Introduction to the rstpm2 package

Mark Clements
Karolinska Institutet

Abstract

This vignette outlines the methods and provides some examples for link-based survival models as implemented in the R **rstpm2** package.

Keywords: survival, splines.

1. Background and theory

Link-based survival models provide a flexible and general approach to modelling survival or time-to-event data. The survival function $S(t|x)$ to time t for covariates x is defined in terms of a link function G and a linear prediction $\eta(t,x)$, such that

$$S(t|x) = G(\eta(t,x))$$

where η is a function of both time and covariates x. The linear predictor can be constructed in a flexible manner. Royston and Parmar (2003) focused on time being modelled using natural splines for log-time, including left truncation and relative survival. We have implemented the Royston-Parmar model class and extended it in several ways, allowing for: (i) general parametric models for $\eta(t,x)$, including B-splines and natural splines for different transformations of time; (ii) general semi-parametric models for $\eta(t,x)$ including penalised smoothers together with unpenalised parametric functions; (iii) interval censoring; and (iv) frailties using Gamma and log-Normal distributions.

A more detailed theoretical development is available from the paper by Liu, Pawitan and Clements (available on request).

2. Mean survival

This has a useful interpretation for causal inference.

$E_Z(S(t|Z,X=1)) - E_Z(S(t|Z,X=0))$

```
fit <- rstpm()
predict(fit,type="meansurvdiff",newdata=data)
```

3. Cure models

For cure, we use the melanoma dataset used by Andersson and colleagues for cure models with Stata's stpm2 (see http://www.pauldickman.com/survival/).

Initially, we merge the patient data with the all cause mortality rates.

```
> data(popmort, package="rstpm2")
> data(colon,package="rstpm2")
> popmort2 <- transform(popmort,exitage=age,exityear=year,age=NULL,year=NULL)
> colon2 <- within(colon, {
+   status <- ifelse(surv_mm>120.5,1,status)
+   tm <- pmin(surv_mm,120.5)/12
+   exit <- dx+tm*365.25
+   sex <- as.numeric(sex)
+   exitage <- pmin(floor(age+tm),99)
+   exityear <- floor(yydx+tm)
+   ##year8594 <- (year8594=="Diagnosed 85-94")
+ })
> colon2 <- merge(colon2,popmort2)
```

For comparisons, we fit the relative survival model without and with cure.

```
> fit0 <- stpm2(Surv(tm,status %in% 2:3)~I(year8594=="Diagnosed 85-94"),
+               data=colon2,
+               bhazard=colon2$rate, df=5)

> summary(fit <- stpm2(Surv(tm,status %in% 2:3)~I(year8594=="Diagnosed 85-94"),
+                      data=colon2,
+                      bhazard=colon2$rate,
+                      df=5,cure=TRUE))

Maximum likelihood estimation

Call:
mle2(minuslogl = negll, start = coef, eval.only = TRUE, vecpar = TRUE,
    gr = function (beta, kappa = 1)
    {
        if (interval)
            stop("Gradient not implemented for interval-censored data.")
        localargs <- args
        localargs$kappa <- kappa
        localargs$return_type <- "gradient"
        return(.Call("model_output", localargs, package = "rstpm2"))
    }, control = list(parscale = c(1, 1, 1, 1, 1, 1, 1), maxit = 300),
    lower = -Inf, upper = Inf)

Coefficients:
```

```
                                    Estimate Std. Error  z value     Pr(z)
(Intercept)                        -3.977323   0.054778 -72.6082 < 2.2e-16
I(year8594 == "Diagnosed 85-94")TRUE -0.155612   0.025088  -6.2027 5.551e-10
nsx(log(tm), df = 5, cure = TRUE)1    3.323191   0.053165  62.5066 < 2.2e-16
nsx(log(tm), df = 5, cure = TRUE)2    3.628630   0.053159  68.2594 < 2.2e-16
nsx(log(tm), df = 5, cure = TRUE)3    1.634847   0.022465  72.7743 < 2.2e-16
nsx(log(tm), df = 5, cure = TRUE)4    6.592021   0.111504  59.1194 < 2.2e-16
nsx(log(tm), df = 5, cure = TRUE)5    3.371809   0.042788  78.8027 < 2.2e-16

(Intercept)                        ***
I(year8594 == "Diagnosed 85-94")TRUE ***
nsx(log(tm), df = 5, cure = TRUE)1   ***
nsx(log(tm), df = 5, cure = TRUE)2   ***
nsx(log(tm), df = 5, cure = TRUE)3   ***
nsx(log(tm), df = 5, cure = TRUE)4   ***
nsx(log(tm), df = 5, cure = TRUE)5   ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

-2 log L: 42190.77
```

```
> predict(fit,head(colon2),se.fit=TRUE)

   Estimate     lower     upper
1 0.8610828 0.8542898 0.8675842
2 0.7934651 0.7850103 0.8016309
3 0.6967400 0.6863191 0.7068926
4 0.8610828 0.8542898 0.8675842
5 0.8221243 0.8143226 0.8296334
6 0.8610828 0.8542898 0.8675842
```

The estimate for the year parameter from the model without cure is within three significant figures with that in Stata. For the predictions, the Stata model gives:

```
     +---------------------------------+
     |      surv   surv_lci   surv_uci |
     |---------------------------------|
  1. | .86108264   .8542898   .8675839 |
  2. | .79346526   .7850106   .8016309 |
  3. | .69674037   .6863196   .7068927 |
  4. | .86108264   .8542898   .8675839 |
  5. | .82212425   .8143227   .8296332 |
     |---------------------------------|
  6. | .86108264   .8542898   .8675839 |
     +---------------------------------+
```

We can estimate the proportion of failures at the end of follow-up using:

```
> newdata.eof <- data.frame(year8594 = unique(colon2$year8594),
+                           tm=max(colon2$tm))
> 1-predict(fit0, newdata.eof, type="surv", se.fit=TRUE)
```

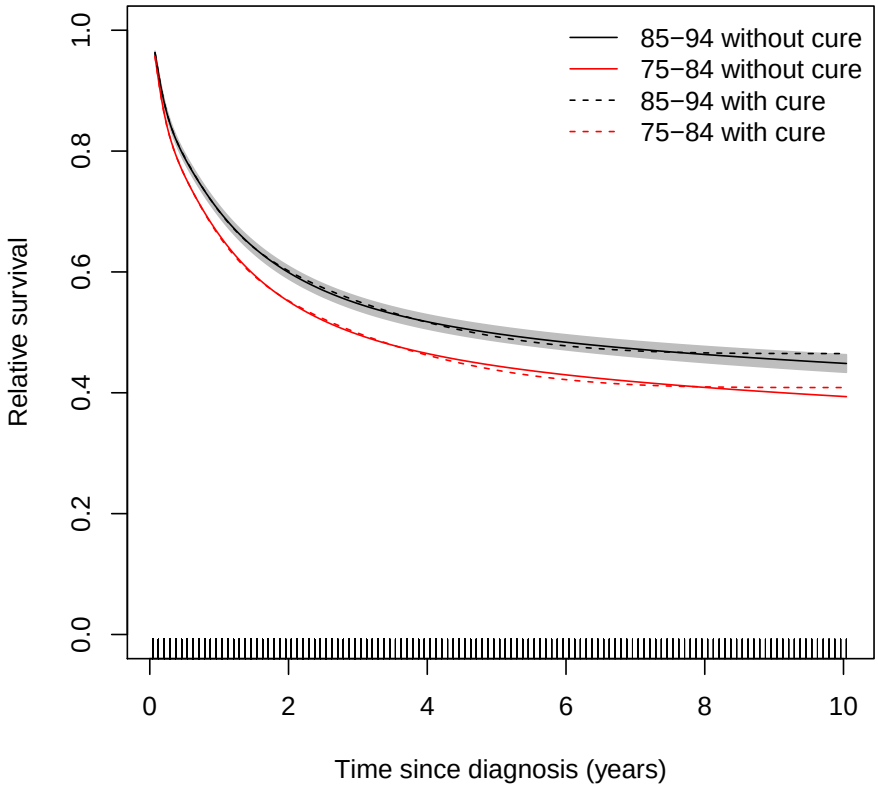
```
   Estimate     lower     upper
1 0.6063703 0.6211752 0.5916057
2 0.5515140 0.5661328 0.5370119
```

```
> 1-predict(fit, newdata.eof, type="surv", se.fit=TRUE)
```

```
   Estimate     lower     upper
1 0.5913317 0.6055025 0.5772183
2 0.5350824 0.5485383 0.5217445
```

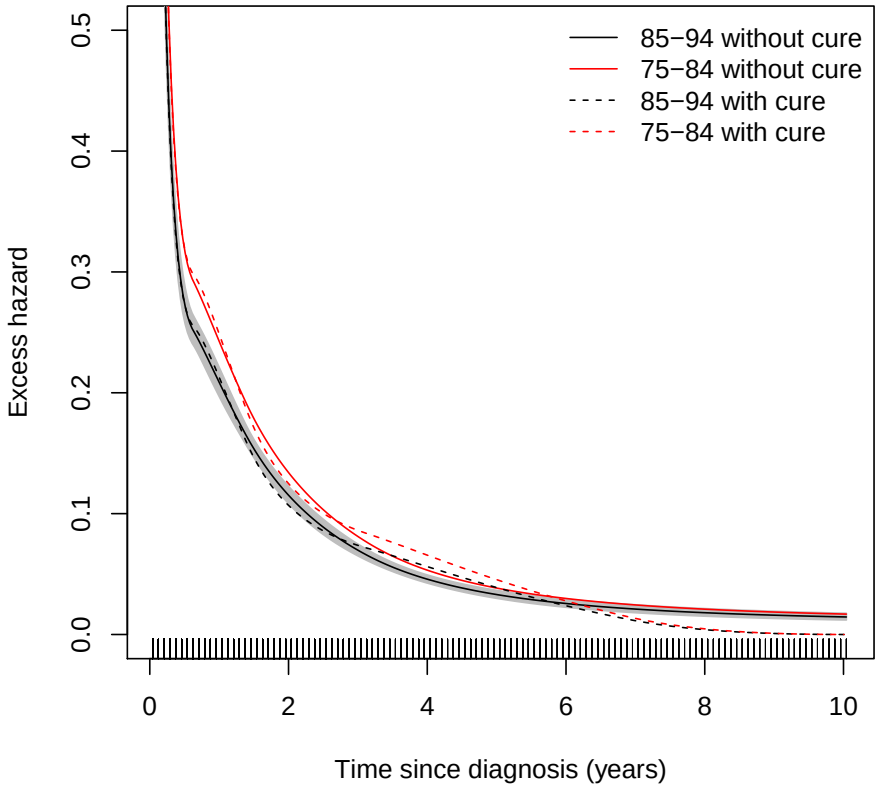
We can plot the predicted survival estimates:

```
> plot(fit0,newdata=data.frame(year8594 = "Diagnosed 85-94"), ylim=0:1,
+      xlab="Time since diagnosis (years)", ylab="Relative survival")
> plot(fit0,newdata=data.frame(year8594 = "Diagnosed 75-84"),
+      add=TRUE,line.col="red",rug=FALSE)
> plot(fit,newdata=data.frame(year8594 = "Diagnosed 85-94"),
+      add=TRUE,ci=FALSE,lty=2,rug=FALSE)
> plot(fit,newdata=data.frame(year8594="Diagnosed 75-84"),
+      add=TRUE,rug=FALSE,line.col="red",ci=FALSE,lty=2)
> legend("topright",c("85-94 without cure","75-84 without cure",
+                     "85-94 with cure","75-84 with cure"),
+        col=c(1,2,1,2), lty=c(1,1,2,2), bty="n")
```



And the hazard curves:

```
> plot(fit0,newdata=data.frame(year8594 = "Diagnosed 85-94"),
+      ylim=c(0,0.5), type="hazard",
+      xlab="Time since diagnosis (years)",ylab="Excess hazard")
> plot(fit0,newdata=data.frame(year8594 = "Diagnosed 75-84"),
+      type="hazard",
+      add=TRUE,line.col="red",rug=FALSE)
> plot(fit,newdata=data.frame(year8594 = "Diagnosed 85-94"),
+      type="hazard",
+      add=TRUE,ci=FALSE,lty=2,rug=FALSE)
> plot(fit,newdata=data.frame(year8594="Diagnosed 75-84"),
+      type="hazard",
+      add=TRUE,rug=FALSE,line.col="red",ci=FALSE,lty=2)
> legend("topright",c("85-94 without cure","75-84 without cure",
+                     "85-94 with cure","75-84 with cure"),
+        col=c(1,2,1,2), lty=c(1,1,2,2), bty="n")
```



Affiliation:

Mark Clements
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet
Email: mark.clements@ki.se