```r
opts_chunk$set (warning = FALSE, message = FALSE, tidy=TRUE, echo=TRUE)
options(warn = -1)

rm(list=ls())

library(survival)
library(knitr)
library(kableExtra)

library(glmnet)

## Loading required package:  Matrix
## Loaded glmnet 4.1-7

library(ggplot2)

# Following loaded in "forest_search_v0.R"
suppressMessages(library(randomForest))
#library(SPlit)

library(grf)
library(policytree)
library(DiagrammeR)

#library(cowplot)

library(data.table)
library(plyr)
library(aVirtualTwins)
# Not sure formatR is needed?
#library(formatR)
suppressMessages(library(gridExtra))

library(speff2trial)

## Loading required package:  leaps

# Location where code is stored
codepath<-c("/Users/larryleon/Documents/GitHub/forestSearch/R/")
source(paste0(codepath,"source_forestsearch_v0.R"))
source_fs_functions(file_loc=codepath)

save_output<-TRUE
```

```r
# NOTE: ZDV+DDI = arm 1, DDI = arm 3
t.start.all <- proc.time()[3]
# GRF analysis To guide selection of binary cutpoints
df.analysis <- subset(ACTG175, arms %in% c(1, 3))
df.analysis <- within(df.analysis, {
    id <- as.numeric(c(1:nrow(df.analysis)))
    time_days <- days
    treat <- ifelse(arms == 1, 1, 0)
})

# plot(survfit(Surv(time_days,cens)~treat,data=df.analysis))
```

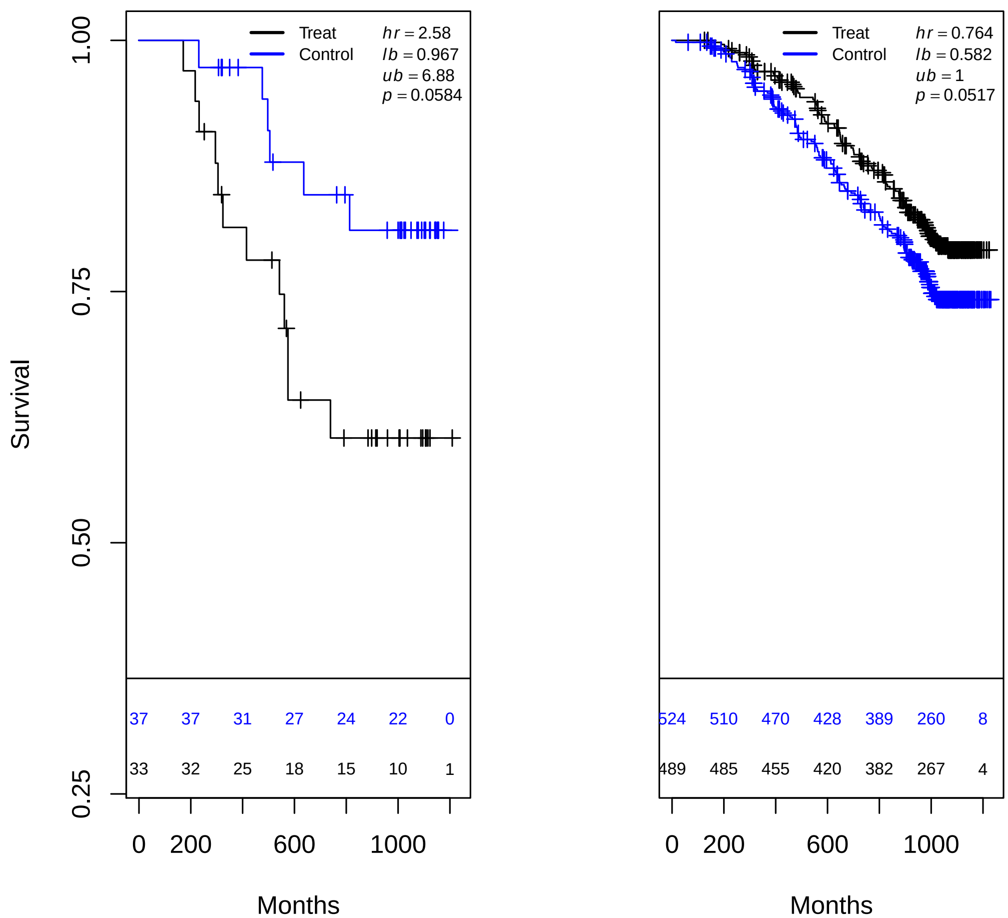
```r
coxph(Surv(time_days, cens) ~ treat, data = df.analysis)

## Call:
## coxph(formula = Surv(time_days, cens) ~ treat, data = df.analysis)
##
##          coef exp(coef) se(coef)      z     p
## treat -0.1751    0.8394   0.1324 -1.323 0.186
##
## Likelihood ratio test=1.76  on 1 df, p=0.1849
## n= 1083, number of events= 231

confounders.name <- c("age", "wtkg", "karnof", "cd40", "cd80", "hemo", "homo", "drugs",
    "race", "gender", "oprior", "symptom")
outcome.name <- c("time_days")
event.name <- c("cens")
id.name <- c("id")
treat.name <- c("treat")

n.min <- 60
dmin.grf <- 12
frac.tau <- 0.8
```

```r
grf.est <- grf.subg.harm.survival(data = df.analysis, confounders.name = confounders.name,
    outcome.name = outcome.name, event.name = event.name, id.name = id.name, treat.name = treat.name,
    n.min = n.min, dmin.grf = dmin.grf, frac.tau = frac.tau, details = TRUE)

## tau= 816.8
##    leaf.node control.mean control.size control.se treated.mean treated.size
## 1          2    -24.43487    854.00000    9.84580     24.43487    854.00000
## 2          3     17.11732    229.00000   15.12873    -17.11732    229.00000
## 3          4     34.31848    147.00000   22.07601    -34.31848    147.00000
## 4          5    -50.00731    381.00000   14.20806     50.00731    381.00000
## 5          6     62.41513    100.00000   27.01085    -62.41513    100.00000
## 6          7    -20.17814    455.00000   12.92982     20.17814    455.00000
## 31        10     85.72443     70.00000   43.28023    -85.72443     70.00000
## 41        11    -60.32406    224.00000   25.83681     60.32406    224.00000
## 51        12     53.97111    100.00000   20.12385    -53.97111    100.00000
## 61        13    -37.71409    449.00000    9.87107     37.71409    449.00000
## 8         15     31.11643    164.00000   12.84153    -31.11643    164.00000
##    treated.se       diff depth
## 1     9.84580  -48.86974     1
## 2    15.12873   34.23465     1
## 3    22.07601   68.63697     2
## 4    14.20806 -100.01462     2
## 5    27.01085  124.83025     2
## 6    12.92982  -40.35629     2
## 31   43.28023  171.44885     3
## 41   25.83681 -120.64812     3
## 51   20.12385  107.94223     3
## 61    9.87107  -75.42819     3
## 8    12.84153   62.23286     3
##    leaf.node control.mean control.size control.se treated.mean treated.size
## 31        10     85.72443     70.00000   43.28023    -85.72443     70.00000
##    treated.se     diff depth
## 31   43.28023 171.4489     3
```

```
cat("Truncation point for RMST:", c(grf.est$tau.rmst), "\n")

## Truncation point for RMST: 816.8

# Plot manually

# plot(grf.est£tree)

# plot(grf.est£tree1)

# plot(grf.est£tree2)

# plot(grf.est£tree3)

df0.grf <- subset(grf.est$data, treat.recommend == 0)
df1.grf <- subset(grf.est$data, treat.recommend == 1)

# Terminal leaf corresponding to selected SG
cat("Terminal leaf:", c(grf.est$sg.harm.id), "\n")

## Terminal leaf: age <= 29

# action=1 --> recommend control

# Manually identify the subgroup looking at tree and terminal leaf
print(dim(df0.grf))

## [1] 70 34

check <- subset(df.analysis, cd40 <= 273 & karnof > 80 & age <= 29)
print(dim(check))

## [1] 70 29

# plot(survfit(Surv(time_days,cens)~treat,data=df.analysis))
# coxph(Surv(time_days,cens)~treat,data=df.analysis)

# if(save_output) save(grf.est,file='output/grf_actg_Arms_1vs3_final.Rdata')
```

```
# Stored results load('output/grf_actg_Arms_1vs3_final.Rdata')

cat("GRF variables in selected tree", "\n")

## GRF variables in selected tree

print(grf.est$tree.names)

## [1] "cd40"   "karnof" "wtkg"   "age"

cat("GRF cuts wrt selected tree:", "\n")

## GRF cuts wrt selected tree:

print(grf.est$tree.cuts)

## [1] "cd40 <= 273"  "karnof <= 80" "wtkg <= 81.7" "age <= 34"    "age <= 29"
## [6] "cd40 <= 311"  "cd40 <= 321"
```

```r
par(mfrow = c(1, 2))
plot.subgroup(sub1 = df0.grf, sub1C = df1.grf, tte.name = "time_days", event.name = "cens",
    treat.name = "treat", fix.rows = FALSE, byrisk = 200, show.med = FALSE, ymin = 0.4)
```




```r
# Reduce dimension via Cox lasso

xx <- as.matrix(df.analysis[, confounders.name])
yy <- as.matrix(df.analysis[, c("time_days", "cens")])
colnames(yy) <- c("time", "status")

cvfit <- cv.glmnet(xx, yy, family = "cox")  #first do 10-fold cross-validation to select lambda

m <- glmnet(xx, yy, family = "cox", lambda = cvfit$lambda.min)  #plugin the optimal lambda

conflasso.name <- confounders.name[which(m$beta != 0)]

cat("Cox-LASSO selected:", c(conflasso.name), "\n")


## Cox-LASSO selected: wtkg karnof cd40 cd80 hemo homo drugs race oprior symptom
```

```r
cat("GRF cuts wrt selected tree:", "\n")

## GRF cuts wrt selected tree:

print(grf.est$tree.cuts)

## [1] "cd40 <= 273"  "karnof <= 80" "wtkg <= 81.7" "age <= 34"    "age <= 29"
## [6] "cd40 <= 311"  "cd40 <= 321"

#'cd40 <= 273'  'karnof <= 80' 'wtkg <= 81.7' 'age <= 34'    'age <= 29'    'cd40 <= 311'  'cd40 <= 321

# Cox-LASSO selected: wtkg karnof cd40 cd80 hemo homo race symptom

# Considering continuous factors per GRF cuts Only considering hemo, homo,
# race, and symptom per lasso
df.analysis <- within(df.analysis, {
    # Age at 29 and 34
    z1a <- ifelse(age <= 29, 1, 0)
    z1b <- ifelse(age <= 34, 1, 0)
    # Wtkg 81.7
    z2 <- ifelse(wtkg <= 82, 1, 0)
    # Karnof 80
    z3 <- ifelse(karnof <= 80, 1, 0)
    # cd80 ---> median
    z4 <- ifelse(cd80 <= median(cd80), 1, 0)
    # cd40 273, 311, 321
    z5a <- ifelse(cd40 <= 273, 1, 0)
    z5b <- ifelse(cd40 <= 311, 1, 0)
    z5c <- ifelse(cd40 <= 321, 1, 0)
    z6 <- hemo
    z7 <- homo
    # z8<-drugs
    z9 <- race
    # z10<-gender z11<-oprior
    z12 <- symptom
    # Convert to factors
    v1a <- as.factor(z1a)
    v1b <- as.factor(z1b)
    v2 <- as.factor(z2)
    v3 <- as.factor(z3)
    v4 <- as.factor(z4)
    v5a <- as.factor(z5a)
    v5b <- as.factor(z5b)
    v5c <- as.factor(z5c)
    v6 <- as.factor(z6)
    v7 <- as.factor(z7)
    v8 <- as.factor(z9)
    v9 <- as.factor(z12)
})

FSconfounders.name <- c("v1a", "v1b", "v2", "v3", "v4", "v5a", "v5b", "v5c", "v6",
    "v7", "v8", "v9")

outcome.name <- c("time_days")
event.name <- c("cens")
id.name <- c("id")
```

```r
treat.name <- c("treat")

df.confounders <- df.analysis[, FSconfounders.name]
df.confounders <- dummy(df.confounders)

hr.threshold <- 1.5  # Initital candidates
hr.consistency <- 1.25  # Candidates for many splits

pconsistency.threshold <- 0.9
maxk <- 4
# maxk is max # of covariates in combination Since we want to allow generation
# of intervals for single covariate allowing for 4 can yield v1, v2 (say), and
# v3,v4 with v3 and v4 generating intervals for a single covariate

# Limit timing for forestsearch
max.minutes <- 60
nmin.fs <- 60
# stop.threshold<-0.60 # If any sg meets this, then choose this (stop here);
m1.threshold <- Inf  # Turning this off (Default)
stop.threshold <- 1
# =1 will run through all sg's meeting HR criteria pconsistency.threshold<-0.70
# # Minimum threshold (will choose max among subgroups satisfying)
fs.splits <- 1000  # How many times to split for consistency
# vi is % factor is selected in cross-validation --> higher more important Set
# liberal here, since LASSO used for selection; VI (variable importance per
# GRF) used for sorting
vi.grf.min <- 0.1
# Null, turns off grf screening Set to 5 for this heavily censored data
d.min <- 5  # Min number of events for both arms (d0.min=d1.min=d.min)
# default=5

sg_focus <- "Nsg"
split_method <- "Random"
pstop_futile <- 0.3

# Stops the consistency evaluation after first subgroup with consistency below
# pstop_futile With idea that since SG's are sorted by hazard ratio estimates,
# once consistency is below pstop_futile it seems unlikely that SG's with lower
# hr's will reach the required consistency criterion

# load('output/fs_actg_Arms_1vs3_final.Rdata') fs.est<-fs_actg_final

fs.est <- forestsearch(df = df.analysis, confounders.name = FSconfounders.name, df.predict = df.analysis
    details = TRUE, sg_focus = sg_focus, split_method = split_method, pstop_futile = pstop_futile,
    outcome.name = outcome.name, treat.name = treat.name, event.name = event.name,
    id.name = id.name, n.min = nmin.fs, hr.threshold = hr.threshold, hr.consistency = hr.consistency,
    fs.splits = fs.splits, stop.threshold = stop.threshold, d0.min = d.min, d1.min = d.min,
    pconsistency.threshold = pconsistency.threshold, max.minutes = max.minutes, maxk = maxk,
    plot.sg = FALSE, vi.grf.min = vi.grf.min)

## Confounders per grf screening v9 v1b v1a v5a v2 v4 v7 v8 v5b v6 v5c v3
## Number of possible subgroups= 16777215
## Number of possible subgroups (in millions)= 16.77722
## # of subgroups based on # variables > k.max and excluded 16764265
## k.max= 4
```

```
## Events criteria for control,exp= 5 5
## # of subgroups with events less than criteria: control, experimental 7657 7990
## # of subgroups meeting all criteria = 2837
## # of subgroups fitted (Cox model estimable) = 2837
## Minutes= 1.126017
## Number of criteria not met for subgroup evaluation
## crit.failure
##        0        1        2        3        4
## 16767102      828     6542      943     1800
## Number of subgroups meeting HR threshold 153
## Subgroups (1st 10) meeting overall screening thresholds (HR, m1) sorted by focus: (m1,sg_focus)= Inf
##     K   n  E d1  m1  m0   HR L(HR) U(HR) v9.0 v9.1 v1b.0 v1b.1 v1a.0 v1a.1
##  1: 3 226 55 32 Inf Inf 1.58  0.92  2.70    0    0     0     1     0     0
##  2: 3 197 36 22 Inf Inf 1.66  0.85  3.24    0    0     0     1     0     0
##  3: 4 192 43 27 Inf Inf 1.67  0.90  3.09    0    0     0     1     0     0
##  4: 4 191 35 22 Inf Inf 1.73  0.87  3.44    0    0     0     1     0     0
##  5: 4 182 41 26 Inf Inf 1.81  0.96  3.42    0    0     0     1     0     0
##  6: 3 177 36 22 Inf Inf 1.61  0.82  3.15    0    0     0     0     0     1
##  7: 4 177 36 22 Inf Inf 1.61  0.82  3.15    0    0     0     1     0     1
##  8: 2 173 21 13 Inf Inf 1.93  0.80  4.66    0    0     0     0     0     0
##  9: 3 173 21 13 Inf Inf 1.93  0.80  4.66    0    0     0     0     0     0
## 10: 4 171 28 17 Inf Inf 1.59  0.75  3.40    1    0     0     1     0     0
##     v5a.0 v5a.1 v2.0 v2.1 v4.0 v4.1 v7.0 v7.1 v8.0 v8.1 v5b.0 v5b.1 v6.0 v6.1
##  1:     0     0    0    0    0    0    0    0    0    0     0     1    0    0
##  2:     1     0    0    0    1    0    0    0    0    0     0     0    0    0
##  3:     0     0    0    1    0    0    0    0    0    0     0     0    0    0
##  4:     1     0    0    0    1    0    0    0    0    0     0     0    0    0
##  5:     0     0    0    1    0    0    0    0    0    0     0     1    0    0
##  6:     0     0    0    0    0    0    0    0    1    0     0     0    0    0
##  7:     0     0    0    0    0    0    0    0    1    0     0     0    0    0
##  8:     0     0    1    0    0    0    0    0    0    0     1     0    0    0
##  9:     1     0    1    0    0    0    0    0    0    0     1     0    0    0
## 10:     1     0    0    0    1    0    0    0    0    0     0     0    0    0
##     v5c.0 v5c.1 v3.0 v3.1
##  1:     0     0    1    0
##  2:     0     0    0    0
##  3:     0     1    1    0
##  4:     0     0    1    0
##  5:     0     0    1    0
##  6:     0     0    1    0
##  7:     0     0    1    0
##  8:     0     0    0    0
##  9:     0     0    0    0
## 10:     0     0    0    0
## Consistency 0.139
## Consistency 0.114
## Consistency 0.174
## Consistency 0.199
## Consistency 0.241
## Consistency 0.112
## Consistency 0.112
## Consistency 0.187
## Consistency 0.187
## Consistency 0.073
## Consistency 0.166
```

```
## Consistency 0.184
## Consistency 0.184
## Consistency 0.514
## Consistency 0.514
## Consistency 0.514
## Consistency 0.514
## Consistency 0.065
## Consistency 0.094
## Consistency 0.094
## Consistency 0.094
## Consistency 0.384
## Consistency 0.384
## Consistency 0.384
## Consistency 0.104
## Consistency 0.1
## Consistency 0.391
## Consistency 0.24
## Consistency 0.099
## Consistency 0.072
## Consistency 0.694
## Consistency 0.09
## Consistency 0.09
## Consistency 0.054
## Consistency 0.109
## Consistency 0.249
## Consistency 0.283
## Consistency 0.283
## Consistency 0.049
## Consistency 0.057
## Consistency 0.284
## Consistency 0.071
## Consistency 0.071
## Consistency 0.056
## Consistency 0.061
## Consistency 0.066
## Consistency 0.697
## Consistency 0.129
## Consistency 0.129
## Consistency 0.042
## Consistency 0.082
## Consistency 0.14
## Consistency 0.111
## Consistency 0.07
## Consistency 0.07
## Consistency 0.92
## Splitting method, # of splits= Random 1000
## Model, % Consistency Met= v1a.1 v5c.1 v3.0 0.92
## Number of subgroups meeting consistency criteria= 1
##    p.consistency Nsg group.id m.index K   M.1   M.2  M.3 M.4
## 1:          0.92 113      132      56 3 v1a.1 v5c.1 v3.0
##    p.consistency Nsg group.id m.index K   M.1   M.2  M.3 M.4
## 1:          0.92 113      132      56 3 v1a.1 v5c.1 v3.0

xx <- fs.est$find.grps$out.found$hr.subgroups
covs.found <- xx[, -c(1:10)]
```

```
covs.most <- apply(covs.found, 2, sum)
covs.most <- covs.most[covs.most > 0]
print(covs.most)
```

```
##  v9.0  v9.1 v1b.1 v1a.0 v1a.1 v5a.0 v5a.1  v2.0  v2.1  v4.0  v4.1  v7.0  v7.1
##    27     3    86    11    50    39     9    34    28    35    22    10    11
##  v8.0 v5b.0 v5b.1  v6.0 v5c.0 v5c.1  v3.0
##    32    18    40    21    14    32    24
```

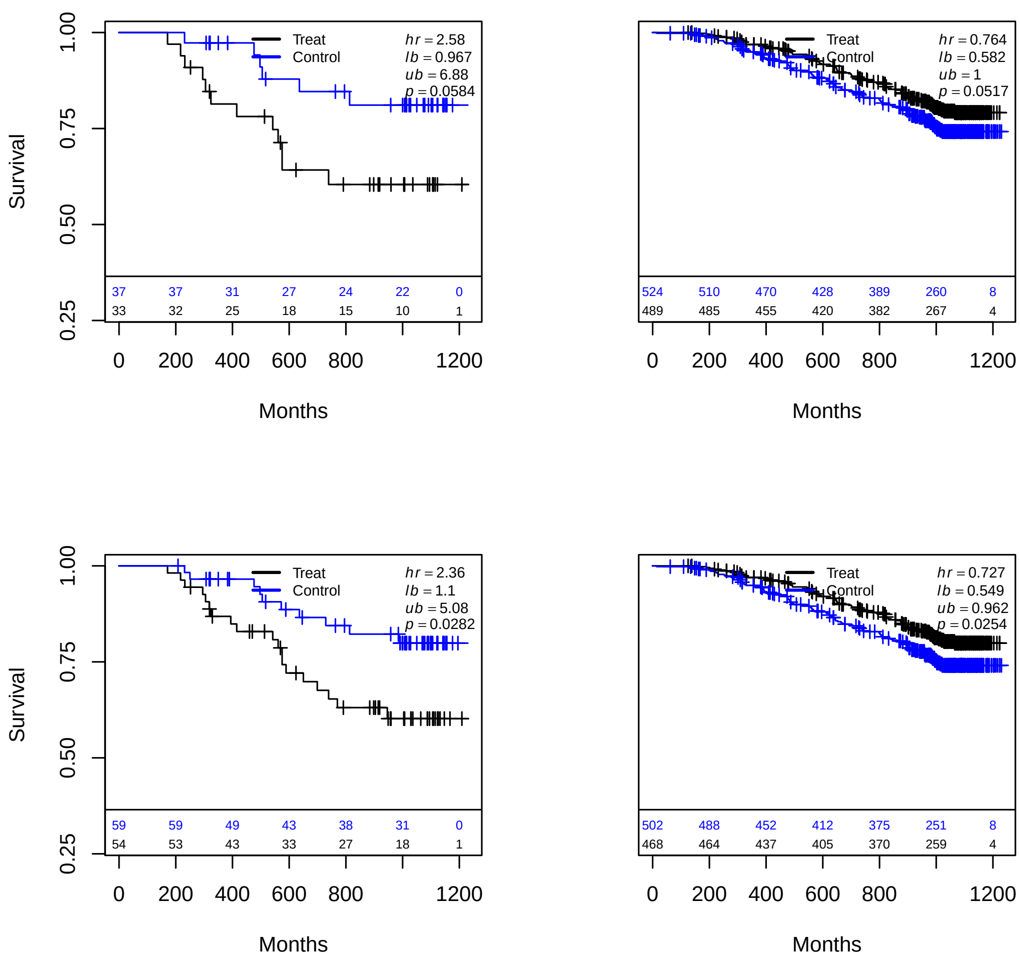
```
print(fs.est$grp.consistency$result)
```

```
##    p.consistency Nsg group.id m.index K   M.1   M.2  M.3 M.4
## 1:          0.92 113      132      56 3 v1a.1 v5c.1 v3.0
```

```
fs_actg_final <- fs.est

df0.fs <- subset(fs.est$df.pred, treat.recommend == 0)
df1.fs <- subset(fs.est$df.pred, treat.recommend == 1)

if (save_output) save(fs_actg_final, df.analysis, FSconfounders.name, file = "output/Nsg-fs_actg_Arms_1
```

```
# Note, the elements above will need to be re-initiated if running separate
# from above E.g., outcome.names, event.name, ... hr.threshold, etc.

# load('output/fs_actg_Arms_1vs3_final.Rdata') fs.est<-fs_actg_final

library(doParallel)
registerDoParallel(parallel::detectCores(logical = FALSE))

cox.formula.boot <- as.formula(paste("Surv(time_days,cens)~treat"))
est.loghr <- TRUE

confounders.name <- FSconfounders.name
stop.threshold <- 0.99
max.minutes <- 6

# Suggest running 50, first ... to get timing estimate
NB <- 20

df_temp <- fs.est$df.pred[, c("id", "treat.recommend")]
dfa <- merge(df.analysis, df_temp, by = "id")
df_boot_analysis <- dfa

fitH <- get_Cox_sg(df_sg = subset(df_boot_analysis, treat.recommend == 0), cox.formula = cox.formula.bo
    est.loghr = est.loghr)
H_obs <- fitH$est_obs  # log(hr) scale
seH_obs <- fitH$se_obs
# Hc observed estimates
fitHc <- get_Cox_sg(df_sg = subset(df_boot_analysis, treat.recommend == 1), cox.formula = cox.formula.b
    est.loghr = est.loghr)
Hc_obs <- fitHc$est_obs
seHc_obs <- fitHc$se_obs
rm("fitH", "fitHc")

Ystar_mat <- bootYstar({
```

```r
# Compare with GRF
layout(matrix(c(1, 2, 3, 4), 2, 2, byrow = TRUE))
plot.subgroup(sub1 = df0.grf, sub1C = df1.grf, tte.name = "time_days", event.name = "cens",
    treat.name = "treat", fix.rows = FALSE, byrisk = 200, show.med = FALSE, ymin = 0.4)
plot.subgroup(sub1 = df0.fs, sub1C = df1.fs, tte.name = "time_days", event.name = "cens",
    treat.name = "treat", fix.rows = FALSE, byrisk = 200, show.med = FALSE, ymin = 0.4)
```




```r
    ystar <- get_Ystar(boot)
}, boots = NB, seed = 8316951, counter = "boot", export = fun_arg_list_boot)
# Check dimension
if (dim(Ystar_mat)[1] != NB | dim(Ystar_mat)[2] != nrow(df_boot_analysis)) stop("Dimension of Ystar_mat

tB.start <- proc.time()[3]
# Bootstraps
resB <- bootPar({
    ans <- fsboot_forparallel(boot)
}, boots = NB, seed = 8316951, counter = "boot", export = fun_arg_list_boot)
tB.now <- proc.time()[3]
tB.min <- (tB.now - tB.start)/60
```

```r
doParallel::stopImplicitCluster()

cat("Minutes for Boots", c(NB, tB.min), "\n")

## Minutes for Boots 20 2.260417

cat("Projection per 100", c(tB.min * (100/NB)), "\n")

## Projection per 100 11.30208

cat("Propn bootstrap subgroups found =", c(sum(!is.na(resB$H_biasadj_1))/NB), "\n")

## Propn bootstrap subgroups found = 1

# How many timmed out
cat("Number timmed out=", c(sum(is.na(resB$H_biasadj_1) & resB$tmins_search > max.minutes)),
    "\n")

## Number timmed out= 0

H_estimates <- get_dfRes(Hobs = H_obs, seHobs = seH_obs, H1_adj = resB$H_biasadj_1,
    ystar = Ystar_mat, cov_method = "standard", cov_trim = 0.05)

Hc_estimates <- get_dfRes(Hobs = Hc_obs, seHobs = seHc_obs, H1_adj = resB$Hc_biasadj_1,
    ystar = Ystar_mat, cov_method = "standard", cov_trim = 0.05)

print(H_estimates)

##           H0      sdH0  H0_lower  H0_upper        H1      sdH1  H1_lower  H1_upper
## 1: 2.360473 0.9240058 1.095965 5.083952 1.435866 0.568245 0.6610745 3.118729

print(Hc_estimates)

##            H0      sdH0  H0_lower  H0_upper        H1      sdH1  H1_lower
## 1: 0.7268405 0.1037692 0.5494336 0.9615305 0.7885755 0.2457578 0.4281227
##    H1_upper
## 1: 1.452507

save(fs.est, Ystar_mat, resB, H_estimates, Hc_estimates, df_boot_analysis, file = "output/Nsg-fsBoot_ac
```

Table 1: ACTG-175 FS Analysis: Cox hazard ratio (HR) estimates for the ITT population and subgroups H and H^c. Cox model estimates are based on subgroups: H true (knowing the actual subgroup, a-priori); the estimated subgroup $\hat{H}$; and the bootstrap ($B = 2,000$) bias-correction to $\hat{H}$ estimates, denoted $\hat{H}_{bc}$. Estimates for the complement H^c are defined analogously. The number of subjects in each population (# Subjects) are listed.

	HR Estimate	Lower	Upper	# Subjects
ITT				
ITT	0.840	0.650	1.090	1083
H subgroup estimates				
$\hat{H}$	2.360	1.096	5.084	113
$\hat{H}_{bc}$	1.436	0.661	3.119	113
H-complement subgroup estimates				
$\hat{H}^c$	0.727	0.549	0.962	970
$\hat{H}^c_{bc}$	0.789	0.428	1.453	970

```r
t.done <- proc.time()[3]
t.min <- (t.done - t.start.all)/60
cat("Minutes and hours to finish", c(t.min, t.min/60), "\n")

## Minutes and hours to finish 6.839667 0.1139944

cat("Machine=", c(Sys.info()[[4]]), "\n")

## Machine= Mac-Studio-M1-Ultra-2022.local

cat("Number of cores=", c(detectCores(logical = FALSE)), "\n")

## Number of cores= 20
```