Recreating a Royston and Altman paper

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August 26, 2021

1 Introduction

The paper by Royston and Altman [1] on Cox model validation is a delightfully clear exposition of the important principles. As well, they made use of, and documented, data sets that others can use. The `rotterdam` and `gbsg` data sets from their work have been incorporated into the survival package.

This short note describes that process, and more importantly, attempts to recreate some of the results of their paper as a way of validating that the data was created correctly.

2 Rotterdam data

The main paper refers to a web site `www.stata-press.com/data/fpsaus.html`. That in turn hosts all of the data sets and Stata code for a book by Royston and Lampert [2]. Following the URL leads to a data set `rott2`, imported from a Stata file `rott2.dta`. Variable labels make it fairly easy to set up the new data set. There were a few variables that we did not copy.

- `mf, mfi`: time to metastisis
- `enodes`: exp(-0.12*nodes)
- `pr_1` : log(pr +1)
- `enod_1`: enodes*enodes
- `recent`: year of surgery dichomized as $\leq$ 1987 (0) vs $\geq$ 1988 (1)
- `_st`: 1 for all rows
- `_d` : equal to `recur` if rtime $<$ 10 years, 0 otherwise
- `_t` : recurrence time, truncated at 10 years
- `_t0`: 0 for all rows

The Rotterdam data contains 2982 subjects.

The article makes the statement that the endpoint for fits to the Rotterdam data is relapse-free survival (RFS), the earlier of death or relapse, censored at 84 months, and that they will omit

those with nodes=0. It also has the statement that "The Rotterdam data (with RFS truncated to 120 months) can be downloaded from www.stat-press.com.", I expect this latter statement has caused many to assume that the `(_t, _d)` pair in that data set contains RFS values, but examination shows that they encode 10 year relapse.

[redacted]< working copy Tabel 1 in the paper shows covariate distributions for 1546 subjects, the number with nodes > 0. The values below, from the R data set, match the values in the table. ======= Table 1 shows the distribution for 1546 subjects, the number with nodes > 0. The distribution below, from the R data set, matches the table with the exception of the mean estrogen receptor (ER) level. If I winsorize that at 2000 to exclude large outliers, however, I match the table. [redacted]> destination

```
> rotterdam2 <- subset(rotterdam, nodes>0)
> table(rotterdam2$size)
 <=20 20-50   >50
  501   783   262
> table(rotterdam2$meno)
  0   1
628 918
> table(rotterdam2$hormon)
   0    1
1207  339
> round(c(mean(rotterdam2$age), sd(rotterdam2$age)), 1)
[1] 56 13
> round(c(mean(rotterdam2$nodes),sd(rotterdam2$nodes)), 1)
[1] 5.2 4.9
> round(c(mean(rotterdam2$pgr),  sd(rotterdam2$pgr)), 1)
[1] 156.2 299.4
> round(c(mean(rotterdam2$er), sd(rotterdam2$er)),1)
[1] 165.1 267.3
```

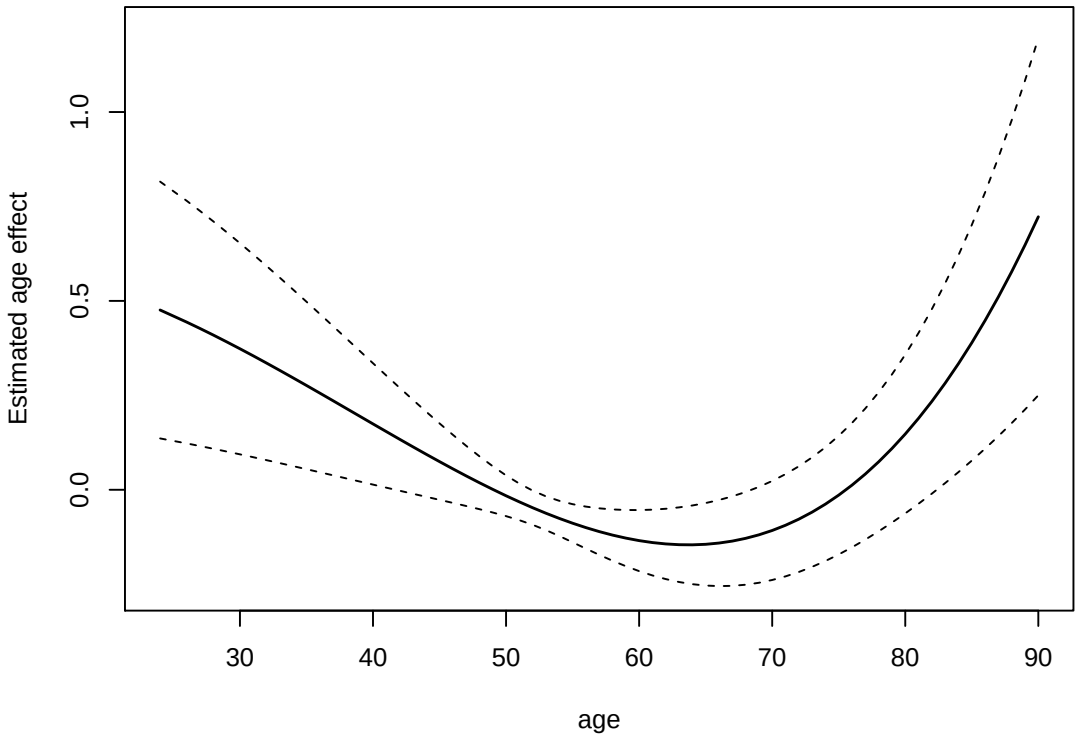
The Cox model in the paper was fit using fractional polynomials. If we use the RPS at 84 months = 7 years, the model fit looks like the following. As noted in the help file for the rotterdam data, there are 43 subjects who have died without recurrence, but whose death time is greater than the censoring time for recurrence; and exactly how best to handle these is debatable. Consider subject 191 who is censored for recurrence at 13 months, with death at 52 months. We could code this subject as censored at 13 or an RFS event at 52. The latter implicitly assumes that there was no recurrence in the unobserved period from 13 to 52 months, over 3 years. For a tertiary care center in the US, where a subject is likely to return to their home physician after the primary cancer treatment, this is not a tenable assumption. If they had recurred, we would not have found out about it due to disjoint medical records systems, and the safer course is to censor at 13. In a national health care system such as the Netherlands, where this study was conducted, such an assumption is more reasonable. In this case, ignoring the gaps and using the later death leads to 965 events, which matches the desciption on page 3 of the paper.

```
> y7 <- round(7*365.25)  # 7 years or 84 months
> r7 <- rotterdam2
> r7$recur <- ifelse(r7$rtime > y7, 0, r7$recur)
> r7$rtime <- pmin(r7$rtime, y7)
> r7$death <- ifelse(r7$dtime > y7, 0, r7$death)
> r7$dtime <- pmin(r7$dtime, y7)
> r7$rfstime <- with(r7, ifelse(recur==1, rtime, dtime))  # time to recur or death
> r7$rfs <- with(r7, pmax(death, recur))
> table(r7$rfs)
  0   1
581 965
> agefun <- function(x) cbind((x/100)^3, (x/100)^3 * log(x/100))
> cfit <- coxph(Surv(rfstime, rfs) ~ agefun(age) + meno + size +
                      I(1/sqrt(nodes)) + I(er/1000) + hormon,
                data= r7, ties="breslow")
> cbind("cfit"= round(coef(cfit),3),
        "paper"= c(1.07, 9.13, 0.46, 0.23, 0.31, -1.74, -0.34, -0.35))
                    cfit paper
agefun(age)1       1.074  1.07
agefun(age)2       9.133  9.13
meno               0.463  0.46
size20-50          0.234  0.23
size>50            0.541  0.31
I(1/sqrt(nodes)) -1.737 -1.74
I(er/1000)       -0.338 -0.34
hormon           -0.346 -0.35
```

The dataset is also available from Sauerbrei et al [3]. That version does not have the overall survival and death variables, but includes two categorical variables `sized1` = 1 if size $>$ 20 and `sized2` = 1 if size $>$ 50, which match the variable names found in table 2, and resolves the coefficent difference we see above for the size $>$ 50 group: our coefficient is the sum of the `sized1` and `sized2` coefficients in their table. They had used contrasts of group 2 vs. 1 and 3 vs. 2, while we have 2 vs. 1 and 3 vs. 1.

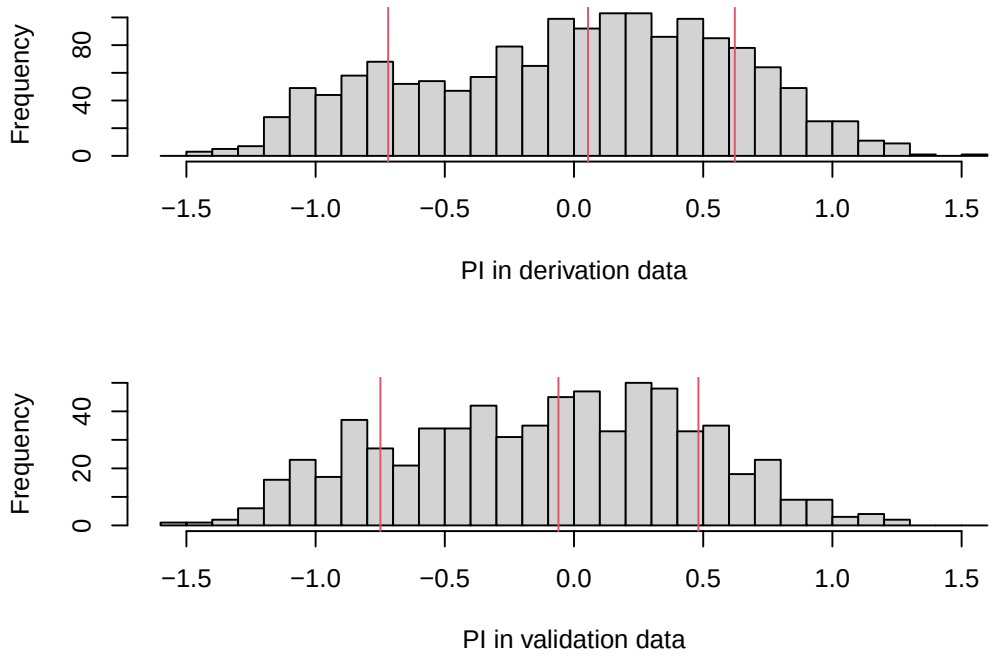
A termplot reveals the non-linear age effect. Both young and old subjects are at higher risk.

```
> termplot(cfit, term=1, ylab="Estimated age effect", col.term=1, col.se=1,
           se=TRUE)
```



<<<<<<< working copy ======= The histogram of the risk scores is not a perfect match, either, but again very close in its overall form.

```
> PI1 <- predict(cfit) - mean(predict(cfit))
> hist(PI1, breaks=seq(-1.5, 1.6, by=.1), xlab="Validation data", man=NULL)
```



An alternate explantion would be that the authors also used the derived variables `_t, _d` that contain 120 month progression. The coefficients with that endpoint are far different, however. We also tried censoring events at 2510 days, which gives 965 events, but that leads to only minor changes in the coefficients and did not improve the agreement with table 1. Likewise for the use of a winsorized value of er. The exact reason for a count of 965 vs. 968 events remains obscure, but we expect it is the underlying cause.

▬> destination

3 GBSG data

The GBSG data set found in the reference is somewhat simpler, in that it only contains the RFS outcome. The GBSG data set has no node-negative subjects, and tumor size is continuous rather than being categorical.

The data set has again, exact agreement with table 1.

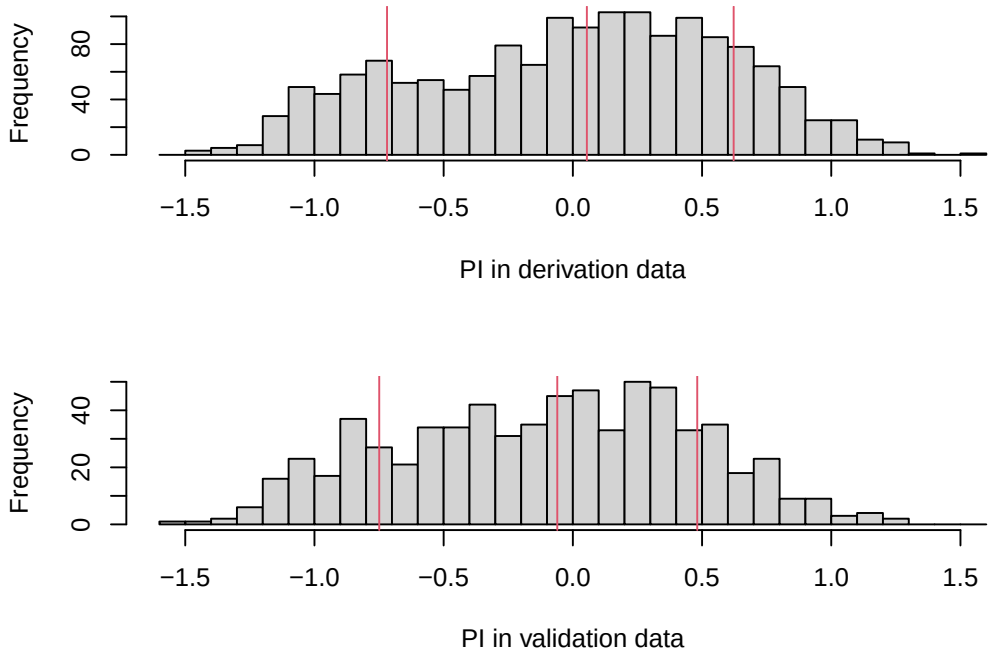
```
> table(cut(gbsg$size, c(0, 20, 50, 150), c("<=20", "20-50", ">50")))
 <=20 20-50   >50
  180   453    53
> table(gbsg$meno)
  0   1
290 396
> table(gbsg$hormon)
```

```
  0   1
440 246
> round(c(mean(gbsg$age), sd(gbsg$age)), 1)
[1] 53.1 10.1
> round(c(mean(gbsg$nodes),sd(gbsg$nodes)), 1)
[1] 5.0 5.5
> round(c(mean(gbsg$pgr), sd(gbsg$pgr)), 1)
[1] 110.0 202.3
> round(c(mean(gbsg$er),  sd(gbsg$er)), 1)
[1]  96.3 153.1
```

Validation is made easier if we create a version of the GBSG data set whose variable names exactly match the Rotterdam derivation data set. Then create a PI variable using the rotterdam fit.

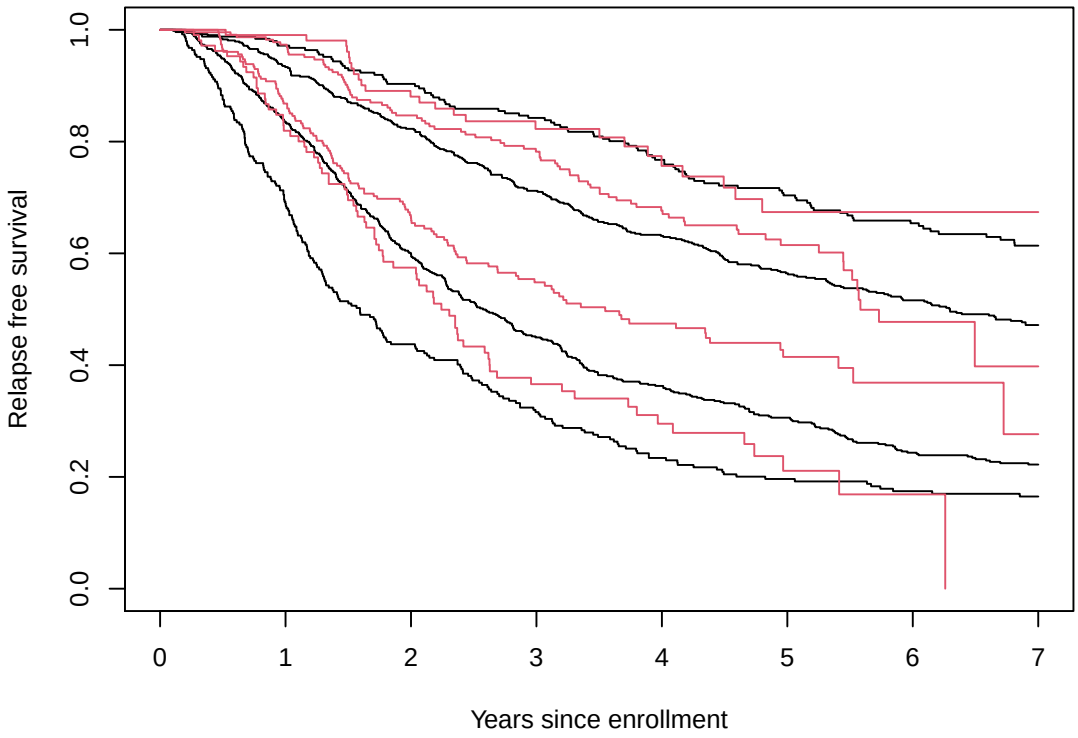
```
> gbsg2 <- gbsg
> gbsg2$size <- cut(gbsg$size, c(0, 20, 50, 150), c("<=20", "20-50", ">50"))
> gbsg2$rfs <- gbsg2$status
> gbsg2$PI <- predict(cfit, newdata=gbsg2)
```

The histogram of the risk scores appears to match that in Figure 1.



And here is figure 2, comparing the KM curves, by PI group.

```
> grp1 <- cut(PI1, quantile(PI1, c(0, .16, .5 , .84, 1)), include.lowest=TRUE)
> km1 <- survfit(Surv(rfstime, rfs) ~ grp1, r7)
> plot(km1, xscale=365.25, xlab="Years since enrollment",
      ylab="Relapse free survival")
> grp2 <- cut(PI2, quantile(PI2, c(0, .16, .5 , .84, 1)), include.lowest=TRUE)
> km2 <- survfit(Surv(rfstime, rfs) ~ grp2, gbsg2)
> lines(km2, col=2)
```



The curves for the validation group have similar spread to those for the development data set. The GBSG data set shows fewer early deaths than predicted; however, this is not surprising. The Rotterdam study enrolled all breast cancer subjects while the GBSG data is from a clinical trial, and cancer clincial trial subjects very often have an initial "death honeymoon", for a variety of reasons: eligibility criteria often explicitly ask for subjects with a minimal expected survival, or implicitly so by excluding those with low Karnofsky scores, while subjects who are in extremis are themselves less likely to volunteer.

References

[1] P. Royston and D. G. Altman. External validation of a Cox prognostic model: principles and methods. *BMC Medical Research Methodology*, 13, 2013.

[2] Patrick Royston and Paul C. Lambert. *Flexible parametric survival analysis using Stata: beyond the Cox model*. Stata Press, 2011.

[3] W. Sauerbrei, P. Royston, and M. Look. A new proposal for multivariable modelling of time-varying effects in survival data based on fractional polynomial time-transformation. *Biom J*, 49:453–73, 2007.