A nonparametric test for the association between longitudinal covariates and censored survival data

Ramon Oller\textsuperscript{1} \hspace{1em} Guadalupe Gómez\textsuperscript{2}

\textsuperscript{1}Universitat de Vic - Universitat Central de Catalunya

\textsuperscript{2}Universitat Politècnica de Catalunya

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Both longitudinal and time-to-event data are relevant in biomedical research and in clinical trials. The methodological and applied literature on these fields is abundant.

Time-to-event data may exhibit complex censoring patterns. Right censoring is the most common form. Interval censoring occurs when the event of interest is only known to be in an interval of time. New methods for interval censoring are increasing fast (Gómez et al. 2009). Methods for interval-censored data can be applied to right-censored data. Unfortunately, the reverse is not generally true.
Joint models are a cutting edge research field.

- Right censoring: book of Elashoff et al. (2016) and R package JM (Rizopoulos 2010).

- Interval censoring have not received much attention to date: Seaman & Bird (2001), Sparling et al. (2006) and Zeng et al. (2016).

- Challenges for joint model research include:
  - Computational problems.
  - Diagnostics of joint models.
  - Practical interpretations of some joint models.
  - Identifiability of certain joint models.
  - Uses of joint models by more applied researchers
Today’s talk is about an extension of the log-rank statistic to test whether or not the time to an event (right- or interval-censored) is independent of a longitudinal covariate.

**Relationship between a time dependent covariate and a survival time**

A preliminar test appears as a valuable resource previously to joint modeling!
OUTLINE

1. Notation
2. Longitudinal log-rank test statistic
3. Longitudinal weighted log-rank test statistic
4. Inference approach
5. Imputed values for $z_i(t)$
6. Simulation study
7. PSA and prostate cancer risk
8. Glucose exposure and retinopathy risk in diabetes
9. Discussion
We focus on testing a possible association between a lifetime $T$ and a time-dependent covariate $z(t)$.

Survival data are usually censored.
- Interval censoring: $T \in (L, R]$
- Right censoring: $R = +\infty$
- Left censoring: $L = 0$
- Uncensored observations: $L = R$

Assumptions for the censoring mechanism:
- It is not informative (Oller et al. 2004, 2007).
- It is independent of $z(t)$. 
Given a random sample \((l_1, r_1], \ldots, (l_N, r_N]\), let \(\hat{S}(t)\) be the Turnbull’s
NPMLE of the survival function \(S(t) = P(T > t)\). Then:

- \(\hat{S}_i(t) = P_{\hat{S}}((t, +\infty) \mid (l_i, r_i])\) is an estimate of the survival function of
the \(i^{th}\) individual (Fay and Shih, 1998).
- \(\hat{S}(t) = \frac{1}{N} \sum_{i=1}^N \hat{S}_i(t)\) (self-consistency property).
- \(\hat{F}(t) = \frac{1}{N} \sum_{i=1}^N \hat{F}_i(t)\) where \(\hat{F}(t) = 1 - \hat{S}(t)\) and \(\hat{F}_i(t) = 1 - \hat{S}_i(t)\).
- To avoid non-specification inside Turnbull’s intervals, we choose \(\hat{S}(t)\)
to jump at the right endpoints \(0 < t_1 < t_2 < \cdots < t_m \leq +\infty\).
- Under right-censored data, the NPMLE reduces to the Kaplan-Meier’s
product-limit estimate and \(\{t_j, j = 1, \cdots, m\}\) coincide with the event
times of the uncensored observations.
Longitudinal log-rank test statistic

**DEFINITION 1**

\[
LLR = \sum_{i=1}^{N} \int_{0}^{+\infty} z_i(t) dC_i(t)
\]

where \(C_i(t)\) is the following step function

\[
C_i(t) = \left( \frac{\hat{S}(l_i) \left( \log(\hat{S}(l_i)) \lor \log(\hat{S}(t)) \right) - \hat{S}(r_i) \left( \log(\hat{S}(r_i)) \lor \log(\hat{S}(t)) \right)}{\hat{S}(l_i) - \hat{S}(r_i)} \right)
\]

and \(a \lor b\) stands for the maximum between \(a\) and \(b\).
3. Longitudinal log-rank test statistic

TOY EXAMPLE

- Interval-censored data sample: (4, 7], (3, 5], (0, 2], (1, 4], (6, 9], (8, 10]
- NPMLE of $S(t)$

![Graph showing survival function](image)

- Assumption: jumps of $\hat{S}(t)$ at $t_1 = 2$, $t_2 = 5$ and $t_3 = 9$.
- Time-dependent covariate sample $(z_i(2), z_i(5), z_i(9))$: (2.7, 1.9, 0.9), (1.1, 2, 3.1), (2.7, 2.2, 1.5), (4.2, 2.9, 1.3), (1.8, 1.7, 1.6), (1.1, 0.9, 0.7)

Test between longitudinal covariates and censored survival data.
3. Longitudinal log-rank test statistic

**TOY EXAMPLE**

- Interval-censored data sample: (4, 7], (3, 5], (0, 2], (1, 4], (6, 9], (8, 10]
- NPMLE of $S(t)$

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- Time-dependent covariate sample $(z_i(2), z_i(5), z_i(9))$: (2.7, 1.9, 0.9), (1.1, 2, 3.1), (2.7, 2.2, 1.5), (4.2, 2.9, 1.3), (1.8, 1.7, 1.6), (1.1, 0.9, 0.7)
3. Longitudinal log-rank test statistic

- Computation of $LLR$:
  
  $$C_i(t) = \frac{\hat{S}(l_i) \left( \log(\hat{S}(l_i)) \vee \log(\hat{S}(t)) \right) - \hat{S}(r_i) \left( \log(\hat{S}(r_i)) \vee \log(\hat{S}(t)) \right)}{\hat{S}(l_i) - \hat{S}(r_i)}$$

  where $\hat{S}(t) = \begin{cases} 
  1 & \text{if } t < 2 \\
  2/3 & \text{if } 2 \leq t < 5 \\
  1/3 & \text{if } 5 \leq t < 9 \\
  0 & \text{if } t \geq 9 
\end{cases}$

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### 3. Longitudinal log-rank test statistic

Test between longitudinal covariates and censored survival data.

\[
\text{LLR} = 3.78
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PROPOSITION 1

When $z_i(t) = z_i$ is a time-independent or baseline covariate, then the longitudinal log-rank statistic $LLR$ simplifies to the log-rank test statistic defined by (Peto & Peto 1972) for interval-censored data, that is,

$$LR = \sum_{i=1}^{N} z_i c_i$$

where $c_i$ is the score defined as

$$c_i = \frac{\hat{S}(l_i) \log(\hat{S}(l_i)) - \hat{S}(r_i) \log(\hat{S}(r_i))}{\hat{S}(l_i) - \hat{S}(r_i)}.$$

Particular cases:

- $z_i$ is a 0-1 group indicator: two-sample problem.
- $z_i$ is a vector of group indicators: k-sample problem.
- $z_i$ is a general time-independent covariate: score test under the grouped proportional hazards model (Finkelstein 1986).
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  - $z_i$ is a general time-independent covariate: score test under the grouped proportional hazards model (Finkelstein 1986).
PROPOSITION 2 (Right-Censored Data)

Let’s consider $LLR = \sum_{i=1}^{N} LLR_i$ where $LLR_i = \int_{0}^{+\infty} z_i(t) dC_i(t)$, then:

(a) For an exact datum ($l_i = r_i = t_i$),

$$LLR_i \overset{d\hat{S}(t_i) \rightarrow 0}{\rightarrow} z_i(t_i) + \int_{0}^{t_i} z_i(t) d\log(\hat{S}(t)).$$

(b) For a right-censored datum ($r_i = +\infty$),

$$LLR_i = \int_{0}^{l_i} z_i(t) d\log(\hat{S}(t)).$$

(c) By replacing $\log(\hat{S}(t))$ by the Nelson-Aalen estimator,

$$LLR_i \approx \begin{cases} 
z_i(t_i) - \sum_{s: t_s \leq t_i} z_i(s) \frac{d_s}{n_s} & \text{when } l_i = r_i = t_i \\
- \sum_{s: t_s \leq l_i} z_i(s) \frac{d_s}{n_s} & \text{when } r_i = +\infty
\end{cases}$$

where $d_s$ and $n_s$ denote, respectively, the number of deaths and the number of individuals at risk at the observed failure time $t_s$.

✓ Under right-censored data, $LLR$ is asymptotically equivalent to the score vector under the Cox proportional hazards model with a time-dependent covariate.
PROPOSITION 2 (Right-Censored Data)

Let’s consider \( LLR = \sum_{i=1}^{N} LLR_i \) where \( LLR_i = \int_0^{+\infty} z_i(t) \, dC_i(t) \), then:

(a) For an exact datum \( (l_i = r_i = t_i) \),
\[
LLR_i \xrightarrow{d\hat{S}(t_i) \to 0} z_i(t_i) + \int_{0}^{t_i} z_i(t) \, d\log(\hat{S}(t)).
\]

(b) For a right-censored datum \( (r_i = +\infty) \),
\[
LLR_i = \int_{0}^{l_i} z_i(t) \, d\log(\hat{S}(t)).
\]

(c) By replacing \( \log(\hat{S}(t)) \) by the Nelson-Aalen estimator,
\[
LLR_i \approx \begin{cases} 
z_i(t_i) - \sum_{s: t_s \leq t_i} z_i(s) \frac{d_s}{n_s} & \text{when } l_i = r_i = t_i \\
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\end{cases}
\]

where \( d_s \) and \( n_s \) denote, respectively, the number of deaths and the number of individuals at risk at the observed failure time \( t_s \).

\( \square \) Under right-censored data, \( LLR \) is asymptotically equivalent to the score vector under the Cox proportional hazards model with a time-dependent covariate.
4. Longitudinal weighted log-rank test statistic

Longitudinal weighted log-rank test statistic

**DEFINITION 2**

A longitudinal weighted log-rank statistic is defined by

\[ LWLR = \sum_{i=1}^{N} \int_{0}^{+\infty} z_i(t) \omega(t) \hat{S}_i(t^-) \left( \frac{d\hat{F}_i(t)}{\hat{S}_i(t^-)} - \frac{d\hat{F}(t)}{\hat{S}(t^-)} \right) \]

where

- \( \omega(t) \) is a weighting function,
- \( \hat{S}(t) = 1 - \hat{F}(t) \) is Turnbull’s NPMLE of \( S(t) \),
- \( \hat{S}_i(t) = 1 - \hat{F}_i(t) = P_{\hat{S}}((t, +\infty) | (l_i, r_i]) \) estimates the survival function restricted to the observed interval corresponding to the \( i^{th} \) individual.
PROPOSITION 3

The statistic \( LLR \) is equivalent to the statistic \( LWLR \) when the weighting function is \( \omega(t) = \frac{d\log(\hat{S}(t))}{d\hat{S}(t)} \hat{S}(t^-). \)

Notice that in this case \( \lim_{d\hat{S}(t) \to 0} \omega(t) = 1 \) at any point \( t \).

Oller\&Gómez (2012), Oller\&Langohr (2017): \( \omega(t) = \frac{d\gamma(\hat{S}(t))}{d\hat{S}(t)} \hat{S}(t^-) \)
where \( \gamma(t) = - \int_0^{1-t} x^\lambda (1 - x)^{\rho-1} dx, \rho \geq 0, \lambda \geq 0. \)

- Earlier hazard differences are reinforced by using \( \lambda = 0 \) and assigning high values of \( \rho \).
- Middle differences by selecting high values of \( \rho = \lambda \).
- Late differences by using \( \rho = 0 \) and assigning high values of \( \lambda \).
- \( LWLR \) simplifies to \( LLR \) when \( \rho = 0 \) and \( \lambda = 0. \)
- \( LWLR \) is an extension of the Wilcoxon test when \( \rho = 1 \) and \( \lambda = 0. \).
PROPOSITION 3

The statistic $LLR$ is equivalent to the statistic $LWLR$ when the weighting function is $\omega(t) = \frac{d\log(\hat{S}(t))}{d\hat{S}(t)} \hat{S}(t^-)$.

Notice that in this case $\lim_{d\hat{S}(t)\to 0} \omega(t) = 1$ at any point $t$.

Oller & Gómez (2012), Oller & Langohr (2017): $\omega(t) = \frac{d\gamma(\hat{S}(t))}{d\hat{S}(t)} \hat{S}(t^-)$ where $\gamma(t) = -\int_0^{1-t} x^\lambda (1 - x)^{\rho - 1} dx$, $\rho \geq 0$, $\lambda \geq 0$.

- Earlier hazard differences are reinforced by using $\lambda = 0$ and assigning high values of $\rho$.
- Middle differences by selecting high values of $\rho = \lambda$.
- Late differences by using $\rho = 0$ and assigning high values of $\lambda$.
- $LWLR$ simplifies to $LLR$ when $\rho = 0$ and $\lambda = 0$.
- $LWLR$ is an extension of the Wilcoxon test when $\rho = 1$ and $\lambda = 0$. 
Our aim is to test the null hypothesis of no relationship between $z(t)$ and $T$.

- $H_0: T$ and $(z(u_1), z(u_2), \ldots, z(u_p))$ are independent for all $p > 0$ and all values $0 < u_1 < u_2 < \cdots < u_p < +\infty$.

We consider a permutation approach to derive the asymptotic distribution of $LLR$ and $LWLR$.

- The main assumption is that the underlying censoring process has to be identical across individuals.
- Notice that counting process techniques are not feasible under interval censoring.
PERMUTATION DISTRIBUTION:

- Let $0 < t_1 < t_2 < \cdots < t_m$ be the right endpoints of the Turnbull’s intervals, under the null hypothesis the covariate vectors $Z_i = (z_i(t_1), z_i(t_2), \ldots, z_i(t_m))$ are interchangeable ($i = 1, \ldots, N$).
- The permutation distribution of $LLR$ and $LWLR$ is then obtained by calculating all possible values of the test statistic under rearrangements of the individual indices on the observed covariate vectors.
- The p-values from the permutation distribution may be calculated either exactly or by an approximation method like the Monte Carlo resampling.
5. Inference approach

- Asymptotically, a version of the Central Limit Theorem for exchange random vectors (Sen 1993) can be used.
- The permutation expectation of LLR and LWLR equal to zero.
- The permutation covariance matrix of LLR is given by

\[
V = \frac{1}{N-1} \sum_{j,k=1}^{m} \left( \sum_{i=1}^{N} (a_{ij} - \bar{a}_j)(a_{ik} - \bar{a}_k) \right) \cdot \left( \sum_{i=1}^{N} b_{ij} b_{ik} \right)
\]

where

- \( a_{ij} = z_i(t_j), \bar{a}_j = \frac{1}{N} \sum_{i=1}^{N} a_{ij} \).
- \( b_{ij} = dC_i(t_j) = C_i(t_j) - C_i(t_j^-) \).
- Note that \( \bar{b}_j = \frac{1}{N} \sum_{i=1}^{N} b_{ij} = 0 \).
6. Imputed values for $z_i(t)$

**Imputed values for $z_i(t)$**

- Computation of $LLR$ (or $LWLR$) and the permutation approach require $z_i(t)$ at the points $0 < t_1 < t_2 < \cdots < t_m$.
  - Realistically, they can be difficult to obtain!

- We propose to replace these values for imputed ones:
  - Last observation carried forward.
  - Fit a mixed model for $z_i(t)$ and use the predicted values at the points $0 < t_1 < t_2 < \cdots < t_m$.

- In a conditional permutation approach:
  - The significance level of the test will not be affected by using imputed values instead of observed values.
  - The power of the test might be highly altered if we fail to adequately fit the unobserved longitudinal observations.
Simulation study

- Evaluate performance of LLR and LWLR in terms of significance level and power.
- Several scenarios including type of association between $T$ and $z(t)$, baseline laws for $T$, measurement error variability and number and timing of longitudinal observations.
  
  - $z_i(t) = m_i(t) + \epsilon_i = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t + \epsilon_i$ with $\beta_0 = 1.44$, $\beta_1 = -0.03$ and $\Sigma_b = \begin{pmatrix} 0.84 & -0.0048 \\ -0.0048 & 0.0012 \end{pmatrix}$
  
  - Scenario 1: $\sigma_\epsilon = 1.26$ and $t_{ij} = 0, 6, 12, 18$; Scenario 2: $\sigma_\epsilon = 1.26$ and $t_j = 0, 3, 6, 9, 12, 15, 18, 21$; Scenario 3: $\sigma_\epsilon = 0.07$ and $t_j = 0, 6, 12, 18$

  - Extended accelerated failure time (AFT) model for association between $T_i$ and $z_i(t)$ (Tseng et al. 2005): $S_i(t) = S_0 \left( \int_0^t \exp(\beta m_i(s))ds \right)$ with $S_0(t)$ being Weibul or Log-logistic.

  - Censoring mechanism for $T_i$ resembles an observational study: 24 months follow-up with periodic visits, in average, every 3 months.
Results from $M = 1000$ replications, a sample size of $N = 400$ and a significance level of 0.05.

Empirical size and power of $LLR$ and $LWL_{1,0}$ (with $\rho = 1$ and $\lambda = 0$) with Weibull baseline distribution $S_0(t) = \exp(-(t/\lambda_1)^{\lambda_2})$

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</tr>
<tr>
<td>0.1</td>
<td>21</td>
<td>2</td>
<td>72.5</td>
</tr>
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</table>
Empirical size and power of $LLR$ and $LWLR$ (with $\rho = 1$ and $\lambda = 0$) with Log-logistic baseline distribution $S_0(t) = 1 - \frac{1}{1+(\alpha_1/t)^{\alpha_2}}$

<table>
<thead>
<tr>
<th>AFT parameters $\beta$</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>Scenario 1 $LLR$</th>
<th>Scenario 1 $LWLR_{1,0}$</th>
<th>Scenario 2 $LLR$</th>
<th>Scenario 2 $LWLR_{1,0}$</th>
<th>Scenario 3 $LLR$</th>
<th>Scenario 3 $LWLR_{1,0}$</th>
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</thead>
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<tr>
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<td>70.4</td>
<td>75.6</td>
<td>82.6</td>
<td>85.4</td>
</tr>
</tbody>
</table>
Screening arm of the Spanish branch of the The European Randomized Screening for Prostate Cancer study (Serrat et al. 2015).

- $T$ is the elapsed time from the protocol screening start (age 45) to diagnosis of PCa. **RIGHT CENSORING**
- $z(t) = LLPSA(t)$ is a double log transformation of prostate-specific antigen (PSA).
Imputed values for $z_i(t)$: we assume a linear average evolution of LLPSA in time.

**MLE for the parameters of a linear mixed-effects model with random intercept and slope**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
<td>-0.2849 (0.0323)</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.0144 (0.0006)</td>
</tr>
<tr>
<td>Standard deviation of $b_0$</td>
<td>0.1036</td>
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<tr>
<td>Standard deviation of $b_1$</td>
<td>0.0055</td>
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<tr>
<td>Correlation of $b_0$ and $b_1$</td>
<td>-0.9843</td>
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<tr>
<td>Standard deviation of $\epsilon$</td>
<td>0.1048</td>
</tr>
</tbody>
</table>

Test between longitudinal covariates and censored survival data.
8. PSA and prostate cancer risk

\[ \text{LLR} = 38.01 \] and \[ \sqrt{V} = 2.46 \] and we conclude that PSA is highly and positively associated with the risk of having prostate cancer.
LLR = 38.01 and $\sqrt{V} = 2.46$ and we conclude that PSA is highly and positively associated with the risk of having prostate cancer.
Study of the Epidemiology of Diabetes Interventions and Complications (EDIC) from subjects in the Diabetes Control and Complications Trial (Sparling et al. 2006).

- \( T \) is the time of progression of retinopathy (eye disease). INTERVAL CENSORING
- \( z(t) = Edic\_Hba(t) \) is a measure of the beta-N-1-deoxy fructosyl component of hemoglobin (HbA\(_{1c}\)) during EDIC.

Test between longitudinal covariates and censored survival data.
Imputed values for $z_i(t)$: we assume a linear average evolution of Edic_Hba in time.

### MLE for the parameters of a linear mixed-effects model with random intercept and slope

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
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<td>$\beta_1$</td>
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<tr>
<td>Standard deviation of $b_0$</td>
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<td>Standard deviation of $b_1$</td>
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<td>Standard deviation of $\varepsilon$</td>
<td>0.762935</td>
</tr>
</tbody>
</table>

Test between longitudinal covariates and censored survival data.
9. Glucose exposure and retinopathy risk in diabetes

\[ LLR = 145.40 \quad \text{and} \quad \sqrt{V} = 14.90 \]

and we conclude that glycemia over times is highly and positively associated with the risk of having diabetic retinopathy.
\( LLR = 145.40 \) and \( \sqrt{V} = 14.90 \) and we conclude that glycemia over times is highly and positively associated with the risk of having diabetic retinopathy.
We have proposed a longitudinal version of the log-rank test.

- It is an extension of the log-rank test proposed in Peto & Peto (1972).
- Under right censoring, it is an analogue of the score vector for the Cox proportional hazards model with a time-dependent covariate.
- It is included in a wide class of weighted log-rank test statistics where the weighting function is geared to emphasize hazard changes at different times.
- The asymptotic distribution is derived by means of a permutation approach.
- The simulation study shows:
  - The empirical size is close to the significance level.
  - The power of the test depends on the strength of association between the covariates and the survival time and on the accuracy of the imputed longitudinal measurements.
One advantage of our methodology is that it applies both to exogenous (or external) and to endogenous (or internal) time-dependent covariates.

One drawback is that the underlying censoring process should be identical across individuals.

Our proposal could be extended to multivariate time-dependent covariates.

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THANK YOU