gestim3.ado -- Summary of Statistical Methodology

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Description

gestim3 extends the methodology of Robins and Tsiatis (1991) for estimation of treatment effects in a 3-arm clinical trial scenario. Two 'active' treatments are compared against 'no treatment' or a placebo for a specified survival-type outcome. Some subjects may 'crossover' to receive the treatment of one of the other arms and treatment combinations are also facilitated. The model is a rank preserving structural failure time model (a class of semi-parametric failure time models) and can be regarded as a structural/strong version of an accelerated failure time model with time-dependent covariates (Cox and Oakes, 1984). The observed event time T is related to an underlying event time U that would have been observed in the absence of treatment. The estimated parameters (values which balance U across arms) represent the effect of treatment; i.e. acceleration or deceleration of the time-to-event.

Two variants of the model are provided (see the section on confidence intervals in this document). The intention is to combine these two variants after testing and validation is complete.

Counterfactual Failure Times

Modelling the impact of treatment combinations:

$$U(\psi_1,\psi_2)=\int_0^T \exp\{\psi_1 D_1(t)+\psi_2 D_2(t)\}dt$$

where

- $D_1(t)$ = 1(0) represents treatment 1 at time t
- $D_2(t)$ = 1(0) represents treatment 2 at time t

Censoring occurs at the minimum of study end (C_i) or death (when investigating morbid events).

Expanding the counterfactual failure time definition

The total time in the trial can be written as

$$T = s_0 + s_1 + s_2 + s_{12}$$

where

- s_0 = time spent on no treatment: $s_0=\int_0^{T_i}(1-D_1(t))(1-D_2(t))dt$
- s_1 = time spent on active treatment 1 only: $s_1=\int_0^{T_i} D_1(t)(1-D_2(t))dt$
- s_2 = time spent on active treatment 2 only: $s_2=\int_0^{T_i}(1-D_1(t))D_2(t)dt$
- s_{12} = time spent on both active treatments: $s_{12}=\int_0^{T_i} D_1(t)D_2(t)dt$

Using these definitions, the counterfactual failutre time can be re-written as

$$\begin{aligned} U_i(\psi_1,\psi_2) &= \int_0^{T_i}\exp[\psi_1 D_{1i}(t)+\psi_2 D_{2i}(t)]dt \\ &= s_{i0}+s_{i1}\exp(\psi_1)+s_{i2}\exp(\psi_2)+s_{i,12}\exp(\psi_1+\psi_2) \end{aligned}$$

Censoring background

If random censoring took place ($T_i = C_i$), then $U_i(\psi_1, \psi_2)$ would typically be censored at

$$\tilde{C}_i(\psi_1, \psi_2) = \int_0^{C_i} \exp[\psi_1 D_{1i}(t) + \psi_2 D_{2i}(t)]dt$$

where C_i is the potential censoring time (known for censored and uncensored patients); usually defined as the trial end.

However, $\tilde{C}_i(\psi_1, \psi_2)$ is a function of the treatment history and may be dependent on the individual's prognosis. If non-random non-compliance is occurring, non-informative censoring on the T-scale may become informative on the transformed U-scale. Therefore, we cannot replace T_i with $Y_i = \min(T_i, C_i)$ when calculating $U_i(\psi_1, \psi_2)$.

Re-Censoring

A number of options are available to counter the issues raised:

Option 1

The adjusted censoring time is

$$C_i(\psi_1, \psi_2) = \begin{cases} C_i \exp(\psi_1 + \psi_2) & ; \psi_1, \psi_2 < 0 \\ C_i \exp(\psi_1) & ; \psi_1 < 0, \psi_2 \geq 0 \\ C_i \exp(\psi_2) & ; \psi_1 \geq 0, \psi_2 < 0 \\ C_i & ; \psi_1, \psi_2 \geq 0 \end{cases}$$

Option 2

Defining $\alpha(\psi_1, \psi_2) = \min_i \{U_i(\psi_1, \psi_2)/T_i\}$, the 'empirical' adjusted censoring time is

$$C_i(\psi_1, \psi_2) = \begin{cases} \alpha(\psi_1, \psi_2) C_i & ; \ 0 \leq \alpha(\psi_1, \psi_2) < 1 \\ C_i & ; \ \alpha(\psi_1, \psi_2) \geq 1 \end{cases}$$

Option 3

The 'empirical' adjusted censoring time is

$$C_i(\psi_1, \psi_2) = (\min_i \{K_i(\psi_1, \psi_2)/T_i\}) C_i$$

where

$$K_i(\psi_1, \psi_2) = \begin{cases} U_i(\psi_1, \psi_2) & ; \ \psi_1, \psi_2 < 0 \\ U_i(\psi_1, 0) & ; \ \psi_1 < 0, \psi_2 \geq 0 \\ U_i(0, \psi_2) & ; \ \psi_1 \geq 0, \psi_2 < 0 \\ U_i(0,0) & ; \ \psi_1, \psi_2 \geq 0 \end{cases}$$

N.B. Option 3 is used in the software routines developed to date.

Estimation

After Re-Censoring

End point: $X_i(\psi_1, \psi_2) = \min[C_i(\psi_1, \psi_2), U_i(\psi_1, \psi_2)]$

Event indicator: $\Delta_i(\psi_1, \psi_2) = \mathrm{I}[U_i(\psi_1, \psi_2) \leq C_i(\psi_1, \psi_2)]$

Determine ψ_1^* and ψ_2^*

Find value of ψ giving $U \perp R$ ($\chi_2^2(\psi_1, \psi_2) = 0$ using log-rank test).

Confidence Intervals

1. Approximate Confidence Intervals

Again, we use a grid search to find:

- 95% confidence interval for ψ_1: $\chi^2_2(\psi_1, \psi_2^*) < 5.99$
- 95% confidence interval for ψ_2: $\chi^2_2(\psi_1^*, \psi_2) < 5.99$

Hazard Ratio Conversion

Firstly, we make the assumption that the counterfactual failure times follow a Weibull distribution; i.e. $U_i(\psi_1^*, \psi_2^*) \sim \text{We}(\lambda, \theta)$. The acceleration parameters can then be converted to hazard ratios (using the estimated shape parameter) as $\text{HR}_1 = \exp[\theta\psi_1^*]$ and $\text{HR}_2 = \exp[\theta\psi_2^*]$.

2. Bootstrapping

This approach utilises sampling with replacement to create multiple extracts from the original data set. The data sets are of the same size as the original but some subjects will appear more than once. The estimation process is undertaken for each extracted data set and the summary statistics are combined to form the 'bootstrapped' estimates. The estimates are combined on the log-hazard ratio scale and backtransformed to obtain the estimated hazard ratio and associated confidence interval.

Reference

Cox, D.R. and Oakes, D. (1984) Analysis of Survival Data, Chapman and Hall: London.

Robins, J.M. and Tsiatis, A.A. (1991) Correcting for non-compliance in randomized trials using rank preserving structural failure time models, Communications in Statistics - Theory and Methods, **20** (8): 2609–2631.