rpsftm: rank-preserving structural failure time models for survival data

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2016-06-25

Summary

The package `rpsftm` provides functions to fit a rank preserving structural failure time model to a two-arm clinical trial with survival outcomes.

Introduction

The rank preserving structural failure time model (RPSFTM) is a method used to adjust for treatment switching in trials with survival outcomes. Treatment switching occurs when patients switch from their randomised arm to the other treatment during the study. The RPSFTM is due to *Robins and Tsiatis (1991)* and has been developed by *White et al. (1997, 1999)* and *Bowden et al. (2015)*.

Methods

RPSFTM assumptions

Let $T_i = T_i^{off} + T_i^{on}$ be the observed event time for subject i, where T_i^{off} and T_i^{on} are the time that the patient spent off and on treatment, respectively. The T_i are related to the counter-factual or treatment-free event times U_i by the causal model

$$U_i = T_i^{off} + T_i^{on} \exp(\psi_0)$$

where $\exp(-\psi_0)$ is the acceleration factor associated with treatment and ψ_0 is the true causal parameter.

To estimate ψ we assume that the U_i are independent of randomised treatment group R, i.e. if the groups are similar with respect to all other characteristics except treatment, the average event times should be the same in each group if no individual were treated. A g-estimation procedure is used to find the value of ψ such that U is independent of R. For each value of ψ considered, the hypothesis $\psi_0 = \psi$ is tested by computing $U_i(\psi)$ and calculating $Z(\psi)$ as the test statistic. This is usually the same test statistic as for the intention-to-treat analysis. In the `rpsftm` function, the test options are log rank (default), Cox, and Weibull. For the parametric Weibull test, the point estimate ($\hat{\psi}$) is the value of ψ for which $Z(\psi) = 0$. For the non-parametric tests (log rank, Cox), $\hat{\psi}$ is the value of ψ for which $Z(\psi)$ crosses 0, since $Z(\psi)$ is a step function. Confidence intervals are similarly found with the $100(1-\alpha)\%$ confidence interval being the set $\{\psi : |Z(\psi)| < z_{1-\alpha/2}\}$, where $z_{1-\alpha/2}$ is the $1-\alpha/2$ percentile of the standard normal distribution.

As well as assuming that the only difference between randomised groups is the treatment received, the RPSFTM also assumes a 'common treatment effect'. The common treatment effect assumption states that the treatment effect is the same for all individuals (with respect to time spent on treatment) regardless of when treatment is received.

Recensoring

The censoring indicators of the observed event times are initially carried over to the counter-factual event times. However, the uninformative censoring on the T_i scale may be informative on the U_i scale. Suppose we have two individuals with the same U_i, one of whom receives the superior treatment. The individual

receiving the superior treatment has their U_i extended so that they are censored whilst the other individual may observe the event. Therefore, on the U_i scale, censoring is informative with respect to treatment group. To overcome this problem, the counter-factual event times are recensored by the minimum U_i that could have been observed for each individual across their possible treatment changes.

Let C_i be the potential censoring time for an individual i. An individual is then recensored at the minimum possible censoring time:

$$D_i^*(\psi) = min(C_i, C_i \exp(\psi)).$$

If $D_i^*(\psi) < U_i$, then U_i is replaced by D_i^* and the censoring indicator is replaced by 0. For treatment arms where switching does not occur, there can be no informative censoring and so recensoring is not applied.

Sensitivity analysis

As previously mentioned, the RPSFTM has two assumptions:

1. The only difference between randomised groups is the treatment received.
2. The treatment effect is the same for all individuals regardless of when treatment is received.

Whilst the first assumption is plausible in a randomised controlled trial, the latter may be unlikely to hold if, for example, control group patients can only switch at disease progression then the treatment benefit may be less in these individuals compared to those randomised to the experimental treatment. The `rpsftm` function allows for investigation of deviations from the common treatment effect assumption by featuring a treatment effect modifier variable which means the treatment effect can be varied across individuals. This is achieved by multiplying ψ_0 by some factor $k_i \in [0, 1]$:

$$U_i = T_i^{off} + T_i^{on} \exp(k_i \psi_0).$$

For example, we can investigate what would happen to the estimate of ψ if the treatment effect in switchers was half of that in the experimental group by setting $k_i = 1$ for patients in the experimental group and $k_i = 0.5$ for patients in the control group.

Recensoring is undertaken in a similar way by recensoring at the minimum possible censoring time:

$$D_i^*(\psi) = min(C_i, C_i \exp(k_i \psi)).$$

Again, if $D_i^*(\psi) < U_i$, then U_i is replaced by D_i^* and the censoring indicator is replaced by 0.

Example

The `rpsftm` function will be illustrated using a simulated dataset `immdef` based on a randomized controlled trial; see *Concorde Coordinating Committee (1994)*. The trial compares two policies (immediate or deferred treatment) of zidovudine treatment in symptom free individuals infected with HIV. The immediate treatment arm received treatment at randomisation whilst the deferred arm received treatment either at onset of AIDS related complex or AIDs or development of persistently low CD4 count. The primary endpoint was time to progression to AIDS or CDC group IV disease, or death.

Data

The `immdef` data frame has 1000 observations and 8 variables:

- **id** participant ID number
- **def** indicator that the participant was assigned to the Deferred treatment arm

- **imm** indicator that the participant was assigned to the Immediate treatment arm
- **censyrs** a real, or theoretical censoring time, corresponding to the close of study minus the time of entry for each participant
- **xo** an indicator that crossover occurred
- **xoyrs** the time at which crossover happened, or 0 for participants in the Immediate arm
- **prog** an indicator of disease progression (1), or censoring (0)
- **entry** the time of entry into the study

The first six entries are:

```
library(rpsftm)
head(immdef)
#>   id def imm censyrs xo    xoyrs prog  progyrs entry
#> 1  1   0   1       3  0 0.000000    0 3.000000     0
#> 2  2   1   0       3  1 2.652797    0 3.000000     0
#> 3  3   0   1       3  0 0.000000    1 1.737838     0
#> 4  4   0   1       3  0 0.000000    1 2.166291     0
#> 5  5   1   0       3  1 2.122100    1 2.884646     0
#> 6  6   1   0       3  1 0.557392    0 3.000000     0
```

For example, subject 2 was randomised to the deferred arm, started treatment at 2.65 years and was censored at 3 years (the end of the study). Subject 3 was randomised to the immediate treatment arm and progressed (observed the event) at 1.74 years. Subject 5 was randomised to the deferred treatment arm, started treatment at 2.12 years and progressed at 2.88 years. The trial lasted 3 years with staggered entry over the first 1.5 years. The variable **censyrs** gives the time from entry to the end of the trial. The table below shows summary statistics for the `immdef` data:

```
library(tableone)
vars       <- c("def", "imm", "censyrs", "xo", "xoyrs", "prog", "progyrs", "entry")
factorVars <- c("def", "imm", "xo", "prog")
CreateTableOne(vars=vars, data=immdef, factorVars=factorVars, includeNA=FALSE, test=FALSE)
#>
#>                        Overall
#>   n                    1000
#>   def = 1 (%)           500 (50.0)
#>   imm = 1 (%)           500 (50.0)
#>   censyrs (mean (sd)) 2.25 (0.45)
#>   xo = 1 (%)            189 (18.9)
#>   xoyrs (mean (sd))   0.78 (0.93)
#>   prog = 1 (%)          312 (31.2)
#>   progyrs (mean (sd)) 1.93 (0.66)
#>   entry (mean (sd))   0.75 (0.45)
```

Fitting the RPSFTM

The main function used in model fitting is `rpsftm` which takes the arguments:

- **formula** a formula with a minimal structure of `ReCen(time, censor_time)~Instr(arm, rx)` where
  - `time` is the observed event time,
  - `censor_time` is the real or theoretical censoring time,
  - `arm` is the randomised treatment arm, and

  - `rx` is the proportion of time spent on treatment, taking values in [0, 1].

  Further terms can be added to the right hand side to adjust for covariates.
- **data** an optional data frame containing the variables.
- **subset** an expression indicating which subset of the rows of data should be used in the fit. This can be a logical vector, a numeric vector indicating which observation numbers are to be included, or a character vector of row names to be included. All observations are included by default.
- **na.action** a missing-data filter function. This is applied to the `model.frame` after any subset argument has been used. Default is `options()$na.action`.
- **test** one of `survdiff`, `coxph` or `survreg`. Describes the test to be used in the estimating equation. Default is `survdiff`.
- **low_psi** the lower limit of the range to search for the causal parameter. Default is -1.
- **hi_psi** the upper limit of the range to search for the causal parameter. Default is 1.
- **alpha** the significance level used to calculate the confidence intervals. Default is 0.05.
- **treat_modifier** an optional parameter that ψ is multiplied by on an individual observation level to give differing impact to treatment. The values are transformed by `abs(.)/max(abs(.))` to ensure 1 is the largest weight. Default is 1.
- **recensor** a logical to perform recensoring if set to TRUE. Default is TRUE.
- **outoswitch** a logical to autodetect cases of no switching. Default is TRUE.

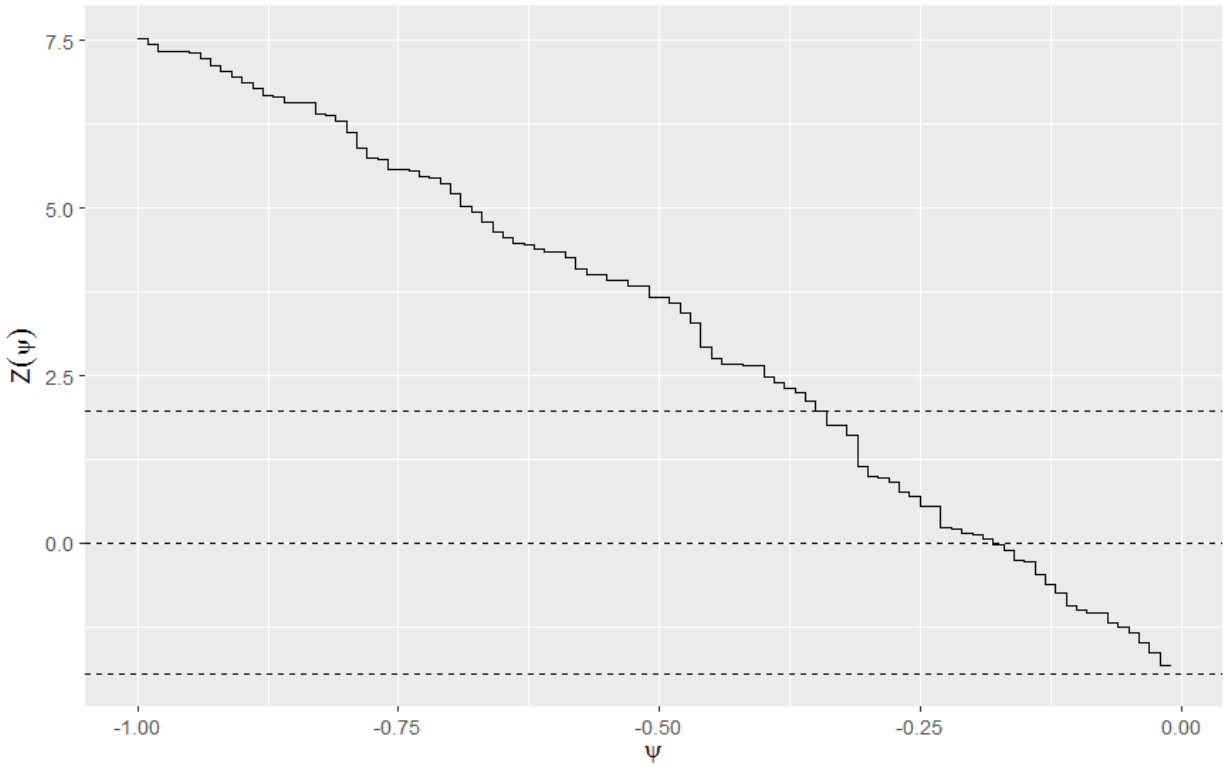
The `rpsftm` function first evaluates $Z(\psi)$ at $\psi =$ `low_psi` and `hi_psi`. If they have the same sign, the procedure is stopped and the following error message is produced

```
#> Error in rpsftm(formula = ReCen(progyrs, censyrs) ~ Instr(imm, rx), data = immdef, :
#> The starting interval (1, 2) to search for a solution for psi
#> gives values of the same sign (-8.95, -12.3).
#> Try a wider interval?
```

This suggests widening the search interval via trial and error until the values of $Z(\psi)$ at `lowpsi` and `hipsi` are of opposite sign. Otherwise, `rpsftm` next uses `uniroot` to search the interval for $\hat{\psi}$ and the $100(1-\alpha)\%$ confidence interval by using the target values 0, $z_{1-\alpha/2}$ and $z_{\alpha/2}$. If the function fails to find $\hat{\psi}$ or either limit of the confidence interval, it will set the value to NA and produce a warning message, for example,

```
#> Warning in rpsftm(formula = ReCen(progyrs, censyrs) ~ Instr(imm, rx), data
#> = immdef, : Evaluation of a limit of the Confidence Interval failed. It is
#> set to NA
```

Investigation of a plot of $Z(\psi)$ against ψ (example shown below) for a range of values of ψ could show why the functions fails to find a root. In this case, the search interval used in `rpsftm` was not be wide enough to find the upper confidence limit.



Recensoring is performed by default unless `recensor=FALSE` is specified in the function parameters. After finding $\hat{\psi}$, `rpsftm` refits the model at $\hat{\psi}$ and produces a `survdiff` object of the counter-factual event times to be used in plotting Kaplan-Meier curves. The function returns

- **psi** the estimated parameter
- **fit** a `survdiff` object to produce Kaplan-Meier curves of the estimated counter-factual event times in each treatment arm using `plot()`
- **formula** a formula representing any adjustments, strata or clusters used
- **regression** the survival regression object at **psi**
- **Sstar** the (possibly) recensored `Surv()` data using **psi**
- **ans** the object returned from `uniroot` used to solve the estimating equation
- **CI** a vector of the confidence interval around **psi**
- **call** the R call object

We now show how to use `rpsftm` with the `immdef` data. First, a variable **rx** for the proportion of time spent on treatment must be created:

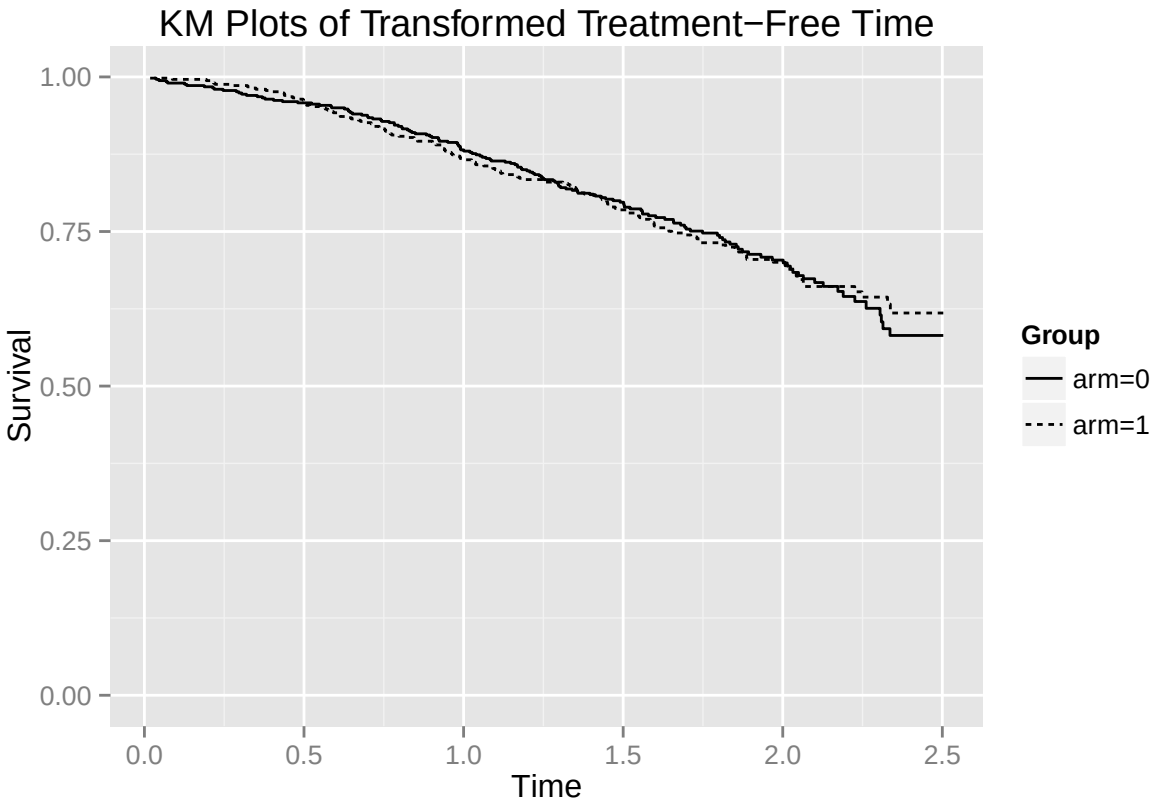
```
rx <- with(immdef,
           ifelse(imm == 1 & xo == 0,
                  1,
                  ifelse(imm == 1 & xo == 1,
                         xoyrs/progyrs,
                         ifelse(imm == 0 & xo == 1,
                                (progyrs-xoyrs)/progyrs,
                                0))))
```

This sets **rx** to 1 in the immediate treatment arm (since no patients could switch to the deferred arm), 0 in the deferred arm patients that did not receive treatment and **(progyrs - xoyrs)/progyrs** in the deferred arm patients that did receive treatment. Using the default options, the fitted model is

```
rpsftm_fit_lr <- rpsftm(formula=ReCen(progyrs, censyrs) ~ Instr(imm, rx),
                        data=immdef)
```

The above formula fits a RPSFTM where `progyrs` is the observed event time, `censyrs` is the real or theoretical censoring time, `imm` is the randomised group indicator and `rx` is the proportion of time spent on treatment. The log rank test is used in finding the point estimate of ψ. The point estimate and 95% confidence interval can be returned using `rpsftm_fit_lr$psi` and `rpsftm_fit_lr$CI` which gives $\hat{\psi} = -0.181$ (-0.35, 0.00199). The function `plot()` produces Kaplan-Meier curves of the counter-factual event times in each group and can be used to check that the distributions are indeed the same at $\hat{\psi}$.

```
plot(rpsftm_fit_lr)
```



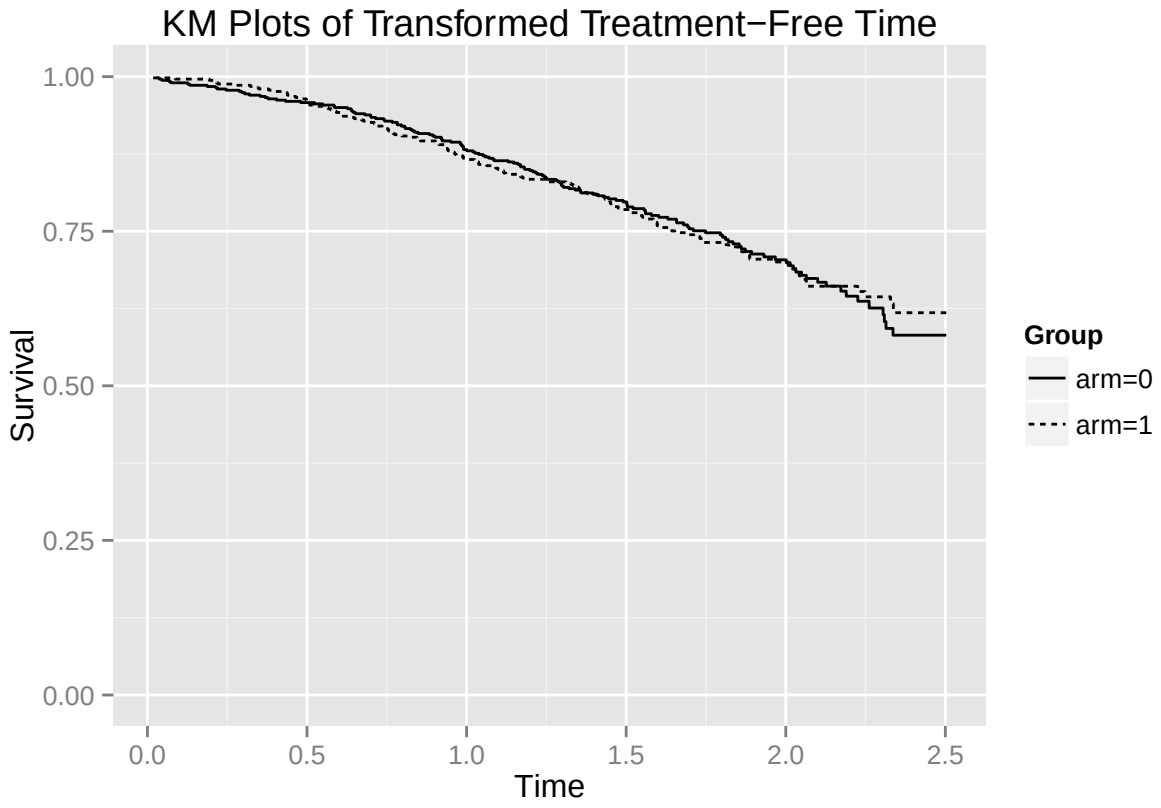
To use the Wald test from a Cox regression model in place of the log rank test, we specify `test=coxph` in the function parameters. Covariates can also be included in the estimation procedure by adding them to the right hand side of the formula. For example, baseline covariates that are included in the intention-to-treat analysis may also be incorporated into the estimation procedure of the RPSFTM. In the following example we add entry time as a covariate and use `summary()` to find the value of $\hat{\psi}$ and its 95% confidence interval:

```
rpsftm_fit_cph <- rpsftm(formula=ReCen(progyrs, censyrs) ~ Instr(imm, rx) + entry,
                         data=immdef,
                         test=coxph)
summary(rpsftm_fit_cph)
#> rpsftm(formula = ReCen(progyrs, censyrs) ~ Instr(imm, rx) + entry,
#>     data = immdef, test = coxph)
#>   n= 1000, number of events= 286
#>
#>            coef exp(coef)  se(coef)      z Pr(>|z|)
```

```
#> arm   -0.002135  0.997867  0.118300 -0.018    0.986
#> entry  0.123541  1.131496  0.148719  0.831    0.406
#>
#>       exp(coef) exp(-coef) lower .95 upper .95
#> arm      0.9979     1.0021    0.7914     1.258
#> entry    1.1315     0.8838    0.8454     1.514
#>
#> Concordance= 0.514  (se = 0.018 )
#> Rsquare= 0.001   (max possible= 0.976 )
#> Likelihood ratio test= 0.69  on 2 df,   p=0.7075
#> Wald test            = 0.69  on 2 df,   p=0.7079
#> Score (logrank) test = 0.69  on 2 df,   p=0.7077
#>
#>
#> psi: -0.1811515
#> exp(psi): 0.834309
#> Confidence Interval, psi -0.3497117 0.00330558
#> Confidence Interval, exp(psi)  0.7048913 1.003311
```

From the output we get $\hat{\psi} = -0.181$ (-0.35, 0.00331). Again, we can plot the Kaplan-Meier curves of the counter-factual event times in each group:

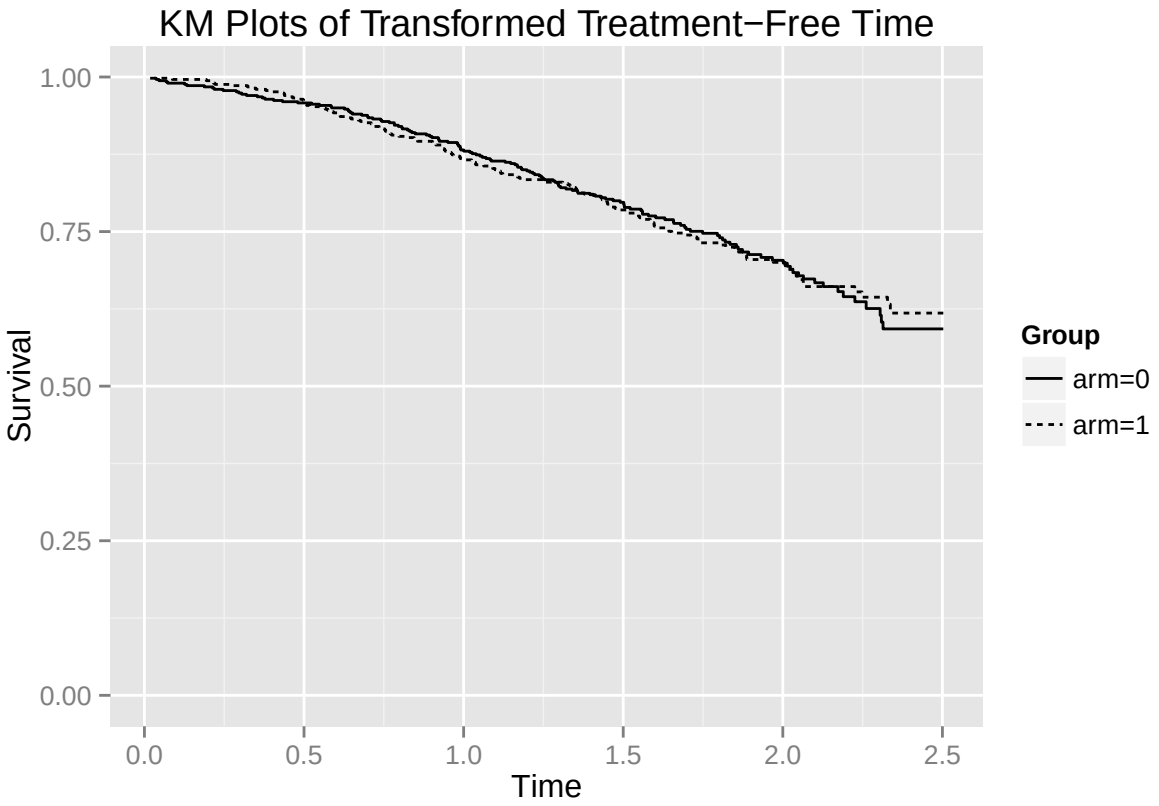
```
plot(rpsftm_fit_cph)
```



Similary, for the Weibull model we have:

```
rpsftm_fit_wb <- rpsftm(formula=ReCen(progyrs, censyrs) ~ Instr(imm, rx) + entry,
                        data=immdef,
                        test=survreg)
summary(rpsftm_fit_wb)
#> rpsftm(formula = ReCen(progyrs, censyrs) ~ Instr(imm, rx) + entry,
#>     data = immdef, test = survreg)
#>
#> Call:
#> NULL
#>                 Value Std. Error       z        p
#> (Intercept)  1.388057     0.0857 16.1963 5.35e-59
#> arm         -0.000461     0.0780 -0.0059 9.95e-01
#> entry       -0.058172     0.0906 -0.6419 5.21e-01
#> Log(scale)  -0.417603     0.0568 -7.3495 1.99e-13
#>
#> Scale= 0.659
#>
#> Weibull distribution
#> Loglik(model)= -759.7   Loglik(intercept only)= -760
#>  Chisq= 0.4 on 2 degrees of freedom, p= 0.82
#> Number of Newton-Raphson Iterations: 6
#> n= 1000
#>
#>
#> psi: -0.181231
#> exp(psi): 0.8342427
#> Confidence Interval, psi -0.3501386 0.005173062
#> Confidence Interval, exp(psi)  0.7045904 1.005186
```

```
plot(rpsftm_fit_wb)
```



The output shows that $\hat{\psi} = -0.181$ (-0.35, 0.00517). In all three cases, the point estimate and 95% confidence interval of ψ are similar.

Limitations

There are a few cases where we may encounter problems with root finding:

1. The interval (`lowpsi`, `hipsi`) may not be wide enough to find one or both of the confidence limits. This can be easily be rectified by extending the range.
2. No confidence limits may exist (i.e. they tail off to $\pm\infty$). In this case they should be reported as $\pm\infty$.
3. There may be multiple solutions to $Z(\psi) = 0$ within the interval (`lowpsi`, `hipsi`). `uniroot` will return one value even if this is the case.

For all of the above a graph of $Z(\psi)$ against ψ would highlight the issue. Another possibility is for the `coxph` function to fail to converge. This occurs when the maximum likelihood estimate of a coefficient is infinity, e.g. if one of the treatment groups has no events. The `coxph` documentation states that the Wald statistic should be ignored in this case and therefore the `rpsftm` output should be taken with caution.

References

Bowden, J., Seamen, S., Huang, X. and White, I.R. (2015). Gaining power and precision by using model-based weights in the analysis of late stage cancer trials with substantial treatment switching. *Statistics in Medicine* 35: 1423-1440.

Concorde Coordinating Committee. (1994). Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 343: 871-881.

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* 20:2609-2631.

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