# Testing examples in saemix 3.0

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## Setup

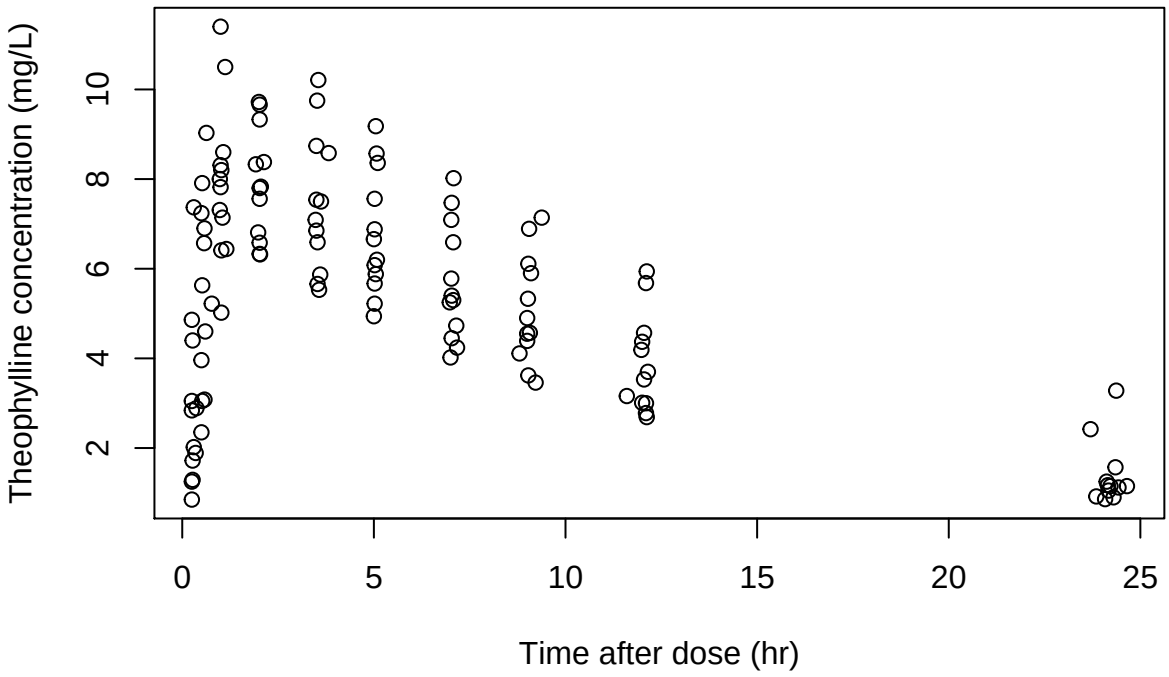
- set up work directories
- two versions toggled by testMode
  - if testMode is FALSE, load the functions in R
  - if testMode is TRUE, load the library in a dev_mode environment
- aim: check the examples used in the online documentation
  - all examples must run without error

## Testing library

### Continuous response model

#### Theophylline

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

#Plotting the theophylline data
plot(Concentration~Time,data=theo.saemix,xlab="Time after dose (hr)",
ylab="Theophylline concentration (mg/L)")
```



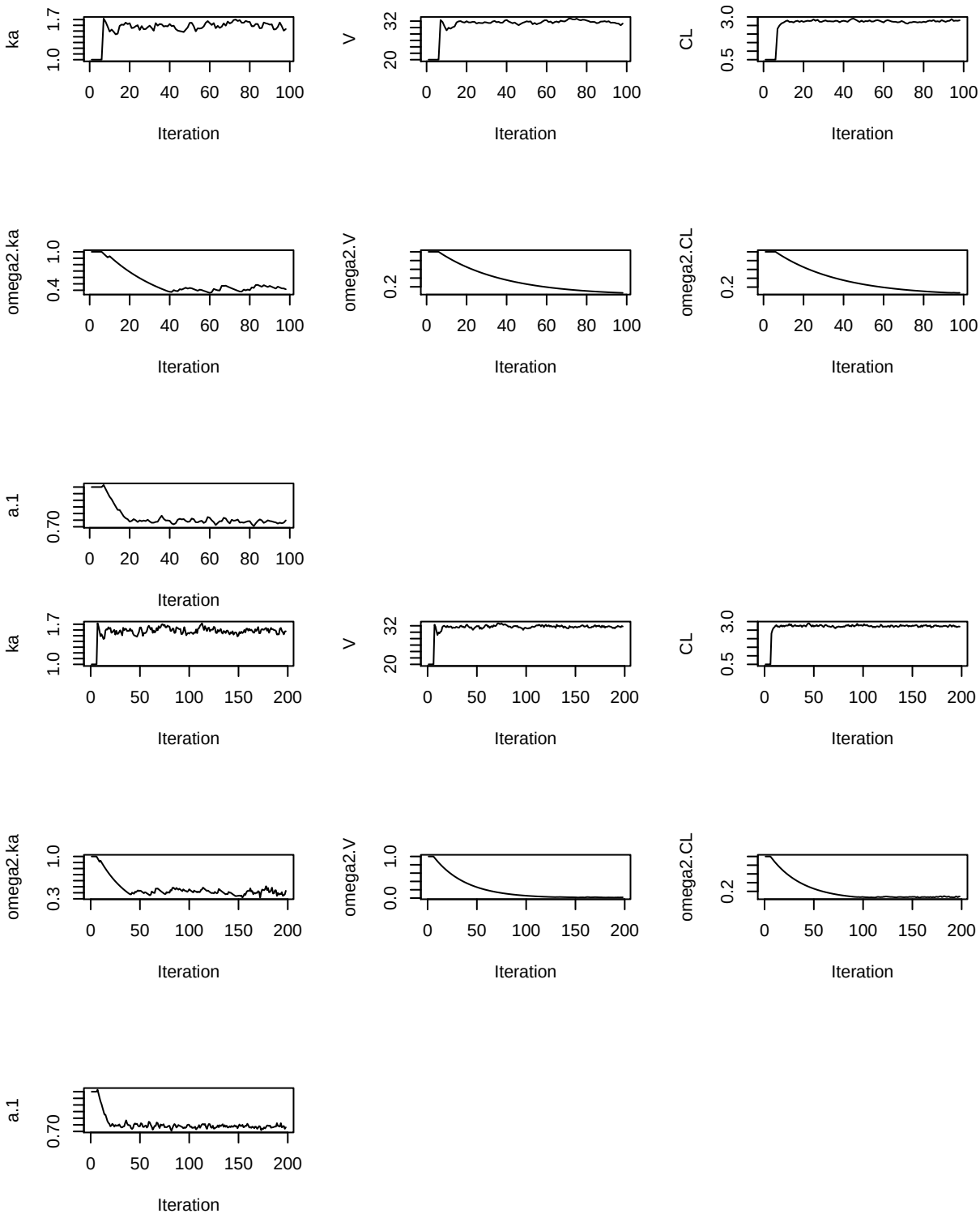

```
saemix.data<-saemixData(name.data=theo.saemix,header=TRUE,sep=" ",na=NA,
  name.group=c("Id"),name.predictors=c("Dose","Time"),
  name.response=c("Concentration"),name.covariates=c("Weight","Sex"),
  units=list(x="hr",y="mg/L",covariates=c("kg","-")), name.X="Time")
```

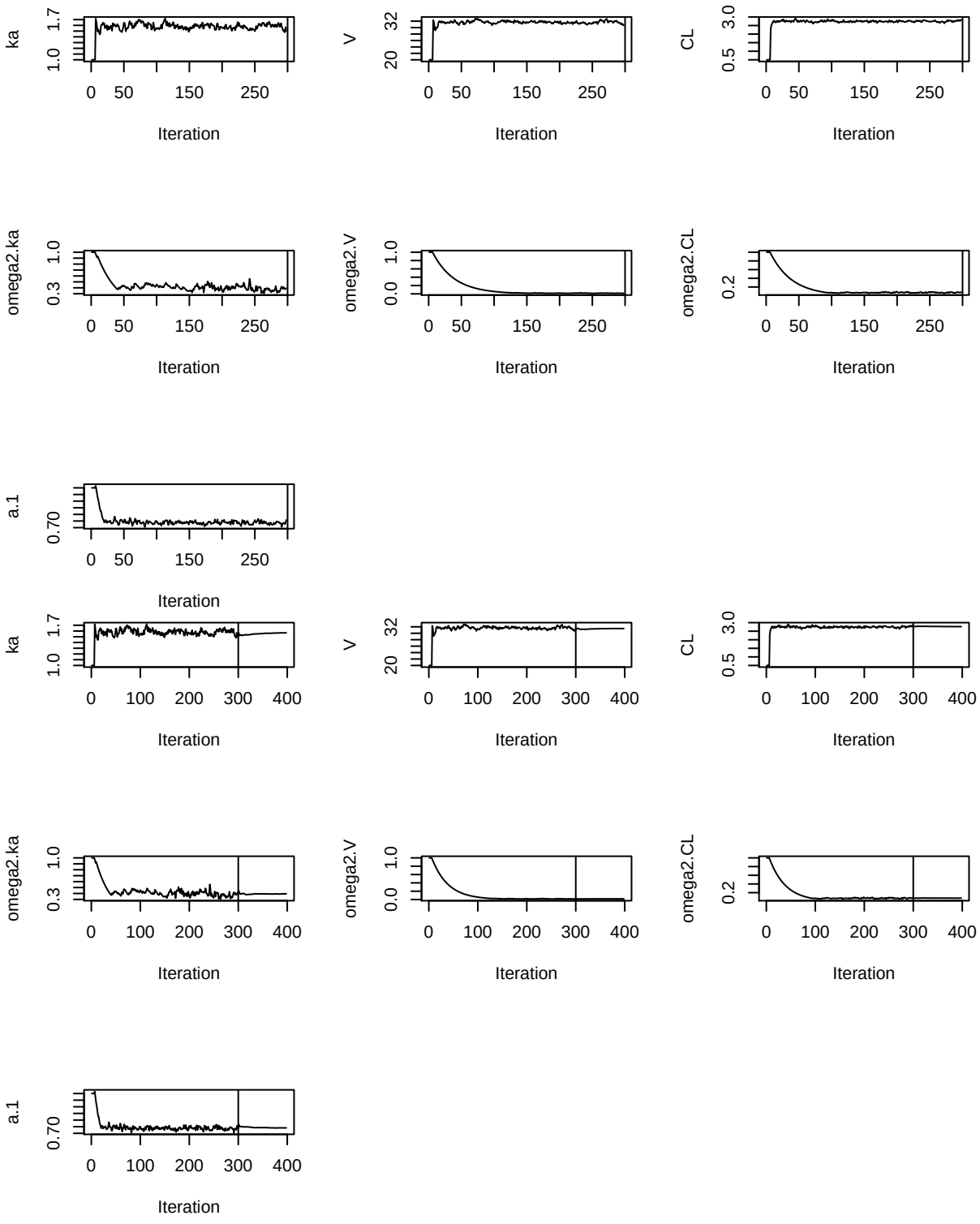
```
## [1] "Weight" "Sex"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset theo.saemix
##     Structured data: Concentration ~ Dose + Time | Id
##     X variable for graphs: Time (hr)
##     covariates: Weight (kg), Sex (-)
##       reference class for covariate Sex :  0
```

```
  model1cpt<-function(psi,id,xidep) {
    dose<-xidep[,1]
    tim<-xidep[,2]
    ka<-psi[id,1]
    V<-psi[id,2]
    CL<-psi[id,3]
    k<-CL/V
    ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
    return(ypred)
    }
# Default model, no covariate
saemix.model<-saemixModel(model=model1cpt,
       description="One-compartment model with first-order absorption",
       psi0=matrix(c(1.,20,0.5,0.1,0,-0.01),ncol=3,byrow=TRUE,
       dimnames=list(NULL, c("ka","V","CL"))),transform.par=c(1,1,1))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  One-compartment model with first-order absorption  Model type:  structural
## function(psi,id,xidep) {
##     dose<-xidep[,1]
##     tim<-xidep[,2]
##     ka<-psi[id,1]
##     V<-psi[id,2]
##     CL<-psi[id,3]
##     k<-CL/V
##     ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
##     return(ypred)
##     }
##   Nb of parameters: 3
##       parameter names:  ka V CL
##       distribution:
##      Parameter Distribution Estimated
## [1,] ka        log-normal   Estimated
## [2,] V         log-normal   Estimated
## [3,] CL        log-normal   Estimated
##   Variance-covariance matrix:
##    ka V CL
## ka  1 0  0
## V   0 1  0
## CL  0 0  1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##               ka  V    CL
## Pop.CondInit 1.0 20  0.50
## Cov.CondInit 0.1  0 -0.01
```

```r
# Note: remove the options save=FALSE and save.graphs=FALSE
# to save the results and graphs
saemix.options<-list(seed=632545,save=FALSE,save.graphs=FALSE)

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


ka
1.0
1.7
V
20
32
CL
0.5
3.0
omega2.ka
0.4
1.0
omega2.V
0.2
omega2.CL
0.2
a.1
0.70
0
20
40
60
80
100
50
150
200
Iteration




```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
```

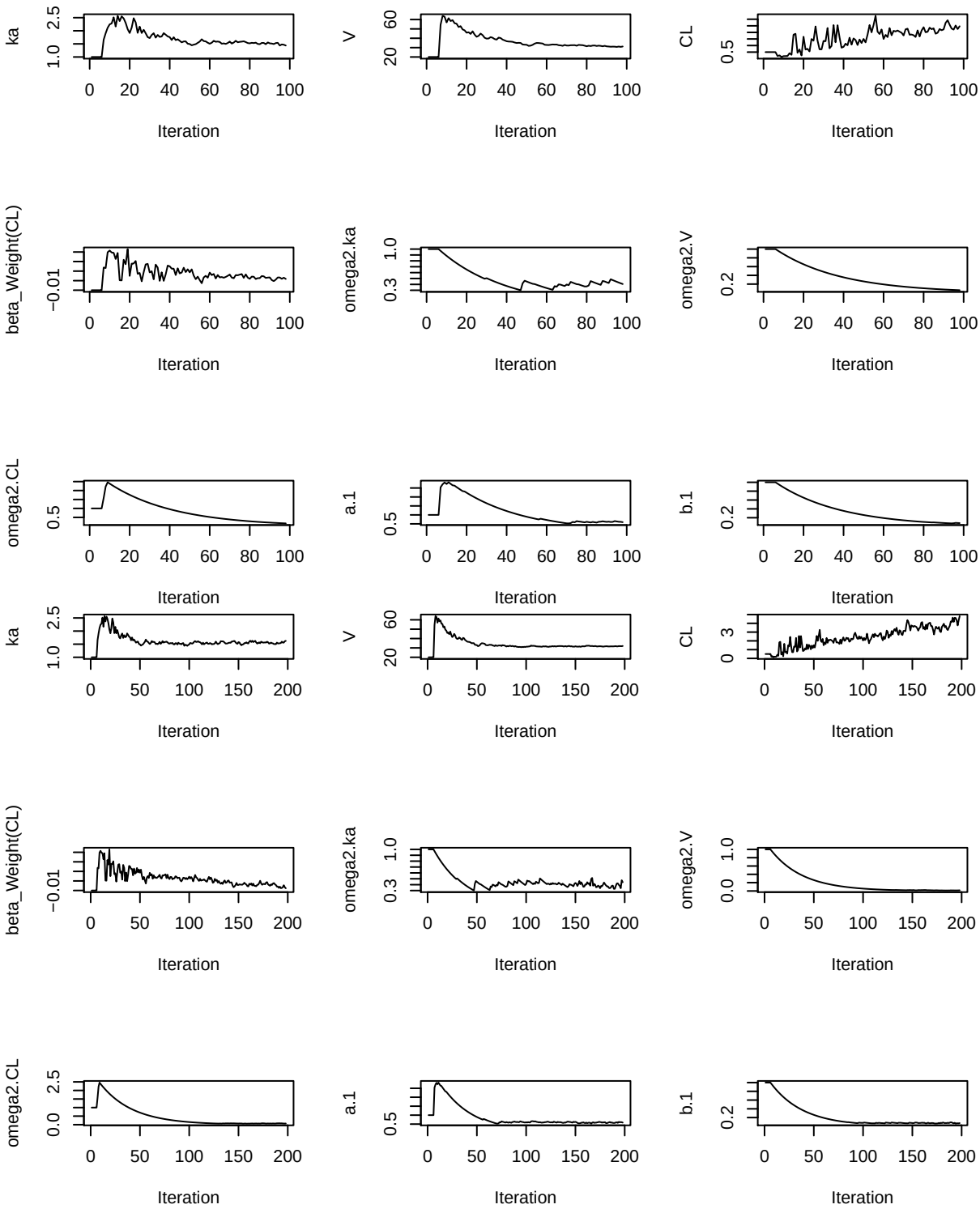
```
## Dataset theo.saemix
##     Structured data: Concentration ~ Dose + Time | Id
##     X variable for graphs: Time (hr)
##     covariates: Weight (kg), Sex (-)
##       reference class for covariate Sex :  0
## Dataset characteristics:
##     number of subjects:     12
##     number of observations: 120
##     average/min/max nb obs: 10.00  /  10  /  10
## First 10 lines of data:
##    Id    Dose  Time Concentration Weight Sex mdv cens occ ytype
## 1   1 319.992  0.25          2.84   79.6   1   0    0   1     1
## 2   1 319.992  0.57          6.57   79.6   1   0    0   1     1
## 3   1 319.992  1.12         10.50   79.6   1   0    0   1     1
## 4   1 319.992  2.02          9.66   79.6   1   0    0   1     1
## 5   1 319.992  3.82          8.58   79.6   1   0    0   1     1
## 6   1 319.992  5.10          8.36   79.6   1   0    0   1     1
## 7   1 319.992  7.03          7.47   79.6   1   0    0   1     1
## 8   1 319.992  9.05          6.89   79.6   1   0    0   1     1
## 9   1 319.992 12.12          5.94   79.6   1   0    0   1     1
## 10  1 319.992 24.37          3.28   79.6   1   0    0   1     1
## -----------------------------------
## ----          Model            ----
## -----------------------------------
## Nonlinear mixed-effects model
##   Model function:  One-compartment model with first-order absorption  Model type:  structural
## function(psi,id,xidep) {
##     dose<-xidep[,1]
##     tim<-xidep[,2]
##     ka<-psi[id,1]
##     V<-psi[id,2]
##     CL<-psi[id,3]
##     k<-CL/V
##     ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
##     return(ypred)
##     }
## <bytecode: 0x556f7a91eae8>
##   Nb of parameters: 3
##       parameter names:  ka V CL
##       distribution:
##      Parameter Distribution Estimated
## [1,] ka        log-normal   Estimated
## [2,] V         log-normal   Estimated
## [3,] CL        log-normal   Estimated
##   Variance-covariance matrix:
##    ka V CL
## ka  1 0  0
## V   0 1  0
## CL  0 0  1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              ka  V  CL
## Pop.CondInit  1 20 0.5
```

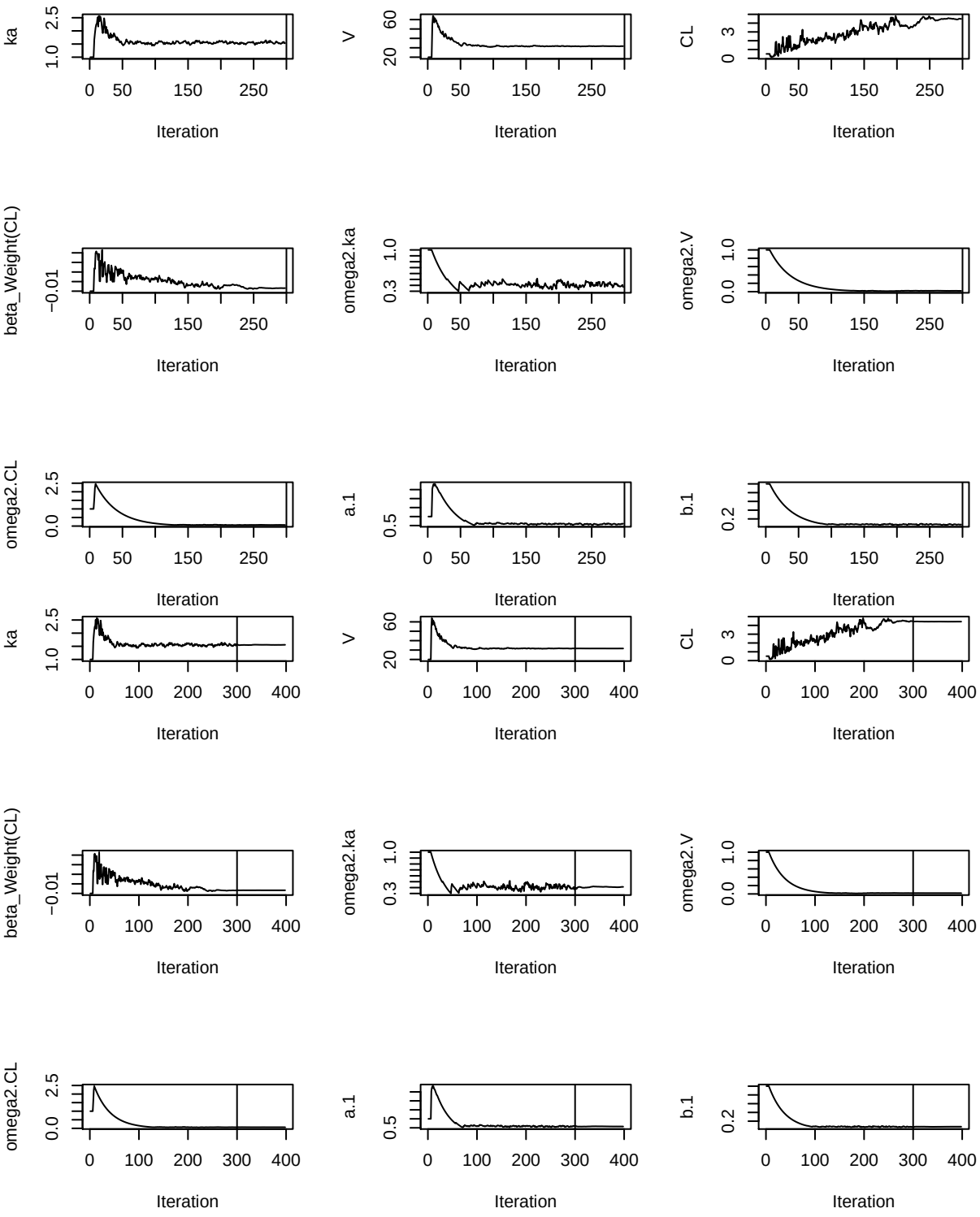
```
## ----------------------------------
## ----    Key algorithm options  ----
## ----------------------------------
##     Estimation of individual parameters (MAP)
##     Estimation of standard errors and linearised log-likelihood
##     Estimation of log-likelihood by importance sampling
##     Number of iterations:  K1=300, K2=100
##     Number of chains:  5
##     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,] ka         1.57    0.304 19.3
## [2,] V         31.47    1.423  4.5
## [3,] CL         2.77    0.239  8.7
## [4,] a.1        0.74    0.057  7.7
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##    Parameter Estimate SE     CV(%)
## ka omega2.ka 0.397    0.1790 45
## V  omega2.V  0.017    0.0096 58
## CL omega2.CL 0.074    0.0360 49
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##           omega2.ka omega2.V omega2.CL
## omega2.ka 1         0        0
## omega2.V  0         1        0
## omega2.CL 0         0        1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 344.1136
##       AIC = 358.1136
##       BIC = 361.5079
##
## Likelihood computed by importance sampling
##       -2LL= 345.4329
##       AIC = 359.4329
##       BIC = 362.8273
## ----------------------------------------------------
```

```r
# Model with covariates
saemix.model<-saemixModel(model=model1cpt,
     description="One-compartment model with first-order absorption",
     psi0=matrix(c(1.,20,0.5,0.1,0,-0.01),ncol=3,byrow=TRUE,
     dimnames=list(NULL, c("ka","V","CL"))),transform.par=c(1,1,1),
     covariate.model=matrix(c(0,0,1,0,0,0),ncol=3,byrow=TRUE),fixed.estim=c(1,1,1),
     covariance.model=matrix(c(1,0,0,0,1,1,0,1,1),ncol=3,byrow=TRUE),
     omega.init=matrix(c(1,0,0,0,1,0,0,0,1),ncol=3,byrow=TRUE),error.model="combined")
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  One-compartment model with first-order absorption  Model type:  structural
## function(psi,id,xidep) {
##     dose<-xidep[,1]
##     tim<-xidep[,2]
##     ka<-psi[id,1]
##     V<-psi[id,2]
##     CL<-psi[id,3]
##     k<-CL/V
##     ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
##     return(ypred)
##     }
## <bytecode: 0x556f7a91eae8>
##   Nb of parameters: 3
##       parameter names:  ka V CL
##       distribution:
##      Parameter Distribution Estimated
## [1,] ka        log-normal   Estimated
## [2,] V         log-normal   Estimated
## [3,] CL        log-normal   Estimated
##   Variance-covariance matrix:
##    ka V CL
## ka  1 0  0
## V   0 1  1
## CL  0 1  1
##   Error model: combined , initial values: a.1=1 b.1=1
##   Covariate model:
##      ka V CL
## [1,]  0 0  1
## [2,]  0 0  0
##     Initial values
##               ka  V    CL
## Pop.CondInit 1.0 20  0.50
## Cov.CondInit 0.1  0 -0.01
```

```r
saemix.options<-list(seed=39546,save=FALSE,save.graphs=FALSE)
saemix.fit<-saemix(saemix.model,saemix.data,saemix.options)
```


ka
V
CL
beta_Weight(CL)
omega2.ka
omega2.V
omega2.CL
a.1
b.1
Iteration




```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset theo.saemix
```

```
##     Structured data: Concentration ~ Dose + Time | Id
##     X variable for graphs: Time (hr)
##     covariates: Weight (kg), Sex (-)
##       reference class for covariate Sex :  0
## Dataset characteristics:
##     number of subjects:     12
##     number of observations: 120
##     average/min/max nb obs: 10.00  /  10  /  10
## First 10 lines of data:
##    Id    Dose  Time Concentration Weight Sex mdv cens occ ytype
## 1   1 319.992  0.25          2.84   79.6   1   0    0   1     1
## 2   1 319.992  0.57          6.57   79.6   1   0    0   1     1
## 3   1 319.992  1.12         10.50   79.6   1   0    0   1     1
## 4   1 319.992  2.02          9.66   79.6   1   0    0   1     1
## 5   1 319.992  3.82          8.58   79.6   1   0    0   1     1
## 6   1 319.992  5.10          8.36   79.6   1   0    0   1     1
## 7   1 319.992  7.03          7.47   79.6   1   0    0   1     1
## 8   1 319.992  9.05          6.89   79.6   1   0    0   1     1
## 9   1 319.992 12.12          5.94   79.6   1   0    0   1     1
## 10  1 319.992 24.37          3.28   79.6   1   0    0   1     1
## ----------------------------------
## ----          Model            ----
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  One-compartment model with first-order absorption  Model type:  structural
## function(psi,id,xidep) {
##     dose<-xidep[,1]
##     tim<-xidep[,2]
##     ka<-psi[id,1]
##     V<-psi[id,2]
##     CL<-psi[id,3]
##     k<-CL/V
##     ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
##     return(ypred)
##     }
## <bytecode: 0x556f7a91eae8>
##   Nb of parameters: 3
##       parameter names:  ka V CL
##       distribution:
##      Parameter Distribution Estimated
## [1,] ka        log-normal   Estimated
## [2,] V         log-normal   Estimated
## [3,] CL        log-normal   Estimated
##   Variance-covariance matrix:
##    ka V CL
## ka  1 0  0
## V   0 1  1
## CL  0 1  1
##   Error model: combined , initial values: a.1=1 b.1=1
##   Covariate model:
##        [,1] [,2] [,3]
## Weight    0    0    1
##     Initial values
##               ka  V    CL
```

```
## Pop.CondInit 1.0 20  0.50
## Cov.CondInit 0.1  0 -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:  5
##     Seed:  39546
##     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,] ka               1.5565  0.3050 19.6  -
## [2,] V               31.6621  1.4946  4.7  -
## [3,] CL               4.4308  1.9206 43.3  -
## [4,] beta_Weight(CL) -0.0067  0.0061 91.3  0.14
## [5,] a.1              0.5734  0.1211 21.1  -
## [6,] b.1              0.0748  0.0223 29.8  -
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##       Parameter Estimate SE    CV(%)
## ka    omega2.ka 0.412    0.179 44
## V     omega2.V  0.019    0.011 56
## CL    omega2.CL 0.064    0.031 48
## covar cov.V.CL  0.035    0.016 45
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##           omega2.ka omega2.V omega2.CL
## omega2.ka 1         0        0
## omega2.V  0         1        1
## omega2.CL 0         1        1
## ----------------------------------------------------
## --------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 330.7213
##       AIC = 350.7213
##       BIC = 355.5704
##
## Likelihood computed by importance sampling
```

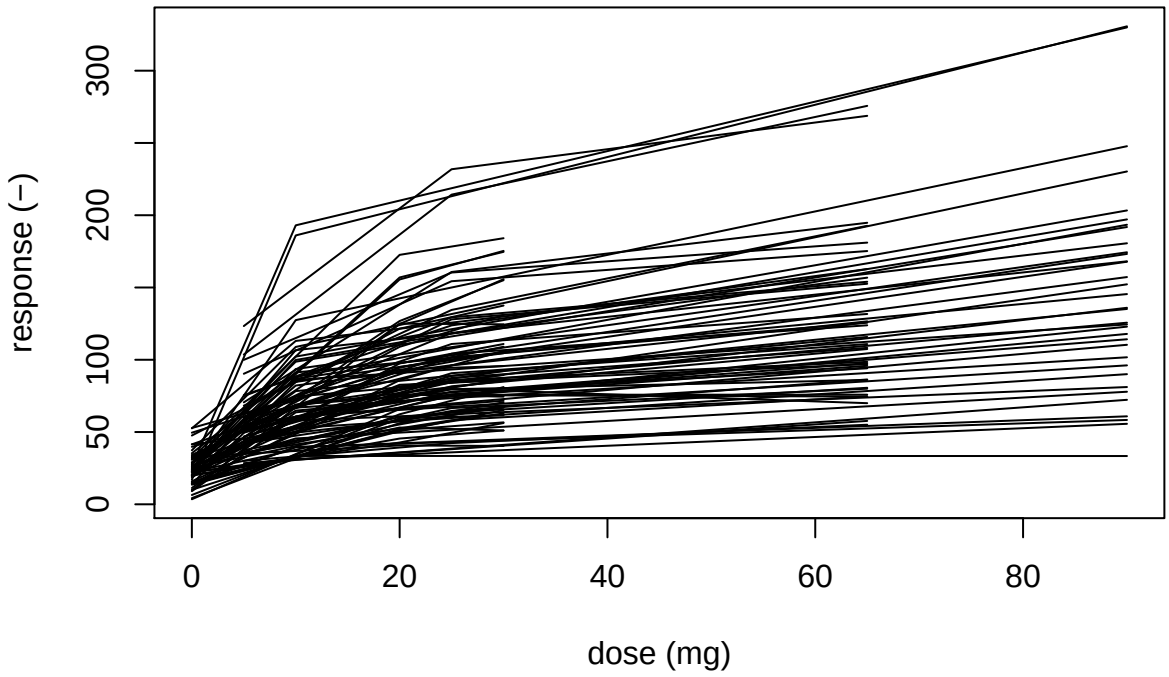
```
##       -2LL= 333.9945
##       AIC = 353.9945
##       BIC = 358.8436
## ----------------------------------------------------
```

### Simulated PD

```
if(testMode) {
  data(PD1.saemix)
  data(PD2.saemix)
  } else {
    PD1.saemix<-read.table(file.path(datDir, "PD1.saemix.tab"), header=TRUE)
    PD2.saemix<-read.table(file.path(datDir, "PD1.saemix.tab"), header=TRUE)
  }

saemix.data<-saemixData(name.data=PD1.saemix,header=TRUE,name.group=c("subject"),
      name.predictors=c("dose"),name.response=c("response"),
      name.covariates=c("gender"), units=list(x="mg",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 PD1.saemix
##     Structured data: response ~ dose | subject
##     Predictor: dose (mg)
##     covariates: gender (-)
##       reference class for covariate gender :  0
```

```
modelemax<-function(psi,id,xidep) {
# input:
#   psi : matrix of parameters (3 columns, E0, Emax, EC50)
#   id : vector of indices
#   xidep : dependent variables (same nb of rows as length of id)
# returns:
#   a vector of predictions of length equal to length of id
  dose<-xidep[,1]
  e0<-psi[id,1]
  emax<-psi[id,2]
  e50<-psi[id,3]
  f<-e0+emax*dose/(e50+dose)
  return(f)
}

# Plotting the data
plot(saemix.data,main="Simulated data PD1")
```




```
# Compare models with and without covariates with LL by Importance Sampling
model1<-saemixModel(model=modelemax,description="Emax growth model",
       psi0=matrix(c(20,300,20,0,0,0),ncol=3,byrow=TRUE,dimnames=list(NULL,
       c("E0","Emax","EC50"))), transform.par=c(1,1,1),
       covariate.model=matrix(c(0,0,0), ncol=3,byrow=TRUE),fixed.estim=c(1,1,1))
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Emax growth model  Model type:  structural
## function(psi,id,xidep) {
## # input:
## #   psi : matrix of parameters (3 columns, E0, Emax, EC50)
## #   id : vector of indices
## #   xidep : dependent variables (same nb of rows as length of id)
## # returns:
## #   a vector of predictions of length equal to length of id
##   dose<-xidep[,1]
##   e0<-psi[id,1]
##   emax<-psi[id,2]
##   e50<-psi[id,3]
##   f<-e0+emax*dose/(e50+dose)
##   return(f)
## }
##   Nb of parameters: 3
##       parameter names:  E0 Emax EC50
##       distribution:
##      Parameter Distribution Estimated
```

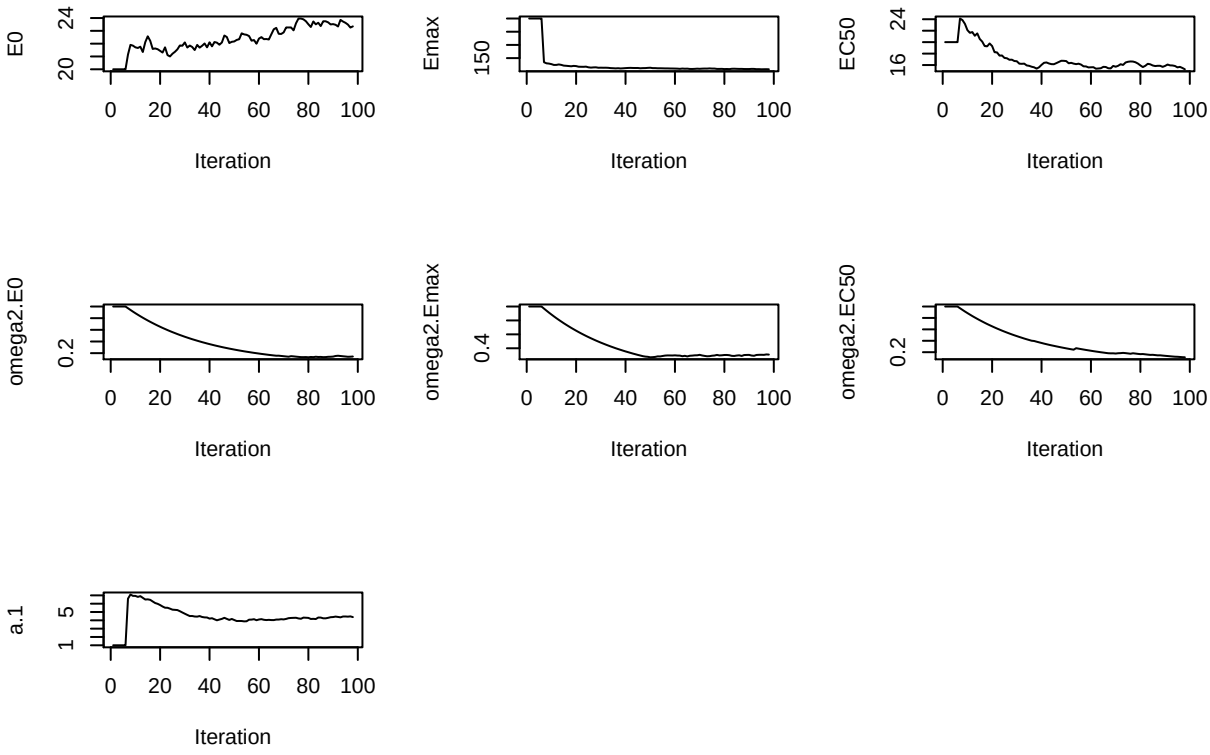
```
## [1,] E0        log-normal   Estimated
## [2,] Emax      log-normal   Estimated
## [3,] EC50      log-normal   Estimated
##   Variance-covariance matrix:
##      E0 Emax EC50
## E0    1    0    0
## Emax  0    1    0
## EC50  0    0    1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              E0 Emax EC50
## Pop.CondInit 20  300   20
## Cov.CondInit  0    0    0
```

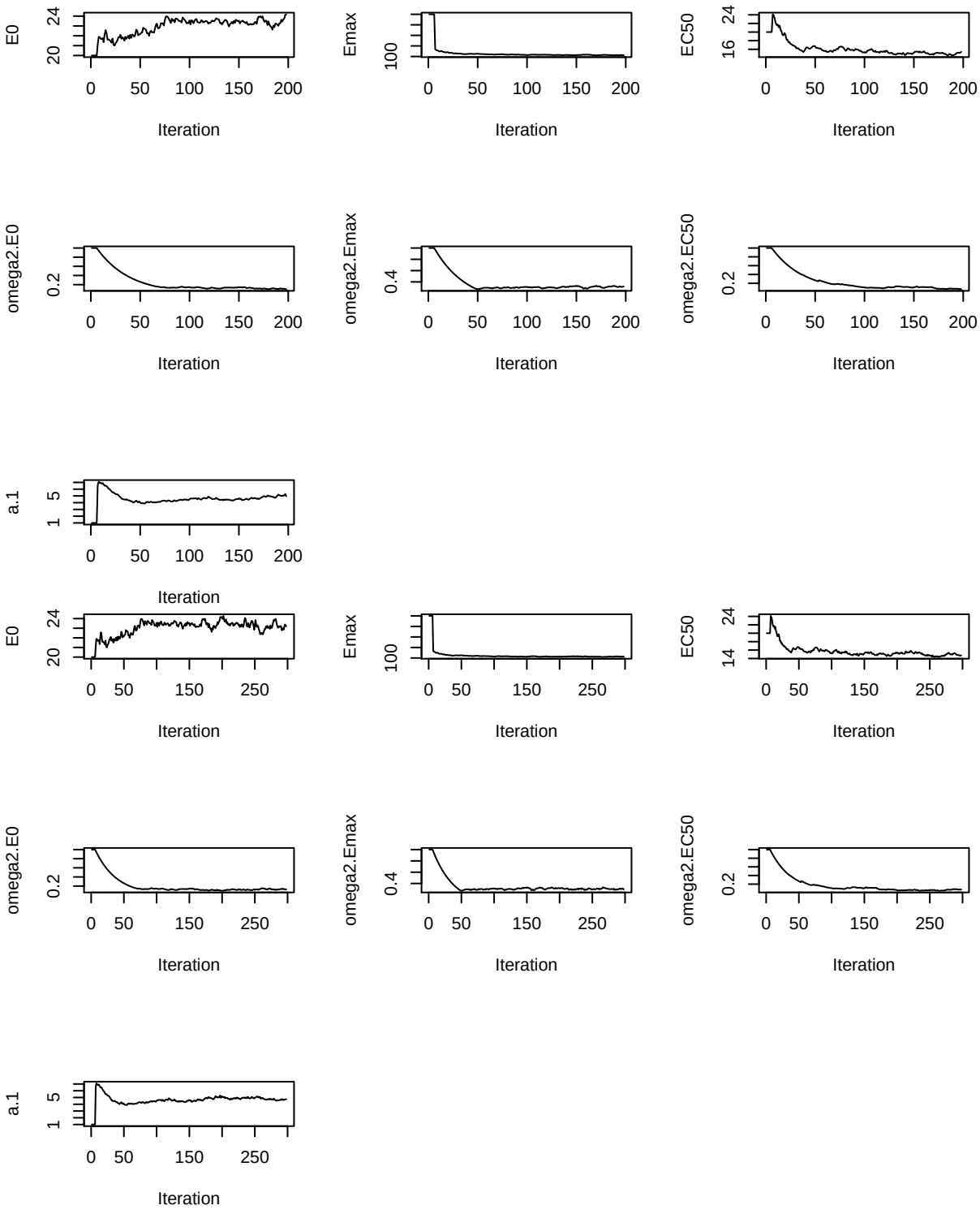
```
model2<-saemixModel(model=modelemax,description="Emax growth model",
       psi0=matrix(c(20,300,20,0,0,0),ncol=3,byrow=TRUE,dimnames=list(NULL,
       c("E0","Emax","EC50"))), transform.par=c(1,1,1),
       covariate.model=matrix(c(0,0,1), ncol=3,byrow=TRUE),fixed.estim=c(1,1,1))
```

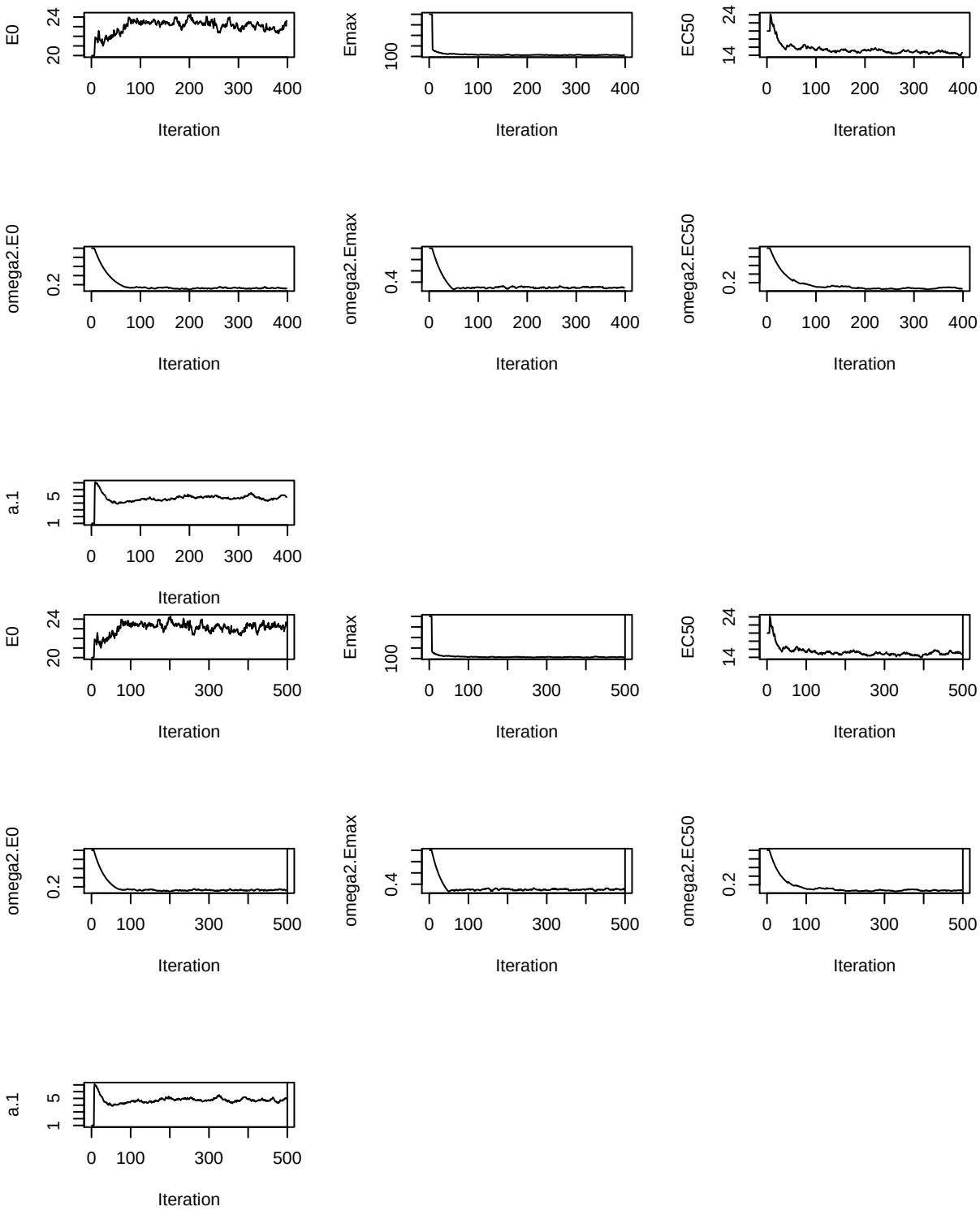
```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Emax growth model  Model type:  structural
## function(psi,id,xidep) {
## # input:
## #   psi : matrix of parameters (3 columns, E0, Emax, EC50)
## #   id : vector of indices
## #   xidep : dependent variables (same nb of rows as length of id)
## # returns:
## #   a vector of predictions of length equal to length of id
##   dose<-xidep[,1]
##   e0<-psi[id,1]
##   emax<-psi[id,2]
##   e50<-psi[id,3]
##   f<-e0+emax*dose/(e50+dose)
##   return(f)
## }
##   Nb of parameters: 3
##       parameter names:  E0 Emax EC50
##       distribution:
##      Parameter Distribution Estimated
## [1,] E0        log-normal   Estimated
## [2,] Emax      log-normal   Estimated
## [3,] EC50      log-normal   Estimated
##   Variance-covariance matrix:
##      E0 Emax EC50
## E0    1    0    0
## Emax  0    1    0
## EC50  0    0    1
##   Error model: constant , initial values: a.1=1
##   Covariate model:
##      E0 Emax EC50
```

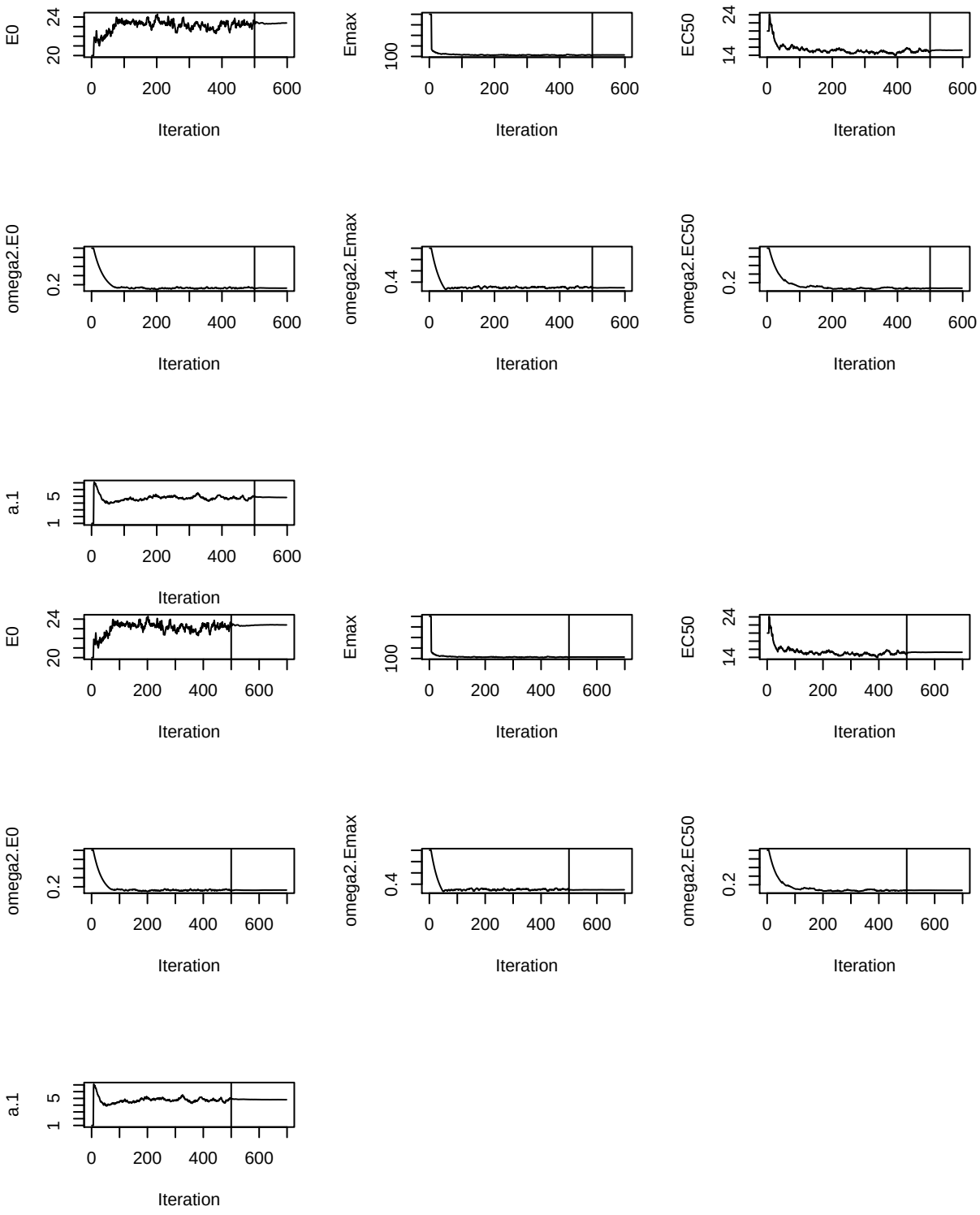
```
## [1,]  0    0    1
##     Initial values
##              E0 Emax EC50
## Pop.CondInit 20  300   20
## Cov.CondInit  0    0    0
```

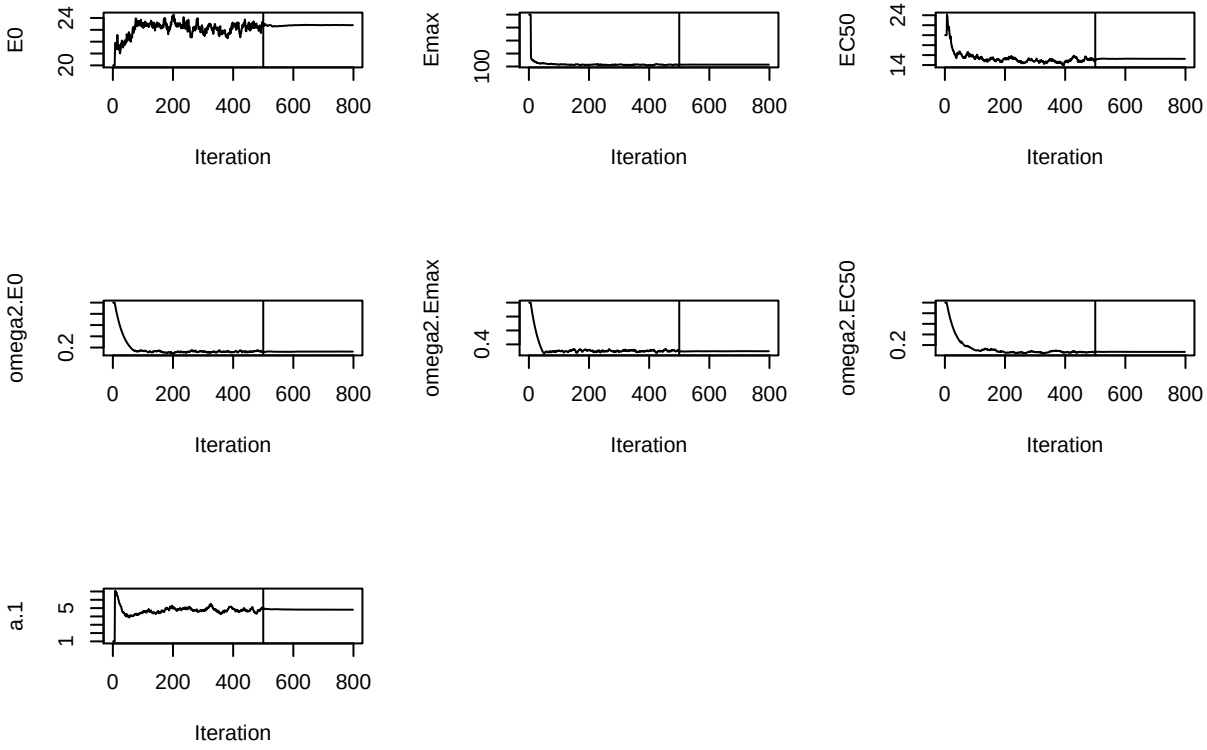
```
# SE not computed as not needed for the test
saemix.options<-list(algorithms=c(0,1,1),nb.chains=3,seed=765754,
       nbiter.saemix=c(500,300),save=FALSE,save.graphs=FALSE)

fit1<-saemix(model1,saemix.data,saemix.options)
```




E0
20
24
0
50
100
150
200
Iteration
Emax
100
0
50
100
150
200
Iteration
EC50
16
24
0
50
100
150
200
Iteration
omega2.E0
0.2
0
50
100
150
200
Iteration
omega2.Emax
0.4
0
50
100
150
200
Iteration
omega2.EC50
0.2
0
50
100
150
200
Iteration
a.1
1
5
0
50
100
150
200
Iteration
E0
20
24
0
50
150
250
Iteration
Emax
100
0
50
150
250
Iteration
EC50
14
24
0
50
150
250
Iteration
omega2.E0
0.2
0
50
150
250
Iteration
omega2.Emax
0.4
0
50
150
250
Iteration
omega2.EC50
0.2
0
50
150
250
Iteration
a.1
1
5
0
50
150
250
Iteration


E0
20
24
0
100
200
300
400
Iteration
Emax
100
0
100
200
300
400
Iteration
EC50
14
24
0
100
200
300
400
Iteration
omega2.E0
0.2
0
100
200
300
400
Iteration
omega2.Emax
0.4
0
100
200
300
400
Iteration
omega2.EC50
0.2
0
100
200
300
400
Iteration
a.1
1
5
0
100
200
300
400
Iteration
E0
20
24
0
100
300
500
Iteration
Emax
100
0
100
300
500
Iteration
EC50
14
24
0
100
300
500
Iteration
omega2.E0
0.2
0
100
300
500
Iteration
omega2.Emax
0.4
0
100
300
500
Iteration
omega2.EC50
0.2
0
100
300
500
Iteration
a.1
1
5
0
100
300
500
Iteration


E0
20
24
0
200
400
600
Iteration
Emax
100
0
200
400
600
Iteration
EC50
14
24
0
200
400
600
Iteration
omega2.E0
0.2
0
200
400
600
Iteration
omega2.Emax
0.4
0
200
400
600
Iteration
omega2.EC50
0.2
0
200
400
600
Iteration
a.1
1
5
0
200
400
600
Iteration
E0
20
24
0
200
400
600
Iteration
Emax
100
0
200
400
600
Iteration
EC50
14
24
0
200
400
600
Iteration
omega2.E0
0.2
0
200
400
600
Iteration
omega2.Emax
0.4
0
200
400
600
Iteration
omega2.EC50
0.2
0
200
400
600
Iteration
a.1
1
5
0
200
400
600
Iteration

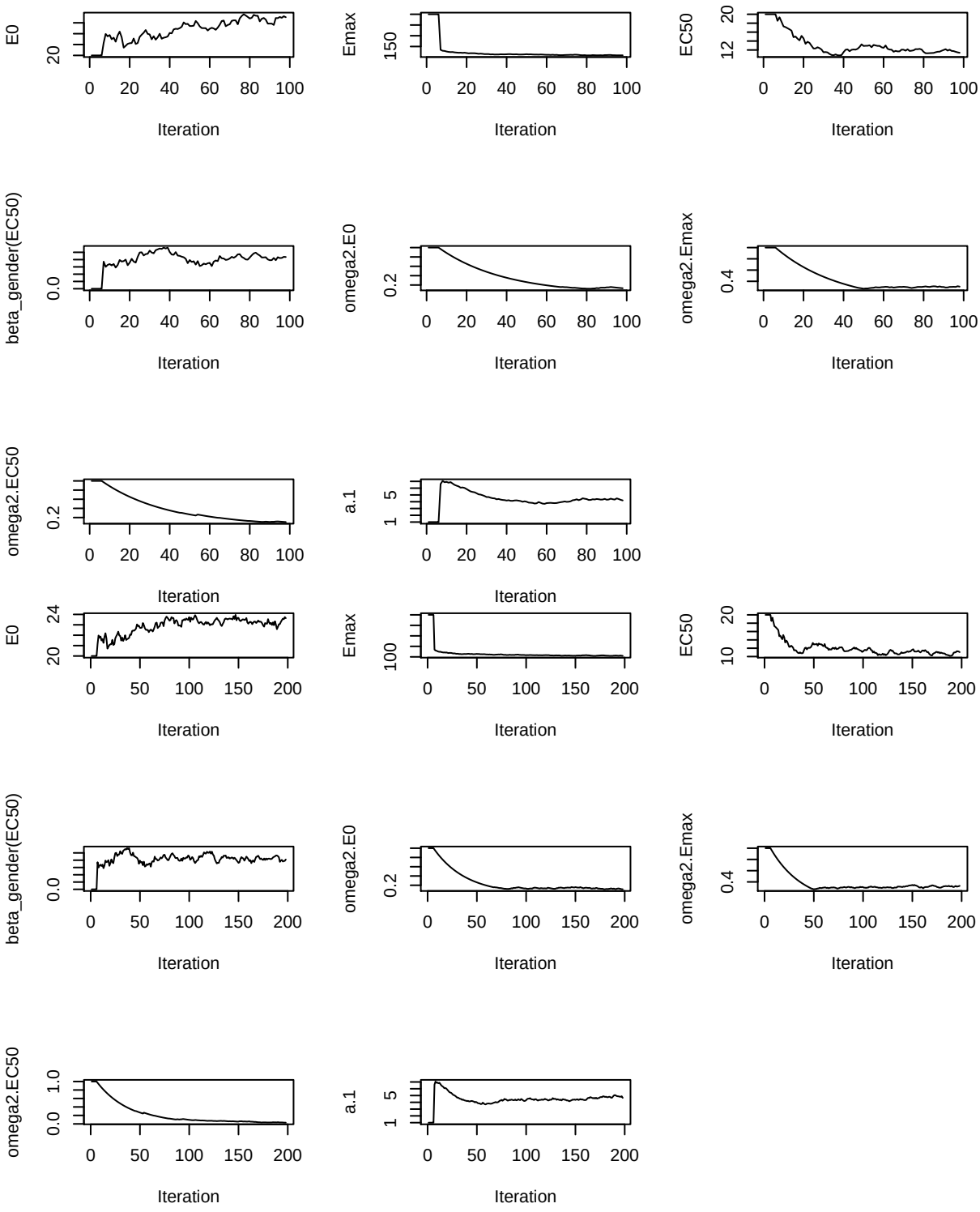


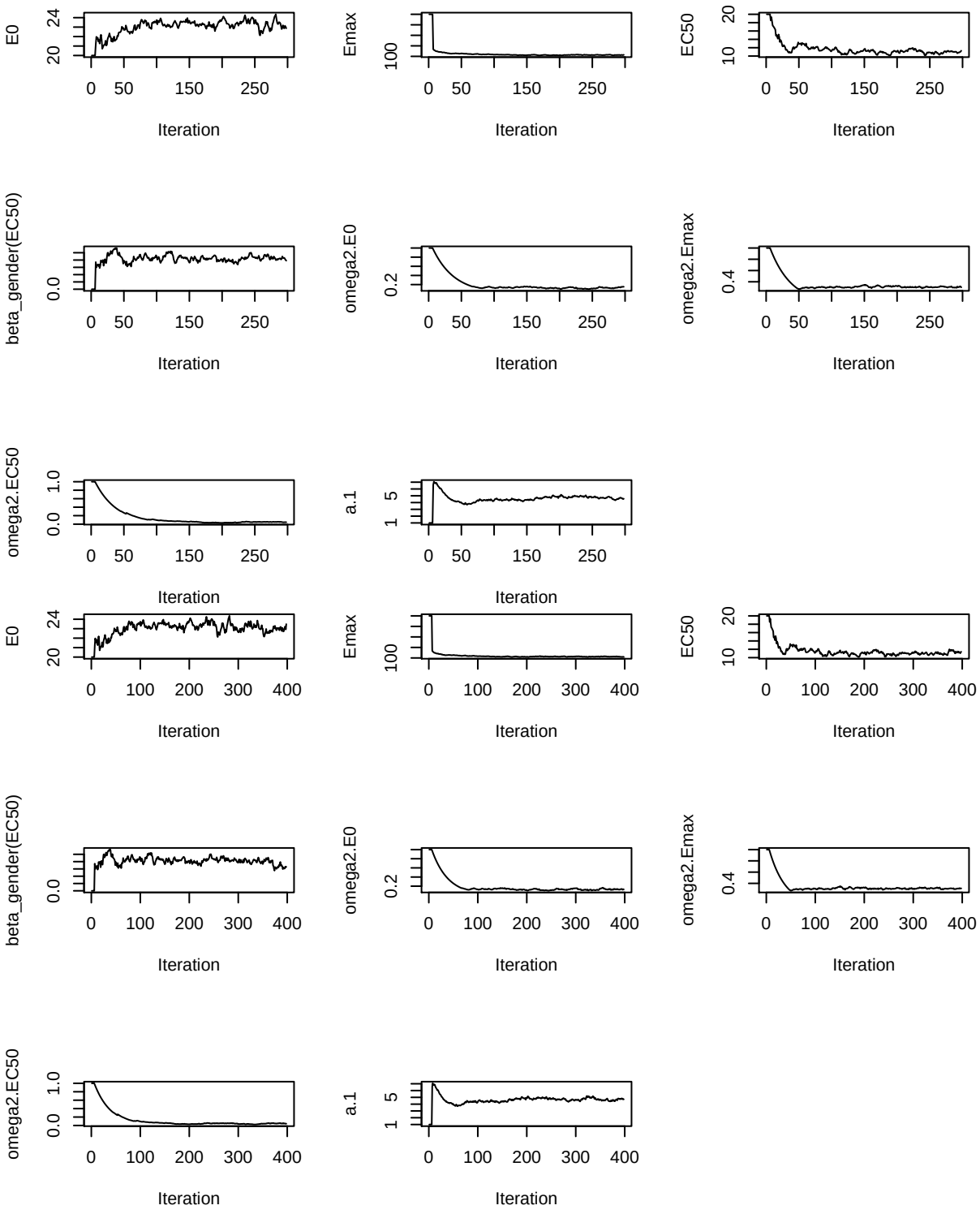

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset PD1.saemix
##     Structured data: response ~ dose | subject
##     Predictor: dose (mg)
##     covariates: gender (-)
##       reference class for covariate gender :  0
## Dataset characteristics:
##     number of subjects:     100
##     number of observations: 300
##     average/min/max nb obs: 3.00  /  3  /  3
## First 10 lines of data:
##    subject dose response gender mdv cens occ ytype
## 1        1    0  11.2870      1   0    0   1     1
## 2        1   10  63.6114      1   0    0   1     1
## 3        1   90 122.9170      1   0    0   1     1
## 4        2    0  15.0514      1   0    0   1     1
## 5        2   10  39.5296      1   0    0   1     1
## 6        2   90  60.8522      1   0    0   1     1
## 7        3    0  25.5390      1   0    0   1     1
## 8        3   10  58.0035      1   0    0   1     1
## 9        3   90  81.1173      1   0    0   1     1
## 10       4    0  22.1446      1   0    0   1     1
## ----------------------------------
## ----          Model             ----
## ----------------------------------
```

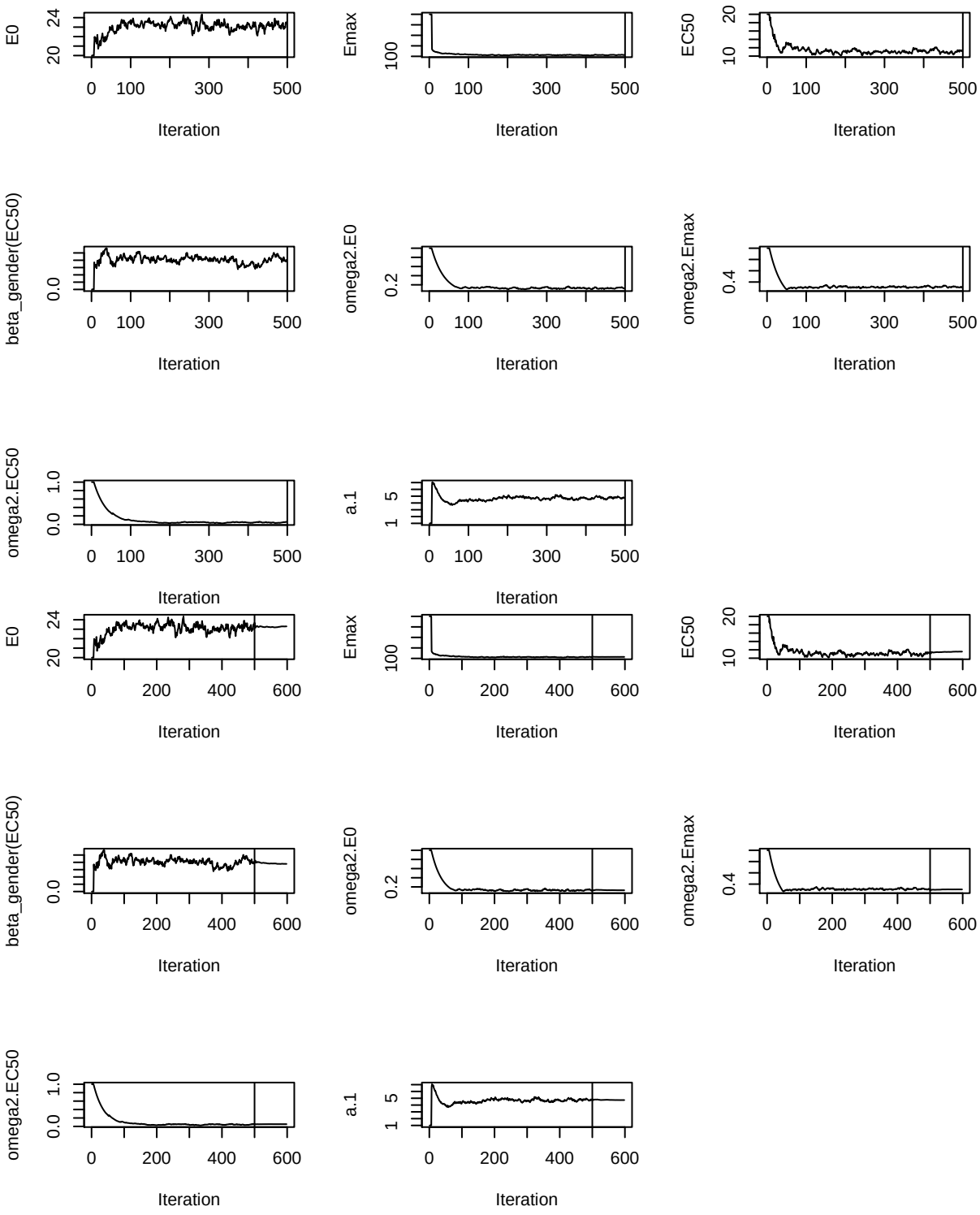
```
## Nonlinear mixed-effects model
##   Model function:  Emax growth model  Model type:  structural
## function(psi,id,xidep) {
## # input:
## #   psi : matrix of parameters (3 columns, E0, Emax, EC50)
## #   id : vector of indices
## #   xidep : dependent variables (same nb of rows as length of id)
## # returns:
## #   a vector of predictions of length equal to length of id
##   dose<-xidep[,1]
##   e0<-psi[id,1]
##   emax<-psi[id,2]
##   e50<-psi[id,3]
##   f<-e0+emax*dose/(e50+dose)
##   return(f)
## }
## <bytecode: 0x556f7def1450>
##   Nb of parameters: 3
##       parameter names:  E0 Emax EC50
##       distribution:
##      Parameter Distribution Estimated
## [1,] E0        log-normal   Estimated
## [2,] Emax      log-normal   Estimated
## [3,] EC50      log-normal   Estimated
##   Variance-covariance matrix:
##      E0 Emax EC50
## E0    1    0    0
## Emax  0    1    0
## EC50  0    0    1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              E0 Emax EC50
## Pop.CondInit 20  300   20
## ----------------------------------
## ----    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=500, K2=300
##     Number of chains:  3
##     Seed:  765754
##     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  ------------------
```

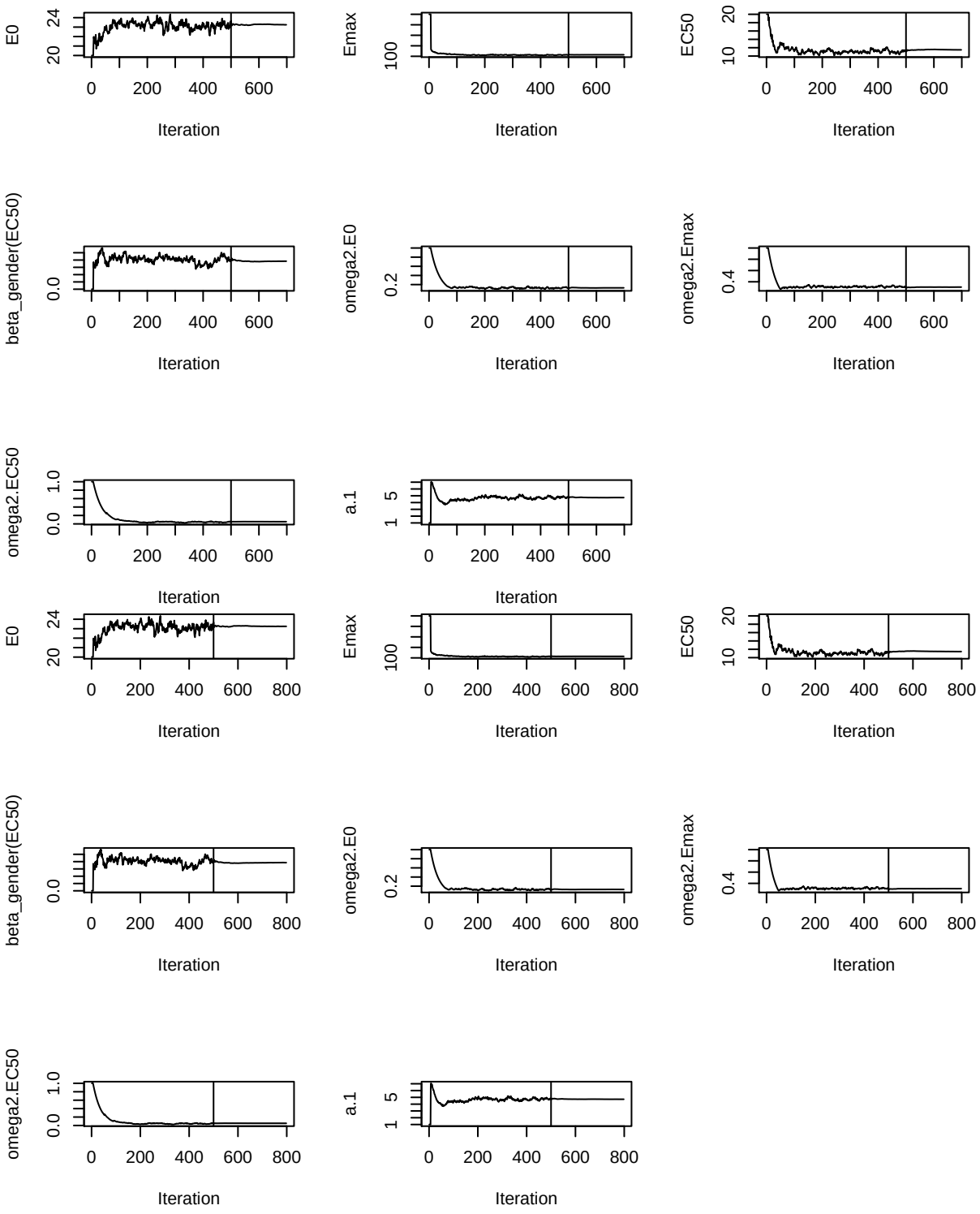
```
## ----------------------------------------------------
##      Parameter Estimate SE   CV(%)
## [1,] E0         23.4    1.08 4.6
## [2,] Emax      107.2    6.09 5.7
## [3,] EC50       15.2    0.77 5.0
## [4,] a.1         4.8    0.42 8.8
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##      Parameter   Estimate SE    CV(%)
## E0   omega2.E0   0.128    0.028 22
## Emax omega2.Emax 0.302    0.045 15
## EC50 omega2.EC50 0.071    0.027 38
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##             omega2.E0 omega2.Emax omega2.EC50
## omega2.E0   1         0           0
## omega2.Emax 0         1           0
## omega2.EC50 0         0           1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 2463.063
##       AIC = 2477.063
##       BIC = 2495.299
##
## Likelihood computed by importance sampling
##       -2LL= 2466.154
##       AIC = 2480.154
##       BIC = 2498.39
## ----------------------------------------------------
```

```
fit2<-saemix(model2,saemix.data,saemix.options)
```


E0
Iteration
Emax
Iteration
EC50
Iteration
beta_gender(EC50)
Iteration
omega2.E0
Iteration
omega2.Emax
Iteration
omega2.EC50
Iteration
a.1
Iteration
E0
Iteration
Emax
Iteration
EC50
Iteration
beta_gender(EC50)
Iteration
omega2.E0
Iteration
omega2.Emax
Iteration
omega2.EC50
Iteration
a.1
Iteration


E0
Emax
EC50
beta_gender(EC50)
omega2.E0
omega2.Emax
omega2.EC50
a.1
Iteration


E0
Emax
EC50
beta_gender(EC50)
omega2.E0
omega2.Emax
omega2.EC50
a.1
Iteration




```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset PD1.saemix
```

```
##     Structured data: response ~ dose | subject
##     Predictor: dose (mg)
##     covariates: gender (-)
##       reference class for covariate gender :  0
## Dataset characteristics:
##     number of subjects:     100
##     number of observations: 300
##     average/min/max nb obs: 3.00  /  3  /  3
## First 10 lines of data:
##    subject dose response gender mdv cens occ ytype
## 1        1    0  11.2870      1   0    0   1     1
## 2        1   10  63.6114      1   0    0   1     1
## 3        1   90 122.9170      1   0    0   1     1
## 4        2    0  15.0514      1   0    0   1     1
## 5        2   10  39.5296      1   0    0   1     1
## 6        2   90  60.8522      1   0    0   1     1
## 7        3    0  25.5390      1   0    0   1     1
## 8        3   10  58.0035      1   0    0   1     1
## 9        3   90  81.1173      1   0    0   1     1
## 10       4    0  22.1446      1   0    0   1     1
## ----------------------------------
## ----          Model            ----
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Emax growth model  Model type:  structural
## function(psi,id,xidep) {
## # input:
## #   psi : matrix of parameters (3 columns, E0, Emax, EC50)
## #   id : vector of indices
## #   xidep : dependent variables (same nb of rows as length of id)
## # returns:
## #   a vector of predictions of length equal to length of id
##   dose<-xidep[,1]
##   e0<-psi[id,1]
##   emax<-psi[id,2]
##   e50<-psi[id,3]
##   f<-e0+emax*dose/(e50+dose)
##   return(f)
## }
## <bytecode: 0x556f7def1450>
##   Nb of parameters: 3
##       parameter names:  E0 Emax EC50
##       distribution:
##      Parameter Distribution Estimated
## [1,] E0        log-normal   Estimated
## [2,] Emax      log-normal   Estimated
## [3,] EC50      log-normal   Estimated
##   Variance-covariance matrix:
##      E0 Emax EC50
## E0    1    0    0
## Emax  0    1    0
## EC50  0    0    1
##   Error model: constant , initial values: a.1=1
##   Covariate model:
```

```
##        [,1] [,2] [,3]
## gender    0    0    1
##     Initial values
##              E0 Emax EC50
## Pop.CondInit 20  300   20
## Cov.CondInit  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=500, K2=300
##     Number of chains:  3
##     Seed:  765754
##     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,] E0                 23.24   1.072  4.6  -
## [2,] Emax              107.20   6.120  5.7  -
## [3,] EC50               11.45   0.980  8.6  -
## [4,] beta_gender(EC50)   0.39   0.099 25.6  4.7e-05
## [5,] a.1                 4.72   0.407  8.6  -
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##      Parameter   Estimate SE    CV(%)
## E0   omega2.E0   0.129    0.028 22
## Emax omega2.Emax 0.307    0.045 15
## EC50 omega2.EC50 0.052    0.022 43
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##             omega2.E0 omega2.Emax omega2.EC50
## omega2.E0   1         0           0
## omega2.Emax 0         1           0
## omega2.EC50 0         0           1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 2448.635
##       AIC = 2464.635
##       BIC = 2485.477
```

```
##
## Likelihood computed by importance sampling
##       -2LL= 2452.279
##       AIC = 2468.279
##       BIC = 2489.121
## -----------------------------------------------------
```

```
wstat<-(-2)*(fit1["results"]["ll.is"]-fit2["results"]["ll.is"])

cat("LRT test for covariate effect on EC50: p-value=",1-pchisq(wstat,1),"\n")
```

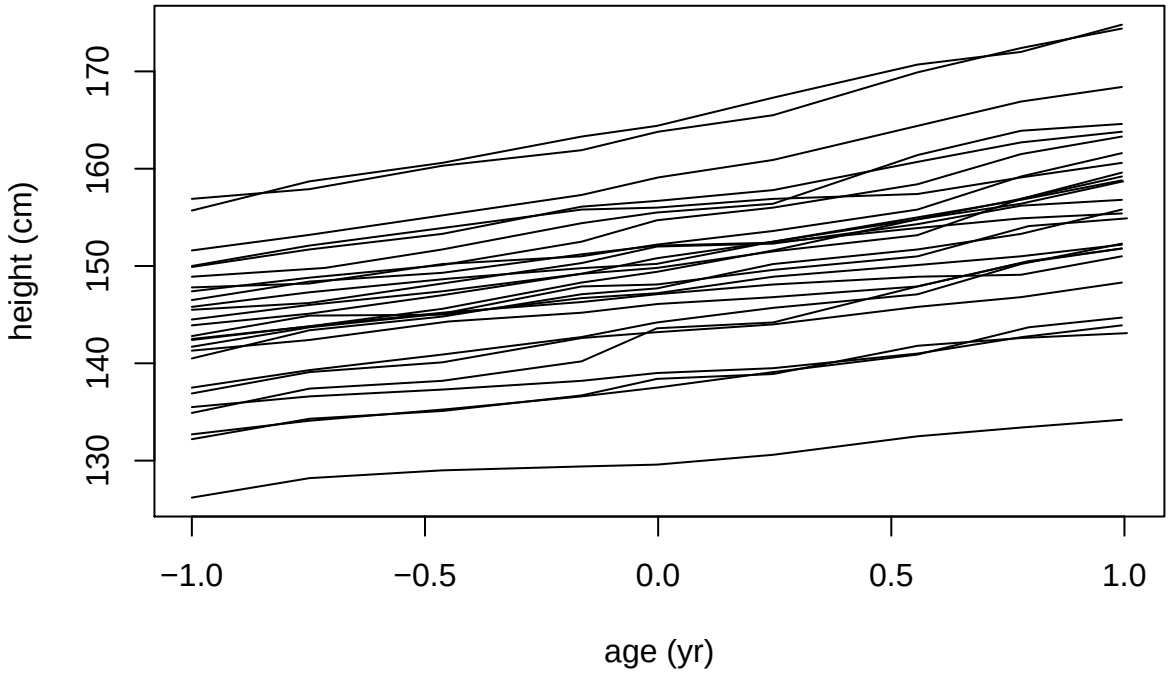
```
## LRT test for covariate effect on EC50: p-value= 0.0001954234
```

### Oxford boys

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

saemix.data<-saemixData(name.data=oxboys.saemix,header=TRUE,
      name.group=c("Subject"),name.predictors=c("age"),name.response=c("height"),
      units=list(x="yr",y="cm"))
```

```
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset oxboys.saemix
##     Structured data: height ~ age | Subject
##     Predictor: age (yr)
```

```
# plot the data
plot(saemix.data)
```



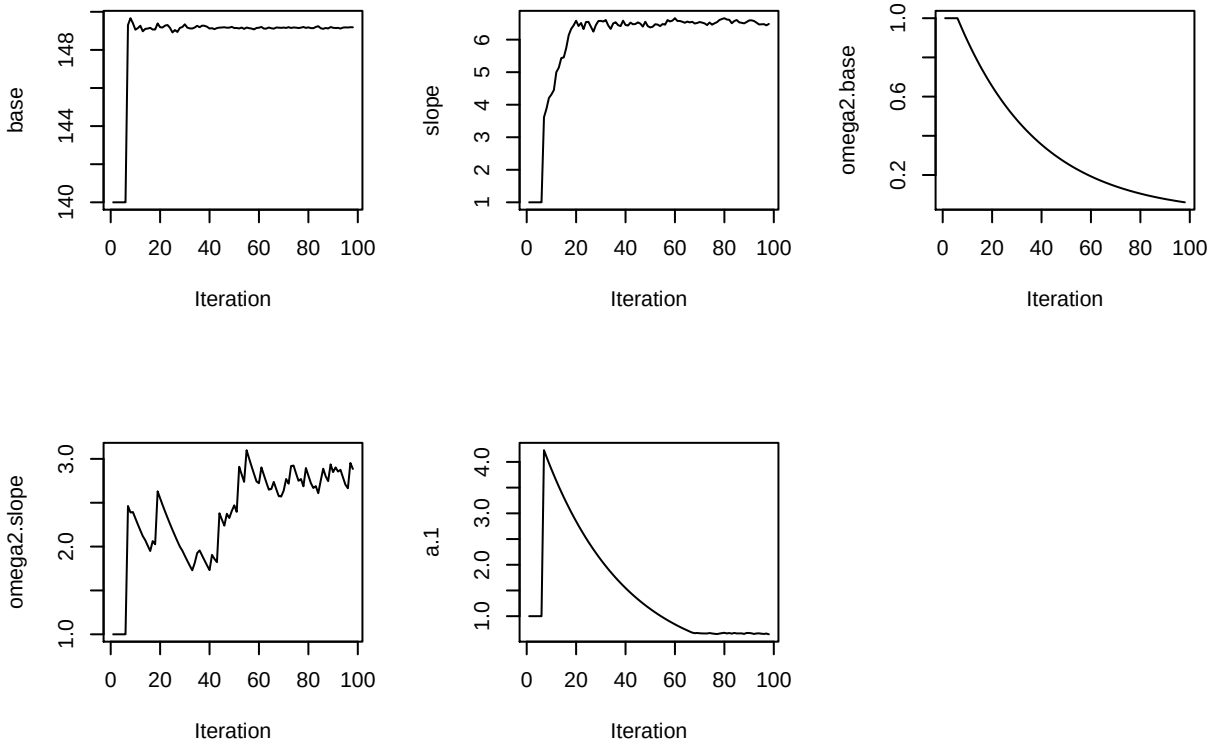

```
growth.linear<-function(psi,id,xidep) {
  x<-xidep[,1]
  base<-psi[id,1]
  slope<-psi[id,2]
  f<-base+slope*x
  return(f)
}
saemix.model<-saemixModel(model=growth.linear,description="Linear model",
      psi0=matrix(c(140,1),ncol=2,byrow=TRUE,dimnames=list(NULL,c("base","slope"))),
      transform.par=c(1,0),covariance.model=matrix(c(1,1,1,1),ncol=2,byrow=TRUE),
      error.model="constant")
```

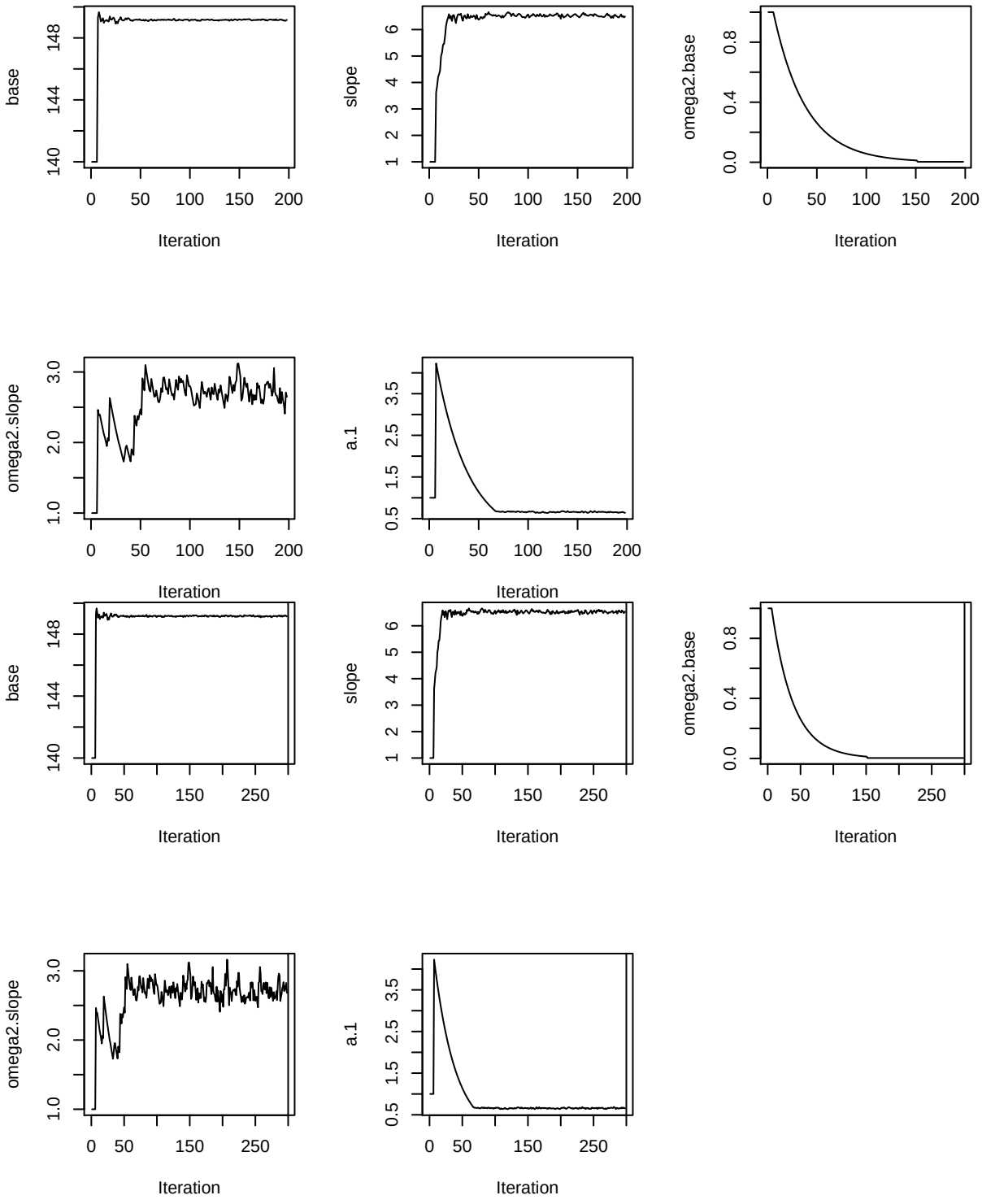
```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Linear model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   base<-psi[id,1]
##   slope<-psi[id,2]
##   f<-base+slope*x
##   return(f)
## }
##   Nb of parameters: 2
##       parameter names:  base slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] base      log-normal   Estimated
## [2,] slope     normal       Estimated
```

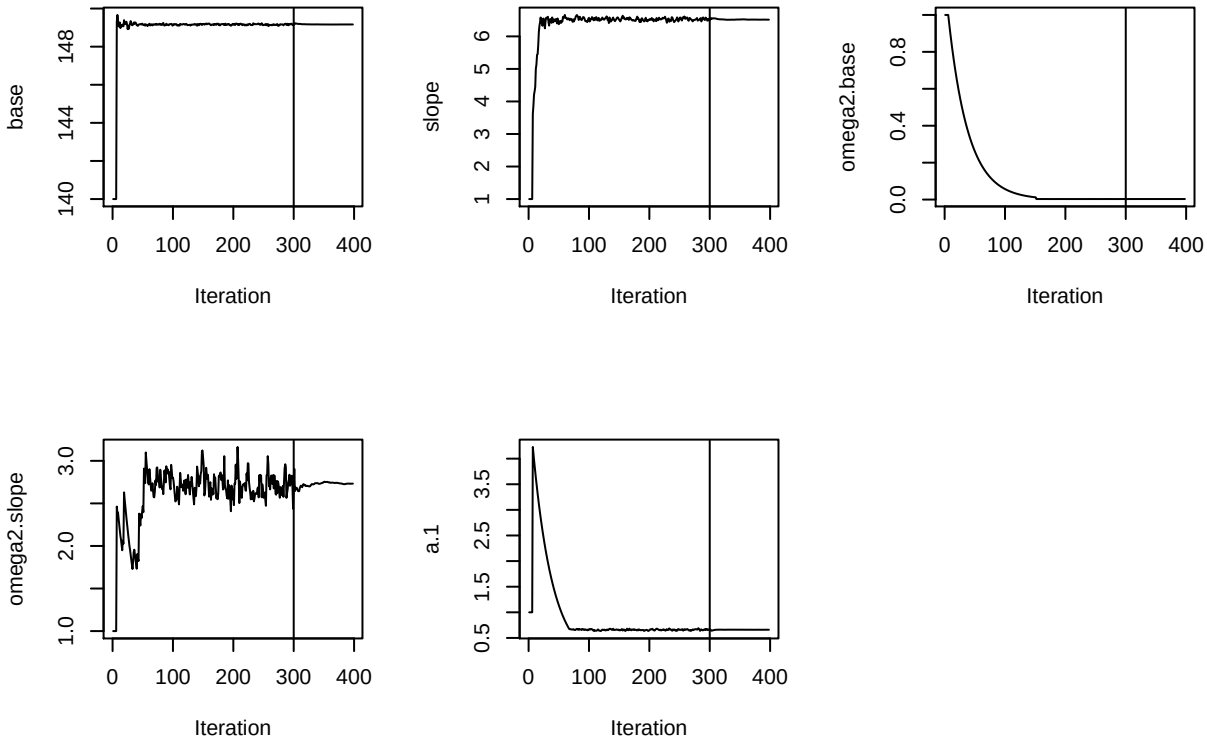
```
##   Variance-covariance matrix:
##       base slope
## base     1     1
## slope    1     1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              base slope
## Pop.CondInit  140     1
```

```
saemix.options<-list(algorithms=c(1,1,1),nb.chains=1,seed=201004,
      save=FALSE,save.graphs=FALSE)
saemix.fit<-saemix(saemix.model,saemix.data,saemix.options)
```

```
## The number of subjects is small, increasing the number of chains to 2 to improve convergence
```




base
slope
omega2.base
omega2.slope
a.1
Iteration




```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset oxboys.saemix
##     Structured data: height ~ age | Subject
##     Predictor: age (yr)
## Dataset characteristics:
##     number of subjects:     26
##     number of observations: 234
##     average/min/max nb obs: 9.00  /  9  /  9
## First 10 lines of data:
##    Subject     age height mdv cens occ ytype
## 1        1 -1.0000  140.5   0    0   1     1
## 2        1 -0.7479  143.4   0    0   1     1
## 3        1 -0.4630  144.8   0    0   1     1
## 4        1 -0.1643  147.1   0    0   1     1
## 5        1 -0.0027  147.7   0    0   1     1
## 6        1  0.2466  150.2   0    0   1     1
## 7        1  0.5562  151.7   0    0   1     1
## 8        1  0.7781  153.3   0    0   1     1
## 9        1  0.9945  155.8   0    0   1     1
## 10       2 -1.0000  136.9   0    0   1     1
## ----------------------------------
## ----          Model             ----
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Linear model  Model type:  structural
```

```
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   base<-psi[id,1]
##   slope<-psi[id,2]
##   f<-base+slope*x
##   return(f)
## }
## <bytecode: 0x556f7b6877c8>
##   Nb of parameters: 2
##       parameter names:  base slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] base      log-normal   Estimated
## [2,] slope     normal       Estimated
##   Variance-covariance matrix:
##       base slope
## base     1     1
## slope    1     1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              base slope
## Pop.CondInit  140     1
## ----------------------------------
## ----    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:  2
##     Seed:  201004
##     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,] base      149.16   1.563 1.0
## [2,] slope       6.51   0.331 5.1
## [3,] a.1         0.66   0.035 5.2
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##       Parameter      Estimate SE      CV(%)
## base  omega2.base    0.0029   0.00079 28
## slope omega2.slope   2.7361   0.79109 29
```

```
## covar cov.base.slope 0.0564   0.02087 37
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##              omega2.base omega2.slope
## omega2.base  1.00        0.64
## omega2.slope 0.64        1.00
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 726.5422
##       AIC = 738.5422
##       BIC = 746.0908
##
## Likelihood computed by importance sampling
##       -2LL= 726.5619
##       AIC = 738.5619
##       BIC = 746.1105
## ----------------------------------------------------
```

**Cow**

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

saemix.data<-saemixData(name.data=cow.saemix,header=TRUE,name.group=c("cow"),
      name.predictors=c("time"),name.response=c("weight"),
      name.covariates=c("birthyear","twin","birthrank"),
      units=list(x="days",y="kg",covariates=c("yr","-","-")))
```

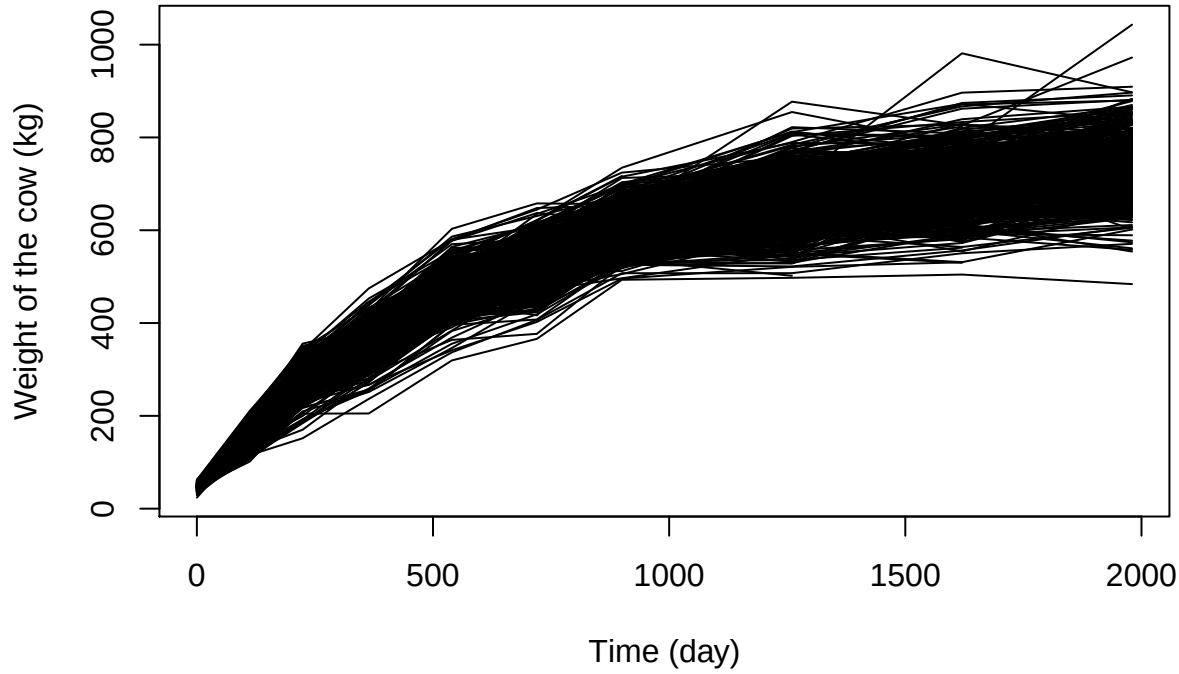
```
## [1] "birthyear" "twin"      "birthrank"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset cow.saemix
##     Structured data: weight ~ time | cow
##     Predictor: time (days)
##     covariates: birthyear (yr), twin (-), birthrank (-)
##       reference class for covariate twin :  1
```

```
growthcow<-function(psi,id,xidep) {
  x<-xidep[,1]
  a<-psi[id,1]
  b<-psi[id,2]
  k<-psi[id,3]
  f<-a*(1-b*exp(-k*x))
  return(f)
}
```

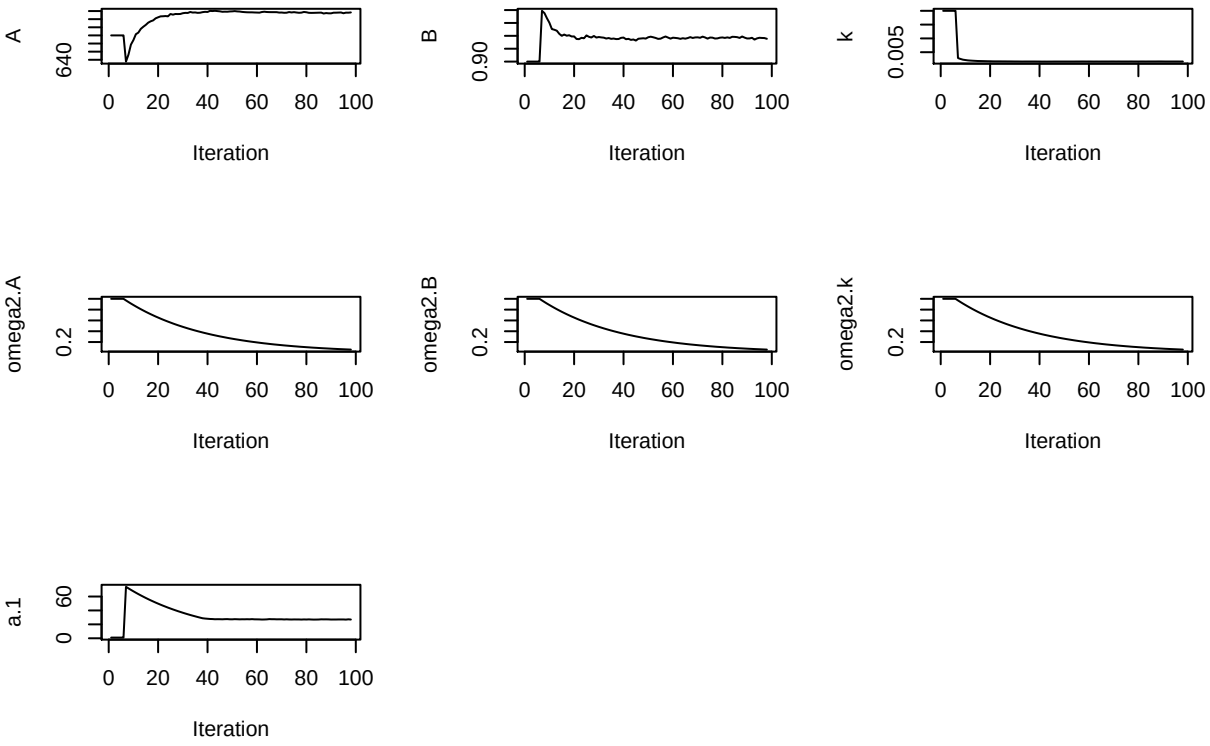
```
saemix.model<-saemixModel(model=growthcow,
      description="Exponential growth model",
      psi0=matrix(c(700,0.9,0.02,0,0,0),ncol=3,byrow=TRUE,
        dimnames=list(NULL,c("A","B","k"))),transform.par=c(1,1,1),fixed.estim=c(1,1,1),
      covariate.model=matrix(c(0,0,0),ncol=3,byrow=TRUE),
      covariance.model=matrix(c(1,0,0,0,1,0,0,0,1),ncol=3,byrow=TRUE),
      omega.init=matrix(c(1,0,0,0,1,0,0,0,1),ncol=3,byrow=TRUE),error.model="constant")
```

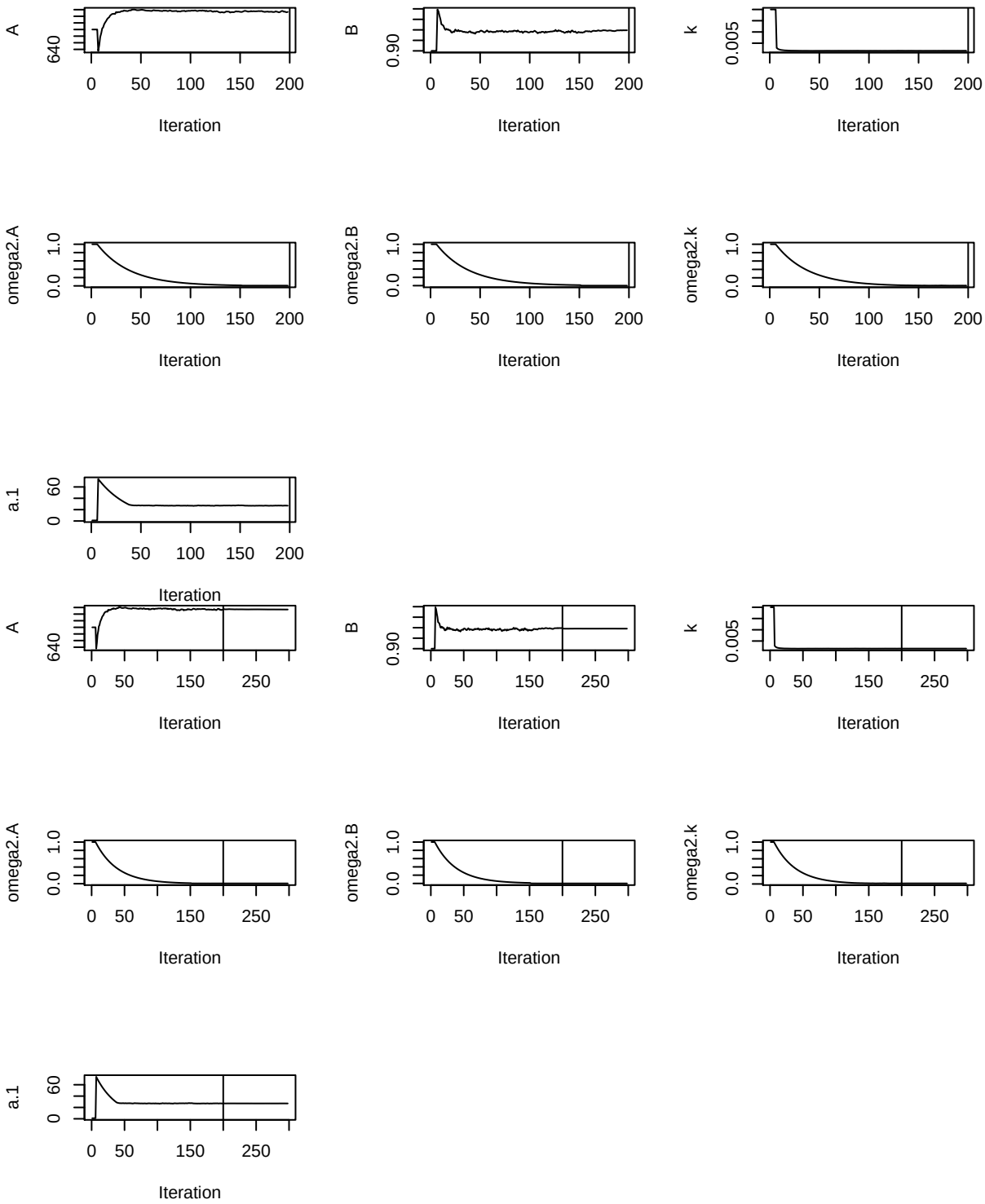
```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Exponential growth model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   a<-psi[id,1]
##   b<-psi[id,2]
##   k<-psi[id,3]
##   f<-a*(1-b*exp(-k*x))
##   return(f)
## }
##   Nb of parameters: 3
##       parameter names:  A B k
##       distribution:
##      Parameter Distribution Estimated
## [1,] A         log-normal   Estimated
## [2,] B         log-normal   Estimated
## [3,] k         log-normal   Estimated
##   Variance-covariance matrix:
##   A B k
## A 1 0 0
## B 0 1 0
## k 0 0 1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##                A   B    k
## Pop.CondInit 700 0.9 0.02
## Cov.CondInit   0 0.0 0.00
```

```
saemix.options<-list(algorithms=c(1,1,1),nb.chains=1,nbiter.saemix=c(200,100),
             seed=4526,save=FALSE,save.graphs=FALSE)

# Plotting the data
plot(saemix.data,xlab="Time (day)",ylab="Weight of the cow (kg)")
```




```
saemix.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 cow.saemix
```

```
##     Structured data: weight ~ time | cow
##     Predictor: time (days)
##     covariates: birthyear (yr), twin (-), birthrank (-)
##       reference class for covariate twin :  1
## Dataset characteristics:
##     number of subjects:     560
##     number of observations: 5455
##     average/min/max nb obs: 9.74  /  7  /  10
## First 10 lines of data:
##        cow time weight birthyear twin birthrank mdv cens occ ytype
## 1  1988005    0   44.0      1988    1         3   0    0   1     1
## 2  1988005  112  173.4      1988    1         3   0    0   1     1
## 3  1988005  224  292.8      1988    1         3   0    0   1     1
## 4  1988005  364  364.6      1988    1         3   0    0   1     1
## 5  1988005  540  490.4      1988    1         3   0    0   1     1
## 6  1988005  720  522.0      1988    1         3   0    0   1     1
## 7  1988005  900  601.1      1988    1         3   0    0   1     1
## 8  1988005 1260  698.1      1988    1         3   0    0   1     1
## 9  1988005 1620  657.7      1988    1         3   0    0   1     1
## 10 1988005 1980  776.7      1988    1         3   0    0   1     1
## ----------------------------------
## ----          Model            ----
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Exponential growth model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   a<-psi[id,1]
##   b<-psi[id,2]
##   k<-psi[id,3]
##   f<-a*(1-b*exp(-k*x))
##   return(f)
## }
## <bytecode: 0x556f7ca400f8>
##   Nb of parameters: 3
##       parameter names:  A B k
##       distribution:
##      Parameter Distribution Estimated
## [1,] A         log-normal   Estimated
## [2,] B         log-normal   Estimated
## [3,] k         log-normal   Estimated
##   Variance-covariance matrix:
##   A B k
## A 1 0 0
## B 0 1 0
## k 0 0 1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##                A   B    k
## Pop.CondInit 700 0.9 0.02
## ----------------------------------
## ----    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=200, K2=100
##     Number of chains:  1
##     Seed:  4526
##     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,] A         7.5e+02  2.9e+00 0.38
## [2,] B         9.4e-01  1.2e-03 0.13
## [3,] k         1.6e-03  1.2e-05 0.72
## [4,] a.1       2.7e+01  3.0e-01 1.11
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##   Parameter Estimate SE      CV(%)
## A omega2.A  6.4e-03  4.4e-04   7.0
## B omega2.B  4.7e-05  5.2e-05 110.6
## k omega2.k  1.4e-02  1.4e-03   9.8
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##          omega2.A omega2.B omega2.k
## omega2.A 1        0        0
## omega2.B 0        1        0
## omega2.k 0        0        1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 53706.64
##       AIC = 53720.64
##       BIC = 53750.93
##
## Likelihood computed by importance sampling
##       -2LL= 53731.51
##       AIC = 53745.51
##       BIC = 53775.8
## ----------------------------------------------------
```

### Wheat yield

```
if(testMode)
  data(yield.saemix) else
    yield.saemix<-read.table(file.path(datDir, "yield.saemix.tab"), header=TRUE)
saemix.data<-saemixData(name.data=yield.saemix,header=TRUE,name.group=c("site"),
      name.predictors=c("dose"),name.response=c("yield"),
      name.covariates=c("soil.nitrogen"),units=list(x="kg/ha",y="t/ha",covariates=c("kg/ha")))
```

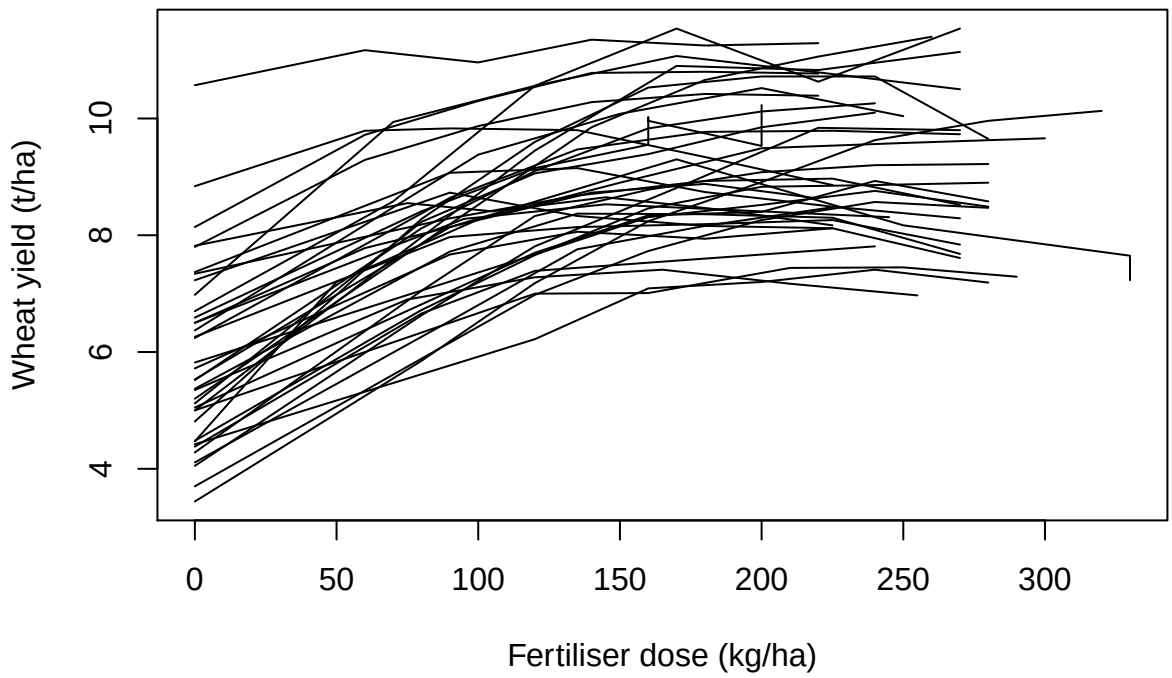
```
## [1] "soil.nitrogen"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset yield.saemix
##     Structured data: yield ~ dose | site
##     Predictor: dose (kg/ha)
##     covariates: soil.nitrogen (kg/ha)
```

```
#  Model: linear + plateau
yield.LP<-function(psi,id,xidep) {
  x<-xidep[,1]
  ymax<-psi[id,1]
  xmax<-psi[id,2]
  slope<-psi[id,3]
  f<-ymax+slope*(x-xmax)
  #'  cat(length(f),"  ",length(ymax),"\n")
  f[x>xmax]<-ymax[x>xmax]
  return(f)
}
saemix.model<-saemixModel(model=yield.LP,description="Linear plus plateau model",
        psi0=matrix(c(8,100,0.2,0,0,0),ncol=3,byrow=TRUE,dimnames=list(NULL,
            c("Ymax","Xmax","slope"))),covariate.model=matrix(c(0,0,0),ncol=3,byrow=TRUE),
        transform.par=c(0,0,0),covariance.model=matrix(c(1,0,0,0,1,0,0,0,1),ncol=3,
            byrow=TRUE),error.model="constant")
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Linear plus plateau model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   ymax<-psi[id,1]
##   xmax<-psi[id,2]
##   slope<-psi[id,3]
##   f<-ymax+slope*(x-xmax)
##   #'  cat(length(f),"  ",length(ymax),"\n")
##   f[x>xmax]<-ymax[x>xmax]
##   return(f)
## }
```

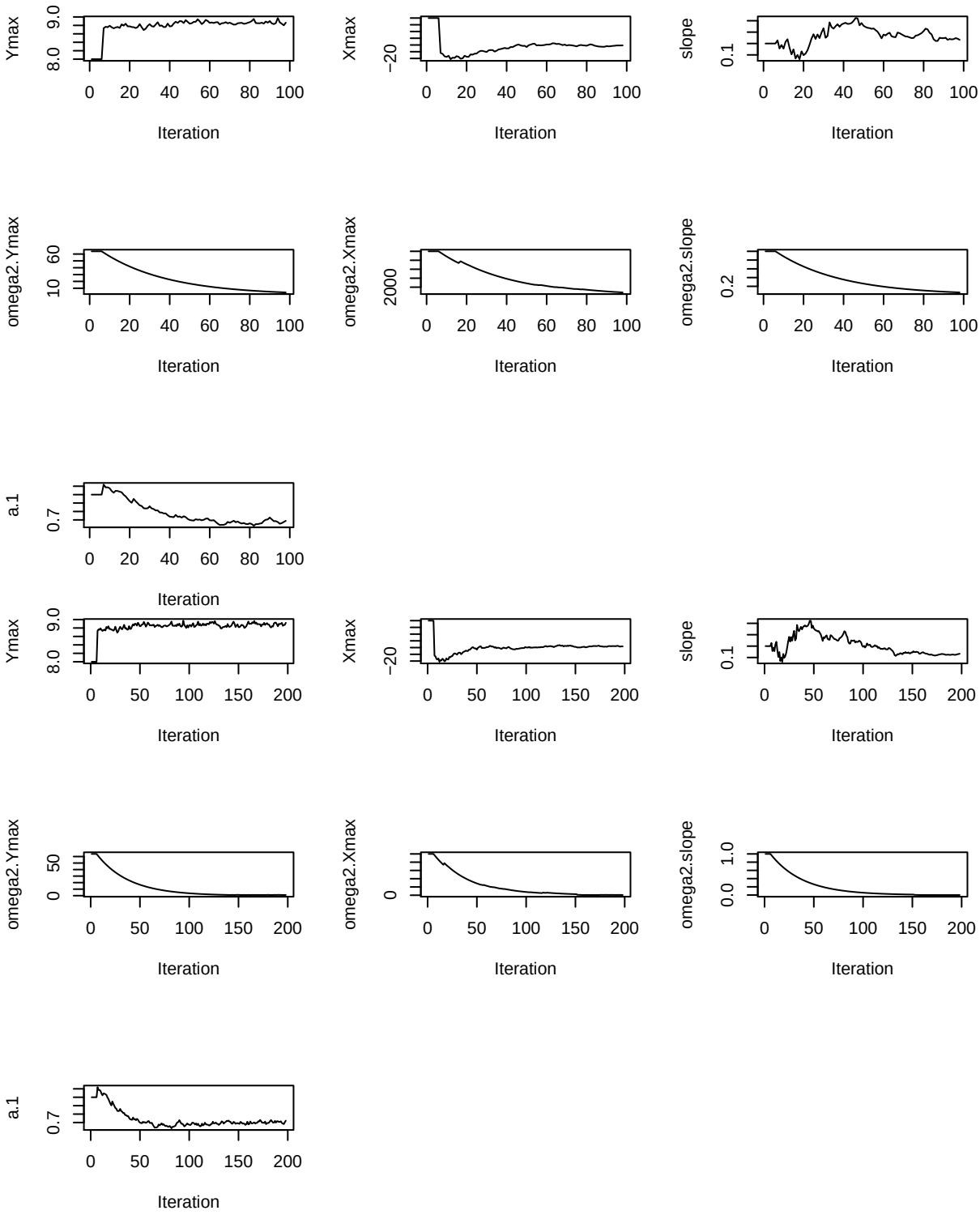
```
##   Nb of parameters: 3
##       parameter names:  Ymax Xmax slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] Ymax      normal       Estimated
## [2,] Xmax      normal       Estimated
## [3,] slope     normal       Estimated
##   Variance-covariance matrix:
##       Ymax Xmax slope
## Ymax     1    0     0
## Xmax     0    1     0
## slope    0    0     1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              Ymax Xmax slope
## Pop.CondInit    8  100   0.2
## Cov.CondInit    0    0   0.0
```

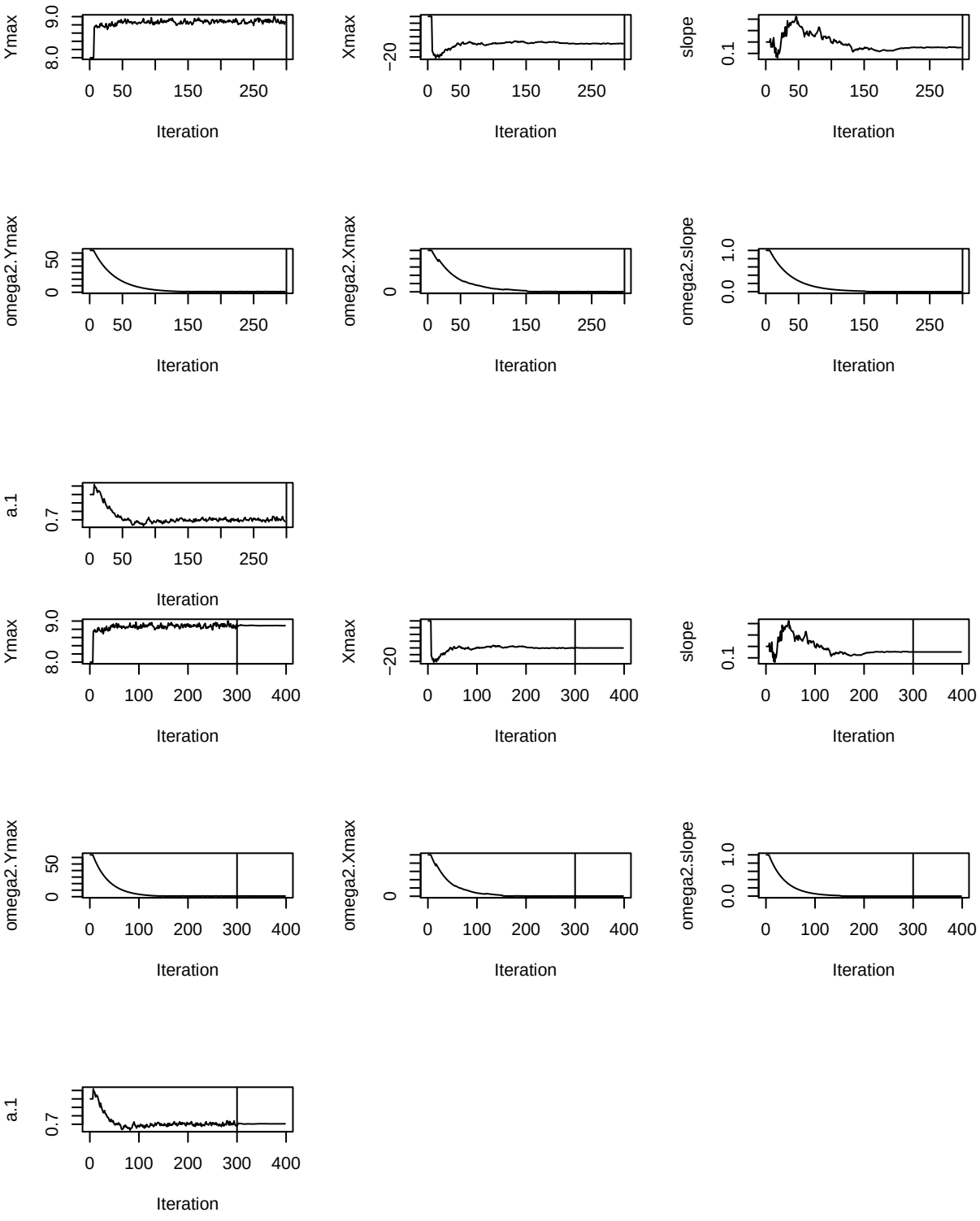
```
saemix.options<-list(algorithms=c(1,1,1),nb.chains=1,seed=666,
       save=FALSE,save.graphs=FALSE)

# Plotting the data
plot(saemix.data,xlab="Fertiliser dose (kg/ha)", ylab="Wheat yield (t/ha)")
```




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

```
## The number of subjects is small, increasing the number of chains to 2 to improve convergence
```


Ymax
8.0
9.0
0
20
40
60
80
100
Iteration
Xmax
−20
0
20
40
60
80
100
Iteration
slope
0.1
0
20
40
60
80
100
Iteration
omega2.Ymax
10
60
0
20
40
60
80
100
Iteration
omega2.Xmax
2000
0
20
40
60
80
100
Iteration
omega2.slope
0.2
0
20
40
60
80
100
Iteration
a.1
0.7
0
20
40
60
80
100
Iteration
Ymax
8.0
9.0
0
50
100
150
200
Iteration
Xmax
−20
0
50
100
150
200
Iteration
slope
0.1
0
50
100
150
200
Iteration
omega2.Ymax
0
50
0
50
100
150
200
Iteration
omega2.Xmax
0
0
50
100
150
200
Iteration
omega2.slope
0.0
1.0
0
50
100
150
200
Iteration
a.1
0.7
0
50
100
150
200
Iteration




```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset yield.saemix
```

```
##     Structured data: yield ~ dose | site
##     Predictor: dose (kg/ha)
##     covariates: soil.nitrogen (kg/ha)
## Dataset characteristics:
##     number of subjects:     37
##     number of observations: 224
##     average/min/max nb obs: 6.05  /  5  /  8
## First 10 lines of data:
##    site dose yield soil.nitrogen mdv cens occ ytype
## 1  1901    0  6.70            70   0    0   1     1
## 2  1901   70  8.58            70   0    0   1     1
## 3  1901  120 10.56            70   0    0   1     1
## 4  1901  170 11.54            70   0    0   1     1
## 5  1901  220 10.63            70   0    0   1     1
## 6  1901  270 11.54            70   0    0   1     1
## 7  1902    0  6.98            80   0    0   1     1
## 8  1902   70  9.94            80   0    0   1     1
## 9  1902  120 10.56            80   0    0   1     1
## 10 1902  170 11.07            80   0    0   1     1
## ------------------------------------
## ----          Model            ----
## ------------------------------------
## Nonlinear mixed-effects model
##   Model function:  Linear plus plateau model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   ymax<-psi[id,1]
##   xmax<-psi[id,2]
##   slope<-psi[id,3]
##   f<-ymax+slope*(x-xmax)
##   #'  cat(length(f),"  ",length(ymax),"\n")
##   f[x>xmax]<-ymax[x>xmax]
##   return(f)
## }
## <bytecode: 0x556f7655ed68>
##   Nb of parameters: 3
##       parameter names:  Ymax Xmax slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] Ymax      normal       Estimated
## [2,] Xmax      normal       Estimated
## [3,] slope     normal       Estimated
##   Variance-covariance matrix:
##       Ymax Xmax slope
## Ymax     1    0     0
## Xmax     0    1     0
## slope    0    0     1
##   Error model: constant , initial values: a.1=1
##     No covariate in the model.
##     Initial values
##              Ymax Xmax slope
## Pop.CondInit    8  100   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:  2
##     Seed:  666
##     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,] Ymax       8.89    0.176  2.0
## [2,] Xmax      19.75    5.089 25.8
## [3,] slope      0.15    0.037 24.7
## [4,] a.1        0.71    0.041  5.8
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##       Parameter    Estimate SE      CV(%)
## Ymax  omega2.Ymax  1.0e+00   0.2659    25
## Xmax  omega2.Xmax  5.3e+01  38.0311    72
## slope omega2.slope 9.2e-06   0.0018 19486
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##              omega2.Ymax omega2.Xmax omega2.slope
## omega2.Ymax  1           0           0
## omega2.Xmax  0           1           0
## omega2.slope 0           0           1
## ----------------------------------------------------
## --------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 616.5701
##       AIC = 630.5701
##       BIC = 641.8466
##
## Likelihood computed by importance sampling
##       -2LL= 616.5048
##       AIC = 630.5048
##       BIC = 641.7812
## ----------------------------------------------------
```

```
# Comparing the likelihoods obtained by linearisation and importance sampling
# to the likelihood obtained by Gaussian Quadrature
```

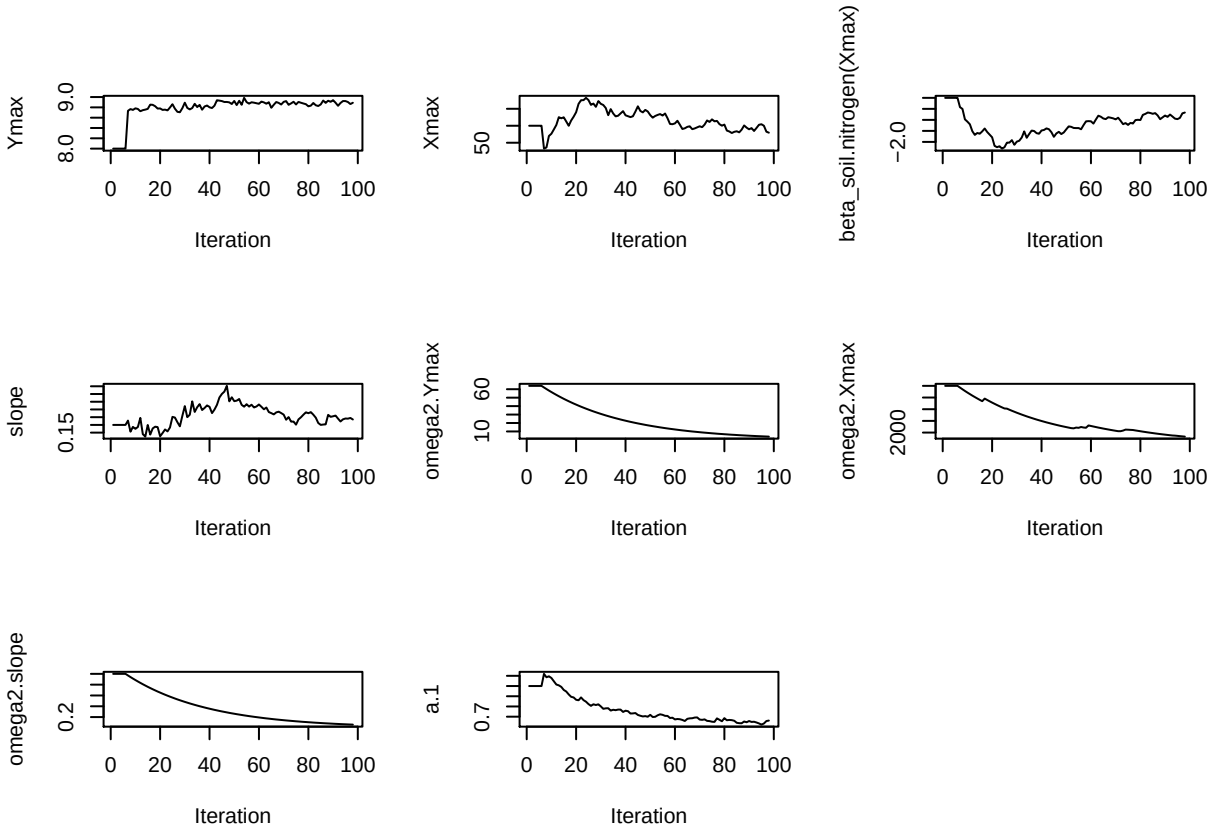
```
saemix.fit<-llgq.saemix(saemix.fit)
{
   cat("LL by Importance sampling, LL_IS=",saemix.fit["results"]["ll.is"],"\n")
   cat("LL by linearisation, LL_lin=",saemix.fit["results"]["ll.lin"],"\n")
   cat("LL by Gaussian Quadrature, LL_GQ=",saemix.fit["results"]["ll.gq"],"\n")
}
```

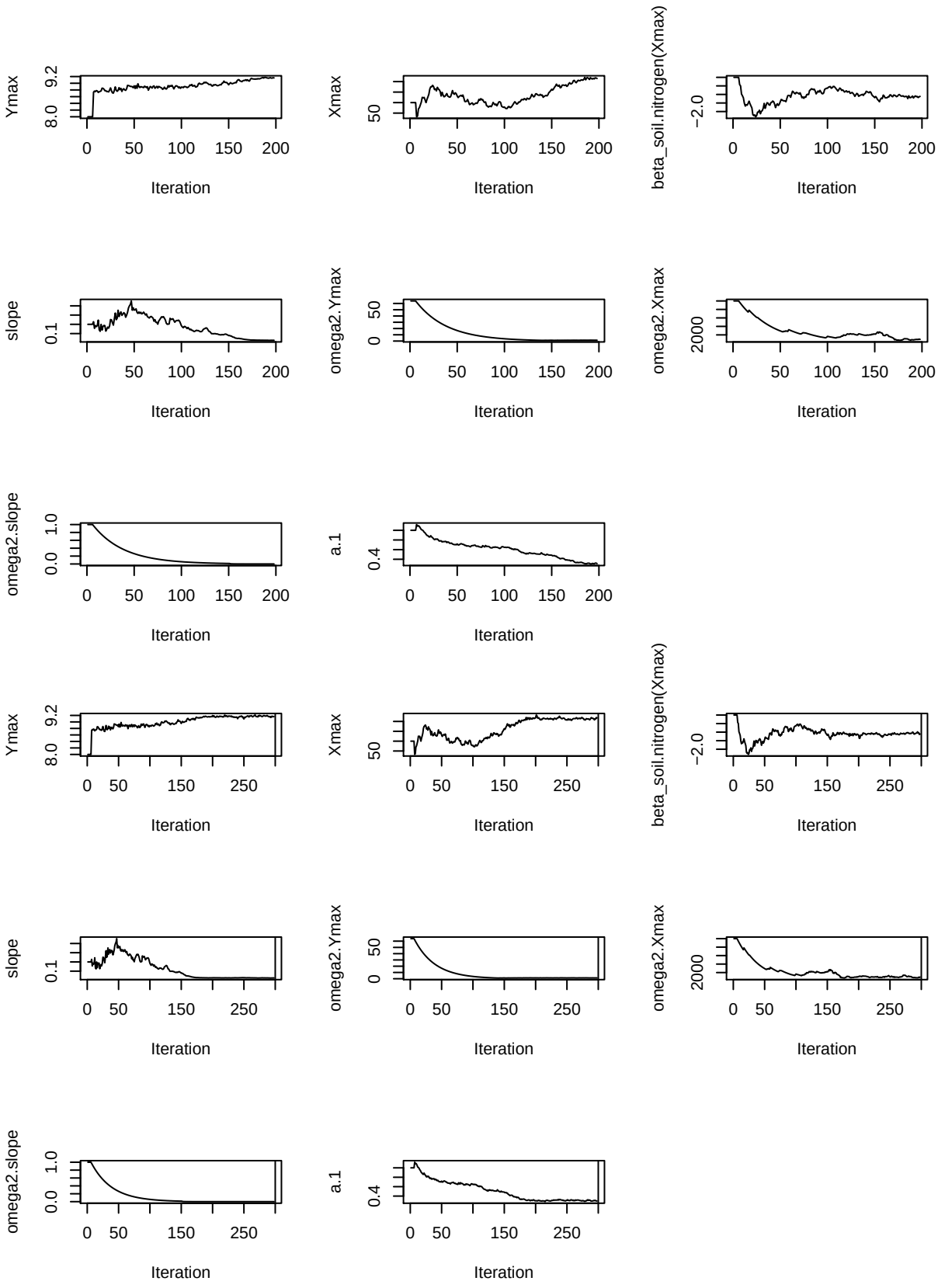
```
## LL by Importance sampling, LL_IS= -308.2524
## LL by linearisation, LL_lin= -308.2851
## LL by Gaussian Quadrature, LL_GQ= -308.2772
```

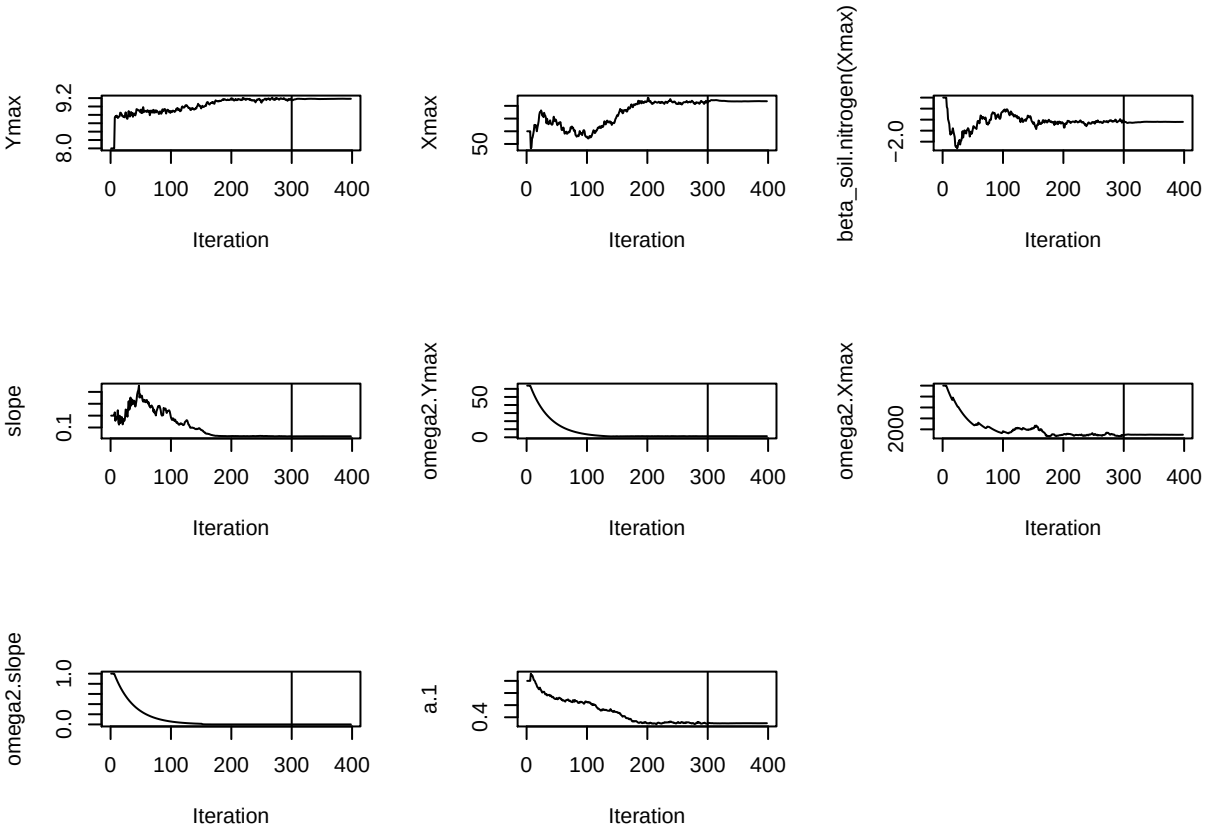
```
# Testing for an effect of covariate soil.nitrogen on Xmax
saemix.model2<-saemixModel(model=yield.LP,description="Linear plus plateau model",
         psi0=matrix(c(8,100,0.2,0,0,0),ncol=3,byrow=TRUE,dimnames=list(NULL,
            c("Ymax","Xmax","slope"))),covariate.model=matrix(c(0,1,0),ncol=3,byrow=TRUE),
         transform.par=c(0,0,0),covariance.model=matrix(c(1,0,0,0,1,0,0,0,1),ncol=3,
             byrow=TRUE),error.model="constant")
```

```
##
##
## The following SaemixModel object was successfully created:
##
## Nonlinear mixed-effects model
##   Model function:  Linear plus plateau model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   ymax<-psi[id,1]
##   xmax<-psi[id,2]
##   slope<-psi[id,3]
##   f<-ymax+slope*(x-xmax)
##   #'  cat(length(f),"  ",length(ymax),"\n")
##   f[x>xmax]<-ymax[x>xmax]
##   return(f)
## }
## <bytecode: 0x556f7655ed68>
##   Nb of parameters: 3
##       parameter names:  Ymax Xmax slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] Ymax      normal       Estimated
## [2,] Xmax      normal       Estimated
## [3,] slope     normal       Estimated
##   Variance-covariance matrix:
##       Ymax Xmax slope
## Ymax     1    0     0
## Xmax     0    1     0
## slope    0    0     1
##   Error model: constant , initial values: a.1=1
##   Covariate model:
##      Ymax Xmax slope
## [1,]    0    1     0
##     Initial values
##              Ymax Xmax slope
## Pop.CondInit    8  100   0.2
## Cov.CondInit    0    0   0.0
```

```
saemix.fit2<-saemix(saemix.model2,saemix.data,saemix.options)

## The number of subjects is small, increasing the number of chains to 2 to improve convergence
```




Ymax
8.0
9.2
0
50
100
150
200
Iteration
Xmax
50
0
50
100
150
200
Iteration
beta_soil.nitrogen(Xmax)
−2.0
0
50
100
150
200
Iteration
slope
0.1
0
50
100
150
200
Iteration
omega2.Ymax
0
50
0
50
100
150
200
Iteration
omega2.Xmax
2000
0
50
100
150
200
Iteration
omega2.slope
0.0
1.0
0
50
100
150
200
Iteration
a.1
0.4
0
50
100
150
200
Iteration
Ymax
8.0
9.2
0
50
150
250
Iteration
Xmax
50
0
50
150
250
Iteration
beta_soil.nitrogen(Xmax)
−2.0
0
50
150
250
Iteration
slope
0.1
0
50
150
250
Iteration
omega2.Ymax
0
50
0
50
150
250
Iteration
omega2.Xmax
2000
0
50
150
250
Iteration
omega2.slope
0.0
1.0
0
50
150
250
Iteration
a.1
0.4
0
50
150
250
Iteration




```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## ----------------------------------
## ----          Data              ----
## ----------------------------------
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset yield.saemix
##     Structured data: yield ~ dose | site
##     Predictor: dose (kg/ha)
##     covariates: soil.nitrogen (kg/ha)
## Dataset characteristics:
##     number of subjects:     37
##     number of observations: 224
##     average/min/max nb obs: 6.05  /  5  /  8
## First 10 lines of data:
##    site dose yield soil.nitrogen mdv cens occ ytype
## 1  1901    0  6.70            70   0    0   1     1
## 2  1901   70  8.58            70   0    0   1     1
## 3  1901  120 10.56            70   0    0   1     1
## 4  1901  170 11.54            70   0    0   1     1
## 5  1901  220 10.63            70   0    0   1     1
## 6  1901  270 11.54            70   0    0   1     1
## 7  1902    0  6.98            80   0    0   1     1
## 8  1902   70  9.94            80   0    0   1     1
## 9  1902  120 10.56            80   0    0   1     1
## 10 1902  170 11.07            80   0    0   1     1
## ----------------------------------
## ----          Model             ----
```

```
## ----------------------------------
## Nonlinear mixed-effects model
##   Model function:  Linear plus plateau model  Model type:  structural
## function(psi,id,xidep) {
##   x<-xidep[,1]
##   ymax<-psi[id,1]
##   xmax<-psi[id,2]
##   slope<-psi[id,3]
##   f<-ymax+slope*(x-xmax)
##   #'  cat(length(f),"  ",length(ymax),"\n")
##   f[x>xmax]<-ymax[x>xmax]
##   return(f)
## }
## <bytecode: 0x556f7655ed68>
##   Nb of parameters: 3
##       parameter names:  Ymax Xmax slope
##       distribution:
##      Parameter Distribution Estimated
## [1,] Ymax      normal       Estimated
## [2,] Xmax      normal       Estimated
## [3,] slope     normal       Estimated
##   Variance-covariance matrix:
##       Ymax Xmax slope
## Ymax     1    0     0
## Xmax     0    1     0
## slope    0    0     1
##   Error model: constant , initial values: a.1=1
##   Covariate model:
##               [,1] [,2] [,3]
## soil.nitrogen    0    1    0
##     Initial values
##              Ymax Xmax slope
## Pop.CondInit    8  100   0.2
## Cov.CondInit    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:  2
##     Seed:  666
##     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,] Ymax                       9.184   0.1919  2.1  -
## [2,] Xmax                     218.403  15.7188  7.2  -
## [3,] beta_soil.nitrogen(Xmax)  -1.106   0.1715 15.5  5.8e-11
## [4,] slope                      0.026   0.0012  4.7  -
## [5,] a.1                        0.302   0.0192  6.4  -
## ----------------------------------------------------
## -----------  Variance of random effects  -----------
## ----------------------------------------------------
##       Parameter    Estimate SE      CV(%)
## Ymax  omega2.Ymax  1.3e+00  3.2e-01 24
## Xmax  omega2.Xmax  1.0e+03  2.9e+02 28
## slope omega2.slope 2.9e-05  1.1e-05 38
## ----------------------------------------------------
## ------  Correlation matrix of random effects  ------
## ----------------------------------------------------
##              omega2.Ymax omega2.Xmax omega2.slope
## omega2.Ymax  1           0           0
## omega2.Xmax  0           1           0
## omega2.slope 0           0           1
## ----------------------------------------------------
## ---------------  Statistical criteria  -------------
## ----------------------------------------------------
## Likelihood computed by linearisation
##       -2LL= 389.099
##       AIC = 405.099
##       BIC = 417.9863
##
## Likelihood computed by importance sampling
##       -2LL= 380.8696
##       AIC = 396.8696
##       BIC = 409.7569
## ----------------------------------------------------
```

```
# BIC for the two models
{
  cat("Model without covariate, BIC=",saemix.fit["results"]["bic.is"],"\n")
  cat("Model with covariate, BIC=",saemix.fit2["results"]["bic.is"],"\n")
  pval<-1-pchisq(-2*saemix.fit["results"]["ll.is"]+2*saemix.fit2["results"]["ll.is"],1)
  cat("        LRT: p=",pval,"\n")
}
```

```
## Model without covariate, BIC= 641.7812
## Model with covariate, BIC= 409.7569
##         LRT: p= 0
```

## Discrete data model

### Binary response model

### Categorical response model

### Count data model

## Time-to-event

### TTE model

### RTTE model