Comparison of treatments via empirical likelihood

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Outline

• Motivating examples
• Background on empirical likelihood (EL)
• EL methods for one-sample problems in survival analysis
• Two-sample problems
• Conclusions
Motivating examples

Mayo Clinic trial

Randomized clinical trial for primary biliary cirrhosis of the liver. Treatment and placebo groups to be compared.

Aim: find an EL-based simultaneous confidence band for the relative survival function:

\[ \theta(t) = \frac{S_1(t)}{S_2(t)} \]

More suitable than the difference \( S_1(t) - S_2(t) \) when the risk of failure is moderate.
Vaccine efficacy estimation

Halloran, Struchiner and Longini (1997)

VE is defined as 1 minus some measure of relative risk in the vaccinated group compared with the unvaccinated group:

\[ VE(t) = 1 - \frac{\alpha_{\text{vaccine}}(t)}{\alpha_{\text{placebo}}(t)} \]

\[ VE_c(t) = 1 - \frac{A_{\text{vaccine}}(t)}{A_{\text{placebo}}(t)} \]

Aim: find an EL-based simultaneous confidence band for \( VE_c(t) \)
Background on empirical likelihood


- First developed for finite-dimensional features $\theta = \theta(F)$ of a cdf (e.g., mean, median, cdf at a single point).
Nonparametric likelihood

\[ L(F) = \prod_{i=1}^{n} (F(X_i) - F(X_i^-)). \]

EL ratio

\[ \tilde{R}(F) = \frac{L(F)}{L(F_n)} = \prod_{i=1}^{n} np_i \]

where (part of) the mass on \( X_i \) is \( p_i \geq 0, \sum_{i=1}^{n} p_i \leq 1 \), and \( F_n \) is the empirical cdf.

EL function

\[ R(\theta_0) = \sup\{ \tilde{R}(F) : \theta(F) = \theta_0 \} \]
Equivalently

\[ R(\theta_0) = \frac{\sup\{L(F) : \theta(F) = \theta_0\}}{\sup\{L(F)\}} \]

**EL hypothesis tests**

Accept \( \theta(F) = \theta_0 \) when \( R(\theta_0) \geq r_0 \) for some threshold \( r_0 \).

**EL confidence regions**

\[ \{ \theta : R(\theta) \geq r_0 \} \]

with \( r_0 \) chosen via an EL analogue of Wilks’s theorem.
EL for means

\[ \mu = E(X) \in \mathbb{R}^d \]

\[ R(\mu) = \max \left\{ \prod_{i=1}^{n} np_i : \sum_{i=1}^{n} p_i X_i = \mu, p_i \geq 0, \sum_{i=1}^{n} p_i = 1 \right\} \]

**Theorem** (ELT, Owen 1990) \( X_1, \ldots, X_n \) iid with finite mean \( \mu_0 \), finite covariance matrix of rank \( q > 0 \). Then

\[ -2 \log R(\mu_0) \xrightarrow{D} \chi_q^2. \]
Extensions

- Smooth functions of means: $\theta = h(\mu)$

- Linear functionals of $F$: $\theta = E(h(X)) = \int h(x) \, dF(x)$.

- Implicitly defined parameters: $E(m(X, \theta)) = 0$ where $m(X, \theta)$ is the estimating function; e.g., median, $m(X, \theta) = 1\{X \leq \theta\} - .5$.

$$R(\theta) = \max \left\{ \prod_{i=1}^{n} np_i : \sum_{i=1}^{n} p_i m(X_i, \theta) = 0, p_i \geq 0, \sum_{i=1}^{n} p_i = 1 \right\}$$
**Theorem** (Owen 1990) Let $X_1, \ldots, X_n$ be iid, and suppose $m(X, \theta_0)$ has finite covariance matrix of rank $q > 0$. If $E(m(X, \theta_0)) = 0$, then

$$-2 \log R(\theta_0) \xrightarrow{D} \chi^2_q.$$ 

**Proof** Immediate from ELT upon some changes in notation: $X$ is replaced by $m(X, \theta)$, which has mean zero when $\theta = \theta_0$. 
EL simultaneous band for $F$

Local EL function at $\theta_0 = F_0(t)$:

$$R(t) = \frac{\sup\{L(F) : F(t) = F_0(t)\}}{\sup\{L(F)\}}$$

$$= \left( \frac{\sqrt{n}(F_n(t) - F_0(t))}{\sqrt{F_0(t)(1 - F_0(t))}} \right)^2 + o_P(1)$$

As a process in $t \in [a, b]$:

$$-2 \log R(t) \xrightarrow{\mathcal{D}} \left( \frac{W^o(F_0(t))}{\sqrt{F_0(t)(1 - F_0(t))}} \right)^2$$

$$\xrightarrow{\mathcal{D}} \left( \frac{W(\sigma^2(t))}{\sigma(t)} \right)^2,$$
$W^o$ standard tied-down Wiener process (Brownian bridge)
$W$ standard Wiener process

$$\sigma^2(t) = \frac{F_0(t)}{1 - F_0(t)}.$$ 

Simultaneous confidence band for $F$ over an interval $[a, b]$:

$$\{(t, F_0(t)) : -2 \log R(t) \leq C_\alpha, t \in [a, b]\}$$

$C_\alpha$ the upper $\alpha$-quantile of

$$\sup_{t \in [\hat{\sigma}^2(a), \hat{\sigma}^2(b)]} \frac{W^2(t)}{t}.$$ 

Survival analysis setting

Right-censored lifetime data

Observe $n$ iid pairs $(Z_i, \delta_i)$

$Z_i = \min(X_i, Y_i), \delta_i = I\{X_i \leq Y_i\}, X_i$ and $Y_i$ independent.

$F$ : cdf of $X_i$

$G$ : cdf of $Y_i$

$S = 1 - F$ : survival function, $S(0) = 1$

$A$: cumulative hazard function

$$A(t) = \int_{(0,t]} \frac{dF(s)}{1 - F(s-)}$$
Nonparametric likelihood

\[ L(S) = L(F) = \prod_{i=1}^{n} (F(Z_i) - F(Z_i-))^{\delta_i} (1 - F(Z_i))^{1-\delta_i}. \]

To maximize \( L(F) \), we only need consider \( F \) supported on the uncensored lifetimes.
EL function

\[ R(\theta_0) = \frac{\sup\{L(S) : \theta(S) = \theta_0\}}{\sup\{L(S)\}} \]

EL suddenly becomes difficult because of the censoring!

Unless \( \theta(S) \) has a particularly simple form, \( R(\theta_0) \) may be intractable.
Known tractable forms of $\theta(S)$ or $\theta(A)$:

- $S(t_0)$
- $A(t_0)$
- quantiles
- linear functionals $\theta(F) = \int h(t) \, dF(t)$
- linear functionals $\theta(A) = \int h(t) \, dA(t)$

EL for the Cox model regression parameters

\[ \alpha(t|z) = \alpha_0(t) \exp(\beta'z) \]

Estimating equation for \( \beta \):

\[ E(U(\beta_0)) = 0 \]

where \( U \) is the partial likelihood score function.

Qin and Jing (2001): standard EL for this estimating equation.

Murphy and van der Vaart (1997): a profile EL for \( \beta \) for current status data.
EL for survival function at a fixed point

\( p = S(t_0), \) with \( t_0 \) fixed, \( 0 < p < 1. \)

Method of Lagrange multipliers is tractable.

**Theorem** If \( S \) is continuous, \( 0 < p = S(t_0) < 1 \) and \( G(t_0) < 1 \), then

\[
-2 \log R(p) \overset{D}{\to} \chi^2_1
\]

Thomas and Grunkemeier (1975), Li (1995), Murphy (1995)
EL simultaneous band for $S$

As a process in $t \in [a, b]$,

$$-2 \log R(t) \xrightarrow{\mathcal{D}} \left( \frac{W(\sigma^2(t))}{\sigma(t)} \right)^2,$$

Simultaneous confidence band for $S$ over an interval $[a, b]$:

$$\{(t, S(t)) : -2 \log R(t) \leq C_\alpha, t \in [a, b]\}$$

$C_\alpha$ the upper $\alpha$-quantile of

$$\sup_{t \in [\hat{\sigma}^2(a), \hat{\sigma}^2(b)]} \frac{W^2(t)}{t}$$


Li and Van Keilegom (2001): adjustment for a covariate effect (continuous one-dimensional covariate).
Two-sample problem

Comparison of treatment and placebo groups.

Notation

Index sample by $j$

Assume $n_j/n \to p_j > 0$

Total sample size $n = n_1 + n_2$

Nonparametric likelihood: $L(S_1, S_2) = L_1(S_1)L_2(S_2)$. 
• Standard method: logrank test for $S_1 = S_2$.

• Wald-type comparison of $S_1$ and $S_2$ using some smooth functional $\varphi(S_1, S_2)$ and the functional delta method typically leads to intractable limiting distributions. Simulation needed.

**Gaussian multiplier simulation technique**

Martingale increments $dM_i(t)$ replaced by $G_i dN_i(t)$, where $G_i \sim N(0,1)$. (Lin, Wei and Ying, 1993)

Parzen, Wei and Ying (1997) constructed a Wald-type confidence band for $S_1(t) - S_2(t)$ using this technique.
Q-Q plot

\{ (F_1^{-1}(p), F_2^{-1}(p)) : 0 < p < 1 \}

Einmahl and McKeague (1999) constructed an EL confidence band for the Q-Q plot:

\{ (t_1, t_2) : -2 \log R(t_1, t_2) \leq C_\alpha, t_1 \in [a, b] \}

where \( C_\alpha \) uses

\[ \sigma^2(t) = \sigma_1^2(t)/p_1 + \sigma_2^2(t')/p_2 \]

and \( t' = F_2^{-1}(F_1(t)) \). Simulation not needed.
Mayo Clinic trial Q-Q plot
Relative survival

\[ \theta(t) = \frac{S_1(t)}{S_2(t)} \]

McKeague and Zhao (2002) construct an EL simultaneous band:

\[ \{(t, \theta(t)) : -2 \log R(t) \leq C_\alpha, t \in [a, b]\} \]

where \( C_\alpha \) uses

\[ \sigma^2(t) = \sigma^2_1(t) / p_1 + \sigma^2_2(t) / p_2. \]

Simulation not needed.
Mayo clinic trail: placebo/treatment relative survival
• Simultaneous band for differences in cumulative hazards:

\[ A_1(t) - A_2(t) = -\log(S_1(t)/S_2(t)) \]

EL works without simulation, McKeague and Zhao (2002).

• Simultaneous band for vaccine efficacy:

\[ VE_c(t) = 1 - \frac{A_{\text{vaccine}}(t)}{A_{\text{placebo}}(t)} \]

EL works, McKeague and Zhao (2002). Gaussian multiplier simulation needed. Reason EL works:

\[ \frac{A_1(t)}{A_2(t)} = \log S_1(t) / \log S_2(t) \]

and the product-limit form of the survival function.
Ratios of cdfs: $F_1(t)/F_2(t)$, EL intractable?
Conclusions

- EL techniques are tractable in the two-sample setting for simultaneous inference concerning *ratios* of survival functions and cumulative hazards.

- EL shows great promise for further development in more complex clinical trial settings.