NSWPCN Predictor Training

January 13, 2015

1 Preparation

```
library(survival)
library(glmulti)

## Error occurred during initialization of VM
## Could not reserve enough space for object heap

## Error:  package or namespace load failed for 'glmulti'

library(flexsurv)
library(randomForestSRC)

library(reshape2)
library(plyr)
library(ggplot2)

library(MASS)
library(boot)

load("03_NSWPCN_subset.rda")
```

2 Cohort selection and transformation

```
x = data[,c("Patient.Sex", "History.Diagnosis.AgeAt.Cent", "Path.LocationBody", "Path.Size.Cent", "Path.
colnames(x) = c("SexM", "AgeCent", "LocBody", "SizeCent", "Ca199", "A2", "A4")
x$SexM = x$Sex == "M"
x$Ca199 = x$Ca199 > 100

y = Surv(as.numeric(data$History.Death.Date - data$History.Diagnosis.Date), data$History.DSDeath.Event)
# Note no surgery dates, though for almost all pts there were only a few days difference.

temp = NA
temp = ls()
rm(list = temp[!(temp %in% c("x", "y"))])

sel = !is.na(y[,1]) & !is.na(y[,2]) & !is.na(x$A2) & !is.na(x$A4) & !is.na(x$LocBody)
x = x[sel,]
y = y[sel,]
rm(sel)
```

```r
# Remove CA-19-9 measurements as they're mostly missing
x = x[,colnames(x) != "Ca199"]

data = as.data.frame(cbind(Time = y[,1], DSD = y[,2], x))
rm(x, y)
data$DSD = data$DSD == 1
```

3 Data splitting

There's going to be an awful lot of model manipulation and black magic going on. Create a holdout validation set for final model comparison and selection.

```r
set.seed(20150110)
sel.val = sample.int(nrow(data), floor(nrow(data)/5))
sel.val = 1:nrow(data) %in% sel.val
mean(sel.val)

## [1] 0.1967

data.val = data[sel.val,,drop = FALSE]
data = data[!sel.val,,drop = FALSE]
```

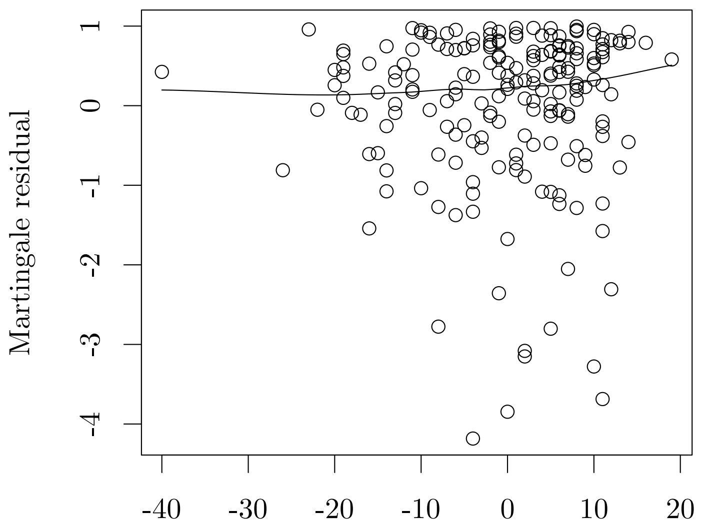
4 EDA

Use the CPH model as a convenient framework for EDA.

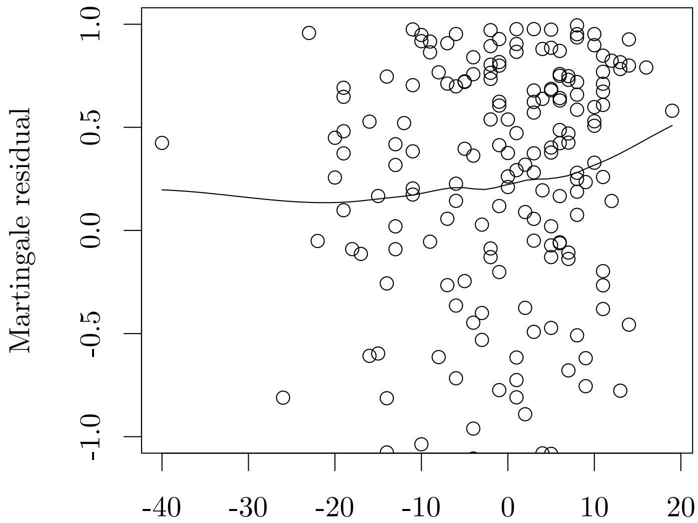
4.1 Functional form

Investigate functional form with martingale residuals.

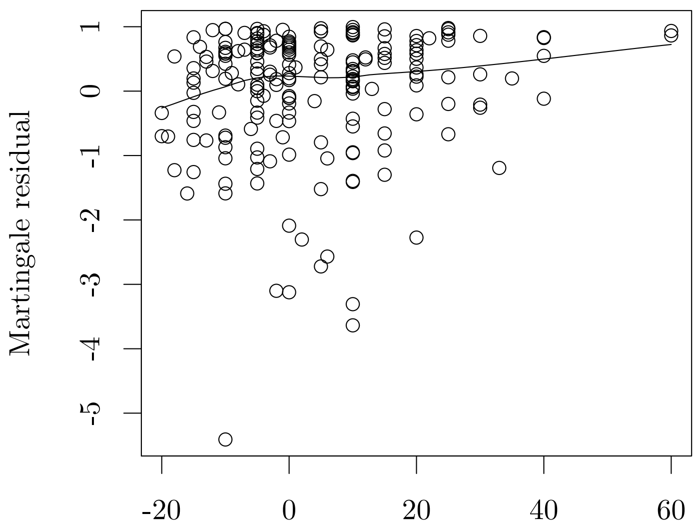
```r
fit.cph.NoAge = coxph(Surv(Time, DSD) ~ SexM + LocBody + SizeCent + A2 + A4, data = data)
scatter.smooth(data$AgeCent, resid(fit.cph.NoAge, type = "martingale"), xlab = "", ylab = "Martingale re
```



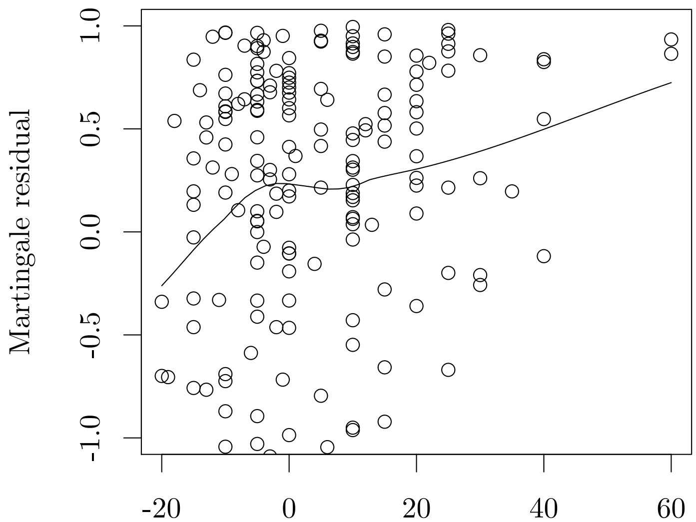
```r
scatter.smooth(data$AgeCent, resid(fit.cph.NoAge, type = "martingale"), xlab = "", ylab = "Martingale re
```




```r
fit.cph.NoSize = coxph(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + A2 + A4, data = data)
scatter.smooth(data$SizeCent, resid(fit.cph.NoSize, type = "martingale"), xlab = "", ylab = "Martingale
```




```r
scatter.smooth(data$SizeCent, resid(fit.cph.NoSize, type = "martingale"), xlab = "", ylab = "Martingale
```



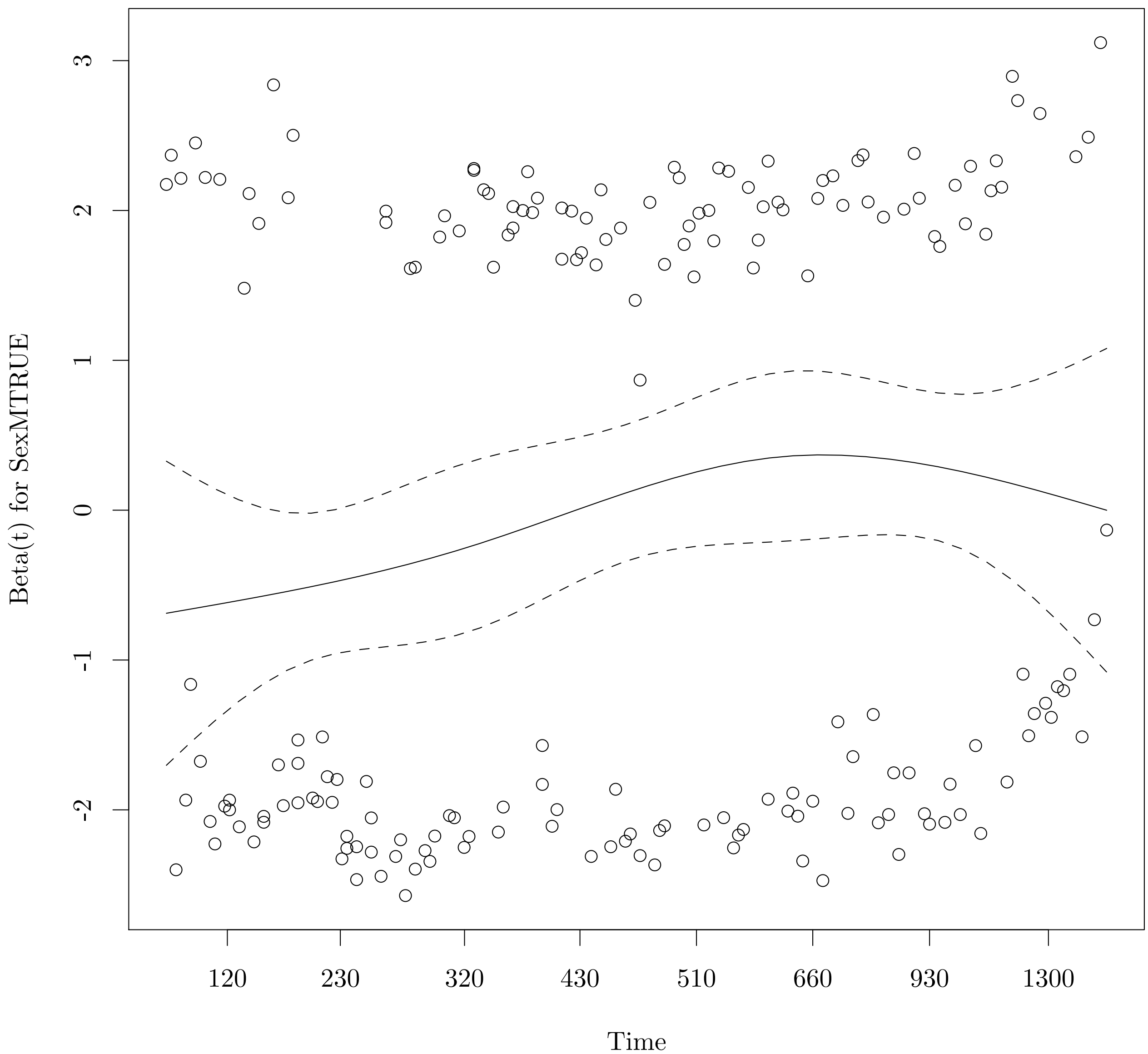
It looks like age has a minor nonlinear component, leading to a quadratic-like U shape. The size relationship appears to have a knee, close to size == 0, around which the relationship is approximately linear.

Model age as: $AgeCent + AgeCent^2$ Model size as: $SizeCent + SizeCentI(SizeCent > 0) \equiv SizeCent + SizeCent_+$

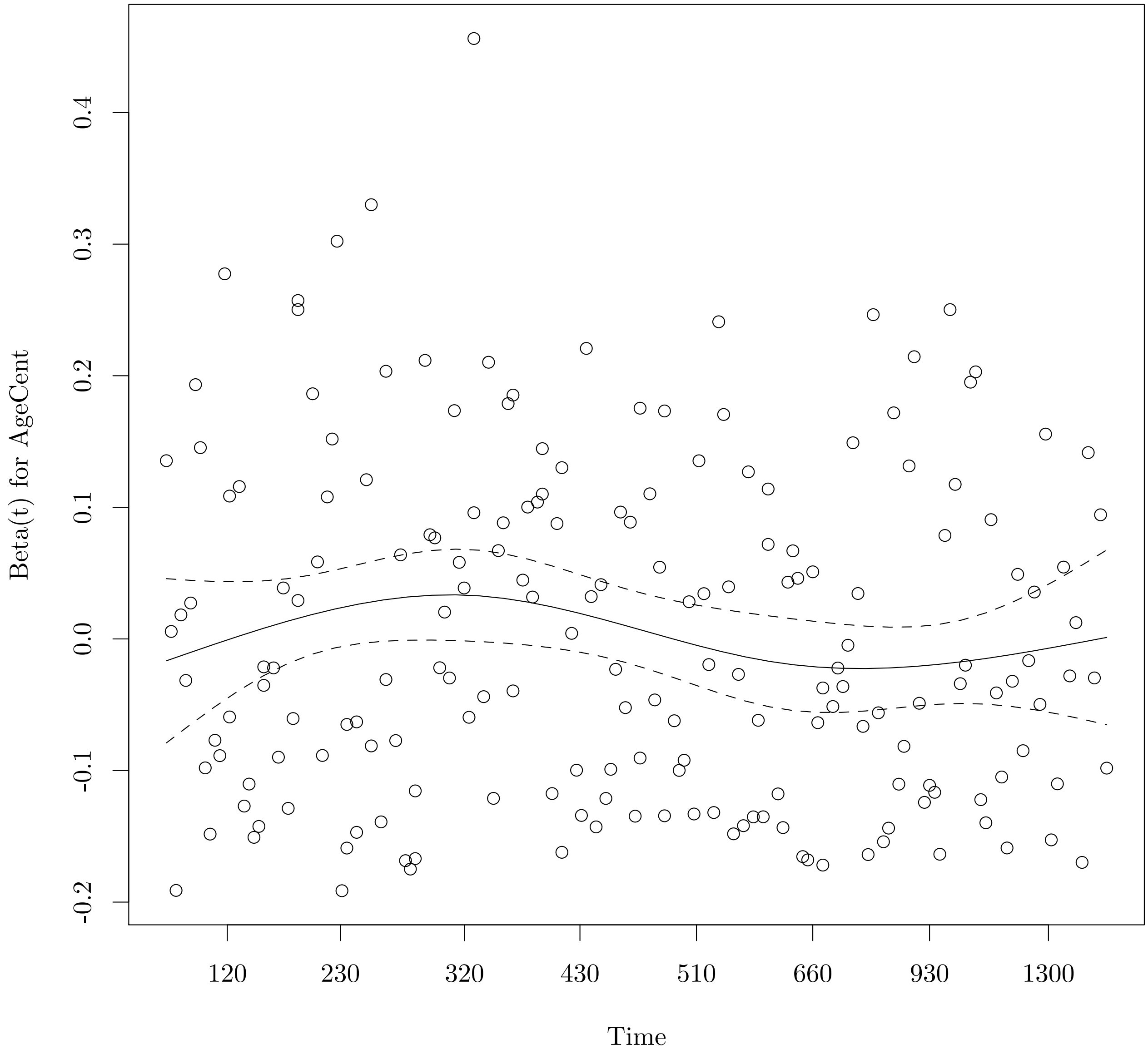
```
data$SizeSmall = data$SizeCent * (data$SizeCent < 0)
data$AgeCent2 = data$AgeCent^2
```

4.2 PH assumption: full model

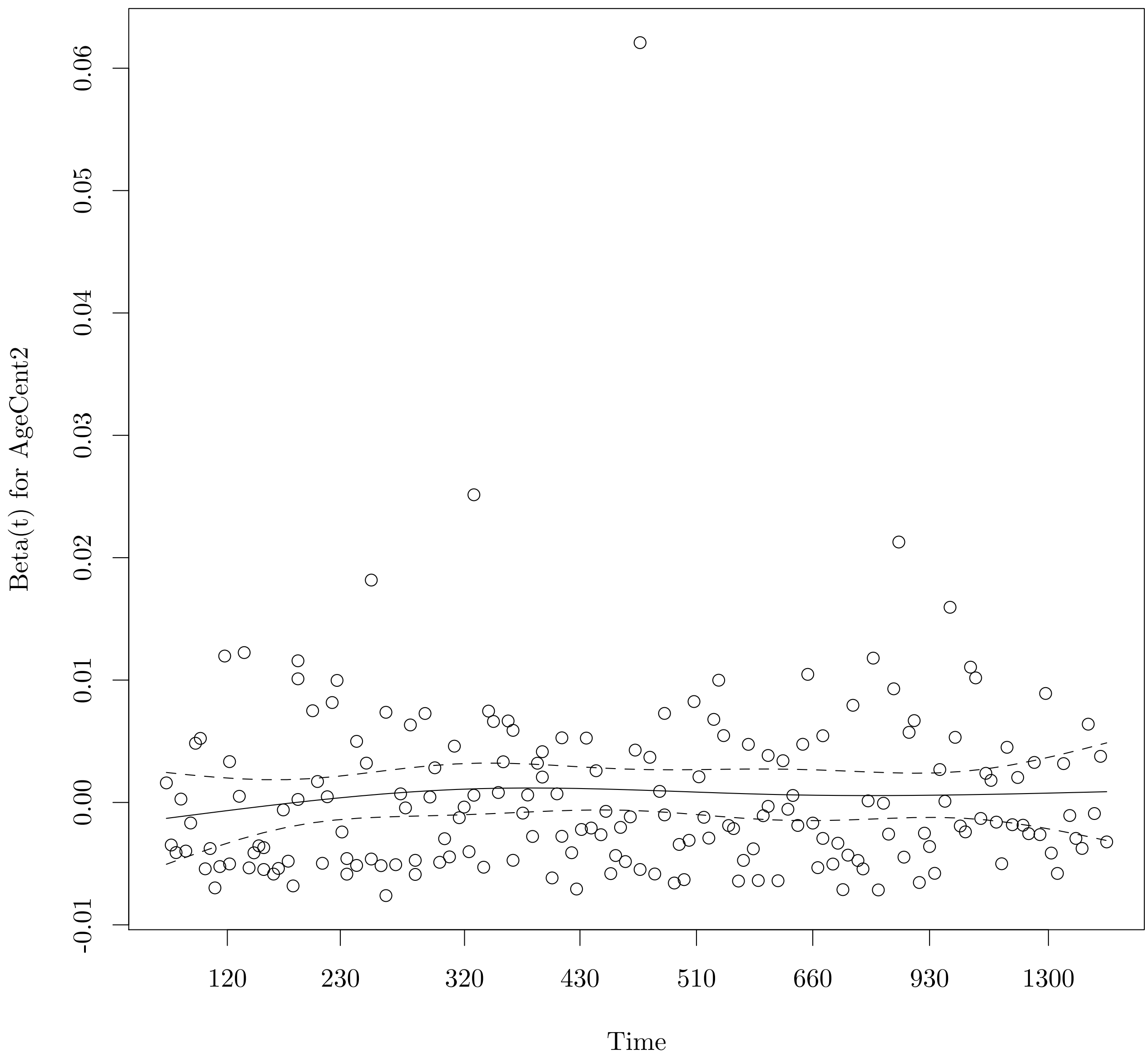
```
fit.cph = coxph(Surv(Time, DSD) ~ SexM + AgeCent + AgeCent2 + LocBody + SizeCent + SizeSmall + A2 + A4,
cox.zph(fit.cph)

##                 rho   chisq      p
## SexMTRUE     0.1520  4.2830 0.0385
## AgeCent     -0.0897  1.5736 0.2097
## AgeCent2     0.0392  0.2733 0.6012
## LocBodyTRUE -0.1287  2.7244 0.0988
## SizeCent     0.0088  0.0168 0.8970
## SizeSmall   -0.0592  0.6803 0.4095
## A2TRUE       0.0533  0.5483 0.4590
## A4TRUE      -0.0596  0.6487 0.4206
## GLOBAL           NA 14.0077 0.0816

plot(cox.zph(fit.cph))
```

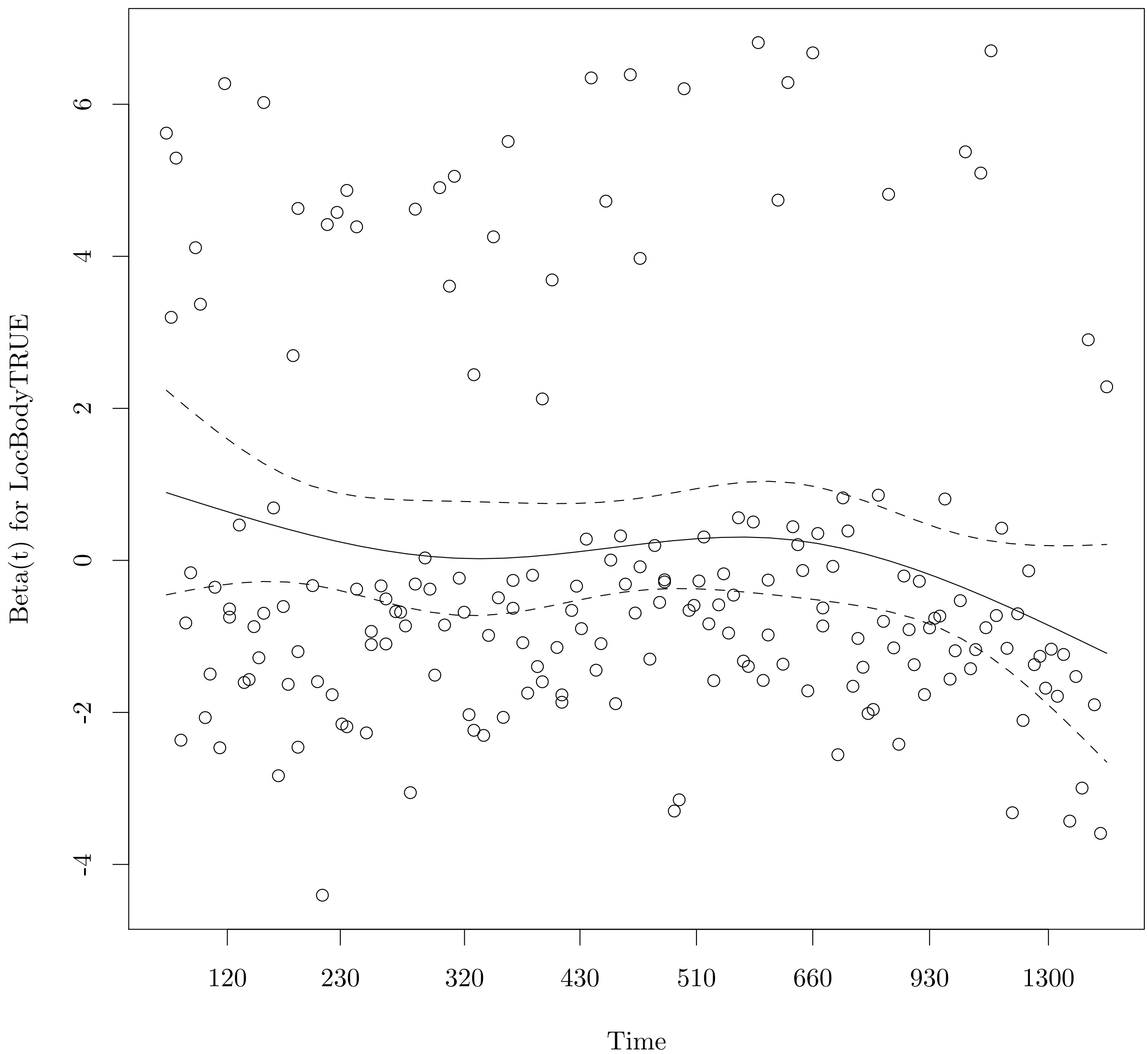


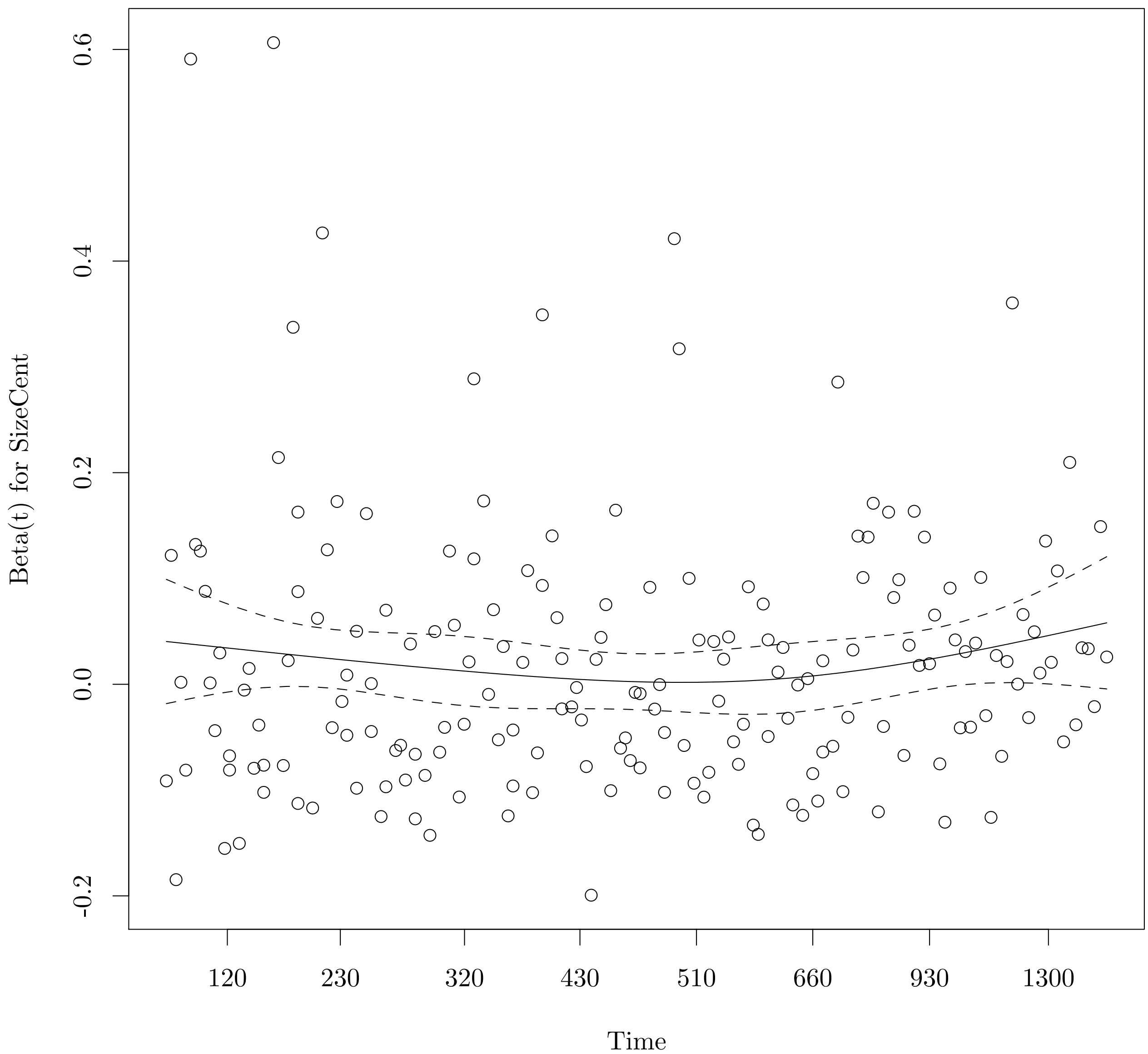
Beta(t) for SexMTRUE
3
2
1
0
-1
-2
120
230
320
430
510
660
930
1300
Time

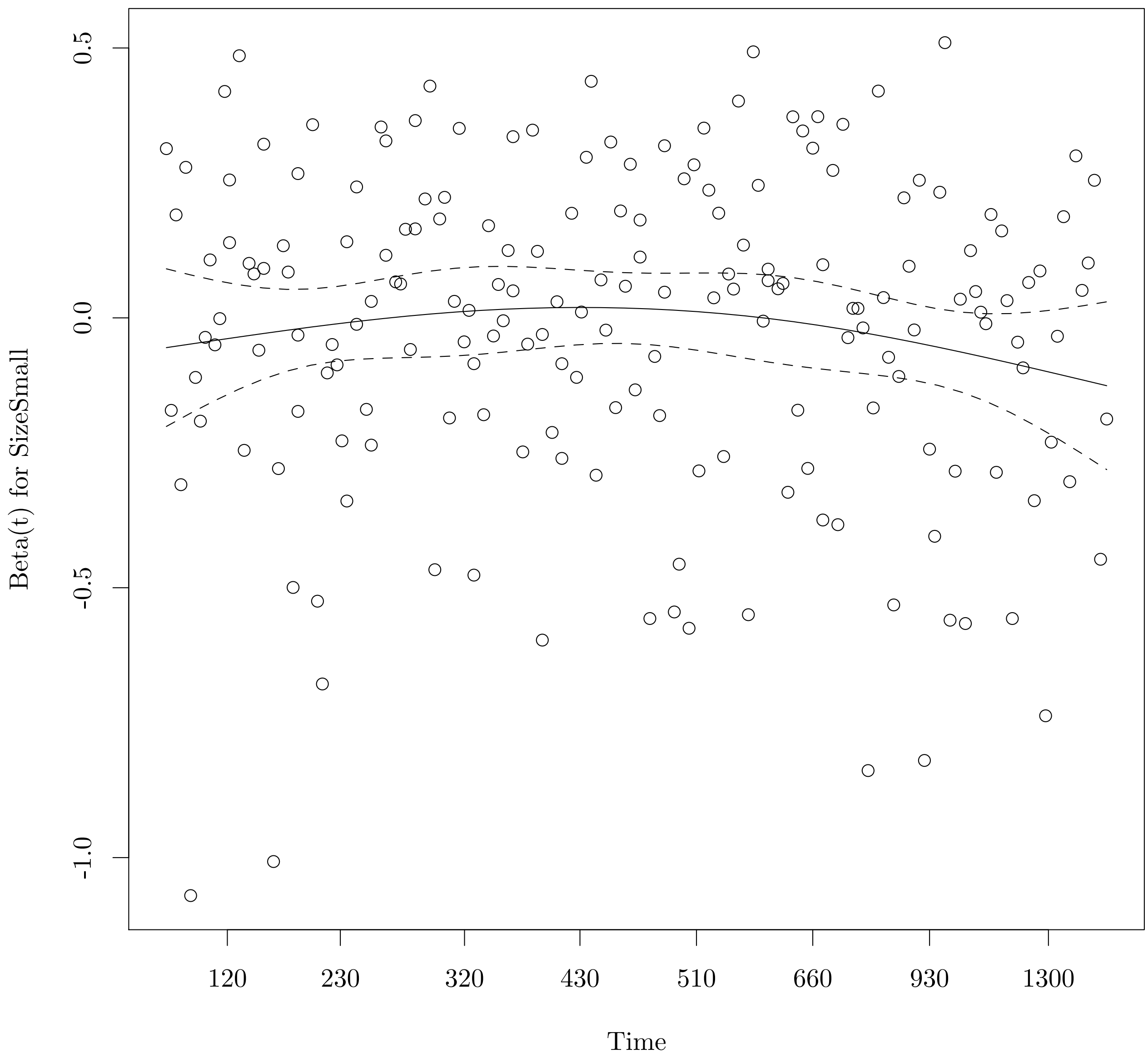


Beta(t) for AgeCent
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
120
230
320
430
510
660
930
1300
Time

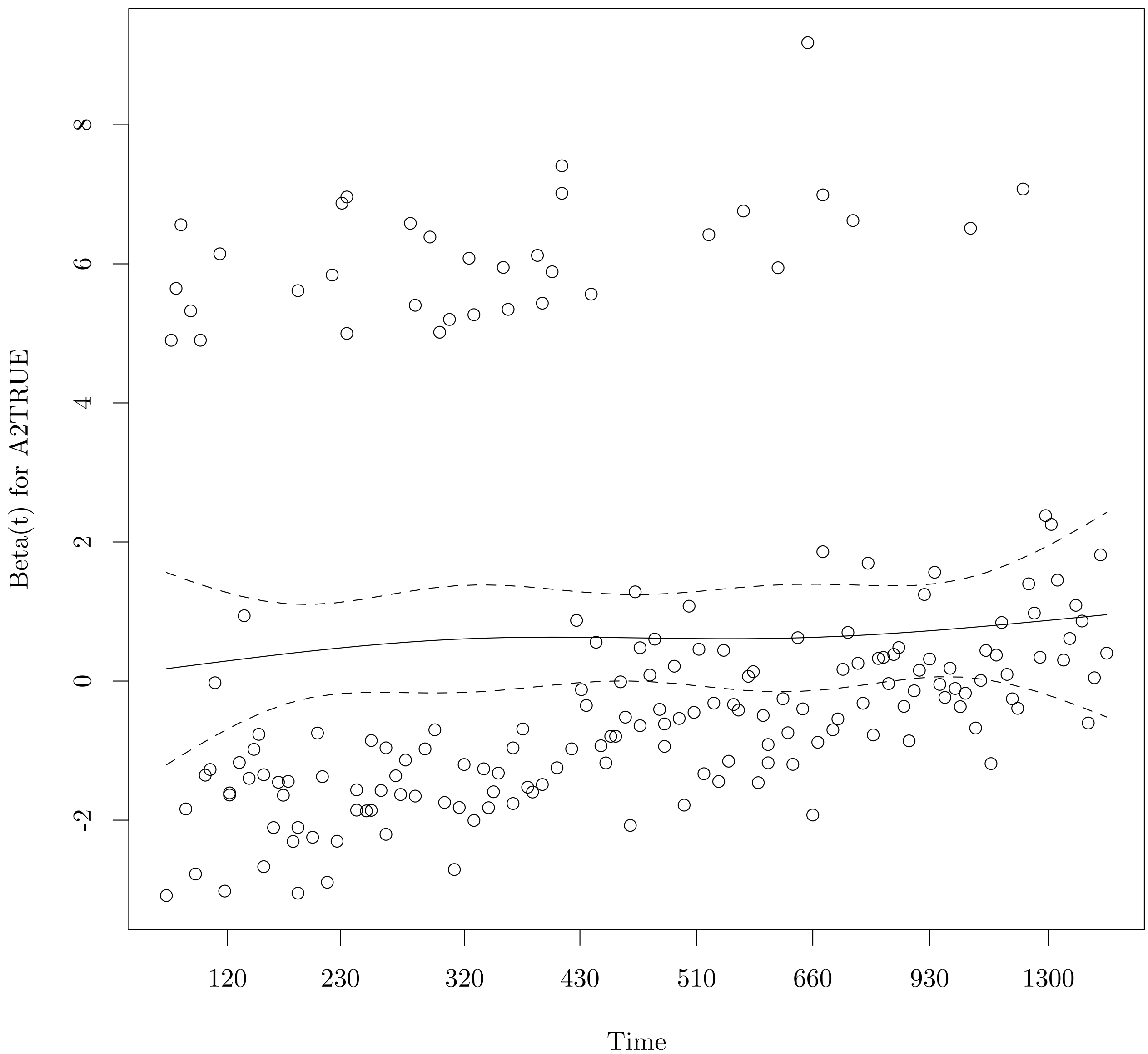

Beta(t) for AgeCent2
0.06
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
120
230
320
430
510
660
930
1300
Time

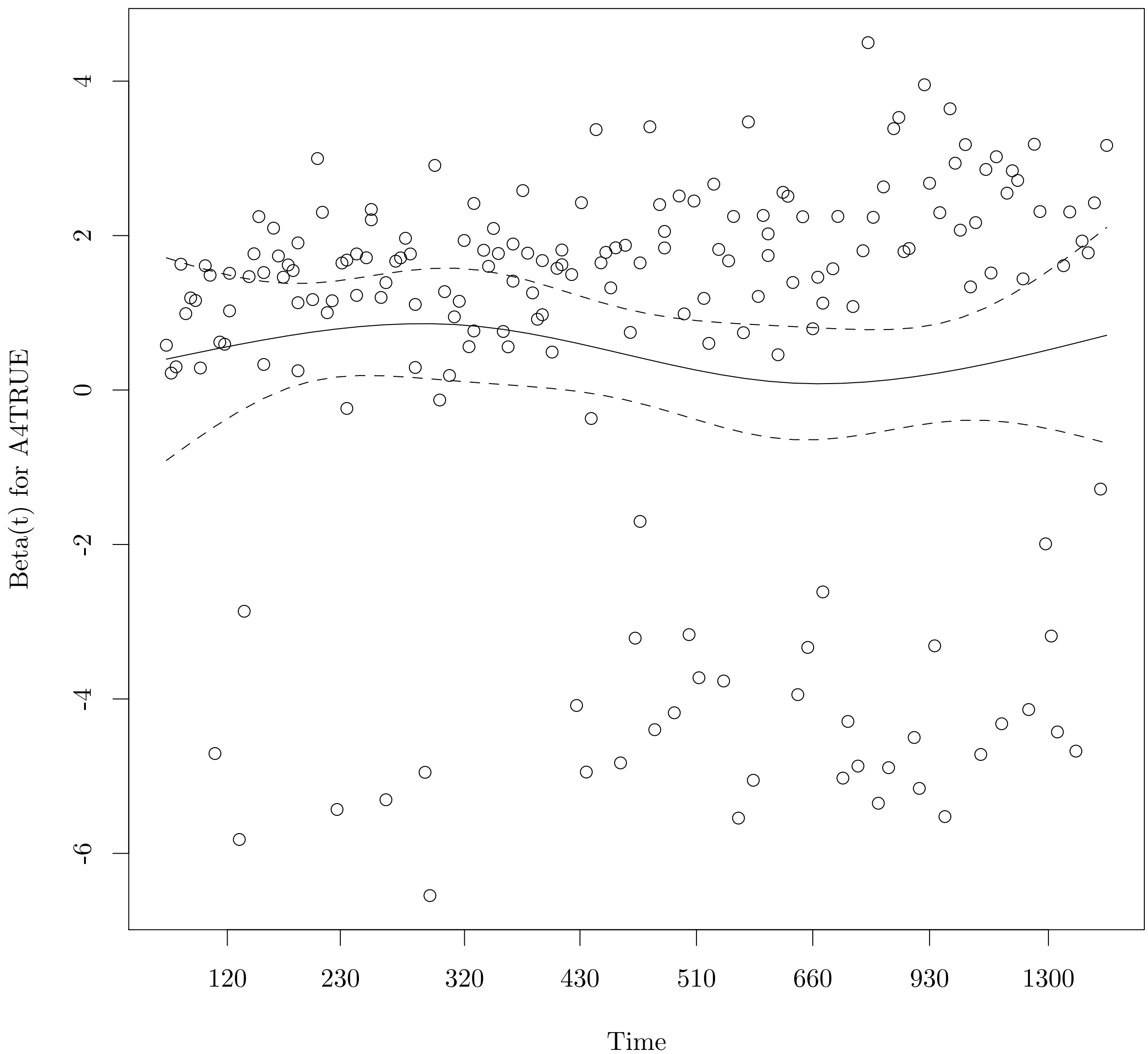

Beta(t) for LocBodyTRUE
-4
-2
0
2
4
6
120
230
320
430
510
660
930
1300
Time


Beta(t) for SizeCent
0.6
0.4
0.2
0.0
-0.2
120
230
320
430
510
660
930
1300
Time



Beta(t) for SizeSmall
0.5
0.0
-0.5
-1.0
120
230
320
430
510
660
930
1300
Time

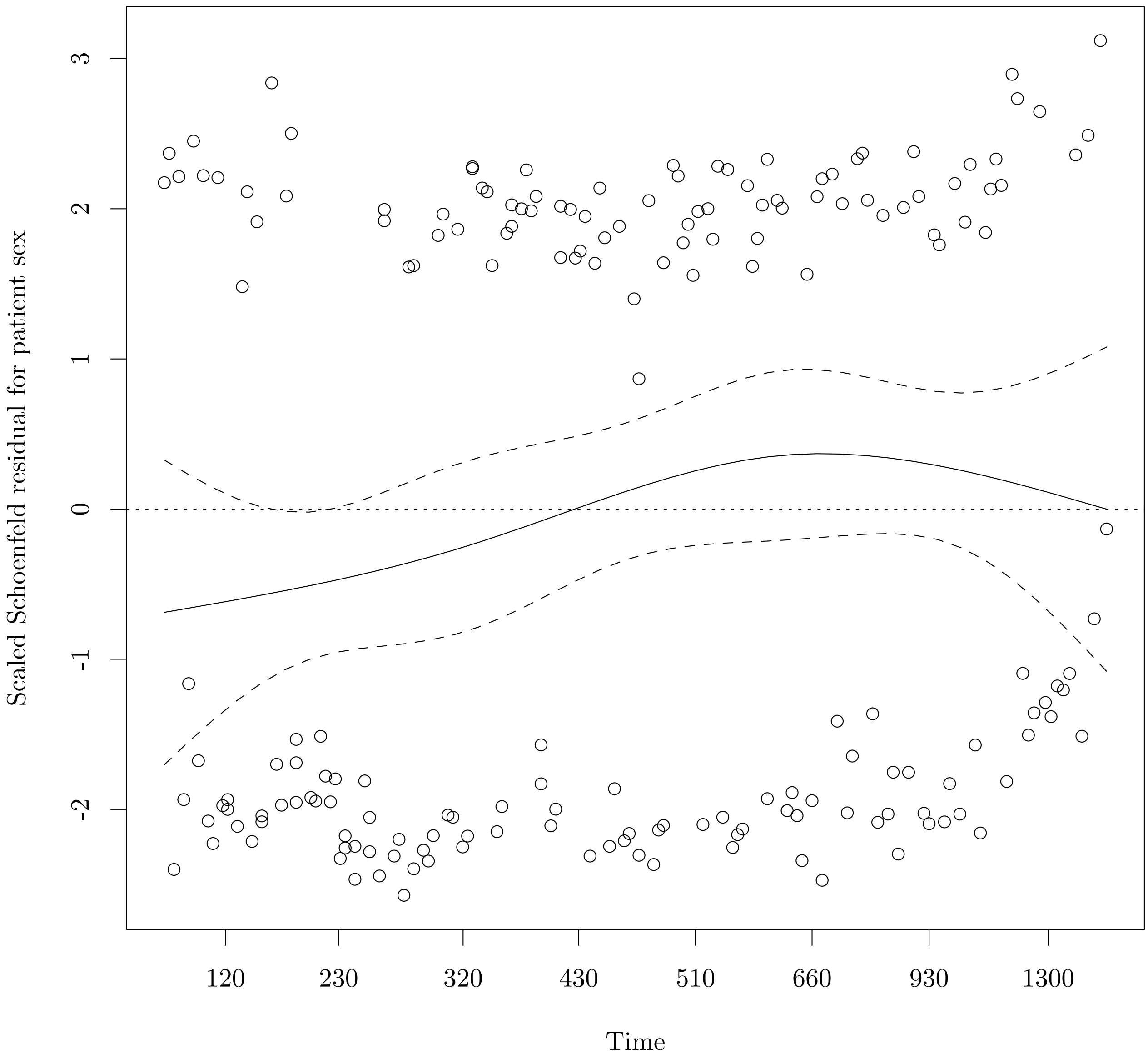

Beta(t) for A2TRUE
-2
0
2
4
6
8
120
230
320
430
510
660
930
1300
Time




```
temp = function (x, resid = TRUE, se = TRUE, df = 4, nsmo = 40, var, ...) {
    xx <- x$x
    yy <- x$y
    d <- nrow(yy)
    df <- max(df)
    nvar <- ncol(yy)
    pred.x <- seq(from = min(xx), to = max(xx), length = nsmo)
    temp <- c(pred.x, xx)
    lmat <- ns(temp, df = df, intercept = TRUE)
    pmat <- lmat[1:nsmo, ]
    xmat <- lmat[-(1:nsmo), ]
    qmat <- qr(xmat)
    if (qmat$rank < df)
        stop("Spline fit is singular, try a smaller degrees of freedom")
    if (se) {
        bk <- backsolve(qmat$qr[1:df, 1:df], diag(df))
        xtx <- bk %*% t(bk)
```

```
        seval <- d * ((pmat %*% xtx) * pmat) %*% rep(1, df)
    }
    ylab <- paste("Beta(t) for", dimnames(yy)[[2]])
    if (missing(var))
        var <- 1:nvar
    else {
        if (is.character(var))
            var <- match(var, dimnames(yy)[[2]])
        if (any(is.na(var)) || max(var) > nvar || min(var) <
            1)
            stop("Invalid variable requested")
    }
    if (x$transform == "log") {
        xx <- exp(xx)
        pred.x <- exp(pred.x)
    }
    else if (x$transform != "identity") {
        xtime <- as.numeric(dimnames(yy)[[1]])
        indx <- !duplicated(xx)
        apr1 <- approx(xx[indx], xtime[indx], seq(min(xx), max(xx),
            length = 17)[2 * (1:8)])
        temp <- signif(apr1$y, 2)
        apr2 <- approx(xtime[indx], xx[indx], temp)
        xaxisval <- apr2$y
        xaxislab <- rep("", 8)
        for (i in 1:8) xaxislab[i] <- format(temp[i])
    }
    for (i in var) {
        y <- yy[, i]
        yhat <- pmat %*% qr.coef(qmat, y)
        if (resid)
            yr <- range(yhat, y)
        else yr <- range(yhat)
        if (se) {
            temp <- 2 * sqrt(x$var[i, i] * seval)
            yup <- yhat + temp
            ylow <- yhat - temp
            yr <- range(yr, yup, ylow)
        }
        if (x$transform == "identity")
            plot(range(xx), yr, type = "n", ...)
        else if (x$transform == "log")
            plot(range(xx), yr, type = "n", log = "x", ...)
        else {
            plot(range(xx), yr, type = "n", axes = FALSE, ...)
            axis(1, xaxisval, xaxislab)
            axis(2)
            box()
        }
        if (resid)
            points(xx, y)
        lines(pred.x, yhat)
        if (se) {
```

```
            lines(pred.x, yup, lty = 2)
            lines(pred.x, ylow, lty = 2)
        }
    }
}

temp(cox.zph(fit.cph), var = 1, ylab = "Scaled Schoenfeld residual for patient sex", xlab = "Time")
abline(h = 0, lty = "dotted")
```



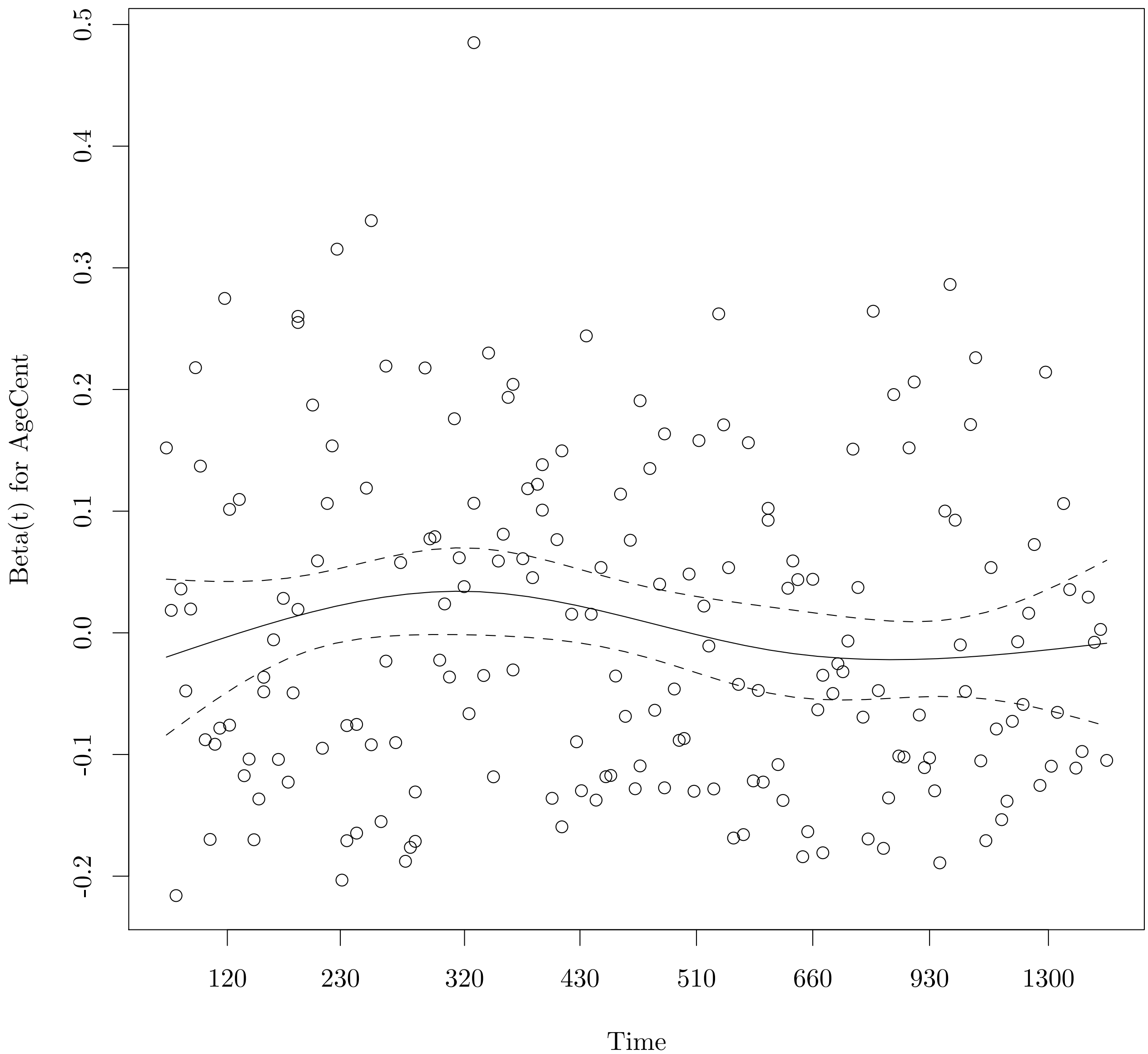
Looks like there's a violation of CPH with gender. Not unexpected. First check whether there is any evidence of gender interaction.

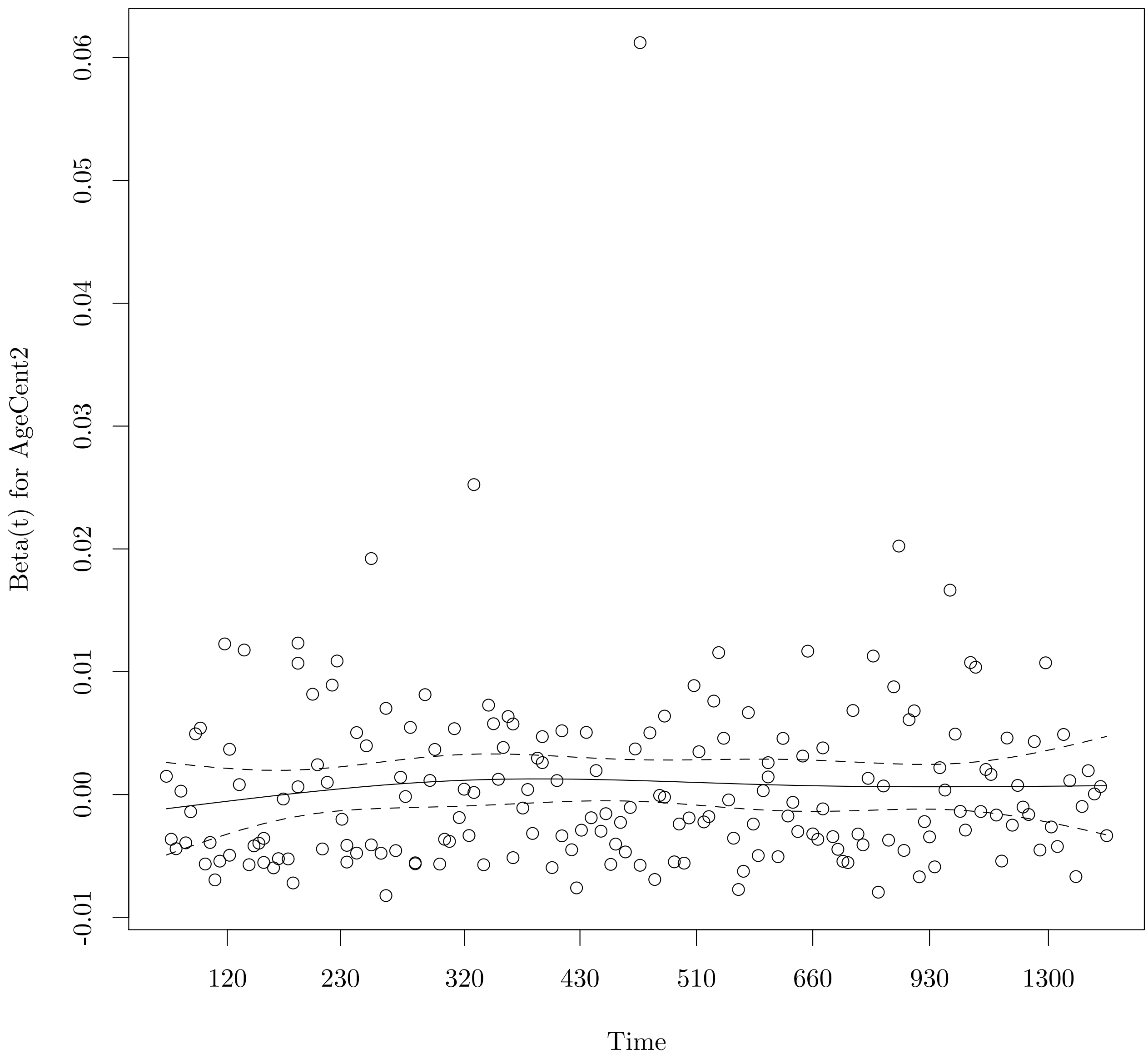
```
anova(coxph(Surv(Time, DSD) ~ SexM*(AgeCent + AgeCent2 + LocBody + SizeCent + SizeSmall + A2 + A4), data

## Analysis of Deviance Table
##  Cox model: response is Surv(Time, DSD)
## Terms added sequentially (first to last)
##
```

```
##                 loglik Chisq Df Pr(>|Chi|)
## NULL              -816
## SexM              -816  0.31  1     0.5770
## AgeCent           -816  0.00  1     0.9623
## AgeCent2          -815  0.78  1     0.3773
## LocBody           -813  3.45  1     0.0634
## SizeCent          -809  7.86  1     0.0050
## SizeSmall         -809  0.00  1     0.9983
## A2                -805  9.64  1     0.0019
## A4                -801  6.85  1     0.0088
## SexM:AgeCent      -800  1.65  1     0.1993
## SexM:AgeCent2     -800  0.00  1     0.9808
## SexM:LocBody      -800  0.10  1     0.7568
## SexM:SizeCent     -800  0.65  1     0.4218
## SexM:SizeSmall    -800  0.01  1     0.9108
## SexM:A2           -800  0.00  1     0.9960
## SexM:A4           -800  0.03  1     0.8537
```

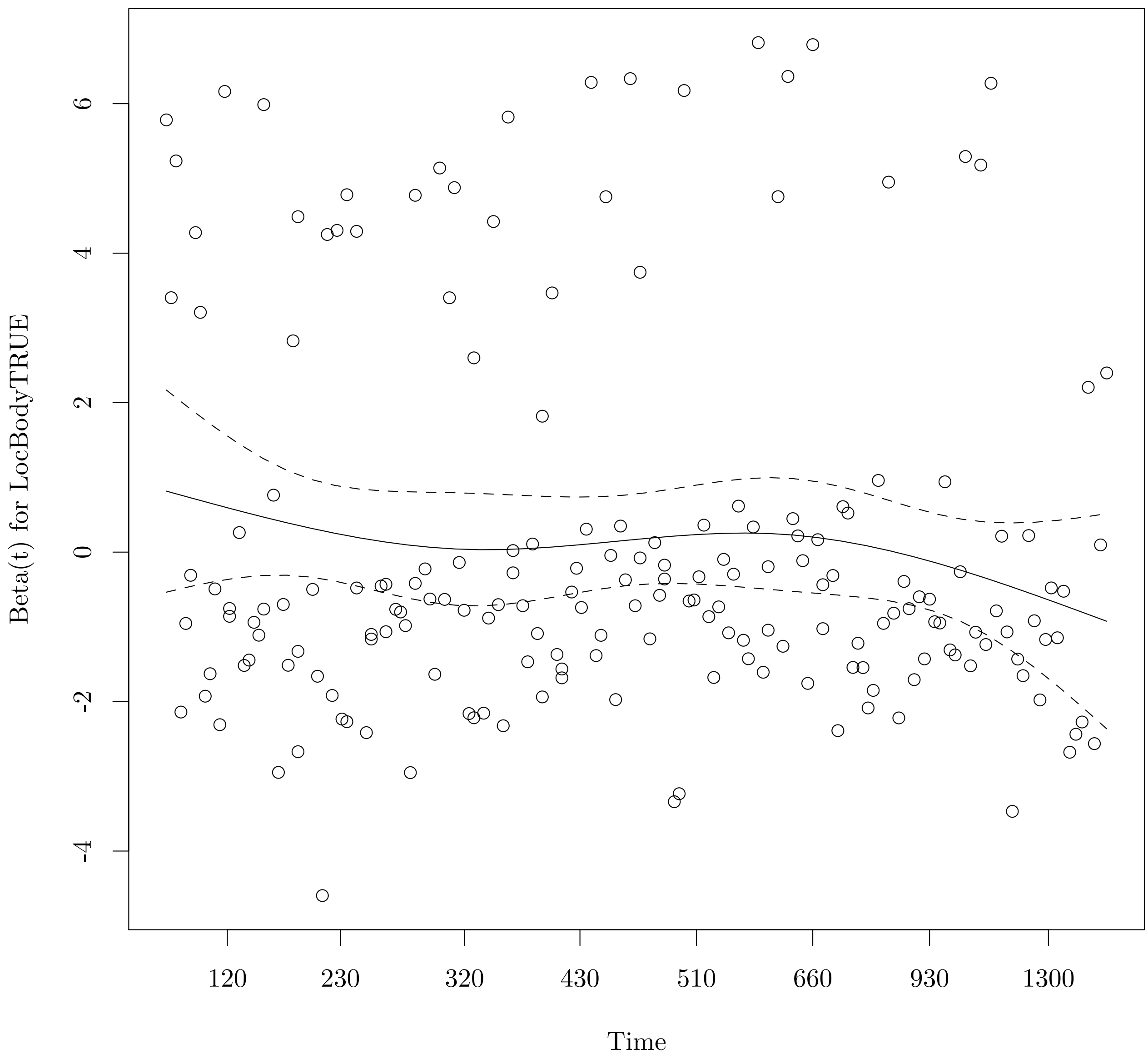
Nope, good. We're not interested in gender effects so just stratify.

```
fit.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + AgeCent + AgeCent2 + LocBody + SizeCent + SizeSmall + A
cox.zph(fit.cph)

##                  rho  chisq     p
## AgeCent     -0.09066 1.6632 0.197
## AgeCent2     0.03371 0.2006 0.654
## LocBodyTRUE -0.10840 1.8729 0.171
## SizeCent    -0.00856 0.0157 0.900
## SizeSmall   -0.04531 0.3927 0.531
## A2TRUE       0.05681 0.6145 0.433
## A4TRUE      -0.06539 0.7755 0.379
## GLOBAL            NA 8.3356 0.304

plot(cox.zph(fit.cph))
```

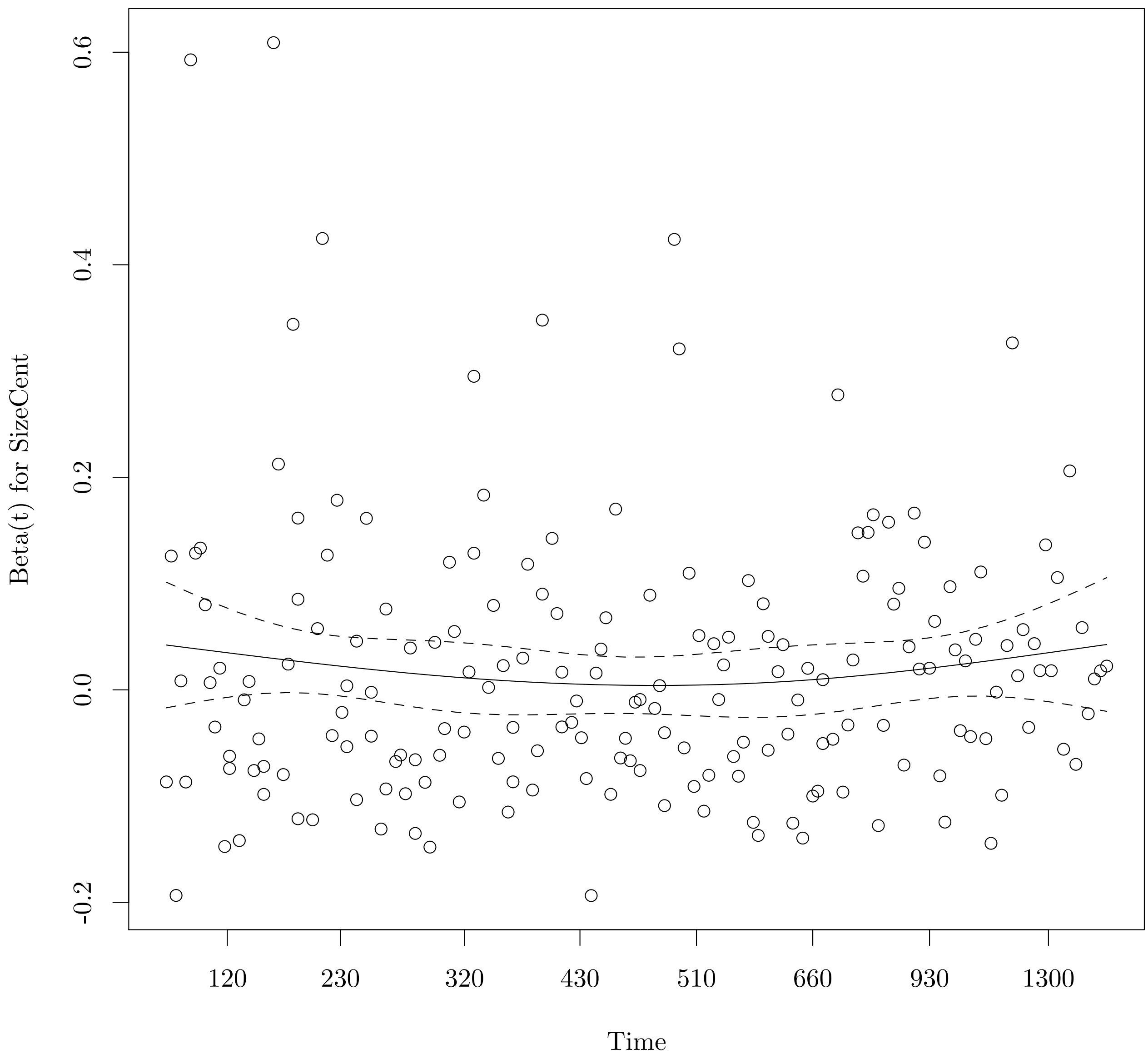

0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
Beta(t) for AgeCent
120
230
320
430
510
660
930
1300
Time



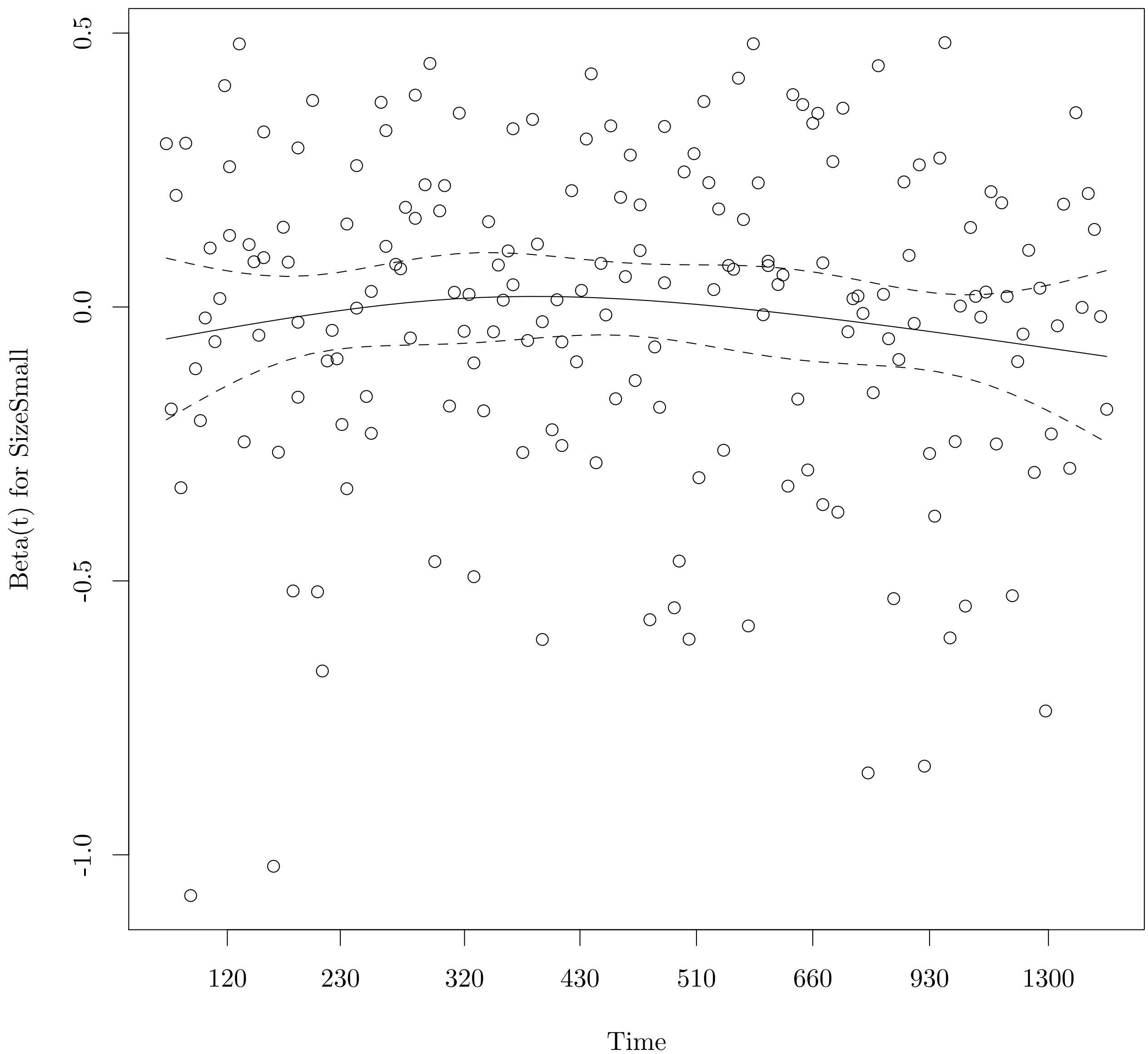
0.06
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
Beta(t) for AgeCent2
120
230
320
430
510
660
930
1300
Time

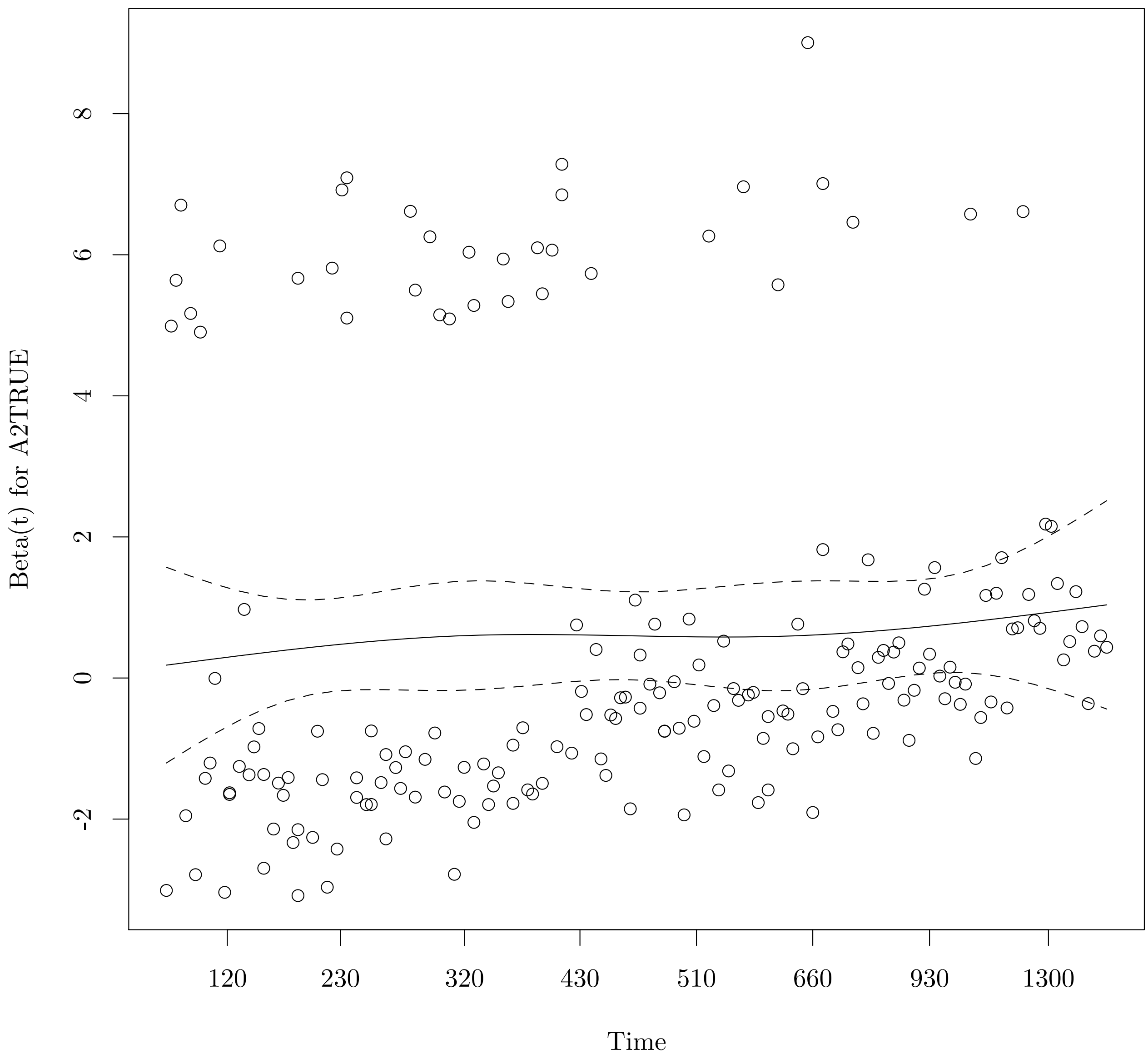


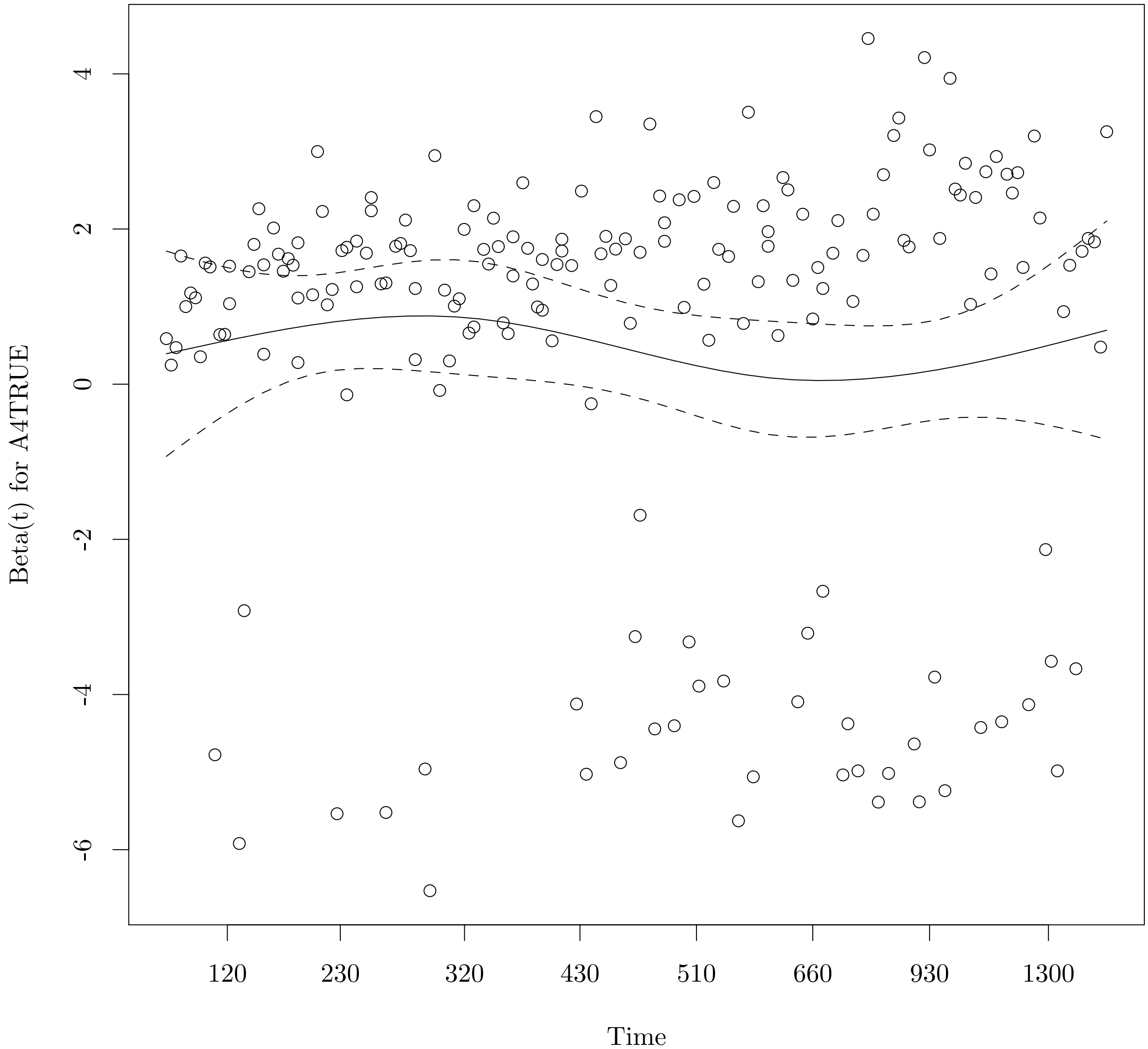
Beta(t) for LocBodyTRUE
-4
-2
0
2
4
6
120
230
320
430
510
660
930
1300
Time



Beta(t) for SizeCent
0.6
0.4
0.2
0.0
-0.2
120
230
320
430
510
660
930
1300
Time

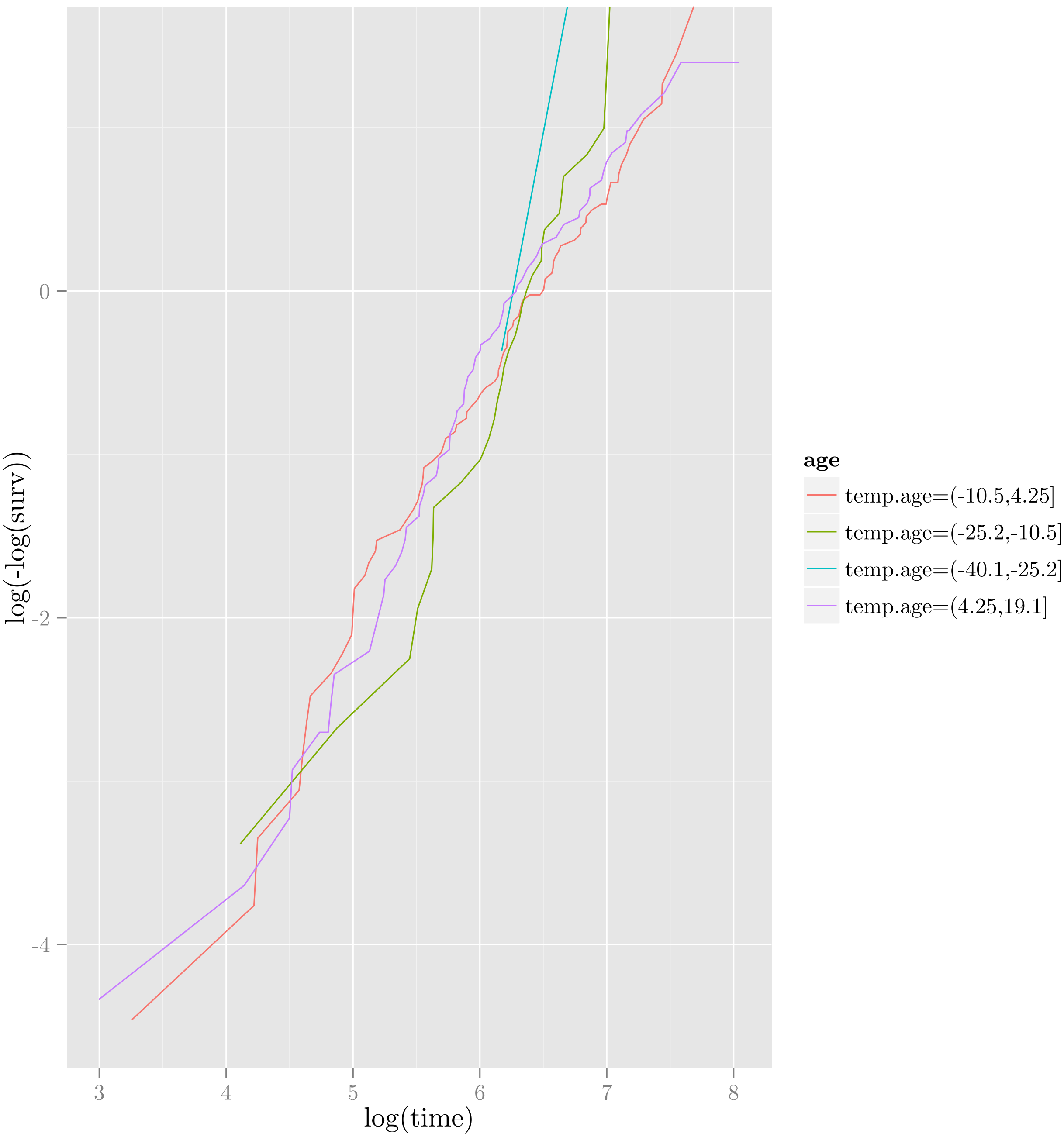

Beta(t) for SizeSmall
0.5
0.0
-0.5
-1.0
120
230
320
430
510
660
930
1300
Time


Beta(t) for A2TRUE
Time
8
6
4
2
0
-2
120
230
320
430
510
660
930
1300



Looks good. Slight snifter with age but I'm not particularly concerned. Split into age groups and do KM plots to verify.

```
temp.age = cut(data$AgeCent, 4)
temp = survfit(Surv(Time, DSD) ~ temp.age, data)
ggplot(data.frame(surv = temp$surv, time = temp$time, age = rep(names(temp$strata), temp$strata)), aes(
```

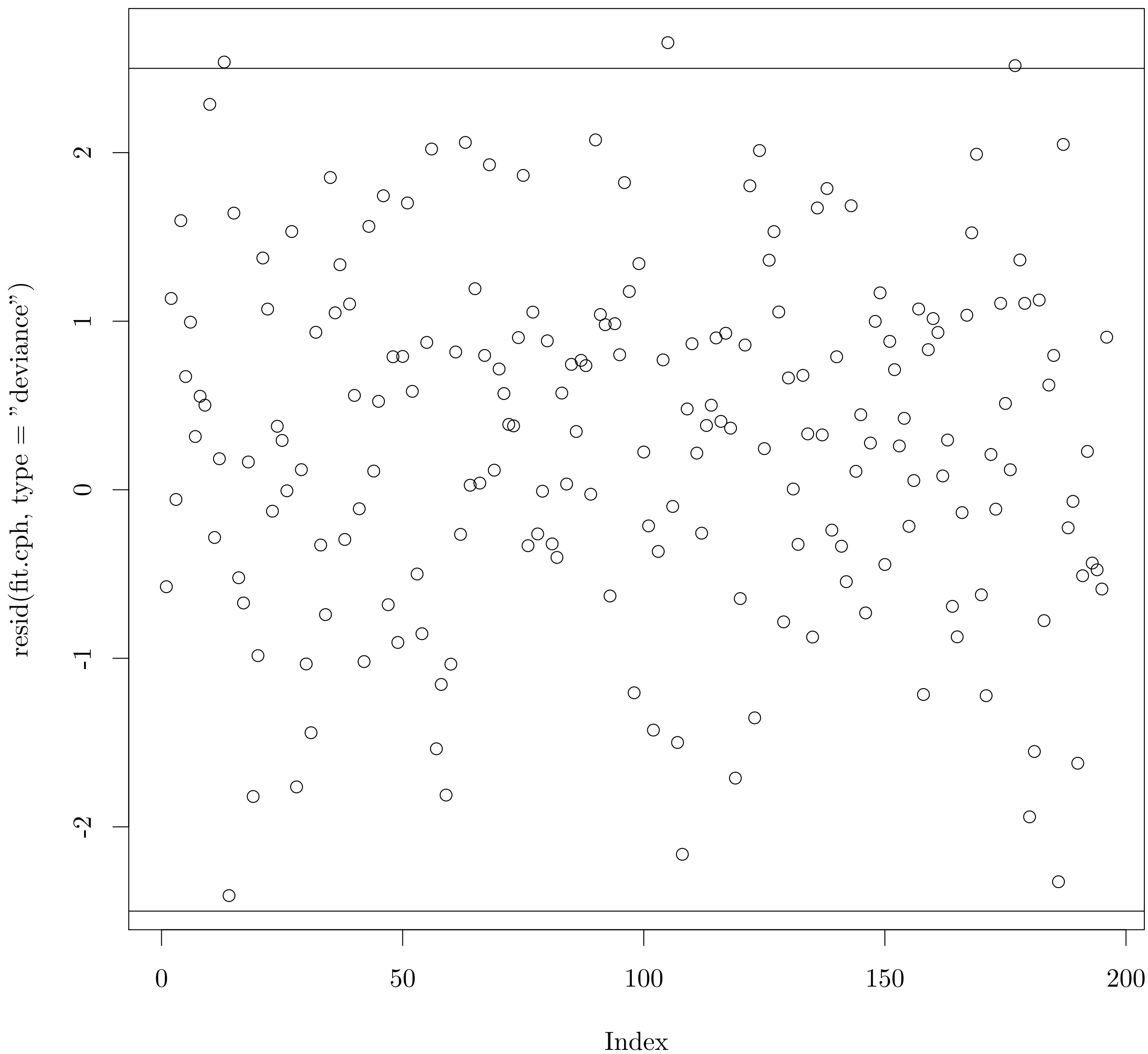


Not perfect but it'll do.

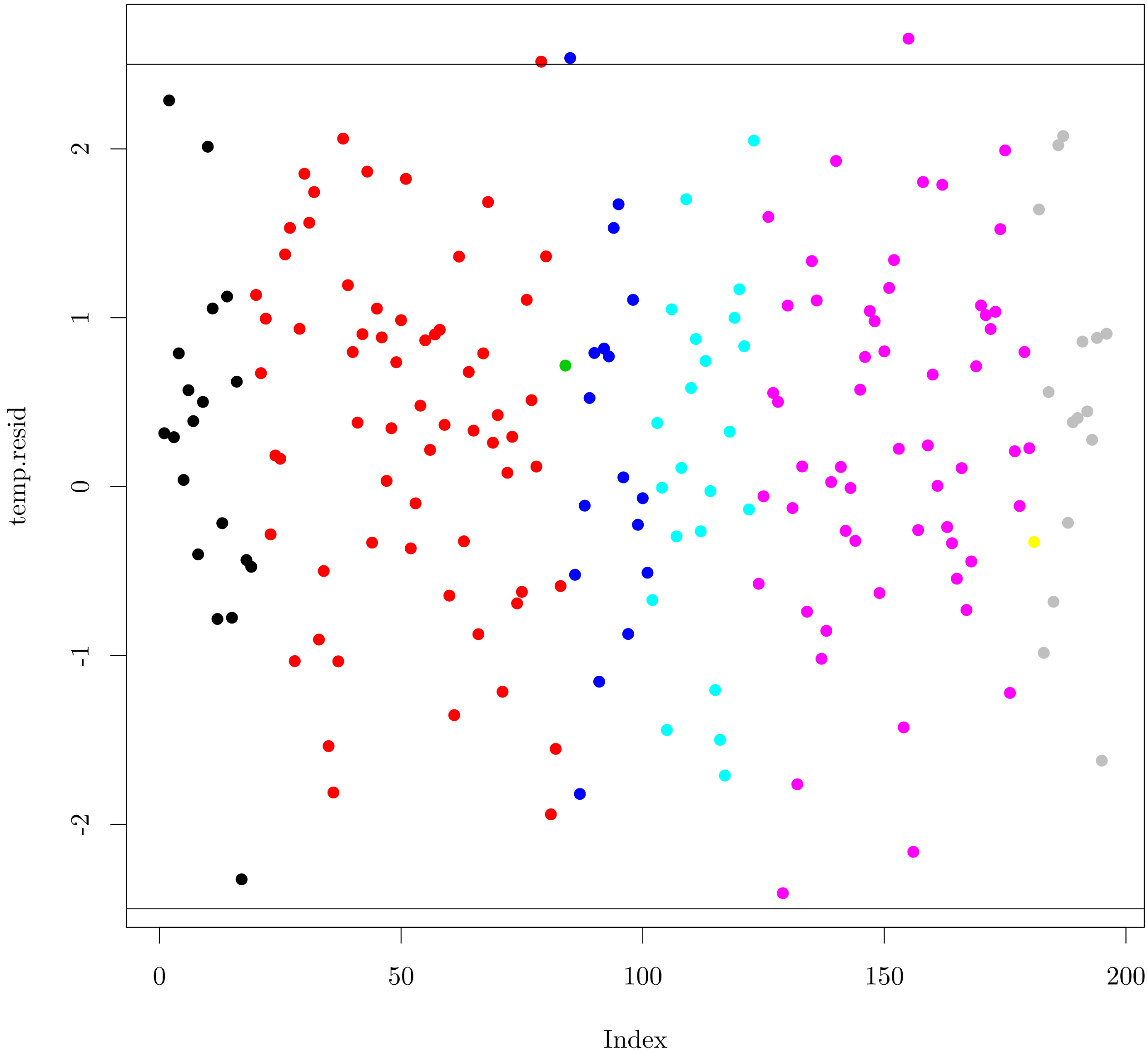
4.3 Outliers: full model

Look at deviance residuals, both marginally and stratified by major subgroups.

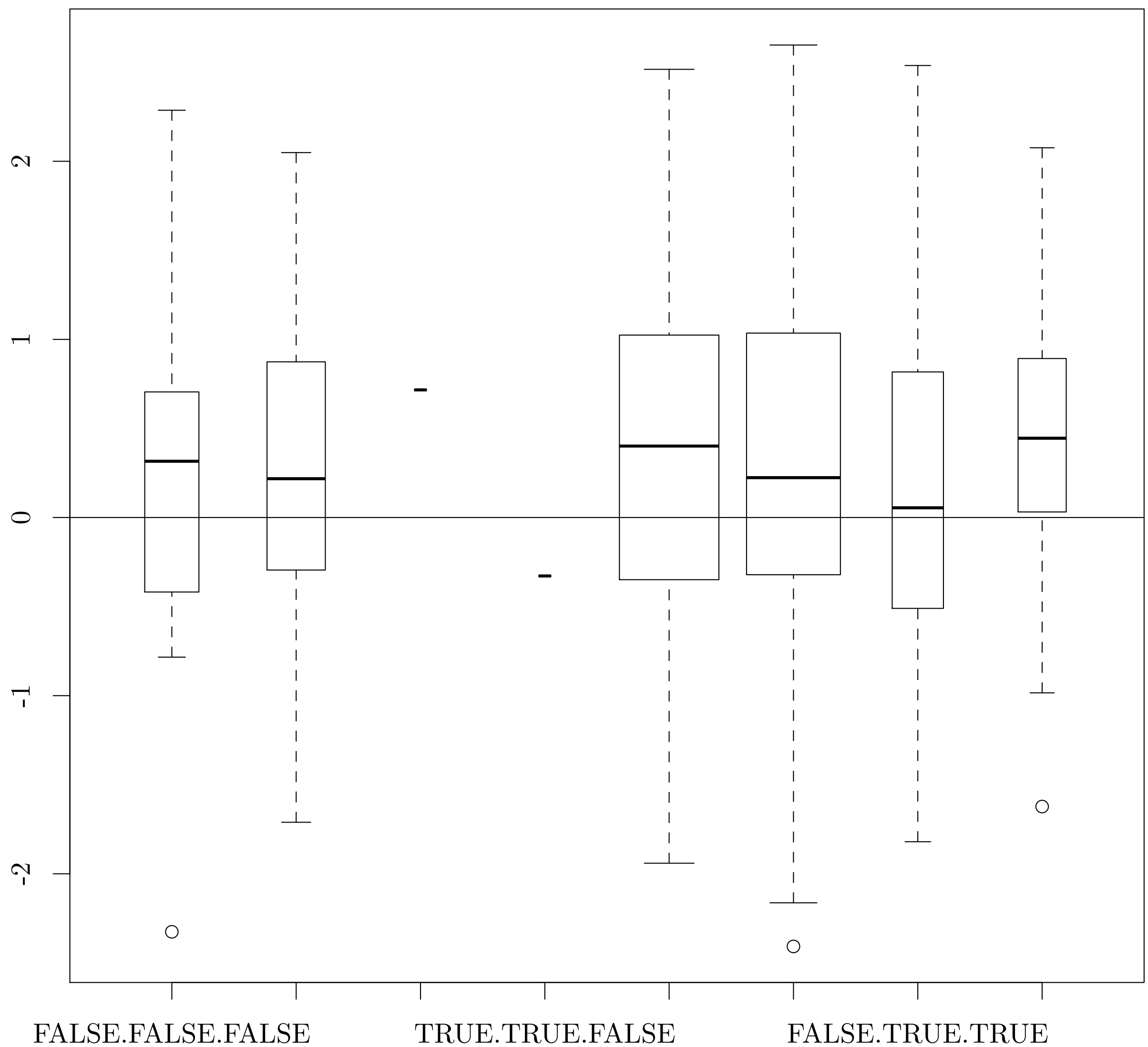
```
plot(resid(fit.cph, type = "deviance"))
abline(h = c(-2.5, 2.5))
```



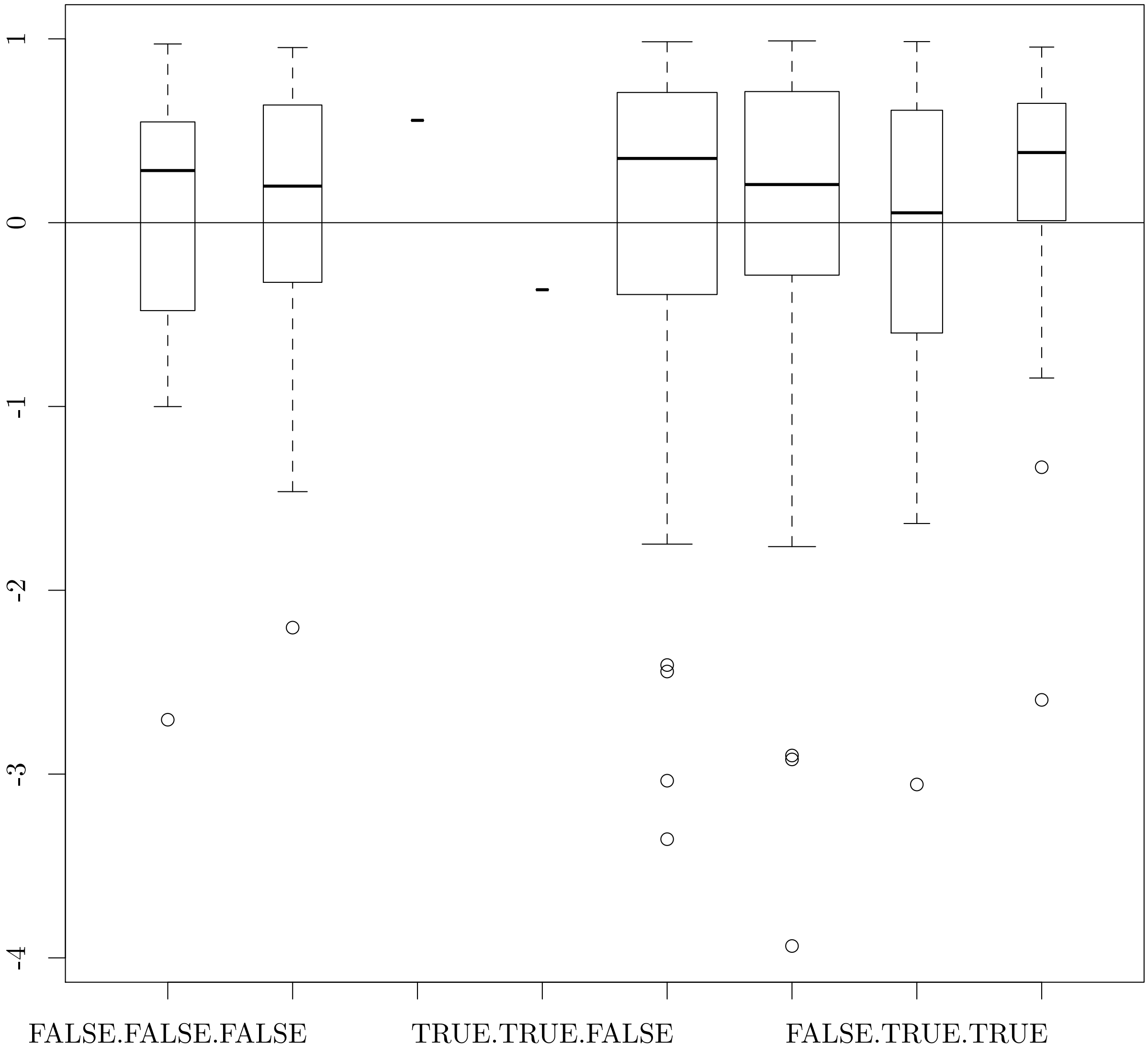

```
temp.ord = order(data$SexM, data$A2, data$A4)
temp.resid = resid(fit.cph, type = "deviance")[temp.ord]
temp.col = (4*data$SexM + 2*data$A2 + data$A4 + 1)[temp.ord]
plot(temp.resid, col = temp.col, pch = 16)
abline(h = c(-2.5, 2.5))
```




```r
boxplot(resid(fit.cph, type = "deviance") ~ data$SexM + data$A2 + data$A4, varwidth = TRUE)
abline(h = 0)
```

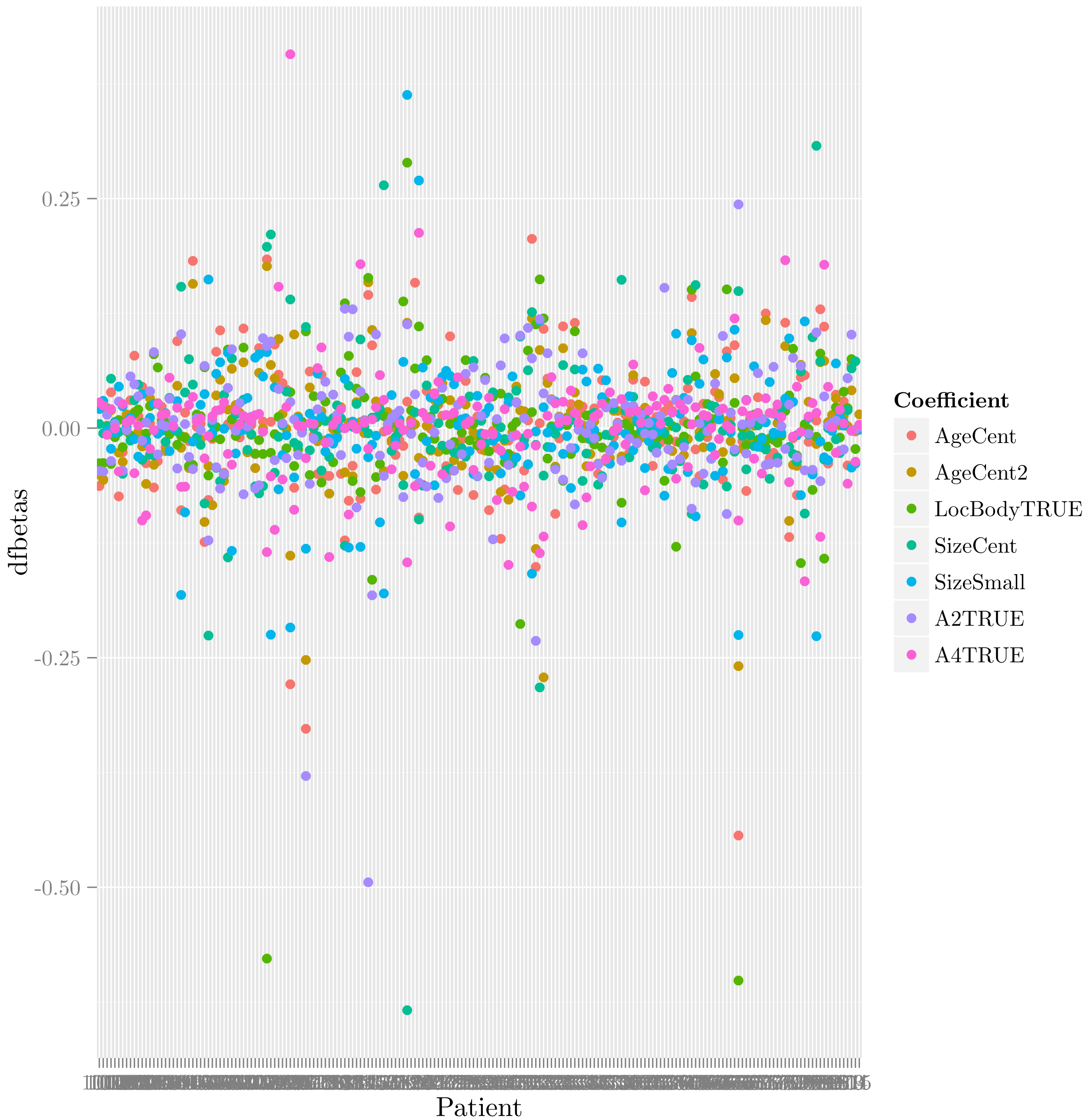



```
boxplot(resid(fit.cph, type = "martingale") ~ data$SexM + data$A2 + data$A4, varwidth = TRUE)
abline(h = 0)
```



Use DFBETAS to examine influence.

```
temp = resid(fit.cph, type = "dfbetas")
colnames(temp) = names(fit.cph$coefficients)
temp = melt(temp)
colnames(temp) = c("Patient", "Coefficient", "dfbetas")
temp$Patient = gsub("NSWPCN_", "", temp$Patient)
ggplot(temp, aes(y = dfbetas, x = Patient, col = Coefficient)) + geom_point()
```



There is quite a number of rather influential observations. These could do with some checking, but first collapse down the model – there's little point doing dfbeta fucking about based on coefficients that will never get fit in the end anyway.

4.4 EDA: Variable selection

```
nobs.coxph <<- function(obj, ...) sum(obj$y[,2])
# Note: Exhaustive search at level 2 is only feasible for at most 5 variables
#fit.cph.as = glmulti(Surv(Time, DSD) ~ strata(SexM) + AgeCent + AgeCent2 + LocBody + SizeCent + SizeSma
set.seed(20150110)
fit.cph.as = glmulti(Surv(Time, DSD) ~ strata(SexM) + AgeCent + AgeCent2 + LocBody + SizeCent + SizeSmal

## Error in eval(expr, envir, enclos):  could not find function "glmulti"
```

```r
# fit.cph.as
# After 830 generations:
# Best model: Surv(Time,DSD)~1+strata(SexM)+SizeCent+A2+A4
# Crit= 1367.16344569113
# Mean crit= 1401.37248769175
# Improvements in best and average IC have bebingo en below the specified goals.
# Algorithm is declared to have converged.
# Completed.
rm(nobs.coxph)
```

Also run BIC stepwise, because we can.

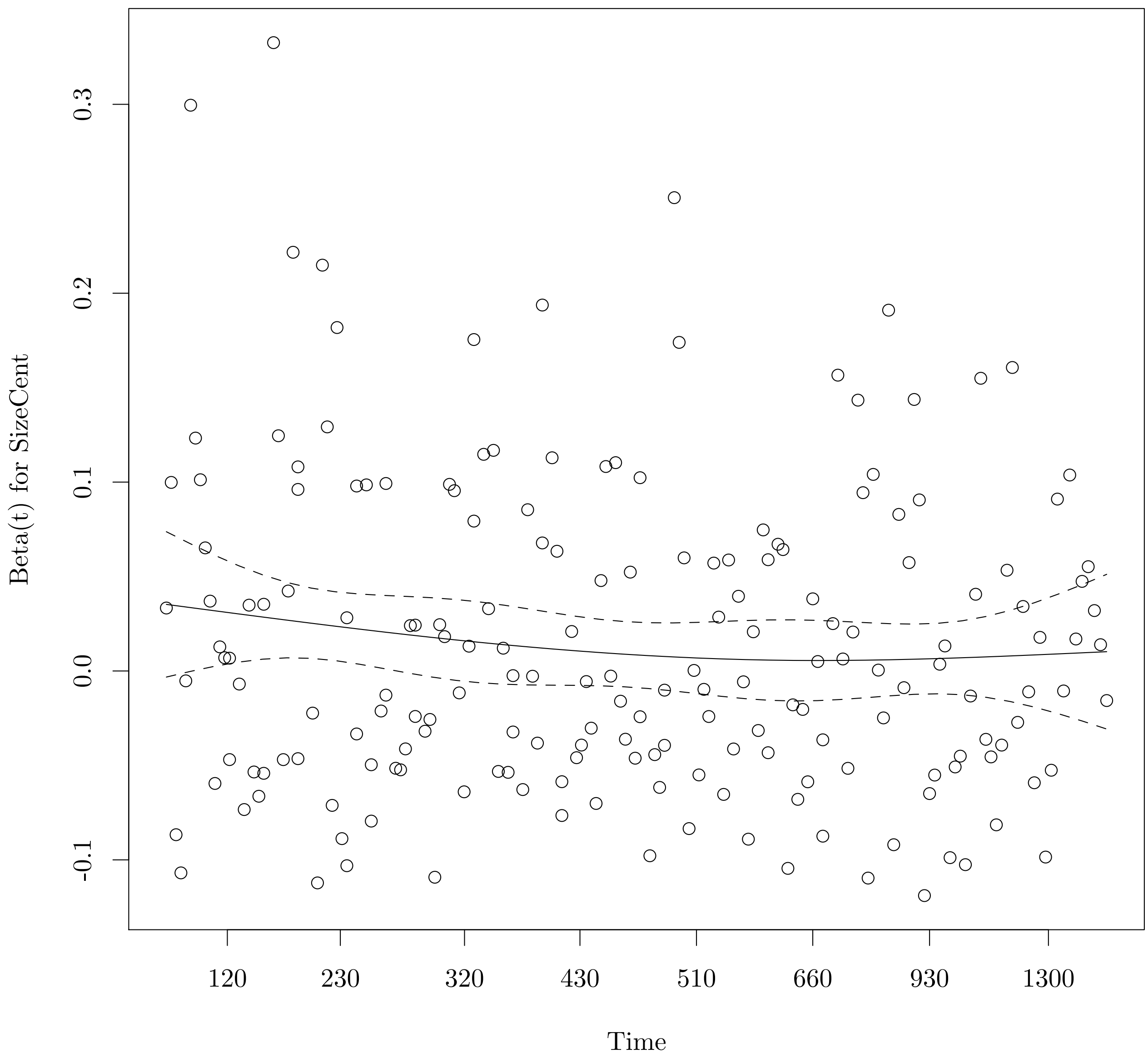
```r
stepAIC(fit.cph, k = log(nrow(data)))

## Start:  AIC=1386
## Surv(Time, DSD) ~ strata(SexM) + AgeCent + AgeCent2 + LocBody +
##     SizeCent + SizeSmall + A2 + A4
##
##             Df  AIC
## - AgeCent    1 1381
## - LocBody    1 1381
## - SizeSmall  1 1381
## - AgeCent2   1 1382
## - SizeCent   1 1385
## <none>         1386
## - A4         1 1387
## - A2         1 1388
##
## Step:  AIC=1381
## Surv(Time, DSD) ~ strata(SexM) + AgeCent2 + LocBody + SizeCent +
##     SizeSmall + A2 + A4
##
##             Df  AIC
## - LocBody    1 1376
## - SizeSmall  1 1376
## - AgeCent2   1 1377
## - SizeCent   1 1379
## <none>         1381
## - A4         1 1382
## - A2         1 1383
##
## Step:  AIC=1376
## Surv(Time, DSD) ~ strata(SexM) + AgeCent2 + SizeCent + SizeSmall +
##     A2 + A4
##
##             Df  AIC
## - SizeSmall  1 1371
## - AgeCent2   1 1372
## - SizeCent   1 1375
## <none>         1376
## - A4         1 1377
## - A2         1 1379
##
## Step:  AIC=1371
```

```
## Surv(Time, DSD) ~ strata(SexM) + AgeCent2 + SizeCent + A2 + A4
##
##            Df  AIC
## - AgeCent2  1 1367
## <none>        1371
## - SizeCent  1 1371
## - A4        1 1372
## - A2        1 1374
##
## Step:  AIC=1367
## Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 + A4
##
##            Df  AIC
## <none>        1367
## - A4        1 1368
## - SizeCent  1 1368
## - A2        1 1370
## Call:
## coxph(formula = Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 +
##     A4, data = data)
##
##
##            coef exp(coef) se(coef)    z      p
## SizeCent 0.0139      1.01  0.00563 2.47 0.0140
## A2TRUE   0.5845      1.79  0.19894 2.94 0.0033
## A4TRUE   0.4311      1.54  0.18733 2.30 0.0210
##
## Likelihood ratio test=25.7  on 3 df, p=1.08e-05  n= 196, number of events= 188
```

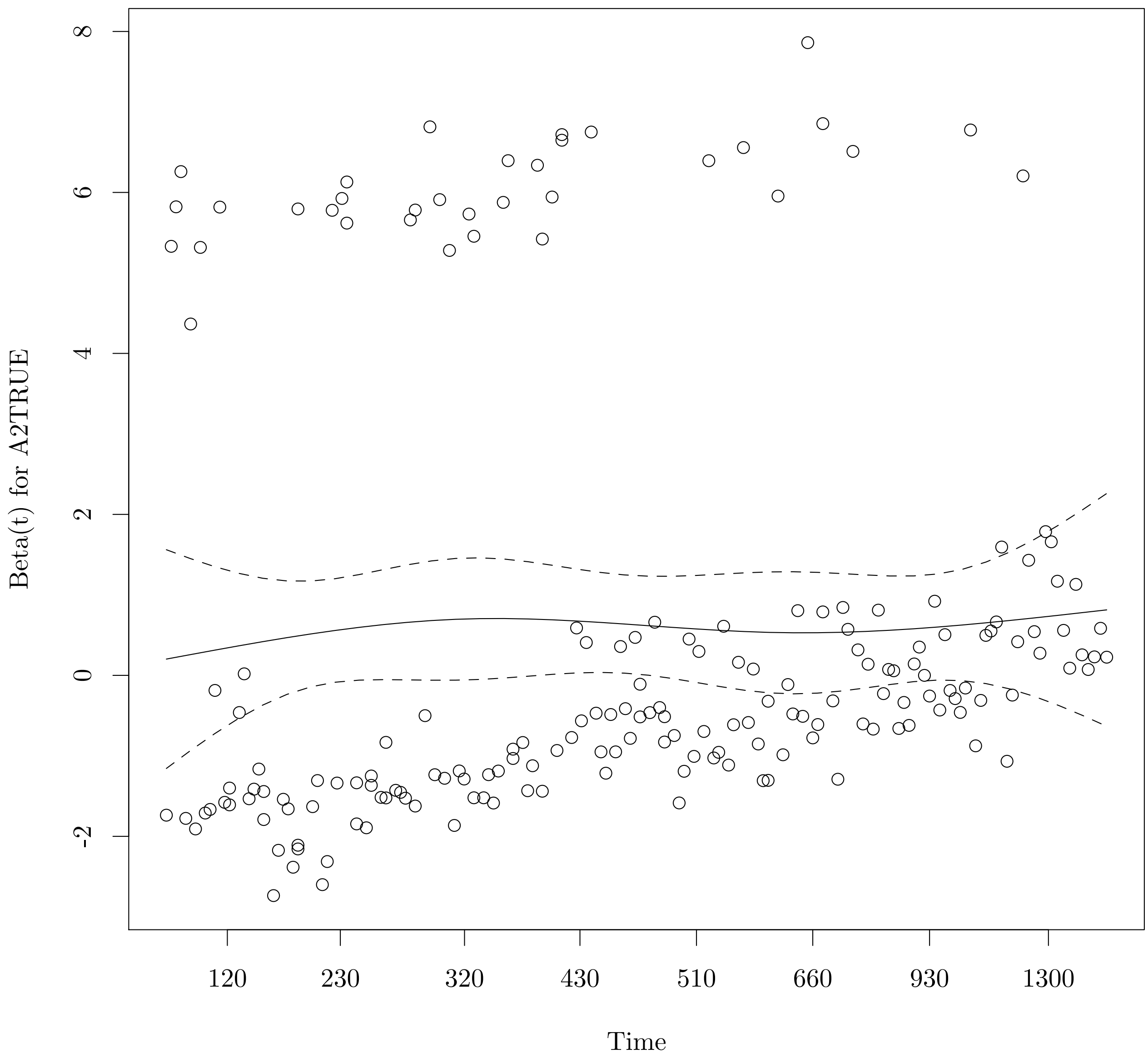
Consensus, excellent.

4.5 PH assumption: reduced model

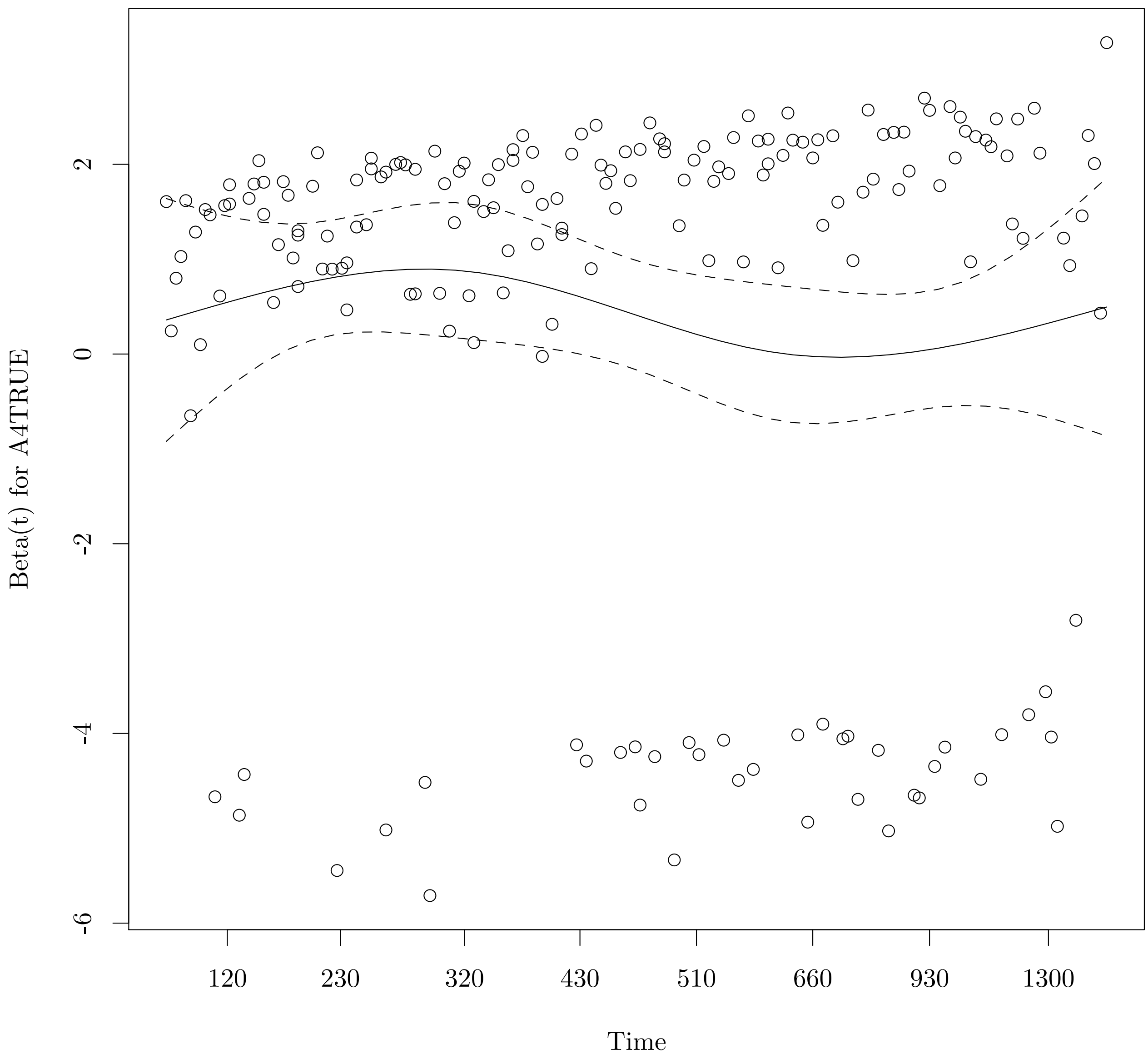
```
fit.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 + A4, data = data)
cox.zph(fit.cph)

##              rho chisq     p
## SizeCent -0.0937 1.894 0.169
## A2TRUE    0.0248 0.115 0.734
## A4TRUE   -0.0890 1.430 0.232
## GLOBAL        NA 3.747 0.290

plot(cox.zph(fit.cph))
```



Beta(t) for SizeCent
0.3
0.2
0.1
0.0
-0.1
120
230
320
430
510
660
930
1300
Time

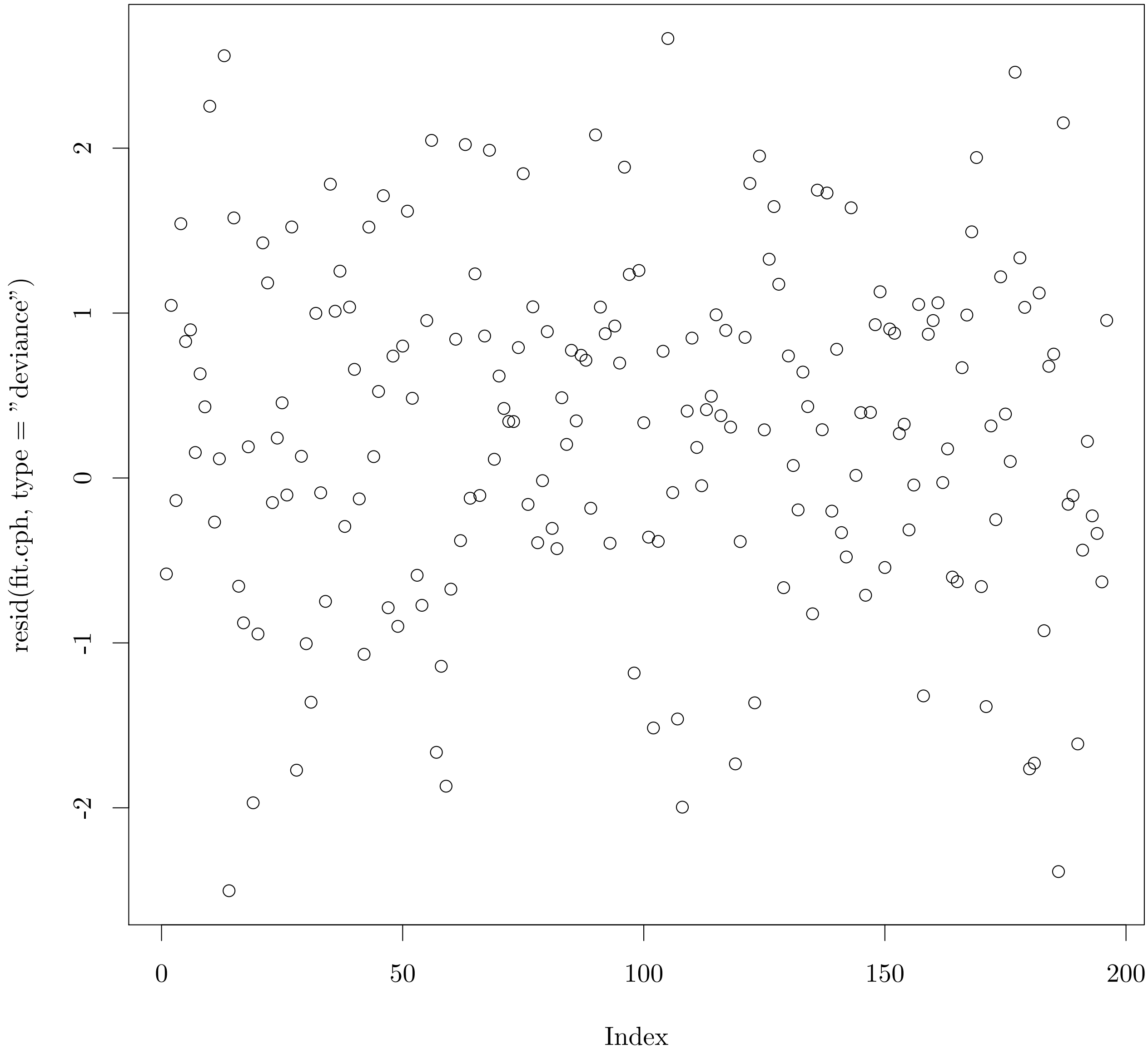


Beta(t) for A2TRUE
Time
-2
0
2
4
6
8
120
230
320
430
510
660
930
1300



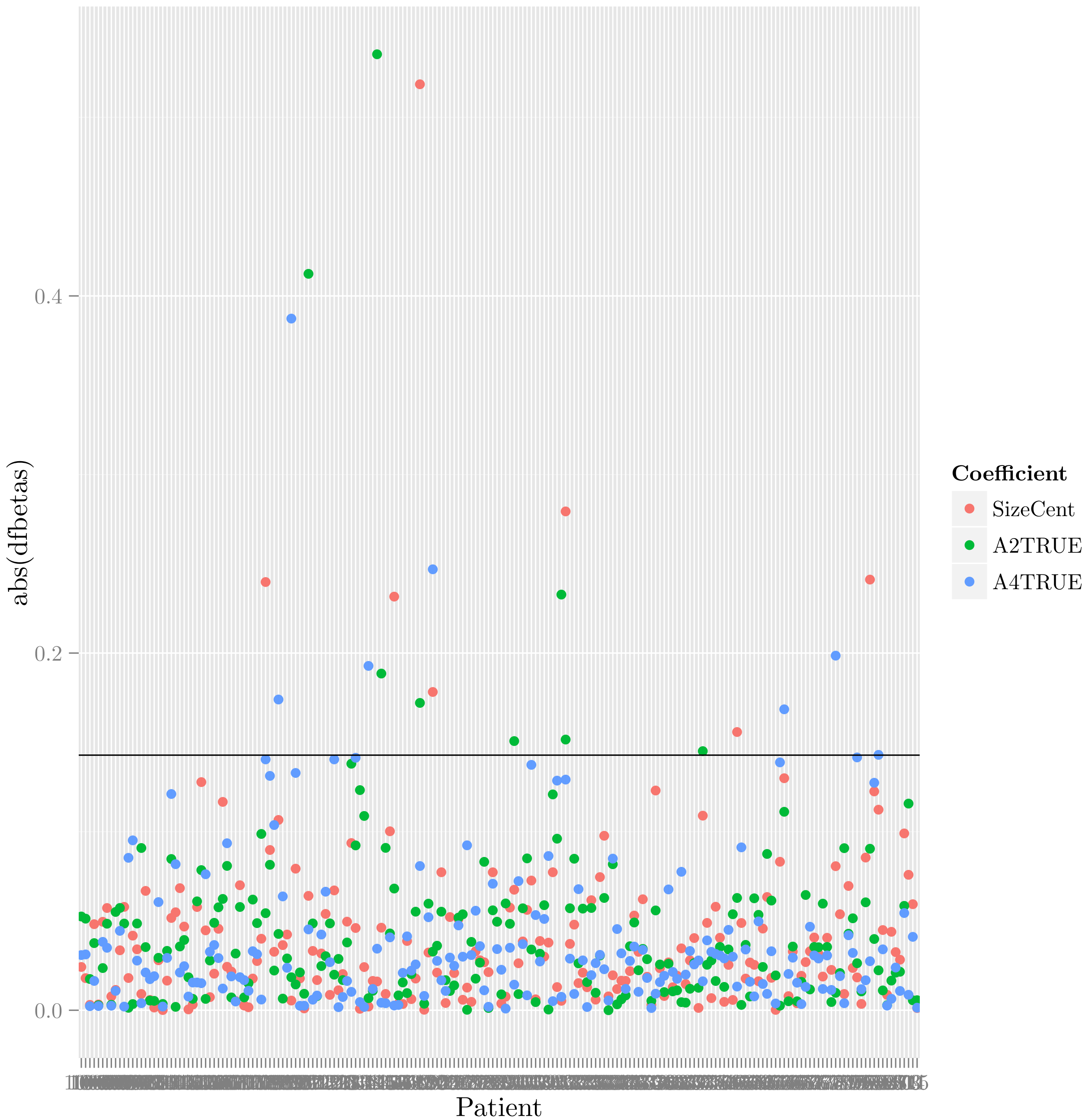
4.6 Outliers: reduced model

```
plot(resid(fit.cph, type = "deviance"))
```



Now generate the restricted fit and examine the DFBETAS on the reduced model.

```
temp = resid(fit.cph, type = "dfbetas")
colnames(temp) = names(fit.cph$coefficients)
temp = melt(temp)
colnames(temp) = c("Patient", "Coefficient", "dfbetas")
temp$Patient = gsub("NSWPCN_", "", temp$Patient)
2/sqrt(nrow(data))             # The classic threshold for concern is 2/sqrt(n).

## [1] 0.1429

ggplot(temp, aes(y = abs(dfbetas), x = Patient, col = Coefficient)) + geom_point() + geom_hline(yinterce
```




```
sort(apply(abs(resid(fit.cph, type = "dfbetas")), 1, max), decreasing = TRUE)

##  NSWPCN_144  NSWPCN_183 NSWPCN_1212 NSWPCN_1195  NSWPCN_318  NSWPCN_195
##    0.535319    0.518522    0.412372    0.387309    0.279328    0.246925
##  NSWPCN_799 NSWPCN_1182  NSWPCN_317  NSWPCN_154  NSWPCN_777  NSWPCN_142
##    0.241159    0.239789    0.232758    0.231619    0.198560    0.192828
##  NSWPCN_145 NSWPCN_1188  NSWPCN_655  NSWPCN_606  NSWPCN_296  NSWPCN_374
##    0.188531    0.174002    0.168515    0.155810    0.150737    0.145092
##  NSWPCN_802  NSWPCN_795  NSWPCN_133  NSWPCN_125  NSWPCN_654  NSWPCN_131
##    0.143009    0.141584    0.141390    0.140472    0.138800    0.138044
##  NSWPCN_307 NSWPCN_1196 NSWPCN_1186  NSWPCN_316 NSWPCN_1155  NSWPCN_801
##    0.137409    0.132883    0.131227    0.128578    0.127761    0.127389
##  NSWPCN_135  NSWPCN_354 NSWPCN_1143  NSWPCN_315 NSWPCN_1167  NSWPCN_814
```

```
##    0.123283    0.123043    0.121087    0.120854    0.116675    0.115720
##  NSWPCN_138 NSWPCN_1187  NSWPCN_152  NSWPCN_813 NSWPCN_1179  NSWPCN_333
##    0.108794    0.103714    0.100222    0.099014    0.098728    0.097707
## NSWPCN_1072 NSWPCN_1168  NSWPCN_269  NSWPCN_636 NSWPCN_1453 NSWPCN_1082
##    0.095141    0.093522    0.092355    0.091215    0.090934    0.090854
##  NSWPCN_789  NSWPCN_647  NSWPCN_312  NSWPCN_798 NSWPCN_1071  NSWPCN_305
##    0.090769    0.087516    0.086378    0.085496    0.085364    0.085038
##  NSWPCN_335  NSWPCN_322  NSWPCN_276 NSWPCN_1145  NSWPCN_364  NSWPCN_200
##    0.084907    0.084847    0.083106    0.081794    0.077536    0.077276
##  NSWPCN_281 NSWPCN_1157  NSWPCN_331  NSWPCN_303 NSWPCN_1172  NSWPCN_790
##    0.077244    0.076161    0.074559    0.072324    0.070007    0.069602
## NSWPCN_1146  NSWPCN_323  NSWPCN_360 NSWPCN_1088 NSWPCN_1222  NSWPCN_664
##    0.068367    0.067802    0.067654    0.066832    0.066379    0.064549
## NSWPCN_1189  NSWPCN_640  NSWPCN_351 NSWPCN_1177  NSWPCN_326  NSWPCN_651
##    0.063748    0.062695    0.062145    0.061975    0.061638    0.061411
## NSWPCN_1153 NSWPCN_1139  NSWPCN_284  NSWPCN_194  NSWPCN_769  NSWPCN_815
##    0.060979    0.060563    0.059802    0.059695    0.059694    0.059379
##  NSWPCN_310  NSWPCN_377 NSWPCN_1031 NSWPCN_1165  NSWPCN_294 NSWPCN_1029
##    0.058826    0.057956    0.057888    0.057640    0.057463    0.057289
## NSWPCN_1023  NSWPCN_320  NSWPCN_304  NSWPCN_324  NSWPCN_272  NSWPCN_182
##    0.057254    0.057106    0.057097    0.056915    0.055722    0.055199
## NSWPCN_1028  NSWPCN_781  NSWPCN_445  NSWPCN_268  NSWPCN_643  NSWPCN_308
##    0.055045    0.053779    0.053775    0.053737    0.053434    0.053314
##  NSWPCN_347   NSWPCN_10   NSWPCN_24  NSWPCN_257  NSWPCN_794 NSWPCN_1016
##    0.053023    0.052498    0.052189    0.051883    0.051498    0.051284
##   NSWPCN_13  NSWPCN_282 NSWPCN_1022 NSWPCN_1160  NSWPCN_375 NSWPCN_1178
##    0.049613    0.049572    0.049531    0.048958    0.048914    0.048792
## NSWPCN_1227 NSWPCN_1213 NSWPCN_1075 NSWPCN_1019 NSWPCN_1147  NSWPCN_665
##    0.048631    0.048614    0.048561    0.048203    0.046858    0.046764
##  NSWPCN_646  NSWPCN_336    NSWPCN_4  NSWPCN_804  NSWPCN_807 NSWPCN_1219
##    0.045742    0.045469    0.045022    0.044914    0.043924    0.042407
## NSWPCN_1190  NSWPCN_164  NSWPCN_666  NSWPCN_381  NSWPCN_770  NSWPCN_370
##    0.042400    0.041379    0.040729    0.040591    0.040581    0.040421
##  NSWPCN_309  NSWPCN_270  NSWPCN_637   NSWPCN_20  NSWPCN_273  NSWPCN_346
##    0.038785    0.038276    0.036619    0.036126    0.035909    0.035845
##  NSWPCN_657    NSWPCN_7 NSWPCN_1141  NSWPCN_369 NSWPCN_1158  NSWPCN_350
##    0.035660    0.035272    0.033258    0.033176    0.032752    0.032716
##  NSWPCN_376  NSWPCN_810  NSWPCN_341 NSWPCN_1171  NSWPCN_384  NSWPCN_126
##    0.032695    0.032560    0.031861    0.031740    0.029033    0.028767
##  NSWPCN_352  NSWPCN_811  NSWPCN_373  NSWPCN_638  NSWPCN_330  NSWPCN_358
##    0.028581    0.028304    0.027879    0.026735    0.026383    0.025635
##  NSWPCN_256  NSWPCN_283  NSWPCN_775  NSWPCN_166 NSWPCN_1170  NSWPCN_362
##    0.024904    0.022669    0.022611    0.022181    0.021654    0.021446
##  NSWPCN_280 NSWPCN_1207  NSWPCN_161  NSWPCN_656  NSWPCN_128  NSWPCN_366
##    0.021341    0.021195    0.020940    0.020342    0.020270    0.019967
##  NSWPCN_653  NSWPCN_363   NSWPCN_36  NSWPCN_662 NSWPCN_1136 NSWPCN_1150
##    0.019505    0.019311    0.019303    0.019302    0.019072    0.018446
## NSWPCN_1018 NSWPCN_1091 NSWPCN_1215 NSWPCN_1175   NSWPCN_21  NSWPCN_345
##    0.017496    0.017407    0.016899    0.016870    0.016860    0.016454
##  NSWPCN_143  NSWPCN_325 NSWPCN_1152  NSWPCN_658 NSWPCN_1176  NSWPCN_797
##    0.016435    0.015767    0.015516    0.015427    0.015148    0.011796
## NSWPCN_1211  NSWPCN_806  NSWPCN_157  NSWPCN_190  NSWPCN_334 NSWPCN_1027
##    0.009221    0.008634    0.008317    0.008019    0.007766    0.007733
##    NSWPCN_9  NSWPCN_353 NSWPCN_1140 NSWPCN_1020
```

```
##     0.005630     0.005273     0.003534     0.003253
sum(apply(abs(resid(fit.cph, type = "dfbetas")), 1, max) > 2/sqrt(nrow(data)))
## [1] 19
```

4.7 Summary of EDA

1. On the basis of pre-operative assessability and data availability, variables were filtered down to Sex, AgeCent, LocBody, SizeCent, A2, A4.
2. Functional forms for the continuous variates AgeCent and SizeCent indicated a possible slight quadratic effect on AgeCent, and a knee on SizeCent. These were modelled by incorporating additional terms.
3. Analysis of a full model fit (with additional nonlinear terms included) indicated violation of PH for gender. This was dealt with by stratification. A slight PH violation by age was deemed unimportant.
4. Variable selection by BIC (both stepwise and genetic all-subset) settled on a final model of Surv(Time,DSD) $\sim 1 +$ strata(SexM) + SizeCent + A2 + A4. This model was refit by coxph.
5. PH was verified on the final model. Deviance residuals showed no egregious outliers. dfBetaS indicated a number of influential observations, which require checking.

5 Final fits

```
fit.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 + A4, data = data)
```

```
set.seed(20150111)
fit.rsf = rfsrc(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + SizeCent + A2 + A4, data = data, mtry = 1,
```

```
fit.gg = flexsurvreg(Surv(Time, DSD) ~ SexM + SizeCent + A2 + A4,
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM),
        data = data, dist = "gengamma")

fit.gf = flexsurvreg(Surv(Time, DSD) ~ SexM + SizeCent + A2 + A4,
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM,
                P = ~ SexM),
        data = data, dist = "genf")

fit.gg$loglik

## [1] -1355

fit.gf$loglik

## [1] -1354

pchisq(2*(fit.gf$loglik - fit.gg$loglik), 2, lower.tail = FALSE)
```

```
## [1] 0.3371
```

```r
AIC(fit.gg)
```

```
## [1] 2727
```

```r
AIC(fit.gf)
```

```
## [1] 2729
```

```r
BIC(fit.gg)
```

```
## [1] 2757
```

```r
BIC(fit.gf)
```

```
## [1] 2765
```

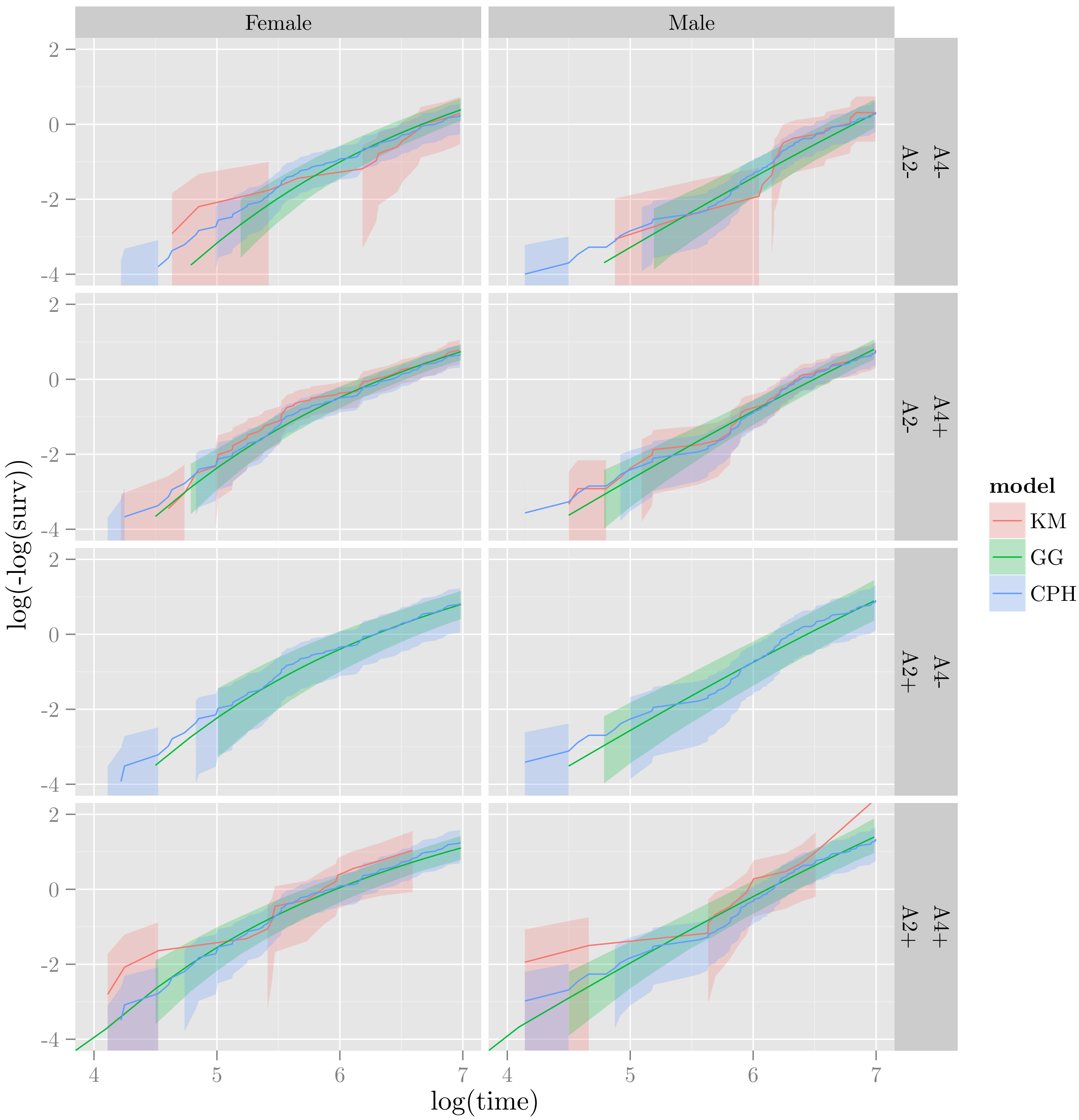
```r
fit.gg
```

```
##
## Call:
## flexsurvreg(formula = Surv(Time, DSD) ~ SexM + SizeCent + A2 +     A4, anc = list(sigma = ~SexM, Q =
##
## Estimates:
##                  data mean  est       L95%      U95%      se
## mu                     NA    6.41920   6.08210   6.75630   0.17199
## sigma                  NA    0.79193   0.68758   0.91211   0.05709
## Q                      NA    0.06489  -0.48729   0.61708   0.28173
## SexMTRUE          0.48469    0.36244   0.03548   0.68940   0.16682
## SizeCent          3.82143   -0.01028  -0.01751  -0.00305   0.00369
## A2TRUE            0.17347   -0.37995  -0.64171  -0.11818   0.13356
## A4TRUE            0.78061   -0.32171  -0.57137  -0.07206   0.12738
## sigma(SexMTRUE)   0.48469   -0.25903  -0.48789  -0.03017   0.11677
## Q(SexMTRUE)       0.48469    0.76270   0.04909   1.47631   0.36409
##                  exp(est)  L95%      U95%
## mu                     NA        NA        NA
## sigma                  NA        NA        NA
## Q                      NA        NA        NA
## SexMTRUE          1.43683   1.03612   1.99251
## SizeCent          0.98977   0.98264   0.99695
## A2TRUE            0.68390   0.52639   0.88854
## A4TRUE            0.72491   0.56475   0.93048
## sigma(SexMTRUE)   0.77180   0.61392   0.97028
## Q(SexMTRUE)       2.14406   1.05032   4.37675
##
## N = 196,  Events: 188,  Censored: 8
## Total time at risk: 113142
## Log-likelihood = -1355, df = 9
## AIC = 2727
```

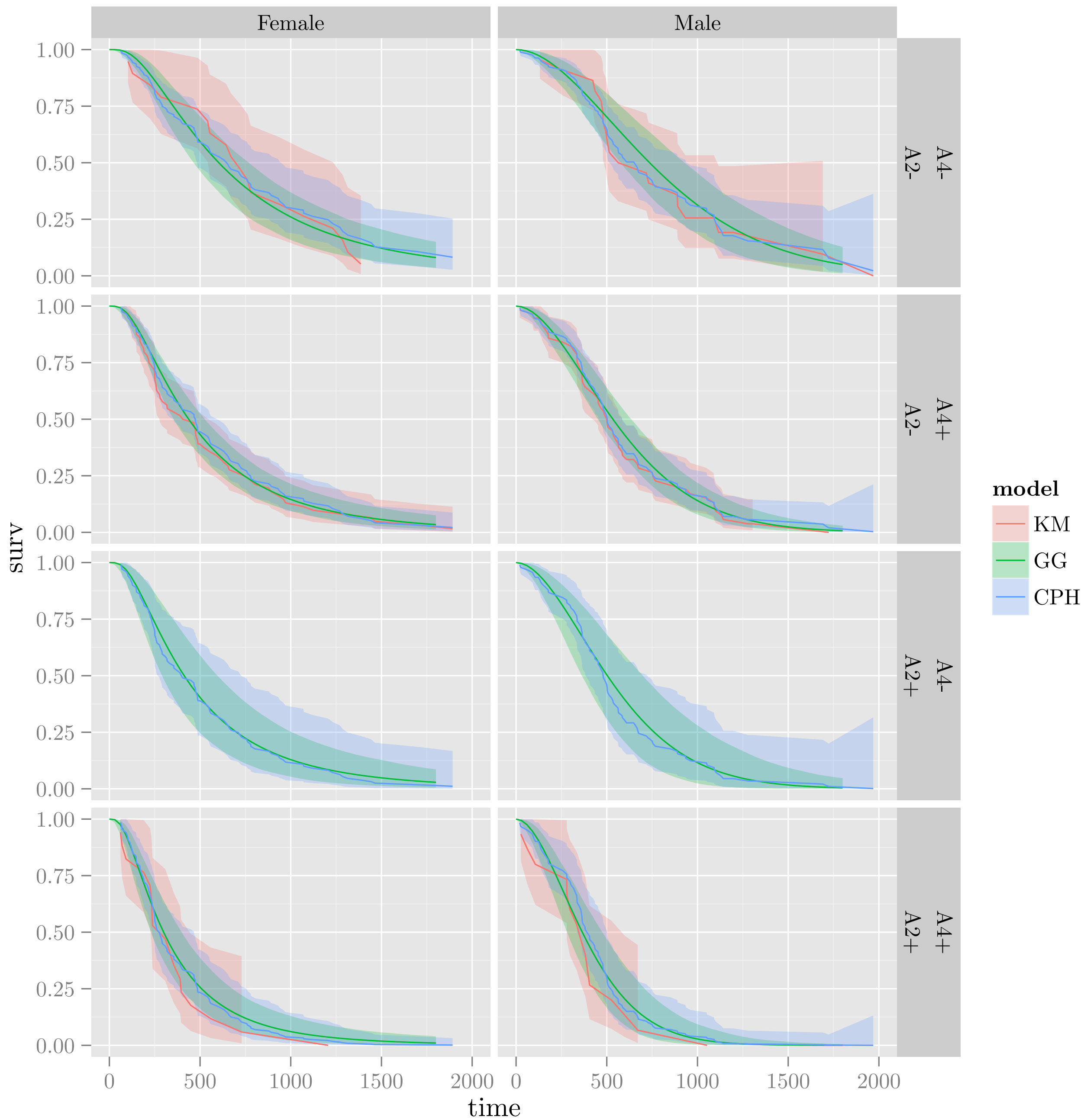
6 Fit assessment

Plot fit stratified by sex, separate curves for A2, A4 status, at median (approx.) Size.

```
temp.grid = expand.grid(A4 = c(FALSE, TRUE), A2 = c(FALSE, TRUE), SexM = c(FALSE, TRUE), SizeCent = 0)
temp.grid$ID = sprintf("SexM=%s, A2=% -5s, A4=% -5s", temp.grid$SexM, temp.grid$A2, temp.grid$A4)
temp.preds = summary(fit.gg, newdata = temp.grid, type = "survival", t = seq(0, 365*5, 30))
temp.preds2 = do.call(rbind, temp.preds)
temp.preds2$group = rep(gsub(".*ID=", "", names(temp.preds)), each = nrow(temp.preds[[1]]))
temp.preds.cox = survfit(fit.cph, newdata = temp.grid)

temp.survfit = survfit(Surv(Time, DSD) ~ SexM + A2 + A4, data)
temp.data = data.frame(time = temp.survfit$time, surv = temp.survfit$surv, upper = temp.survfit$lower, l
temp.data = rbind(temp.data, data.frame(time = temp.preds2$time, surv = temp.preds2$est, upper = temp.pr
temp.data = rbind(temp.data, data.frame(time = temp.preds.cox$time, surv = temp.preds.cox$surv, upper =

temp.data$Sex = c("Male", "Female")[grepl("SexM=FALSE", temp.data$group)+1]
temp.data$A2 = c("A2-", "A2+")[grepl("A2=TRUE", temp.data$group)+1]
temp.data$A4 = c("A4-", "A4+")[grepl("A4=TRUE", temp.data$group)+1]

ggplot(temp.data, aes(x = log(time), y = log(-log(surv)), ymin = log(-log(lower)), ymax = log(-log(upper
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() +
        xlim(4, 7) + ylim(-4, 2) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 46 rows containing missing values (geom_path).
## Warning:  Removed 41 rows containing missing values (geom_path).
## Warning:  Removed 48 rows containing missing values (geom_path).
## Warning:  Removed 44 rows containing missing values (geom_path).
## Warning:  Removed 39 rows containing missing values (geom_path).
## Warning:  Removed 37 rows containing missing values (geom_path).
## Warning:  Removed 40 rows containing missing values (geom_path).
## Warning:  Removed 38 rows containing missing values (geom_path).
```




```
ggplot(temp.data, aes(x = time, y = surv, ymin = lower, ymax = upper, colour = model, fill = model)) +
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() + xlim(0, 2000) + ylim(0, 1) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
```



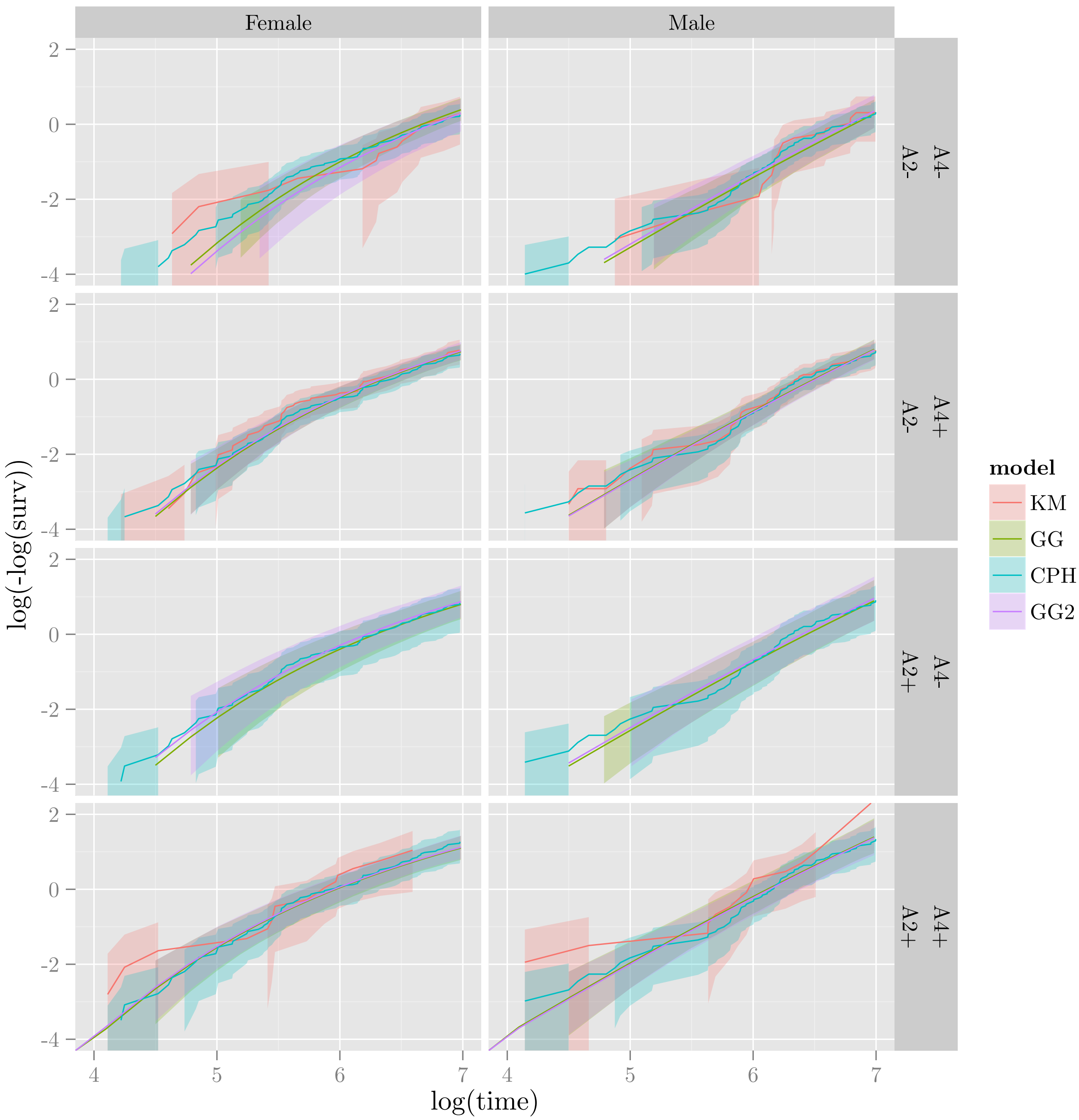
Some deviation though not significant. Most concerning is the A2- A4- female group, survival of which is underestimated by the flexsurv model. To approach this in a modelling sense would require interaction terms between Sex and A2, A4. Overfitting seems likely considering the very few data available for the A2+/A4- group. Perhaps just add a single "DoubleNegFemale" term.

```
fit.gg2 = flexsurvreg(Surv(Time, DSD) ~ SexM + SizeCent + A2 + A4 + I(SexM == FALSE & A2 == FALSE & A4 =
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM),
        data = data, dist = "gengamma")

AIC(fit.gg)

## [1] 2727
```

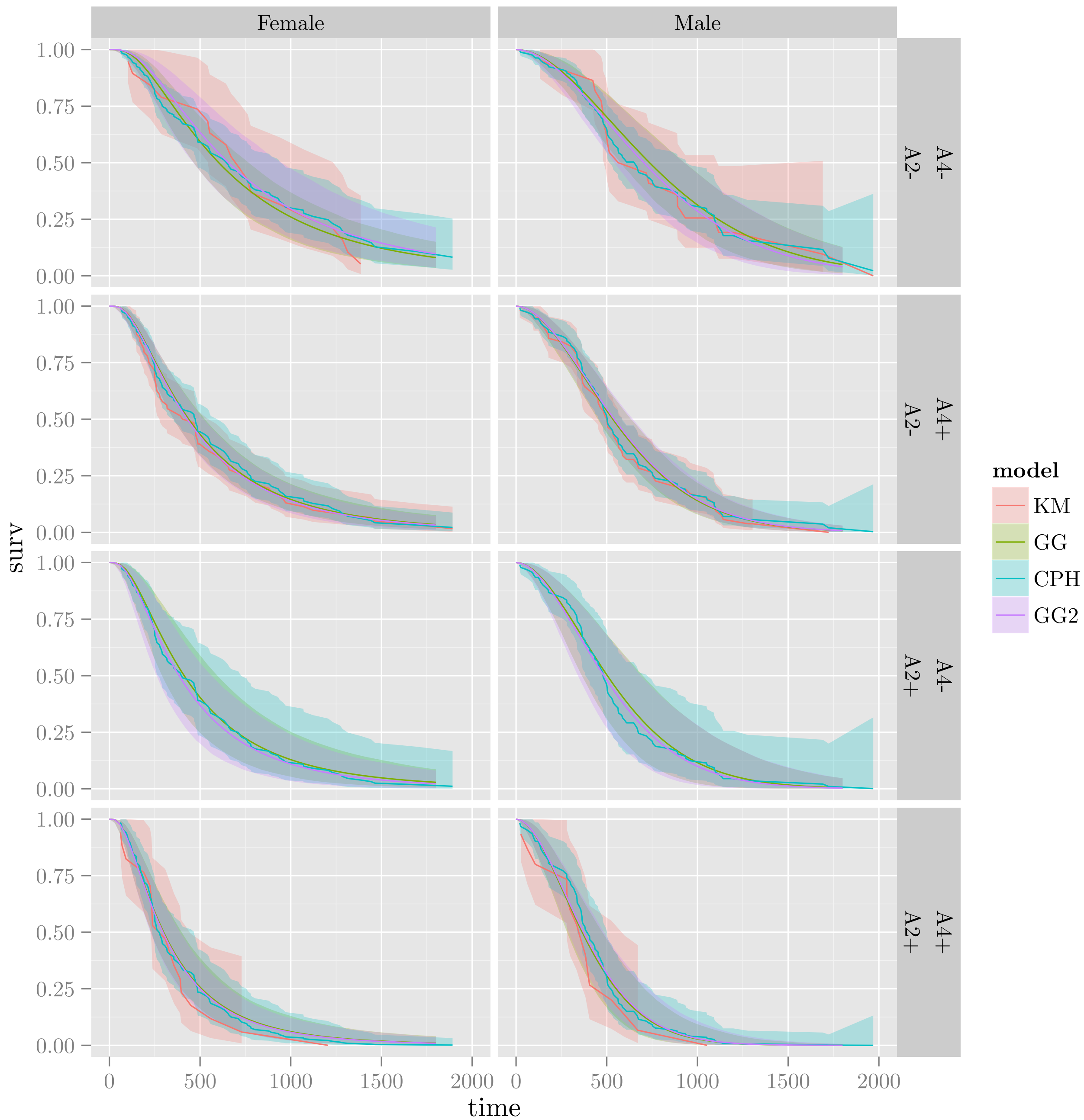
```
AIC(fit.gg2)

## [1] 2729

AIC(fit.gg) - AIC(fit.gg2)

## [1] -1.604

# Equivocal on AIC.  BIC would favour gg then.

pchisq(-2*(fit.gg$loglik - fit.gg2$loglik), 1, lower.tail = FALSE)

## [1] 0.5291

# Not good evidence on LRT
```

See how it plots relative to the others.

```
temp.preds = summary(fit.gg2, newdata = temp.grid, type = "survival", t = seq(0, 365*5, 30))
temp.preds2 = do.call(rbind, temp.preds)
temp.preds2$group = rep(gsub(".*ID=", "", names(temp.preds)), each = nrow(temp.preds[[1]]))
temp.data = rbind(temp.data, data.frame(time = temp.preds2$time, surv = temp.preds2$est, upper = temp.pr
temp.data$Sex = c("Male", "Female")[grepl("SexM=FALSE", temp.data$group)+1]
temp.data$A2 = c("A2-", "A2+")[grepl("A2=TRUE", temp.data$group)+1]
temp.data$A4 = c("A4-", "A4+")[grepl("A4=TRUE", temp.data$group)+1]

ggplot(temp.data, aes(x = log(time), y = log(-log(surv)), ymin = log(-log(lower)), ymax = log(-log(upper
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() +
        xlim(4, 7) + ylim(-4, 2) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 71 rows containing missing values (geom_path).
## Warning:  Removed 66 rows containing missing values (geom_path).
## Warning:  Removed 73 rows containing missing values (geom_path).
## Warning:  Removed 69 rows containing missing values (geom_path).
## Warning:  Removed 64 rows containing missing values (geom_path).
## Warning:  Removed 62 rows containing missing values (geom_path).
## Warning:  Removed 65 rows containing missing values (geom_path).
## Warning:  Removed 63 rows containing missing values (geom_path).
```



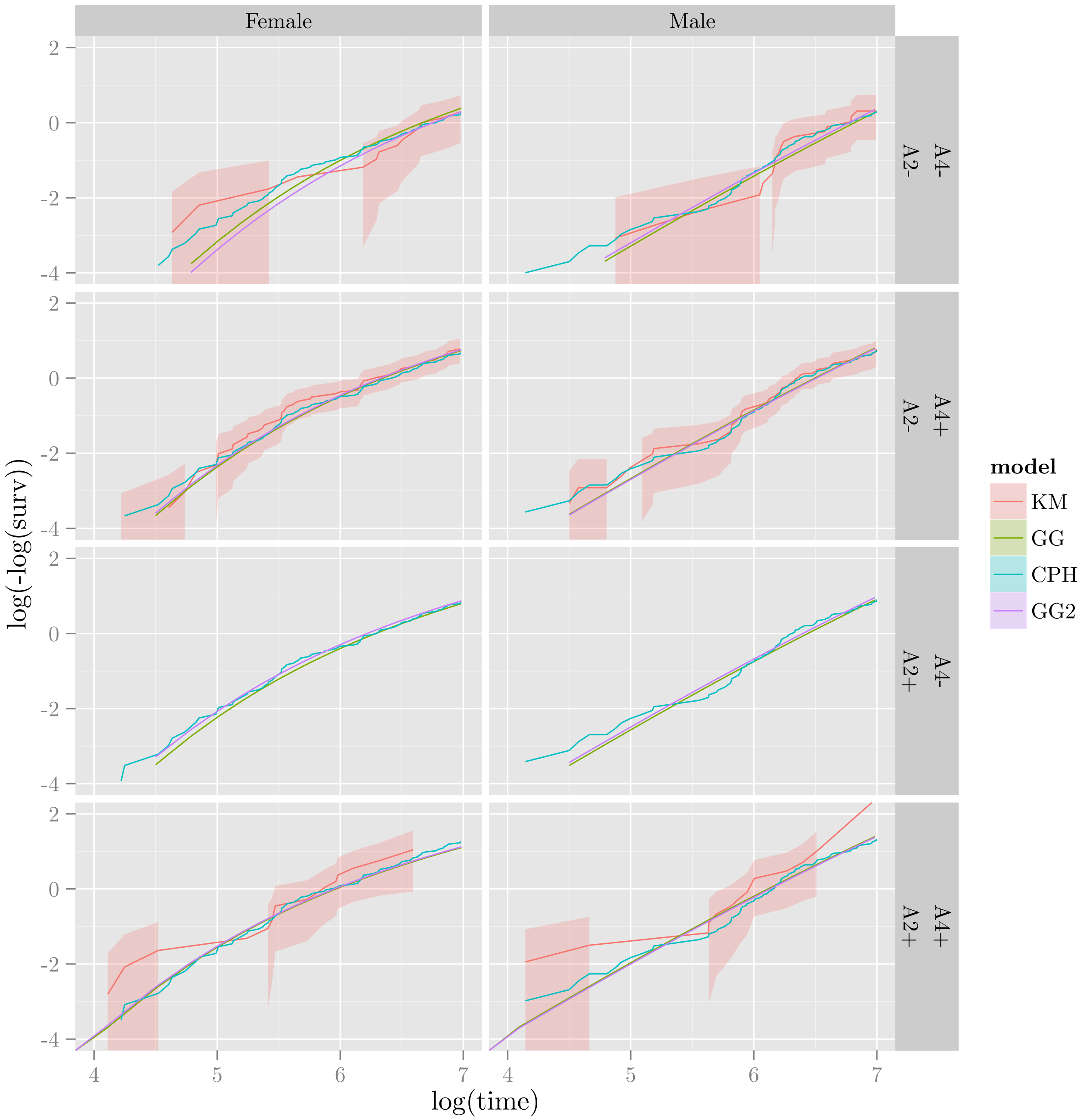

```
ggplot(temp.data, aes(x = time, y = surv, ymin = lower, ymax = upper, colour = model, fill = model)) +
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() + xlim(0, 2000) + ylim(0, 1) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
```



An alternative take, showing errors with the KMs only.

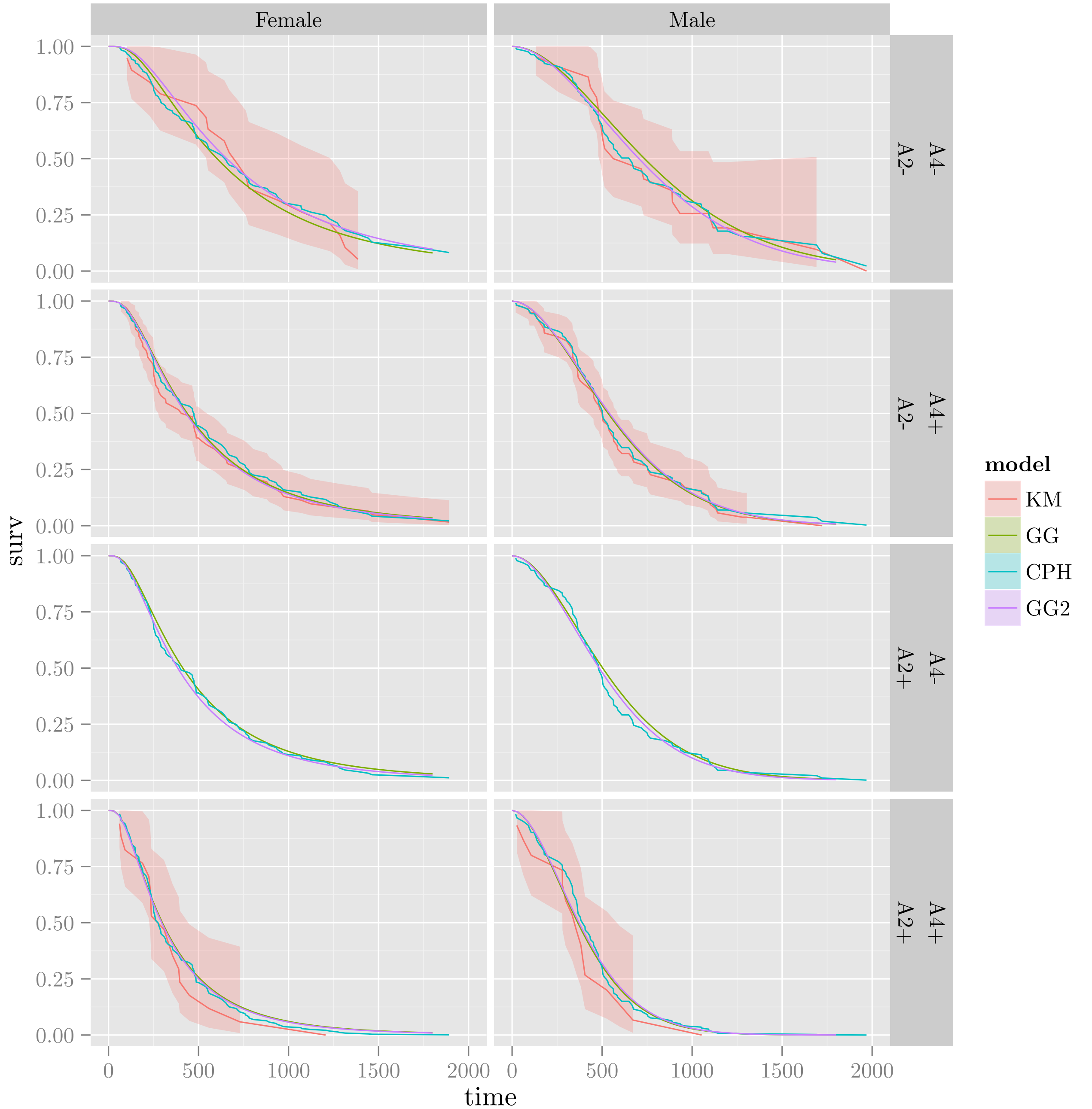
```
temp.data$lower[temp.data$model != "KM"] = NA
temp.data$upper[temp.data$model != "KM"] = NA
ggplot(temp.data, aes(x = log(time), y = log(-log(surv)), ymin = log(-log(lower)), ymax = log(-log(upper
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() +
        xlim(4, 7) + ylim(-4, 2) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 71 rows containing missing values (geom_path).
## Warning:  Removed 66 rows containing missing values (geom_path).
## Warning:  Removed 73 rows containing missing values (geom_path).
## Warning:  Removed 69 rows containing missing values (geom_path).
```

```
## Warning:  Removed 64 rows containing missing values (geom_path).
## Warning:  Removed 62 rows containing missing values (geom_path).
## Warning:  Removed 65 rows containing missing values (geom_path).
## Warning:  Removed 63 rows containing missing values (geom_path).
```



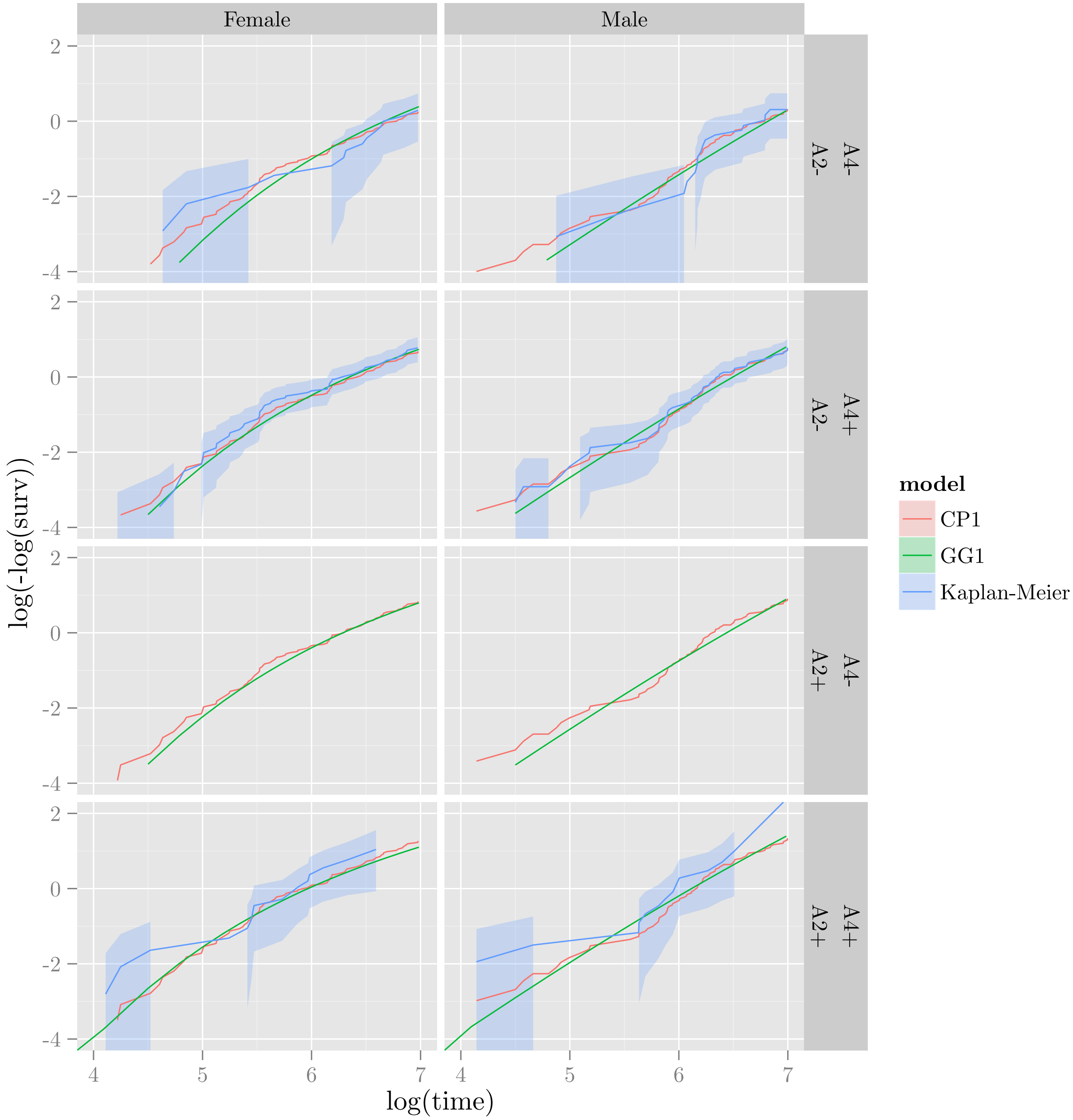

```
ggplot(temp.data, aes(x = time, y = surv, ymin = lower, ymax = upper, colour = model, fill = model)) +
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() + xlim(0, 2000) + ylim(0, 1) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
```

```
## Warning:  Removed 2 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
```



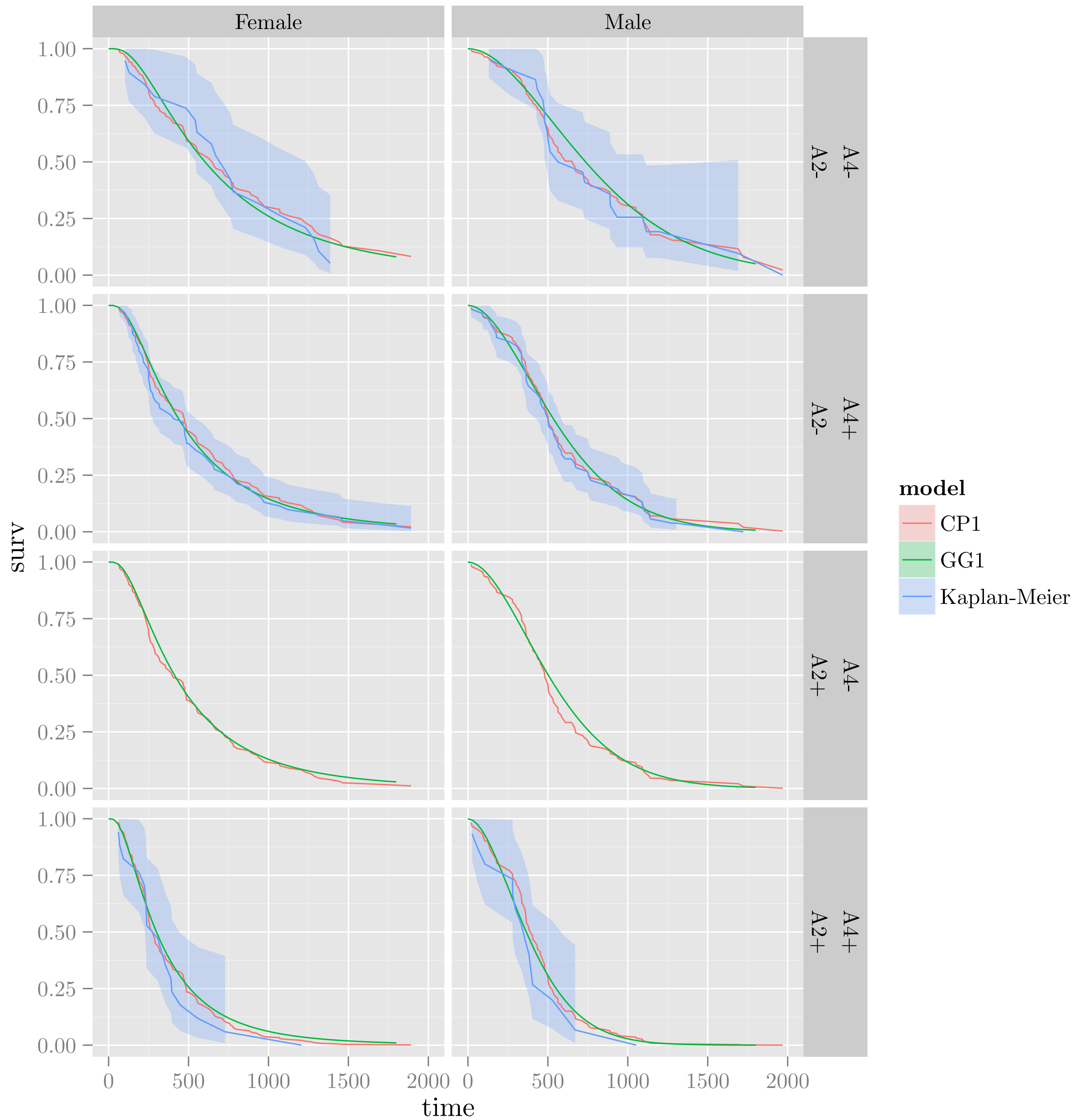

```
temp.data$lower[temp.data$model != "KM"] = NA
temp.data$upper[temp.data$model != "KM"] = NA
temp.data = temp.data[temp.data$model != "GG2",]
temp.data$model = c("KM" = "Kaplan-Meier", "GG" = "GG1", "CPH" = "CP1")[temp.data$model]
ggplot(temp.data, aes(x = log(time), y = log(-log(surv)), ymin = log(-log(lower)), ymax = log(-log(upper
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() +
        xlim(4, 7) + ylim(-4, 2) +
        facet_grid(A2 ~ A4 ~ Sex)
```

```
## Warning:  Removed 46 rows containing missing values (geom_path).
## Warning:  Removed 41 rows containing missing values (geom_path).
## Warning:  Removed 48 rows containing missing values (geom_path).
## Warning:  Removed 44 rows containing missing values (geom_path).
## Warning:  Removed 39 rows containing missing values (geom_path).
## Warning:  Removed 37 rows containing missing values (geom_path).
## Warning:  Removed 40 rows containing missing values (geom_path).
## Warning:  Removed 38 rows containing missing values (geom_path).
```




```
ggplot(temp.data, aes(x = time, y = surv, ymin = lower, ymax = upper, colour = model, fill = model)) +
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() + xlim(0, 2000) + ylim(0, 1) +
```

```
       facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
## Warning:  Removed 2 rows containing missing values (geom_path).
```



7 Model selection

It looks like that's as far as we can go with tweaking the fits. Time to put the different models against each other on the holdout data, and choose a winner.

DIY IBS, wooo.

```
calcIBS = function(surv, pred, pred_times, max_time)
{
        stopifnot(nrow(surv) == nrow(pred) && length(pred_times) == ncol(pred))

        n = nrow(surv)
        marg_survfit = survfit(surv ~ 1)
        marg_censfit = survfit(Surv(surv[,1], !surv[,2]) ~ 1)
        marg_surv_func = approxfun(marg_survfit$time, marg_survfit$surv, method = "constant", yleft = 1,
        marg_cens_func = approxfun(marg_censfit$time, marg_censfit$surv, method = "constant", yleft = 1,

        pred_funcs = apply(pred, 1, function(pat_preds) approxfun(pred_times, pat_preds, yleft = 1, yrig

        indiv_patient_bsc = function(pat_i, tstars)
        {
                observed_time = surv[pat_i, 1]
                observed_event = surv[pat_i, 2]
                pred_func = pred_funcs[[pat_i]]
                category = 1*(observed_time <= tstars & observed_event) + 2*(observed_time > tstars) + 3
                bsc = rep(NA, length(tstars))
                bsc[category == 1] = pred_func(tstars[category == 1])^2 / marg_cens_func(observed_time)
                bsc[category == 2] = (1 - pred_func(tstars[category == 2]))^2 / marg_cens_func(tstars[ca
                bsc[category == 3] = 0
                bsc
        }

        bsc_func = function(tstars) { rowMeans(sapply(1:n, function(pat_i) indiv_patient_bsc(pat_i, tsta

        weight_func = function(tstars) { (1 - marg_surv_func(tstars)) / (1 - marg_surv_func(max_time)) }

        # Be slack and do trapezoidal int. with a fine grid.  It should be possible
        # to calulate the int. exactly but I cbfed.
        int_grid = seq(0, max_time, length.out = 1e3)
        bsc_vals = bsc_func(int_grid)
        weight_vals = weight_func(int_grid)
        int_vals = bsc_vals * weight_vals
        ibsc = (2*sum(int_vals) - int_vals[1] - int_vals[length(int_vals)]) * (diff(range(int_grid))) /

        return(list(bsc = bsc_vals, weights = weight_vals, eval_times = int_grid, ibsc = ibsc))
}
```

Calculate survival probability predictions for each of the models, on the validation data.

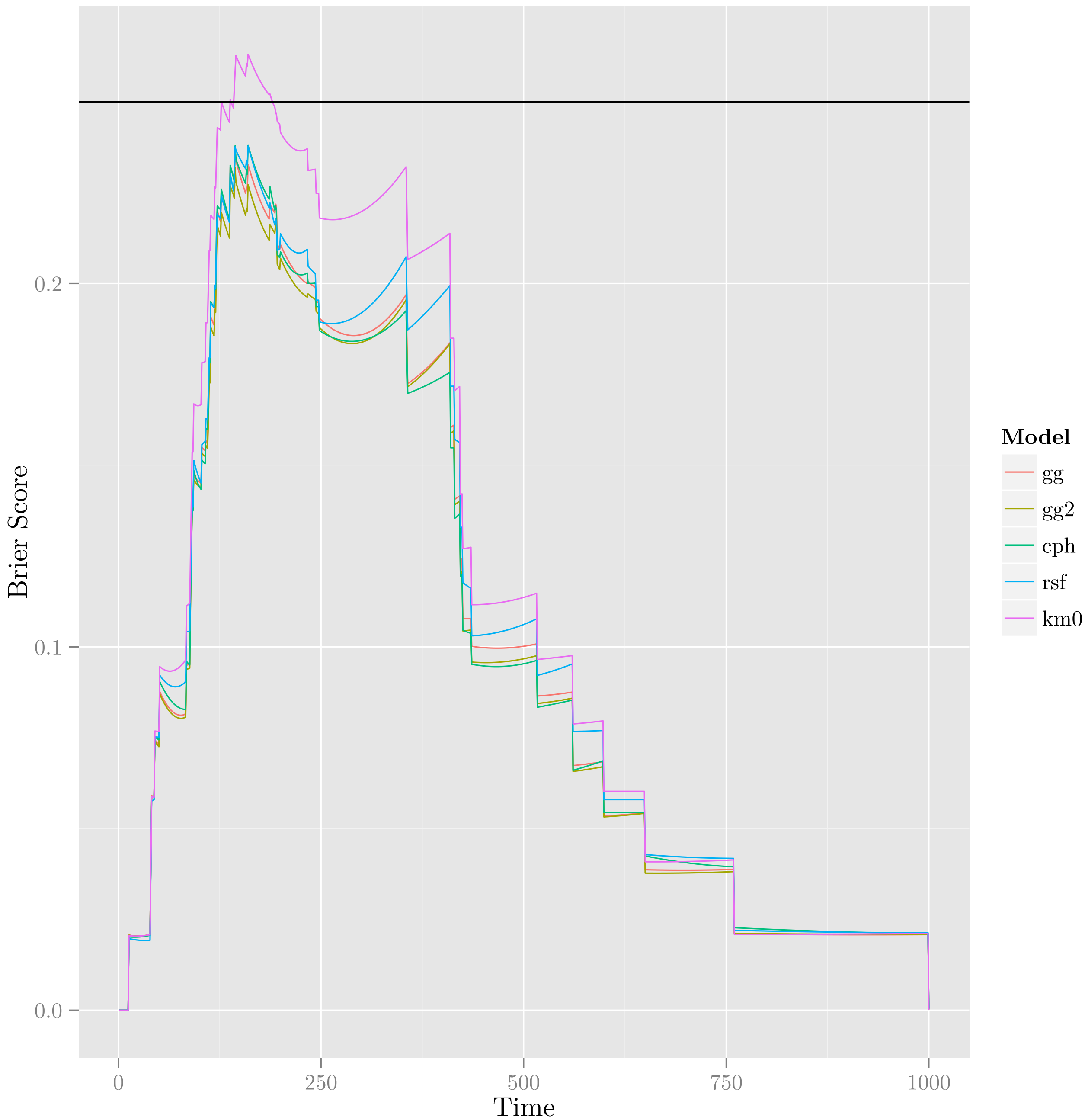
```
ibs_times = sort(unique(data.val$Time))
ibs_preds_gg = as.matrix(t(sapply(summary(fit.gg, newdata = data.val, type = "survival", t = ibs_times),
ibs_preds_gg2 = as.matrix(t(sapply(summary(fit.gg2, newdata = data.val, type = "survival", t = ibs_times
temp_cox_preds = survfit(fit.cph, newdata = data.val)
ibs_preds_cph = simplify2array(tapply(1:length(temp_cox_preds$time), rep(names(temp_cox_preds$strata), t
        approx(x = temp_cox_preds$time[strat_i], y = temp_cox_preds$surv[strat_i], xout = ibs_times, met
ibs_preds_cph = t(ibs_preds_cph[,rownames(data.val)])
temp_rsf_preds = predict(fit.rsf, newdata = data.val)
ibs_preds_rsf = t(apply(temp_rsf_preds$survival, 1, function(survs) approx(temp_rsf_preds$time.interest,
# Patients (from data.val) are in rows, times (from ibs_times) in columns.

# Add a no-information KM predictor
```

```
temp_km0 = survfit(Surv(Time, DSD) ~ 1, data)
ibs_preds_km0 = t(matrix(rep(approx(temp_km0$time, temp_km0$surv, xout = ibs_times, method = "constant",
ibs_preds_all = list(gg = ibs_preds_gg, gg2 = ibs_preds_gg2, cph = ibs_preds_cph, rsf = ibs_preds_rsf, k
```

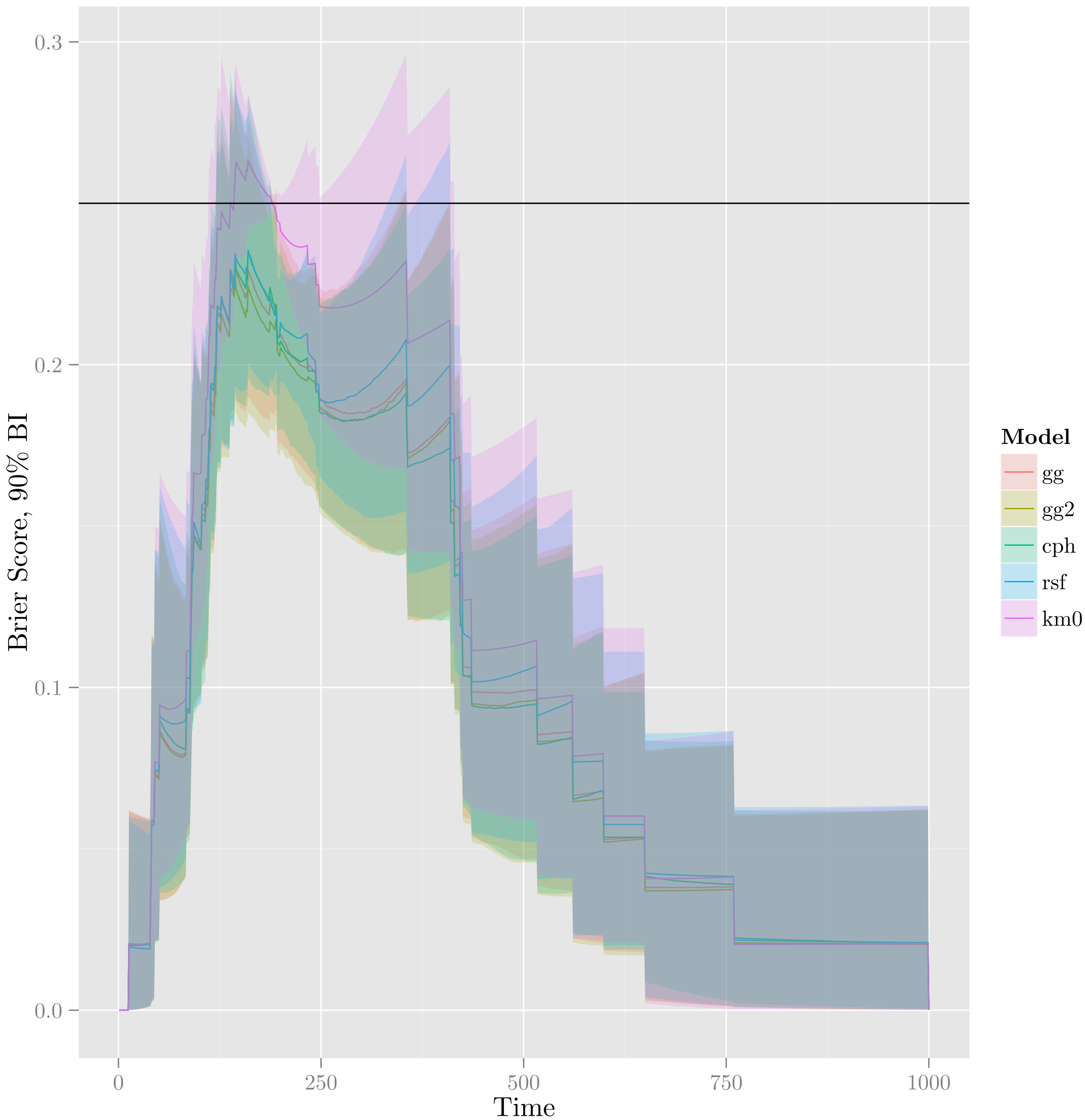
Evaluate IBS point estimates. BS paths over time on bootstrap samples of the holdout set.

```
set.seed(20150111)
ibs_eval_times = calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_gg, ibs_times, max(data.val$Time))
# bsc_boot2 = lapply(ibs_preds_all, function(preds) boot(data.val, statistic = function(d, i) calcIBS(Su
# bsc_boot2ci = lapply(bsc_boot2, function(single_boot) t(sapply(1:length(ibs_eval_times), function(time
#  temp = try(boot.ci(single_boot, index = time_index, type = "bca")£bca, silent = TRUE)
#  if (class(temp) == "try-error" || is.null(temp)) { temp = rep(NA, 5) }
#  temp })))
bsc_boots = laply(1:500, function(i) {
        if (i %% 50 == 0)       { message(i) }
        boot_samp = sample.int(nrow(data.val), replace = TRUE)
        gg = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_gg[boot_samp,], ibs_times,
        gg2 = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_gg2[boot_samp,], ibs_time
        cph = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_cph[boot_samp,], ibs_time
        rsf = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_rsf[boot_samp,], ibs_time
        km0 = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_km0[boot_samp,], ibs_time
        rbind(gg, gg2, cph, rsf, km0)
})

## 50
## 100
## 150
## 200
## 250
## 300
## 350
## 400
## 450
## 500
```

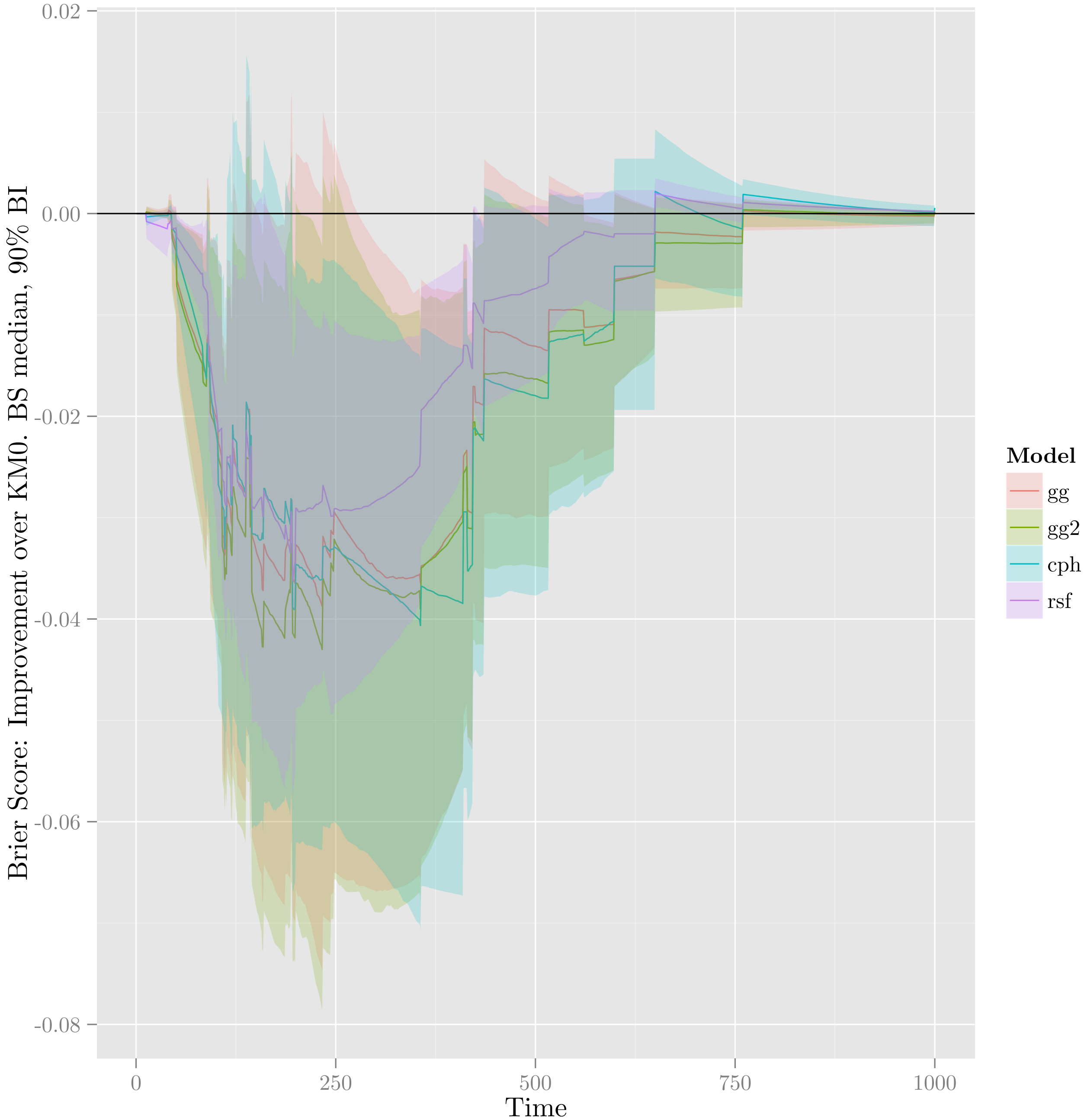
```
temp = sapply(list(gg = ibs_preds_gg, gg2 = ibs_preds_gg2, cph = ibs_preds_cph, rsf = ibs_preds_rsf, km0
temp = melt(temp)
colnames(temp) = c("Time", "Model", "BS")
ggplot(temp, aes(x = Time, y = BS, colour = Model)) + geom_line() + ylab("Brier Score") + geom_hline(yin
```




```r
temp = melt(aaply(bsc_boots, 2:3, quantile, probs = c(0.05, 0.5, 0.95)))
colnames(temp) = c("Model", "Time", "Quantile", "Value")
temp$Quantile = paste("Q", gsub("%", "", temp$Quantile), sep = "")
temp = dcast(temp, Model + Time ~ Quantile, value.var = "Value")
ggplot(temp, aes(x = Time, y = Q50, ymin = Q5, ymax = Q95, colour = Model, fill = Model)) + geom_line()
```



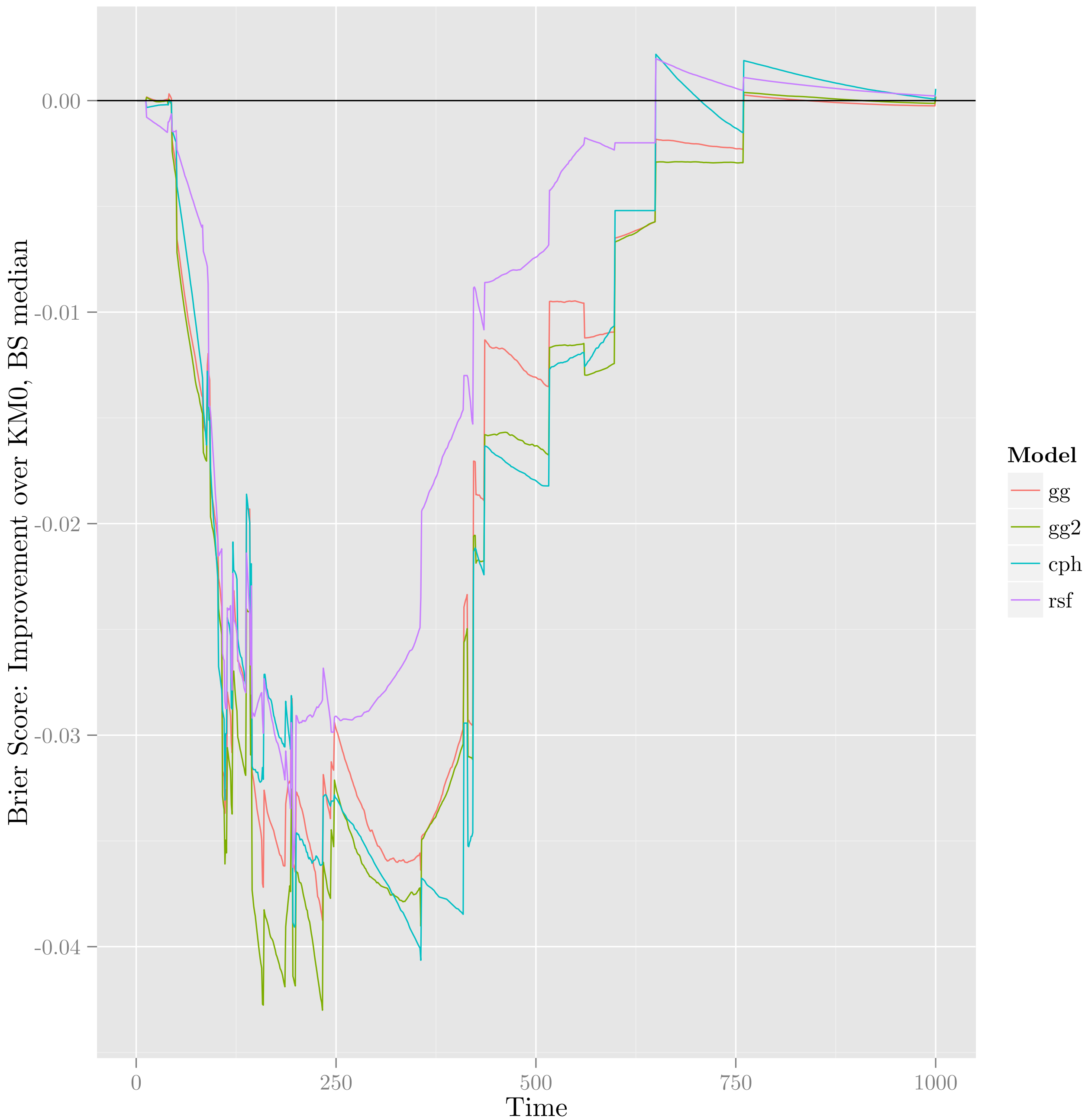

```
bsc_boots_diff = aaply(bsc_boots, 2, function(x) x - bsc_boots[,5,])[1:4,,]
temp = melt(aaply(bsc_boots_diff, c(1,3), quantile, probs = c(0.05, 0.5, 0.95)))
colnames(temp) = c("Model", "Time", "Quantile", "Value")
temp$Quantile = paste("Q", gsub("%", "", temp$Quantile), sep = "")
temp = dcast(temp, Model + Time ~ Quantile, value.var = "Value")
ggplot(temp, aes(x = Time, y = Q50, ymin = Q5, ymax = Q95, colour = Model, fill = Model)) + geom_line()
```




```
ggplot(temp, aes(x = Time, y = Q50, ymin = Q5, ymax = Q95, colour = Model, fill = Model)) + geom_line()

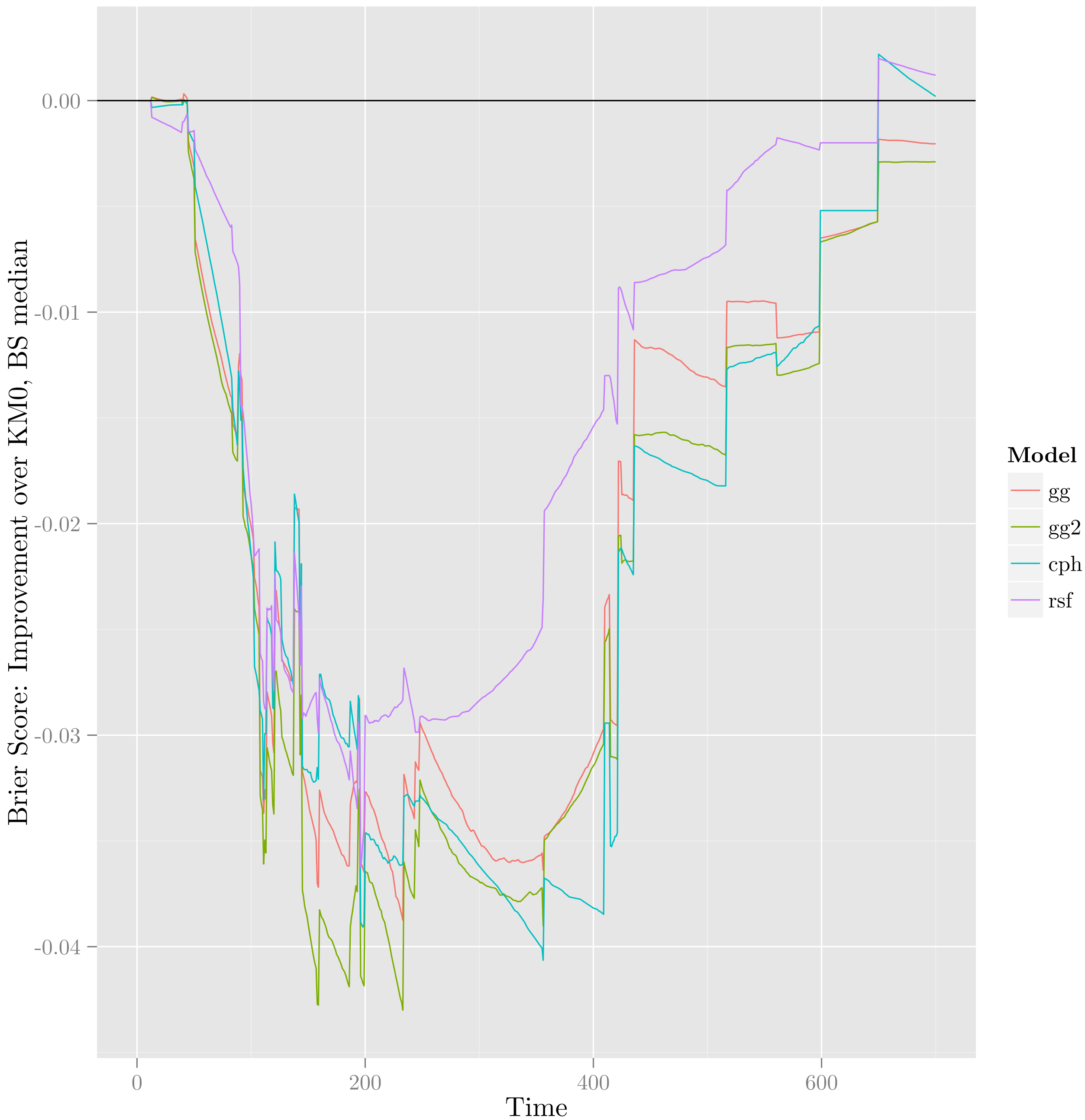
## Warning: Removed 1200 rows containing missing values (geom_path).
```


```
ggplot(temp, aes(x = Time, y = Q50, colour = Model)) + geom_line() + ylab("Brier Score: Improvement over
```




```
ggplot(temp, aes(x = Time, y = Q50, colour = Model)) + geom_line() + ylab("Brier Score: Improvement over
```

```
## Warning:  Removed 1200 rows containing missing values (geom_path).
```

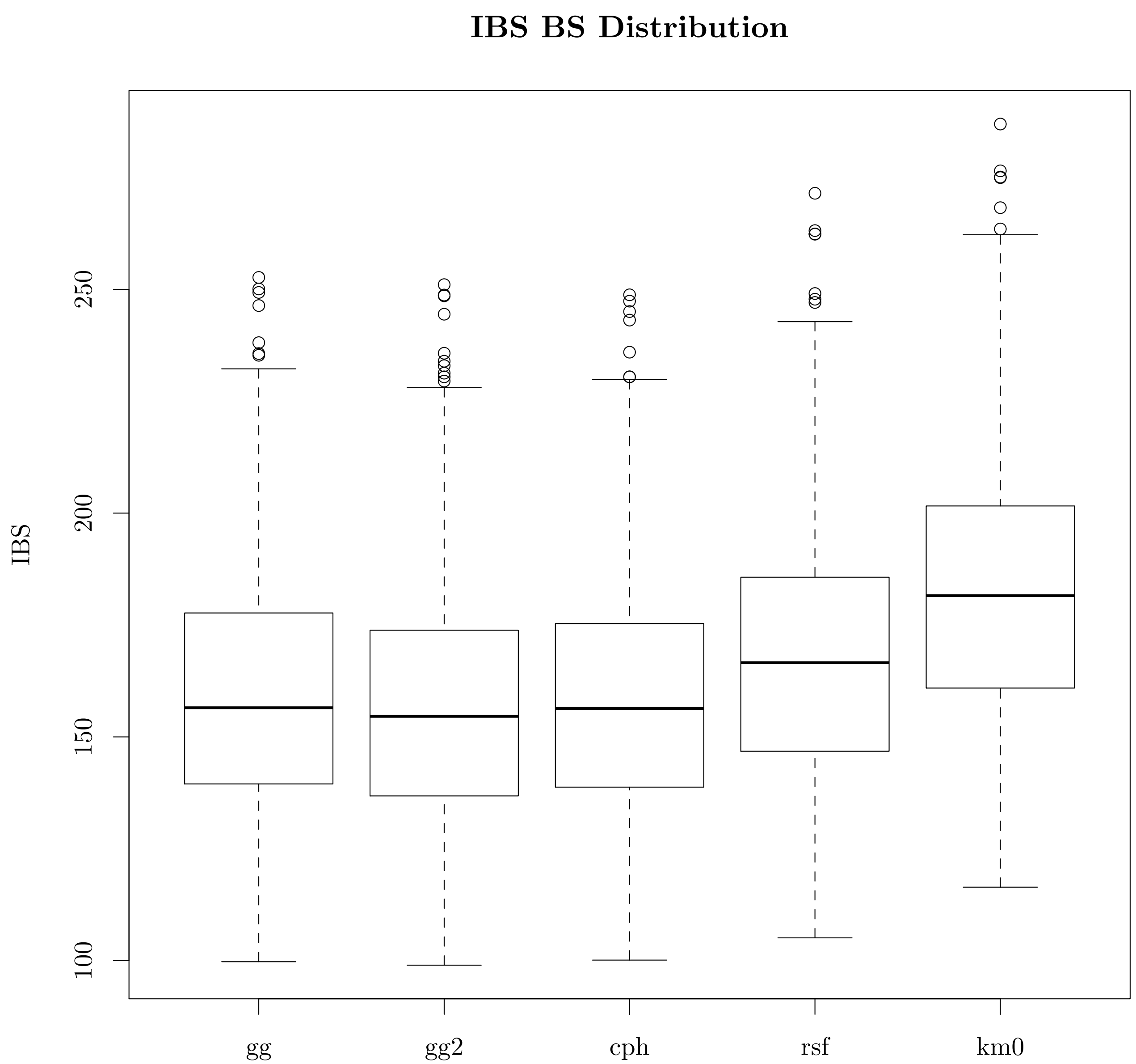


IBS comparisons.

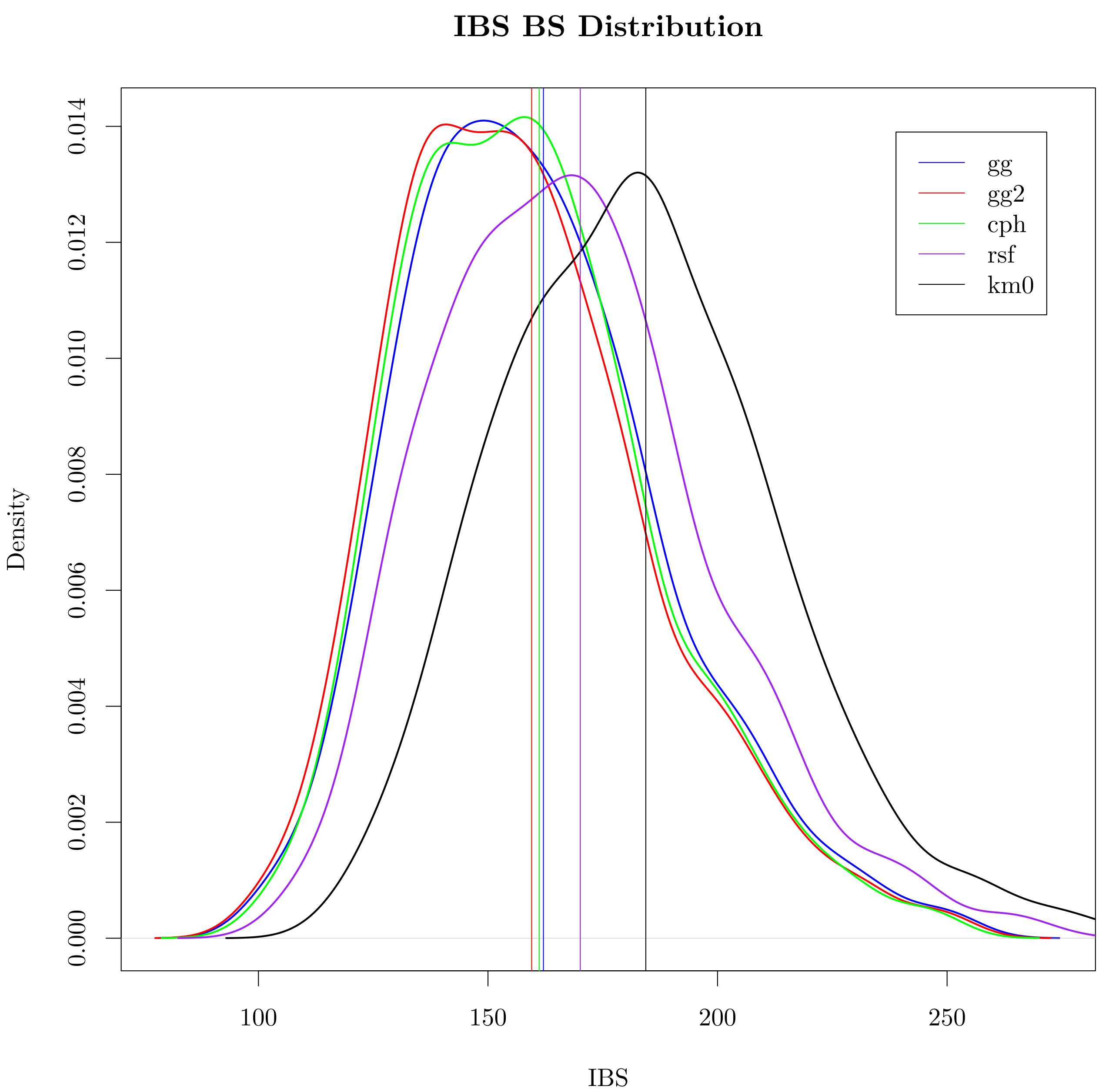
```
set.seed(20150111)
ibsc_boots = t(sapply(1:5e2, function(i) {
        if (i %% 5e1 == 0)      { message(i) }
        boot_samp = sample.int(nrow(data.val), replace = TRUE)
        gg = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_gg[boot_samp,], ibs_times,
        gg2 = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_gg2[boot_samp,], ibs_time
        cph = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_cph[boot_samp,], ibs_time
        rsf = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_rsf[boot_samp,], ibs_time
        km0 = calcIBS(Surv(data.val$Time, data.val$DSD)[boot_samp,], ibs_preds_km0[boot_samp,], ibs_time
        c(gg, gg2, cph, rsf, km0)
}))
```

```
## 50
## 100
## 150
## 200
## 250
## 300
## 350
## 400
## 450
## 500
colnames(ibsc_boots) = c("gg", "gg2", "cph", "rsf", "km0")
```

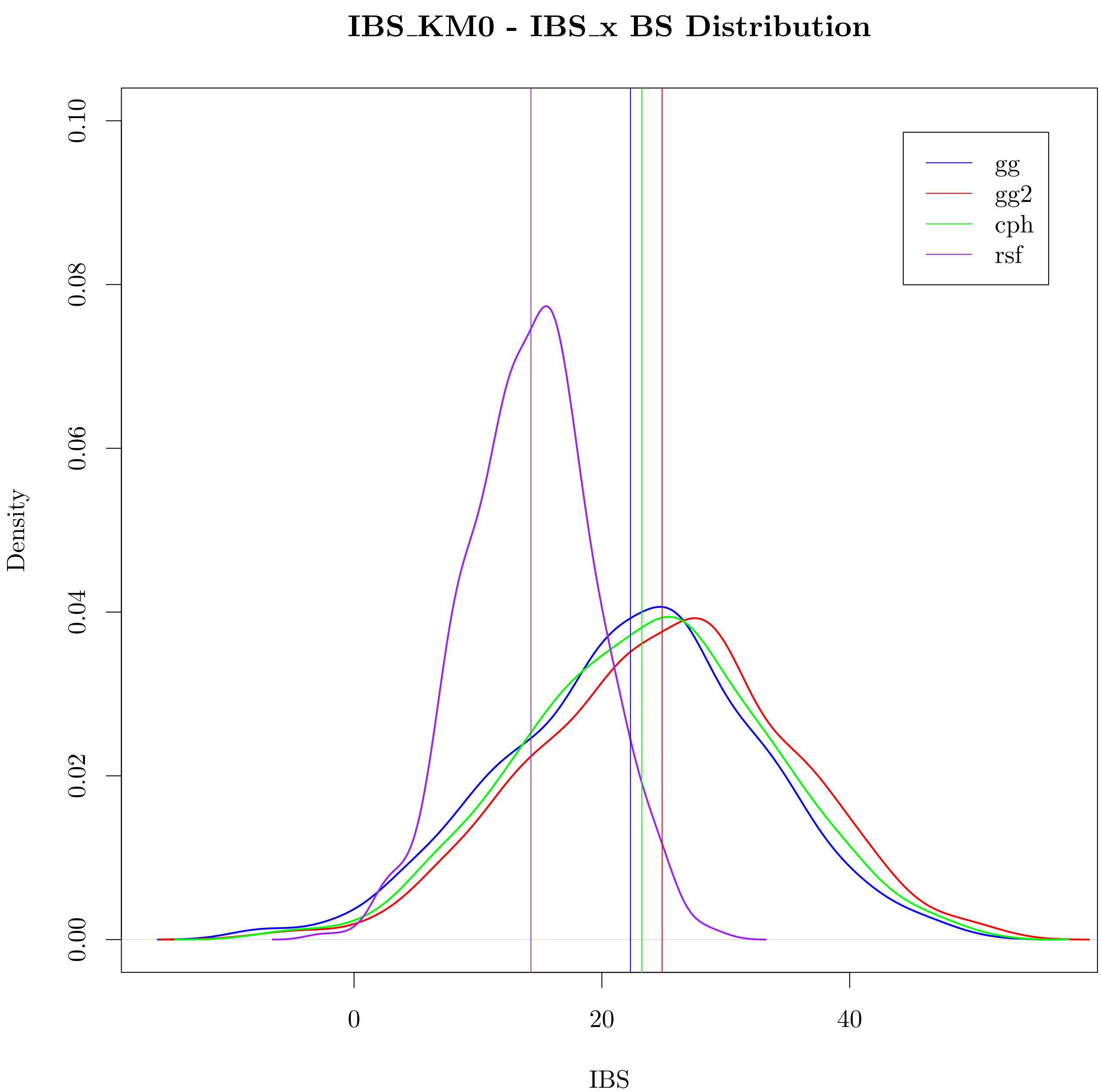
```
calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_gg, ibs_times, max(data.val$Time))$ibs
## [1] 162.1
calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_gg2, ibs_times, max(data.val$Time))$ibs
## [1] 159.5
calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_cph, ibs_times, max(data.val$Time))$ibs
## [1] 161.2
calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_rsf, ibs_times, max(data.val$Time))$ibs
## [1] 170.1
calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_km0, ibs_times, max(data.val$Time))$ibs
## [1] 184.4
boxplot(ibsc_boots, main = "IBS BS Distribution", ylab = "IBS")
```




```
plot(density(ibsc_boots[,1]), col = "blue", lwd = 2, main = "IBS BS Distribution", xlab = "IBS")
lines(density(ibsc_boots[,2]), col = "red", lwd = 2)
lines(density(ibsc_boots[,3]), col = "green", lwd = 2)
lines(density(ibsc_boots[,4]), col = "purple", lwd = 2)
lines(density(ibsc_boots[,5]), col = "black", lwd = 2)
abline(v = calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_gg, ibs_times, max(data.val$Time))$ibs,
abline(v = calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_gg2, ibs_times, max(data.val$Time))$ibs,
abline(v = calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_cph, ibs_times, max(data.val$Time))$ibs,
abline(v = calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_rsf, ibs_times, max(data.val$Time))$ibs,
abline(v = calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_km0, ibs_times, max(data.val$Time))$ibs,
legend("topright", legend = c("gg", "gg2", "cph", "rsf", "km0"), col = c("blue", "red", "green", "purple
```




```
plot(density(ibsc_boots[,5] - ibsc_boots[,1]), col = "blue", lwd = 2, main = "IBS\\_KM0 - IBS\\_x BS Dis
lines(density(ibsc_boots[,5] - ibsc_boots[,2]), col = "red", lwd = 2)
lines(density(ibsc_boots[,5] - ibsc_boots[,3]), col = "green", lwd = 2)
lines(density(ibsc_boots[,5] - ibsc_boots[,4]), col = "purple", lwd = 2)
abline(v = (calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_km0, ibs_times, max(data.val$Time))$ibs
abline(v = (calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_km0, ibs_times, max(data.val$Time))$ibs
abline(v = (calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_km0, ibs_times, max(data.val$Time))$ibs
abline(v = (calcIBS(Surv(data.val$Time, data.val$DSD), ibs_preds_km0, ibs_times, max(data.val$Time))$ibs
legend("topright", legend = c("gg", "gg2", "cph", "rsf"), col = c("blue", "red", "green", "purple"), lty
```



Do some proper BCA bootstrapping on the differences, just as a double-check test.

```
set.seed(20150111)
ibsc_boots2 = boot(data.val, statistic = function(d, i) {
        gg = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_gg[i,], ibs_times, max(d$Time[i]))$ibs
        gg2 = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_gg2[i,], ibs_times, max(d$Time[i]))$ibs
        cph = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_cph[i,], ibs_times, max(d$Time[i]))$ibs
        rsf = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_rsf[i,], ibs_times, max(d$Time[i]))$ibs
        km0 = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_km0[i,], ibs_times, max(d$Time[i]))$ibs
        c(gg - km0, gg2 - km0, cph - km0, rsf - km0, gg - rsf, gg2 - rsf, cph - rsf, gg - cph, gg2 - cph
}, R = 500)
ibsc_boots2_ci = t(sapply(1:length(ibsc_boots2$t0), function(i) boot.ci(ibsc_boots2, index = i, type = '
rownames(ibsc_boots2_ci) = c("gg-km0", "gg2-km0", "cph-km0", "rsf-km0", "gg-rsf", "gg2-rsf", "cph-rsf",
colnames(ibsc_boots2_ci) = c("level", "orderi1", "orderi2", "lci", "uci")
ibsc_boots2
```

```
##
## ORDINARY NONPARAMETRIC BOOTSTRAP
##
##
## Call:
## boot(data = data.val, statistic = function(d, i) {
##     gg = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_gg[i, ],
##         ibs_times, max(d$Time[i]))$ibs
##     gg2 = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_gg2[i,
##         ], ibs_times, max(d$Time[i]))$ibs
##     cph = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_cph[i,
##         ], ibs_times, max(d$Time[i]))$ibs
##     rsf = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_rsf[i,
##         ], ibs_times, max(d$Time[i]))$ibs
##     km0 = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_km0[i,
##         ], ibs_times, max(d$Time[i]))$ibs
##     c(gg - km0, gg2 - km0, cph - km0, rsf - km0, gg - rsf, gg2 -
##         rsf, cph - rsf, gg - cph, gg2 - cph, gg - gg2)
## }, R = 500)
##
##
## Bootstrap Statistics :
##      original   bias    std. error
## t1*  -22.3076 -0.17520       9.532
## t2*  -24.8647 -0.09403       9.606
## t3*  -23.2248 -0.37205       9.365
## t4*  -14.2733 -0.06822       4.884
## t5*   -8.0342 -0.10698       5.437
## t6*  -10.5914 -0.02581       5.507
## t7*   -8.9515 -0.30383       5.362
## t8*    0.9172  0.19685       2.317
## t9*   -1.6399  0.27802       1.538
## t10*   2.5571 -0.08117       1.750
```

```
ibsc_boots2_ci
```

```
##         level orderi1 orderi2      lci    uci
## gg-km0   0.95   13.01   488.9 -40.3228 -1.913
## gg2-km0  0.95   13.15   489.0 -43.6730 -5.025
## cph-km0  0.95   14.97   490.4 -41.7017 -4.139
## rsf-km0  0.95   10.17   486.0 -24.5684 -5.101
## gg-rsf   0.95   19.02   493.1 -17.1187  5.000
## gg2-rsf  0.95   14.32   490.0 -20.9064  1.084
## cph-rsf  0.95   15.74   490.9 -19.3549  3.149
## gg-cph   0.95   11.40   487.1  -3.3813  5.809
## gg2-cph  0.95    6.39   477.7  -4.6303  1.218
## gg-gg2   0.95   26.24   496.2  -0.1672  7.060
```

All models perform equivalently on the validation set. Select the simplest: gg.

Final model fitting:

```
data.all = rbind(data[colnames(data.val)], data.val)
head(data.all)
```

```
##           Time  DSD  SexM AgeCent LocBody SizeCent    A2   A4
```

```
## NSWPCN_4   937 TRUE  TRUE     -16   FALSE       -1 FALSE TRUE
## NSWPCN_7   247 TRUE FALSE      -1   FALSE       -2 FALSE TRUE
## NSWPCN_9   587 TRUE  TRUE       5   FALSE       10 FALSE TRUE
## NSWPCN_10  177 TRUE  TRUE      -9   FALSE       10 FALSE TRUE
## NSWPCN_13  247 TRUE FALSE     -19    TRUE       20 FALSE TRUE
## NSWPCN_20  256 TRUE FALSE      -8   FALSE        0 FALSE TRUE

fit.final.gg = flexsurvreg(Surv(Time, DSD) ~ SexM + SizeCent + A2 + A4,
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM),
        data = data.all, dist = "gengamma")
fit.final.gg2 = flexsurvreg(Surv(Time, DSD) ~ SexM + SizeCent + A2 + A4 + I(SexM == FALSE & A2 == FALSE
    anc = list(
        sigma = ~ SexM,
        Q = ~ SexM),
    data = data.all, dist = "gengamma")
fit.final.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 + A4, data = data.all, x = TRUE, y
set.seed(20150111)
fit.final.rsf = rfsrc(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + SizeCent + A2 + A4, data = data.all,
fit.final.km0 = survfit(Surv(Time, DSD) ~ 1, data.all)
saveRDS(list(gg = fit.final.gg, km0 = fit.final.km0, gg2 = fit.final.gg2, cph = fit.final.cph, rsf = fit
```

8 Session information

```
sessionInfo()

## R version 3.1.1 (2014-07-10)
## Platform: x86_64-unknown-linux-gnu (64-bit)
##
## locale:
##  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
##  [3] LC_TIME=en_US.UTF-8        LC_COLLATE=en_US.UTF-8
##  [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
##  [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
##  [9] LC_ADDRESS=C               LC_TELEPHONE=C
## [11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
##
## attached base packages:
## [1] parallel  splines   methods   stats     graphics  grDevices utils
## [8] datasets  base
##
## other attached packages:
##  [1] boot_1.3-13           MASS_7.3-35           ggplot2_1.0.0
##  [4] plyr_1.8.1            reshape2_1.4          randomForestSRC_1.5.5
##  [7] flexsurv_0.5          rJava_0.9-6           survival_2.37-7
## [10] tikzDevice_0.7.0      filehash_2.2-2        knitr_1.8
##
## loaded via a namespace (and not attached):
##  [1] codetools_0.2-9  colorspace_1.2-4 deSolve_1.11     digest_0.6.4
##  [5] evaluate_0.5.5   formatR_1.0      grid_3.1.1       gtable_0.1.2
##  [9] highr_0.4        labeling_0.3     muhaz_1.2.6      munsell_0.4.2
```

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## [13] mvtnorm_1.0-1    proto_0.3-10     Rcpp_0.11.3      scales_0.2.4
## [17] stringr_0.6.2    tools_3.1.1
```