Saemix 3 - showcasing binary and categorical models

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Version

Use saemix version ≥ 3.2

Objective

Run binary and categorical models in **saemix**

This notebook uses additional result files from the **saemix** development github (https://github.com/sae mixdevelopment/saemixextension), not integrated in the package to avoid bloating. The *workDir* folder in the next chunk of code points to the folder where the user stored this code, and is needed to run the notebook (*workDir* defaults to the current working directory). Specifically, the notebook loads the results for the bootstrap runs performed using different approaches (see Comets et al. Pharm Res 2021). Bootstraps can be run instead by switching the *runBootstrap* variable to TRUE in the first chunk of code:

- in the code, the number of bootstraps is set to 10 for speed but we recommend to use at least 200 for a 90% CI.
- this can be changed in the following change of code by uncommenting the line *nboot<-200* and setting the number of bootstrap samples (this may cause memory issues in **Rstudio** with older machines, if this is the case we recommend executing the code in a separate script)

The current notebook can be executed to create an HMTL or PDF output with comments and explanations. A script version containing only the R code is also given as *saemix3_categoricalModel.R* in the same folder.

Binary response model

Data description   The *toenail.saemix* dataset in the **saemix** package contains binary data from a randomised clinical trial comparing two treatments for fungal toenail infection. The original data is available in **R** as the *toenail* dataset in the package **prLogistic** and has been reformatted for **saemix**.

The data was collected in a multi-center randomised comparison of two oral treatments (A and B) for toenail infection. 294 patients are measured at seven visits, i.e. at baseline (week 0), and at weeks 4, 8, 12, 24, 36, and 48 thereafter, comprising a total of 1908 measurements. The primary end point was the presence of toenail infection and the outcome of interest is the binary variable "onycholysis" which indicates the degree of separation of the nail plate from the nail-bed (0=none or mild versus 1=moderate or severe).

To create the data object using saemixData, we need to specify the response column both as a response (*name.response="y"*) and as a predictor (here, time is the first predictor and we add the response in the argument *name.predictors*).

```
data(toenail.saemix)

saemix.data<-saemixData(name.data=toenail.saemix,name.group=c("id"),name.predictors=c("time","y"), name
                        name.covariates=c("treatment"), verbose=FALSE)
```

Exploring data The usual plot of the data object is not very informative as it alternates between 0 and 1's. Instead we plot the evolution of the frequency of infection over time in the population, stratifying by treatment. We use the *plotDiscreteData()* function from the package, setting the *outcome* argument to '*binary*'.

```
# Distribution of times
if(FALSE) hist(toenail.saemix$time, breaks=c(-1,0.25,1.25,2.25, 3.25, 7,10,15,20), freq=T)
table(cut(toenail.saemix$time, breaks=c(-1,0.25,1.25,2.25, 3.25, 7,10,15,20)))
```

```
##
##   (-1,0.25] (0.25,1.25] (1.25,2.25] (2.25,3.25]   (3.25,7]    (7,10]
##         294         278         272         240        291         245
##    (10,15]    (15,20]
##        282          6
```

```
# Proportion of 0's and 1's across time
plotDiscreteData(saemix.data, outcome='binary', which.cov="treatment")
```
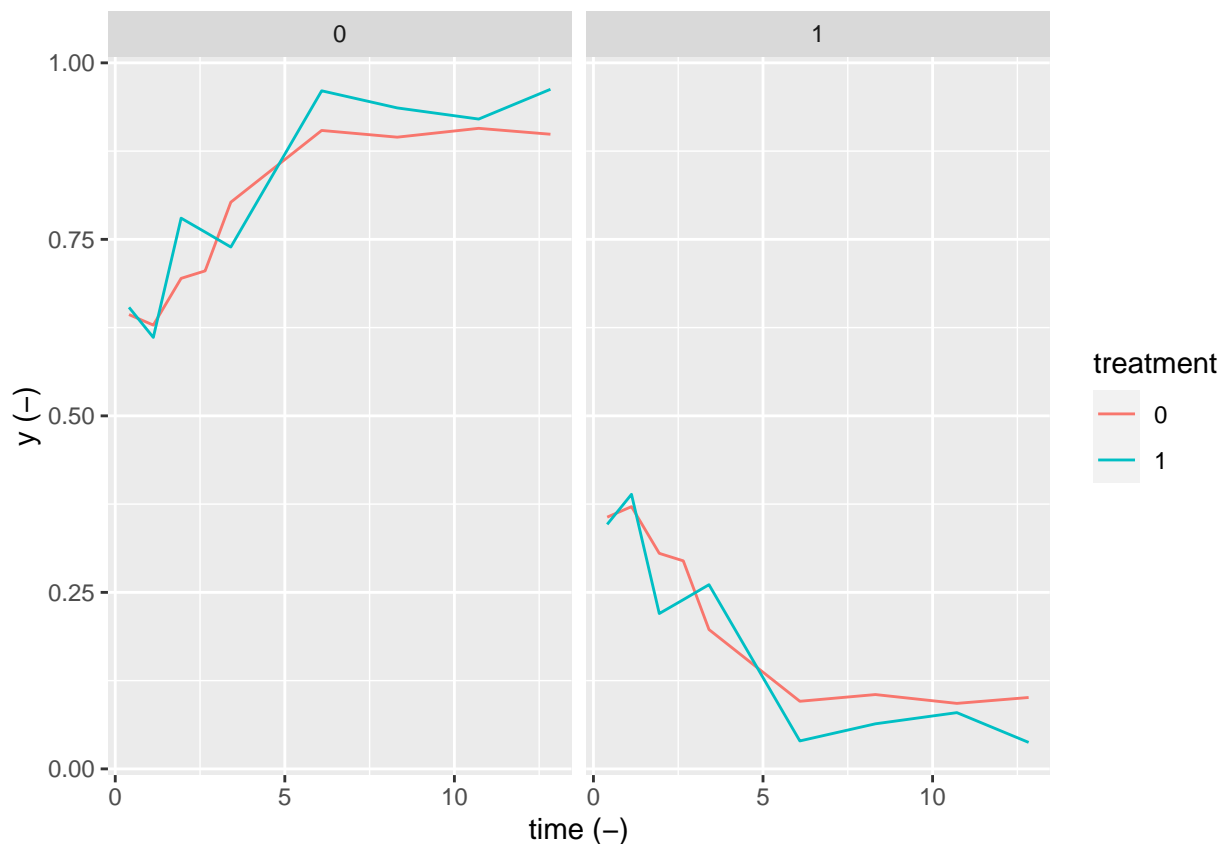

We can also present the results as a barplot of the proportion of events, using **ggplot2** and **tidyverse**.

```
# Barplots across time
toe1 <- toenail.saemix %>%
  group_by(visit, treatment) %>%
  summarise(nev = sum(y), n=n()) %>%
  mutate(freq = nev/n, sd=sqrt((1-nev/n)/nev)) %>%
  mutate(lower=freq-1.96*sd, upper=freq+1.96*sd)
```

```
## `summarise()` has grouped output by 'visit'. You can override using the
## `.groups` argument.
```

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```
toe1$lower[toe1$lower<0] <-0 # we should use a better approximation for CI
toe1$treatment <- factor(toe1$treatment, labels=c("A","B"))

plot1<-ggplot(toe1, aes(x=visit, y=freq, group=treatment)) + geom_line(aes(colour=treatment)) +
  geom_point(aes(colour=treatment)) +
  geom_ribbon(aes(ymin=lower, ymax=upper, fill=treatment), alpha=0.2) +
  ylim(c(0,1)) + theme_bw() + theme(legend.position = "top") +
  xlab("Visit number") + ylab("Observed frequency of infection")

print(plot1)
```
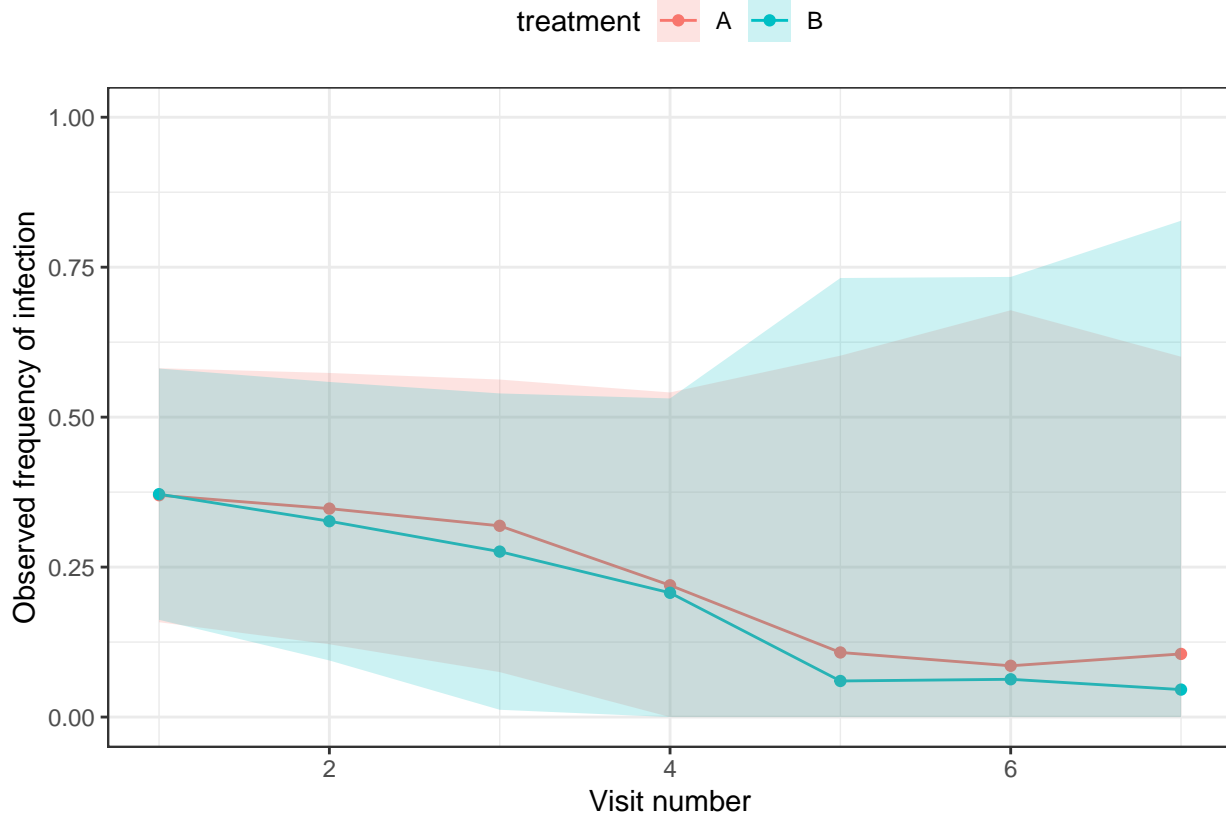


```
if(saveFigs) {
  namfig<-"toenail_infectionFreq.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  plot(plot1)
  dev.off()
}
```

Statistical model   The model fit here is a logistic random effect model developed by (Hedeker et al. 1994). This model includes a random intercept (θ_1 and ω_1), a time effect (θ_2) and treatment (A or B) (β) as a covariate affecting the slope θ_2. We considered the interaction term between time and treatment but no treatment effect alone as it would impact the intercept which shouldn't be different between arms due to the randomisation process. The time course was assumed to be similar across subjects as no significant interindividual variability was found when testing different models.

- Model for repeated binary data
  - the probability that y_{ij} outcome observed in subject i at visit j (time t_{ij} in months) is 1 is modelled as a logistic model

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– linear model on the logit scale $(\text{logit}(p) = \ln\left(\frac{p}{1-p}\right))$

$$\text{logit}(P(y_{ij} = 1)) = \theta_{1,i} + \theta_{2,i} t_{ij}$$

- Statistical model
  - $\theta_{1,i}$ assumed to follow a normal distribution $N(\mu_{\theta_1}, \omega_{\theta_1})$
  - $\theta_{2,i}$ assumed to depend on treatment as in $\theta_{2,i} = \mu_\beta + 1_{trt=B}$

In the following chunk of code, we define the model and the simulate function, then create the saemixModel object.

```
# saemix model
binary.model<-function(psi,id,xidep) {
  tim<-xidep[,1]
  y<-xidep[,2]
  inter<-psi[id,1]
  slope<-psi[id,2]
  logit<-inter+slope*tim
  pevent<-exp(logit)/(1+exp(logit))
  logpdf<-rep(0,length(tim))
  P.obs = (y==0)*(1-pevent)+(y==1)*pevent
  logpdf <- log(P.obs)
  return(logpdf)
}

# simulation function (used for diagnostics)
simulBinary<-function(psi,id,xidep) {
  tim<-xidep[,1]
  y<-xidep[,2]
  inter<-psi[id,1]
  slope<-psi[id,2]
  logit<-inter+slope*tim
  pevent<-1/(1+exp(-logit))
  ysim<-rbinom(length(tim),size=1, prob=pevent)
  return(ysim)
}

saemix.model<-saemixModel(model=binary.model,description="Binary model",
                simulate.function=simulBinary, modeltype="likelihood",
                psi0=matrix(c(-0.5,-.15,0,0),ncol=2,byrow=TRUE,
                          dimnames=list(NULL,c("theta1","theta2"))),
                transform.par=c(0,0), covariate.model=c(0,1),
                covariance.model=matrix(c(1,0,0,0),ncol=2),
                omega.init=diag(c(0.5,0.3)), verbose=FALSE)
```

Fitting the model

- Fit with saemix and store the results to the object *binary.fit*
  - setting options
  - 10 chains
  - don't display intermediate graphs or save graphs
  - don't compute the FIM (approximation not suited to discrete data models)

```
# saemix fit
saemix.options<-list(seed=1234567,save=FALSE,save.graphs=FALSE,
                  displayProgress=FALSE, nb.chains=10, fim=FALSE, print=FALSE)
```

```
binary.fit<-saemix(saemix.model,saemix.data,saemix.options)
summary(binary.fit)
```

```
## ----------------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------------
##                 Parameter Estimate
## 1                  theta1   -1.71
## 2                  theta2   -0.39
## 3 beta_treatment(theta2)    -0.15
## ----------------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------------
##              Parameter Estimate
## theta1 omega2.theta1     16.11
## ----------------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------------
##                  omega2.theta1
## omega2.theta1 1.00
## ----------------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------------
##
## Likelihood computed by importance sampling
##        -2LL= 1250.678
##        AIC = 1260.678
##        BIC = 1279.096
## ----------------------------------------------------------
```

```
plot(binary.fit, plot.type="convergence")
```

theta1

theta2

beta_treatment(theta2)

omega2.theta1
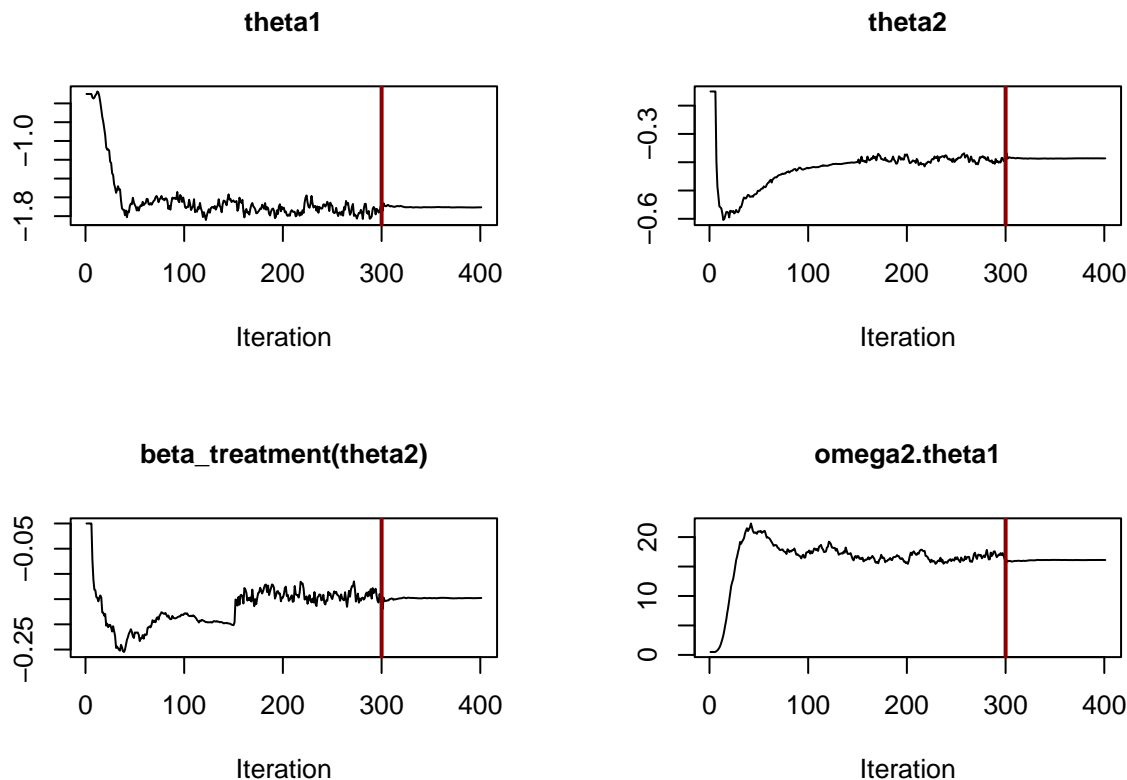
- Results -
numerical output - note that the estimated value of μ_{θ_1} is -1.71, corresponding to an estimated probability of event of 0.154 - this is lower than the observed probability of infection at time 0 (around 0.37) because the logistic model is highly non-linear and $E(f(\theta))$ is very different from $f(E(\theta))$ - convergence plots show good convergence for all parameters

Diagnostics

- Simulation function to simulate from a binary model
  - the model function defines directly the log-pdf, so the user needs to define a function to simulate from the appropriate binomial function
  - note the similarities between the model function (*binary.model()*) and the simulation function (*simulBinary()*)
    * same setting of dependent variables (*tim* and *y*) from *xidep* and parameters (*inter* and *slope*) from *psi*
      · note that we don't use *y* in *simulBinary()*
    * same definition of pevent ($=P(Y_{ij} = 1)$, the probability of observing an event)
    * in *binary.model()* we then compute the probability of the observed outcome using the observed value of Y_{ij} contained in *y* for each observation
    * in *simulBinary()*, we use the individual $P(Y_{ij} = 1)$ predictions to simulate from a Bernouilli distribution using the *rbinom()* function
- once the simulation function has been defined and associated with the model component of the object, we use the *simulateDiscreteSaemix()* function from the **saemix** package to simulate *nsim* values (here 100) with the population parameters estimated in *binary.fit*
  - this adds a *simdata* element to the *binary.fit*
  - the simulations are used to produce VPC via the *discreteVPC()* function, again specifying the outcome to be binary. Here, we stratify the plot on the treatment covariate

```
#  $1_{Y_{ij}=0} \times (1-P(Y_{ij}=1)) + 1_{Y_{ij}=1} \times P(Y_{ij}=1) $
# simulate from model (nsim=100)
nsim<-1000
```

```
binary.fit <- simulateDiscreteSaemix(binary.fit, nsim=nsim)

discreteVPC(binary.fit, outcome="binary", which.cov="treatment")
```
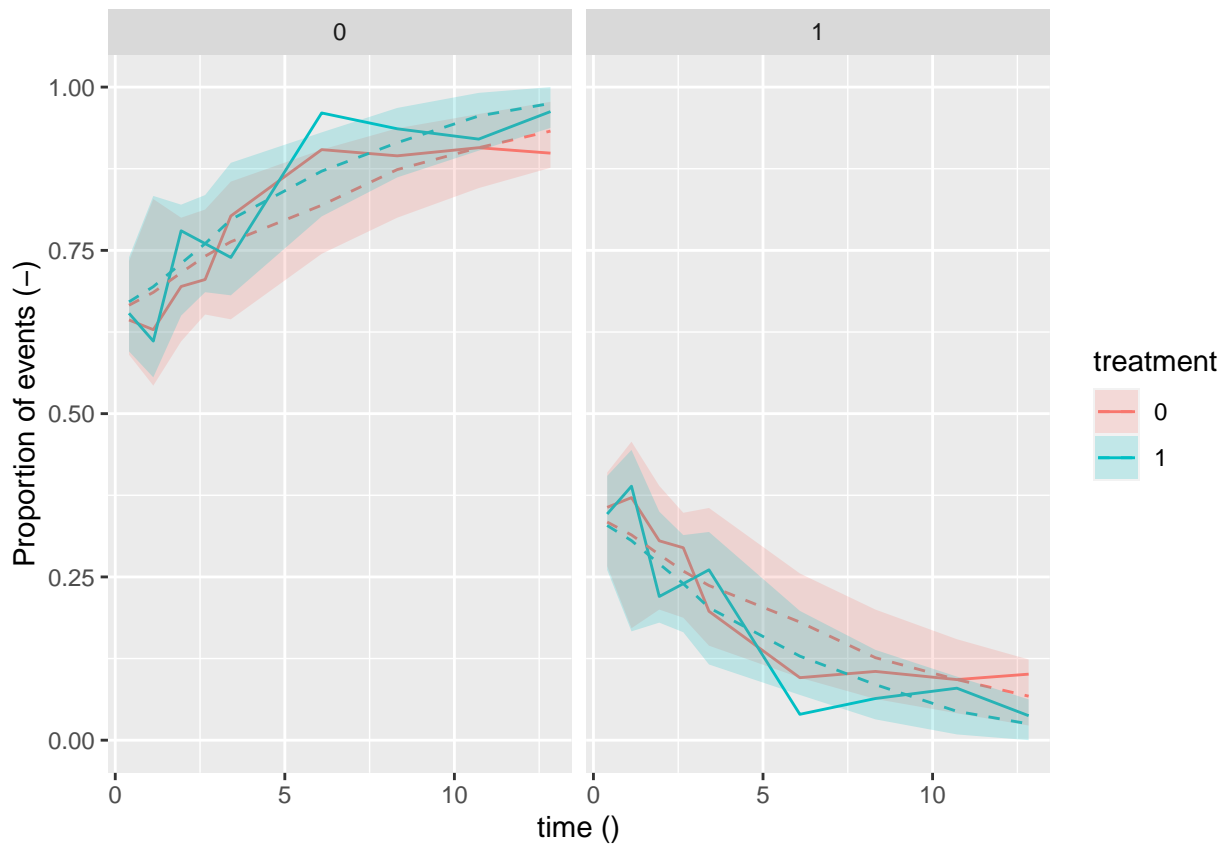


```
if(saveFigs) {
  namfig<-"toenail_vpcByTreatment.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  discreteVPC(binary.fit, outcome="binary", which.cov="treatment")
  dev.off()
}
```

We can also extract dataframe with the simulated data ($binary.fit@sim.data@datasim$) and produce
diagnostics in R. Below, using **tidyverse**, we add columns *visit* and *treatment* to plot the frequency of
infection over time for each treatment.

```
simdat <-binary.fit@sim.data@datasim
simdat$visit<-rep(toenail.saemix$visit,nsim)
simdat$treatment<-rep(toenail.saemix$treatment,nsim)
# VPC-type diagnostic
ytab<-NULL
for(irep in 1:nsim) {
  xtab<-simdat[simdat$irep==irep,]
  suppressMessages(
  xtab1 <- xtab %>%
    group_by(visit, treatment) %>%
    summarise(nev = sum(ysim), n=n()) %>%
    mutate(freq = nev/n)
  )
```

```
  ytab<-rbind(ytab,xtab1[,c("visit","freq","treatment")])
}
gtab <- ytab %>%
  group_by(visit, treatment) %>%
  summarise(lower=quantile(freq, c(0.05)), median=quantile(freq, c(0.5)), upper=quantile(freq, c(0.95))]
  mutate(treatment=ifelse(treatment==1,"B","A"))
gtab$freq<-1

plot2 <- ggplot(toe1, aes(x=visit, y=freq, group=treatment)) + geom_line(aes(colour=treatment)) +
  geom_point(aes(colour=treatment)) +
  geom_line(data=gtab, aes(x=visit, y=median), linetype=2, colour='lightblue') +
  geom_ribbon(data=gtab,aes(ymin=lower, ymax=upper), alpha=0.5, fill='lightblue') +
  ylim(c(0,0.5)) + theme_bw() + theme(legend.position = "none") + facet_wrap(.~treatment) +
  xlab("Visit number") + ylab("Frequency of infection")

print(plot2)
```
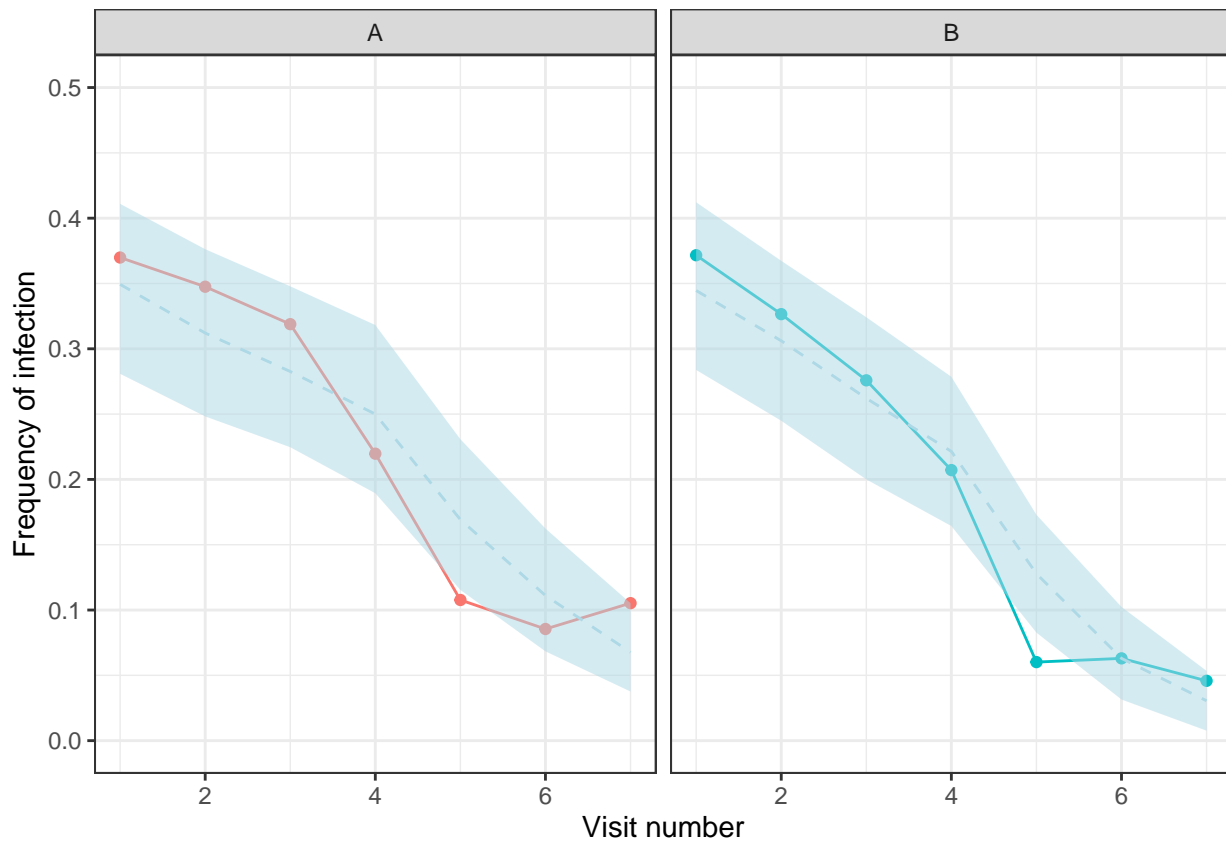


```
if(saveFigs) {
  namfig<-"toenail_ggplot2VPCTreatment.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  plot(plot2)
  dev.off()
}
```

Work in progress

- npde for categorical data (submitted)

– **TODO** using code from Marc Cerou

```
# npd
```

Standard errors of estimation   The computation of the FIM in **saemix** uses the so-called FOCE method, an approximation where the model function f is linearised around the conditional expectation of the individual parameters. This approximation is particularly poor for discrete data models, which is why currently **saemix** doesn't provide estimation errors for categorical/binary data models. In this document we show how to obtain SE through the computation of the exact FIM using numerical integration, as well as a bootstrap approach. Because all subjects have different times, for the binary data we will use bootstrap approaches as computing the exact FIM is time-consuming and we would need to compute it for each subject separately before summing the individual FIMs.

Different bootstrap approaches can be used in non-linear mixed effect models and have been implemented for **saemix** in Comets et al. 2021, with code available on the github.

Case bootstrap   The first bootstrap approach we can use is case bootstrap, where we resample at the level of the individual. We plot the bootstrap distribution for the 4 parameters (intercept, slope, treatment effect on slope, and variability of intercept). The red vertical line represents the estimate obtained on the original data while the blue line shows the mean of the bootstrap distribution.

```
if(!runBootstrap) {
  case.bin <- read.table(file.path(saemixDir,"paperSaemix3","bootstrapCase_toenail.res"), header=T)
# case.bin <- read.table(file.path(saemixDir,"bootstrap","results","toenail_caseBootstrap.res"), heade
  nboot<-dim(case.bin)[1]
} else case.bin <- saemix.bootstrap(binary.fit, method="case", nboot=nboot)
head(case.bin)
```

```
##   Replicate     theta1      theta2 beta_treatment.theta2. omega2.theta1
## 1         1 -1.849570 -0.2902835            -0.21074995      13.17395
## 2         2 -1.586745 -0.3967016            -0.14629305      21.68146
## 3         3 -1.293854 -0.4130704            -0.43070091      23.02703
## 4         4 -1.841955 -0.4209368            -0.17205499      19.53466
## 5         5 -1.452577 -0.4220905            -0.01978366      11.77808
## 6         6 -1.728391 -0.3969421            -0.18977969      13.30204
```

```
# Bootstrap distributions
if(nboot<200) cat("The number of bootstrap samples is too low to provide good estimates of the confiden
  resboot1<-case.bin
  ypd2<-NULL
  for(icol in 1:4) {
    ypd2<-rbind(ypd2,data.frame(rep=resboot1[,1],Param=colnames(resboot1)[(icol+1)],value=resboot1[,(ic
  }

  ypd2$Param<-factor(ypd2$Param, levels = unique(ypd2$Param))
  ypd2.fix<-ypd2[ypd2$Param %in% unique(ypd2$Param)[1:3],]
  ypd2.iiv<-ypd2[ypd2$Param %in% unique(ypd2$Param)[4],]
  ypd <- ypd2

  par.estim<-c(binary.fit@results@fixed.effects,diag(binary.fit@results@omega)[binary.fit@results@indx.
  mean.bootDist<-apply(resboot1, 2, mean)[-c(1)]
  df<-data.frame(Param=unique(ypd2$Param), mean.boot=mean.bootDist, est.saemix=par.estim, Bootstrap="Ca

  plot.density2<-ggplot(data=ypd2) + geom_density(aes(value,fill="red4"), alpha=0.5) +
    geom_vline(data=df,aes(xintercept=est.saemix),colour="red",size=1.2) +
    geom_vline(data=df,aes(xintercept=mean.boot),colour="blue",size=1.2) +
```
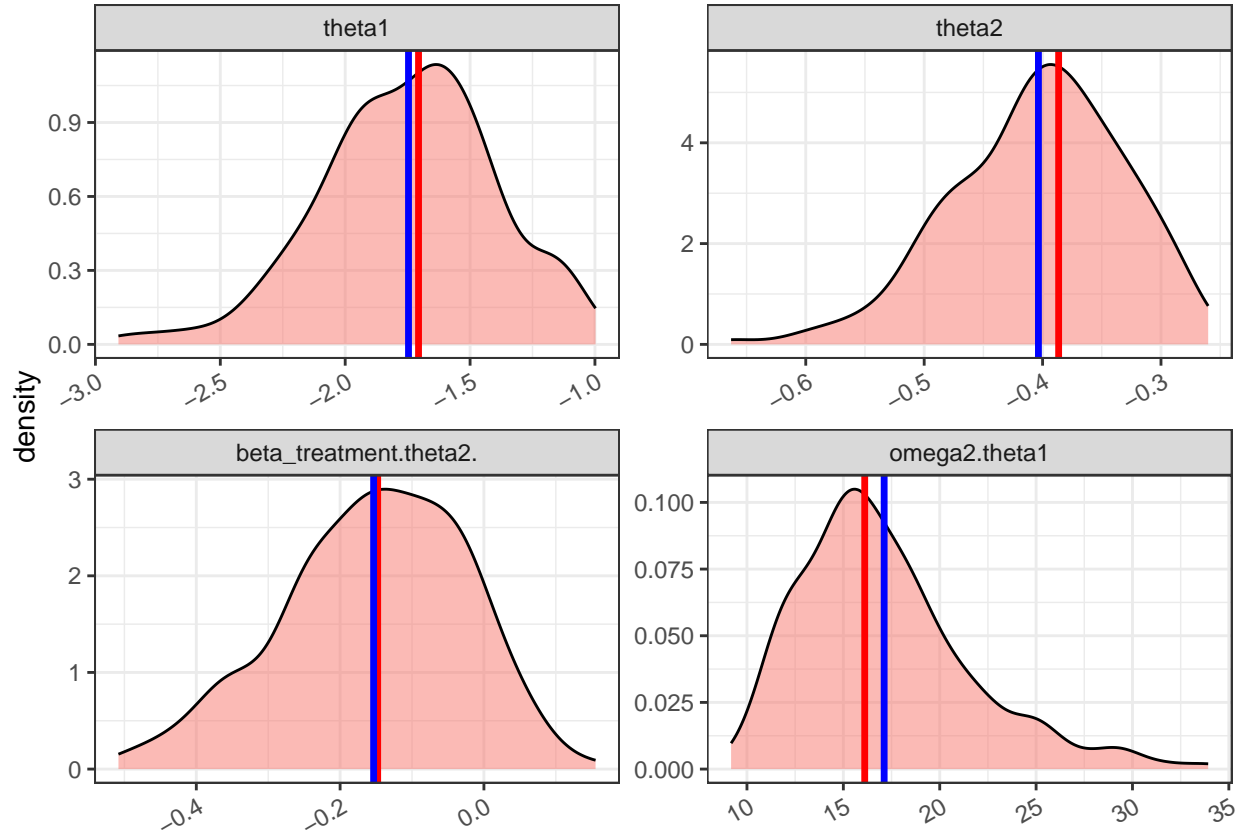
```
    theme_bw() + theme(axis.title.x = element_blank(),axis.text.x = element_text(size=9, angle=30, hjust
    facet_wrap(~Param, ncol=2, scales = 'free')

  print(plot.density2)
}
```


Conditional bootstrap We can also use conditional bootstrap, a non-parametric residual bootstrap which bootstraps samples from the conditional distributions and preserves the exact structure of the original dataset.

```
if(!runBootstrap) {
# cond.bin <- read.table(file.path(saemixDir,"bootstrap","results","toenail_condBootstrap.res"), heade
  cond.bin <- read.table(file.path(saemixDir,"paperSaemix3","bootstrapCond_toenail.res"), header=T)
  nboot<-dim(cond.bin)[1]
  } else
    cond.bin <- saemix.bootstrap(binary.fit, method="conditional", nboot=nboot)
summary(cond.bin)
```

```
##    Replicate          theta1             theta2        beta_treatment.theta2.
## Min.   :  1.00   Min.   :-2.3705   Min.   :-0.5303   Min.   :-0.38948
## 1st Qu.: 50.75   1st Qu.:-1.7310   1st Qu.:-0.4257   1st Qu.:-0.18420
## Median :100.50   Median :-1.4959   Median :-0.3974   Median :-0.14188
## Mean   :100.50   Mean   :-1.5284   Mean   :-0.3972   Mean   :-0.14057
## 3rd Qu.:150.25   3rd Qu.:-1.3374   3rd Qu.:-0.3717   3rd Qu.:-0.09399
## Max.   :200.00   Max.   :-0.6744   Max.   :-0.2878   Max.   : 0.02641
##  omega2.theta1
## Min.   : 9.37
## 1st Qu.:12.71
```

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```
##  Median :14.27
##  Mean   :14.49
##  3rd Qu.:16.29
##  Max.   :23.46
# Bootstrap distributions
if(nboot<200) cat("The number of bootstrap samples is too low to provide good estimates of the confiden
  resboot1<-cond.bin
  ypd2<-NULL
  for(icol in 1:4) {
    ypd2<-rbind(ypd2,data.frame(rep=resboot1[,1],Param=colnames(resboot1)[(icol+1)],value=resboot1[,(ic
  }

  ypd2$Param<-factor(ypd2$Param, levels = unique(ypd2$Param))
  ypd2.fix<-ypd2[ypd2$Param %in% unique(ypd2$Param)[1:3],]
  ypd2.iiv<-ypd2[ypd2$Param %in% unique(ypd2$Param)[4],]
  ypd <- rbind(ypd,ypd2)

  par.estim<-c(binary.fit@results@fixed.effects,diag(binary.fit@results@omega)[binary.fit@results@indx.
  mean.bootDist<-apply(resboot1, 2, mean)[-c(1)]
  df2<-data.frame(Param=unique(ypd2$Param), mean.boot=mean.bootDist, est.saemix=par.estim, Bootstrap="C
  df<-rbind(df,df2)

    plot.density2<-ggplot(data=ypd2) + geom_density(aes(value,fill="red4"), alpha=0.5) +
    geom_vline(data=df2,aes(xintercept=est.saemix),colour="red",size=1.2) +
    geom_vline(data=df2,aes(xintercept=mean.boot),colour="blue",size=1.2) +
    theme_bw() + theme(axis.title.x = element_blank(),axis.text.x = element_text(size=9, angle=30, hjus
    facet_wrap(~Param, ncol=2, scales = 'free')
  print(plot.density2)

  plot.density3<-ggplot(data=ypd) + geom_density(aes(value,fill="red4"), alpha=0.5) +
    geom_vline(data=df,aes(xintercept=est.saemix),colour="red",size=1.2) +
    geom_vline(data=df,aes(xintercept=mean.boot),colour="blue",size=1.2) +
    theme_bw() + theme(axis.title.x = element_blank(),axis.text.x = element_text(size=9, angle=30, hjus
    facet_grid(Bootstrap~Param, scales = 'free')
#    facet_wrap(Bootstrap~Param, nrow=2, scales = 'free')

  print(plot.density3)
}
```
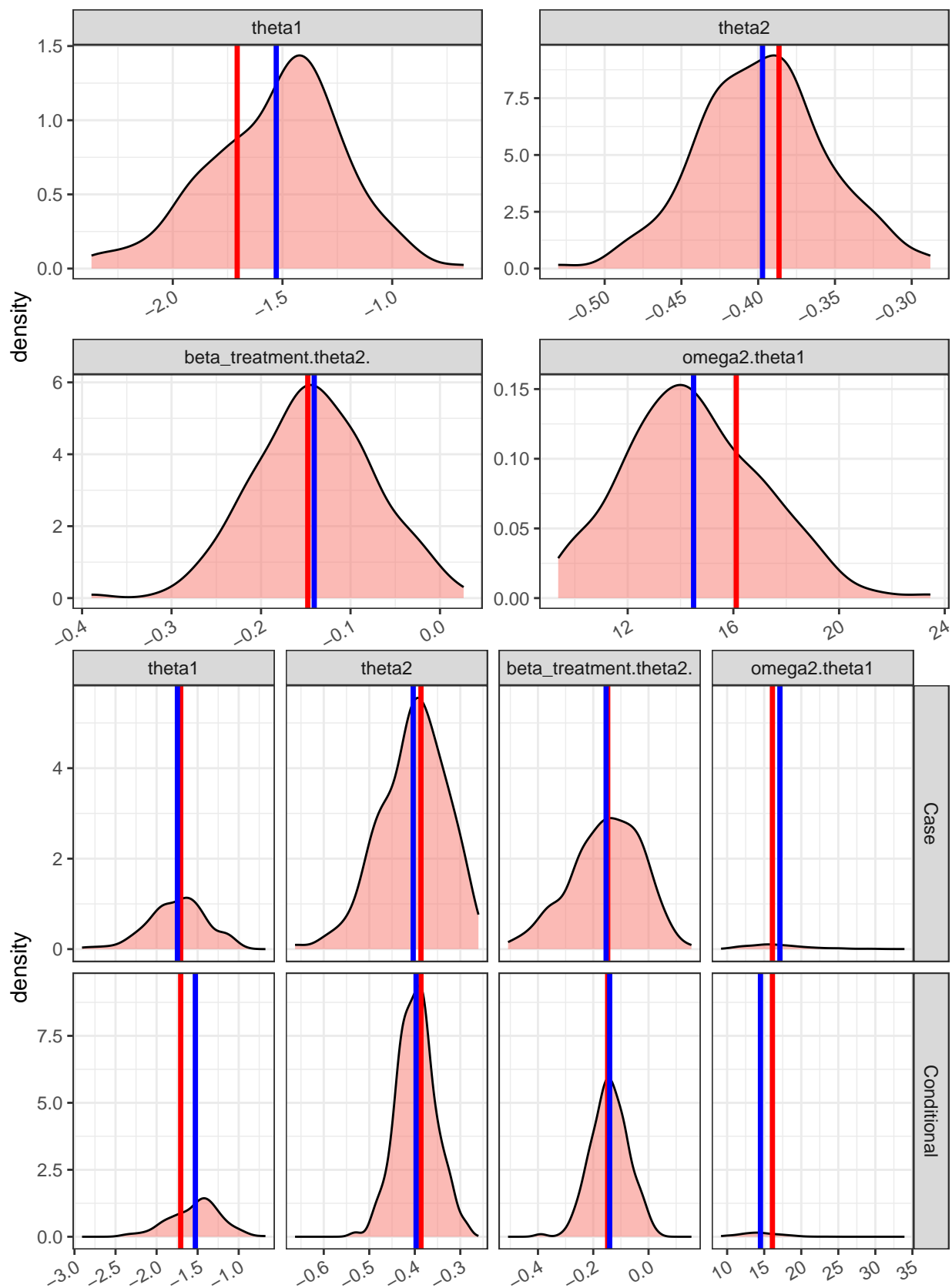
Bootstrap results Here we produce a table showing tbe parameters estimated on the original dataset along with the bootstrap estimates (mean (SD) of the bootstrap distribution) and the 95% CI. The table is produced when the number of bootstrap is higher than 200 in the code below.

```r
if(nboot<200) cat("The number of bootstrap samples is too low to provide good estimates of the confidenc
  par.estim<-c(binary.fit@results@fixed.effects,diag(binary.fit@results@omega)[binary.fit@results@indx.
  namsd<-paste0("SD.",colnames(binary.fit@results@omega)[binary.fit@results@indx.omega])
  df2<-data.frame(parameter=c(colnames(case.bin)[-c(1)],namsd), saemix=par.estim)
  for(i in 1:2) {
    if(i==1) {
      resboot1<-case.bin
      namboot<-"case"
      } else {
      resboot1<-cond.bin
      namboot <-"cNP"
      }
    ncol<-dim(resboot1)[2]
    resboot1<-cbind(resboot1, sqrt(resboot1[,ncol]))
    mean.bootDist<-apply(resboot1, 2, mean)[-c(1)]
    sd.bootDist<-apply(resboot1, 2, sd)[-c(1)]
    quant.bootDist<-apply(resboot1[-c(1)], 2, quantile, c(0.025, 0.975))
    l1<-paste0(format(mean.bootDist, digits=2)," (",format(sd.bootDist,digits=2, trim=T),")")
    l2<-paste0("[",format(quant.bootDist[1,], digits=2),", ",format(quant.bootDist[2,],digits=2, trim=T
    df2<-cbind(df2, l1, l2)
    i1<-3+2*(i-1)
    colnames(df2)[i1:(i1+1)]<-paste0(namboot,".",c("estimate","CI"))
  }
  print(df2)
}
```

```
##                 parameter     saemix case.estimate         case.CI  cNP.estimate
## 1                  theta1 -1.7063992 -1.75 (0.351) [-2.44, -1.114] -1.53 (0.305)
## 2                  theta2 -0.3864426 -0.40 (0.072) [-0.56, -0.285] -0.40 (0.042)
## 3 beta_treatment.theta2. -0.1477510 -0.15 (0.127)  [-0.42, 0.054] -0.14 (0.067)
## 4          omega2.theta1 16.1090732 17.12 (4.464) [10.89, 28.927] 14.49 (2.596)
## 5              SD.theta1  4.0136110  4.10 (0.520)  [ 3.30, 5.378]  3.79 (0.340)
##            cNP.CI
## 1 [-2.18, -0.980]
## 2 [-0.48, -0.313]
## 3 [-0.26, -0.015]
## 4 [ 9.84, 19.401]
## 5  [ 3.14, 4.405]
```

```r
print(xtable(df2),only.contents=TRUE, include.rownames=FALSE)
```

```
## % latex table generated in R 4.3.2 by xtable 1.8-4 package
## % Sun Jun  9 14:00:10 2024
## parameter & saemix & case.estimate & case.CI & cNP.estimate & cNP.CI \\
##   \hline
## theta1 & -1.71 & -1.75 (0.351) & [-2.44, -1.114] & -1.53 (0.305) & [-2.18, -0.980] \\
##   theta2 & -0.39 & -0.40 (0.072) & [-0.56, -0.285] & -0.40 (0.042) & [-0.48, -0.313] \\
##   beta\_treatment.theta2. & -0.15 & -0.15 (0.127) & [-0.42, 0.054] & -0.14 (0.067) & [-0.26, -0.015]
##   omega2.theta1 & 16.11 & 17.12 (4.464) & [10.89, 28.927] & 14.49 (2.596) & [ 9.84, 19.401] \\
##   SD.theta1 & 4.01 &  4.10 (0.520) & [ 3.30, 5.378] &  3.79 (0.340) & [ 3.14, 4.405] \\
##    \hline
```

```
# Bootstrap SE on omega instead of omega2
# sd(sqrt(case.bin$omega2.theta1))
# sd(sqrt(cond.bin$omega2.theta1))
```

Categorical response model

Data   The *knee.saemix* data represents pain scores recorded in a clinical study in 127 patients with sport related injuries treated with two different therapies. The pain occuring during knee movement was observed after 3,7 and 10 days of treatment. It was taken from the **catdata** package in R (Schauberger and Tutz 2020) (dataset *knee*) and reformatted as follows:

- a time column was added representing the day of the measurement (with 0 being the baseline value) and each observation corresponds to a different line in the dataset
- treatment was recoded as 0/1 (placebo/treatment), gender as 0/1 (male/female)
- *Age2* represents the square of centered *Age*.

We can visualise the evolution of the proportion of each score over time using the *plotDiscreteData()* function with the outcome set to *categorical*, stratifying by treatment. In both treatment groups, the probability of lower scores (1 or 2) increases with time while the probability to obtain a high (4 or 5) pain score decreases.
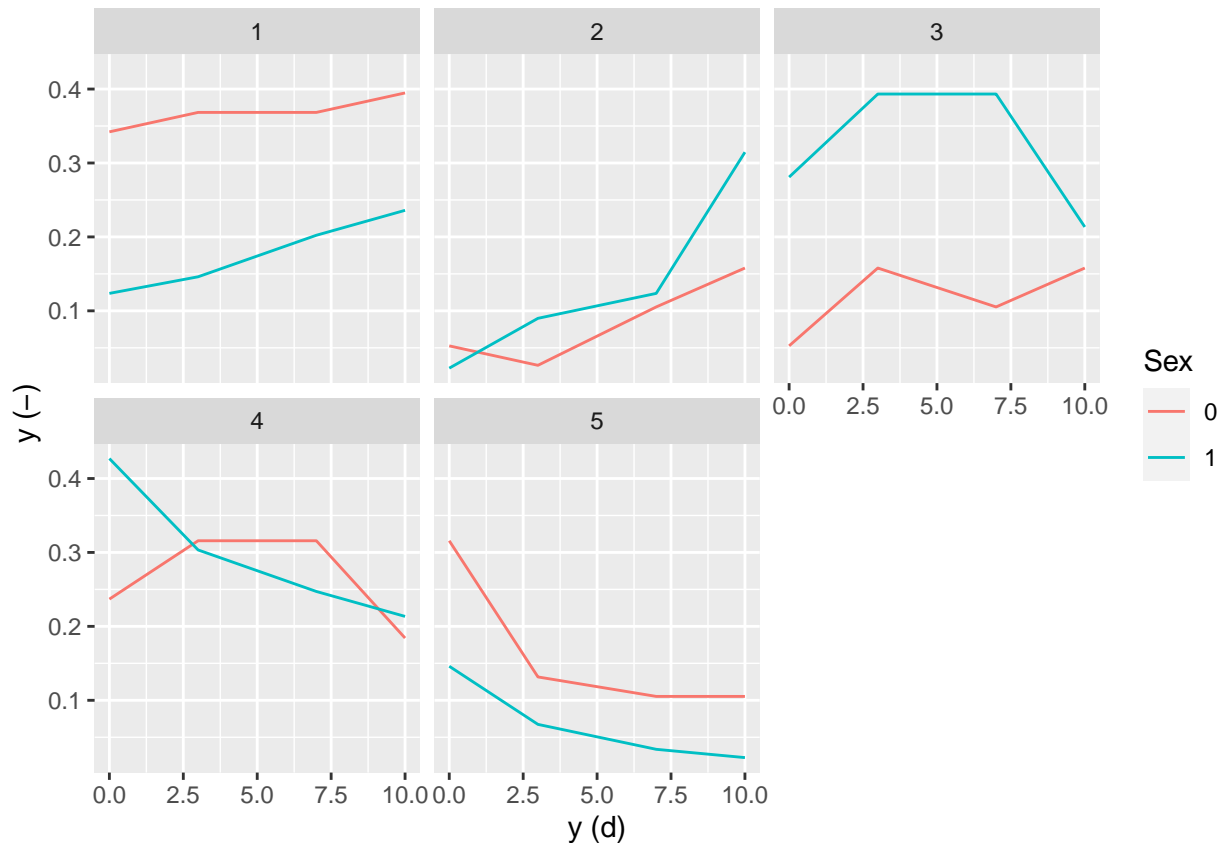
```
data(knee.saemix)

# Data
ordknee.data<-saemixData(name.data=knee.saemix,name.group=c("id"),
                         name.predictors=c("y", "time"), name.X=c("time"),
                         name.covariates = c("Age","Sex","treatment","Age2"),
                         units=list(x="d",y="", covariates=c("yr","-","-","yr2")), verbose=FALSE)

plotDiscreteData(ordknee.data, outcome="categorical", which.cov="treatment")
```
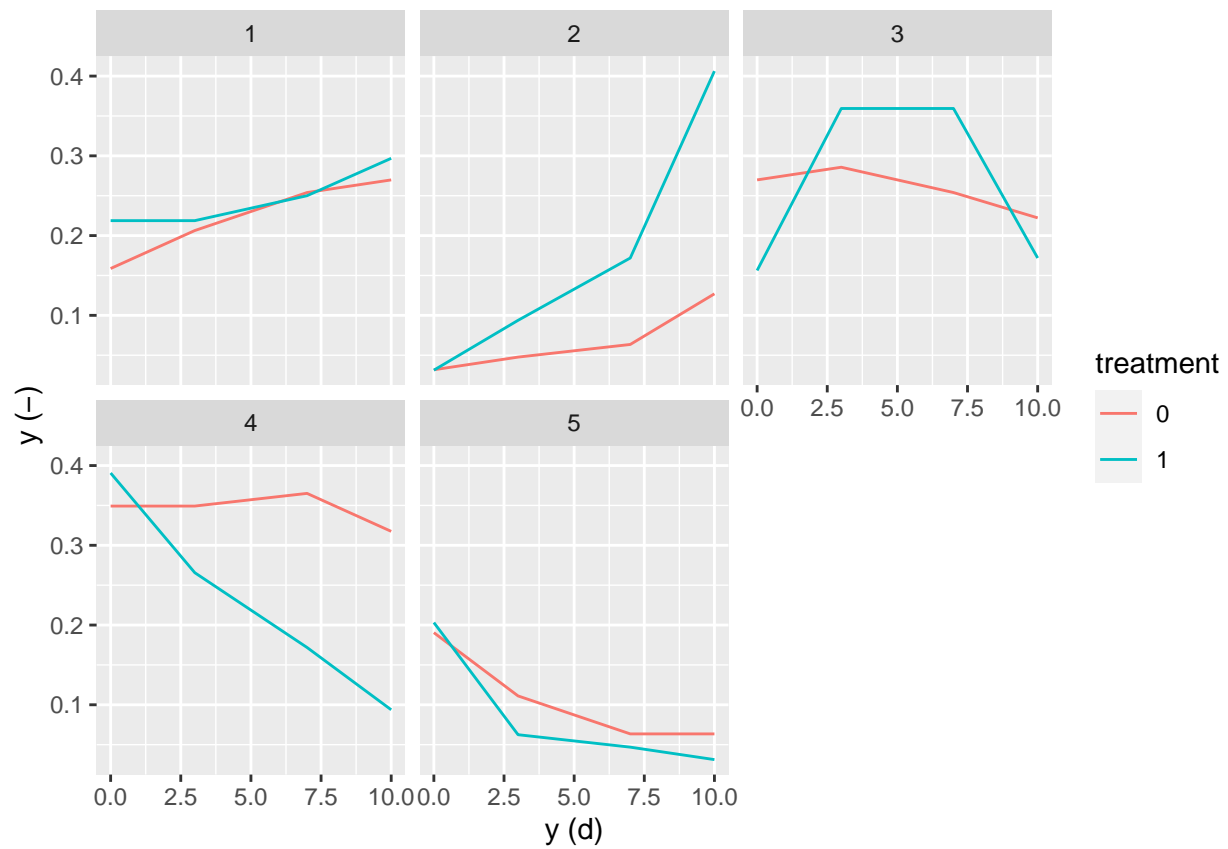
```
plotDiscreteData(ordknee.data, outcome="categorical", which.cov="Sex")
```

```
if(saveFigs) {
  namfig<-"knee_rawDataPropTime.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  plotDiscreteData(saemix.data, outcome="categorical", which.cov="treatment")
  dev.off()
}
```

The following R code represents the data as barplots of the different pain scores as a function of time in study, also illustrating a recovery as the proportion of lower pain scores increases. Other graphs can be created to explore this data, such as the evolution of mean scores over time.

```
gtab <- knee.saemix %>%
  group_by(time, y) %>%
  summarise(n=length(y)) %>%
  mutate(y=as.factor(y))
```

```
## `summarise()` has grouped output by 'time'. You can override using the
## `.groups` argument.
```

```
ggplot(data = gtab, aes(x = time, y=n, group=y, fill=y)) +
  geom_bar(stat="identity", position = "dodge") + theme_bw() +
  scale_fill_brewer(palette = "Reds") + theme(legend.position = "top") +
  labs(fill = "Score") + xlab("Time (d)") + ylab("Counts")
```
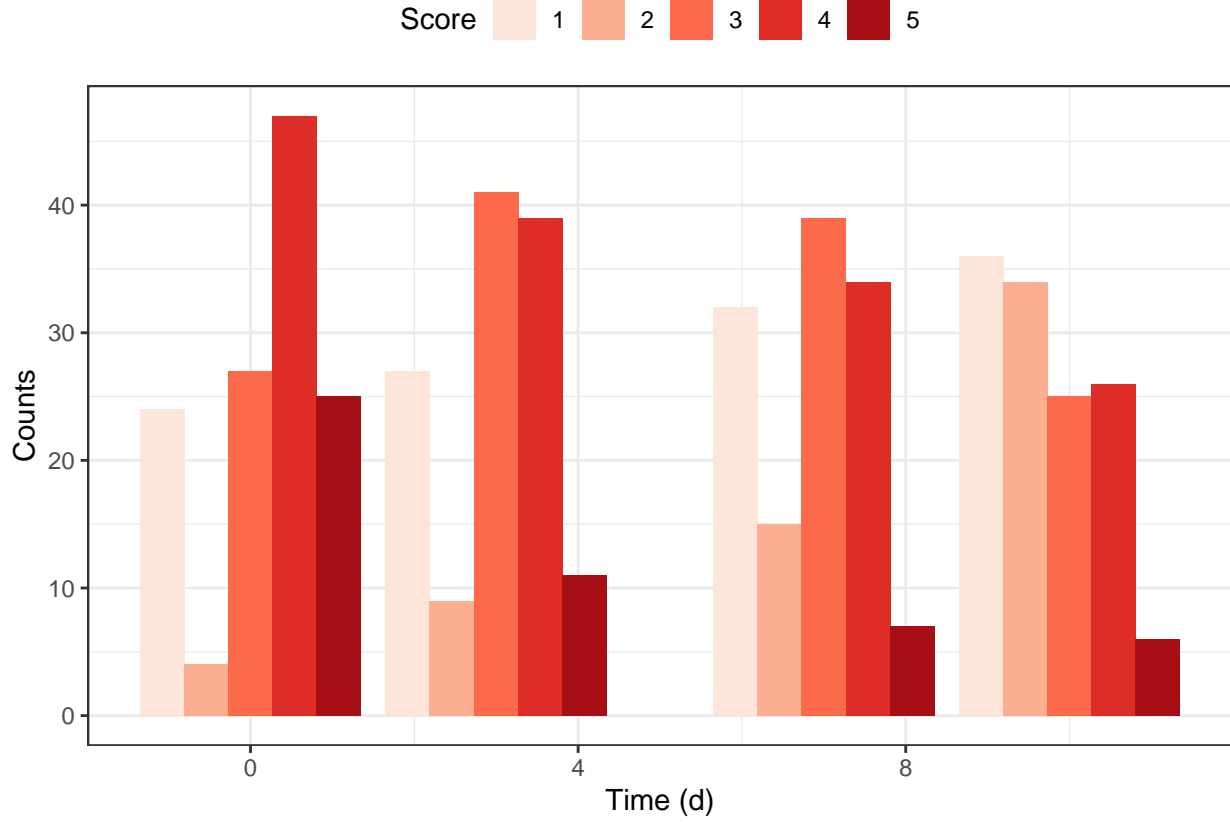
```
# Gender effect ?
if(FALSE) {
  gtab2 <- knee.saemix %>%
    group_by(time, Sex) %>%
    summarise(meanscore=mean(y))

  ggplot(data = gtab2, aes(x = time, y=meanscore, group=Sex, fill=Sex)) +
    geom_line() + theme_bw() + theme(legend.position = "top") +
    labs(fill = "Score") + xlab("Time (d)") + ylab("Mean score")
}
```

Model The dataset is part of the datasets analysed in (Tutz 2012) with various methods described in the vignettes in the documentation of the *knee* dataset, but mainly as logistic regression on the response after 10 days, or as mixed binary regression after dichotomising the response. Here, we fit a proportional odds model to the full data. The probability $p_{ij} = P(Y_{ij} = 1 | \theta_{1,i}, \theta_{2,i})$ associated with an event Y_{ij} at time t_{ij} is given by the following equation for the logit:

$$
\begin{aligned}
logit(P(Y_{ij} = 1 | \psi_i)) &= \theta_{1,i} + \beta_i t_{ij} \\
logit(P(Y_{ij} = 2 | \psi_i)) &= \theta_{1,i} + \theta_2 \\
logit(P(Y_{ij} = 3 | \psi_i)) &= \theta_{1,i} + \theta_2 + \theta_3 \\
logit(P(Y_{ij} = 4 | \psi_i)) &= \theta_{1,i} + \theta_2 + \theta_3 + \theta_4 \\
P(Y_{ij} = 4 | \psi_i) &= 1 - \sum_{k=1}^{4} P(Y_{ij} = k | \psi_i)
\end{aligned}
\tag{1}
$$

where θ_1 and β are assumed to have interindividual variability and to follow a normal distribution. β is the effect of time, θ_1 is the probability of a pain score of 1 and the other parameters represent an incremental risk to move into the higher pain category.

The following segment of code defines the ordinal model, computing the different logits for the different categories and deriving the corresponding probability given the observed data passed in *xidep*. We first fit a base model without covariate.

```r
# Model for ordinal responses
ordinal.model<-function(psi,id,xidep) {
  y<-xidep[,1]
  time<-xidep[,2]
  alp1<-psi[id,1]
  alp2<-psi[id,2]
  alp3<-psi[id,3]
  alp4<-psi[id,4]
  beta<-psi[id,5]

  logit1<-alp1 + beta*time
  logit2<-logit1+alp2
  logit3<-logit2+alp3
  logit4<-logit3+alp4
  pge1<-exp(logit1)/(1+exp(logit1))
  pge2<-exp(logit2)/(1+exp(logit2))
  pge3<-exp(logit3)/(1+exp(logit3))
  pge4<-exp(logit4)/(1+exp(logit4))
  pobs = (y==1)*pge1+(y==2)*(pge2 - pge1)+(y==3)*(pge3 - pge2)+(y==4)*(pge4 - pge3)+(y==5)*(1 - pge4)
  logpdf <- log(pobs)

  return(logpdf)
}
# simulate function
simulateOrdinal<-function(psi,id,xidep) {
  y<-xidep[,1]
  time<-xidep[,2]
  alp1<-psi[id,1]
  alp2<-psi[id,2]
  alp3<-psi[id,3]
  alp4<-psi[id,4]
  beta<-psi[id,5]

  logit1<-alp1 + beta*time
  logit2<-logit1+alp2
  logit3<-logit2+alp3
  logit4<-logit3+alp4
  pge1<-exp(logit1)/(1+exp(logit1))
  pge2<-exp(logit2)/(1+exp(logit2))
  pge3<-exp(logit3)/(1+exp(logit3))
  pge4<-exp(logit4)/(1+exp(logit4))
  x<-runif(length(time))
  ysim<-1+as.integer(x>pge1)+as.integer(x>pge2)+as.integer(x>pge3)+as.integer(x>pge4)
  return(ysim)
}

# Saemix model
saemix.model<-saemixModel(model=ordinal.model,description="Ordinal categorical model",modeltype="likeli
                simulate.function=simulateOrdinal, psi0=matrix(c(0,0.2, 0.6, 3, 0.2),ncol=5, byrow=TRUE
                dimnames=list(NULL,c("alp1","alp2","alp3","alp4","beta"))), transform.par=c(0,1,1,1,1),
```

```
                omega.init=diag(c(100, 1, 1, 1, 1)), covariance.model = diag(c(1,0,0,0,1)), verbose=FALS

# Fitting
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, fim=FALSE, nb.chains=10, nbiter.saemix=c
#saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, nb.chains=10, fim=FALSE)

ord.fit<-saemix(saemix.model,ordknee.data,saemix.options)
summary(ord.fit)

## ---------------------------------------------------------
## ----------------- Fixed effects ------------------
## ---------------------------------------------------------
##   Parameter Estimate
## 1      alp1   -15.21
## 2      alp2     6.51
## 3      alp3     8.49
## 4      alp4    12.48
## 5      beta     0.87
## ---------------------------------------------------------
## ----------- Variance of random effects -----------
## ---------------------------------------------------------
##           Parameter Estimate
## alp1 omega2.alp1   189.79
## beta omega2.beta     0.55
## ---------------------------------------------------------
## ------   Correlation matrix of random effects  ------
## ---------------------------------------------------------
##              omega2.alp1 omega2.beta
## omega2.alp1 1.00          0.00
## omega2.beta 0.00          1.00
## ---------------------------------------------------------
## --------------- Statistical criteria -------------
## ---------------------------------------------------------
##
## Likelihood computed by importance sampling
##        -2LL= 859.7992
##        AIC = 875.7992
##        BIC = 898.5527
## ---------------------------------------------------------
plot(ord.fit, plot.type="convergence")
```
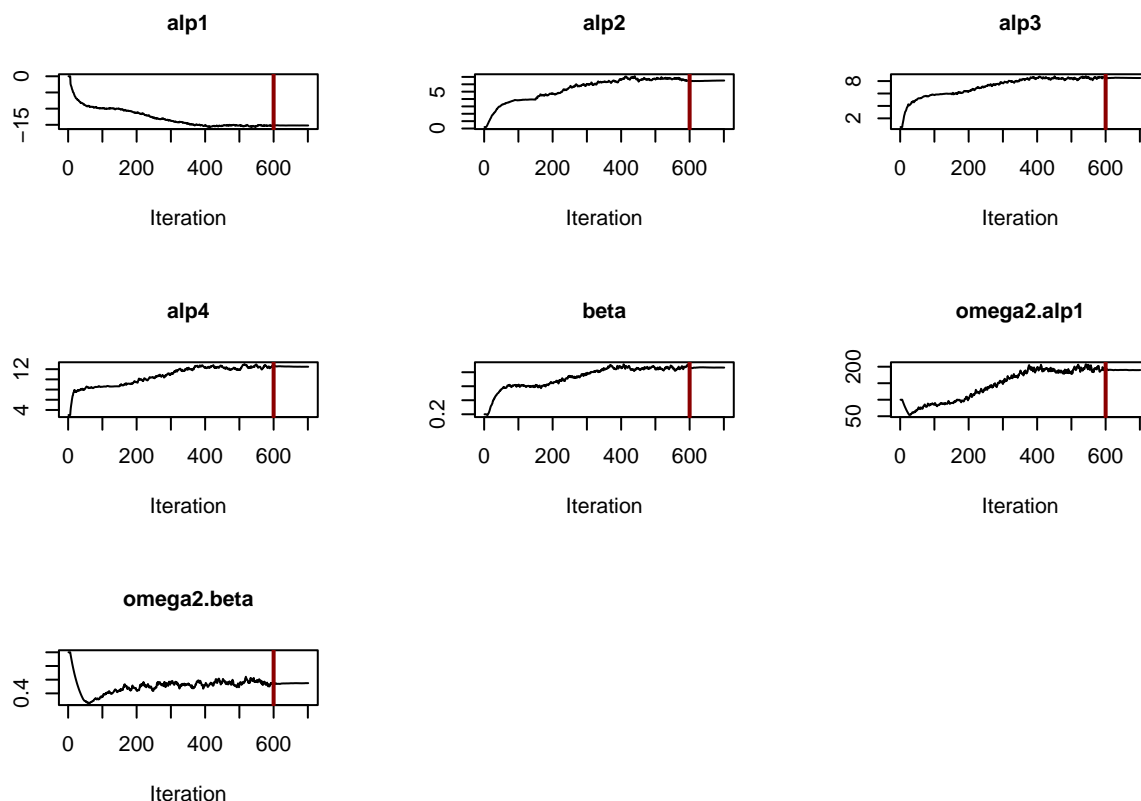
alp1   **alp2**   **alp3**

alp4   **beta**   **omega2.alp1**

omega2.beta

```
## Note: comparable estimates obtained with Monolix (not same, but within CI)
## quite a lot of sensitivity to distributions (when using eg normal distributions in Monolix the parame
```

We then applied the stepwise algorithm proposed by Delattre et al. to simultaneously investigate the covariate model and variability structure. This was run outside Rstudio because of memory issues. The resulting model has variability on all the α parameters, and included treatment on α_2 and β and age squared on α_1. Comparing the two models through the *compare.saemix()* function shows about 30 points improvement in the BIC.

```
# Do not run, Rstudio fails (ran in a script as "R CMD BATCH paper_kneeCovModel.R paper_kneeCovModel.ou
#if(runCovKnee) cov.ordfit <- step.saemix(ord.fit, trace=TRUE, direction='both')

# Resulting model
## IIV: all alphas, none on beta :-/
## Covariates:   alp1(Age2)alp2(treatment)beta(treatment)
covariate.model <- matrix(data=0, nrow=4, ncol=5)
covariate.model[3,2]<-covariate.model[3,5]<-covariate.model[4,1]<-1
ordmodel.cov<-saemixModel(model=ordinal.model,description="Ordinal categorical model",modeltype="likeli
                simulate.function=simulateOrdinal, psi0=matrix(c(0,0.2, 0.6, 3, 0.2),ncol=5, byrow=TRUE
                dimnames=list(NULL,c("alp1","alp2","alp3","alp4","beta"))), transform.par=c(0,1,1,1,1),
                omega.init=diag(c(100, 1, 1, 1, 1)), covariate.model=covariate.model, covariance.model =

# Fitting
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, fim=FALSE, nb.chains=10, nbiter.saemix=c
#saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, nb.chains=10, fim=FALSE)

ord.fit.cov<-saemix(ordmodel.cov,ordknee.data,saemix.options)
summary(ord.fit.cov)
```

```
## -------------------------------------------------------
## ----------------- Fixed effects  ------------------
## -------------------------------------------------------
##                Parameter Estimate
## 1                    alp1  -23.349
## 2      beta_Age2(alp1)     0.062
## 3                    alp2    3.499
## 4 beta_treatment(alp2)     0.977
## 5                    alp3    8.538
## 6                    alp4   16.436
## 7                    beta    0.884
## 8 beta_treatment(beta)     0.557
## -------------------------------------------------------
## ----------- Variance of random effects  -----------
## -------------------------------------------------------
##         Parameter Estimate
## alp1 omega2.alp1   244.71
## alp2 omega2.alp2     0.18
## alp3 omega2.alp3     0.55
## alp4 omega2.alp4     0.47
## -------------------------------------------------------
## ------  Correlation matrix of random effects  ------
## -------------------------------------------------------
##             omega2.alp1 omega2.alp2 omega2.alp3 omega2.alp4
## omega2.alp1 1.00        0.00        0.00        0.00
## omega2.alp2 0.00        1.00        0.00        0.00
## omega2.alp3 0.00        0.00        1.00        0.00
## omega2.alp4 0.00        0.00        0.00        1.00
## -------------------------------------------------------
## --------------- Statistical criteria  -------------
## -------------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 807.0315
##       AIC = 833.0315
##       BIC = 870.0059
## -------------------------------------------------------
```

```
# Compare the base and covariate model
compare.saemix(ord.fit, ord.fit.cov)
```

```
## Likelihoods calculated by importance sampling
```

```
##        AIC       BIC
## 1 875.7992 898.5527
## 2 833.0315 870.0059
```

Model evaluation In the code below we produce VPC plots with the *discreteVPC()* function (see details above for the binary example) for the model with covariates. The VPC show some model misspecification, especially in the intermediate pain scores, as well as a tendency to overestimate the improvement, driven by the increase in the lowest pain score. This suggests the impact of time and treatment are not well taken into account in the current model. A second plot stratified by treatment also suggests treatment effect is not properly accounted for the three lowest pain categories and across time. Finally, although Sex was not retained in the covariate model, VPC stratified on Sex seem to indicate different distributions of the pain scores between men and women, especially in the first and third categories (no or middle pain levels).
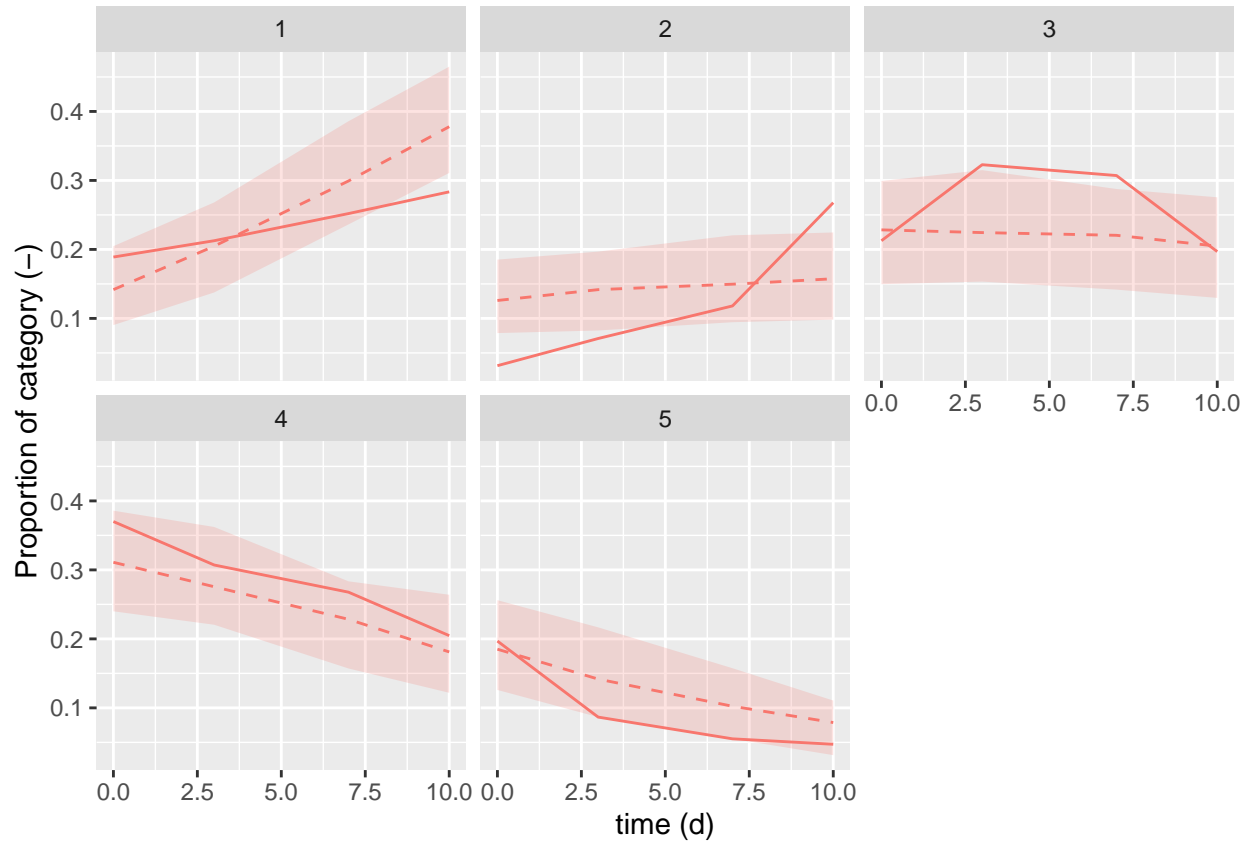
```
### Simulations for VPC
nsim<-100
yfit<-ord.fit.cov
yfit<-simulateDiscreteSaemix(yfit, nsim=nsim)
discreteVPC(yfit, outcome="categorical")
```
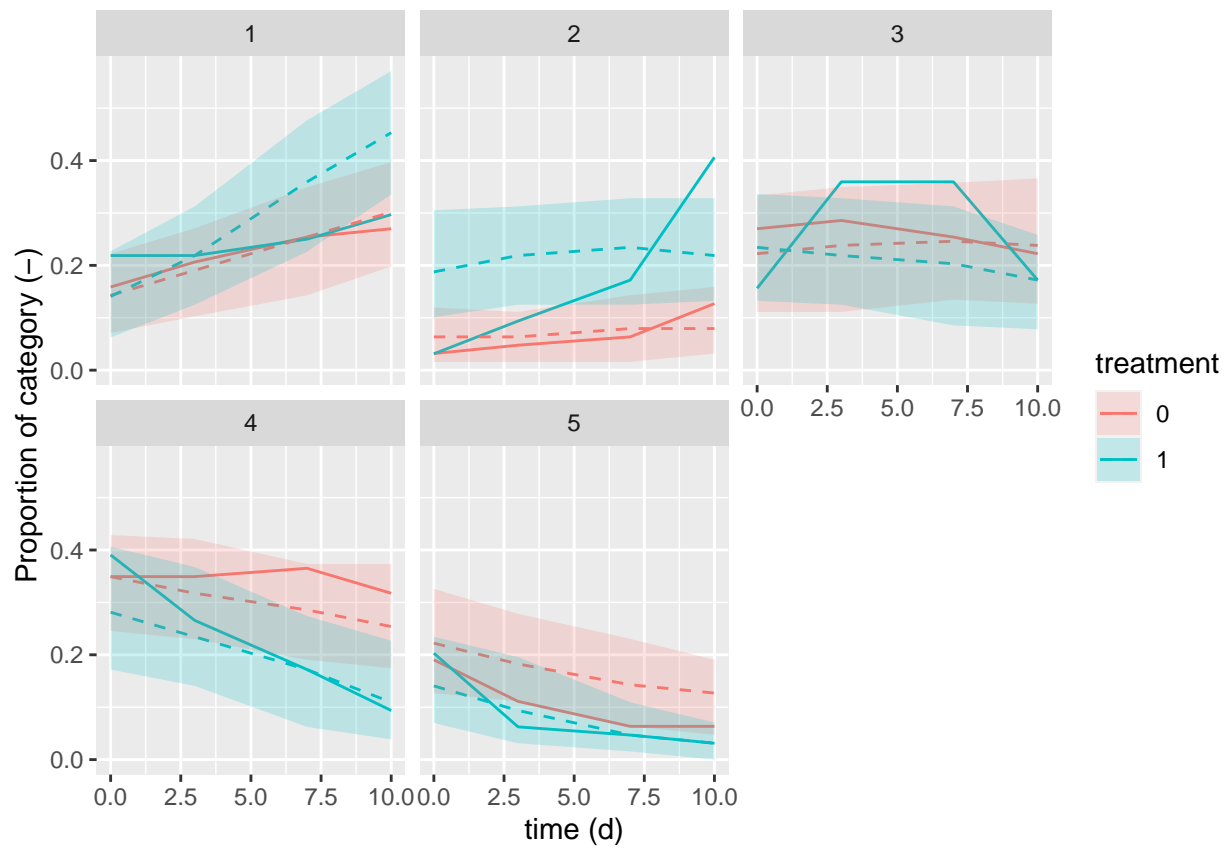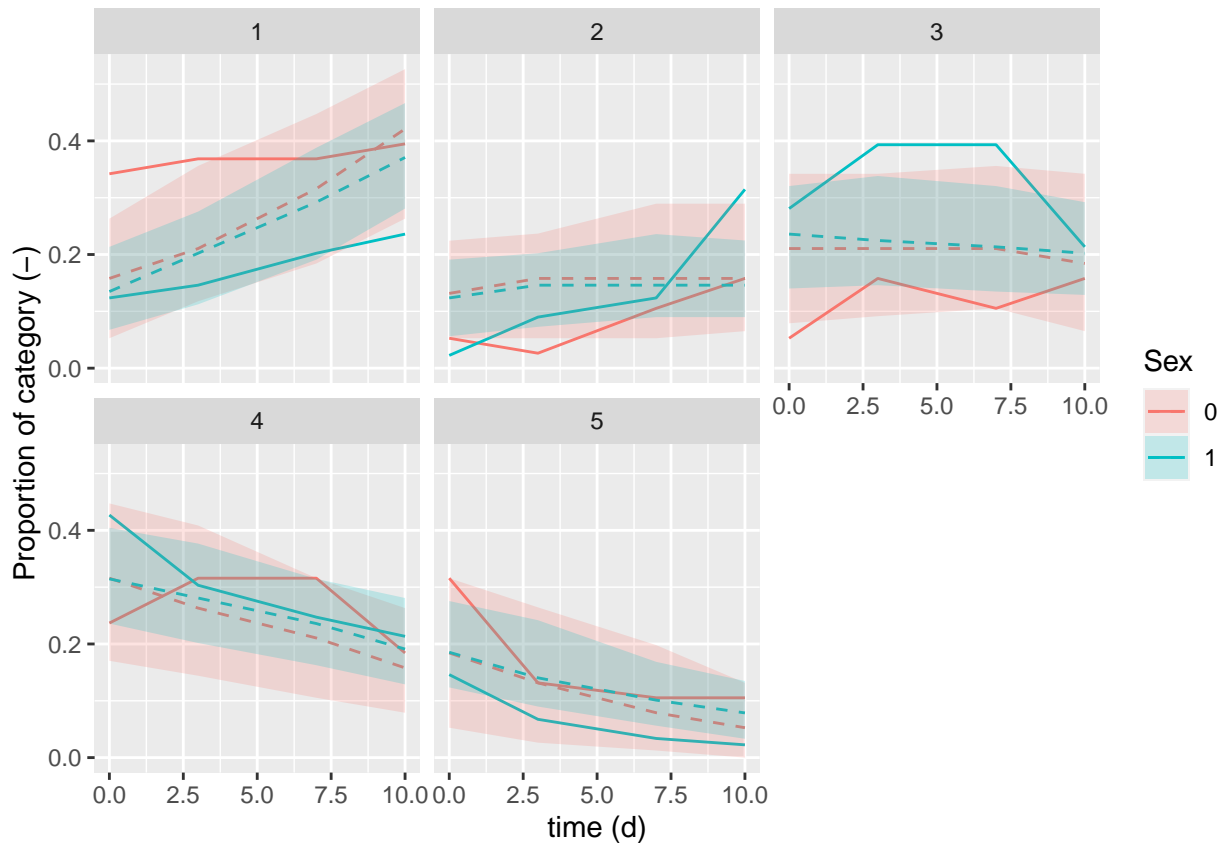


```
discreteVPC(yfit, outcome='categorical',covsplit=TRUE, which.cov="treatment")
```

```
discreteVPC(yfit, outcome='categorical',covsplit=TRUE, which.cov="Sex")
```

```r
if(saveFigs) {
  namfig<-"knee_VPCbytreatment.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  discreteVPC(yfit, outcome='categorical',covsplit=TRUE, which.cov="treatment")
  dev.off()
  namfig<-"knee_VPCbySex.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  discreteVPC(yfit, outcome='categorical',covsplit=TRUE, which.cov="Sex")
  dev.off()
}

if(FALSE) {
  ### Simulations for VPC - model without covariates
  nsim<-100
  yfit<-ord.fit
  yfit<-simulateDiscreteSaemix(yfit, nsim=nsim)
  discreteVPC(yfit, outcome="categorical")
}
```

We can also look at the VPC for the median score in each treatment group to find that the model tends to underpredict the pain scores, especially in the group receiving therapy 1.

```r
# VPC for median score in each group
knee3 <- knee.saemix %>%
  group_by(time, treatment) %>%
  summarise(mean=mean(y))
```

```
## `summarise()` has grouped output by 'time'. You can override using the
```

```
## `.groups` argument.
simdat <-yfit@sim.data@datasim
simdat$time<-rep(yfit@data@data$time,nsim)
simdat$treatment<-rep(yfit@data@data$treatment,nsim)
ytab<-NULL
for(irep in 1:nsim) {
  xtab<-simdat[simdat$irep==irep,]
  suppressMessages(
  xtab1 <- xtab %>%
    group_by(time, treatment) %>%
    summarise(mean=mean(ysim))
  )
  ytab<-rbind(ytab,xtab1[,c("time","treatment","mean")])
}
gtab <- ytab %>%
  group_by(time, treatment) %>%
  summarise(lower=quantile(mean, c(0.05)), mean=median(mean), upper=quantile(mean, c(0.95)))

## `summarise()` has grouped output by 'time'. You can override using the
## `.groups` argument.
kneeMedvpc <- ggplot(data = knee3, aes(x = time, y=mean, group=treatment)) +
  geom_ribbon(data=gtab, aes(x=time, ymin=lower, ymax=upper), alpha=0.5, fill="lightblue") +
  geom_point(colour='blue') + theme_bw() +
  scale_fill_brewer(palette = "Blues") + theme(legend.position = "top") +
  labs(fill = "Score") + xlab("Time (d)") + ylab("Median value of score over time") + facet_wrap(.~trea

print(kneeMedvpc)
```
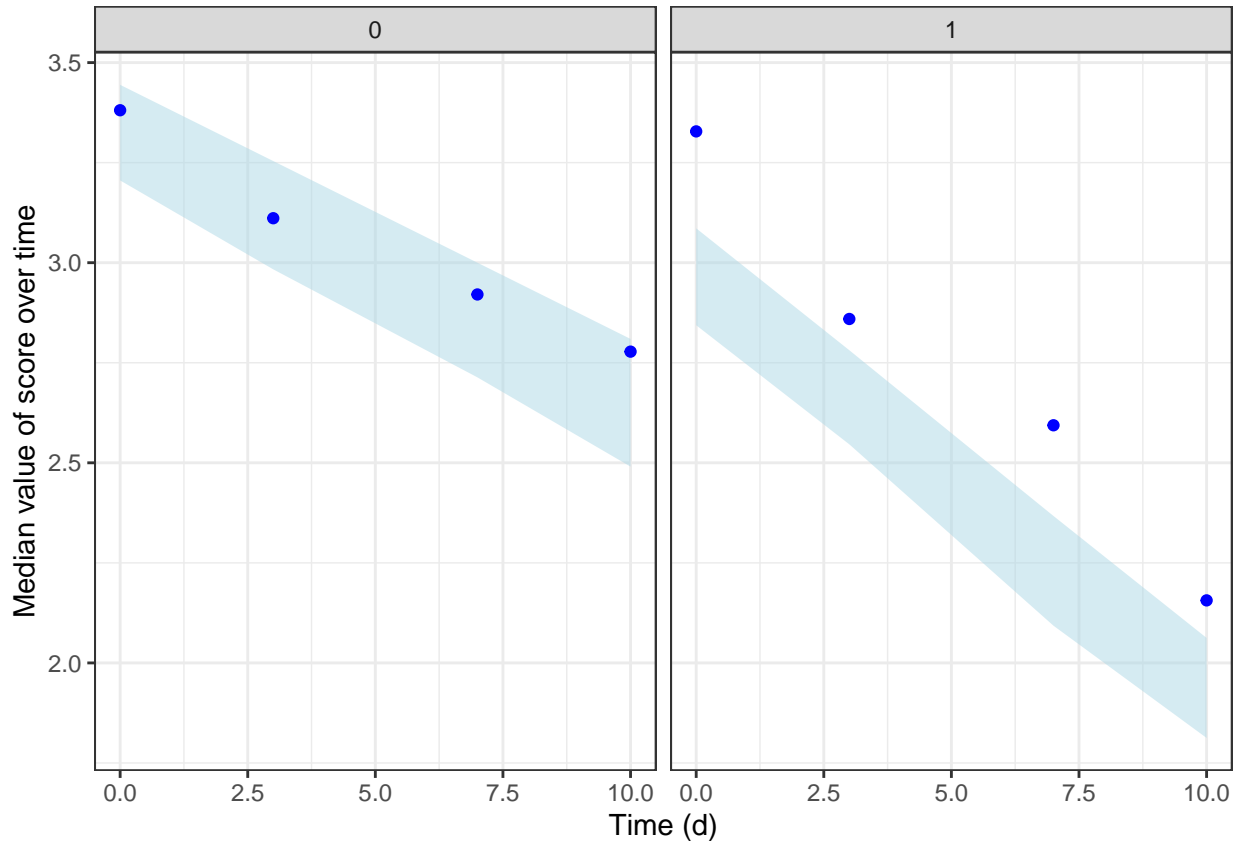
```
if(saveFigs) {
  namfig<-"knee_medianScoreVPC.eps"
  cairo_ps(file = file.path(figDir, namfig), onefile = TRUE, fallback_resolution = 600, height=8.27, wid
  plot(kneeMedvpc)
  dev.off()
}
```

Taken together, these results suggest that the proportional odds model may not be adequate to describe this data. We could investigate multinomial models to allow for different time trends within each value of score, or consider different types of models such as Markov models, but these are currently out of scope in **saemix**.

Estimation errors

Boostrap methods   As previously, we can assess parameters uncertainty using bootstrap approaches. Here we load the results from the two bootstrap files prepared beforehand by running the *saemix.bootstrap()* function with 500 simulations. We compute the bootstrap quantiles for the 95% CI, as well as the SD of the bootstrap distribution, corresponding to a normal approximation of the SE.

```
if(runBootstrap) {
  case.ordinal <- saemix.bootstrap(ord.fit, method="case", nboot=nboot)
  cond.ordinal <- saemix.bootstrap(ord.fit, method="conditional", nboot=nboot)
} else {
# case.ordinal <- read.table(file.path(saemixDir,"bootstrap","results","knee_caseBootstrap.res"), header
# cond.ordinal <- read.table(file.path(saemixDir,"bootstrap","results","knee_condBootstrap.res"), header
 case.ordinal <- read.table(file.path(saemixDir,"paperSaemix3","bootstrapCase_knee.res"), header=T)
 cond.ordinal <- read.table(file.path(saemixDir,"paperSaemix3","bootstrapCond_knee.res"), header=T)
}
```

```r
case.ordinal <- case.ordinal[!is.na(case.ordinal[,2]),]
cond.ordinal <- cond.ordinal[!is.na(cond.ordinal[,2]),]
nboot<-dim(case.ordinal)[1]
for(icol in 7:8) {
  case.ordinal[,icol]<-sqrt(case.ordinal[,icol]) # compute SD (omega) from omega2
  cond.ordinal[,icol]<-sqrt(cond.ordinal[,icol])
}

par.estim<-format(c(ord.fit@results@fixed.effects,sqrt(diag(ord.fit@results@omega)[ord.fit@results@indx
df2<-data.frame(parameter=colnames(case.ordinal)[-c(1)], saemix=par.estim)
for(i in 1:2) {
  if(i==1) {
    resboot1<-case.ordinal
    namboot<-"case"
  } else {
    resboot1<-cond.ordinal
    namboot <-"cNP"
  }
  mean.bootDist<-apply(resboot1, 2, mean, na.rm=T)[-c(1)]
  sd.bootDist<-apply(resboot1, 2, sd, na.rm=T)[-c(1)]
  quant.bootDist<-apply(resboot1[-c(1)], 2, quantile, c(0.025, 0.975), na.rm=T)
  l1<-paste0(format(mean.bootDist, digits=2)," (",format(sd.bootDist,digits=2, trim=T),")")
  l2<-paste0("[",format(quant.bootDist[1,], digits=2),", ",format(quant.bootDist[2,],digits=2, trim=T),"
  df2<-cbind(df2, l1, l2)
  i1<-3+2*(i-1)
  colnames(df2)[i1:(i1+1)]<-paste0(namboot,".",c("estimate","CI"))
}
print(df2)
```

```
##      parameter saemix case.estimate         case.CI  cNP.estimate
## 1        alp1 -15.21 -16.40 (2.26) [-20.29, -11.96] -14.88 (2.07)
## 2        alp2   6.51   7.15 (0.87)   [  5.31, 8.54]   6.05 (0.85)
## 3        alp3   8.49   9.07 (1.38)   [  6.71, 11.78]   8.47 (1.07)
## 4        alp4  12.48  13.26 (2.43)   [  9.81, 18.76]  12.88 (1.91)
## 5        beta   0.87   0.92 (0.11)   [  0.73, 1.13]   0.82 (0.11)
## 6 omega2.alp1  13.78  14.83 (2.24)  [ 11.22, 19.66]  13.37 (1.74)
## 7 omega2.beta   0.74   0.74 (0.12)   [  0.53, 0.96]   0.75 (0.11)
##            cNP.CI
## 1 [-18.99, -10.69]
## 2   [  4.63, 7.74]
## 3   [  6.58, 10.62]
## 4   [  9.68, 16.98]
## 5   [  0.62, 1.04]
## 6   [ 10.47, 17.02]
## 7   [  0.55, 0.95]
```

```r
df3<-df2[,c(2,4)] # case bootstrap
rownames(df3)<-c("$\\alpha_1$","$\\alpha_2$","$\\alpha_3$","$\\alpha_4$","$\\beta$", "$\\omega_{\\alpha_
# print(xtable(df3), only.contents=TRUE, include.rownames=TRUE,  floating=F, sanitize.rownames.function

df3<-df2[,c(2,5)] # conditional bootstrap
rownames(df3)<-c("$\\alpha_1$","$\\alpha_2$","$\\alpha_3$","$\\alpha_4$","$\\beta$", "$\\omega_{\\alpha_
# print(xtable(df3), only.contents=TRUE, include.rownames=TRUE,  floating=F, sanitize.rownames.function
```

Model with covariates

```
if(runBootstrap) {
  case.ordinal <- saemix.bootstrap(ord.fit.cov, method="case", nboot=nboot)
  cond.ordinal <- saemix.bootstrap(ord.fit.cov, method="conditional", nboot=nboot)
} else {
 case.ordinal <- read.table(file.path(saemixDir,"paperSaemix3","bootstrapCase_kneeCov.res"), header=T)
 cond.ordinal <- read.table(file.path(saemixDir,"paperSaemix3","bootstrapCond_kneeCov.res"), header=T)
}
case.ordinal <- case.ordinal[!is.na(case.ordinal[,2]),]
cond.ordinal <- cond.ordinal[!is.na(cond.ordinal[,2]),]
nboot<-dim(case.ordinal)[1]
for(icol in 10:13) {
  case.ordinal[,icol]<-sqrt(case.ordinal[,icol]) # compute SD (omega) from omega2
  cond.ordinal[,icol]<-sqrt(cond.ordinal[,icol])
}


par.estim<-format(c(ord.fit.cov@results@fixed.effects,sqrt(diag(ord.fit.cov@results@omega)[ord.fit.cov@:
df2<-data.frame(parameter=colnames(case.ordinal)[-c(1)], saemix=par.estim)
for(i in 1:2) {
  if(i==1) {
    resboot1<-case.ordinal
    namboot<-"case"
  } else {
    resboot1<-cond.ordinal
    namboot <-"cNP"
  }
  mean.bootDist<-apply(resboot1, 2, mean, na.rm=T)[-c(1)]
  sd.bootDist<-apply(resboot1, 2, sd, na.rm=T)[-c(1)]
  quant.bootDist<-apply(resboot1[-c(1)], 2, quantile, c(0.025, 0.975), na.rm=T)
  l1<-paste0(format(mean.bootDist, digits=2)," (",format(sd.bootDist,digits=2, trim=T),")")
  l2<-paste0("[",format(quant.bootDist[1,], digits=2),", ",format(quant.bootDist[2,],digits=2, trim=T),
  df2<-cbind(df2, l1, l2)
  i1<-3+2*(i-1)
  colnames(df2)[i1:(i1+1)]<-paste0(namboot,".",c("estimate","CI"))
}
print(df2)
```

```
##               parameter  saemix  case.estimate            case.CI
## 1                  alp1 -23.349 -21.917 (4.065) [-30.235, -14.84]
## 2        beta_Age2.alp1.   0.062   0.058 (0.021) [  0.022, 0.10]
## 3                  alp2   3.499   3.160 (1.209) [  1.243, 5.51]
## 4  beta_treatment.alp2.   0.977   1.111 (0.386) [  0.490, 1.93]
## 5                  alp3   8.538   8.466 (1.824) [  5.484, 12.03]
## 6                  alp4  16.436  15.226 (3.176) [  9.654, 22.18]
## 7                  beta   0.884   0.838 (0.193) [  0.497, 1.20]
## 8  beta_treatment.beta.   0.557   0.566 (0.199) [  0.223, 0.97]
## 9           omega2.alp1  15.643  14.472 (2.674) [ 10.097, 20.36]
## 10          omega2.alp2   0.426   0.204 (0.172) [  0.023, 0.60]
## 11          omega2.alp3   0.742   0.681 (0.240) [  0.205, 1.09]
## 12          omega2.alp4   0.688   0.596 (0.228) [  0.163, 1.04]
##      cNP.estimate            cNP.CI
## 1  -19.682 (3.546) [-28.117, -13.576]
## 2    0.054 (0.016)   [  0.026, 0.091]
```

```
## 3     2.809 (0.835)   [  1.353, 4.839]
## 4     0.934 (0.310)   [  0.428, 1.573]
## 5     8.162 (1.544)   [  5.841, 11.233]
## 6    14.081 (3.167)   [  9.418, 20.727]
## 7     0.767 (0.134)   [  0.555, 1.031]
## 8     0.501 (0.149)   [  0.206, 0.831]
## 9    12.750 (2.270)   [  9.277, 17.827]
## 10    0.081 (0.082)   [  0.014, 0.324]
## 11    0.536 (0.167)   [  0.247, 0.889]
## 12    0.570 (0.233)   [  0.185, 1.072]
```

```r
# pretty print for paper
df3<-df2[,c(2,4)] # case bootstrap
rownames(df3)<-c("$\\alpha_1$","$\\beta_{Age2,\\alpha_1}$","$\\alpha_2$","$\\beta_{trt,\\alpha_2}$","$\
print(xtable(df3), only.contents=TRUE, include.rownames=TRUE,  floating=F, sanitize.rownames.function =
```

```
## % latex table generated in R 4.3.2 by xtable 1.8-4 package
## % Sun Jun  9 14:02:14 2024
##   & saemix & case.CI \\
##     \hline
## $\alpha_1$ & -23.349 & [-30.235, -14.84] \\
##     $\beta_{Age2,\alpha_1}$ &   0.062 & [  0.022, 0.10] \\
##     $\alpha_2$ &   3.499 & [  1.243, 5.51] \\
##     $\beta_{trt,\alpha_2}$ &   0.977 & [  0.490, 1.93] \\
##     $\alpha_3$ &   8.538 & [  5.484, 12.03] \\
##     $\alpha_4$ &  16.436 & [  9.654, 22.18] \\
##     $\beta$ &   0.884 & [  0.497, 1.20] \\
##     $\beta_{trt,\beta}$ &   0.557 & [  0.223, 0.97] \\
##     $\omega_{\alpha_1}$ &  15.643 & [ 10.097, 20.36] \\
##     $\omega_{\alpha_2}$ &   0.426 & [  0.023, 0.60] \\
##     $\omega_{\alpha_3}$ &   0.742 & [  0.205, 1.09] \\
##     $\omega_{\alpha_4}$ &   0.688 & [  0.163, 1.04] \\
##     \hline
```

```r
df3<-df2[,c(2,6)] # conditional bootstrap
rownames(df3)<-c("$\\alpha_1$","$\\beta_{Age2,\\alpha_1}$","$\\alpha_2$","$\\beta_{trt,\\alpha_2}$","$\
print(xtable(df3), only.contents=TRUE, include.rownames=TRUE,  floating=F, sanitize.rownames.function =
```

```
## % latex table generated in R 4.3.2 by xtable 1.8-4 package
## % Sun Jun  9 14:02:14 2024
##   & saemix & cNP.CI \\
##     \hline
## $\alpha_1$ & -23.349 & [-28.117, -13.576] \\
##     $\beta_{Age2,\alpha_1}$ &   0.062 & [  0.026, 0.091] \\
##     $\alpha_2$ &   3.499 & [  1.353, 4.839] \\
##     $\beta_{trt,\alpha_2}$ &   0.977 & [  0.428, 1.573] \\
##     $\alpha_3$ &   8.538 & [  5.841, 11.233] \\
##     $\alpha_4$ &  16.436 & [  9.418, 20.727] \\
##     $\beta$ &   0.884 & [  0.555, 1.031] \\
##     $\beta_{trt,\beta}$ &   0.557 & [  0.206, 0.831] \\
##     $\omega_{\alpha_1}$ &  15.643 & [  9.277, 17.827] \\
##     $\omega_{\alpha_2}$ &   0.426 & [  0.014, 0.324] \\
##     $\omega_{\alpha_3}$ &   0.742 & [  0.247, 0.889] \\
##     $\omega_{\alpha_4}$ &   0.688 & [  0.185, 1.072] \\
##     \hline
```

References

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