

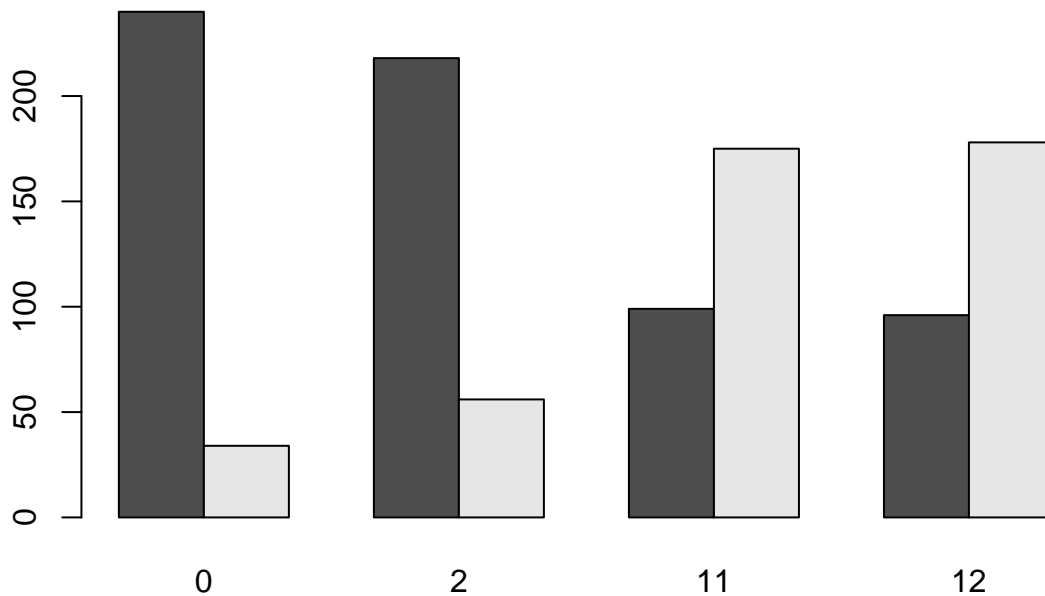
Calcul SE simulations Marilou

Setting up the system

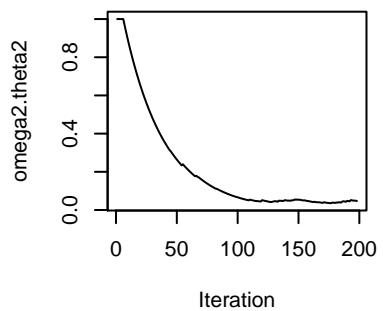
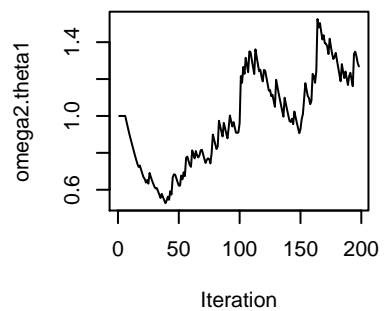
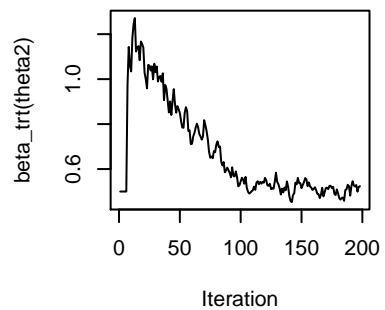
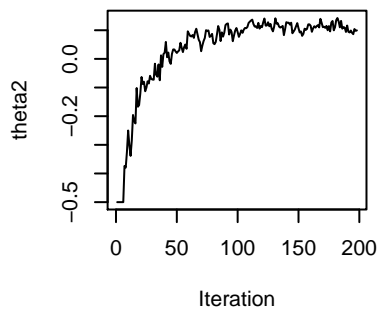
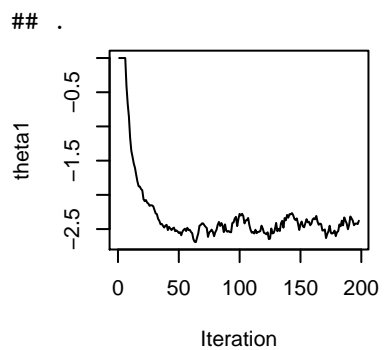
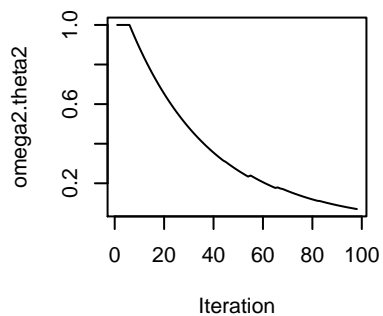
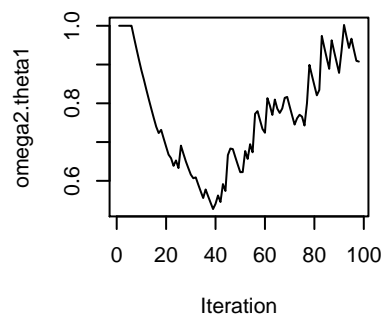
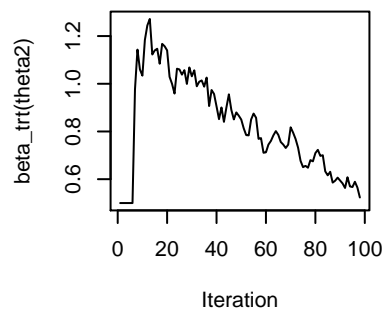
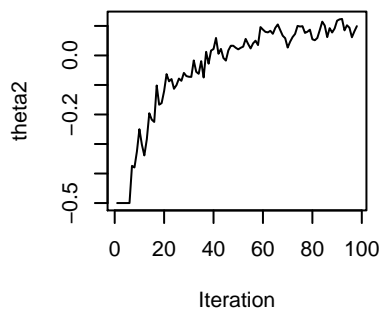
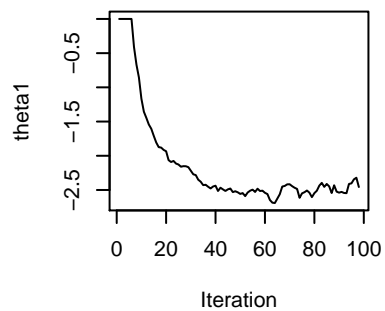
Binomial model in saemix

```
##
##
## 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
```

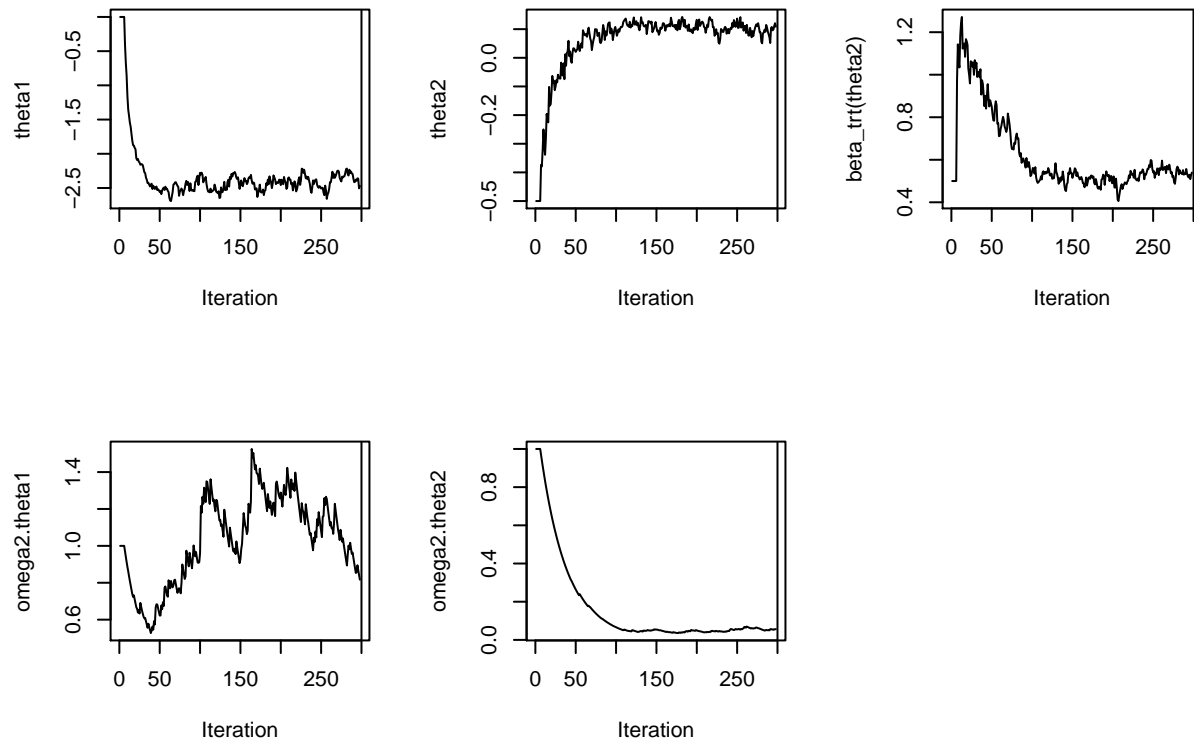
Run saemix sur le premier jeu de données pour vérifier que ça colle



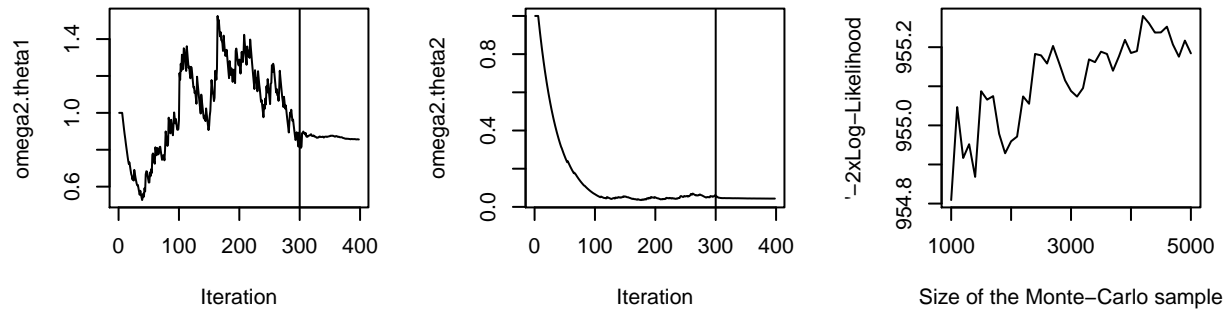
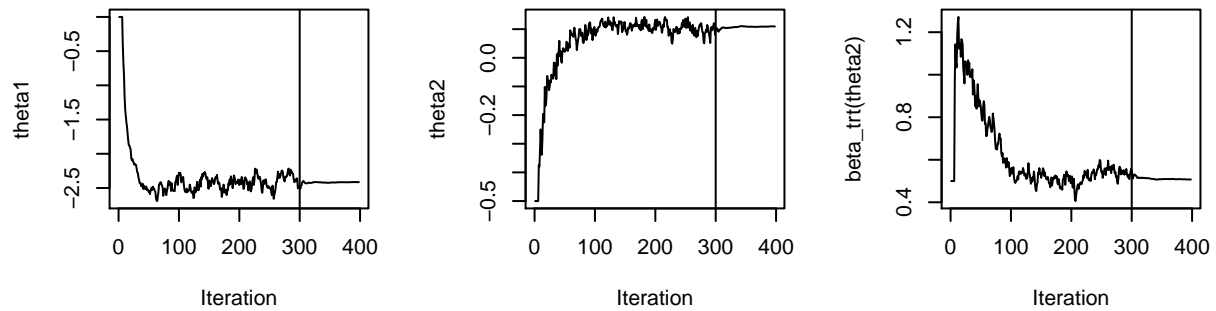
```
## Reading data from file /home/eco/work/theses/sirM2marilou/simulations/data/data1.txt
## These are the first lines of the dataset as read into R. Please check the format of the data is appropriate
##      id   theta1   theta2 betacov trt time   logitp      p y
## 1     1 -3.096707 0.16248408   0.45  0   0 -3.096707 0.04324328 0
## 275   1 -3.096707 0.16248408   0.45  0   2 -2.771739 0.05887058 0
## 549   1 -3.096707 0.16248408   0.45  0  11 -1.309382 0.21259020 0
## 823   1 -3.096707 0.16248408   0.45  0  12 -1.146898 0.24105606 0
## 2     2 -2.821699 0.06527274   0.45  0   0 -2.821699 0.05616282 0
## 276   2 -2.821699 0.06527274   0.45  0   2 -2.691153 0.06349740 0
## 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] "trt"
##
##
## The following SaemixData object was successfully created:
##
## Object of class SaemixData
##      longitudinal data for use with the SAEM algorithm
## Dataset /home/eco/work/theses/sirM2marilou/simulations/data/data1.txt
##      Structured data: y ~ time + y | id
##      X variable for graphs: time ( )
##      covariates: trt (-)
##      reference class for covariate trt : 0
##
## Running main SAEM algorithm
## [1] "Sat Jul  6 20:20:12 2019"
## .
```



.



```
## .
##
##      Minimisation finished
## [1] "Sat Jul  6 20:20:15 2019"
## Error in solve.default(F0) :
##   le système est numériquement singulier : conditionnement de la réciproque = 2.99566e-17
## Error computing the Fisher Information Matrix: singular system.
```



Estimation of the log-likelihood

```
## Nonlinear mixed-effects model fit by the SAEM algorithm
## -----
## ----          Data          ----
## -----
## Object of class SaemixData
##   longitudinal data for use with the SAEM algorithm
## Dataset /home/eco/work/theses/sirM2marilou/simulations/data/data1.txt
##   Structured data: y ~ time + y | id
##   X variable for graphs: time ()
##   covariates: trt (-)
##   reference class for covariate trt : 0
## Dataset characteristics:
##   number of subjects:      274
##   number of observations: 1096
##   average/min/max nb obs: 4.00 / 4 / 4
## First 10 lines of data:
##   id time y y.1 trt mdv cens occ ytype
## 1    1   0 0   0 0 0 0 1   1
## 275  1   2 0   0 0 0 0 1   1
## 549  1  11 0   0 0 0 0 1   1
## 823  1  12 0   0 0 0 0 1   1
## 2    2   0 0   0 0 0 0 1   1
## 276  2   2 0   0 0 0 0 1   1
## 550  2  11 0   0 0 0 0 1   1
## 824  2  12 0   0 0 0 0 1   1
## 3    3   0 0   0 0 0 0 1   1
## 277  3   2 0   0 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: 0x774ca88>
## 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]
## trt    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 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: 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 SE  CV(%) p-value

```

```

## [1,] theta1          -2.42    0.21  8.5  -
## [2,] theta2           0.11    0.10 95.2  -
## [3,] beta_trt(theta2) 0.51    0.18 36.1  0.0028
## -----
## ----- Variance of random effects -----
## -----
##      Parameter      Estimate SE CV(%)
## theta1 omega2.theta1 0.856    NA NA
## theta2 omega2.theta2 0.043    NA NA
## -----
## ----- Correlation matrix of random effects -----
## -----
##      omega2.theta1 omega2.theta2
## omega2.theta1 1          0
## omega2.theta2 0          1
## -----
## ----- Statistical criteria -----
## -----
## Likelihood computed by linearisation
##      -2LL= 3252.623
##      AIC = 3264.623
##      BIC = 3286.301
##
## Likelihood computed by importance sampling
##      -2LL= 955.1842
##      AIC = 967.1842
##      BIC = 988.8629
## -----

```

Run saemix sur les 200 simulations de Marilou, et récupération des résultats dans un tableau, fait dans computeSEemp_binomial.R

Calcul SE par bootstrap pour 1 jeu de données

Test rapide avec 10 échantillons bootstrap seulement, juste pour tester les codes

```

## Warning in rm(.Random.seed): objet '.Random.seed' introuvable

## Warning in rm(.Random.seed): objet '.Random.seed' introuvable

## Warning in rm(.Random.seed): objet '.Random.seed' introuvable

## Warning in rm(.Random.seed): objet '.Random.seed' introuvable

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## Warning in rm(.Random.seed): objet '.Random.seed' introuvable

## Warning in rm(.Random.seed): objet '.Random.seed' introuvable

```

```
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
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## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
## Warning in rm(.Random.seed): objet '.Random.seed' introuvable
```

Summary, SD and quantiles of bootstrap distributions for the 2 fixed, effect, the covariate effect and the 2 variabilities.

```
apply(res.boot[,2:6],2,summary)
```

```
##          theta1      theta2 beta_trt(theta2) omega2.theta1 omega2.theta2
## Min.    -2.879033 0.0809111      0.3693210      0.3391882      0.01386664
## 1st Qu. -2.688144 0.1086251      0.4437737      0.9001025      0.02448749
## Median -2.544041 0.1212871      0.5163572      1.2770004      0.03805155
## Mean    -2.519576 0.1258515      0.5053262      1.2546404      0.03943791
## 3rd Qu. -2.350707 0.1466459      0.5660670      1.5937432      0.04766536
## Max.    -2.128179 0.1672035      0.6018643      2.1754994      0.07907715
```

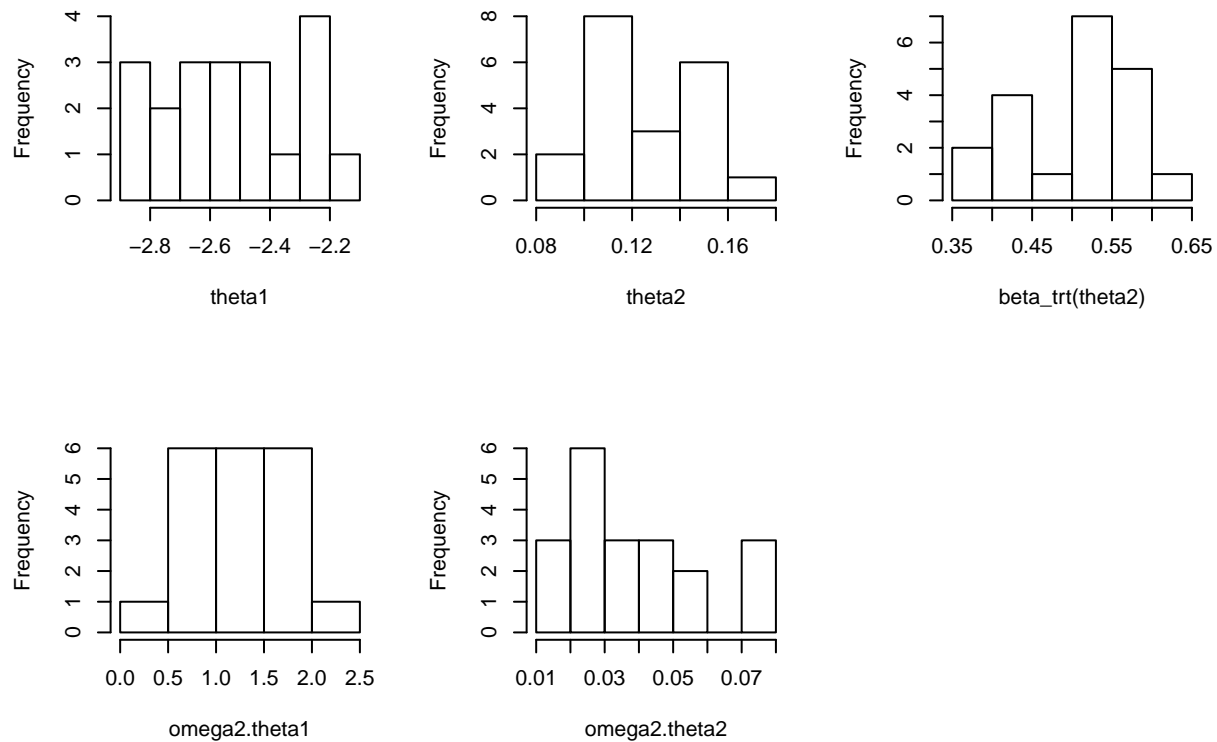
```
apply(res.boot[,2:6],2,sd)
```

```
##          theta1          theta2 beta_trt(theta2)      omega2.theta1
##      0.22495423      0.02378150      0.07213049      0.48297218
##      omega2.theta2
##      0.01976853
```

```
apply(res.boot[,2:6],2,quantile,c(0.025,0.5,0.975))
```

```
##          theta1      theta2 beta_trt(theta2) omega2.theta1 omega2.theta2
## 2.5%  -2.873633 0.08529847      0.3784378      0.4890779      0.01587834
## 50%   -2.544041 0.12128714      0.5163572      1.2770004      0.03805155
## 97.5% -2.180187 0.16323033      0.5964226      2.0346047      0.07777023
```

Bootstrap distributions



Calcul SE par la AGQ (méthode de Sebastian, code ad hoc)

```
##           mu1      mu2      mu3  omega1.1  omega2.2
## mu1      59.72529 186.72123  77.07814 12.136375 -28.76754
## mu2     186.72123 2133.38367 761.53398 -7.881850 -881.84773
## mu3      77.07814 761.53398 761.53398 -10.076503 -1797.41995
## omega1.1 12.13637  -7.88185 -10.07650  7.735019  77.02905
## omega2.2 -28.76754 -881.84773 -1797.41995 77.029050 8663.43890

##           mu1      mu2      mu3  omega1.1  omega2.2
## -9.039789 30.771085 13.426490 62.569823 39.293465

##           param      se
## mu1      -2.4160841 0.21840891
## mu2       0.1102140 0.03391403
## mu3       0.5063923 0.06799071
## omega1.1  0.8562196 0.53573506
## omega2.2  0.0433050 0.01701604
```

Calcul SE empirique simulations Marilou

```
##           Simulation  theta1      theta2      beta  omega2.theta1
## Min.              1.00 -2.788802 -0.009588763 0.3551997  0.3467233
## 1st Qu.           50.75 -2.330911  0.070810643 0.4763961  0.8026750
## Median          100.50 -2.200969  0.088915945 0.5244584  1.0636280
## Mean            100.50 -2.215034  0.090789687 0.5341374  1.1031808
## 3rd Qu.         150.25 -2.096785  0.110608475 0.5889836  1.3084848
## Max.            200.00 -1.729065  0.170173200 0.8098407  2.2509190
##           omega2.theta2
```

```
## Min.      0.01356832
## 1st Qu.   0.03139451
## Median    0.04040995
## Mean      0.04473278
## 3rd Qu.   0.05563287
## Max.      0.11319040

##      Simulation      theta1      theta2      beta omega2.theta1
## 57.87918451 0.19709055 0.02866786 0.07997905 0.41631827
## omega2.theta2
##      0.01855807
```

Comparaison des différentes estimations des SE

SE empiriques (sur 200 simulations), SE bootstrap (avec seulement 20 échantillons) et SE prédites par AGQ

SE empiriques:

```
##      Simulation      theta1      theta2      beta omega2.theta1
## 57.87918451 0.19709055 0.02866786 0.07997905 0.41631827
## omega2.theta2
##      0.01855807
```

SE bootstrap:

```
##      theta1      theta2 beta_trt(theta2) omega2.theta1
## 0.22495423 0.02378150 0.07213049 0.48297218
## omega2.theta2
##      0.01976853
```

SE :

```
##      mu1      mu2      mu3 omega1.1 omega2.2
## 0.21840891 0.03391403 0.06799071 0.53573506 0.01701604
```

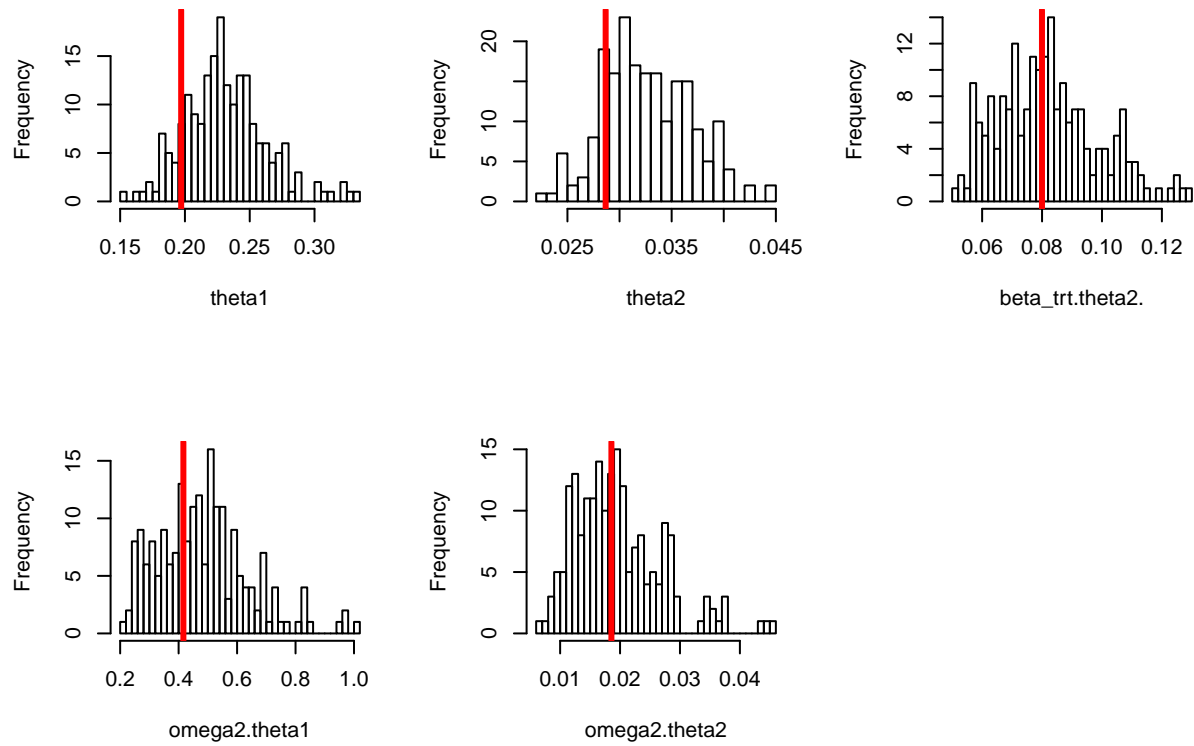
Calcul SE par bootstrap pour l'ensemble des jeux de données binomial

Test du bootstrap pour un modèle binomial

- Code bootstrap - en mode batch
- R CMD BATCH run_bootstrapBinomial.R

```
##      Simulation      theta1      theta2      beta omega2.theta1
## Min.      1.00 -2.788802 -0.009588763 0.3551997 0.3467233
## 1st Qu.    50.75 -2.330911 0.070810643 0.4763961 0.8026750
## Median    100.50 -2.200969 0.088915945 0.5244584 1.0636280
## Mean      100.50 -2.215034 0.090789687 0.5341374 1.1031808
## 3rd Qu.   150.25 -2.096785 0.110608475 0.5889836 1.3084848
## Max.      200.00 -1.729065 0.170173200 0.8098407 2.2509190
##      omega2.theta2
## Min.      0.01356832
## 1st Qu.    0.03139451
## Median    0.04040995
## Mean      0.04473278
## 3rd Qu.    0.05563287
## Max.      0.11319040
```

```
## [1] 0.770 0.950 0.840 0.405 0.870
```



```
##      Simulation      theta1      theta2      beta omega2.theta1
## Min.          1.00 -56.3193900 -3.12236000 0.1738997 0.223212
## 1st Qu.       50.75 -4.0538180 -0.03661100 0.5390754 1.116581
## Median      100.50 -2.9313175 0.10879830 0.8599547 2.500230
## Mean       100.50 -4.0110940 0.04312205 1.3753507 18.214142
## 3rd Qu.    150.25 -2.1993073 0.22945390 1.3842012 7.153019
## Max.       200.00 -0.8060751 1.77272400 22.9010700 1555.417000
##      omega2.theta2
## Min.      0.006106888
## 1st Qu.   0.049973110
## Median    0.108420050
## Mean      0.757804043
## 3rd Qu.   0.267611100
## Max.     32.921850000
## [1] 0.735 0.875 0.640 0.410 0.815
```

