Appendix

Proof of Theorem 1

We restrict our attention to a neighborhood around \( t \) and cause \( j \) i.e. \( N_t^{(j)}(h_n) = \{ t_k : |t - t_k| < h_n, \delta_k = j \} \) with size \( |N_t^{(j)}(h_n)| = m_t^{(j)} \). Other causes can be treated in a similar way. For simplicity, we assume that no subjects are censored.

Let \( B_t \) denote the number of subjects at the start of the neighborhood i.e. at time \( t - h_n \). We assume that no failures other than cause \( j \) within neighborhood. We also assume no two subjects fail at the same time. The ordered unique event time for \( i \)-th subject is \( T_i = t_i \). The indices of the observed event times due to cause \( j \) within the neighborhood \( N_t^{(j)}(h_n) \) are then \( B_t + 1, B_t + 2, ..., B_t + m_t^{(j)} \) and that \( t_{(B_t + 1)}, t_{(B_t + 2)}, ..., t_{(B_t + m_t^{(j)})} \) are the corresponding ordered unique event times within \( N_t^{(j)}(h_n) \). The \( j \)-th cause-specific weighted mean rank estimator can be written as

\[
cWMR_t^{(j)} = \frac{1}{|N_t^{(j)}(h_n)|} \sum_{t(i) \in N_t^{(j)}(h_n)} A^{(j)}(t(i)),
\]

\[
= \frac{1}{m_t^{(j)}} \sum_{i = B_t + 1}^{B_t + m_t^{(j)}} A^{(j)}(t(i)),
\]

\[
= \frac{1}{m_t^{(j)}} \sum_{i = B_t + 1}^{B_t + m_t^{(j)}} \frac{1}{n_{t(i)}} \sum_{k = i + 1}^{n} 1\{M_i > M_k\} 1\{T_i < T_k\} 1\{\delta_i = j\},
\]

\[
= \sum_{i \neq k} \frac{1}{2 \times m_t^{(j)} \times n_{t(i)}} 1\{M_i > M_k\} 1\{T_i < T_k\} 1\{\delta_i = j\}
\]

From the above representation of \( cWMR_t^{(j)} \), it can be seen that \( cWMR_t^{(j)} \) is a linear transformation of weighted U-statistic i.e. \( cWMR_t^{(j)} = 2 \left( U^{(j)} + 1 \right) \) where

\[
U^{(j)} = \sum_{i \neq k} w_{ik}^{(j)} 1\{k > i\} 1\{R_i > R_k\} 1\{\delta_i = j\},
\]
where $R_i$ is the rank of the marker $M$ corresponding to the $i$-th ordered observed failure time and $u_{ik}^{(j)} = \frac{1}{2 \times m_{t_i}^{(j)} \times n_{t_i}^{(j)}}$. According to [1], $W_n = \sum_{n,k} W(S)\phi(S)$ be a weighted U-statistic of order 2 with $w_{i,n} = \sum_{i \in S} w_i \phi_i(X_i)$. Suppose that, as $n \to \infty$, the following conditions hold

1. $\max_{1 \leq i \leq n} |w_{i,n}|^2 \to 0,$

2. $\frac{\sum_{(n,2)} w^2(S)}{\sum_i w^2_{i,n}} \to 0$ and

3. $\mathbb{E}|\phi_i(X_i)|^{(2+\delta)} \leq \infty$ for some $\delta > 0$.

Then

$$\frac{(W_n - \theta)}{\sqrt{\text{Var}(W_n)}} \overset{D}{\to} N(0, 1).$$

To prove asymptotic Normality of $cWMR_{(j)}^{(j)}$ we need to verify the conditions (1)-(3). Similar to the arguments and derivation in [2], we will verify them. To simplify notations we will drop the subscript $n$ from $w_{i,n}^{(j)}$. Let $w_i^{(j)}$ denote as

$$w_i^{(j)} = \sum_k w_{ik}^{(j)},$$

$$= \begin{cases} 
\frac{1}{2 \times m_{t_i}^{(j)}} \left(1 + \sum_{k < i} \frac{1}{|R_{t_i(k)}|}\right) & i = B_t + 1, \ldots, B_t + n_{t_i}^{(j)}, \\
\frac{1}{2 \times m_{t_i}^{(j)}} \sum_k \frac{1}{|R_{t_i(k)}|} & i > B_t + n_{t_i}^{(j)}.
\end{cases}$$

To prove condition (1), let’s begin with

$$\max_{B_t + 1 \leq i \leq n} |w_i^{(j)}|^2 = \left[\frac{w_i^{(j)}}{B_t + m_t^{(j)}}\right]^2 = \sum_{k = B_t}^{n} \left[\frac{w_i^{(j)}}{B_t + m_t^{(j)}}\right]^2$$

$$= \frac{1}{4 \times [m_{t_i}^{(j)}]^2} \left(1 + \frac{1}{n_{B_t+1}} + \frac{1}{n_{B_t+2}} + \cdots + \frac{1}{n_{B_t+m_t^{(j)}-1}}\right)^2$$

$$\leq \frac{1}{4 \times [m_{t_i}^{(j)}]^2} \left(1 + \frac{m_t^{(j)}}{n_{B_t+m_t^{(j)}}}\right)^2.$$
Again,

\[
4 \times [m_i^{(j)}]^2 \sum_i |w_i^{(j)}|^2 = 1 + \left(1 + \frac{1}{n_{B_{t+1}}} \right)^2 + \left(1 + \frac{1}{n_{B_{t+2}}} \right)^2 + \ldots \\
+ \left(1 + \frac{1}{n_{B_{t+1}}} + \frac{1}{n_{B_{t+2}}} + \ldots + \frac{1}{n_{B_{t+m_{i}^{(j)}-1}}} \right)^2 \\
+(n - B_t + m_i^{(j)}) \left(1 + \frac{1}{n_{B_{t+1}}} + \frac{1}{n_{B_{t+2}}} + \ldots + \frac{1}{n_{B_{t+m_{i}^{(j)}-1}}} \right)^2 \\
\geq (n - B_t + m_i^{(j)}) \left(\frac{m_i^{(j)}}{n_{B_{t+1}}} \right)^2
\]

If \(n \to \infty\) then \((n - B_t + m_i^{(j)}) \to \infty\), therefore

\[
\max_{B_{t+1} \leq i \leq n} |w_i^{(j)}|^2 \leq \frac{(1 + \frac{m_i^{(j)}}{n_{B_{t} + m_i^{(j)}}})^2}{(n - B_t + m_i^{(j)}) \left(\frac{m_i^{(j)}}{n_{B_{t+1}}} \right)^2} \rightarrow 0,
\]

condition (1) is satisfied. Again, for condition (2) we are following the algebraic arguments provided on page 16 of [2], and therefore, we can write

\[
4 \times [m_i^{(j)}]^2 \sum_{k \neq i} |w_{ik}^{(j)}|^2 \leq 2 \times \frac{m_i^{(j)}}{n_{B_{t} + m_i^{(j)}}}.
\]

Also,

\[
\sum_{k \neq i} |w_{ik}^{(j)}|^2 \leq \frac{2 \times m_i^{(j)}}{(n - B_t + m_i^{(j)}) \left(\frac{m_i^{(j)}}{n_{B_{t+1}}} \right)^2} \rightarrow 0 \text{ as } n \to \infty
\]

and hence condition (2) is satisfied. Again, for condition (3), let \(\psi(X_i, X_j) = 1\{k > i\} \cdot 1\{R_i > R_k\} \cdot 1\{\delta_i = j\}\). The expectation of \(\psi(X_i, X_j)\), \(E[\psi(X_i, X_j)]\) is \(\infty\) since \(|\psi(X_i, X_j)| \leq 1\). So, \(E[\psi(X_i, X_j)]^{(2+\delta)} \leq \infty\) for some \(\delta > 0\).

**Estimation of variance of cWMR**

The variance of cWMR\(_t^{(j)}\), \(V_n^{(j)}\), is written as

\[
V_n^{(j)} = \frac{1}{[m_t^{(j)}]^2} \left[ \sum_{t(i) \in T_t^{(j)}(h_n)} \text{var}[A^{(j)}(t(i))] + \sum_{t(i) \neq t(k)} \text{cov}[A^{(j)}(t(i)), A^{(j)}(t(k))] \right],
\]

In order to compute \(\text{var}[A^{(j)}(t(i))]\) and \(\text{cov}[A^{(j)}(t(i)), A^{(j)}(t(k))]\) we propose the following estimators in the spirit of variance calculation of AUC proposed in [3].
and \[2\]
\[
\text{var}[A^{(j)}(t)] = \left(\frac{n_t - 1}{n_t}\right)\{P_1^{(j)}(t) - [P_0^{(j)}(t)]^2\} + \frac{1}{n_t}\{P_0^{(j)}(t)(1 - P_0^{(j)}(t))\},
\]
\[
\text{cov}[A^{(j)}(t), A^{(j)}(s)] = \frac{1}{n_t}\{P_2^{(j)}(t, s) - P_2^{(j)}(t, 0)\} + \{P_3^{(j)}(t, s) - P_3^{(j)}(t, 0)\},
\]
where
\[
P_0^{(j)}(t) = \Pr(M_i > M_k \mid T_i = t, \delta_i = j, T_k > t),
\]
\[
P_1^{(j)}(t) = \Pr(M_i > M_k, M_i > M_k_i \mid T_i = t, \delta_i = j, T_k > t, T_k > t),
\]
\[
P_2^{(j)}(t, s) = \Pr(M_i > M_k, M_i > M_k_i \mid T_i = t, \delta_i = j, T_l = s, \delta_l = j, T_k > s),
\]
\[
P_2^{(j)}(t, s) = \Pr(M_i > M_k \mid T_i = t, \delta_i = j, T_k > s) \times \Pr(M_i > M_k \mid T_l = s, \delta_l = j, T_k > s)
\]
\[
P_3^{(j)}(t, s) = \Pr(M_i > M_k, M_i > M_k_i \mid T_i = t, \delta_i = j, T_l = s, \delta_l = j, T_k > s),
\]
\[
P_3^{(j)}(t, s) = \Pr(M_i > M_k_i \mid T_i = t, \delta_i = j, T_l = s, \delta_l = j, T_k > s),
\]

To estimate \(P_0^{(j)}(\cdot), P_1^{(j)}(\cdot)\) etc. we use a Normal approximation for the case due to \(j\)-th cause and control markers after a rank-based Z-score transformation and then empirically estimating the parameters of the approximating Normal distributions. Let \(\mu_1^{(j)}(t)\) and \(\sigma_1^{(j)}(t)\) can be estimated as the mean and variance of the marker of the \(j\)-the cause-specific cases at \(t\). While \(\mu_0(t)\) and \(\sigma_0(t)\) can be estimated as the mean and variance of the marker of the controls at \(t\).

\[
\hat{P}_0^{(j)}(t) = \phi\left(\frac{\mu_1^{(j)}(t) - \mu_0(t)}{\sqrt{(\sigma_1^{(j)}(t))^2 + \sigma_0^2(t)}}\right),
\]

\[
\hat{P}_1^{(j)}(t) = \phi_2(0|\mu_2, \Sigma_2),
\]

where

\[
\mu_2 = \left(\begin{array}{c}
\mu_0(t) - \mu_1^{(j)}(t) \\
\mu_0(t) - \mu_1^{(j)}(t)
\end{array}\right),
\quad \Sigma_2 = \left(\begin{array}{cc}
(\sigma_1^{(j)}(t))^2 + \sigma_0^2(t) & (\sigma_1^{(j)}(t))^2 \\
(\sigma_1^{(j)}(t))^2 & (\sigma_1^{(j)}(t))^2 + \sigma_0^2(t)
\end{array}\right).
\]

\[
\hat{P}_2^{(j)}(t, s) = \phi_2(0|\mu_3, \Sigma_3),
\]

where

\[
\mu_3 = \left(\begin{array}{c}
\mu_0(s) - \mu_1^{(j)}(t) \\
\mu_0(s) - \mu_1^{(j)}(s)
\end{array}\right),
\quad \Sigma_3 = \left(\begin{array}{cc}
(\sigma_1^{(j)}(t))^2 + \sigma_0^2(s) & \sigma_0^2(s) \\
\sigma_0^2(s) & (\sigma_1^{(j)}(s))^2 + \sigma_0^2(s)
\end{array}\right).
\]
\[ \hat{P}_{2,0}(t, s) = \phi\left( \frac{\mu_1^{(j)}(t) - \mu_0(s)}{\sqrt{(\sigma_1^{(j)}(t))^2 + \sigma_0^2(s)}} \right) \times \phi\left( \frac{\mu_1^{(j)}(s) - \mu_0(s)}{\sqrt{(\sigma_1^{(j)}(s))^2 + \sigma_0^2(s)}} \right), \]

\[ \hat{P}_{3,0}(t, s) = \phi_2(0 | \mu_4, \Sigma_4), \]

where

\[ \mu_4 = \left( \frac{\mu_1^{(j)}(s) - \mu_1^{(j)}(t)}{\mu_0(t) - \mu_1^{(j)}(s)} \right), \]

\[ \Sigma_4 = \begin{pmatrix} (\sigma_1^{(j)}(s))^2 + (\sigma_1^{(j)}(t))^2 & -\sigma_0^2(s) \\ -\sigma_0^2(s) & (\sigma_1^{(j)}(s))^2 + \sigma_0^2(s) \end{pmatrix} \]

\[ \hat{P}_{3,0}(t, s) = \phi\left( \frac{\mu_1^{(j)}(t) - \mu_1^{(j)}(s)}{\sqrt{(\sigma_1^{(j)}(t))^2 + (\sigma_1^{(j)}(s))^2}} \right) \times \phi\left( \frac{\mu_1^{(j)}(s) - \mu_0(s)}{\sqrt{(\sigma_1^{(j)}(s))^2 + \sigma_0^2(s)}} \right). \]

**Proof of Theorem 2**

In order to establish the asymptotic properties of \( \text{AUC}_{t}^{(j)}(\tilde{\beta}_j) \) the key step to our theoretical development is the establishment of asymptotic theory for the \( \tilde{\beta}_j \). When there is a single cause of failure, [4] provided procedures for making inference about the maximum likelihood estimator of partial likelihood. We generalize their idea in the case of cause-specific partial likelihood estimator.

We assume the following regularity conditions hold for \( i = 1, 2, \ldots, n \)

1. \( \Pr(N_1^{(j)}(\tau) > 0) > 0 \), where \( N_1^{(j)}(\tau) \) counts number of events due to \( j \)-th cause of failure occurring over \([0, \tau]\).

2. Positive-definiteness of the matrices, \( \Sigma_{j1} \) and \( \Sigma_{j2} \) where

\[ \Sigma_{j1} = E\{- \frac{d}{d\beta_j} f_{ik}(\beta_j) ; \beta_{0j} \}, \]

\[ \Sigma_{j2} = 4 \text{ Cov}\{g_{ik}(\beta_j), g_{ik'}(\beta_j) ; \beta_{0j} \}, \]

where, \( g_{ik}(\beta_j) = \frac{(f_{ik}(\beta_j) + f_{ik}(\beta_j))}{2} \)

\[ f_{ik}(\beta_j) = \int_{0}^{\tau} \int_{0}^{\tau} \mathbb{1}\{t > s\} \{1\{M_t > M_k\} \frac{d}{d\beta_j} \text{AUC}_{t}^{(j)}(\beta_j) \} \frac{d}{d\beta_j} \text{AUC}_{t}^{(j)}(\beta_j) - 1\{M_t \leq M_k\} \frac{d}{d\beta_j} \text{AUC}_{t}^{(j)}(\beta_j) \} dN_i^{(j)}(s)dN_k^{(j)}(t), \]

3. Assume that \( 0 \leq \text{AUC}_{t}^{(j)}(\beta_j) \leq 1 \) and it is twice differentiable with respect to \( \beta_j \). Also, we assume that \( \frac{\delta^2 \text{AUC}_{t}^{(j)}(\beta_j)}{\delta \beta_j \delta \beta_j^T} \) negative-definite for any \( t \in (0, \tau) \) in a neighborhood of \( \beta_{0j} \).
In practice, condition (1) can be enforced simply by not choosing \( \tau \) to be greater than the maximum observation time. Condition (2) can be interpreted that the sample covariance among the covariates is asymptotically non-singular. For simplicity we assume \( \beta_j \) is one-dimensional and its corresponding true value is \( \beta_{0j} \). Multi-dimensional cases can be treated in a similar way.

To begin with, we prove the consistency of \( \hat{\beta}_j \). Consider the Taylor expansion of \( j \)-th cause specific partial likelihood \( L(\beta_j) \) around \( \beta_{0j} \),

\[
\frac{1}{n^2}\{L(\hat{\beta}_j) - L(\beta_{0j})\} = \frac{1}{n^2} \frac{\delta L(\beta_{0j})}{\delta \beta_j} \hat{\beta}_j + \frac{1}{2} \frac{\delta^2 L(\beta_{0j})}{\delta \beta_j^2} \hat{\beta}_j^2 + O_p(1)\vert \hat{\beta}_j \vert^3.
\]

Note that as \( n \to \infty \), because the first order derivative of \( \text{AUC}^{(j)}(\beta_j) \) is bounded, therefore, \( \frac{1}{n^2} \frac{\delta L(\beta_{0j})}{\delta \beta_j} \to 0 \). Furthermore, because of assumption (3), \( \frac{1}{n^2} \frac{\delta^2 L(\beta_{0j})}{\delta \beta_j^2} < 0 \). As a result, \( \frac{1}{n^2} \{L(\hat{\beta}_j) - L(\beta_{0j})\} \to 0 \), with probability going to 1. The consistency result follows. To prove asymptotic normality of \( \hat{\beta}_j \), we restate the score equation \( U(\beta_j) \) with respect to an underlying counting process \( \{N_i(t)\}_{i=1}^{n} \), \( t > 0 \) which counts number of events due to \( j \)-th cause of failure occurring over \([0,\tau]\) and it is

\[
U(\beta_j) = \sum_{i=1}^{n} \sum_{k=1}^{n} \int_{0}^{\tau} \int_{0}^{\tau} 1\{t > s\} \{1\{M_i > M_k\} \frac{d}{d \beta_j} \text{AUC}^{(j)}_{Z_i}(\beta_j) - 1\{M_i \leq M_k\} \frac{d}{d \beta_j} \text{AUC}^{(j)}_{Z_k}(\beta_j) \} dN_i(t) dN_j(t),
\]

\[
= \sum_{i=1}^{n} \sum_{k=1}^{n} f_{ik}(\beta_j).
\]

To show the asymptotic Normality results of \( \hat{\beta}_j \), we apply the Taylor expansion of \( U(\beta_j) \) at \( \beta_{0j} \)

\[
\sum_{i=1}^{n} \sum_{k=1}^{n} f_{ik}(\beta_j) = 0,
\]

or, \( \sum_{i=1}^{n} \sum_{k=1}^{n} f_{ik}(\beta_{0j}) + \sum_{i=1}^{n} \sum_{k=1}^{n} (\beta_j - \beta_{0j})^T \frac{d f_{ik}(\beta_{0j})}{d \beta_j} + O_p(n^{-3/2}) = 0, \)

or, \( \sqrt{n} (\hat{\beta}_j - \beta_{0j}) = \sqrt{n} \left[ - \sum_{i=1}^{n} \sum_{k=1}^{n} \frac{d f_{ik}(\beta_{0j})}{d \beta_j} \right]^{-1} \left[ \frac{\sum_{i=1}^{n} \sum_{k=1}^{n} f_{ik}(\beta_{0j})}{\sqrt{n} B_{nj}} \right] + O_p(n^{-1/2}), \)

or, \( \sqrt{n} (\hat{\beta}_j - \beta_{0j}) = A^{-1}_{nj} \sqrt{n} B_{nj} \)
where

\[ A_{nj} = \frac{-1}{n^2} \sum_{i=1}^{n} \sum_{k=1}^{n} \int_{0}^{\tau} \int_{0}^{\tau} 1\{t > s\} \{1\{M_i > M_k\} \frac{d}{d\beta_j} AUC_{\tau}^{(j)}(\beta_{0j}) \} \]

\[ = \frac{1}{n^2} \sum_{i=1}^{n} \sum_{k=1}^{n} f_{ik}(\beta_{0j}) \]

\[ = \frac{1}{n^2} \sum_{i=1}^{n} \left( \sum_{k \neq i} f_{ik}(\beta_{0j}) \right) \text{ since } f_{ii}(\beta_{0j}) = 0, \]

\[ = \frac{1}{n^2} \sum_{i=1}^{n} \left( \sum_{k < i} \left( f_{ik}(\beta_{0j}) + f_{ki}(\beta_{0j}) \right) \right), \]

\[ = \left( \frac{n}{2} \right) \sum_{i=1}^{n} \left( \sum_{k < i} \frac{f_{ik}(\beta_{0j}) + f_{ki}(\beta_{0j})}{2} \right). \]

and as \( n \to \infty \), \( A_{nj} \to \Sigma_{1j}. \) Also,

\[ B_{nj} = \frac{1}{n^2} \sum_{i=1}^{n} \sum_{k=1}^{n} f_{ik}(\beta_{0j}) \]

\[ = \frac{1}{n^2} \sum_{i=1}^{n} \sum_{k \neq i} f_{ik}(\beta_{0j}) \]

\[ = \frac{1}{n^2} \sum_{i=1}^{n} \left( \sum_{k < i} f_{ik}(\beta_{0j}) \right) \text{ since } f_{ii}(\beta_{0j}) = 0, \]

\[ = \frac{1}{n^2} \sum_{i=1}^{n} \left( \sum_{k < i} \left( f_{ik}(\beta_{0j}) + f_{ki}(\beta_{0j}) \right) \right), \]

\[ = \left( \frac{n}{2} \right) \sum_{i=1}^{n} \left( \sum_{k < i} \frac{f_{ik}(\beta_{0j}) + f_{ki}(\beta_{0j})}{2} \right). \]

Here, \( B_{nj} \) is a U-statistic of degree 2. Therefore, the asymptotic Normality follows by the projection theory in [5].

**Proof of Corollary 1**

Since \( \hat{\beta}_j \) is consistent for \( \beta_{0j} \) and \( AUC_t^{(j)}(\cdot) \) is a continuous function, therefore, \( AUC_t^{(j)}(\hat{\beta}_j) \) is a consistent estimator of \( AUC_t^{(j)}(\beta_{0j}) \). In order to prove the Normality of \( AUC_t^{(j)}(\hat{\beta}_j) \), following the proof of theorem 2, we can write the

\[ \hat{\beta}_j = \beta_{0j} + \Sigma_{1j}^{-1} \frac{1}{n^2} \sum_{i=1}^{n} \sum_{k=1}^{n} g_{ik}(\beta_{0j}) + O_p(n^{-1}). \]

Now, consider the Taylor expansion of \( AUC_t^{(j)}(\hat{\beta}_j) \) around \( AUC_t^{(j)}(\beta_{0j}) \)

\[ AUC_t^{(j)}(\hat{\beta}_j) = AUC_t^{(j)}(\beta_{0j}) + \frac{dAUC_t^{(j)}(\beta_{0j})}{d\beta_j}(\hat{\beta}_j - \beta_{0j}) + O_p(n^{-1}), \]

\[ = AUC_t^{(j)}(\beta_{0j}) + \frac{1}{n^2} \sum_{i=1}^{n} \sum_{k=1}^{n} \Sigma_{1j}^{-1} g_{ik}(\beta_{0j}) \frac{dAUC_t^{(j)}(\beta_{0j})}{d\beta_j} + O_p(n^{-1}). \]

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Note that $\sum_{i=1}^{n} \sum_{k=1}^{n} g_{ik}(\beta_{0j}) \frac{dAUC_t^{(j)}(\beta_{0j})}{d\beta_j}$ is a U-statistic, which implies the asymptotic Normality result by the projection theorem. Again, the covariance matrix of $\hat{\beta}_j$ is $\Sigma_{j1}^{-1} \Sigma_{j2} \Sigma_{j1}^{-1}$. The AUC$_t^{(j)}$ after transformation with link function $\eta$ can be rewritten as

$$\eta(AUC_t^{(j)}(\beta_j)) = \beta_{j0} + \sum_{l=1}^{7} \beta_{jl} t(p_l) = A \beta_j^T$$

where $A = (1, t^{p_1}, t^{p_2}, \ldots, t^{p_7})$, and $\beta_j = (\beta_{j0}, \beta_{j1}, \ldots, \beta_{j7})$. Using the delta method we can obtain the variance of AUC$_t^{(j)}(\hat{\beta}_j)$ as

$$\frac{d}{d\beta_j} \eta^{-1}(A \beta_j^T)|_{\beta_j = \hat{\beta}_j} \Sigma_{j1}^{-1} \Sigma_{j2} \Sigma_{j1}^{-1} A^T.$$

References


