MarkovTestExample

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07/07/2020

```
####
library(survival)
```

```
## Warning: package 'survival' was built under R version 3.6.3
```

```
library(mstate)
library(frailtyEM)
source("cox_markov_test.R")
source("simulation_code.R")
source("plotMarkovTest.R")
```

```
## Loading required package: lattice
```

```
set.seed(2072020)
```

#Simulate the dataset

```
N<-70
v <- c(0.5,1.5,0.4,0.1,0.3,0.1)
simdata <-  sim_data_sleep(N,v=v,frailties=TRUE,
                           a=c(42.39,  0.08 , 4.79,  0.78 , 1.92,  3.92),
                           b=c(0.9, 1.5,1,1.5,1.5,0.8))
simdata <- collapse_data(simdata,times=seq(0,10,by=30/3600))

#Convert the data to mstate format
  simdata1 <- simdata
  simdata1$status <- 1*(simdata1$from==1 & simdata1$to==2) + 1*(simdata1$from==2 & simdata1$to==3) +
                           1*(simdata1$from==3 & simdata1$to==1)
  simdata1$to[simdata1$from==1]<-2
  simdata1$to[simdata1$from==2]<-3
  simdata1$to[simdata1$from==3]<-1
  simdata2 <- simdata
  simdata2$status <- 1*(simdata2$from==1 & simdata2$to==3) + 1*(simdata2$from==2 & simdata2$to==1) +
                          1*(simdata2$from==3 & simdata2$to==2)
  simdata2$to[simdata2$from==1]<-3
  simdata2$to[simdata2$from==2]<-1
  simdata2$to[simdata2$from==3]<-2
  msdata <- rbind(simdata1,simdata2)
  msdata <- msdata[order(msdata$id,msdata$entry),]
  msdata$trans <- as.numeric(factor(paste(msdata$from,msdata$to,sep=" ")))
```

##Commenges-Andersen Test

```
  #Fit each of the intensities
  fit_trans <- coxph(Surv(entry,exit,status)~strata(trans),control=coxph.control(timefix=TRUE),
```

```
                          data=msdata,x=TRUE,model=TRUE)
  #Commenges-Andersen test across all transitions
  caALL <- ca_test(fit_trans,id=msdata$id)
  caALL
```

```
##        tstat          var         pval
## 3.342320e+04 3.661068e+06 2.509830e-68
```

##Add the estimated frailty effects to the data as offsets

```
  #Fit a frailty model to the Awake -> Non-REM transition.
  fit1 <- coxph(Surv(entry,exit,status)~frailty(id),control=coxph.control(timefix=TRUE),
                  data=msdata,subset=(trans==1))
  #W/o frailty
  fit1_0 <- coxph(Surv(entry,exit,status)~1,control=coxph.control(timefix=TRUE),
                   data=msdata,subset=(trans==1),x=TRUE)

  simdata$offs1 <- fit1$frail[simdata$id] #Frailty for the 1->2 transition
```

##Calculate the proposed weights

```
  #Time grid
  tseq <- seq(1/60,8,by=1/60) #1 minute intervals up to 8 hours.

  #Obtain the weights functions for the 1->2 transition
  owm1 <- weights_multiple(simdata,grid=tseq,from=1,to=2,min_time=0)
  opw_ind1 <- weights_matrix(simdata,grid=tseq,from=1,to=2,min_time=0,
          other_weights=list(function(x) mean(abs(x),na.rm=TRUE),
                             function(x) max(abs(x),na.rm=TRUE)))

  tmat <- transMat(x = list( c(2, 3), c(1,3), c(1,2) ),
                   names = c("Awake", "REM", "Non-REM"))
  B <- 1000
```

##Compute the test statistics and perform the wild bootstrap

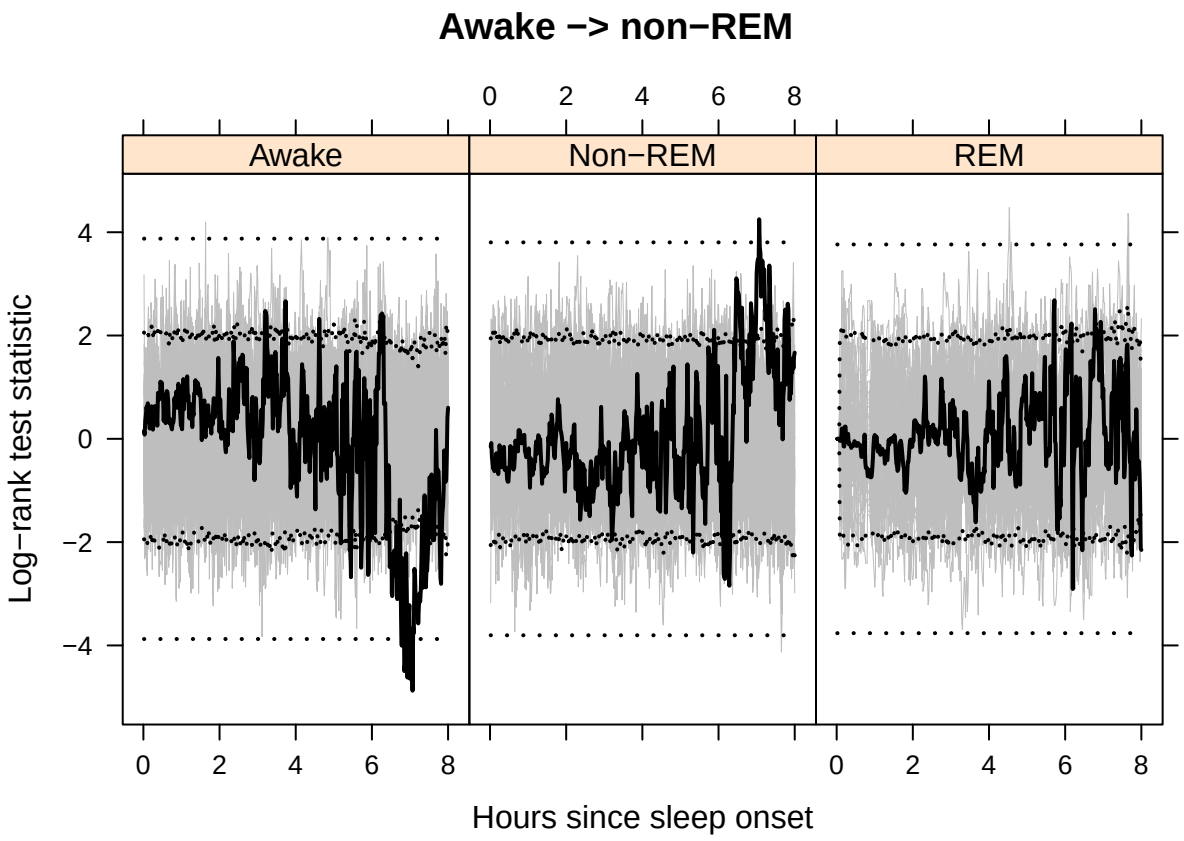
```
  #Version without correcting for frailty
  ct1_0 <- cox_markov_test(simdata,formula=NULL,tfrom=1,tto=2,trans=tmat,
                  grid = tseq,B = B,fn=opw_ind1,
                  fn2=list(function(x) weighted.mean(abs(x),w=owm1,na.rm=TRUE),
                  function(x) mean(abs(x),na.rm=TRUE),function(x) max(abs(x),na.rm=TRUE)))
```

```
  #Version treating estimated frailties as offsets.
  ct1 <- cox_markov_test(simdata,formula="offset(offs1)",
                  tfrom=1,tto=2,trans=tmat,grid = tseq,B = B,fn=opw_ind1,
                  fn2=list(function(x) weighted.mean(abs(x),w=owm1,na.rm=TRUE),
                  function(x) mean(abs(x),na.rm=TRUE),function(x) max(abs(x),na.rm=TRUE)))
```

##Plot the resulting output

```
  #Figure S16 in the Supplementary Materials
   plot.MarkovTest(ct1, tseq, what="states", idx=1:50, qsup=3, states=c("Awake","Non-REM","REM"),
                   xlab="Hours since sleep onset", ylab="Log-rank test statistic",
                   main="Awake -> non-REM")
```

```
## [1] 3.875581 3.803563 3.762734
```


Awake −> non−REM
Awake
Non−REM
REM
Log−rank test statistic
Hours since sleep onset
0
2
4
6
8
−4
−2
0
2
4