Research Article

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Supporting Web Materials to "Weighted win loss approach for analyzing prioritized outcomes"†

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1. Proof of $W_D(G_1, G_2) = W_D(g_1, g_2) + o_p(n^{3/2})$

For $i, j = 1, \ldots, n$, let $G_{2ij} = G_2(Y_{2i} \wedge Y_{2j})$, $g_{2ij} = g_2(Y_{2i} \wedge Y_{2j})$, $G_{1ij} = G_1(Y_{1i} \wedge Y_{1j}, Y_{2i} \wedge Y_{2j})$ and $g_{1ij} = g_1(Y_{1i} \wedge Y_{1j}, Y_{2i} \wedge Y_{2j})$. We can write $W_D(G_1, G_2) = W_D(g_1, g_2) + SR_1 + SR_2$, where $SR_1 = SR_{12} + SR_{11}$ and $SR_2 = SR_{21} + SR_{22}$

$$
\begin{aligned}
SR_{12} &= -\sum_{i=1}^{n}\sum_{j=1}^{n} Z_i(1-Z_j)(W_{2ij} - L_{2ij})\frac{G_{2ij} - g_{2ij}}{g_{2ij}^2}, \\
SR_{11} &= -\sum_{i=1}^{n}\sum_{j=1}^{n} Z_i(1-Z_j)\Omega_{2ij}(W_{1ij} - L_{1ij})\frac{G_{1ij} - g_{1ij}}{g_{1ij}^2}, \\
SR_{22} &= \sum_{i=1}^{n}\sum_{j=1}^{n} Z_i(1-Z_j)(W_{2ij} - L_{2ij})\frac{(G_{2ij} - g_{2ij})^2}{G_{2ij}g_{2ij}^2}, \\
SR_{21} &= -\sum_{i=1}^{n}\sum_{j=1}^{n} Z_i(1-Z_j)\Omega_{2ij}(W_{1ij} - L_{1ij})\frac{(G_{1ij} - g_{1ij})^2}{G_{1ij}g_{1ij}^2}.
\end{aligned}
$$

By Conditions 1 and 2, $\inf_{i,j} \min\{G_{2ij}, g_{2ij}, G_{1ij}, g_{1ij}\}$ is bounded away from zero and that $\sup_{i,j} |G_{2ij} - g_{2ij}| = o(n^{-1/4})$ and $\sup_{i,j} |G_{1ij} - g_{1ij}| = o(n^{-1/4})$ almost surely, therefore, the remainders $SR_{22} = o(n^{3/2})$ and $SR_{21} = o(n^{3/2})$ almost surely. Next we shall show $SR_{12} = o_p(n^{3/2})$ and $SR_{11} = o_p(n^{3/2})$. We shall only show the case for SR_{11} because the case for SR_{12} can be similarly proved. Let $V_{1kij} = V_{1k}(Y_{1i} \wedge Y_{1j}, Y_{2i} \wedge Y_{2j})$, Condition 1 indicates that $SR_{11} = \widetilde{SR}_{11} + o(n^{3/2})$ almost surely, where

$$
\widetilde{SR}_{11} = -\sum_{i=1}^{n}\sum_{j=1}^{n} Z_i(1-Z_j)\Omega_{2ij}(W_{1ij} - L_{1ij})\frac{n^{-1}\sum_{k=1}^{n} V_{1kij}}{g_{1ij}^2}.
$$

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Apparently, $\widetilde{SR}_{11}$ is a U-statistic of order 3. We denote the summand in $\widetilde{SR}_{11}$ as $X_{ijk},\ i,j,k=1,\ldots,n$. For mutually different i,j,k, by the conditions on $V_{1k}(y_1,y_2)$, $E(X_{ijk}\mid O_i)=E\{E(X_{ijk}\mid O_i,O_j)\}=0$ and $E(X_{ijk}\mid O_j)=E\{E(X_{ijk}\mid O_i,O_j)\}=0$. And, under H_0, because V_{1kij} is symmetric in i and j, a similar calculation like the proof of the formula (3) in the Appendix of the main body will show that $E(X_{ijk}\mid O_k)=0$. Therefore, the U-statistic $\widetilde{SR}_{11}$ is degenerate with var$\{\widetilde{SR}_{11}\}=o(n^3)$, which, by Chebyshev's inequality, implies $\widetilde{SR}_{11}=o_p(n^{3/2})$ as desired.

2. Proof of Eq. (5) the approximation for $n^{-1}W_D(g_1,g_2)$

Using the notations in Section 1 of this supporting web materials, we can denote the summand of the U-statistic $n^{-1}W_D(g_1,g_2)$ as $Q_{ij},\ i,j=1,\ldots,n$, where

$$Q_{ij}=Z_i(1-Z_j)\Big\{\frac{W_{2ij}-L_{2ij}}{g_{2ij}}+\frac{\Omega_{2ij}(W_{1ij}-L_{1ij})}{g_{1ij}}\Big\}.$$

Because $Q_{ij},\ i,j=1,\ldots,n$ are bounded with mean zero under H_0, using the exponential inequalities for U-statistics[1, 2], we can show that

$$n^{-1}W_D(g_1,g_2)=\sum_{i=1}^{n}E(Q_{ij}\mid O_i)+\sum_{j=1}^{n}E(Q_{ij}\mid O_j)+o(n^{1/2})$$

almost surely. Note the main terms on the right hand side are the Hajek's projection [3] of the U-statistic $n^{-1}W_D(g_1,g_2)$. Switching i and j in the second term and then combining it with the first term, we get $\sum_{i=1}^{n}E(Q_{ij}+Q_{ji}\mid O_i)$. By definition, for any $i,j=1,\ldots,n$ and $k=1,2$, $W_{kji}=L_{kij}$, $\Omega_{2ij}=\Omega_{2ji}$, $g_{2ij}=g_{2ji}$ and $g_{1ij}=g_{1ji}$, therefore $Z_i(1-Z_j)(W_{2ij}-L_{2ij})+Z_j(1-Z_i)(W_{2ji}-L_{2ji})=(Z_i-Z_j)(W_{2ij}-L_{2ij})$ and $Z_i(1-Z_j)\Omega_{2ij}(W_{1ij}-L_{1ij})+Z_j(1-Z_i)\Omega_{2ij}(W_{1ji}-L_{1ji})=(Z_i-Z_j)\Omega_{2ji}(W_{1ij}-L_{1ij})$. With these, we find

$$Q_{ij}+Q_{ji}=(Z_i-Z_j)\Big\{\frac{W_{2ij}-L_{2ij}}{g_{2ij}}+\frac{\Omega_{2ij}(W_{1ij}-L_{1ij})}{g_{1ij}}\Big\},$$

which completes the proof.

3. Optimality of $W_D(g_1,g_2)$ under contiguous alternatives

For simplicity, we further assume that the study ends at a time point τ such that subjects survive at τ will be censored and the cumulative hazards Λ_{c1} and Λ_{c0} are continuous in $(0,\tau)$ with only a jump at τ. Let $\mu_2(dt_2)=\{r_{20}(t_2)r_{21}(t_2)/r_2(t_2)\}\lambda_2(t_2)dt_2$ and $\mu_1(dt_1,dt_2)=\{r_{10}(t_1,t_2)r_{11}(t_1,t_2)/r_1(t_1,t_2)\}\lambda_1(t_1\mid t_2)dt_1\Lambda_a(dt_2)$.

Under a sequence of contiguous alternatives: $\lambda_2^{(n)}(t_2)=\{1-n^{-1/2}\Theta_{2n}(t_2)\}\lambda_2(t_2)$ and $\lambda_1^{(n)}(t_1\mid t_2)=\{1-n^{-1/2}\Theta_{1n}(t_1,t_2)\}\lambda_1(t_1\mid t_2)$ such that $\Theta_{2n}(t_2)\to\theta_2(t_2)$ and $\Theta_{1n}(t_1,t_2)\to\theta_1(t_1,t_2)$ with $\theta_2\geq 0$ and $\theta_1\geq 0$, we calculate

$$\begin{aligned}
n^{-3/2}E\{W_D(g_1,g_2)\} &= \int_{t_2\leq\tau}\frac{r_2(t_2)\theta_2(t_2)}{g_2(t_2)}\mu_2(dt_2)+\int_{t_1\leq t_2\leq\tau}\frac{r_1(t_1,t_2)\theta_1(t_1,t_2)}{g_1(t_1,t_2)}\mu_1(dt_1,dt_2)+o(1)\\
&= \int_{0\leq t_1\leq t_2\leq\tau}\frac{r(t_1,t_2)\theta(t_1,t_2)}{g(t_1,t_2)}\mu(dt_1,dt_2)+o(1)
\end{aligned}$$

where $r(t_1,t_2)=I(t_1=0)r_2(t_2)+I(t_1>0)r_1(t_1,t_2)$, $\theta(t_1,t_2)=I(t_1=0)\theta_2(t_2)+I(t_1>0)\theta_1(t_1,t_2)$, $g(t_1,t_2)=I(t_1=0)g_2(t_2)+I(t_1>0)g_1(t_1,t_2)$ and $\mu(dt_1,dt_2)=dI(t_1\geq 0)\mu_2(dt_2)+\mu_1(dt_1,dt_2)$.

In the end of this section, we calculate that, under the sequence of contiguous alternatives,

$$\mathrm{var}\{n^{-3/2}W_D(g_1,g_2)\} \;=\; \int_{0\le t_1\le t_2\le\tau}\psi(t_1,t_2)\mu(dt_1,dt_2)+o(1), \tag{S1}$$

where $\psi(t_1,t_2)=I(t_1=0)\psi_2(t_2)+I(t_1>0)\psi_1(t_1,t_2)$ with $\psi_2(t_2)=r_2^2(t_2)/g_2^2(t_2)$ and

$$\begin{aligned}\psi_1(t_1,t_2) \;=\;& \frac{r_1^2(t_1,t_2)}{g_1^2(t_1,t_2)}\Big\{1+\tilde\Lambda_c(dt_2)-\frac{\tilde\Lambda_c(dt_2)}{\Lambda_a(dt_2)}\Big\}\\ &+2\int_{t_1\le t_2'<t_2\le\tau}\frac{r_1(t_1,t_2)}{g_1(t_1,t_2)}\frac{r_1(t_1,t_2')}{g_1(t_1,t_2')}\tilde\Lambda_c(dt_2')\\ &+2\int_{t_1'\le t_1}\frac{r_1(t_1',t_2)}{g_1(t_1',t_2)}\lambda_1(t_1'\mid t_2)dt_1'\eta_{g_1}(t_1,t_2)\\ &+2I(t_2<\tau)\frac{r_2(t_2)}{g_2(t_2)}\xi_{g_2}(t_2)\eta_{g_1}(t_1,t_2),\end{aligned}$$

with

$$\begin{aligned}\tilde\Lambda_c(dt_2)&=\frac{r_{10}(t_1,t_2)\Lambda_{c0}(dt_2)+r_{11}(t_1,t_2)\Lambda_{c1}(dt_2)}{r_1(t_1,t_2)}=\frac{r_{20}(t_2)\Lambda_{c0}(dt_2)+r_{21}(t_2)\Lambda_{c1}(dt_2)}{r_2(t_2)},\\ \eta_{g_1}(t_1,t_2)&=\int_{t_1\le t_2'<t_2\le\tau}\frac{r_1(t_1,t_2')}{g_1(t_1,t_2')}\Big\{\frac{\lambda_1(t_1\mid t_2')}{\lambda_1(t_1\mid t_2)}-1\Big\}\tilde\Lambda_c(dt_2')\end{aligned}$$

and

$$\begin{aligned}\xi_{g_2}(t_2) \;&=\; 1+\frac{2\Lambda_2(dt_2)+g_2(dt_2)/g_2(t_2)}{\Lambda_a(dt_2)}\\ &=\begin{cases}1+\frac{2\Lambda_2(dt_2)}{\Lambda_a(dt_2)}, & \text{if } g_2=1,\\ 1+\frac{\Lambda_2(dt_2)}{\Lambda_a(dt_2)}-\frac{\tilde\Lambda_c(dt_2)}{\Lambda_a(dt_2)}, & \text{if } g_2=r_2.\end{cases}\end{aligned}$$

If $\lambda_1(t_1\mid t_2)$ is a nonincreasing function of t_2 for any given t_1, then $\eta_{g_1}(t_1,t_2)\ge 0$, which implies $\psi_1(t_1,t_2)>0$. To maximize the power, one needs to maximize

$$e_{g_1,g_2}=\frac{\displaystyle\int_{0\le t_1\le t_2\le\tau}\frac{r(t_1,t_2)\theta(t_1,t_2)}{g(t_1,t_2)}\mu(dt_1,dt_2)}{\{\int_{0\le t_1\le t_2\le\tau}\psi(t_1,t_2)\mu(dt_1,dt_2)\}^{1/2}}.$$

We can apply the Cauchy-Schwartz inequality to get

$$e_{g_1,g_2}^2\le\int_{0\le t_1\le t_2\le\tau}\frac{r^2(t_1,t_2)\theta^2(t_1,t_2)}{g^2(t_1,t_2)\psi(t_1,t_2)}\mu(dt_1,dt_2).$$

The equality is obtained when

$$\frac{r(t_1,t_2)\theta(t_1,t_2)}{g(t_1,t_2)}=\text{constant}\times\psi(t_1,t_2). \tag{S2}$$

If θ_2 and θ_1 are fixed, we can use this relationship to find the best weights g_2 and g_1. On the contrary, if g_2 and g_1 are fixed, one may find θ_2 and θ_1 and the corresponding contiguous alternatives under which the weighted win-loss statistic is optimal. In particular, if $\theta_2(t_2)$ is a constant so the proportional hazards assumption holds for the terminal event, one may choose $g_2=r_2$ to maximize the power, in which case, log-rank test statistic is used for the terminal event. However, in the presence of related non-terminal event, this solution is not unique. For example, if $g_2=r_2$ and $g_1=r_1$, we have

$\theta_2(t_2) =$ constant and $\theta_1(t_1,t_2) =$ constant $\times\, \psi_1(t_1,t_2)$, but since we can also write

$$\text{var}\{n^{-3/2}W_D(G_1,G_2)\} \quad = \quad \int_{t_2\le\tau} \psi_2(t_2)\mu_2(dt_2) + \int_{t_2\le\tau} \tilde{\psi}_2(t_2)\mu_2(dt_2)$$

where $\tilde{\psi}_2(t_2) = \int_{t_1\le t_2} \frac{\psi_1(t_1,t_2)\mu_1(dt_1,dt_2)}{\mu_2(dt_2)}$, then $\theta_2(t_2) =$ constant $\times \{1+\tilde{\psi}_2(t_2)\}$ and $\theta_1(t_1,t_2)=0$ is also a solution. Please note that in this case, the maximum obtainable power is not changed but the ways of achieving it are not unique. Furthermore, because $r\theta/g \ge r_2\theta_2/g_2$, the weighted win difference has a better efficiency than the weighted log-rank statistic based on the terminal event only.

To assume that $\lambda_1(t_1 \mid t_2)$ is a nonincreasing function of t_2 for any given t_1, we actually assume that for any $t_1 \le t_2$,

$$\frac{\text{pr}(T_2 = t_2, T_1 = t_1)}{\text{pr}(T_2 \ge t_2, T_1 = t_1)} \ge \frac{\text{pr}(T_2 = t_2, T_1 \ge t_1)}{\text{pr}(T_2 \ge t_2, T_1 \ge t_1)} \tag{S3}$$

which is satisfied if for all $t_1 \le \min(t_1', t_2)$

$$\frac{\text{pr}(T_2 = t_2, T_1 = t_1)}{\text{pr}(T_2 \ge t_2, T_1 = t_1)} \ge \frac{\text{pr}(T_2 = t_2, T_1 = t_1')}{\text{pr}(T_2 \ge t_2, T_1 = t_1')}.$$

Apparently, if the condition (S3) is satisfied, then under the contiguous alternatives, the weighted win difference will have a better power than the weighted log-rank statistic for the terminal event, provided that the weight function for the nonterminal event is suitably selected. This makes sense as when the nonterminal event and terminal event are positively correlated satisfying the condition (S3), the inclusion of the nonterminal event can improve the efficiency of the marginal analysis of the terminal event.

It remains to find the variance of $W_D(g_1,g_2)$ under H_0 in (S1). To do so, we find

$$\begin{aligned}
& E\Big\{\frac{(Z_i-Z_j)(L_{2ij}-W_{2ij})}{g_2(Y_{2i}\wedge Y_{2j})}\Big| O_i\Big\} \\
= \quad & \frac{\delta_{2i}r_2(Y_{2i})}{g_2(Y_{2i})}\Big\{Z_i - \frac{r_{21}(Y_{2i})}{r_2(Y_{2i})}\Big\} - \int \frac{r_2(t_2)}{g_2(t_2)}\Big\{Z_i - \frac{r_{21}(t_2)}{r_2(t_2)}\Big\} I(Y_{2i}\ge t_2)\lambda_2(t_2)dt_2 \\
= \quad & B_{11i} - B_{12i}, \qquad \text{say.}
\end{aligned}$$

and

$$\begin{aligned}
& E\Big\{\frac{(Z_i-Z_j)\Omega_{2ij}(L_{1ij}-W_{1ij})}{g_1(Y_{1i}\wedge Y_{1j}, Y_{2i}\wedge Y_{2j})}\Big| O_i\Big\} \\
= \quad & \frac{\delta_{1i}(1-\delta_{2i})r_1(Y_{1i},Y_{2i})}{g_1(Y_{1i},Y_{2i})}\Big\{Z_i - \frac{r_{11}(Y_{1i},Y_{2i})}{r_1(Y_{1i},Y_{2i})}\Big\} \\
& -(1-\delta_{2i})\int \frac{r_1(t_1,Y_{2i})}{g_1(t_1,Y_{2i})}\Big\{Z_i - \frac{r_{11}(t_1,Y_{2i})}{r_1(t_1,Y_{2i})}\Big\} I(Y_{1i}\ge t_1)\lambda_1(t_1\mid Y_{2i})dt_1 \\
& +\delta_{1i}\int \frac{r_1(Y_{1i},t_2)}{g_1(Y_{1i},t_2)} I(Y_{2i} > t_2 \ge Y_{1i}) Q_i(Y_{1i},dt_2) \\
& -\int_{t_1\le t_2} \frac{r_1(t_1,t_2)}{g_1(t_1,t_2)} I(Y_{1i}\ge t_1, Y_{2i} > t_2) Q_i(t_1,dt_2)\lambda_1(t_1\mid t_2)dt_1 \\
= \quad & B_{21i} - B_{22i} + B_{31i} - B_{32i}, \qquad \text{say,}
\end{aligned}$$

where, for $i = 1,\ldots,n$,

$$Q_i(t_1,t_2) = \int_{t_1\le s\le t_2} \frac{Z_i r_{10}(t_1,s)\Lambda_{c0}(ds) - (1-Z_i)r_{11}(t_1,s)\Lambda_{c1}(ds)}{r_1(t_1,s)}.$$

We need to compute $E\{(B_{11i} - B_{12i} + B_{21i} - B_{22i} + B_{31i} - B_{32i})^2\}$. By definition, we have $E\{(B_{11i} - B_{12i})(B_{21i} - B_{22i})\} = 0$. We calculate

$$
\begin{aligned}
E\{(B_{11i} - B_{12i})^2\} &= \int_{t_2 \le \tau} \frac{r_2^2(t_2)}{g_2^2(t_2)} \mu_2(dt_2), \\
E\{(B_{21i} - B_{22i} + B_{31i} - B_{32i})^2\} &= \int_{t_1 \le t_2 \le \tau} \frac{r_1^2(t_1, t_2)}{g_1^2(t_1, t_2)} \Big\{ 1 + \tilde{\Lambda}_c(dt_2) - \frac{\tilde{\Lambda}_c(dt_2)}{\Lambda_a(dt_2)} \Big\} \mu_1(dt_1, dt_2) \\
&\quad + 2 \int_{t_1 \le t_2' < t_2 \le \tau} \frac{r_1(t_1, t_2)}{g_1(t_1, t_2)} \frac{r_1(t_1, t_2')}{g_1(t_1, t_2')} \tilde{\Lambda}_c(dt_2') \mu_1(dt_1, dt_2) \\
&\quad + 2 \int_{t_1 \le t_2 \le \tau} \Big\{ \int_{t_1' \le t_1} \frac{r_1(t_1', t_2)}{g_1(t_1', t_2)} \lambda_1(t_1' \mid t_2) dt_1' \Big\} \eta_{g_1}(t_1, t_2) \mu_1(dt_1, dt_2) \\
2E\{(B_{11i} - B_{12i})(B_{31i} - B_{32i})\} &= 2 \int_{t_1 \le t_2 < \tau} \frac{r_2(t_2)}{g_2(t_2)} \xi_{g_2}(t_2) \eta_{g_1}(t_1, t_2) \mu_1(dt_1, dt_2).
\end{aligned}
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References

1. Giné E, Latała R, Zinn J. Exponential and moment inequalities for U-statistics. *High Dimensional Probability II. Progress in Probability* 2000; **47**: 13–38.
2. Houdré C, Reynaud-Bouret P. Exponential Inequalities, with Constants, for U-statistics of Order Two. *Stochastic inequalities and applications. Progress in Probability* 2003; **56**: 55–69.
3. Hájek J. Asymptotic normality of simple linear rank statistics under alternatives. *Ann. Math. Statist.* 1968; **39**: 325–346.