Testing examples in saemix 3.0 - discrete models

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Objective

Check saemix for discrete data models

Setup

- set up work directories
- two versions toggled by testMode
  - if testMode is FALSE, load the functions in R
  - if testMode is TRUE, load the library in a dev_mode environment
- aim: check the examples used in the online documentation
  - all examples must run without error

```
if(testMode) cat("Testing package\n") else cat("Loading libraries\n")
```

```
## Loading libraries
```

Testing library

Binary response model

- Toenail data
  - using the full model with 2 random effects (better than with only random effect on intercept according to AIC/BIC)
  - quick diagnostics using a simulation function
- **TODO**
  - add diagnostics (npd-categorical ?)
  - maybe check SE's with package by S. Ueckert

```
if(testMode)
  data(toenail.saemix) else
    toenail.saemix<-read.table(file.path(datDir, "toenail.saemix.tab"), header=TRUE)

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

```
## [1] "treatment"
##
##
## The following SaemixData object was successfully created:
```

```
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset toenail.saemix
##     Structured data: y ~ time + y | id
##     X variable for graphs: time ()
##     covariates: treatment (-)
##       reference class for covariate treatment :  0
```

```
# Explore data
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.
```

```
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")

# 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)
}

saemix.model<-saemixModel(model=binary.model,description="Binary model",
                          modeltype="likelihood",
                          psi0=matrix(c(0,-.5,0,0.5),ncol=2,byrow=TRUE,dimnames=list(NULL,c("theta1","th
                          transform.par=c(0,0), covariate.model=c(0,1),covariance.model=matrix(c(1,0,0,
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Binary model
##   Model type:  likelihood
## 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)
## }
##   Nb of parameters: 2
##       parameter names:  theta1 theta2
##       distribution:
##      Parameter Distribution Estimated
## [1,] theta1    normal       Estimated
## [2,] theta2    normal       Estimated
##   Variance-covariance matrix:
##        theta1 theta2
## theta1      1      0
## theta2      0      1
##   Covariate model:
##      theta1 theta2
## [1,]      0      1
##     Initial values
##              theta1 theta2
## Pop.CondInit      0   -0.5
## Cov.CondInit      0    0.5
```

```
saemix.options<-list(seed=1234567,save=FALSE,save.graphs=FALSE, displayProgress=FALSE, nb.chains=10, fi

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

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data              ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset toenail.saemix
##     Structured data: y ~ time + y | id
##     X variable for graphs: time ()
##     covariates: treatment (-)
##       reference class for covariate treatment :  0
## Dataset characteristics:
##     number of subjects:     294
##     number of observations: 1908
##     average/min/max nb obs: 6.49  /  1  /  7
## First 10 lines of data:
##    id       time y y.1 treatment mdv cens occ ytype
## 1   1  0.0000000 1   1         1   0    0   1     1
## 2   1  0.8571429 1   1         1   0    0   1     1
## 3   1  3.5357143 1   1         1   0    0   1     1
## 4   1  4.5357143 0   0         1   0    0   1     1
## 5   1  7.5357143 0   0         1   0    0   1     1
```

```
## 6   1 10.0357143 0   0         1   0    0   1     1
## 7   1 13.0714286 0   0         1   0    0   1     1
## 8   2  0.0000000 0   0         0   0    0   1     1
## 9   2  0.9642857 0   0         0   0    0   1     1
## 10  2  2.0000000 1   1         0   0    0   1     1
## -----------------------------------
## ----          Model           ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Binary model
##   Model type:  likelihood
## 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)
## }
## <bytecode: 0x55e9dd526cd0>
##   Nb of parameters: 2
##       parameter names:  theta1 theta2
##       distribution:
##      Parameter Distribution Estimated
## [1,] theta1    normal       Estimated
## [2,] theta2    normal       Estimated
##   Variance-covariance matrix:
##        theta1 theta2
## theta1      1      0
## theta2      0      1
##   Covariate model:
##           [,1] [,2]
## treatment    0    1
##     Initial values
##              theta1 theta2
## Pop.CondInit      0   -0.5
## Cov.CondInit      0    0.5
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  10
##     Seed:  1234567
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
```

```
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  -----------------
## ----------------------------------------------------
##      Parameter              Estimate
## [1,] theta1                 -2.20
## [2,] theta2                 -1.25
## [3,] beta_treatment(theta2) -0.47
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##        Parameter     Estimate
## theta1 omega2.theta1 59.3
## theta2 omega2.theta2  1.1
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.theta1 omega2.theta2
## omega2.theta1 1             0
## omega2.theta2 0             1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 1116.755
##       AIC = 1128.755
##       BIC = 1150.856
## ----------------------------------------------------
```

```
# simulate from model (nsim=100)
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)
}

yfit<-binary.fit
nsim<-100
yfit <- simulateDiscreteSaemix(yfit, simulBinary, nsim=nsim)
simdat <-yfit@sim.data@datasim
simdat$visit<-rep(toenail.saemix$visit,nsim)
simdat$treatment<-rep(toenail.saemix$treatment,nsim)

# VPC-type diagnostic
ytab<-NULL
```

```r
for(irep in 1:nsim) {
  xtab<-simdat[simdat$irep==irep,]
  xtab1 <- xtab %>%
    group_by(visit, treatment) %>%
    summarise(nev = sum(ysim), n=n()) %>%
    mutate(freq = nev/n)
  ytab<-rbind(ytab,xtab1[,c("visit","freq","treatment")])
}
```

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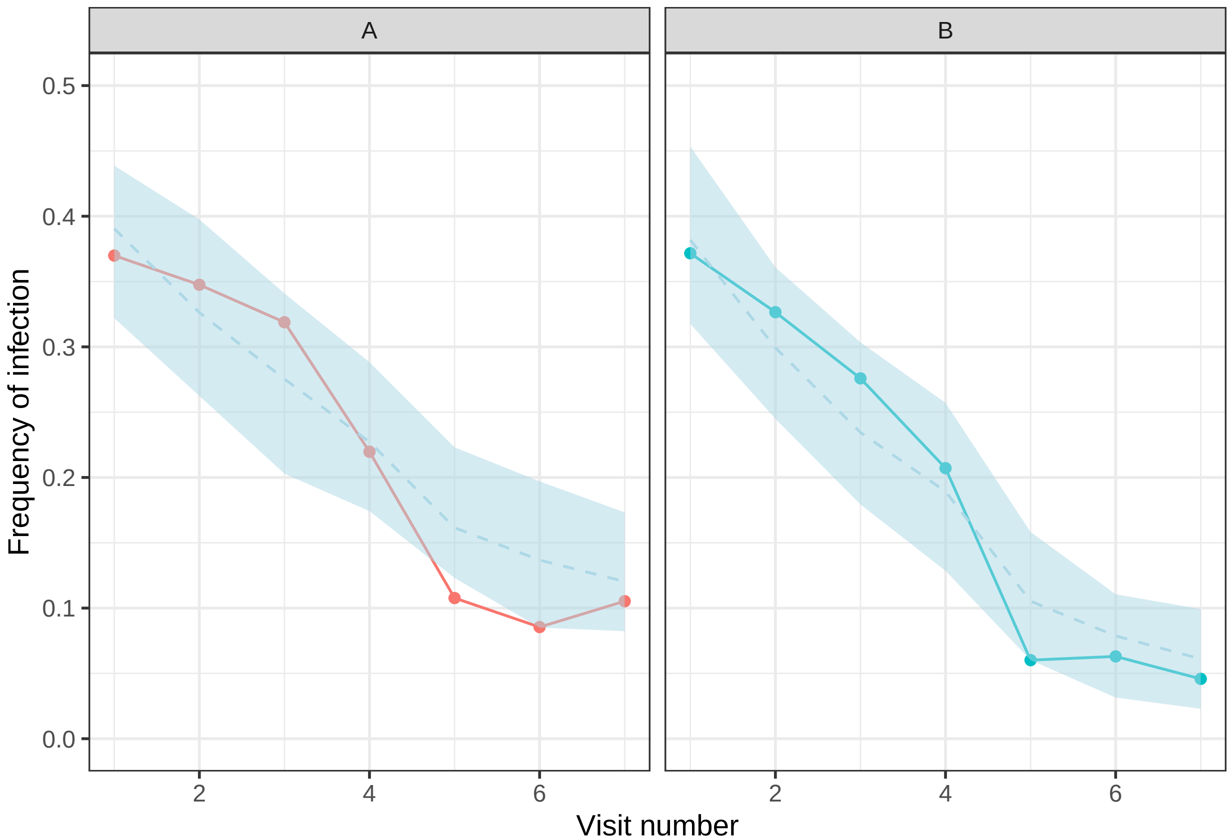

```
## `summarise()` has grouped output by 'visit'. You can override using the `.groups` argument.
```

```
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"))
```

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

```
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)
```



Categorical response model

- Knee pain after 3, 7 and 10 days of treatment compared to baseline (time=0)
  - longitudinal ordinal model with 5 categories
  - similar results to Monolix in terms of parameter estimates
  - SE don't seem so off, but still higher than Monolix (but computed with linearisation anyway)
- Comparing the 3 covariate models - model with Age on alp1 and treatment on beta best

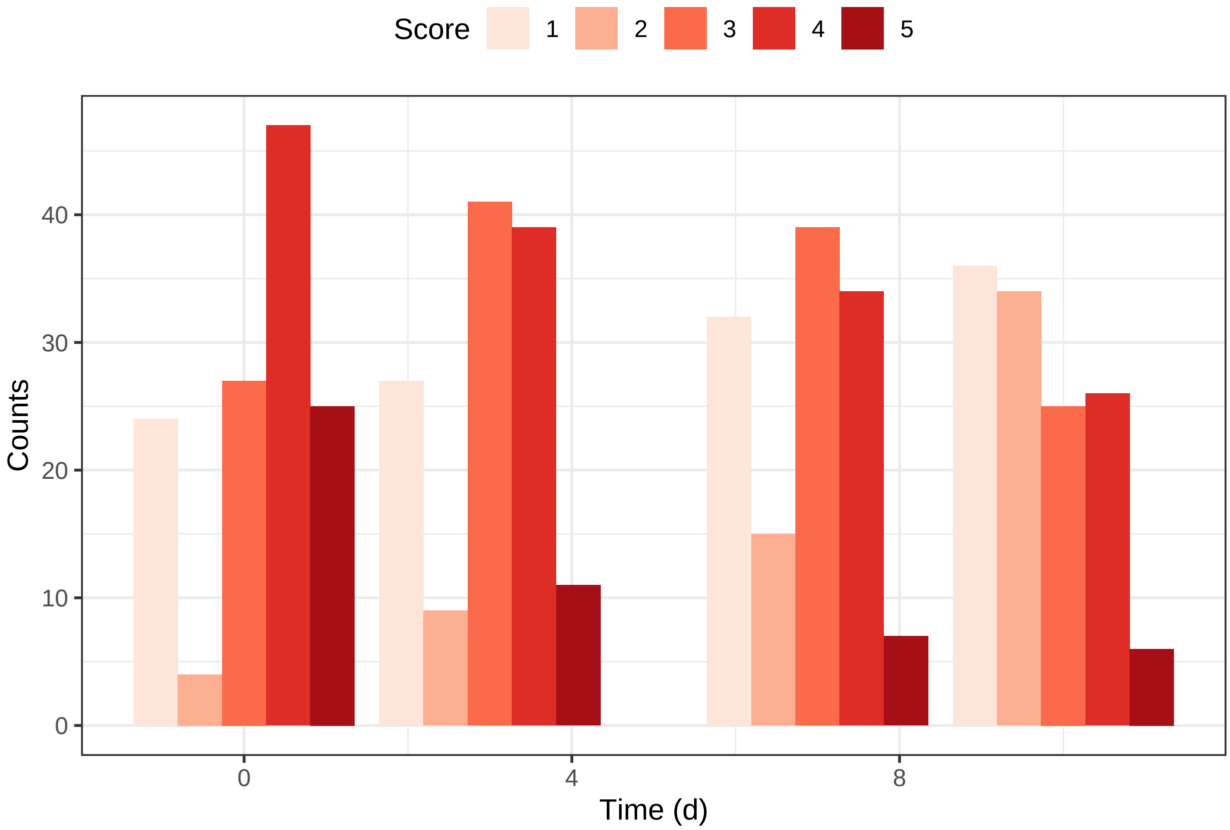
```r
if(testMode)
  data(knee.saemix) else
    knee.saemix<-read.table(file.path(datDir, "knee.saemix.tab"), header=TRUE)

# Data
saemix.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")))
```

```
## Column name(s)  do(es) not exist in the dataset, please check
## Remove columns 1 (  )
## No valid name given, attempting automatic recognition
## Automatic recognition of columns y successful
## [1] "Age"       "Sex"       "treatment" "Age2"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset knee.saemix
##     Structured data: y ~ y + time | id
##     X variable for graphs: time (d)
##     covariates: Age (yr), Sex (-), treatment (-), Age2 (yr2)
##       reference class for covariate Sex :  0
##       reference class for covariate treatment :  0
```

```r
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.
```

```r
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")
```




```
# 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)
}

# Fitting
covmodel2<-covmodel1<-matrix(data=0,ncol=5,nrow=4)
covmodel1[,1]<-1
```

```
covmodel1[,5]<-1
covmodel2[3,5]<-covmodel2[4,1]<-1

saemix.model<-saemixModel(model=ordinal.model,description="Ordinal categorical model",modeltype="likeli
                          psi0=matrix(c(0,0.2, 0.6, 3, 0.2),ncol=5,byrow=TRUE,dimnames=list(NULL,c("alp
                          transform.par=c(0,1,1,1,1),omega.init=diag(rep(1,5)), covariance.model = diag
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Ordinal categorical model
##   Model type:  likelihood
## 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)
## }
##   Nb of parameters: 5
##       parameter names:  alp1 alp2 alp3 alp4 beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] alp1      normal       Estimated
## [2,] alp2      log-normal   Estimated
## [3,] alp3      log-normal   Estimated
## [4,] alp4      log-normal   Estimated
## [5,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##      alp1 alp2 alp3 alp4 beta
## alp1    1    0    0    0    0
## alp2    0    0    0    0    0
## alp3    0    0    0    0    0
## alp4    0    0    0    0    0
## beta    0    0    0    0    1
##     No covariate in the model.
##     Initial values
```

```
##               alp1 alp2 alp3 alp4 beta
## Pop.CondInit    0  0.2  0.6    3  0.2
```

```
saemix.model.cov1<-saemixModel(model=ordinal.model,description="Ordinal categorical model",modeltype="li
                              psi0=matrix(c(0,0.2, 0.6, 3, 0.2),ncol=5,byrow=TRUE,dimnames=list(NULL,c(
                              transform.par=c(0,1,1,1,1),omega.init=diag(rep(1,5)), covariance.model = c
                              covariate.model = covmodel1)
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Ordinal categorical model
##   Model type:  likelihood
## 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)
## }
##   Nb of parameters: 5
##       parameter names:  alp1 alp2 alp3 alp4 beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] alp1      normal       Estimated
## [2,] alp2      log-normal   Estimated
## [3,] alp3      log-normal   Estimated
## [4,] alp4      log-normal   Estimated
## [5,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##      alp1 alp2 alp3 alp4 beta
## alp1    1    0    0    0    0
## alp2    0    0    0    0    0
## alp3    0    0    0    0    0
## alp4    0    0    0    0    0
## beta    0    0    0    0    1
##   Covariate model:
##      alp1 alp2 alp3 alp4 beta
```

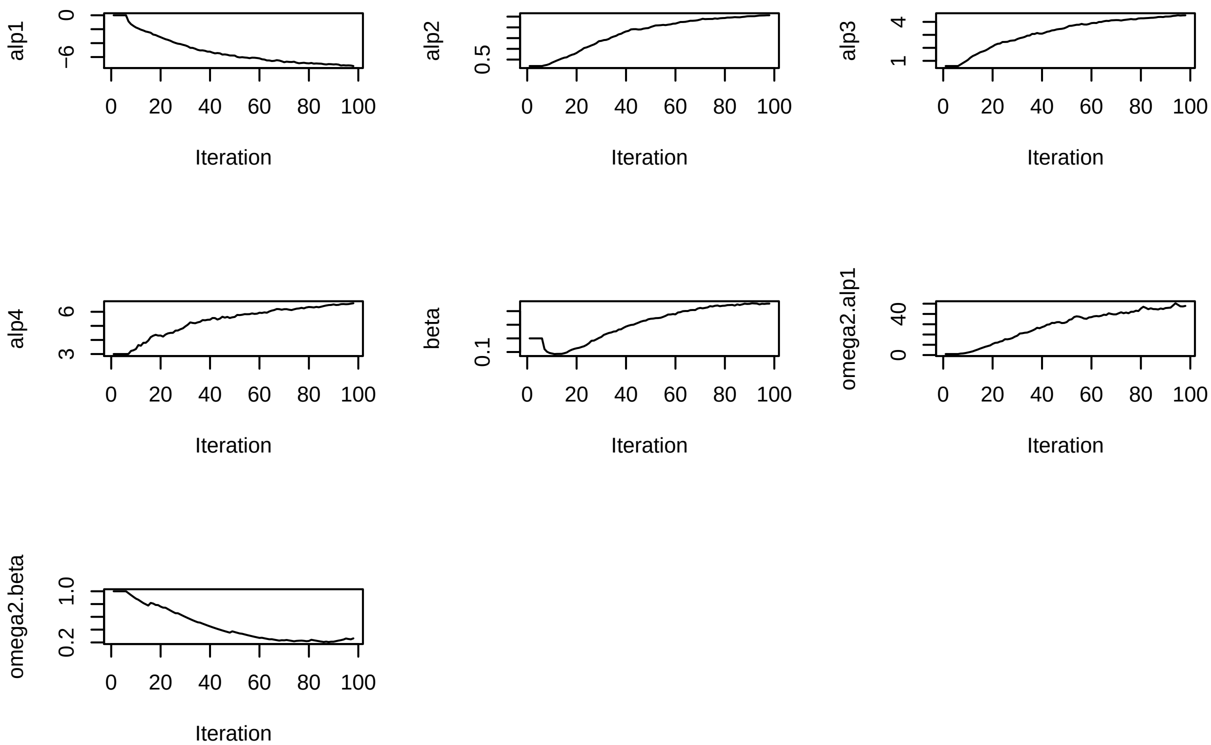
```
## [1,]    1    0    0    0    1
## [2,]    1    0    0    0    1
## [3,]    1    0    0    0    1
## [4,]    1    0    0    0    1
##     Initial values
##              alp1 alp2 alp3 alp4 beta
## Pop.CondInit    0  0.2  0.6    3  0.2
## Cov.CondInit    0  0.0  0.0    0  0.0
```

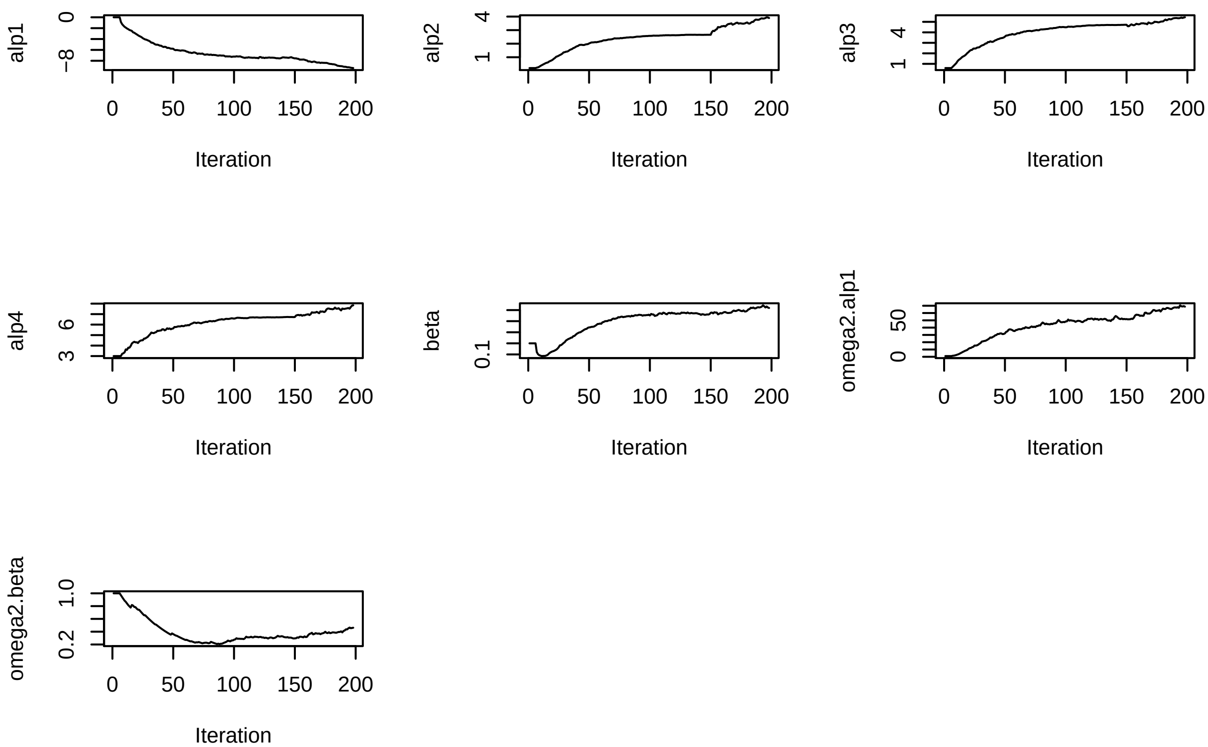
```
saemix.model.cov2<-saemixModel(model=ordinal.model,description="Ordinal categorical model",modeltype="li
                              psi0=matrix(c(0,0.2, 0.6, 3, 0.2),ncol=5,byrow=TRUE,dimnames=list(NULL,c
                              transform.par=c(0,1,1,1,1),omega.init=diag(rep(1,5)), covariance.model =
                              covariate.model = covmodel2)
```

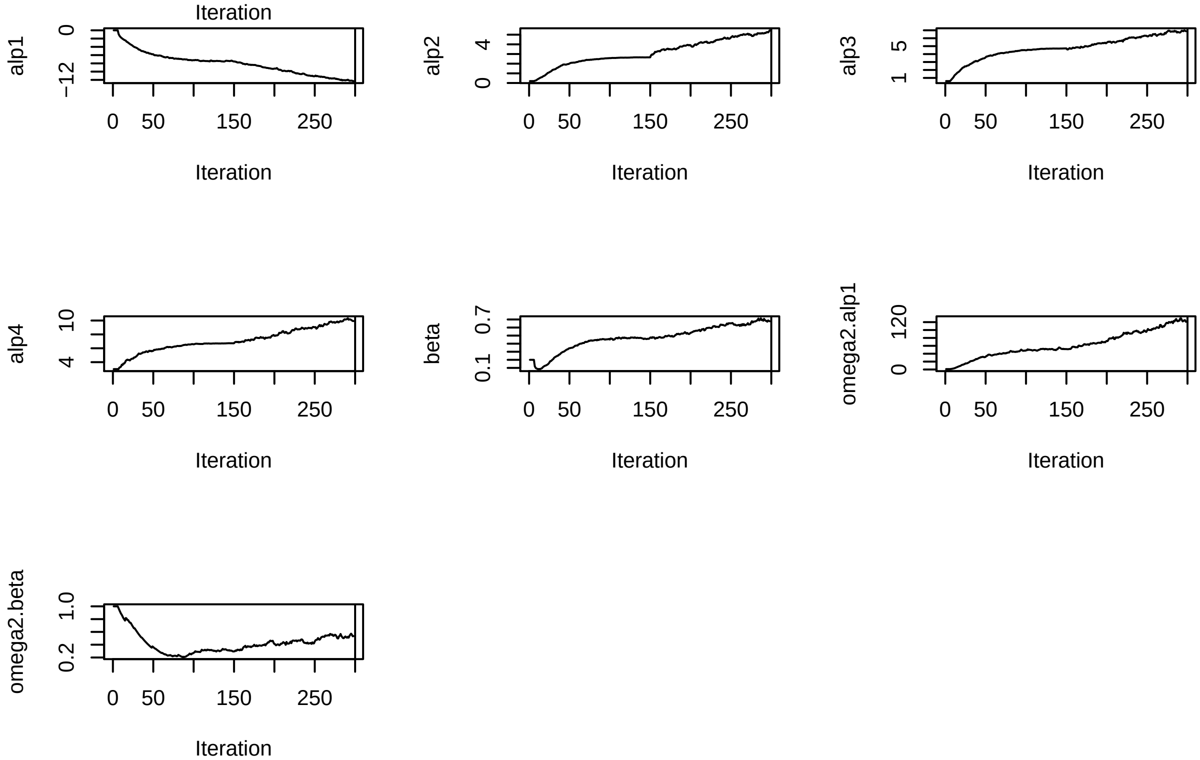
```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Ordinal categorical model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,1]
##   time<-xidep[,2]
##   alp1<-psi[id,1]
##   alp2<-psi[id,2]
##   alp3<-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)
## }
##   Nb of parameters: 5
##       parameter names:  alp1 alp2 alp3 alp4 beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] alp1      normal       Estimated
## [2,] alp2      log-normal   Estimated
## [3,] alp3      log-normal   Estimated
## [4,] alp4      log-normal   Estimated
## [5,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##      alp1 alp2 alp3 alp4 beta
## alp1    1    0    0    0    0
```

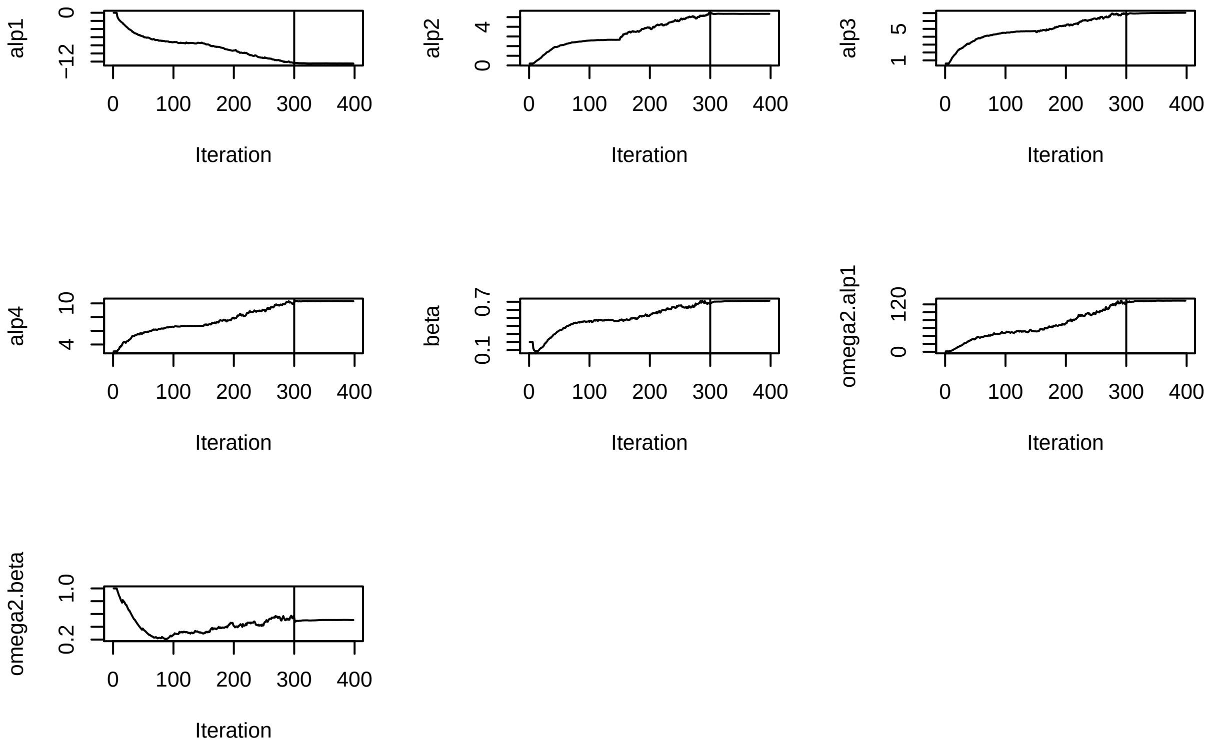
```
## alp2    0    0    0    0    0
## alp3    0    0    0    0    0
## alp4    0    0    0    0    0
## beta    0    0    0    0    1
##   Covariate model:
##       alp1 alp2 alp3 alp4 beta
## [1,]    0    0    0    0    0
## [2,]    0    0    0    0    0
## [3,]    0    0    0    0    1
## [4,]    1    0    0    0    0
##     Initial values
##                 alp1 alp2 alp3 alp4 beta
## Pop.CondInit    0  0.2  0.6    3  0.2
## Cov.CondInit    0  0.0  0.0    0  0.0
```

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

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




alp1
alp2
alp3
alp4
beta
omega2.alp1
omega2.beta
Iteration


alp1
alp2
alp3
alp4
beta
omega2.alp1
omega2.beta
Iteration




```
## Error in solve.default(FO) :
##   le système est numériquement singulier : conditionnement de la réciproque = 3.8767e-17
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset knee.saemix
##     Structured data: y ~ y + time | id
##     X variable for graphs: time (d)
##     covariates: Age (yr), Sex (-), treatment (-), Age2 (yr2)
##       reference class for covariate Sex :  0
##       reference class for covariate treatment :  0
## Dataset characteristics:
##     number of subjects:     127
##     number of observations: 508
##     average/min/max nb obs: 4.00  /  4  /  4
## First 10 lines of data:
##    id y time y.1 Age Sex treatment Age2 mdv cens occ ytype
## 1   1 4    0   4  -2   1         0    4   0    0   1     1
## 2   1 4    3   4  -2   1         0    4   0    0   1     1
## 3   1 4    7   4  -2   1         0    4   0    0   1     1
## 4   1 4   10   4  -2   1         0    4   0    0   1     1
## 5   2 4    0   4   2   1         0    4   0    0   1     1
## 6   2 4    3   4   2   1         0    4   0    0   1     1
## 7   2 4    7   4   2   1         0    4   0    0   1     1
## 8   2 4   10   4   2   1         0    4   0    0   1     1
## 9   3 3    0   3  11   1         0  121   0    0   1     1
## 10  3 3    3   3  11   1         0  121   0    0   1     1
```

```
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Ordinal categorical model
##   Model type:  likelihood
## 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)
## }
## <bytecode: 0x55e9ded79f10>
##   Nb of parameters: 5
##       parameter names:  alp1 alp2 alp3 alp4 beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] alp1      normal       Estimated
## [2,] alp2      log-normal   Estimated
## [3,] alp3      log-normal   Estimated
## [4,] alp4      log-normal   Estimated
## [5,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##      alp1 alp2 alp3 alp4 beta
## alp1    1    0    0    0    0
## alp2    0    0    0    0    0
## alp3    0    0    0    0    0
## alp4    0    0    0    0    0
## beta    0    0    0    0    1
##     No covariate in the model.
##     Initial values
##              alp1 alp2 alp3 alp4 beta
## Pop.CondInit    0  0.2  0.6    3  0.2
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
```

```
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  10
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter Estimate SE   CV(%)
## [1,] alp1      -12.47   1.96 16
## [2,] alp2        5.34   1.93 36
## [3,] alp3        7.05   1.56 22
## [4,] alp4       10.31   3.03 29
## [5,] beta        0.71   0.15 22
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##      Parameter   Estimate SE CV(%)
## alp1 omega2.alp1 129.61   NA NA
## beta omega2.beta   0.51   NA NA
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##             omega2.alp1 omega2.beta
## omega2.alp1 1           0
## omega2.beta 0           1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 5970.576
##       AIC = 5986.576
##       BIC = 6009.33
##
## Likelihood computed by importance sampling
##       -2LL= 864.4609
##       AIC = 880.4609
##       BIC = 903.2144
## ----------------------------------------------------
```

```
ord.fit.cov1<-saemix(saemix.model.cov1,saemix.data,saemix.options)
```

```
## Error in plot.new() : figure margins too large
```

```
## Error in plot.new() : figure margins too large
```

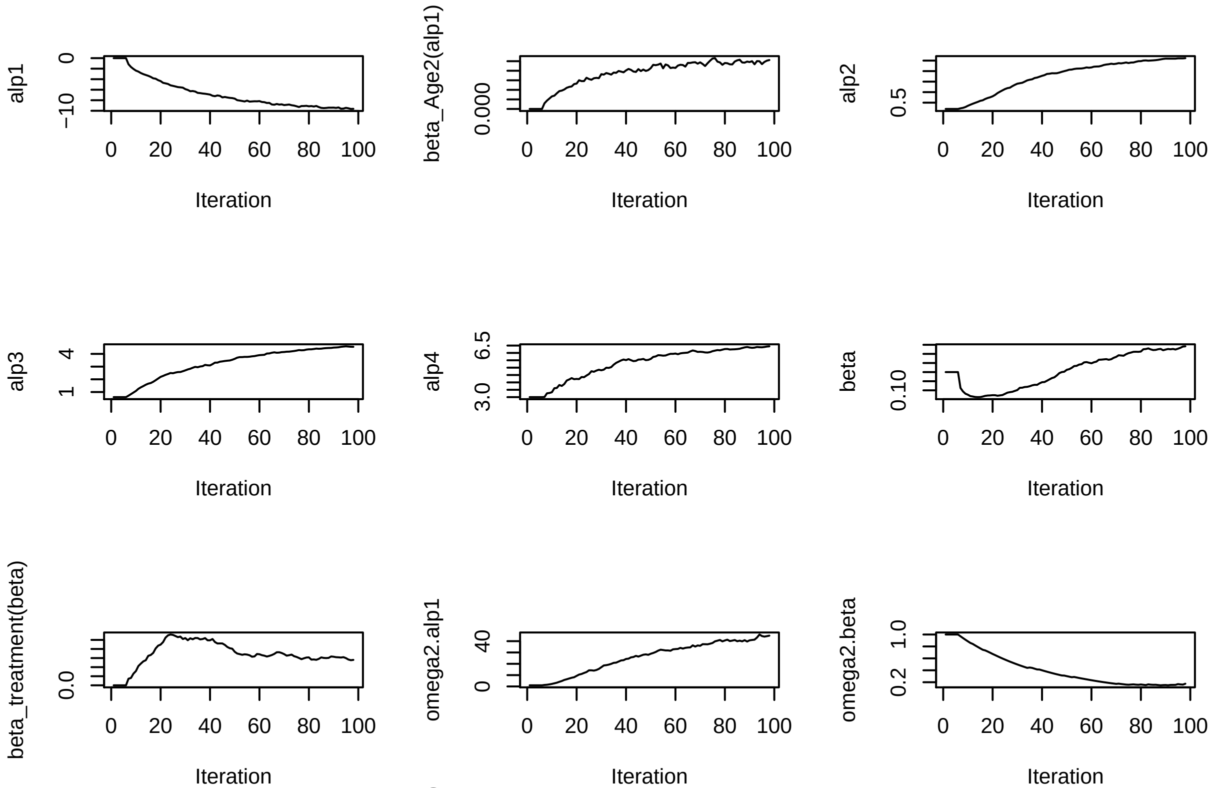
```
## Error in plot.new() : figure margins too large
```

```
## Error in plot.new() : figure margins too large
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset knee.saemix
##     Structured data: y ~ y + time | id
##     X variable for graphs: time (d)
##     covariates: Age (yr), Sex (-), treatment (-), Age2 (yr2)
##       reference class for covariate Sex :  0
##       reference class for covariate treatment :  0
## Dataset characteristics:
##     number of subjects:     127
##     number of observations: 508
##     average/min/max nb obs: 4.00  /  4  /  4
## First 10 lines of data:
##    id y time y.1 Age Sex treatment Age2 mdv cens occ ytype
## 1   1 4    0   4  -2   1         0    4   0    0   1     1
## 2   1 4    3   4  -2   1         0    4   0    0   1     1
## 3   1 4    7   4  -2   1         0    4   0    0   1     1
## 4   1 4   10   4  -2   1         0    4   0    0   1     1
## 5   2 4    0   4   2   1         0    4   0    0   1     1
## 6   2 4    3   4   2   1         0    4   0    0   1     1
## 7   2 4    7   4   2   1         0    4   0    0   1     1
## 8   2 4   10   4   2   1         0    4   0    0   1     1
## 9   3 3    0   3  11   1         0  121   0    0   1     1
## 10  3 3    3   3  11   1         0  121   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Ordinal categorical model
##   Model type:  likelihood
## 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))
```

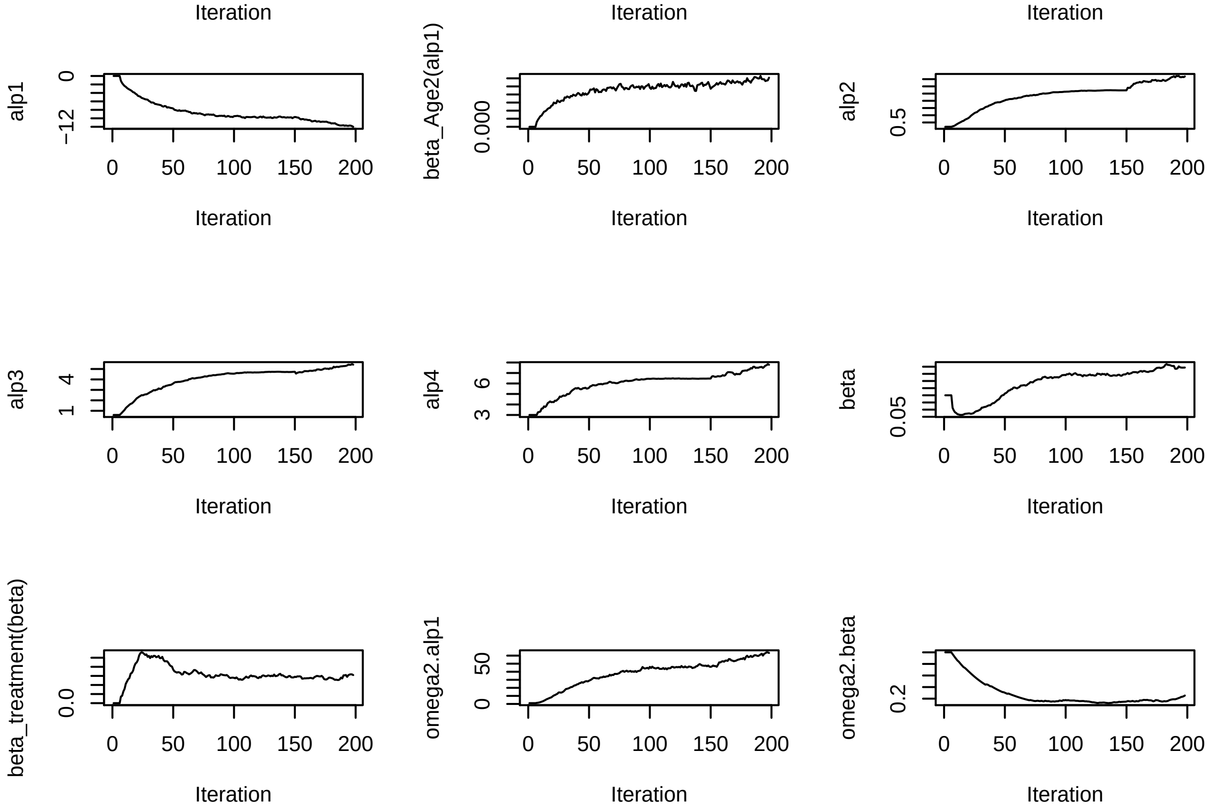
```
##   pobs = (y==1)*pge1+(y==2)*(pge2 - pge1)+(y==3)*(pge3 - pge2)+(y==4)*(pge4 - pge3)+(y==5)*(1 - pge4)
##   logpdf <- log(pobs)
##
##   return(logpdf)
## }
## <bytecode: 0x55e9ded79f10>
##   Nb of parameters: 5
##       parameter names:  alp1 alp2 alp3 alp4 beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] alp1      normal       Estimated
## [2,] alp2      log-normal   Estimated
## [3,] alp3      log-normal   Estimated
## [4,] alp4      log-normal   Estimated
## [5,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##      alp1 alp2 alp3 alp4 beta
## alp1    1    0    0    0    0
## alp2    0    0    0    0    0
## alp3    0    0    0    0    0
## alp4    0    0    0    0    0
## beta    0    0    0    0    1
##   Covariate model:
##           [,1] [,2] [,3] [,4] [,5]
## Age          1    0    0    0    1
## Sex          1    0    0    0    1
## treatment    1    0    0    0    1
## Age2         1    0    0    0    1
##     Initial values
##              alp1 alp2 alp3 alp4 beta
## Pop.CondInit    0  0.2  0.6    3  0.2
## Cov.CondInit    0  0.0  0.0    0  0.0
## psi1            0  0.0  0.0    0  0.0
## psi1            0  0.0  0.0    0  0.0
## psi1            0  0.0  0.0    0  0.0
## ----------------------------------
## ----    Key algorithm options  ----
## ----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  10
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
```

```
## -----------------  Fixed effects  ------------------
## ---------------------------------------------------
##       Parameter            Estimate SE     CV(%) p-value
##  [1,] alp1                 -1.6e+01 3.4778   22  -
##  [2,] beta_Age(alp1)        1.2e-01 0.1171   95  0.146
##  [3,] beta_Sex(alp1)       -6.9e-01 2.5495  370  0.394
##  [4,] beta_treatment(alp1)  1.7e+00 2.1382  124  0.210
##  [5,] beta_Age2(alp1)       3.4e-02 0.0166   49  0.021
##  [6,] alp2                  5.2e+00 1.8170   35  -
##  [7,] alp3                  6.9e+00 1.5416   22  -
##  [8,] alp4                  9.8e+00 2.8741   29  -
##  [9,] beta                  4.8e-01 0.2935   61  -
## [10,] beta_Age(beta)       -1.6e-02 0.0229  142  0.240
## [11,] beta_Sex(beta)        3.4e-02 0.4957 1446  0.472
## [12,] beta_treatment(beta)  5.1e-01 0.4301   85  0.119
## [13,] beta_Age2(beta)       7.4e-04 0.0028  381  0.397
## ---------------------------------------------------
## -----------  Variance of random effects  -----------
## ---------------------------------------------------
##      Parameter   Estimate SE CV(%)
## alp1 omega2.alp1 108.43   NA NA
## beta omega2.beta   0.41   NA NA
## ---------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ---------------------------------------------------
##             omega2.alp1 omega2.beta
## omega2.alp1 1           0
## omega2.beta 0           1
## ---------------------------------------------------
## ---------------  Statistical criteria  -------------
## ---------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 5958.536
##       AIC = 5990.536
##       BIC = 6036.043
##
## Likelihood computed by importance sampling
##       -2LL= 840.4144
##       AIC = 872.4144
##       BIC = 917.9213
## ---------------------------------------------------
```

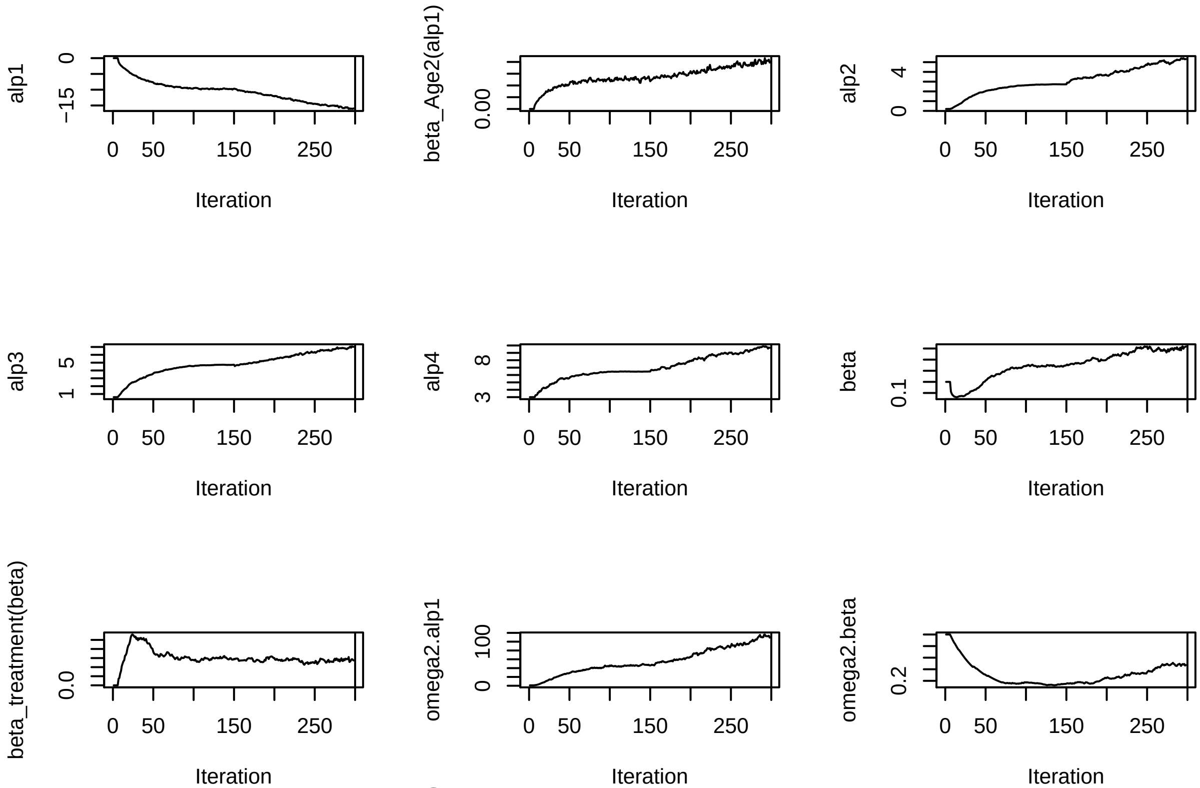
```
ord.fit.cov2<-saemix(saemix.model.cov2,saemix.data,saemix.options)
```

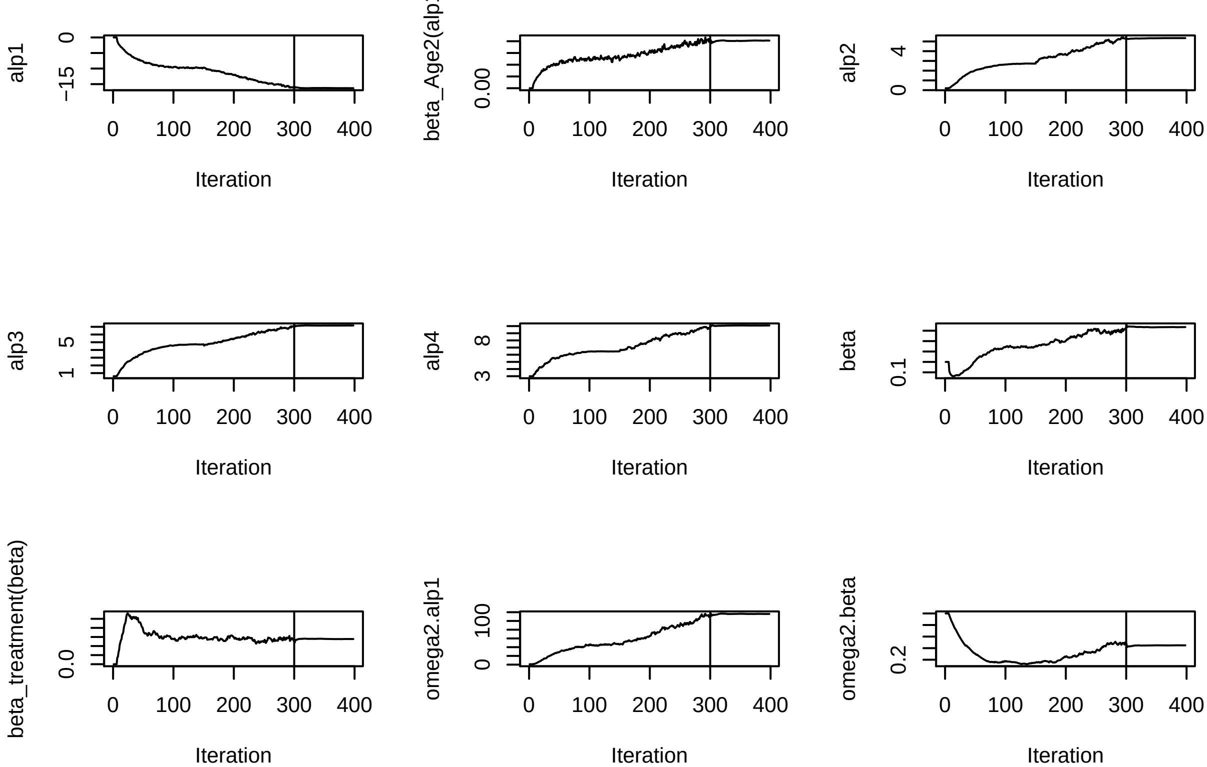


alp1
0
−10
beta_Age2(alp1)
0.000
alp2
0.5
alp3
4
1
alp4
6.5
3.0
beta
0.10
beta_treatment(beta)
0.0
omega2.alp1
40
0
omega2.beta
1.0
0.2
0 20 40 60 80 100
Iteration



alp1
0
−12
beta_Age2(alp1)
0.000
alp2
0.5
alp3
4
1
alp4
6
3
beta
0.05
beta_treatment(beta)
0.0
omega2.alp1
50
0
omega2.beta
0.2
0 50 100 150 200
Iteration






```
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
```

```
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset knee.saemix
##     Structured data: y ~ y + time | id
##     X variable for graphs: time (d)
##     covariates: Age (yr), Sex (-), treatment (-), Age2 (yr2)
##       reference class for covariate Sex :  0
##       reference class for covariate treatment :  0
## Dataset characteristics:
##     number of subjects:     127
##     number of observations: 508
##     average/min/max nb obs: 4.00  /  4  /  4
## First 10 lines of data:
##    id y time y.1 Age Sex treatment Age2 mdv cens occ ytype
## 1   1 4    0   4  -2   1         0    4   0    0   1     1
## 2   1 4    3   4  -2   1         0    4   0    0   1     1
## 3   1 4    7   4  -2   1         0    4   0    0   1     1
## 4   1 4   10   4  -2   1         0    4   0    0   1     1
## 5   2 4    0   4   2   1         0    4   0    0   1     1
## 6   2 4    3   4   2   1         0    4   0    0   1     1
## 7   2 4    7   4   2   1         0    4   0    0   1     1
## 8   2 4   10   4   2   1         0    4   0    0   1     1
## 9   3 3    0   3  11   1         0  121   0    0   1     1
## 10  3 3    3   3  11   1         0  121   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Ordinal categorical model
##   Model type:  likelihood
## 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)
## }
```

```
## <bytecode: 0x55e9ded79f10>
##   Nb of parameters: 5
##       parameter names:  alp1 alp2 alp3 alp4 beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] alp1      normal       Estimated
## [2,] alp2      log-normal   Estimated
## [3,] alp3      log-normal   Estimated
## [4,] alp4      log-normal   Estimated
## [5,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##      alp1 alp2 alp3 alp4 beta
## alp1    1    0    0    0    0
## alp2    0    0    0    0    0
## alp3    0    0    0    0    0
## alp4    0    0    0    0    0
## beta    0    0    0    0    1
##   Covariate model:
##           [,1] [,2] [,3] [,4] [,5]
## treatment    0    0    0    0    1
## Age2         1    0    0    0    0
##     Initial values
##              alp1 alp2 alp3 alp4 beta
## Pop.CondInit    0  0.2  0.6    3  0.2
## Cov.CondInit    0  0.0  0.0    0  0.0
## psi1            0  0.0  0.0    0  0.0
## ----------------------------------
## ----    Key algorithm options  ----
## ----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  10
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter           Estimate SE    CV(%) p-value
## [1,] alp1                -16.300  2.406 15    -
## [2,] beta_Age2(alp1)       0.041  0.014 33    0.0014
## [3,] alp2                  5.340  1.814 34    -
## [4,] alp3                  7.173  1.587 22    -
## [5,] alp4                 10.079  3.010 30    -
## [6,] beta                  0.535  0.176 33    -
```

```
## [7,] beta_treatment(beta)   0.554  0.347 63    0.0552
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##      Parameter   Estimate SE CV(%)
## alp1 omega2.alp1 116.22   NA NA
## beta omega2.beta   0.45   NA NA
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##             omega2.alp1 omega2.beta
## omega2.alp1 1           0
## omega2.beta 0           1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 5980.122
##       AIC = 6000.122
##       BIC = 6028.564
##
## Likelihood computed by importance sampling
##       -2LL= 843.57
##       AIC = 863.57
##       BIC = 892.0119
## ----------------------------------------------------
```

```r
BIC(ord.fit)
```

```
## [1] 903.2144
```

```r
BIC(ord.fit.cov1)
```

```
## [1] 917.9213
```

```r
BIC(ord.fit.cov2)
```

```
## [1] 892.0119
```

```r
# Comparing the 3 covariate models - model with Age2 on alp1 and treatment on beta best
compare.saemix(ord.fit, ord.fit.cov1, ord.fit.cov2)
```

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

```
##        AIC      BIC  BIC.cov
## 1 880.4609 903.2144 892.8407
## 2 872.4144 917.9213 907.5477
## 3 863.5700 892.0119 881.6382
```

```r
###################
# But VPC not good
### Simulations for VPC
simulateOrdinal<-function(psi,id,xidep) {
  y<-xidep[,1]
  time<-xidep[,2]
  alp1<-psi[id,1]
  alp2<-psi[id,2]
  alp3<-psi[id,3]
```

```r
  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)
}

nsim<-100
yfit<-ord.fit.cov2
yfit<-simulateDiscreteSaemix(yfit, simulateOrdinal, nsim=nsim)

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,]
  xtab1 <- xtab %>%
    group_by(time, treatment, ysim) %>%
    summarise(n=length(ysim))
  ytab<-rbind(ytab,xtab1[,c("time","ysim","n","treatment")])
}
```

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```

```r
gtab <- ytab %>%
  group_by(time, treatment, ysim) %>%
  summarise(lower=quantile(n, c(0.05)), n=quantile(n, c(0.5)), upper=quantile(n, c(0.95))) %>%
  mutate(y=as.factor(ysim))
```

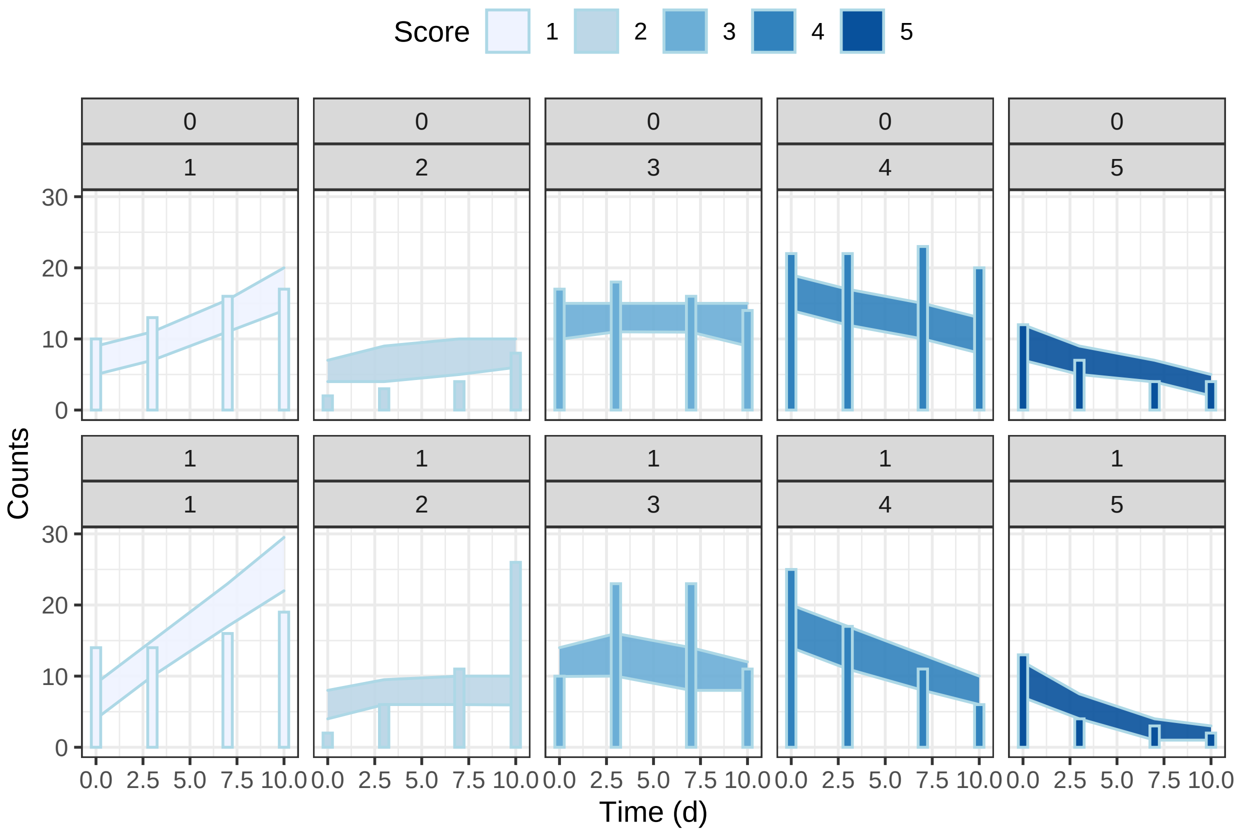
```
## `summarise()` has grouped output by 'time', 'treatment'. You can override using the `.groups` argumen
```

```r
knee2 <- knee.saemix %>%
  group_by(time, treatment, y) %>%
  summarise(n=length(y)) %>%
  mutate(y=as.factor(y))
```

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

```r
kneevpc <- ggplot(data = knee2, aes(x = time, y=n, fill=y, group=treatment)) +
  geom_ribbon(data=gtab, aes(x=time, ymin=lower, ymax=upper), alpha=0.9, colour="lightblue") +
  geom_col(position = "dodge", width=0.5, colour="lightblue") + theme_bw() +
  scale_fill_brewer(palette = "Blues") + theme(legend.position = "top") +
  labs(fill = "Score") + xlab("Time (d)") + ylab("Counts") + facet_wrap(treatment~y, nrow=2)

print(kneevpc)
```




```
# 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.
```

```
ytab<-NULL
for(irep in 1:nsim) {
  xtab<-simdat[simdat$irep==irep,]
  xtab1 <- xtab %>%
    group_by(time, treatment) %>%
    summarise(mean=mean(ysim))
  ytab<-rbind(ytab,xtab1[,c("time","treatment","mean")])
}
```

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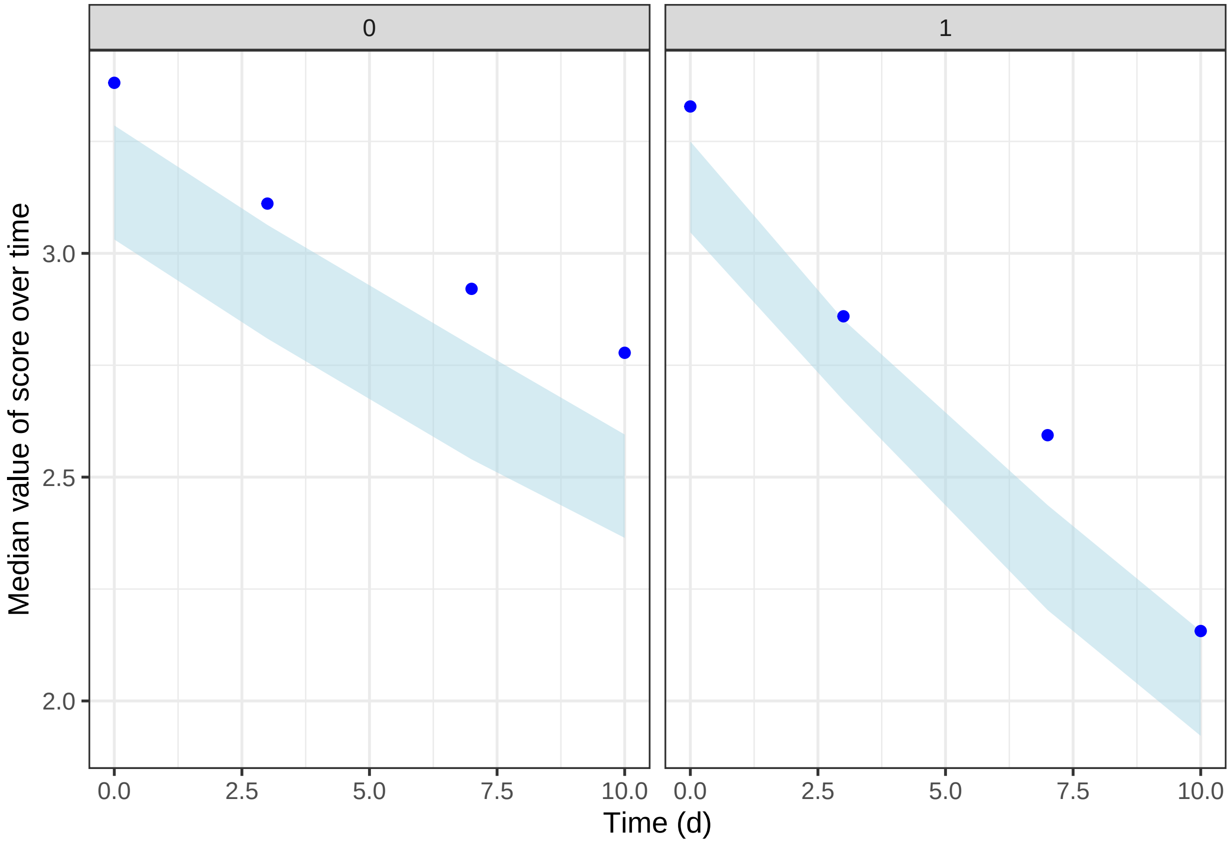

```r
gtab <- ytab %>%
  group_by(time, treatment) %>%
  summarise(lower=quantile(mean, c(0.05)), mean=median(mean), upper=quantile(mean, c(0.95)))
```

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

```r
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)
```



Count data model

- Epilepsy
  - dataset epil from MASS
  - very basic model with only one parameter
- Drinking patterns amongst students (David Atkins from tutorial)
  - dataset rapi.saemix
  - lambda parameter from Poisson model with a time-effect, gender effects on both intercept and slope
  - different models can be adjusted to the data, accounting for overdispersion

Epilepsy data

```
epilepsy<-MASS::epil
saemix.data<-saemixData(name.data=epilepsy, name.group=c("subject"),
                        name.predictors=c("period","y"),name.response=c("y"),
                        name.covariates=c("trt","base", "age"),
                        units=list(x="2-week",y="",covariates=c("","","yr")))
```

```
## [1] "trt"  "base" "age"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
```

```
## Dataset epilepsy
##     Structured data: y ~ period + y | subject
##     X variable for graphs: period (2-week)
##     covariates: trt (), base (), age (yr)
##       reference class for covariate trt :  placebo
```

```r
## Poisson model with one parameter
countmodel.poisson<-function(psi,id,xidep) {
  y<-xidep[,2]
  lambda<-psi[id,1]
  logp <- -lambda + y*log(lambda) - log(factorial(y))
  return(logp)
}

# Adding a period effect
countmodel.periodpoi<-function(psi,id,xidep) {
  tim <- xidep[,1]
  y<-xidep[,2]
  lam<-psi[id,1]
  betaT<-psi[id,2]
  lambda<-lam*exp(beta*log(tim))
  logp <- -lambda + y*log(lambda) - log(factorial(y))
  return(logp)
}

## Generalised Poisson model
countmodel.genpoisson<-function(psi,id,xidep) {
  y<-xidep[,1]
  delta<-psi[id,1]
  lambda<-psi[id,2]
  logp <- -lambda
  pos.ind <- which(y>0)
  lp1 <-log(lambda) + (y-1)*log(lambda+y*delta) - (lambda+y*delta) - log(factorial(y))
  logp[pos.ind] <- lp1[pos.ind]
  return(logp)
}

## Poisson model wtih Zero-Inflation
countmodel.zip<-function(psi,id,xidep) {
  y<-xidep[,2]
  lambda<-psi[id,1]
  p0<-psi[id,2]
  logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y))
  logp0 <- log(p0+(1-p0)*exp(-lambda))
  logp[y==0]<-logp0[y==0]
  return(logp)
}

saemix.model.poi<-saemixModel(model=countmodel.poisson,description="count model Poisson",modeltype="lik
                          psi0=matrix(c(0.5),ncol=1,byrow=TRUE,dimnames=list(NULL, c("lambda"))),
                          transform.par=c(1))
```

```
##
##
## The following SaemixModel object was successfully created:
```

```
##
## Nonlinear mixed-effects model
##   Model function:  count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,2]
##   lambda<-psi[id,1]
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
##   Nb of parameters: 1
##       parameter names:  lambda
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
##   Variance-covariance matrix:
##        lambda
## lambda      1
##     No covariate in the model.
##     Initial values
##              lambda
## Pop.CondInit    0.5
```

```
saemix.model.zip<-saemixModel(model=countmodel.zip,description="count model ZIP",modeltype="likelihood"
                              psi0=matrix(c(0.5,0.2),ncol=2,byrow=TRUE,dimnames=list(NULL, c("lambda","
                              transform.par=c(1,3), #omega.init=matrix(c(0.5,0,0,0.3),ncol=2,byrow=TRUE
                              covariance.model=matrix(c(1,0,0,0),ncol=2,byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,2]
##   lambda<-psi[id,1]
##   p0<-psi[id,2]
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y))
##   logp0 <- log(p0+(1-p0)*exp(-lambda))
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
##   Nb of parameters: 2
##       parameter names:  lambda p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] p0        logit        Estimated
##   Variance-covariance matrix:
##        lambda p0
## lambda      1  0
## p0          0  0
##     No covariate in the model.
```

```
##     Initial values
##              lambda  p0
## Pop.CondInit    0.5 0.2
```

```
saemix.model.gp<-saemixModel(model=countmodel.zip,description="Generalised Poisson model",modeltype="li
                              psi0=matrix(c(0.5,0.2),ncol=2,byrow=TRUE,dimnames=list(NULL, c("delta","l
                              transform.par=c(1,1), #omega.init=matrix(c(0.5,0,0,0.3),ncol=2,byrow=TRUE
                              covariance.model=matrix(c(1,0,0,0),ncol=2,byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Generalised Poisson model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,2]
##   lambda<-psi[id,1]
##   p0<-psi[id,2]
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y))
##   logp0 <- log(p0+(1-p0)*exp(-lambda))
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
##   Nb of parameters: 2
##       parameter names:  delta lambda
##       distribution:
##      Parameter Distribution Estimated
## [1,] delta     log-normal   Estimated
## [2,] lambda    log-normal   Estimated
##   Variance-covariance matrix:
##        delta lambda
## delta      1      0
## lambda     0      0
##     No covariate in the model.
##     Initial values
##              delta lambda
## Pop.CondInit   0.5    0.2
```

```
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, displayProgress=FALSE)

poisson.fit<-saemix(saemix.model.poi,saemix.data,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset epilepsy
##     Structured data: y ~ period + y | subject
##     X variable for graphs: period (2-week)
##     covariates: trt (), base (), age (yr)
##       reference class for covariate trt :  placebo
```

```
## Dataset characteristics:
##     number of subjects:     59
##     number of observations: 236
##     average/min/max nb obs: 4.00  /  4  /  4
## First 10 lines of data:
##    subject period y y.1     trt base age mdv cens occ ytype
## 1        1      1 5   5 placebo   11  31   0    0   1     1
## 2        1      2 3   3 placebo   11  31   0    0   1     1
## 3        1      3 3   3 placebo   11  31   0    0   1     1
## 4        1      4 3   3 placebo   11  31   0    0   1     1
## 5        2      1 3   3 placebo   11  30   0    0   1     1
## 6        2      2 5   5 placebo   11  30   0    0   1     1
## 7        2      3 3   3 placebo   11  30   0    0   1     1
## 8        2      4 3   3 placebo   11  30   0    0   1     1
## 9        3      1 2   2 placebo    6  25   0    0   1     1
## 10       3      2 4   4 placebo    6  25   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,2]
##   lambda<-psi[id,1]
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
## <bytecode: 0x55e9dc358bf0>
##   Nb of parameters: 1
##       parameter names:  lambda
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
##   Variance-covariance matrix:
##        lambda
## lambda      1
##     No covariate in the model.
##     Initial values
##              lambda
## Pop.CondInit    0.5
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
```

```
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter Estimate SE   CV(%)
## [1,] lambda    5.1      0.71 14
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##        Parameter     Estimate SE   CV(%)
## lambda omega2.lambda 0.9      0.21 23
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.lambda
## omega2.lambda 1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 60096.92
##       AIC = 60102.92
##       BIC = 60109.15
##
## Likelihood computed by importance sampling
##       -2LL= 1402.095
##       AIC = 1408.095
##       BIC = 1414.327
## ----------------------------------------------------
```

```
genpoisson.fit<-saemix(saemix.model.gp,saemix.data,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset epilepsy
##     Structured data: y ~ period + y | subject
##     X variable for graphs: period (2-week)
##     covariates: trt (), base (), age (yr)
##       reference class for covariate trt :  placebo
## Dataset characteristics:
##     number of subjects:     59
##     number of observations: 236
##     average/min/max nb obs: 4.00  /  4  /  4
## First 10 lines of data:
##    subject period y y.1     trt base age mdv cens occ ytype
## 1        1      1 5   5 placebo   11  31   0    0   1     1
## 2        1      2 3   3 placebo   11  31   0    0   1     1
```

```
## 3       1      3 3   3 placebo   11  31   0    0   1     1
## 4       1      4 3   3 placebo   11  31   0    0   1     1
## 5       2      1 3   3 placebo   11  30   0    0   1     1
## 6       2      2 5   5 placebo   11  30   0    0   1     1
## 7       2      3 3   3 placebo   11  30   0    0   1     1
## 8       2      4 3   3 placebo   11  30   0    0   1     1
## 9       3      1 2   2 placebo    6  25   0    0   1     1
## 10      3      2 4   4 placebo    6  25   0    0   1     1
## -----------------------------------
## ----         Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Generalised Poisson model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,2]
##   lambda<-psi[id,1]
##   p0<-psi[id,2]
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y))
##   logp0 <- log(p0+(1-p0)*exp(-lambda))
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
## <bytecode: 0x55e9de3c01a0>
##   Nb of parameters: 2
##       parameter names:  delta lambda
##       distribution:
##      Parameter Distribution Estimated
## [1,] delta     log-normal   Estimated
## [2,] lambda    log-normal   Estimated
##   Variance-covariance matrix:
##        delta lambda
## delta      1      0
## lambda     0      0
##     No covariate in the model.
##     Initial values
##              delta lambda
## Pop.CondInit   0.5    0.2
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
```

```
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter Estimate SE    CV(%)
## [1,] delta     5.314    0.747 14
## [2,] lambda    0.041    0.024 58
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##       Parameter    Estimate SE   CV(%)
## delta omega2.delta 0.86     0.21 24
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##              omega2.delta
## omega2.delta 1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 60647.88
##       AIC = 60655.88
##       BIC = 60664.19
##
## Likelihood computed by importance sampling
##       -2LL= 1381.329
##       AIC = 1389.329
##       BIC = 1397.639
## ----------------------------------------------------
```

```
zippoisson.fit<-saemix(saemix.model.zip,saemix.data,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset epilepsy
##     Structured data: y ~ period + y | subject
##     X variable for graphs: period (2-week)
##     covariates: trt (), base (), age (yr)
##       reference class for covariate trt :  placebo
## Dataset characteristics:
##     number of subjects:     59
##     number of observations: 236
##     average/min/max nb obs: 4.00  /  4  /  4
## First 10 lines of data:
##    subject period y y.1     trt base age mdv cens occ ytype
## 1        1      1 5   5 placebo   11  31   0    0   1     1
## 2        1      2 3   3 placebo   11  31   0    0   1     1
## 3        1      3 3   3 placebo   11  31   0    0   1     1
## 4        1      4 3   3 placebo   11  31   0    0   1     1
```

```
## 5        2      1 3   3 placebo   11  30   0    0   1     1
## 6        2      2 5   5 placebo   11  30   0    0   1     1
## 7        2      3 3   3 placebo   11  30   0    0   1     1
## 8        2      4 3   3 placebo   11  30   0    0   1     1
## 9        3      1 2   2 placebo    6  25   0    0   1     1
## 10       3      2 4   4 placebo    6  25   0    0   1     1
## -----------------------------------
## ----          Model           ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   y<-xidep[,2]
##   lambda<-psi[id,1]
##   p0<-psi[id,2]
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y))
##   logp0 <- log(p0+(1-p0)*exp(-lambda))
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
## <bytecode: 0x55e9de3c01a0>
##   Nb of parameters: 2
##       parameter names:  lambda p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] p0        logit        Estimated
##   Variance-covariance matrix:
##        lambda p0
## lambda      1  0
## p0          0  0
##     No covariate in the model.
##     Initial values
##             lambda  p0
## Pop.CondInit    0.5 0.2
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
```

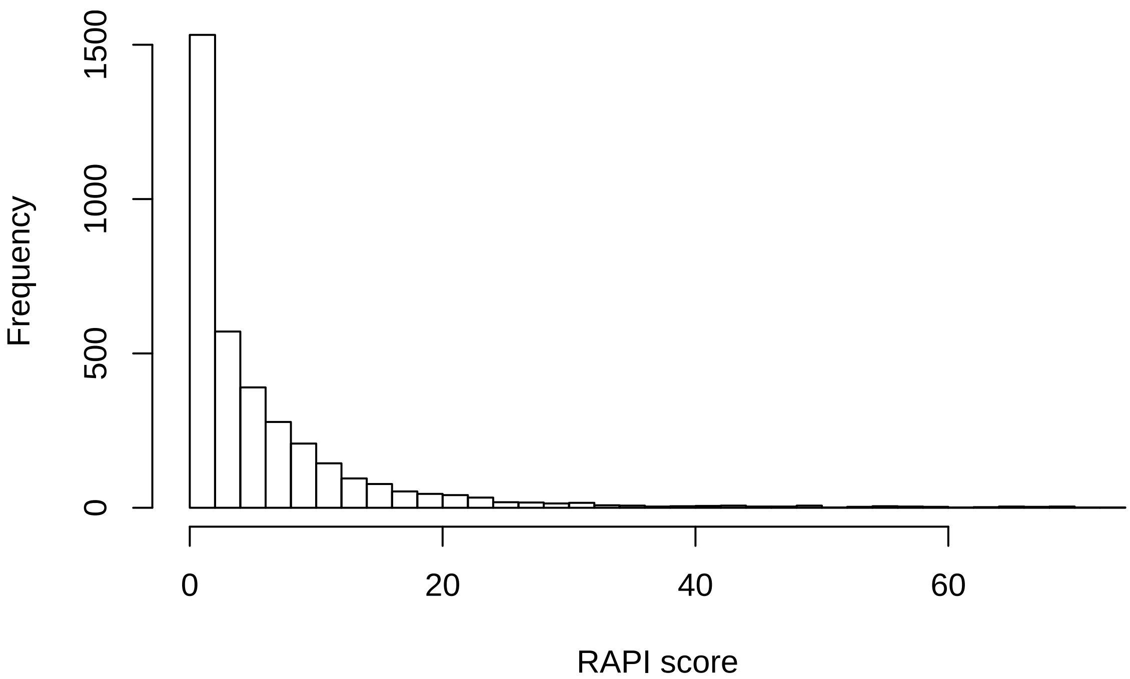
```
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter Estimate SE    CV(%)
## [1,] lambda    5.320    0.748 14
## [2,] p0        0.041    0.024 58
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##        Parameter     Estimate SE   CV(%)
## lambda omega2.lambda 0.86     0.21 24
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.lambda
## omega2.lambda 1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 61045.94
##       AIC = 61053.94
##       BIC = 61062.25
##
## Likelihood computed by importance sampling
##       -2LL= 1381.314
##       AIC = 1389.314
##       BIC = 1397.624
## ----------------------------------------------------
```

RAPI

```
if(testMode)
  data(rapi.saemix) else
    rapi.saemix<-read.table(file.path(datDir, "rapi.saemix.tab"), header=TRUE)

# Data
saemix.data<-saemixData(name.data=rapi.saemix, name.group=c("id"),
                        name.predictors=c("time","rapi"),name.response=c("rapi"),
                        name.covariates=c("gender"),
                        units=list(x="months",y="",covariates=c("")))
```

```
## [1] "gender"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (months)
##     covariates: gender ()
##       reference class for covariate gender :  Men
```

```r
hist(rapi.saemix$rapi, main="", xlab="RAPI score", breaks=30)
```




```r
## Models
# Poisson with a time effect
count.poisson<-function(psi,id,xidep) {
  time<-xidep[,1]
  y<-xidep[,2]
  intercept<-psi[id,1]
  slope<-psi[id,2]
  lambda<- exp(intercept + slope*time)
  logp <- -lambda + y*log(lambda) - log(factorial(y))
  return(logp)
}

## ZIP Poisson model with time effect
count.poissonzip<-function(psi,id,xidep) {
  time<-xidep[,1]
  y<-xidep[,2]
  intercept<-psi[id,1]
  slope<-psi[id,2]
  p0<-psi[id,3] # Probability of zero's
  lambda<- exp(intercept + slope*time)
  logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
  logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
  logp[y==0]<-logp0[y==0]
  return(logp)
}

## Generalized Poisson model with time effect
count.genpoisson<-function(psi,id,xidep) {
  time<-xidep[,1]
  y<-xidep[,2]
```

```r
  intercept<-psi[id,1]
  slope<-psi[id,2]
  lambda<- exp(intercept + slope*time)
  delta<-psi[id,3]
  logp <- log(lambda) + (y-1)*log(lambda+y*delta) - lambda - y*delta - log(factorial(y))
  return(logp)
}

## Negative binomial model with time effect
count.NB<-function(psi,id,xidep) {
  time<-xidep[,1]
  y<-xidep[,2]
  intercept<-psi[id,1]
  slope<-psi[id,2]
  k<-psi[id,3]
  lambda<- exp(intercept + slope*time)
  logp <- log(factorial(y+k-1)) - log(factorial(y)) - log(factorial(k-1)) + y*log(lambda) - y*log(lambda
  return(logp)
}

# Fits
## Poisson
### Model without covariate
saemix.model.poi<-saemixModel(model=count.poisson,description="Count model Poisson",modeltype="likeliho
                              psi0=matrix(c(log(5),0.01),ncol=2,byrow=TRUE,dimnames=list(NULL, c("inter
                              transform.par=c(0,0), omega.init=diag(c(0.5, 0.5)))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   lambda<- exp(intercept + slope*time)
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
##   Nb of parameters: 2
##       parameter names:  intercept slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##           intercept slope
## intercept         1     0
## slope             0     1
##     No covariate in the model.
```

```
##     Initial values
##              intercept slope
## Pop.CondInit  1.609438  0.01
```

```r
### Gender effect on intercept and slope
saemix.model.poi.cov2<-saemixModel(model=count.poisson,description="Count model Poisson",modeltype="lik
                                   psi0=matrix(c(log(5),0.01),ncol=2,byrow=TRUE,dimnames=list(NULL, c("
                                   transform.par=c(0,0), omega.init=diag(c(0.5, 0.5)),
                                   covariance.model =matrix(data=1, ncol=2, nrow=2),
                                   covariate.model=matrix(c(1,1), ncol=2, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   lambda<- exp(intercept + slope*time)
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
##   Nb of parameters: 2
##       parameter names:  intercept slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##           intercept slope
## intercept         1     1
## slope             1     1
##   Covariate model:
##      intercept slope
## [1,]         1     1
##     Initial values
##              intercept slope
## Pop.CondInit  1.609438  0.01
## Cov.CondInit  0.000000  0.00
```

```r
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, displayProgress=FALSE)

### Fit with saemix
poisson.fit<-saemix(saemix.model.poi,saemix.data,saemix.options)
```

```
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
```

```
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (months)
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
##     number of subjects:     818
##     number of observations: 3616
##     average/min/max nb obs: 4.42  /  1  /  5
## First 10 lines of data:
##    id time rapi rapi.1 gender mdv cens occ ytype
## 1   1    0    0      0    Men   0    0   1     1
## 2   1    6    0      0    Men   0    0   1     1
## 3   1   18    0      0    Men   0    0   1     1
## 4   2    0    3      3  Women   0    0   1     1
## 5   2    6    6      6  Women   0    0   1     1
## 6   2   12    5      5  Women   0    0   1     1
## 7   2   18    4      4  Women   0    0   1     1
## 8   2   24    5      5  Women   0    0   1     1
## 9   3    0    9      9    Men   0    0   1     1
## 10  3   12    1      1    Men   0    0   1     1
## ----------------------------------
## ----          Model            ----
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   lambda<- exp(intercept + slope*time)
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
## <bytecode: 0x55e9e5cf2928>
##   Nb of parameters: 2
##       parameter names:  intercept slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##           intercept slope
## intercept         1     0
## slope             0     1
##     No covariate in the model.
##     Initial values
##              intercept slope
## Pop.CondInit  1.609438  0.01
```

```
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter Estimate SE    CV(%)
## [1,] intercept  1.577   0.041   2.6
## [2,] slope     -0.033   0.036 107.6
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##           Parameter        Estimate SE CV(%)
## intercept omega2.intercept 0.9039   NA NA
## slope     omega2.slope     0.0039   NA NA
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept 1                0
## omega2.slope     0                1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 475787.9
##       AIC = 475797.9
##       BIC = 475821.4
##
## Likelihood computed by importance sampling
##       -2LL= 21486.75
##       AIC = 21496.75
##       BIC = 21520.29
## ----------------------------------------------------
```

```
poisson.fit.cov2<-saemix(saemix.model.poi.cov2,saemix.data,saemix.options)
```

```
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Error in data.frame(name = namallpar, estimate = estpar, se = estSE) :
```

```
##   arguments imply differing number of rows: 10, 11
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (months)
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
##     number of subjects:     818
##     number of observations: 3616
##     average/min/max nb obs: 4.42  /  1  /  5
## First 10 lines of data:
##    id time rapi rapi.1 gender mdv cens occ ytype
## 1   1    0    0      0    Men   0    0   1     1
## 2   1    6    0      0    Men   0    0   1     1
## 3   1   18    0      0    Men   0    0   1     1
## 4   2    0    3      3  Women   0    0   1     1
## 5   2    6    6      6  Women   0    0   1     1
## 6   2   12    5      5  Women   0    0   1     1
## 7   2   18    4      4  Women   0    0   1     1
## 8   2   24    5      5  Women   0    0   1     1
## 9   3    0    9      9    Men   0    0   1     1
## 10  3   12    1      1    Men   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   lambda<- exp(intercept + slope*time)
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
## <bytecode: 0x55e9e5cf2928>
##   Nb of parameters: 2
##       parameter names:  intercept slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##           intercept slope
## intercept         1     1
## slope             1     1
```

```
##   Covariate model:
##        [,1] [,2]
## gender    1    1
##     Initial values
##              intercept slope
## Pop.CondInit  1.609438  0.01
## Cov.CondInit  0.000000  0.00
## ----------------------------------
## ----    Key algorithm options  ----
## ----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter              Estimate
## [1,] intercept               1.683
## [2,] beta_gender(intercept) -0.196
## [3,] slope                  -0.022
## [4,] beta_gender(slope)     -0.017
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##           Parameter        Estimate
## intercept omega2.intercept 0.9179
## slope     omega2.slope     0.0039
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept  1.00            -0.14
## omega2.slope     -0.14             1.00
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 21454.94
##       AIC = 21470.94
##       BIC = 21508.59
## ----------------------------------------------------
```

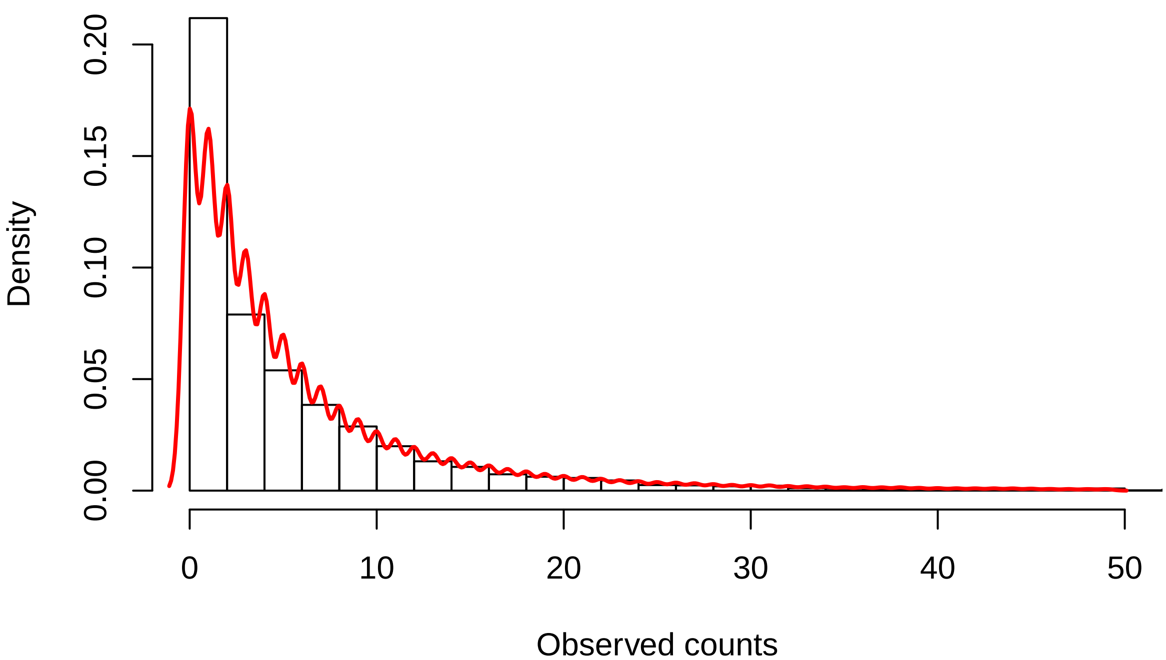
```r
exp(poisson.fit@results@fixed.effects)
```

```
## [1] 4.8394604 0.9673886
```

```r
exp(poisson.fit.cov2@results@fixed.effects)
```

```
## [1] 5.3842360 0.8217414 0.9780800 0.9833256
```

```r
### Simulations
saemix.simulatePoisson<-function(psi, id, xidep) {
  time<-xidep[,1]
  y<-xidep[,2]
  intercept<-psi[id,1]
  slope<-psi[id,2]
  lambda<- exp(intercept + slope*time)
  y<-rpois(length(time), lambda=lambda)
  return(y)
}

yfit1<-simulateDiscreteSaemix(poisson.fit.cov2, saemix.simulatePoisson, 100)

hist(yfit1@data@data$rapi, xlim=c(0,50), freq=F, breaks=30, xlab="Observed counts", main="")
lines(density(yfit1@sim.data@datasim$ysim[yfit1@sim.data@datasim$ysim<50]), lwd = 2, col = 'red')
```




```r
cat("Observed proportion of 0's", length(yfit1@data@data$rapi[yfit1@data@data$rapi==0])/yfit1@data@ntot
```

```
## Observed proportion of 0's 0.2090708
```

```r
cat("      Poisson model, p=",length(yfit1@sim.data@datasim$ysim[yfit1@sim.data@datasim$ysim==0])/lengt
```

```
##       Poisson model, p= 0.1518501
```

Overdispersion

```r
## ZIP
### base model
saemix.model.zip<-saemixModel(model=count.poissonzip,description="count model ZIP",modeltype="likelihood
                              psi0=matrix(c(1.5, 0.01, 0.2),ncol=3,byrow=TRUE,dimnames=list(NULL, c("in
                              transform.par=c(0,0,3), covariance.model=diag(c(1,1,0)), omega.init=diag(
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   p0<-psi[id,3] # Probability of zero's
##   lambda<- exp(intercept + slope*time)
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
##   logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
##   Nb of parameters: 3
##       parameter names:  intercept slope p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
## [3,] p0        logit        Estimated
##   Variance-covariance matrix:
##           intercept slope p0
## intercept         1     0  0
## slope             0     1  0
## p0                0     0  0
##     No covariate in the model.
##     Initial values
##              intercept slope  p0
## Pop.CondInit       1.5  0.01 0.2
```

```r
### ZIP Poisson with gender on both intercept
saemix.model.zip.cov1<-saemixModel(model=count.poissonzip,description="count model ZIP",modeltype="likel
                                   psi0=matrix(c(1.5, 0.01, 0.2),ncol=3,byrow=TRUE,dimnames=list(NULL, c
                                   transform.par=c(0,0,3), covariance.model=diag(c(1,1,0)), omega.init=c
                                   covariate.model = matrix(c(1,0,0),ncol=3, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
```

```
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   p0<-psi[id,3] # Probability of zero's
##   lambda<- exp(intercept + slope*time)
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
##   logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
##   Nb of parameters: 3
##       parameter names:  intercept slope p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
## [3,] p0        logit        Estimated
##   Variance-covariance matrix:
##           intercept slope p0
## intercept         1     0  0
## slope             0     1  0
## p0                0     0  0
##   Covariate model:
##      intercept slope p0
## [1,]         1     0  0
##     Initial values
##              intercept slope  p0
## Pop.CondInit       1.5  0.01 0.2
## Cov.CondInit       0.0  0.00 0.0
```

```
### ZIP Poisson with gender on both intercept and slope
saemix.model.zip.cov2<-saemixModel(model=count.poissonzip,description="count model ZIP",modeltype="likel
                                  psi0=matrix(c(1.5, 0.01, 0.2),ncol=3,byrow=TRUE,dimnames=list(NULL, c
                                  transform.par=c(0,0,3), covariance.model=diag(c(1,1,0)), omega.init=d
                                  covariate.model = matrix(c(1,1,0),ncol=3, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   p0<-psi[id,3] # Probability of zero's
##   lambda<- exp(intercept + slope*time)
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
##   logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
##   logp[y==0]<-logp0[y==0]
```

```
##   return(logp)
## }
##   Nb of parameters: 3
##       parameter names:  intercept slope p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
## [3,] p0        logit        Estimated
##   Variance-covariance matrix:
##           intercept slope p0
## intercept         1     0  0
## slope             0     1  0
## p0                0     0  0
##   Covariate model:
##      intercept slope p0
## [1,]         1     1  0
##     Initial values
##              intercept slope  p0
## Pop.CondInit       1.5  0.01 0.2
## Cov.CondInit       0.0  0.00 0.0
```

```
zippoisson.fit<-saemix(saemix.model.zip,saemix.data,saemix.options)
```

```
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (months)
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
##     number of subjects:     818
##     number of observations: 3616
##     average/min/max nb obs: 4.42  /  1  /  5
## First 10 lines of data:
##    id time rapi rapi.1 gender mdv cens occ ytype
## 1   1    0    0      0    Men   0    0   1     1
## 2   1    6    0      0    Men   0    0   1     1
## 3   1   18    0      0    Men   0    0   1     1
## 4   2    0    3      3  Women   0    0   1     1
## 5   2    6    6      6  Women   0    0   1     1
## 6   2   12    5      5  Women   0    0   1     1
## 7   2   18    4      4  Women   0    0   1     1
## 8   2   24    5      5  Women   0    0   1     1
## 9   3    0    9      9    Men   0    0   1     1
## 10  3   12    1      1    Men   0    0   1     1
## -----------------------------------
## ----          Model            ----
```

```
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   p0<-psi[id,3] # Probability of zero's
##   lambda<- exp(intercept + slope*time)
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
##   logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
## <bytecode: 0x55e9dd608e88>
##   Nb of parameters: 3
##       parameter names:  intercept slope p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
## [3,] p0        logit        Estimated
##   Variance-covariance matrix:
##           intercept slope p0
## intercept         1     0  0
## slope             0     1  0
## p0                0     0  0
##     No covariate in the model.
##     Initial values
##              intercept slope  p0
## Pop.CondInit       1.5  0.01 0.2
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
```

```
##      Parameter Estimate SE     CV(%)
## [1,] intercept  1.657   0.0425   2.6
## [2,] slope     -0.029   0.0357 123.5
## [3,] p0         0.076   0.0085  11.2
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##           Parameter        Estimate SE CV(%)
## intercept omega2.intercept 0.7977   NA NA
## slope     omega2.slope     0.0032   NA NA
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept 1                0
## omega2.slope     0                1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 459470.4
##       AIC = 459482.4
##       BIC = 459510.7
##
## Likelihood computed by importance sampling
##       -2LL= 20479.88
##       AIC = 20491.88
##       BIC = 20520.12
## ----------------------------------------------------
```

```
zippoisson.fit.cov1<-saemix(saemix.model.zip.cov1,saemix.data,saemix.options)
```

```
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (months)
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
##     number of subjects:     818
##     number of observations: 3616
##     average/min/max nb obs: 4.42  /  1  /  5
## First 10 lines of data:
##    id time rapi rapi.1 gender mdv cens occ ytype
## 1   1    0    0      0    Men   0    0   1     1
## 2   1    6    0      0    Men   0    0   1     1
## 3   1   18    0      0    Men   0    0   1     1
## 4   2    0    3      3  Women   0    0   1     1
```

```
## 5   2    6    6      6  Women   0    0   1     1
## 6   2   12    5      5  Women   0    0   1     1
## 7   2   18    4      4  Women   0    0   1     1
## 8   2   24    5      5  Women   0    0   1     1
## 9   3    0    9      9    Men   0    0   1     1
## 10  3   12    1      1    Men   0    0   1     1
## -----------------------------------
## ----          Model           ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   p0<-psi[id,3] # Probability of zero's
##   lambda<- exp(intercept + slope*time)
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
##   logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
## <bytecode: 0x55e9dd608e88>
##   Nb of parameters: 3
##       parameter names:  intercept slope p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
## [3,] p0        logit        Estimated
##   Variance-covariance matrix:
##           intercept slope p0
## intercept         1     0  0
## slope             0     1  0
## p0                0     0  0
##   Covariate model:
##        [,1] [,2] [,3]
## gender    1    0    0
##     Initial values
##              intercept slope  p0
## Pop.CondInit       1.5  0.01 0.2
## Cov.CondInit       0.0  0.00 0.0
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
```

```
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter              Estimate SE     CV(%) p-value
## [1,] intercept               1.786   0.0638   3.6 -
## [2,] beta_gender(intercept) -0.226   0.0852  37.7 0.004
## [3,] slope                  -0.029   0.0357 123.4 -
## [4,] p0                      0.076   0.0085  11.2 -
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##           Parameter        Estimate SE CV(%)
## intercept omega2.intercept 0.7849   NA NA
## slope     omega2.slope     0.0033   NA NA
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept 1                0
## omega2.slope     0                1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 454429.7
##       AIC = 454443.7
##       BIC = 454476.6
##
## Likelihood computed by importance sampling
##       -2LL= 20469.41
##       AIC = 20483.41
##       BIC = 20516.35
## ----------------------------------------------------
```

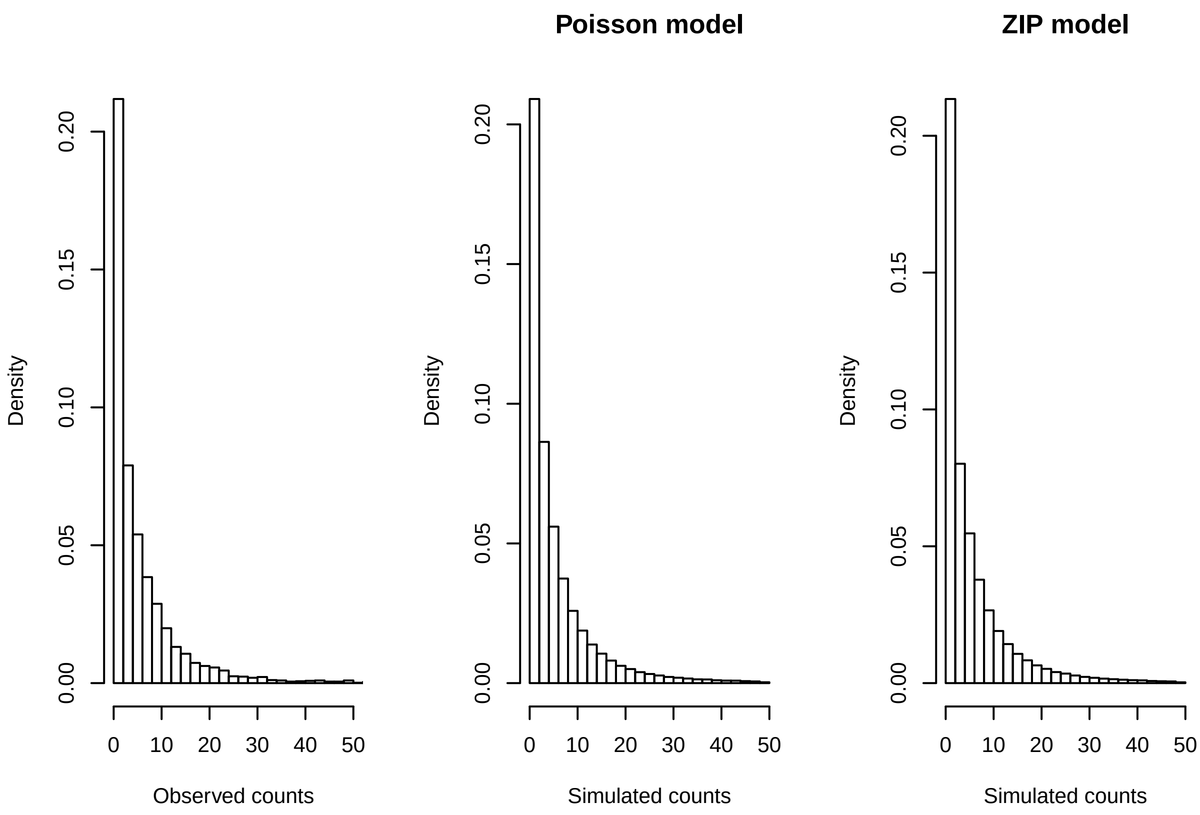
```
zippoisson.fit.cov2<-saemix(saemix.model.zip.cov2,saemix.data,saemix.options)
```

```
## Error in solve.default(FO) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (months)
```

```
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
##     number of subjects:     818
##     number of observations: 3616
##     average/min/max nb obs: 4.42  /  1  /  5
## First 10 lines of data:
##    id time rapi rapi.1 gender mdv cens occ ytype
## 1   1    0    0      0    Men   0    0   1     1
## 2   1    6    0      0    Men   0    0   1     1
## 3   1   18    0      0    Men   0    0   1     1
## 4   2    0    3      3  Women   0    0   1     1
## 5   2    6    6      6  Women   0    0   1     1
## 6   2   12    5      5  Women   0    0   1     1
## 7   2   18    4      4  Women   0    0   1     1
## 8   2   24    5      5  Women   0    0   1     1
## 9   3    0    9      9    Men   0    0   1     1
## 10  3   12    1      1    Men   0    0   1     1
## ----------------------------------
## ----          Model            ----
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  count model ZIP
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   p0<-psi[id,3] # Probability of zero's
##   lambda<- exp(intercept + slope*time)
##   logp <- log(1-p0) -lambda + y*log(lambda) - log(factorial(y)) # Poisson
##   logp0 <- log(p0+(1-p0)*exp(-lambda)) # Zeroes
##   logp[y==0]<-logp0[y==0]
##   return(logp)
## }
## <bytecode: 0x55e9dd608e88>
##   Nb of parameters: 3
##       parameter names:  intercept slope p0
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
## [3,] p0        logit        Estimated
##   Variance-covariance matrix:
##           intercept slope p0
## intercept         1     0  0
## slope             0     1  0
## p0                0     0  0
##   Covariate model:
##        [,1] [,2] [,3]
## gender    1    1    0
##     Initial values
##              intercept slope  p0
```

```
## Pop.CondInit       1.5  0.01 0.2
## Cov.CondInit       0.0  0.00 0.0
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter              Estimate SE     CV(%) p-value
## [1,] intercept               1.773   0.0637   3.6 -
## [2,] beta_gender(intercept) -0.197   0.0853  43.3 0.011
## [3,] slope                  -0.020   0.0552 270.1 -
## [4,] beta_gender(slope)     -0.016   0.0724 460.4 0.414
## [5,] p0                      0.075   0.0085  11.2 -
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##           Parameter        Estimate SE CV(%)
## intercept omega2.intercept 0.7826   NA NA
## slope     omega2.slope     0.0033   NA NA
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept 1                0
## omega2.slope     0                1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 458502.9
##       AIC = 458518.9
##       BIC = 458556.5
##
## Likelihood computed by importance sampling
##       -2LL= 20459.27
##       AIC = 20475.27
##       BIC = 20512.93
## ----------------------------------------------------
```

```
### Simulations
saemix.simulatePoissonZIP<-function(psi, id, xidep) {
  time<-xidep[,1]
  y<-xidep[,2]
  intercept<-psi[id,1]
  slope<-psi[id,2]
  p0<-psi[id,3] # Probability of zero's
  lambda<- exp(intercept + slope*time)
  prob0<-rbinom(length(time), size=1, prob=p0)
  y<-rpois(length(time), lambda=lambda)
  y[prob0==1]<-0
  return(y)
}

yfit2<-simulateDiscreteSaemix(zippoisson.fit.cov2, saemix.simulatePoissonZIP, 100)

par(mfrow=c(1,3))
hist(yfit1@data@data$rapi, xlim=c(0,50), freq=F, breaks=30, xlab="Observed counts", main="")
hist(yfit1@sim.data@datasim$ysim[yfit1@sim.data@datasim$ysim<50], xlim=c(0,50), freq=F, breaks=20, xlab=
hist(yfit2@sim.data@datasim$ysim[yfit2@sim.data@datasim$ysim<50], xlim=c(0,50), freq=F, breaks=20, xlab=
```



Hurdle model

```
## Hurdle - 2 models
saemix.data1<-saemixData(name.data=rapi.saemix[rapi.saemix$rapi>0,], name.group=c("id"),
                         name.predictors=c("time","rapi"),name.response=c("rapi"),
                         name.covariates=c("gender"),
```

```r
                         units=list(x="week",y="",covariates=c("")))
```

```
## [1] "gender"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix[rapi.saemix$rapi > 0, ]
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (week)
##     covariates: gender ()
##       reference class for covariate gender :  Men
```

```r
rapi.saemix$y0<-as.integer(rapi.saemix$rapi>0)
saemix.data0<-saemixData(name.data=rapi.saemix, name.group=c("id"),
                         name.predictors=c("time","y0"),name.response=c("y0"),
                         name.covariates=c("gender"),
                         units=list(x="week",y="",covariates=c("")))
```

```
## [1] "gender"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: y0 ~ time + y0 | id
##     X variable for graphs: time (week)
##     covariates: gender ()
##       reference class for covariate gender :  Men
```

```r
# Fit Binomial model to saemix.data0
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)
}

saemix.hurdle0<-saemixModel(model=binary.model,description="Binary model",
                            modeltype="likelihood",
                            psi0=matrix(c(-1.5,-.1,0,0),ncol=2,byrow=TRUE,dimnames=list(NULL,c("theta1"
                            transform.par=c(0,0), covariate.model=c(1,1),
                            covariance.model=matrix(c(1,0,0,1),ncol=2), omega.init=diag(c(1,0.3)))
```

```
##
```

```
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Binary model
##   Model type:  likelihood
## 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)
## }
##   Nb of parameters: 2
##       parameter names:  theta1 theta2
##       distribution:
##      Parameter Distribution Estimated
## [1,] theta1    normal       Estimated
## [2,] theta2    normal       Estimated
##   Variance-covariance matrix:
##        theta1 theta2
## theta1      1      0
## theta2      0      1
##   Covariate model:
##      theta1 theta2
## [1,]      1      1
##     Initial values
##              theta1 theta2
## Pop.CondInit   -1.5   -0.1
## Cov.CondInit    0.0    0.0
```

```
saemix.options<-list(seed=1234567,save=FALSE,save.graphs=FALSE, displayProgress=FALSE, nb.chains=10, fi

hurdlefit0<-saemix(saemix.hurdle0,saemix.data0,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix
##     Structured data: y0 ~ time + y0 | id
##     X variable for graphs: time (week)
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
##     number of subjects:     818
##     number of observations: 3616
##     average/min/max nb obs: 4.42  /  1  /  5
```

```
## First 10 lines of data:
##    id time y0 y0.1 gender mdv cens occ ytype
## 1   1    0  0    0    Men   0    0   1     1
## 2   1    6  0    0    Men   0    0   1     1
## 3   1   18  0    0    Men   0    0   1     1
## 4   2    0  1    1  Women   0    0   1     1
## 5   2    6  1    1  Women   0    0   1     1
## 6   2   12  1    1  Women   0    0   1     1
## 7   2   18  1    1  Women   0    0   1     1
## 8   2   24  1    1  Women   0    0   1     1
## 9   3    0  1    1    Men   0    0   1     1
## 10  3   12  1    1    Men   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Binary model
##   Model type:  likelihood
## 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)
## }
## <bytecode: 0x55e9db532fe0>
##   Nb of parameters: 2
##       parameter names:  theta1 theta2
##       distribution:
##      Parameter Distribution Estimated
## [1,] theta1    normal       Estimated
## [2,] theta2    normal       Estimated
##   Variance-covariance matrix:
##        theta1 theta2
## theta1      1      0
## theta2      0      1
##   Covariate model:
##        [,1] [,2]
## gender    1    1
##     Initial values
##              theta1 theta2
## Pop.CondInit   -1.5   -0.1
## Cov.CondInit    0.0    0.0
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
```

```
##     Number of chains:  10
##     Seed:  1234567
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter           Estimate
## [1,] theta1               2.696
## [2,] beta_gender(theta1) -0.062
## [3,] theta2              -0.029
## [4,] beta_gender(theta2) -0.034
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##        Parameter     Estimate
## theta1 omega2.theta1 2.3052
## theta2 omega2.theta2 0.0072
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.theta1 omega2.theta2
## omega2.theta1 1             0
## omega2.theta2 0             1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 3248.691
##       AIC = 3262.691
##       BIC = 3295.639
## ----------------------------------------------------
```

```
# proportion of 0's in the data
rapi.tab <- table(rapi.saemix$rapi == 0)
rapi.tab/sum(rapi.tab)
```

```
##
##     FALSE      TRUE
## 0.7909292 0.2090708
```

```
# Fit Poisson model to saemix.data1
saemix.hurdle1.cov2<-saemixModel(model=count.poisson,description="Count model Poisson",modeltype="likeli
                                 psi0=matrix(c(log(5),0.01),ncol=2,byrow=TRUE,dimnames=list(NULL, c("in
                                 transform.par=c(0,0), omega.init=diag(c(0.5, 0.5)),
                                 covariance.model =matrix(data=1, ncol=2, nrow=2),
                                 covariate.model=matrix(c(1,1), ncol=2, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   lambda<- exp(intercept + slope*time)
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
## <bytecode: 0x55e9e5cf2928>
##   Nb of parameters: 2
##       parameter names:  intercept slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##           intercept slope
## intercept         1     1
## slope             1     1
##   Covariate model:
##      intercept slope
## [1,]         1     1
##     Initial values
##              intercept slope
## Pop.CondInit  1.609438  0.01
## Cov.CondInit  0.000000  0.00
```

```
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, displayProgress=FALSE)

hurdlefit1<-saemix(saemix.hurdle1.cov2,saemix.data1,saemix.options)
```

```
## Error in solve.default(F0) :
##   routine Lapack dgesv : le système est exactement singulier : U[2,2] = 0
## Error in data.frame(name = namallpar, estimate = estpar, se = estSE) :
##   arguments imply differing number of rows: 10, 11
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset rapi.saemix[rapi.saemix$rapi > 0, ]
##     Structured data: rapi ~ time + rapi | id
##     X variable for graphs: time (week)
##     covariates: gender ()
##       reference class for covariate gender :  Men
## Dataset characteristics:
```

```
##     number of subjects:     802
##     number of observations: 2860
##     average/min/max nb obs: 3.57  /  1  /  5
## First 10 lines of data:
##    id time rapi rapi.1 gender mdv cens occ ytype
## 4   2    0    3      3  Women   0    0   1     1
## 5   2    6    6      6  Women   0    0   1     1
## 6   2   12    5      5  Women   0    0   1     1
## 7   2   18    4      4  Women   0    0   1     1
## 8   2   24    5      5  Women   0    0   1     1
## 9   3    0    9      9    Men   0    0   1     1
## 10  3   12    1      1    Men   0    0   1     1
## 12  4    0    3      3  Women   0    0   1     1
## 13  4    6    2      2  Women   0    0   1     1
## 14  5    0   35     35  Women   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Count model Poisson
##   Model type:  likelihood
## function(psi,id,xidep) {
##   time<-xidep[,1]
##   y<-xidep[,2]
##   intercept<-psi[id,1]
##   slope<-psi[id,2]
##   lambda<- exp(intercept + slope*time)
##   logp <- -lambda + y*log(lambda) - log(factorial(y))
##   return(logp)
## }
## <bytecode: 0x55e9e5cf2928>
##   Nb of parameters: 2
##       parameter names:  intercept slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] intercept normal       Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##           intercept slope
## intercept         1     1
## slope             1     1
##   Covariate model:
##        [,1] [,2]
## gender    1    1
##     Initial values
##              intercept slope
## Pop.CondInit  1.609438  0.01
## Cov.CondInit  0.000000  0.00
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
```

```
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter              Estimate
## [1,] intercept               1.8656
## [2,] beta_gender(intercept) -0.1972
## [3,] slope                  -0.0059
## [4,] beta_gender(slope)     -0.0085
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##           Parameter        Estimate
## intercept omega2.intercept 0.6000
## slope     omega2.slope     0.0017
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept  1.00            -0.32
## omega2.slope     -0.32             1.00
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 17628.18
##       AIC = 17644.18
##       BIC = 17681.67
## ----------------------------------------------------
```

```r
summary(hurdlefit0)
```

```
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##             Parameter Estimate
## 1              theta1    2.696
## 2 beta_gender(theta1)   -0.062
## 3              theta2   -0.029
## 4 beta_gender(theta2)   -0.034
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
```

```
##            Parameter Estimate
## theta1 omega2.theta1   2.3052
## theta2 omega2.theta2   0.0072
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.theta1 omega2.theta2
## omega2.theta1 1.00          0.00
## omega2.theta2 0.00          1.00
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 3248.691
##       AIC = 3262.691
##       BIC = 3295.639
## ----------------------------------------------------
```

```r
summary(hurdlefit1)
```

```
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##                Parameter Estimate
## 1              intercept   1.8656
## 2 beta_gender(intercept)  -0.1972
## 3                  slope  -0.0059
## 4     beta_gender(slope)  -0.0085
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##                    Parameter Estimate
## intercept omega2.intercept   0.6000
## slope         omega2.slope   0.0017
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##                  omega2.intercept omega2.slope
## omega2.intercept  1.00            -0.32
## omega2.slope     -0.32             1.00
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 17628.18
##       AIC = 17644.18
##       BIC = 17681.67
## ----------------------------------------------------
```

```r
# Table form - compare to column B in Table 2
yfit0<-hurdlefit0
yfit1<-hurdlefit1
```

```
rr.tab<-data.frame(param=c("intercept", "beta.Male.inter", "slope", "beta.Male.slope", "omega.inter","om
                  poissonNoZero=c(yfit1@results@fixed.effects, c(sqrt(diag(yfit1@results@omega)))),
                  logistic=c(yfit0@results@fixed.effects, c(sqrt(diag(yfit0@results@omega)))))

print(rr.tab)
```

```
##             param poissonNoZero    logistic
## 1       intercept   1.865583452  2.69565710
## 2 beta.Male.inter  -0.197211376 -0.06199618
## 3           slope  -0.005943599 -0.02895852
## 4 beta.Male.slope  -0.008525854 -0.03367309
## 5     omega.inter   0.774608111  1.51828371
## 6     omega.slope   0.041313987  0.08465239
```

Time-to-event

TTE model - simulated data

TTE data simulated according to a Weibull model, hazard defined by shape (β) and scale (λ) as:

$$h(t) = \frac{\beta}{\lambda}\left(\frac{t}{\lambda}\right)^{\beta-1}$$

```
# Simulating TTE data
set.seed(12345)

nsuj<-50
xtim<-c(0)
tte.data<-data.frame(id=rep(1:nsuj,each=length(xtim)),time=rep(xtim,nsuj))
psiM<-data.frame(lambda=seq(1.6,2,length.out=length(unique(tte.data$id))),beta = 2)

simul.tte<-function(psi,id,xidep) {
  T<-xidep
  N <- nrow(psi)
  Nj <- length(T)
  censoringtime = 3
  lambda <- psi[id,1]
  beta <- psi[id,2]
  obs <-rep(0,length(T))
  for (i in (1:N)){
    obs[id==i] <- rweibull(n=length(id[id==i]), shape=beta[i], scale=lambda[i])
  }
  obs[obs>censoringtime]<-censoringtime
  return(obs)
}

preds <- simul.tte(psiM, tte.data$id, tte.data[,c("time")])
tte.data$y<-0
tte.data$tlat<-preds
dat1<-tte.data[,c("id","time","y")]
dat2<-tte.data[,c("id","tlat","y")]
dat2$y<-as.integer(dat2$tlat>0 & dat2$tlat<3)
colnames(dat2)[2]<-"time"
```

```r
tte.data<-rbind(dat1,dat2)
tte.data<-tte.data[order(tte.data$id, tte.data$time),]
tte.psiM<-psiM

# Simulate T from Weibull (check)
if(FALSE) {
  lambda<-2
  beta<-2
  nsim<-5000
  # By hand
  q1<-runif(nsim)
  #  tevent<-lambda*exp(log(q1)/beta)
  tevent<-lambda*exp(log(-log(q1))/beta)
  tevent<-sort(tevent)
#  plot(tevent, exp(-(tevent/lambda)^beta))
  tevent2<-sort(rweibull(nsim, shape=beta, scale=lambda))
  plot(tevent, tevent2)
  abline(0,1)

}
```

```r
saemix.data<-saemixData(name.data=tte.data, name.group=c("id"),
  name.predictors=c("time"), name.response="y")
```

```
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset tte.data
##     Structured data: y ~ time | id
##     Predictor: time ()
```

```r
tte.model<-function(psi,id,xidep) {
  T<-xidep[,1]
  N <- nrow(psi)
  Nj <- length(T)
  # censoringtime = 6
  censoringtime = max(T)
  lambda <- psi[id,1]
  beta <- psi[id,2]
  init <- which(T==0)
  cens <- which(T==censoringtime)
  ind <- setdiff(1:Nj, append(init,cens))
  hazard <- (beta/lambda)*(T/lambda)^(beta-1)
  H <- (T/lambda)^beta
  logpdf <- rep(0,Nj)
  logpdf[cens] <- -H[cens] + H[cens-1]
  logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind])
  return(logpdf)
}

saemix.model<-saemixModel(model=tte.model,description="time model",modeltype="likelihood",
```

```r
  psi0=matrix(c(1,2),ncol=2,byrow=TRUE,dimnames=list(NULL,  c("lambda","beta"))),
  transform.par=c(1,1),covariance.model=matrix(c(1,0,0,1),ncol=2, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  time model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   N <- nrow(psi)
##   Nj <- length(T)
##   # censoringtime = 6
##   censoringtime = max(T)
##   lambda <- psi[id,1]
##   beta <- psi[id,2]
##   init <- which(T==0)
##   cens <- which(T==censoringtime)
##   ind <- setdiff(1:Nj, append(init,cens))
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1)
##   H <- (T/lambda)^beta
##   logpdf <- rep(0,Nj)
##   logpdf[cens] <- -H[cens] + H[cens-1]
##   logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind])
##   return(logpdf)
## }
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    1
##     No covariate in the model.
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
```

```r
saemix.model<-saemixModel(model=tte.model,description="time model",modeltype="likelihood",
  psi0=matrix(c(1,2),ncol=2,byrow=TRUE,dimnames=list(NULL,  c("lambda","beta"))),
  transform.par=c(1,1),covariance.model=matrix(c(1,0,0,0),ncol=2, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  time model
##   Model type:  likelihood
```

```
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   N <- nrow(psi)
##   Nj <- length(T)
##   # censoringtime = 6
##   censoringtime = max(T)
##   lambda <- psi[id,1]
##   beta <- psi[id,2]
##   init <- which(T==0)
##   cens <- which(T==censoringtime)
##   ind <- setdiff(1:Nj, append(init,cens))
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1)
##   H <- (T/lambda)^beta
##   logpdf <- rep(0,Nj)
##   logpdf[cens] <- -H[cens] + H[cens-1]
##   logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind])
##   return(logpdf)
## }
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    0
##     No covariate in the model.
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
```

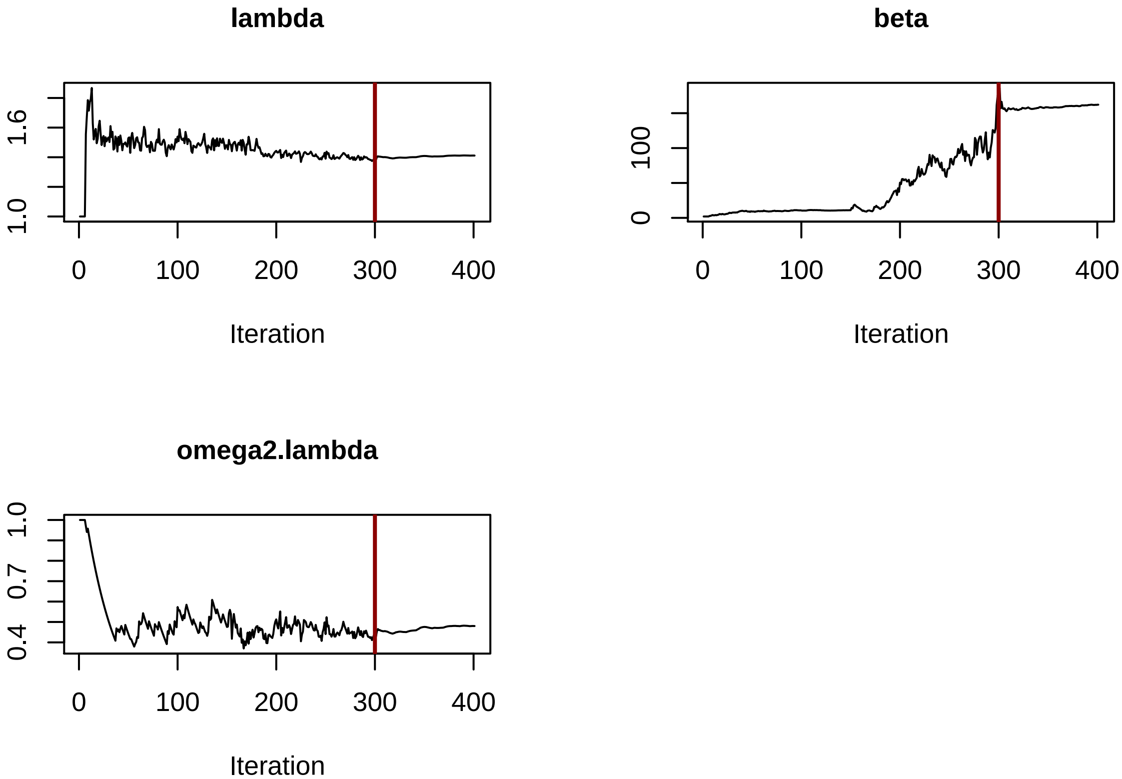
```
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, displayProgress=FALSE)
tte.fit<-saemix(saemix.model,saemix.data,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset tte.data
##     Structured data: y ~ time | id
##     Predictor: time ()
## Dataset characteristics:
##     number of subjects:     50
##     number of observations: 100
##     average/min/max nb obs: 2.00  /  2  /  2
## First 10 lines of data:
##    id      time y mdv cens occ ytype
## 1   1 0.0000000 0   0    0   1     1
## 51  1 0.9152915 1   0    0   1     1
## 2   2 0.0000000 0   0    0   1     1
## 52  2 0.5857074 1   0    0   1     1
```

```
## 3   3 0.0000000 0   0    0   1     1
## 53  3 0.8447454 1   0    0   1     1
## 4   4 0.0000000 0   0    0   1     1
## 54  4 0.5648408 1   0    0   1     1
## 5   5 0.0000000 0   0    0   1     1
## 55  5 1.4458047 1   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  time model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   N <- nrow(psi)
##   Nj <- length(T)
##   # censoringtime = 6
##   censoringtime = max(T)
##   lambda <- psi[id,1]
##   beta <- psi[id,2]
##   init <- which(T==0)
##   cens <- which(T==censoringtime)
##   ind <- setdiff(1:Nj, append(init,cens))
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1)
##   H <- (T/lambda)^beta
##   logpdf <- rep(0,Nj)
##   logpdf[cens] <- -H[cens] + H[cens-1]
##   logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind])
##   return(logpdf)
## }
## <bytecode: 0x55e9df7a8478>
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    0
##     No covariate in the model.
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
```

```
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  -----------------
## ----------------------------------------------------
##      Parameter Estimate SE      CV(%)
## [1,] lambda      1.4       0.58   41
## [2,] beta      162.2    5675.89 3500
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##        Parameter     Estimate SE   CV(%)
## lambda omega2.lambda 0.48     0.21 44
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.lambda
## omega2.lambda 1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 573.0104
##       AIC = 581.0104
##       BIC = 588.6585
##
## Likelihood computed by importance sampling
##       -2LL= 122.2899
##       AIC = 130.2899
##       BIC = 137.938
## ----------------------------------------------------
```

```r
plot(tte.fit, plot.type="convergence")
```



TTE model - lung cancer

- create dataset for saemix (once) using the lung data from the survival package
- changes
  - saemix format: added time=0
  - created one column for status (dead or alive, recoded as 1/0) and one for censoring (0/1)
  - removed subjects with missing age, institution, sex, or ph scores (ecog and karno)

Checks

- The `Surv` function from the `survival` package creates a survival object for use as the response in a model formula.
  - one entry for each subject that is the survival time, which is followed by a `+` if the subject was censored
  - transform lung.saemix in the Surv format to check the survival function w/r saemix fit
- Weibull model
  - parametric survival function

$$S(t) = e^{-\left(\frac{t}{\lambda}\right)^{\beta}}$$

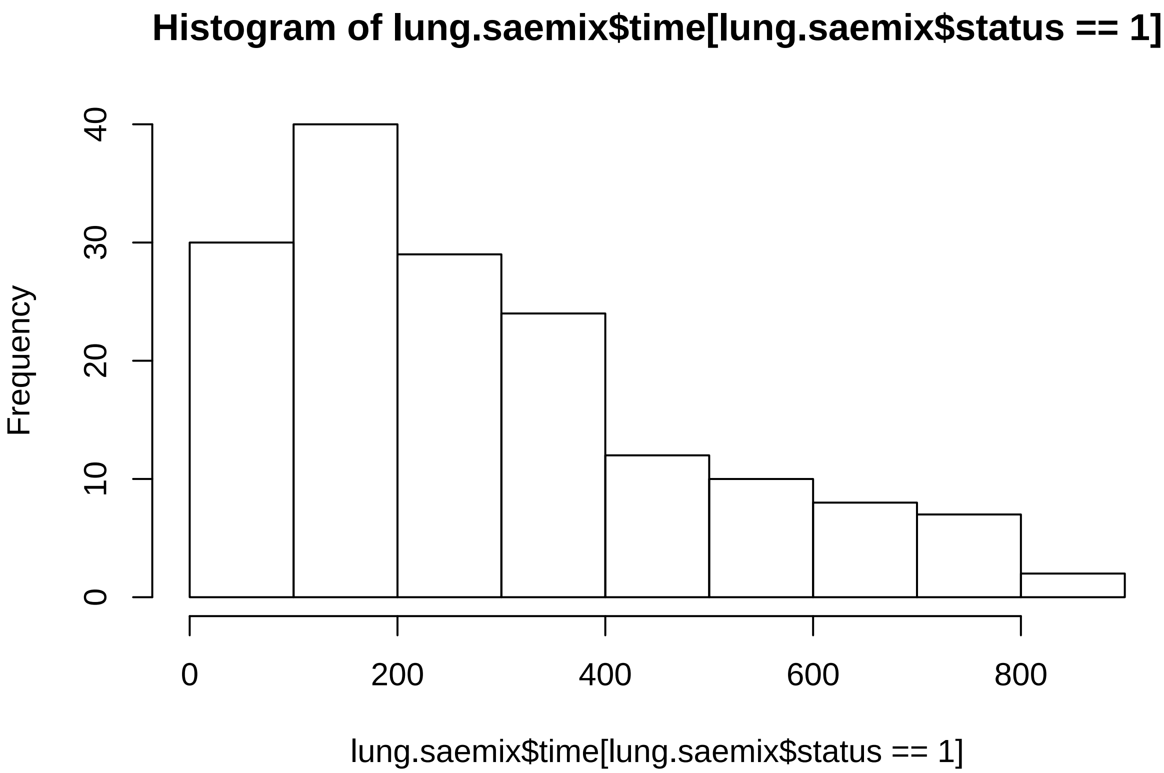
- Also tried computing a SE for $S(t)$ using the delta-method where the vector of derivatives for the survival function of Weibull model are:

$$\begin{pmatrix} \frac{\delta S}{\delta \lambda} \\ \frac{\delta S}{\delta \beta} \end{pmatrix} = \begin{pmatrix} \frac{\beta}{\lambda} \ \left(\frac{t}{\lambda}\right)^{\beta} e^{-\left(\frac{t}{\lambda}\right)^{\beta}} \\ -\ln\left(\frac{t}{\lambda}\right) \ \left(\frac{t}{\lambda}\right)^{\beta} e^{-\left(\frac{t}{\lambda}\right)^{\beta}} \end{pmatrix}$$

- works pretty well compared to the non-parametric KM estimate

```
if(testMode)
  data(lung.saemix) else
```

```r
    lung.saemix<-read.table(file.path(datDir, "lung.saemix.tab"), header=TRUE)

hist(lung.saemix$time[lung.saemix$status==1])
```




```r
# Note: missing data in pat.karno, wt.loss and meal.cal
if(FALSE)
    print(summary(lung.saemix))

saemix.data<-saemixData(name.data=lung.saemix,header=TRUE,name.group=c("id"),
      name.predictors=c("time","status","cens"),name.response=c("status"),
      name.covariates=c("age", "sex", "ph.ecog", "ph.karno", "pat.karno", "wt.loss","meal.cal"),
      units=list(x="days",y="",covariates=c("yr","","-","%","%","cal","pounds")))
```

```
## [1] "age"       "sex"       "ph.ecog"   "ph.karno"  "pat.karno" "wt.loss"
## [7] "meal.cal"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset lung.saemix
##     Structured data: status ~ time + status + cens | id
##     X variable for graphs: time (days)
##     covariates: age (yr), sex (), ph.ecog (-), ph.karno (%), pat.karno (%), wt.loss (cal), meal.cal
##       reference class for covariate sex :  0
```

```r
weibulltte.model<-function(psi,id,xidep) {
  T<-xidep[,1]
  y<-xidep[,2] # events (1=event, 0=no event)
```

```r
  cens<-which(xidep[,3]==1) # censoring times (subject specific)
  init <- which(T==0)
  lambda <- psi[id,1] # Parameters of the Weibull model
  beta <- psi[id,2]
  Nj <- length(T)

  ind <- setdiff(1:Nj, append(init,cens)) # indices of events
  hazard <- (beta/lambda)*(T/lambda)^(beta-1) # ln(H')
  H <- (T/lambda)^beta # ln(H)
  logpdf <- rep(0,Nj) # ln(l(T=0))=0
  logpdf[cens] <- -H[cens] + H[cens-1] # ln(l(T=censoring time))
  logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind]) # ln(l(T=event time))
  return(logpdf)
}

saemix.model<-saemixModel(model=weibulltte.model,description="time model",modeltype="likelihood",
  psi0=matrix(c(1,2),ncol=2,byrow=TRUE,dimnames=list(NULL,  c("lambda","beta"))),
  transform.par=c(1,1),covariance.model=matrix(c(1,0,0,0),ncol=2, byrow=TRUE))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  time model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   y<-xidep[,2] # events (1=event, 0=no event)
##   cens<-which(xidep[,3]==1) # censoring times (subject specific)
##   init <- which(T==0)
##   lambda <- psi[id,1] # Parameters of the Weibull model
##   beta <- psi[id,2]
##   Nj <- length(T)
##
##   ind <- setdiff(1:Nj, append(init,cens)) # indices of events
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1) # ln(H')
##   H <- (T/lambda)^beta # ln(H)
##   logpdf <- rep(0,Nj) # ln(l(T=0))=0
##   logpdf[cens] <- -H[cens] + H[cens-1] # ln(l(T=censoring time))
##   logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind]) # ln(l(T=event time))
##   return(logpdf)
## }
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    0
##     No covariate in the model.
```

```
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
```

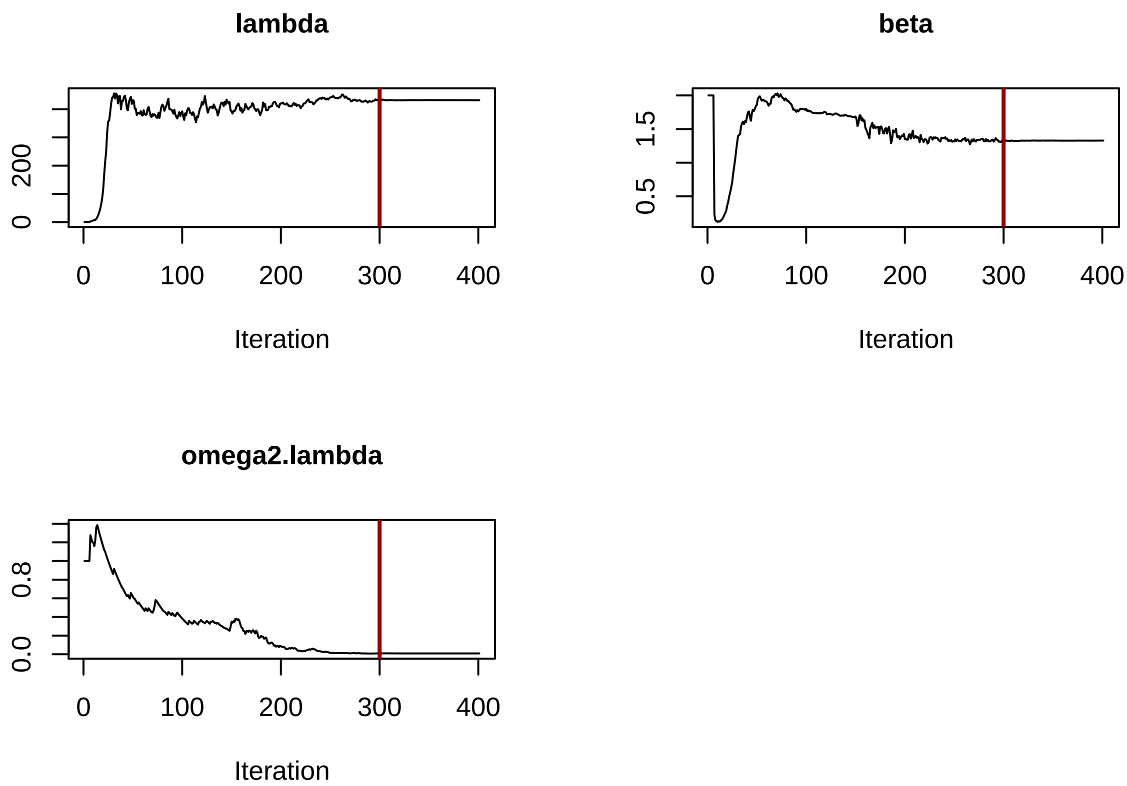
```
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, displayProgress=FALSE)
tte.fit<-saemix(saemix.model,saemix.data,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data              ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset lung.saemix
##     Structured data: status ~ time + status + cens | id
##     X variable for graphs: time (days)
##     covariates: age (yr), sex (), ph.ecog (-), ph.karno (%), pat.karno (%), wt.loss (cal), meal.cal
##       reference class for covariate sex :  0
## Dataset characteristics:
##     number of subjects:     225
##     number of observations: 450
##     average/min/max nb obs: 2.00  /  2  /  2
## First 10 lines of data:
##    id time status cens status.1 age sex ph.ecog ph.karno pat.karno wt.loss
## 1   1    0      0    0        0  74   0       1       90       100      NA
## 2   1  306      1    0        1  74   0       1       90       100      NA
## 3   2    0      0    0        0  68   0       0       90        90      15
## 4   2  455      1    0        1  68   0       0       90        90      15
## 5   3    0      0    0        0  56   0       0       90        90      15
## 6   3 1010      0    1        0  56   0       0       90        90      15
## 7   4    0      0    0        0  57   0       1       90        60      11
## 8   4  210      1    0        1  57   0       1       90        60      11
## 9   5    0      0    0        0  60   0       0      100        90       0
## 10  5  883      1    0        1  60   0       0      100        90       0
##    meal.cal mdv cens.1 occ ytype
## 1      1175   0      0   1     1
## 2      1175   0      0   1     1
## 3      1225   0      0   1     1
## 4      1225   0      0   1     1
## 5        NA   0      0   1     1
## 6        NA   0      0   1     1
## 7      1150   0      0   1     1
## 8      1150   0      0   1     1
## 9        NA   0      0   1     1
## 10       NA   0      0   1     1
## -----------------------------------
## ----          Model             ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  time model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   y<-xidep[,2] # events (1=event, 0=no event)
##   cens<-which(xidep[,3]==1) # censoring times (subject specific)
```

```
##   init <- which(T==0)
##   lambda <- psi[id,1] # Parameters of the Weibull model
##   beta <- psi[id,2]
##   Nj <- length(T)
##
##   ind <- setdiff(1:Nj, append(init,cens)) # indices of events
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1) # ln(H')
##   H <- (T/lambda)^beta # ln(H)
##   logpdf <- rep(0,Nj) # ln(l(T=0))=0
##   logpdf[cens] <- -H[cens] + H[cens-1] # ln(l(T=censoring time))
##   logpdf[ind] <- -H[ind] + H[ind-1] + log(hazard[ind]) # ln(l(T=event time))
##   return(logpdf)
## }
## <bytecode: 0x55e9e4ee0798>
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    0
##     No covariate in the model.
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
## ----------------------------------
## ----    Key algorithm options  ----
## ----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter Estimate SE    CV(%)
## [1,] lambda    431.8    51.60 12
## [2,] beta        1.3     0.19 14
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
```

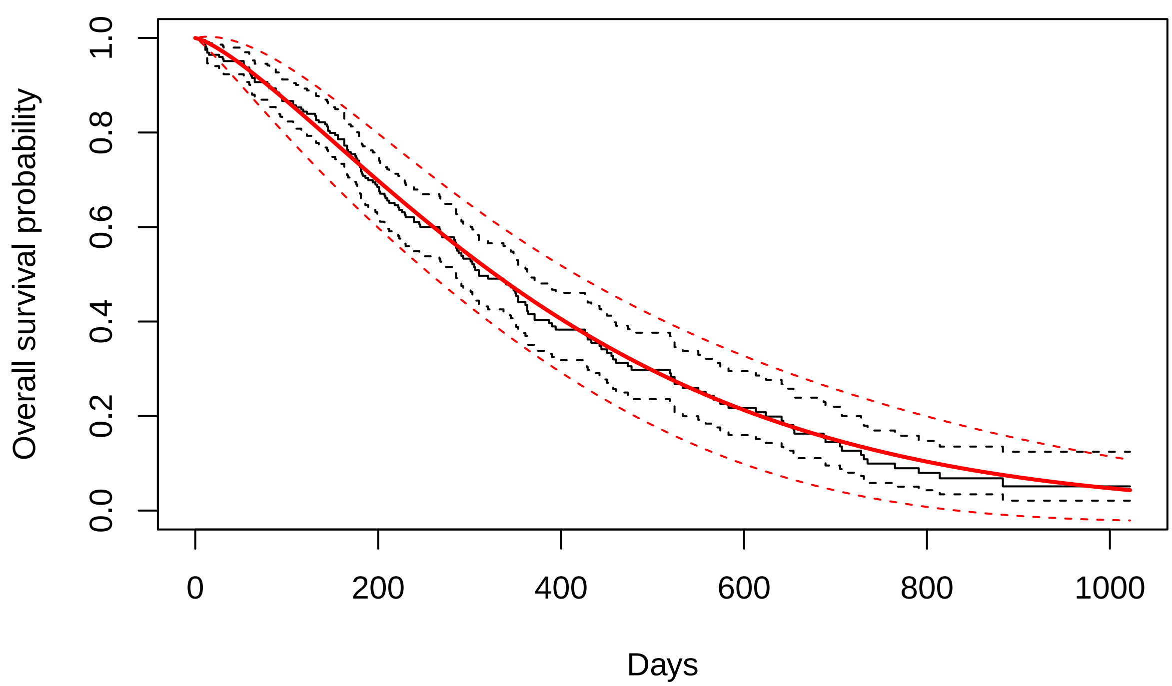
```
## ----------------------------------------------------
##        Parameter     Estimate SE   CV(%)
## lambda omega2.lambda 0.009    0.17 1858
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.lambda
## omega2.lambda 1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 5189.352
##       AIC = 5197.352
##       BIC = 5211.017
##
## Likelihood computed by importance sampling
##       -2LL= 2269.357
##       AIC = 2277.357
##       BIC = 2291.021
## ----------------------------------------------------
```

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




```
ypred<-predict(tte.fit)

# Use survival package to assess Survival curve
if(TRUE) {
  library(survival)
  lung.surv<-lung.saemix[lung.saemix$time>0,]
```

```
  lung.surv$status<-lung.surv$status+1
  Surv(lung.surv$time, lung.surv$status) # 1=censored, 2=dead
  f1 <- survfit(Surv(time, status) ~ 1, data = lung.surv)
  xtim<-seq(0,max(lung.saemix$time), length.out=200)
  estpar<-tte.fit@results@fixed.effects
  estse<-tte.fit@results@se.fixed
  ypred<-exp(-(xtim/estpar[1])^(estpar[2]))

# Computing SE for the survival curve based on linearised FIM (probably not a good idea) through the de
  invfim<-solve(tte.fit@results@fim[1:2,1:2])
  xcal<- (xtim/estpar[1])^estpar[2]
  dsdbeta<- -log(xtim/estpar[1]) * xcal *exp(-xcal)
  dsdalpha<- estpar[2]/estpar[1] * xcal *exp(-xcal)
  xmat<-rbind(dsdalpha, dsdbeta)
  #    x1<-t(xmat[,1:3]) %*% invfim %*% xmat[,1:3]
  sesurv<-rep(0,length(xcal))
  for(i in 1:length(xcal))
    sesurv[i]<-sqrt(t(xmat[,i]) %*% invfim %*% xmat[,i])
  plot(f1, xlab = "Days", ylab = "Overall survival probability")
  lines(xtim,ypred, col="red",lwd=2)
  lines(xtim,ypred+1.96*sesurv, col="red",lwd=1, lty=2)
  lines(xtim,ypred-1.96*sesurv, col="red",lwd=1, lty=2)

  # ypred2<-exp(-(xtim/(estpar[1]-1.96*sqrt(invfim[1,1])))^(estpar[2]+1.96*sqrt(invfim[2,2])))
  # ypred3<-exp(-(xtim/(estpar[1]+1.96*sqrt(invfim[1,1])))^(estpar[2]+1.96*sqrt(invfim[2,2])))
  # lines(xtim,ypred2, col="blue",lwd=1, lty=2)
  # lines(xtim,ypred3, col="blue",lwd=1, lty=2)
}
```



RTTE model

- again difficult to find real data
- simulated data
  - Exemple simulé de Belhal **TODO**
  - data from the Monolix documentation: absolutely no indication where the data comes from (weibull_data.txt for the weibullRTTE.mlxtran project in the demo)
- search for real data
  - asked Ulrika Simonsson for the RTTE data on post-operative pain (Pain Medicine 2015)
  - data on events in Gaucher disease used for the ENSAI workshops (but few events)
  - discretised PCA events during warfarin treatment ? (from the warfarin PK/PD) (but threshold ?)

```
# Simulating RTTE data by simulating from U(0,1) and inverting the cdf
simul.rtte.unif<-function(psi) { # xidep, id not important, we only use psi
  censoringtime <- 3
  maxevents <- 30
  lambda <- psi[,1]
  beta <- psi[,2]
  simdat<-NULL
  N<-nrow(psi)
  for(i in 1:N) {
    eventTimes<-c(0)
    T<-0
    Vj<-runif(1)
    #    T <- (-log(Vj)*lambda[i])^(beta[i])
    T<-lambda[i]*(-log(Vj))^(1/beta[i])
    nev<-0
    while (T < censoringtime & nev<maxevents){
      eventTimes <- c(eventTimes, T)
      nev<-nev+1
      Vj<-runif(1)
      #      T <- T+(-log(Vj)*lambda[i])^(beta[i])
      #      T<-(-log(Vj)*lambda[i] + T^(1/beta[i]))^(beta[i])
      T<-lambda[i]*(-log(Vj) + (T/lambda[i])^(beta[i]))^(1/beta[i])
    }
    if(nev==maxevents) {
      message("Reached maximum number of events\n")
    }
    eventTimes<-c(eventTimes, censoringtime)
    cens<-rep(1,length(eventTimes))
    cens[1]<-cens[length(cens)]<-0
    simdat<-rbind(simdat,
                  data.frame(id=i, T=eventTimes, status=cens))
  }
  return(simdat)
}

# Subjects
set.seed(12345)
param<-c(2, 1.5, 0.5)
# param<-c(4, 1.2, 0.3)
omega<-c(0.25,0.25)
nsuj<-200
risk<-rep(0,nsuj)
```

```
risk[(nsuj/2+1):nsuj]<-1
psiM<-data.frame(lambda=param[1]*exp(rnorm(nsuj,sd=omega[1])), beta=param[2]*exp(param[3]*risk+rnorm(nsu
simdat <- simul.rtte.unif(psiM)
```

```
## Reached maximum number of events
```

```
simdat$risk<-as.integer(simdat$id>(nsuj/2))

# Simulate T from Weibull (check)
if(FALSE) {
  lambda<-2
  beta<-2
  nsim<-5000
  # By hand
  q1<-runif(nsim)
  #  tevent<-lambda*exp(log(q1)/beta)
  tevent<-lambda*exp(log(-log(q1))/beta)
  tevent<-sort(tevent)
#  plot(tevent, exp(-(tevent/lambda)^beta))
  tevent2<-sort(rweibull(nsim, shape=beta, scale=lambda))
  plot(tevent, tevent2)
  abline(0,1)

}
```

```
saemix.data<-saemixData(name.data=simdat, name.group=c("id"), name.predictors=c("T"), name.response="sta
```

```
## [1] "risk"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset simdat
##     Structured data: status ~ T | id
##     Predictor: T ()
##     covariates: risk (-)
##       reference class for covariate risk :  0
```

```
rtte.model<-function(psi,id,xidep) {
  T<-xidep[,1]
  N <- nrow(psi) # nb of subjects
  Nj <- length(T) # nb of events (including 0 and censoring times)
  # censoringtime = 6
  censoringtime = max(T) # same censoring for everyone
  lambda <- psi[id,1]
  beta <- psi[id,2]
  tinit <- which(T==0) # indices of beginning of observation period
  tcens <- which(T==censoringtime) # indices of censored events
  tevent <- setdiff(1:Nj, append(tinit,tcens)) # indices of non-censored event times
  hazard <- (beta/lambda)*(T/lambda)^(beta-1)
  H <- (T/lambda)^beta
  logpdf <- rep(0,Nj)
  logpdf[tcens] <- -H[tcens] + H[tcens-1]
```

```
  logpdf[tevent] <- -H[tevent] + H[tevent-1] + log(hazard[tevent])
  return(logpdf)
}

saemix.model.base<-saemixModel(model=rtte.model,description="Repeated TTE model",modeltype="likelihood"
                               psi0=matrix(c(1,2),ncol=2,byrow=TRUE,dimnames=list(NULL,  c("lambda","be
                               transform.par=c(1,1),covariance.model=matrix(c(1,0,0,1),ncol=2, byrow=TR
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Repeated TTE model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   N <- nrow(psi) # nb of subjects
##   Nj <- length(T) # nb of events (including 0 and censoring times)
##   # censoringtime = 6
##   censoringtime = max(T) # same censoring for everyone
##   lambda <- psi[id,1]
##   beta <- psi[id,2]
##   tinit <- which(T==0) # indices of beginning of observation period
##   tcens <- which(T==censoringtime) # indices of censored events
##   tevent <- setdiff(1:Nj, append(tinit,tcens)) # indices of non-censored event times
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1)
##   H <- (T/lambda)^beta
##   logpdf <- rep(0,Nj)
##   logpdf[tcens] <- -H[tcens] + H[tcens-1]
##   logpdf[tevent] <- -H[tevent] + H[tevent-1] + log(hazard[tevent])
##   return(logpdf)
## }
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    1
##     No covariate in the model.
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
```

```
saemix.model<-saemixModel(model=rtte.model,description="Repeated TTE model",modeltype="likelihood",
                          psi0=matrix(c(1,2),ncol=2,byrow=TRUE,dimnames=list(NULL,  c("lambda","beta"))
                          transform.par=c(1,1),covariate.model=matrix(c(0,1),ncol=2),
                          covariance.model=matrix(c(1,0,0,1),ncol=2, byrow=TRUE))
```

```
##
```

```
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Repeated TTE model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   N <- nrow(psi) # nb of subjects
##   Nj <- length(T) # nb of events (including 0 and censoring times)
##   # censoringtime = 6
##   censoringtime = max(T) # same censoring for everyone
##   lambda <- psi[id,1]
##   beta <- psi[id,2]
##   tinit <- which(T==0) # indices of beginning of observation period
##   tcens <- which(T==censoringtime) # indices of censored events
##   tevent <- setdiff(1:Nj, append(tinit,tcens)) # indices of non-censored event times
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1)
##   H <- (T/lambda)^beta
##   logpdf <- rep(0,Nj)
##   logpdf[tcens] <- -H[tcens] + H[tcens-1]
##   logpdf[tevent] <- -H[tevent] + H[tevent-1] + log(hazard[tevent])
##   return(logpdf)
## }
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    1
##   Covariate model:
##      lambda beta
## [1,]      0    1
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
## Cov.CondInit      0    0
```

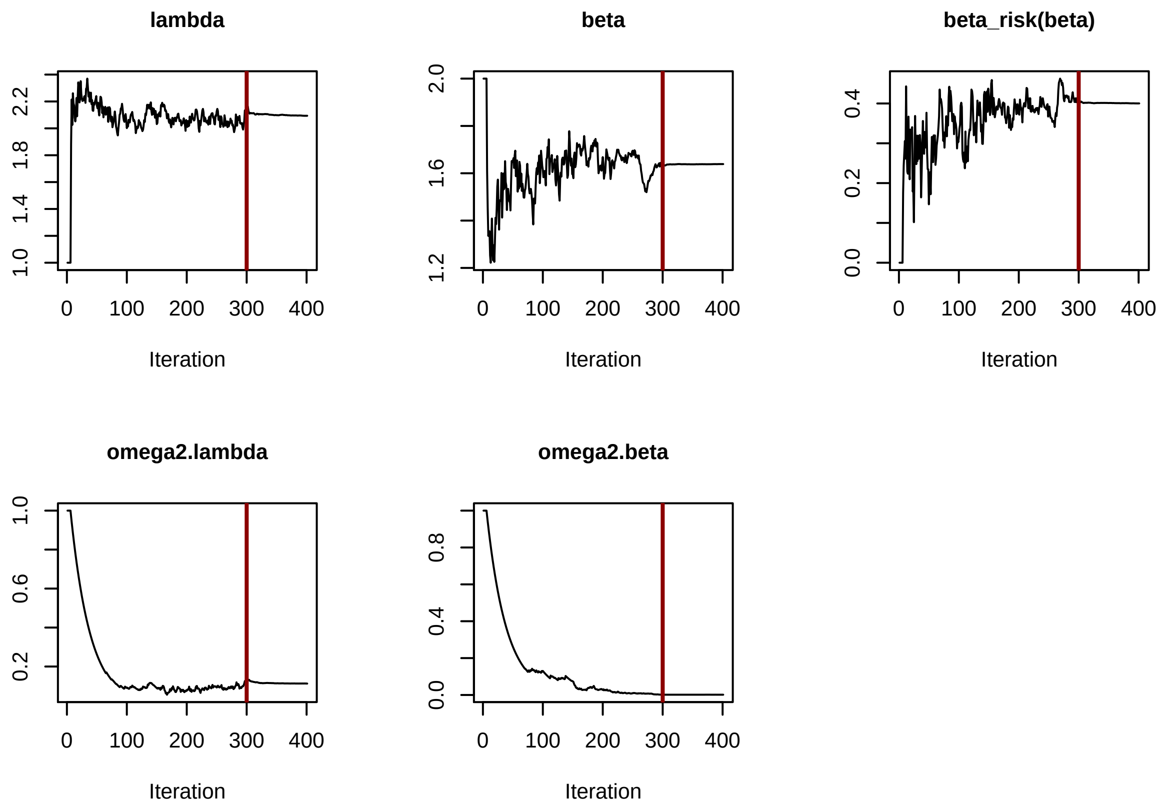
```
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE, fim=FALSE, displayProgress=FALSE)
rtte.fit<-saemix(saemix.model,saemix.data,saemix.options)
```

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----------------------------------
## ----          Data             ----
## -----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset simdat
##     Structured data: status ~ T | id
##     Predictor: T ()
##     covariates: risk (-)
```

```
##       reference class for covariate risk :  0
## Dataset characteristics:
##     number of subjects:     200
##     number of observations: 967
##     average/min/max nb obs: 4.83  /  2  /  32
## First 10 lines of data:
##    id         T status risk mdv cens occ ytype
## 1   1 0.0000000      0    0   0    0   1     1
## 2   1 0.7520145      1    0   0    0   1     1
## 3   1 0.8775847      1    0   0    0   1     1
## 4   1 2.4331650      1    0   0    0   1     1
## 5   1 3.0000000      0    0   0    0   1     1
## 6   2 0.0000000      0    0   0    0   1     1
## 7   2 1.3712351      1    0   0    0   1     1
## 8   2 3.0000000      0    0   0    0   1     1
## 9   3 0.0000000      0    0   0    0   1     1
## 10  3 2.8564910      1    0   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Repeated TTE model
##   Model type:  likelihood
## function(psi,id,xidep) {
##   T<-xidep[,1]
##   N <- nrow(psi) # nb of subjects
##   Nj <- length(T) # nb of events (including 0 and censoring times)
##   # censoringtime = 6
##   censoringtime = max(T) # same censoring for everyone
##   lambda <- psi[id,1]
##   beta <- psi[id,2]
##   tinit <- which(T==0) # indices of beginning of observation period
##   tcens <- which(T==censoringtime) # indices of censored events
##   tevent <- setdiff(1:Nj, append(tinit,tcens)) # indices of non-censored event times
##   hazard <- (beta/lambda)*(T/lambda)^(beta-1)
##   H <- (T/lambda)^beta
##   logpdf <- rep(0,Nj)
##   logpdf[tcens] <- -H[tcens] + H[tcens-1]
##   logpdf[tevent] <- -H[tevent] + H[tevent-1] + log(hazard[tevent])
##   return(logpdf)
## }
## <bytecode: 0x55e9de24a7d0>
##   Nb of parameters: 2
##       parameter names:  lambda beta
##       distribution:
##      Parameter Distribution Estimated
## [1,] lambda    log-normal   Estimated
## [2,] beta      log-normal   Estimated
##   Variance-covariance matrix:
##        lambda beta
## lambda      1    0
## beta        0    1
##   Covariate model:
##      [,1] [,2]
```

```
## risk    0    1
##     Initial values
##              lambda beta
## Pop.CondInit      1    2
## Cov.CondInit      0    0
## -----------------------------------
## ----    Key algorithm options  ----
## -----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  1
##     Seed:  632545
##     Number of MCMC iterations for IS:  5000
##     Simulations:
##         nb of simulated datasets used for npde:  1000
##         nb of simulated datasets used for VPC:  100
##     Input/output
##         save the results to a file:  FALSE
##         save the graphs to files:  FALSE
## ----------------------------------------------------
## ----                  Results                   ----
## ----------------------------------------------------
## -----------------  Fixed effects  ------------------
## ----------------------------------------------------
##      Parameter       Estimate
## [1,] lambda          2.1
## [2,] beta            1.6
## [3,] beta_risk(beta) 0.4
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##        Parameter     Estimate
## lambda omega2.lambda 0.1125
## beta   omega2.beta   0.0015
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##               omega2.lambda omega2.beta
## omega2.lambda 1             0
## omega2.beta   0             1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
##
## Likelihood computed by importance sampling
##       -2LL= 690.2485
##       AIC = 702.2485
##       BIC = 722.0384
## ----------------------------------------------------
```

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




```
saemix.data<-saemixData(name.data=tte.data, name.group=c("id"),
  name.predictors=c("time"), name.response="y")
```

```
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset tte.data
##     Structured data: y ~ time | id
##     Predictor: time ()
```

Exiting

```
if(testMode) {
  dev_mode()
}
```