0| = \left( \max_{1 \leq i \leq n} \left| \hat{\psi}_0 - \psi_0 \right|^2 \right)^{1/2} + \max_{1 \leq i \leq n} |\psi_0| $$

$$ \leq n^{1/2} \left( \frac{1}{n} \sum_{i=1}^{n} \left| \hat{\psi}_0 - \psi_0 \right|^2 \right)^{1/2} + o_p(n^{1/2}), $$

we only need to prove $n^{-1} \sum_{i=1}^{n} \hat{\psi}_0 - \psi_0 \right|^2 = o_p(1)$. Note that

$$ \frac{1}{n} \sum_{i=1}^{n} \hat{\psi}_0 - \psi_0 \right|^2 = \sum_{k=1}^{3} \left( \frac{1}{n} \sum_{i=1}^{n} \left| \psi(W_i, k; \theta_0, \hat{\xi}) - \psi(W_i, k; \theta_0, \xi) \right|_{(\theta_i = k)} \right) $$

$$ = \sum_{k=1}^{3} \int \left( \psi(w, k; \theta_0, \hat{\xi}) - \psi(w, k; \theta_0, \xi) \right)^2 \hat{d}H_k(w) = \sum_{k=1}^{3} \Gamma_k, $$

where

$$ \Gamma_1 = \int \left( \psi(w, 1; \theta_0, \hat{\xi}) - \psi(w, 1; \theta_0, \xi) \right)^2 \hat{d}H_1(w), $$

$$ \Gamma_2 = \int \left( \psi(w, 2; \theta_0, \hat{\xi}) - \psi(w, 2; \theta_0, \xi) \right)^2 \left( 1 - \hat{F}(w) \right) \hat{d}G_2(w), $$

$$ \Gamma_3 = \int \left( \psi(w, 3; \theta_0, \hat{\xi}) - \psi(w, 3; \theta_0, \xi) \right)^2 \hat{F}(w) \hat{d}G_3(w). $$

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Using Lemma B.1, we have

\[ I_1 = \int \left( \ell_f \hat{h}_0(w, 1) - \ell_f h_0(w, 1) \right)^2 \, d\hat{H}_1(w) = \int \left( \hat{h}_0(w) - h_0(w) \right)^2 \, d\hat{H}_1(w) \leq \left\| \hat{h}_0 - h_0 \right\|_\infty^2 \to 0. \]

For the second part,

\[ I_2 = \int \left( \ell_f \hat{h}_0(w, 2) - \ell_f h_0(w, 2) \right)^2 \left( 1 - \hat{F}(w) \right) \, d \left( \hat{G}_R(w) - G_R(w) \right) + \int \left( \ell_f \hat{h}_0(w, 2) - \ell_f h_0(w, 2) \right)^2 \left( 1 - \hat{F}(w) \right) \, dG_R(w). \]

From Lemma 3.1 in Chang (1990), we know that the first part of above equation is \( o(1) \). Since \( \ell_f \hat{h}_0(w, 2) - \ell_f h_0(w, 2) \to 0 \), together with dominated convergence theorem, the second part of above equation is \( o(1) \). Therefore \( I_2 \to 0 \), and \( I_3 \) converges to 0 can be proved similarly. Hence part (1) is proved.

[2.] Using Eqs. (2)–(4), we have

\[ \frac{1}{n} \sum_{i=1}^n \hat{\psi}_{i0} = \frac{3}{n} \int \psi(w, k; \theta_0, \xi) \, d\hat{H}_k(w) = \int \hat{h}_0 \left( \hat{G}_R - \hat{G}_L \right) \, d\hat{F} + \int \left( 1 - \hat{G}_R \right) \hat{h}_0 \, d\hat{F} + \int \hat{G}_L \hat{h}_0 \, d\hat{F} = \int \hat{h}_0(w) \, d\hat{F}(w) = \int \hat{\theta}_0 \, d\left( \hat{F} - F \right). \]

Due to the definition of efficient influence function and the proof of Lemma A.3 in Murphy and van der Vaart (1997), we have

\[ \sqrt{n} \left( \frac{1}{n} \sum_{i=1}^n \hat{\psi}_{i0} \right) \to N(0, \sigma^2). \]

Therefore

\[ \sqrt{n} \left( \frac{1}{n} \sum_{i=1}^n \hat{\psi}_{i0} \right) \sim N(0, \sigma^2). \]

[3.] Since

\[ \frac{1}{n} \sum_{i=1}^n \hat{\psi}_{i0}^2 = \frac{1}{n} \sum_{i=1}^n \left( \hat{\psi}_{i0} - \psi_{i0} \right)^2 + \frac{2}{n} \sum_{i=1}^n \left( \hat{\psi}_{i0} - \psi_{i0} \right) \psi_{i0} + \frac{1}{n} \sum_{i=1}^n \psi_{i0}^2, \]

and

\[ \left| \frac{1}{n} \sum_{i=1}^n \left( \hat{\psi}_{i0} - \psi_{i0} \right) \psi_{i0} \right| \leq \left| \frac{1}{n} \sum_{i=1}^n \left( \hat{\psi}_{i0} - \psi_{i0} \right) \right|^{1/2} \left| \frac{1}{n} \sum_{i=1}^n \psi_{i0}^2 \right|^{1/2} = o_p(1), \]

we get

\[ \frac{1}{n} \sum_{i=1}^n \hat{\psi}_{i0}^2 = \frac{1}{n} \sum_{i=1}^n \psi_{i0}^2 + o_p(1) = \sigma^2 + o_p(1). \]

Appendix C. Proof of Corollary 2.1

**Proof.** From the definition, the least favorable direction \( h_\theta = (\ell^* \ell_f)^{-1} \hat{h}_0(x; \theta) \) satisfies the equation \( \langle \ell^* \ell_f \rangle h_\theta = \hat{h}_0(x; \theta) \), that is

\[ \left( G_L(x) - G_R(x) \right) h_\theta(x) + \int \left( \int_{[x, \infty)} \frac{dG_L}{F} + \int_{[0, x]} \frac{dG_R}{1-F} \right) h_\theta(s) \, dF(s) = \hat{h}_0(x; \theta). \]

(C.1)

Since

\[ dF(s) = \frac{dH_1(s)}{G_L(s) - G_R(s)}, \quad dG_R(s) = \frac{dH_2(s)}{1 - F(s)}, \quad dG_L(s) = \frac{dH_3(s)}{F(s)}. \]
therefore
\[
\int \left( \frac{d G_t}{F} + \int_{[0, x_s \wedge \infty)} \frac{d G_R}{1 - F} \right) \hat{h}_0(s) d F(s) = \int \frac{1}{G_t(s) - G_R(s-)} \left( \int_{[0, x_s \wedge \infty)} \frac{d H_2(u)}{(1 - F(u))^2} + \int_{[x_s \wedge \infty, \infty)} \frac{d H_2(u)}{F^2(u)} \right) \hat{h}_0(s) d H_1(s) = \int \frac{1}{G_t(s) - G_R(s-)} \left( K_1(x \wedge s) + K_2(x \vee s) \right) \hat{h}_0(s) d H_1(s),
\]
where
\[
K_1(t) = \int_{[0, t]} \frac{d H_2(u)}{(1 - F(u))^2}, \quad K_2(t) = \int_{[t, \infty)} \frac{d H_3(u)}{F^2(u)}.
\]
Hence, Eq. \((C.1)\) can be rewritten as
\[
\left( G_t(x) - G_R(x-) \right) \hat{h}_0(x) + \int \frac{\left( K_1(x \wedge s) + K_2(x \vee s) \right) \hat{h}_0(s) d H_1(s) = \theta_0(x; \theta). \tag{C.2}
\]
Substituting \(\hat{F}, \hat{G}_R\), and \(\hat{G}_t\) into \(K_1, K_2\) and \((C.2)\), we get \(\hat{K}_1(t), \hat{K}_2(t)\) and
\[
\hat{\theta}(x; \theta) = \left( \hat{G}_t(x) = \hat{G}_R(x-) \right) \hat{h}_0(x) + \int \frac{\left( \hat{K}_1(x \wedge s) + \hat{K}_2(x \vee s) \right) \hat{h}_0(s) d H_1(s) + \frac{1}{n} \sum_{j=1}^{n} \left( \hat{K}_1(W_j) + \hat{K}_2(W_j \wedge s) \right) \hat{h}_0(W_j) I_{(\delta_j=1)}.
\tag{C.3}
\]
Set \(x = W_i\) \((i = 1, 2, \ldots, n)\) in Eq. \((C.3)\), we get Eq. \((7)\). □

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