R code used on the PRIMO data for the function F2:

```
#Creation of the database containing the information useful for the model:
#TM is the value of the biomarker TM
#V3 is the value of the biomarker V3
#tps is the time between the infection and the visit measure (in days)
base=data.frame(id=base_primo$id,TM=base_primo$TM,
                V3=base_primo$V3, tps=base_primo$time)

#Database transformation for the brms package
dt=base%>% gather(gp, y, V3,TM) %>% mutate (gp=as.factor(gp))

#Prior specifications
prior1 <- prior(normal(0,10000), nlpar = "b", lb=0)+
  prior(normal(0,10000), nlpar = "c", lb=0)+
  prior(normal(0,10000), nlpar = "num", class="b", lb=0)+
  prior(uniform(0,10000),nlpar = "num", class="sd", group = "id")+
  prior(uniform(0,10000),nlpar = "num", class="sd")

#Model specification with the function F2 and random effet in a1 (fixed parameter b1)
fit_F2_a1 <- brm(bf(y ~ num*exp(-b*exp(-tps/c)),
                   num~-1+gp+(gp+0|id),
                   b~-1+gp,
                   c~-1+gp,
                   sigma~-1+gp,
                   nl = TRUE),
                 data = dt,prior = prior1,
                 chains = 4,iter=20000, control=list(adapt_delta=0.9))

#Model specification with the function F2 and random effet in a2 (fixed parameter b2)
fit_F2_a2 <- brm(bf(y ~ b*exp(-num*exp(-tps/c)),
                   num~-1+gp+(gp+0|id),
                   b~-1+gp,
                   c~-1+gp,
                   sigma~-1+gp,
                   nl = TRUE),
                 data = dt,prior = prior1,
                 chains = 4,iter=20000, control=list(adapt_delta=0.9))
```

```
#Model specification with the function F2 and random effet in a3 (fixed parameter b3)
fit_F2_a3 <- brm(bf(y ~ b*exp(-c*exp(-tps/num)),
                    num~-1+gp+(gp+0|id),
                    b~-1+gp,
                    c~-1+gp,
                    sigma~-1+gp,
                    nl = TRUE),
                 data = dt,prior = prior1,
                 chains = 4,iter=20000, control=list(adapt_delta=0.99))

#WAIC calculation
WAIC_fit_F2_a1=waic(fit_F2_a1)
WAIC_fit_F2_a2=waic(fit_F2_a2)
WAIC_fit_F2_a3=waic(fit_F2_a3)
```

VPC calculation details for a given biomarker:

$VPC = \frac{\sigma_a^2}{\sigma_a^2+\sigma_\epsilon^2}$

We need to calculate the variance of the random effect:

$g_b(t,a) = b_1 exp(-(b_2 + a_2) exp(\frac{-t}{b_3}))$

$g_b(t,a) = b_1 exp(-b_2 exp(\frac{-t}{b_3}) - a_2 exp(\frac{-t}{b_3}))$

$g_b(t,a) = b_1 exp(-b_2 exp(\frac{-t}{b_3})) exp(-a_2 exp(\frac{-t}{b_3}))$

We note $\lambda = b_1 exp(-b_2 exp(\frac{-t}{b_3}))$ and $k(t) = exp(\frac{-t}{b_3})$

$g_b(t,a) = \lambda exp(-a_2 k(t))$

$-a_2 k(t) \sim \mathbb{N}(0, \sigma_a^2 k(t)^2)$

$V(exp(-a_2 k(t))) = exp(\sigma_a^2 k(t)^2)(exp(\sigma_a^2 k(t)^2) - 1)$

$V(g_b(t,a)) = \lambda^2 exp(\sigma_a^2 k(t)^2)(exp(\sigma_a^2 k(t)^2) - 1)$

$V(g_b(t,a)) = \lambda^2 \sigma_a^2 k(t)^2$ if $\sigma_a^2 k(t)^2$ is small

For a given marker of our model:

$$VPC = \frac{\lambda^2 \sigma_a^2 k(t)^2}{\lambda^2 \sigma_a^2 k(t)^2 + \sigma_\epsilon^2}$$

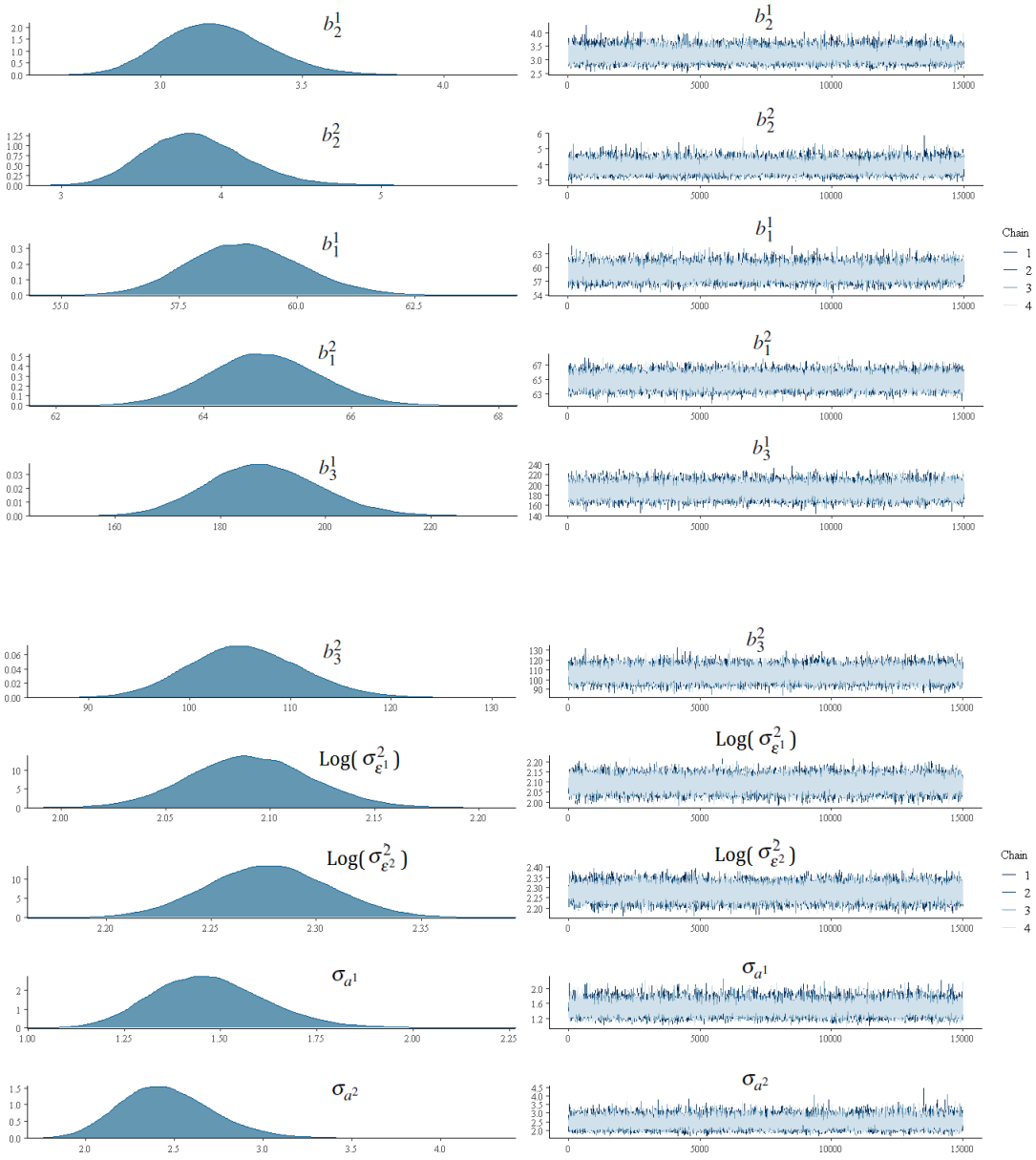
R code used for the simulation design:

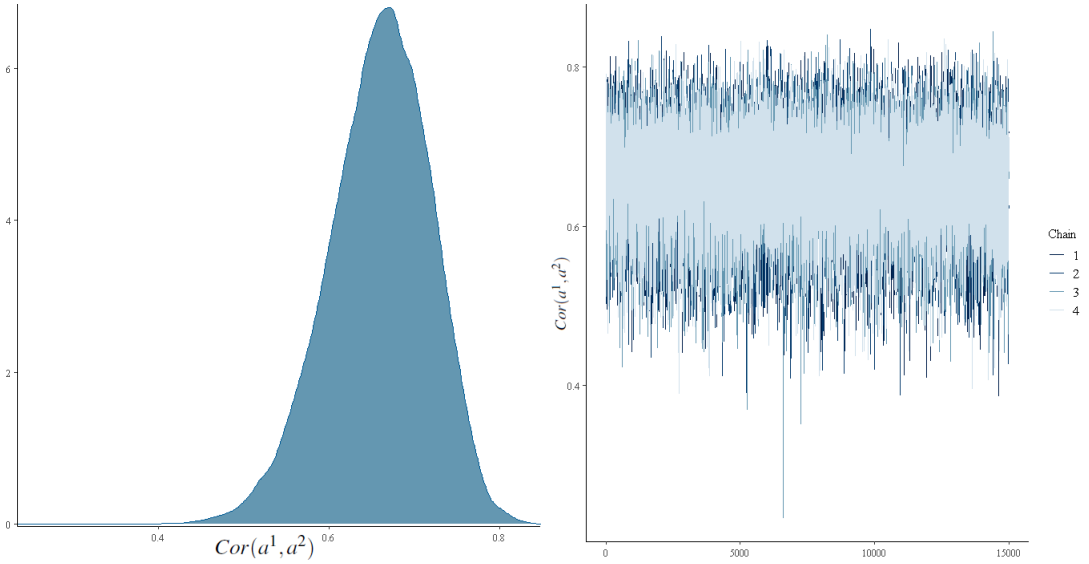
```
#We fixed  n=272 individuals as in the PRIMO ANRS C06 cohort
  n<-272

#We start by generating a number of measurements per patient according to
the distribution of Primo:
#134 patients with one measure [0,0.49[
#8 patients with two measures [0.49,0.497[
#12 patients with three measures [0.497,0.54[
#47 patients with four measures [0.54,0.71[
#13 patients with five measures[0.71,0.76[
#33 patients with six measures [0.76, 0.88[
#25 patients with seven measures [0.88,1]

  nb_mesure=runif(n)

  nb_mesure=replace(nb_mesure, nb_mesure<0.49,1)
  nb_mesure=replace(nb_mesure, nb_mesure>=0.49 & nb_mesure<0.497,2)
  nb_mesure=replace(nb_mesure, nb_mesure>=0.497 & nb_mesure<0.54,3)
  nb_mesure=replace(nb_mesure, nb_mesure>=0.54 & nb_mesure<0.71,4)
  nb_mesure=replace(nb_mesure, nb_mesure>=0.71 & nb_mesure<0.76,5)
  nb_mesure=replace(nb_mesure, nb_mesure>=0.76 & nb_mesure<0.88,6)
  nb_mesure=replace(nb_mesure, nb_mesure!=1 & nb_mesure!=2 & nb_mesure!=3 &
 nb_mesure!=4 & nb_mesure!=5 & nb_mesure!=6 ,7)

#We generate the date of the first measurement
  tps_J0=round(rlnorm(n, meanlog =4, sdlog = 0.50),0)

#We create the times t of measurements of individuals according
 to the number of measurements:
  time_individu=matrix(NA, ncol=n, nrow=7)
  for (i in 1:n){
    time_individu[1,i]=tps_J0[i]
    if (nb_mesure[i]==2) {
      time_individu[2,i]=time_individu[1,i]+30
    } else if (nb_mesure[i]==3) {
      time_individu[2,i]=time_individu[1,i]+30
      time_individu[3,i]=time_individu[1,i]+3*30
    } else if  (nb_mesure[i]==4) {
      time_individu[2,i]=time_individu[1,i]+30
      time_individu[3,i]=time_individu[1,i]+3*30
```

```
      time_individu[4,i]=time_individu[1,i]+6*30
    } else if  (nb_mesure[i]==5) {
    time_individu[2,i]=time_individu[1,i]+30
    time_individu[3,i]=time_individu[1,i]+3*30
    time_individu[4,i]=time_individu[1,i]+6*30
    time_individu[5,i]=time_individu[1,i]+12*30
    } else if  (nb_mesure[i]==6) {
      time_individu[2,i]=time_individu[1,i]+30
      time_individu[3,i]=time_individu[1,i]+3*30
      time_individu[4,i]=time_individu[1,i]+6*30
      time_individu[5,i]=time_individu[1,i]+12*30
      time_individu[6,i]=time_individu[1,i]+18*30
    }
    else if  (nb_mesure[i]==7) {
      time_individu[2,i]=time_individu[1,i]+30
      time_individu[3,i]=time_individu[1,i]+3*30
      time_individu[4,i]=time_individu[1,i]+6*30
      time_individu[5,i]=time_individu[1,i]+12*30
      time_individu[6,i]=time_individu[1,i]+18*30
      time_individu[7,i]=time_individu[1,i]+24*30
    }
  else {
    time_individu[1,i]=time_individu[1,i]

    }
}

#We repeat the id of the individual according to the number of measurements
  id=rep(1:n,nb_mesure)
  base=data.frame(id=id)
  vector_time=c(time_individu)

#We add the different times in the base:
 base$tps=vector_temps

#We generate the values of TM and V3 for each time and for each individual:
 b11<-70
 b21<-65
 b12<-3
 b22<-4
 b13<-200
 b23<-100
```

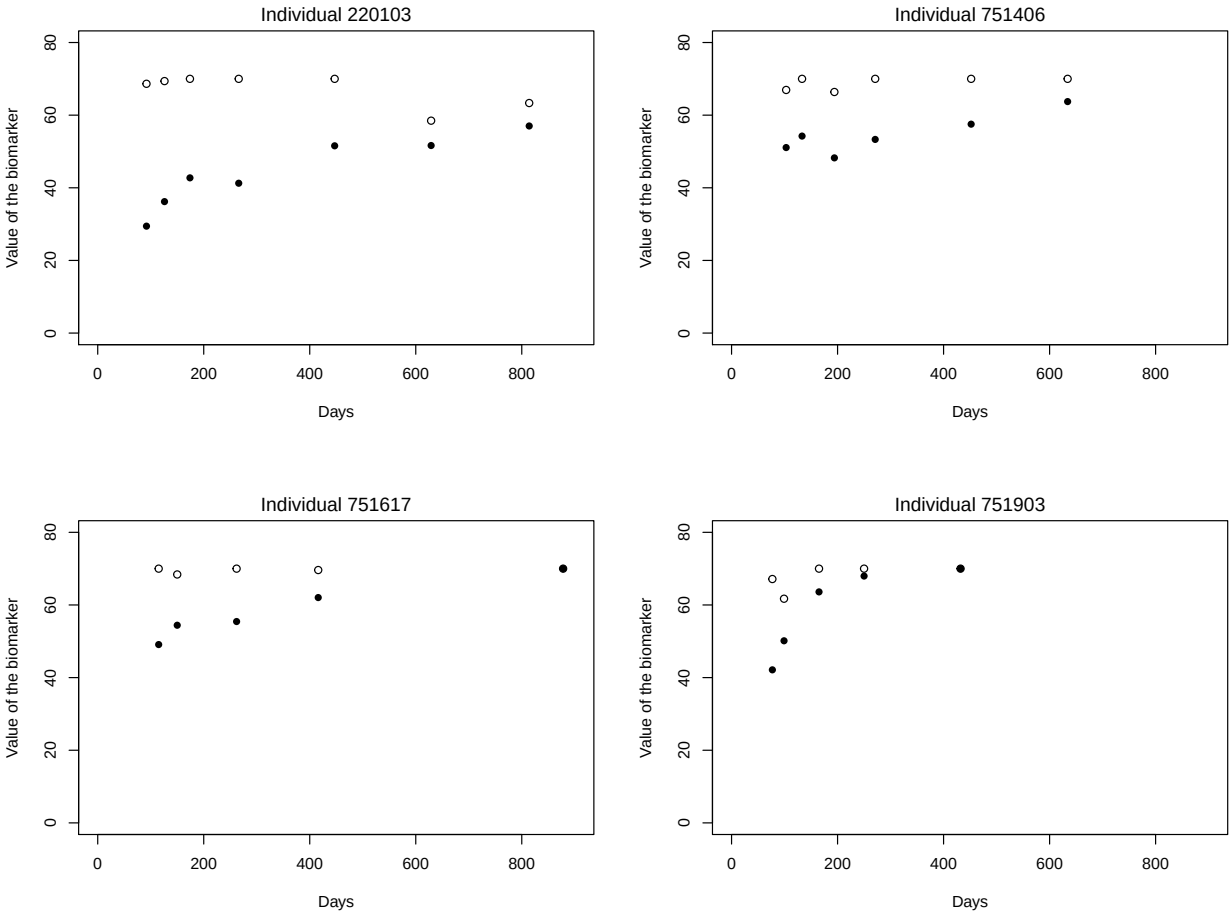
```
mu=c(0,0)
Sigma=matrix(c(4,2,2,6.25),ncol=2)
a<-MASS::mvrnorm(n=n,mu=mu,Sigma=Sigma)
alea=data.frame(id=1:272,a1=a[,1], a2=a[,2])

base=right_join(base,alea,by=c("id"))

TM_mean=NULL
V3_mean=NULL
 for (i in 1: nrow(base)){
   TM_mean[i]=b11*exp(-(b12+base$a1[i])*exp(-base$tps[i]/b13))
   V3_mean[i]=b21*exp(-(b22+base$a2[i])*exp(-base$tps[i]/b23))
 }

Sigma=diag(c(8.08,9.78))
for (i in 1:nrow(base)){
  base$TM[i]=MASS::mvrnorm(n=1,mu=c(TM_mean[i],V3_mean[i]),Sigma=Sigma)[1]
  base$V3[i]=MASS::mvrnorm(n=1,mu=c(TM_mean[i],V3_mean[i]),Sigma=Sigma)[2]
}

#We apply the biomarkers censorship:

base=base %>% mutate(TM = ifelse(TM >70, 70, TM))
base=base %>% mutate(V3 = ifelse(V3 > 70, 70, V3))

base=base %>% mutate(TM = ifelse(TM <0, 0 , TM))
base=base %>% mutate(V3 = ifelse(V3 < 0 , 0 , V3))

base$TM=round(base$TM,1)
base$V3=round(base$V3,1)

base
```

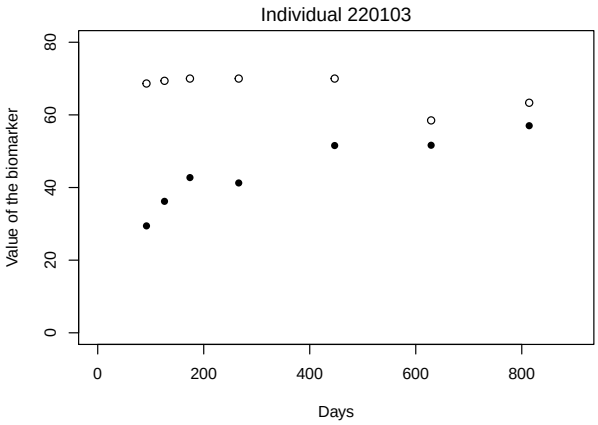
Trace plots and marginal posterior distributions for the PRIMO ANRS C06 results:

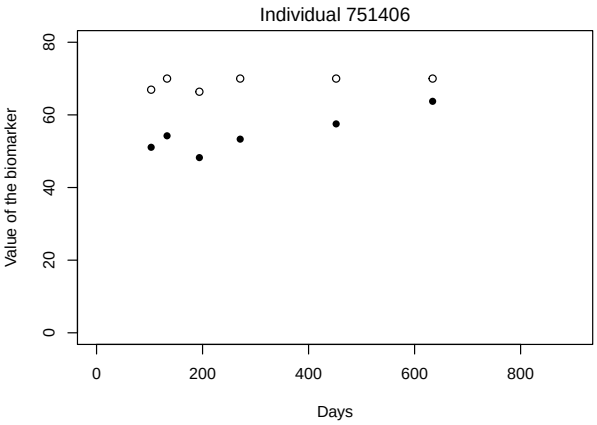


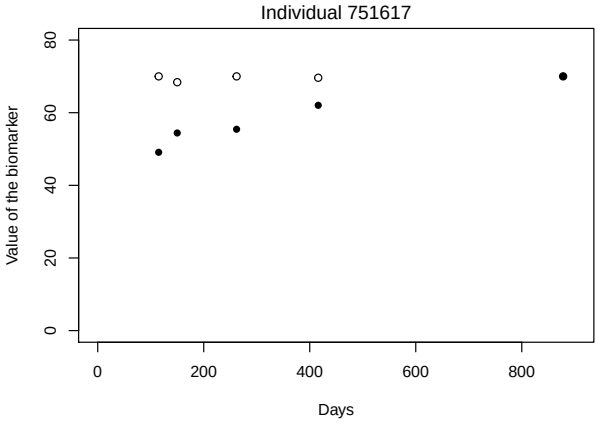

6
4
2
0
0.4
0.6
0.8
$Cor(a^1, a^2)$
0.8
0.6
0.4
$Cor(a^1, a^2)$
0
5000
10000
15000
Chain
1
2
3
4

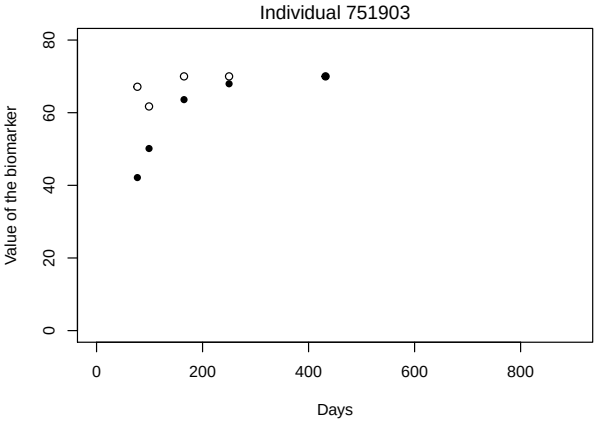
Evolution of the TM and V3 biomarkers for the four individuals who did not converge:




Individual 220103
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


Individual 751406
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


Individual 751617
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


Individual 751903
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

R code used and results for the univariate models:

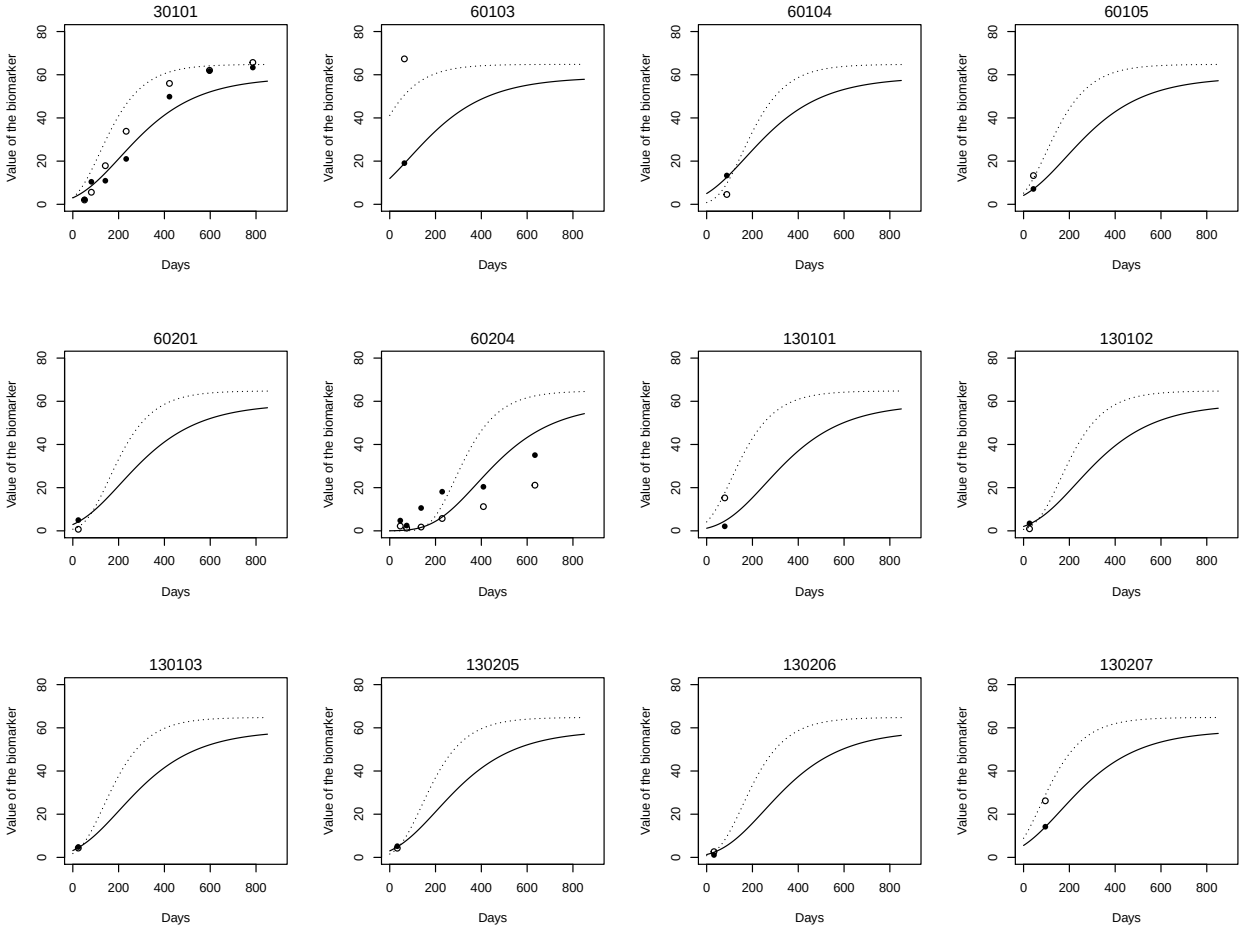
```
#We load the 200 simulated databases
base_simul=readRDS( "base_primo_simul.rds")

#We define the sigmoid function of the estimate, namely the function F2
sigmoid.model <- function(psi, id, xidep) {
  tps <- xidep[, 1]
  A <- psi[id, 1]
  B <- psi[id, 2]
  C <- psi[id, 3]
  resp <- A*exp(-B*exp(-tps/C))
  return(resp)
}

#We estimate the parameters for the function F2 with the random
 effect in a2 for the biomarker TM
saemix_F2_A2_TM=list()
for (i in 1:200){

  base=base_simul[[i]]

  modele <- saemixData(name.data = base, name.group = "id",
                       name.predictors = "tps", name.response = "TM",
                       units = list(x = "Days"))
  #Parametrisation
  opt <- list(save = FALSE, save.graphs = FALSE)

  base.modelA2 <- saemixModel(model = sigmoid.model,
                              description = "Sigmoid growth",
                              psi0 = matrix(c(24.63, 3.48, 49.47),ncol = 3, byrow = TRUE,
                         dimnames = list(NULL, c("A", "B", C"))),
 covariance.model = matrix(c(0, 0, 0, 0, 1, 0, 0, 0, 0), ncol = 3, byrow = TRUE))

  saemix_F2_A2_TM[[i]]=saemix(base.modelA2, modele, opt)
}

#We estimate the parameters for the function F2 with the random
 effect in a2 for the biomarker V3
saemix_F2_A2_V3=list()
for (i in 1:200){

  base=base_simul[[i]]
```

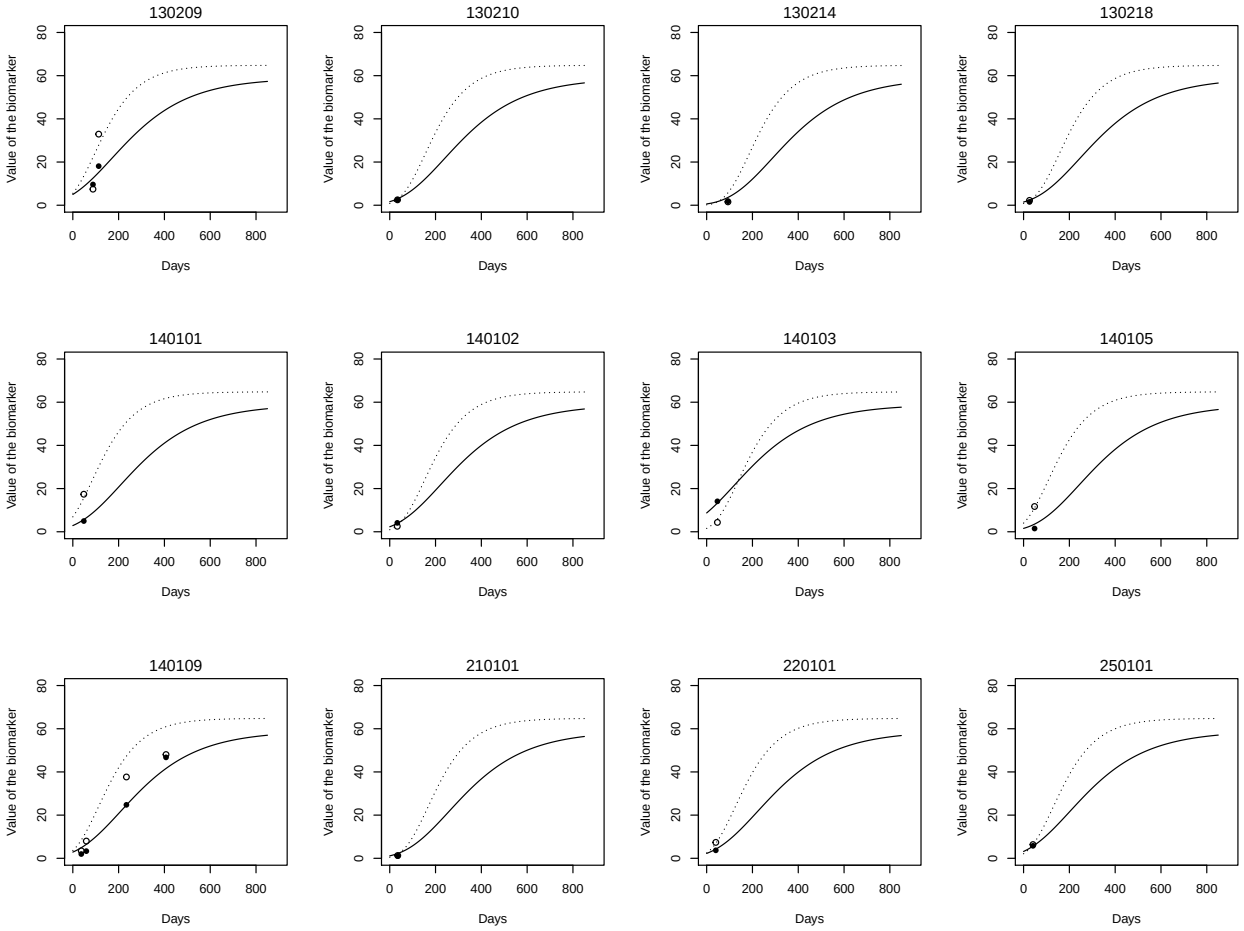
```
  modele <- saemixData(name.data = base, name.group = "id",
                       name.predictors = "tps", name.response = "V3",
                       units = list(x = "Days"))

  base.modelA2 <- saemixModel(model = sigmoid.model,
                              description = "Sigmoid growth",
                              psi0 = matrix(c(24.63, 3.48, 49.47),ncol = 3, byrow = TRUE,
 dimnames = list(NULL, c("A", "B", "C"))),
                              covariance.model = matrix(c(0, 0, 0, 0, 1, 0, 0, 0, 0),
    ncol = 3, byrow = TRUE))

  saemix_F2_A2_V3[[i]]=saemix(base.modelA2, modele, opt)
}
```

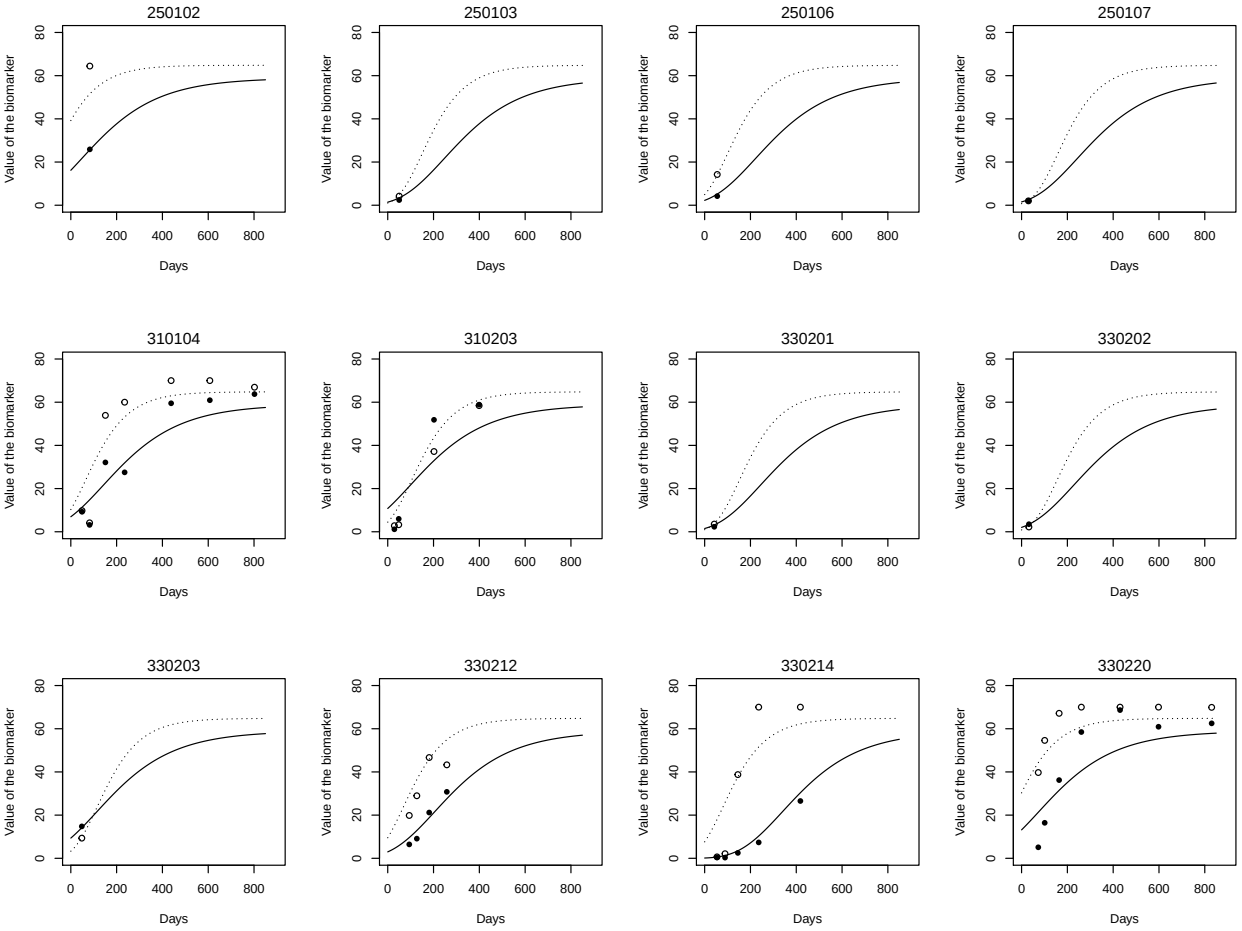
Table 1: True value of the parameters, mean, absolute relative bias (ARB), empirical root mean squared error (RMSE), and coverage rate (CR) of the credibility interval at 95% of the estimated parameters for the 200 simulations

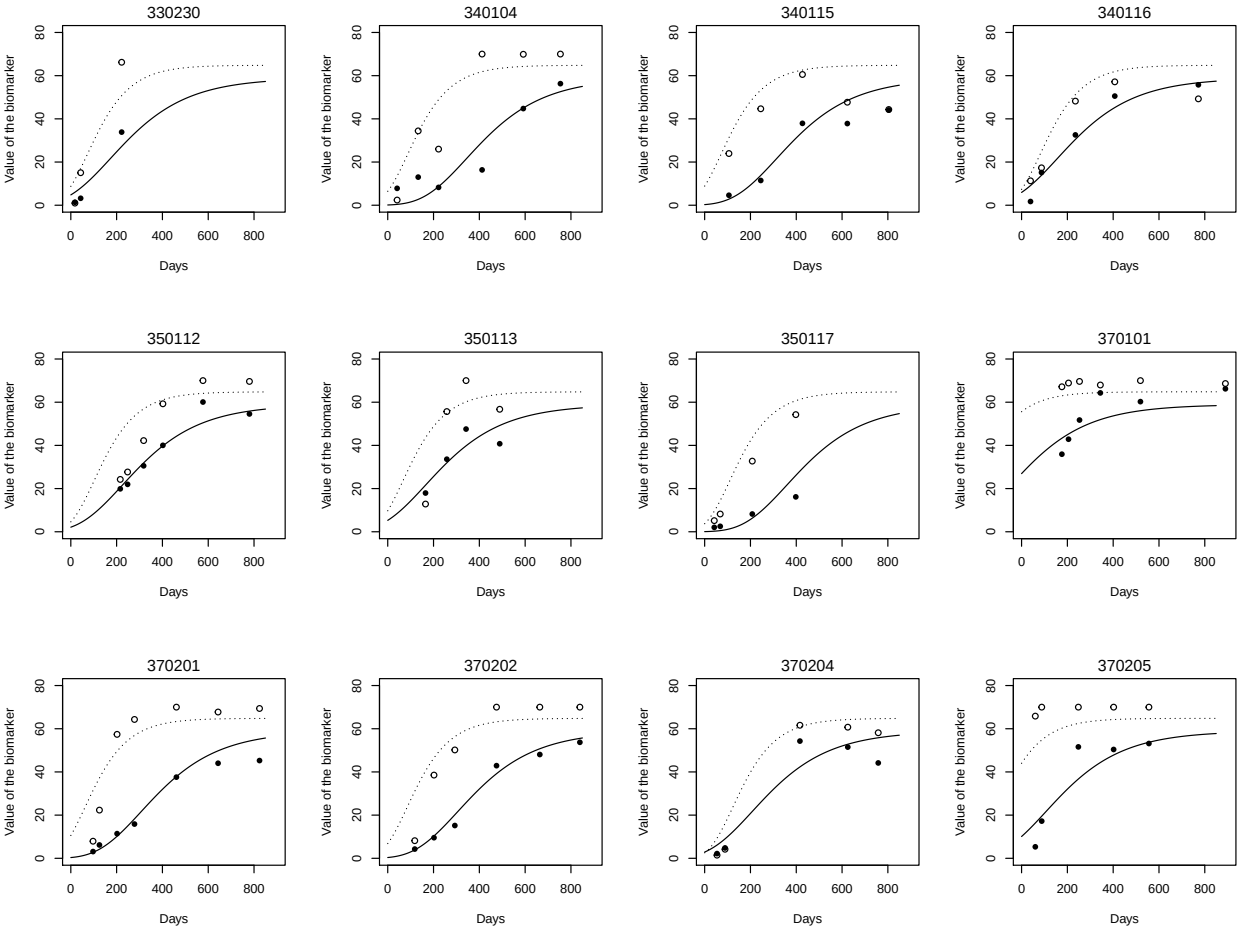
Parameters	**True value**	**Mean**	**ARB**	**RMSE**	**CR**
b_1^1	70	69.9	0.09%	0.38	96.5
b_2^1	3	3	0%	0.11	96.5
b_3^1	200	201.7	0.9%	3.5	87
b_1^2	65	65.3	0.46%	0.39	78
b_2^2	4	3.9	2.5%	0.19	88.5
b_3^2	100	101.9	1.9%	2.6	66
σ_{a^1}	2	1.8	10%	0.8	25
σ_{a^2}	2.5	2.2	12%	1.3	33
σ_{ϵ^1}	2.8	2.6	7%	0.2	30
σ_{ϵ^2}	3.1	3	3.5%	0.16	63

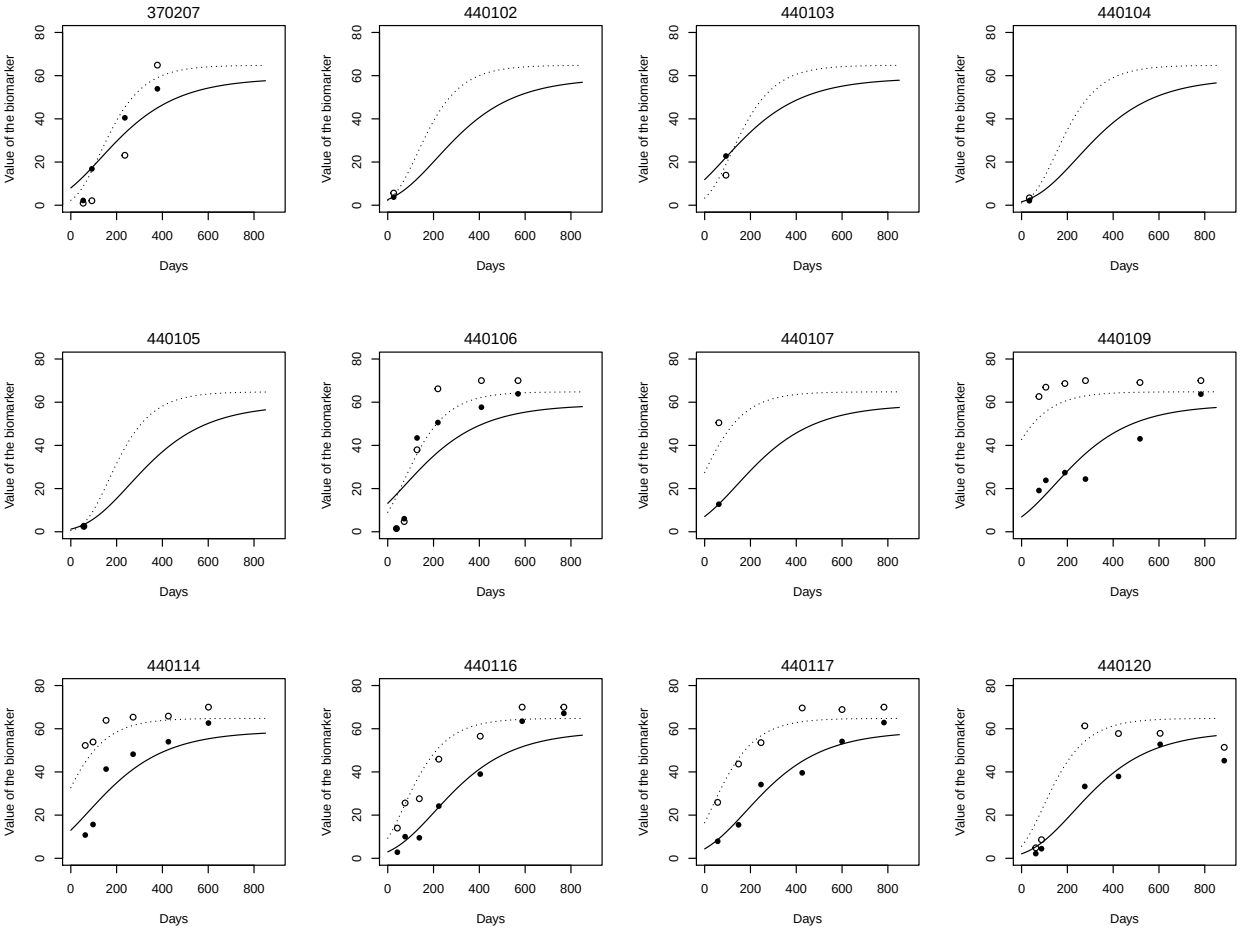
Values of the TM and V3 biomarkers with the observed (full circle for TM and empty circle for V3) and predicted trajectories (solid curve for TM and dotted line for V3) for all subjects of the PRIMO-ANRS C06 cohort

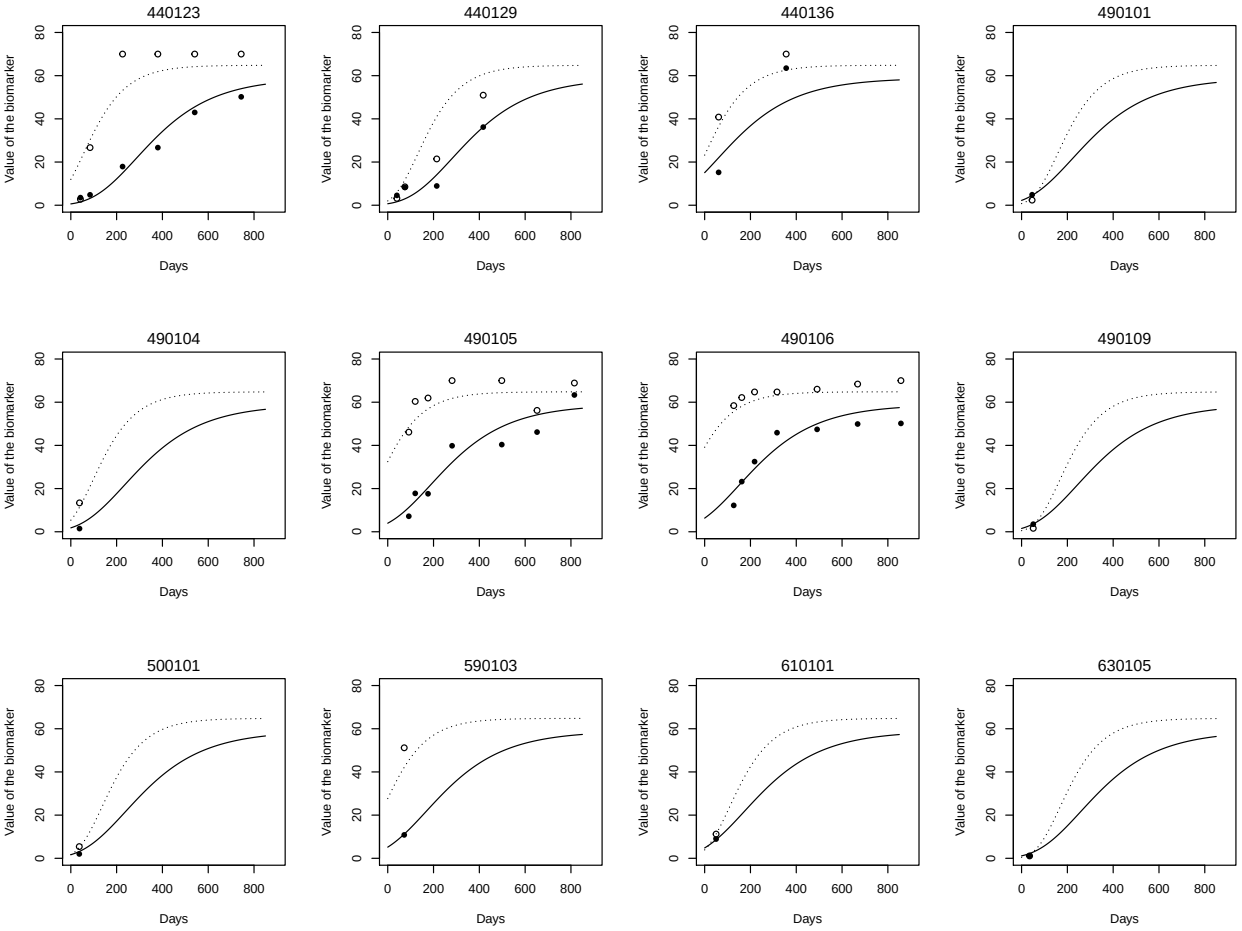


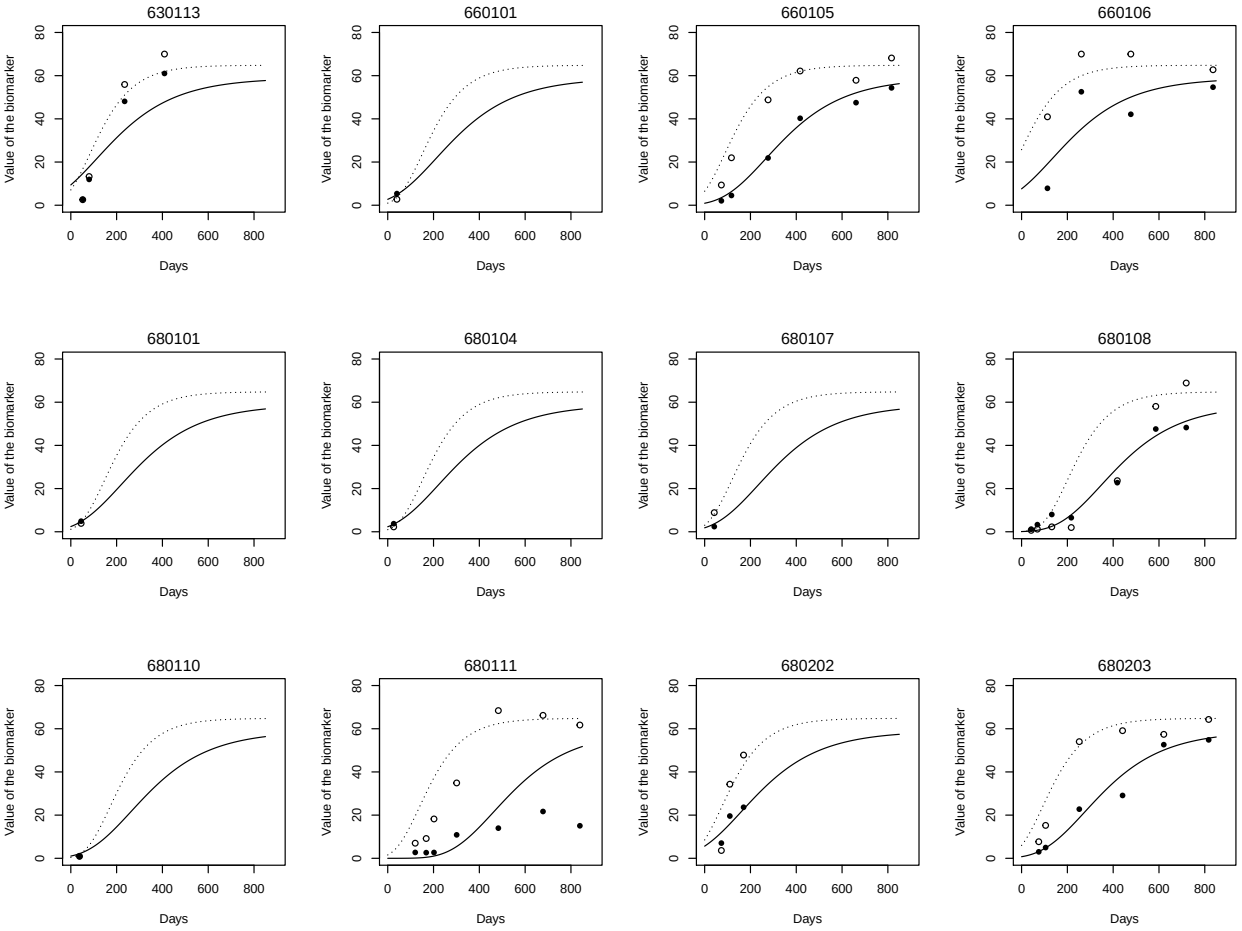

130209
130210
130214
130218
140101
140102
140103
140105
140109
210101
220101
250101
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

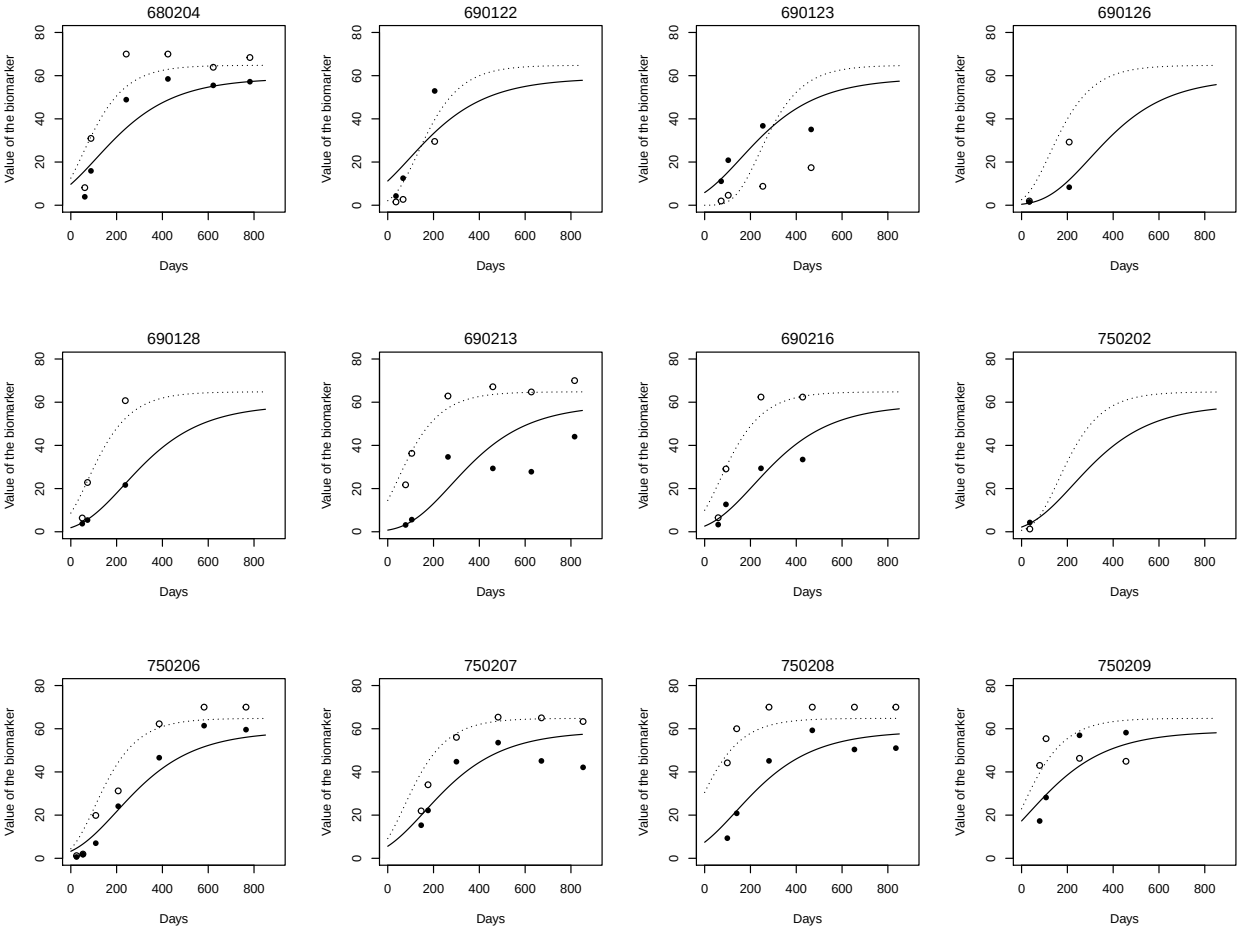

250102
250103
250106
250107
310104
310203
330201
330202
330203
330212
330214
330220
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

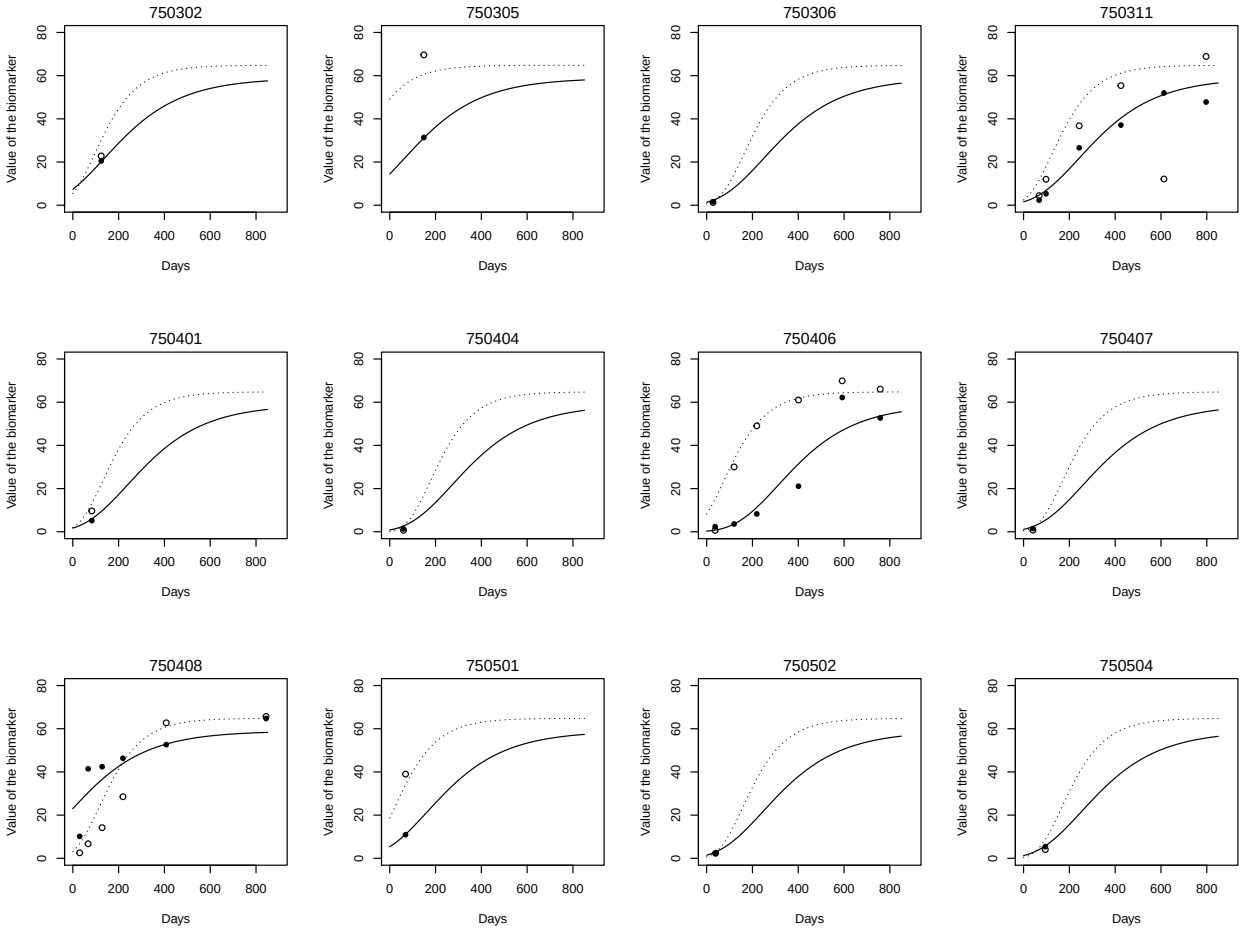

330230
340104
340115
340116
350112
350113
350117
370101
370201
370202
370204
370205
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

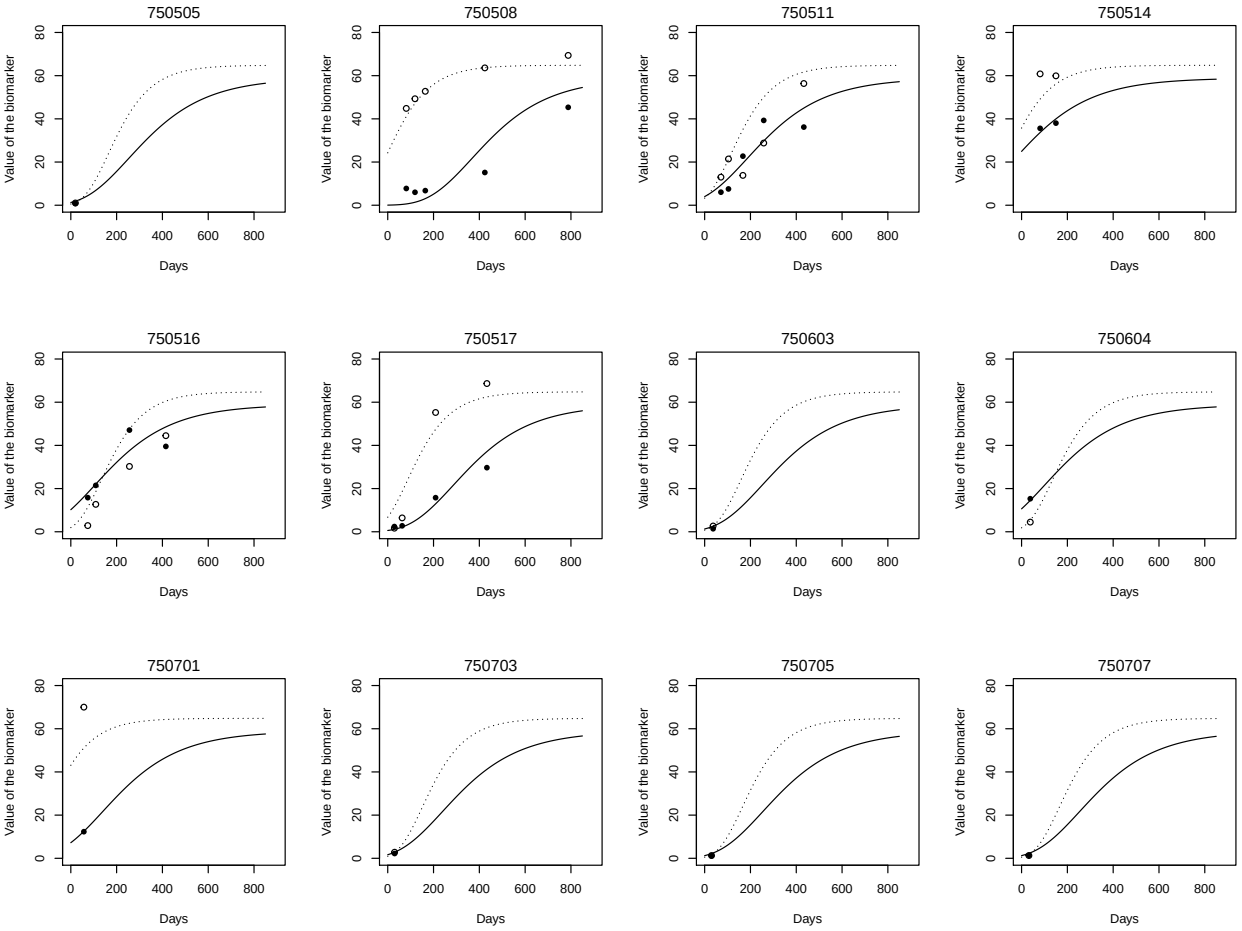

370207
440102
440103
440104
440105
440106
440107
440109
440114
440116
440117
440120
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

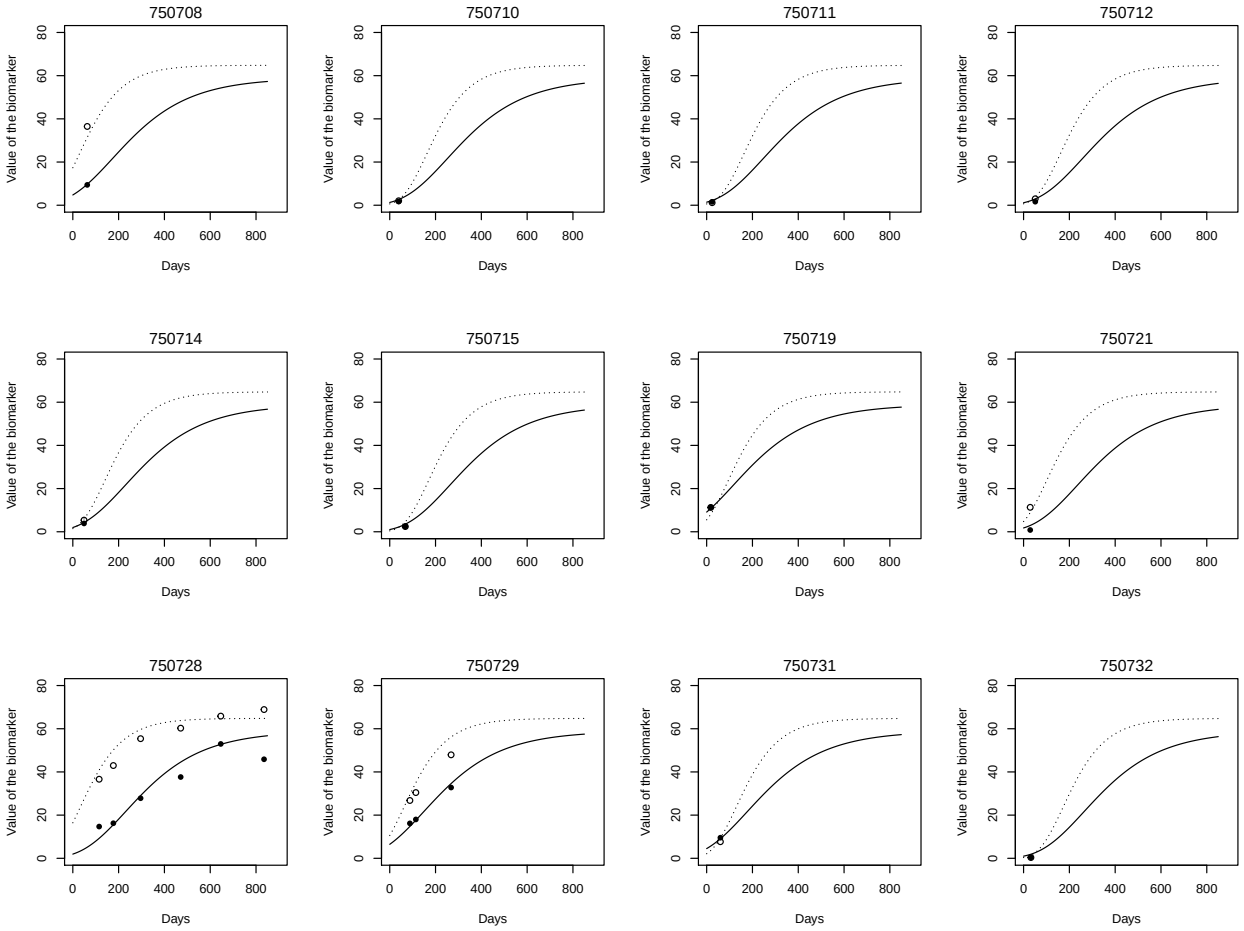

440123
440129
440136
490101
490104
490105
490106
490109
500101
590103
610101
630105
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

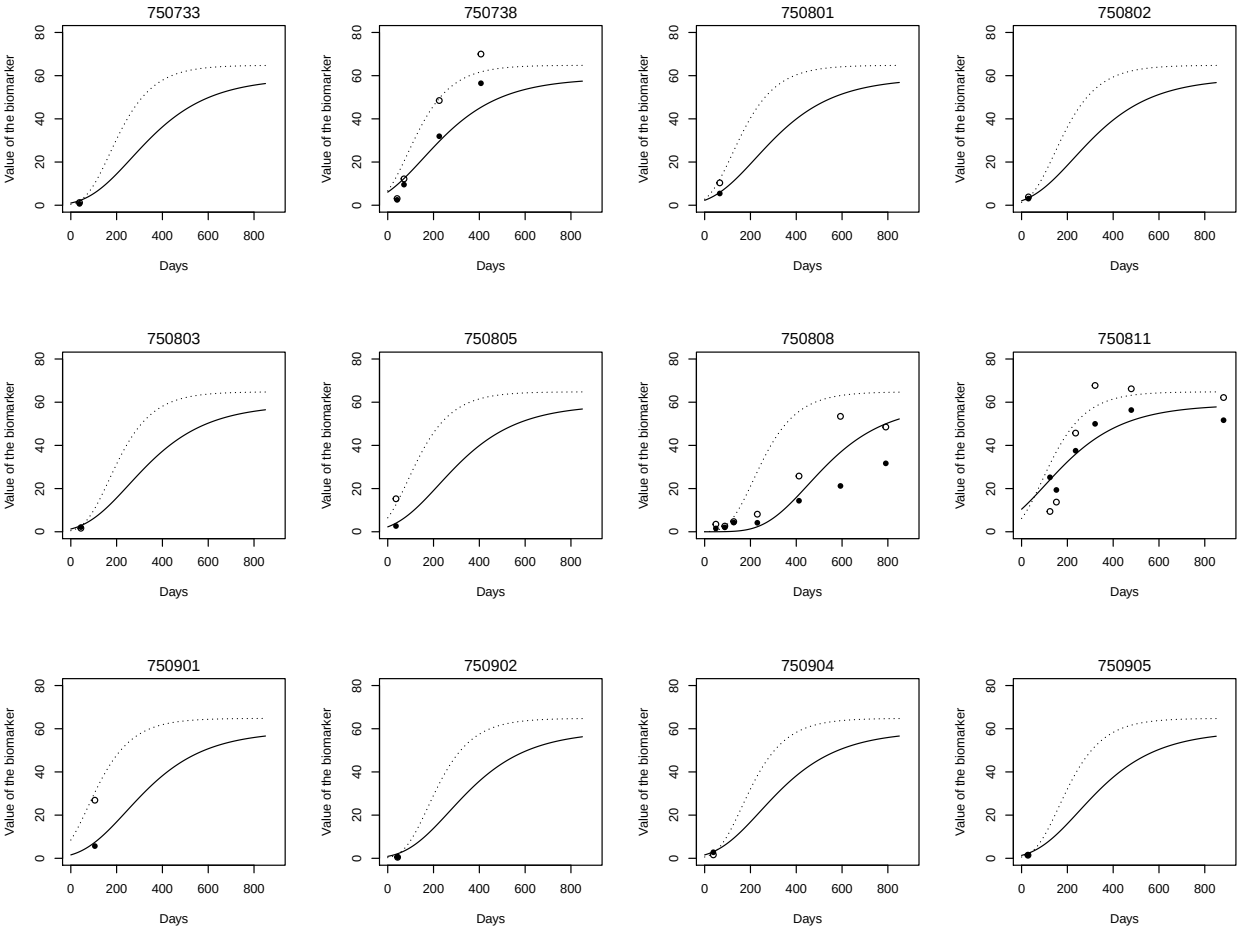

630113
660101
660105
660106
680101
680104
680107
680108
680110
680111
680202
680203
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800

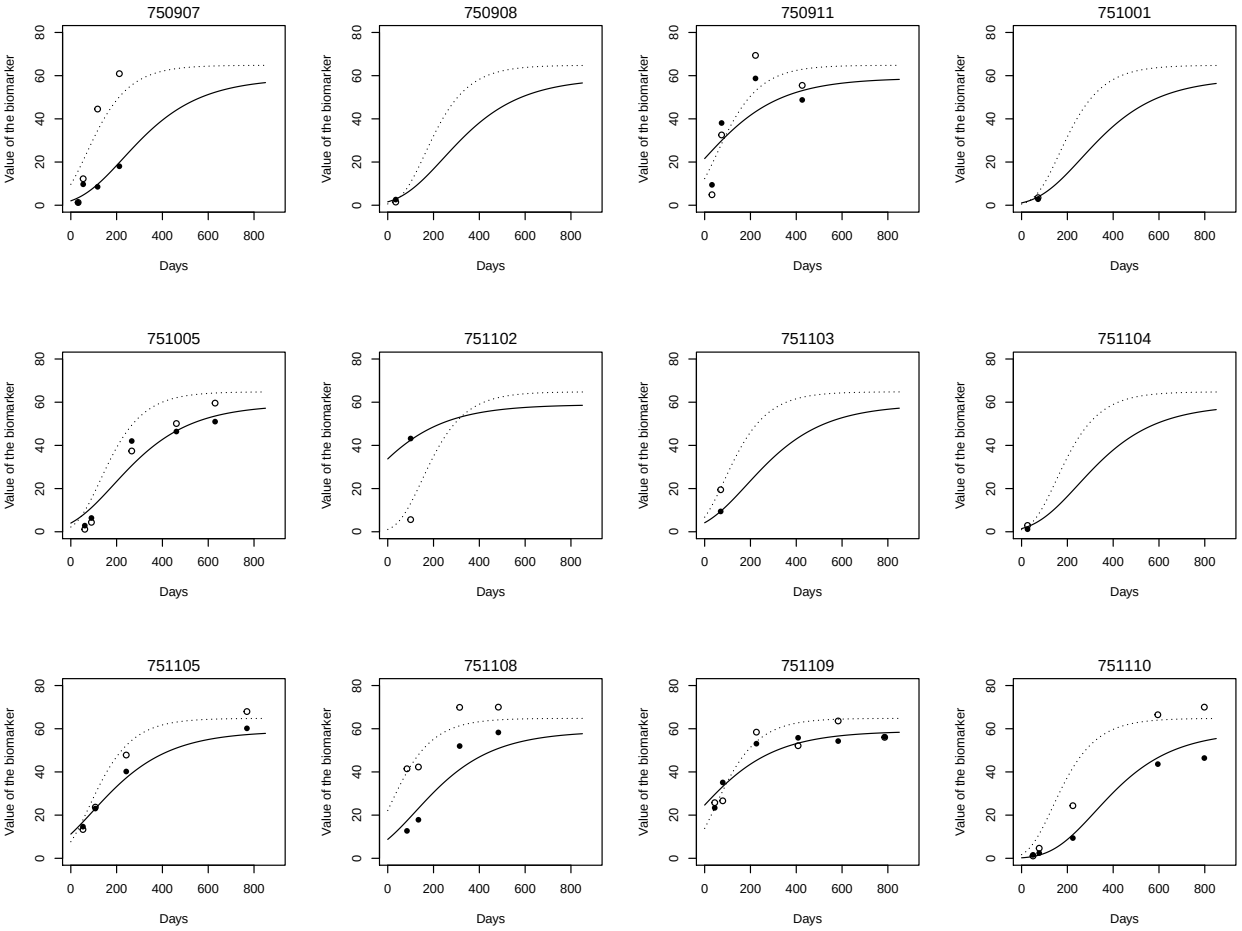

680204
690122
690123
690126
690128
690213
690216
750202
750206
750207
750208
750209
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


750302
750305
750306
750311
750401
750404
750406
750407
750408
750501
750502
750504
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


750505
750508
750511
750514
750516
750517
750603
750604
750701
750703
750705
750707
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


750708
750710
750711
750712
750714
750715
750719
750721
750728
750729
750731
750732
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


750733
750738
750801
750802
750803
750805
750808
750811
750901
750902
750904
750905
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


750907
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750911
751001
751005
751102
751103
751104
751105
751108
751109
751110
Value of the biomarker
Days
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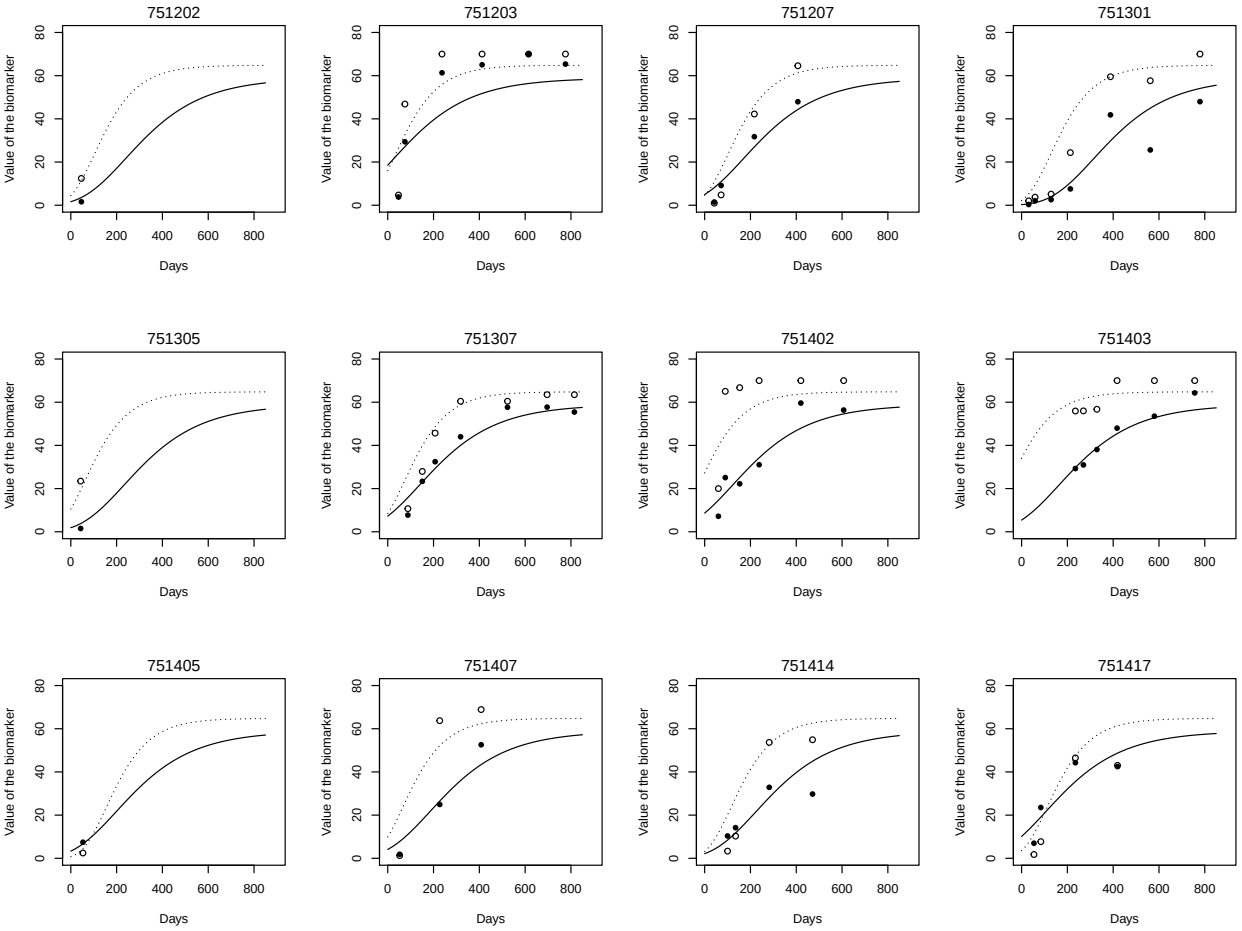
800


751202
751203
751207
751301
751305
751307
751402
751403
751405
751407
751414
751417
Value of the biomarker
Days
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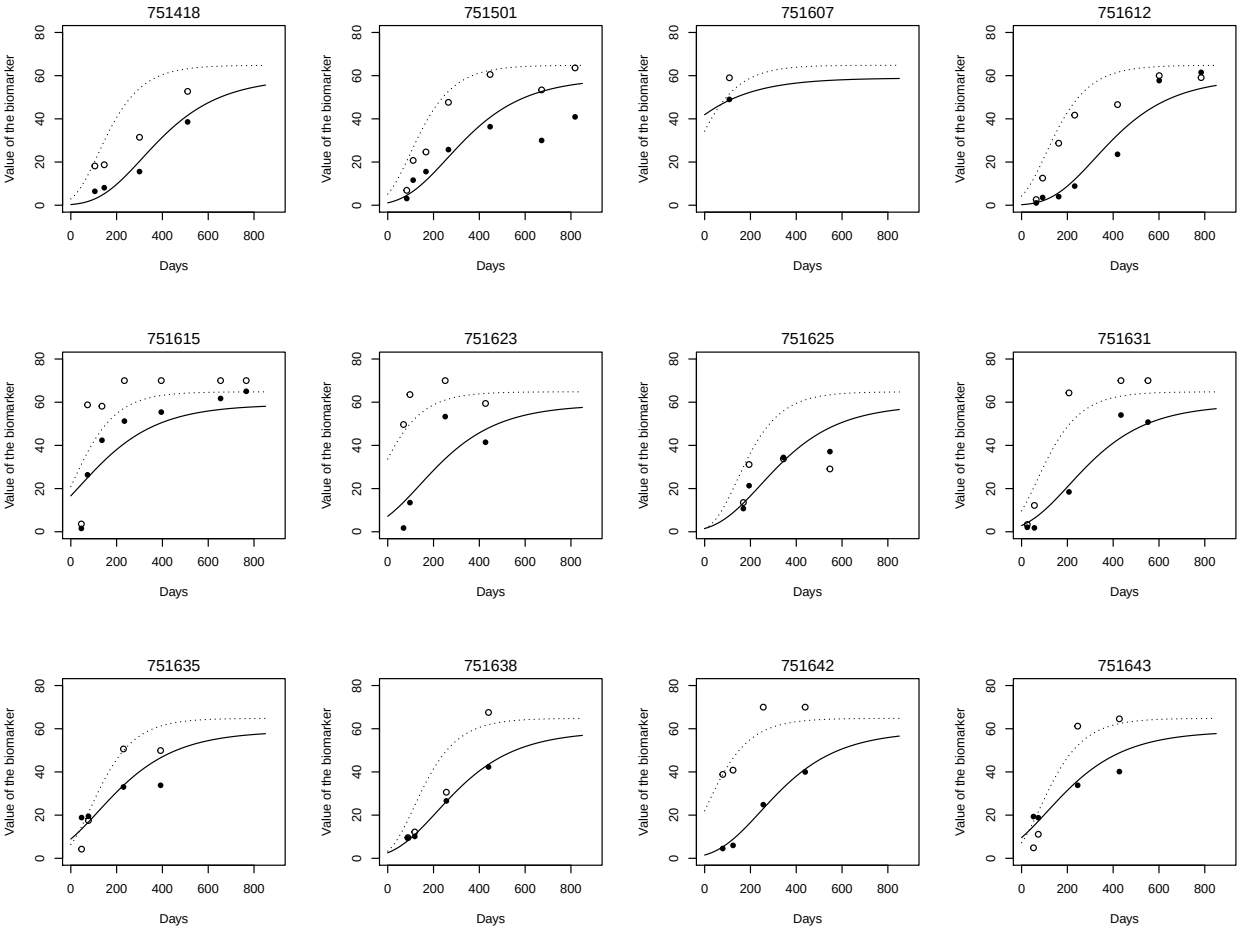
751418
751501
751607
751612
751615
751623
751625
751631
751635
751638
751642
751643
Value of the biomarker
Days
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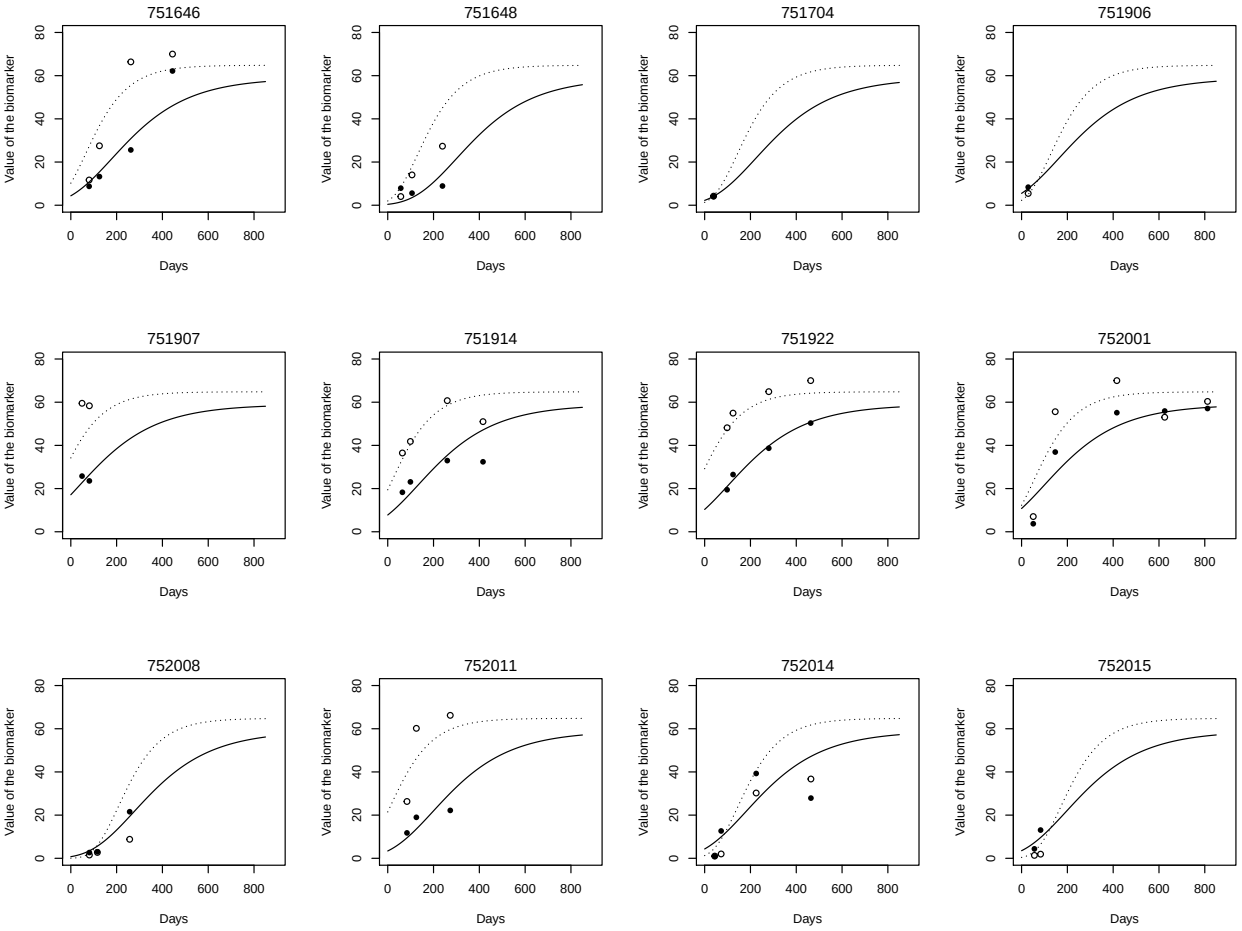
400
600
800


751646
751648
751704
751906
751907
751914
751922
752001
752008
752011
752014
752015
Value of the biomarker
Days
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80
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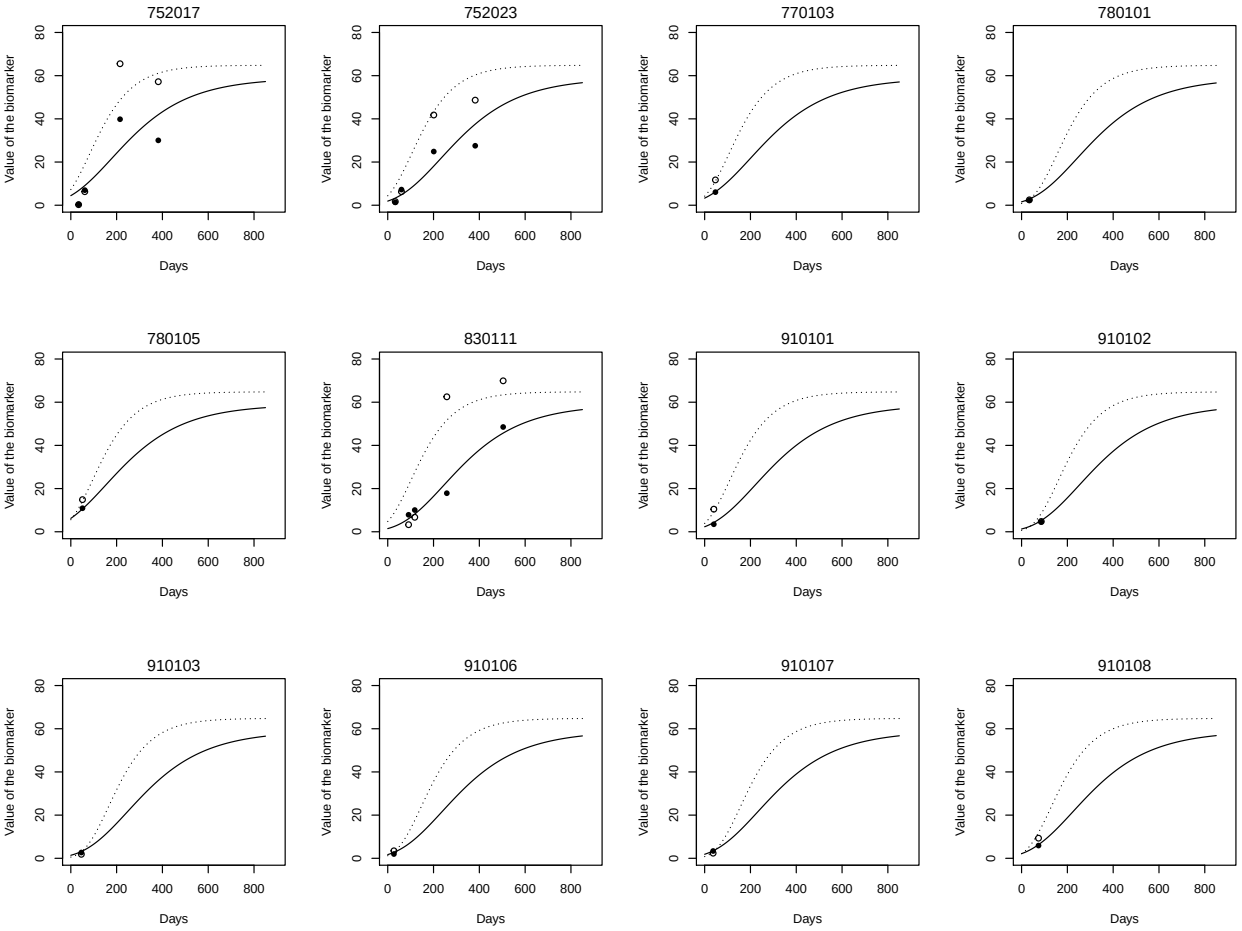
400
600
800


752017
752023
770103
780101
780105
830111
910101
910102
910103
910106
910107
910108
Value of the biomarker
Days
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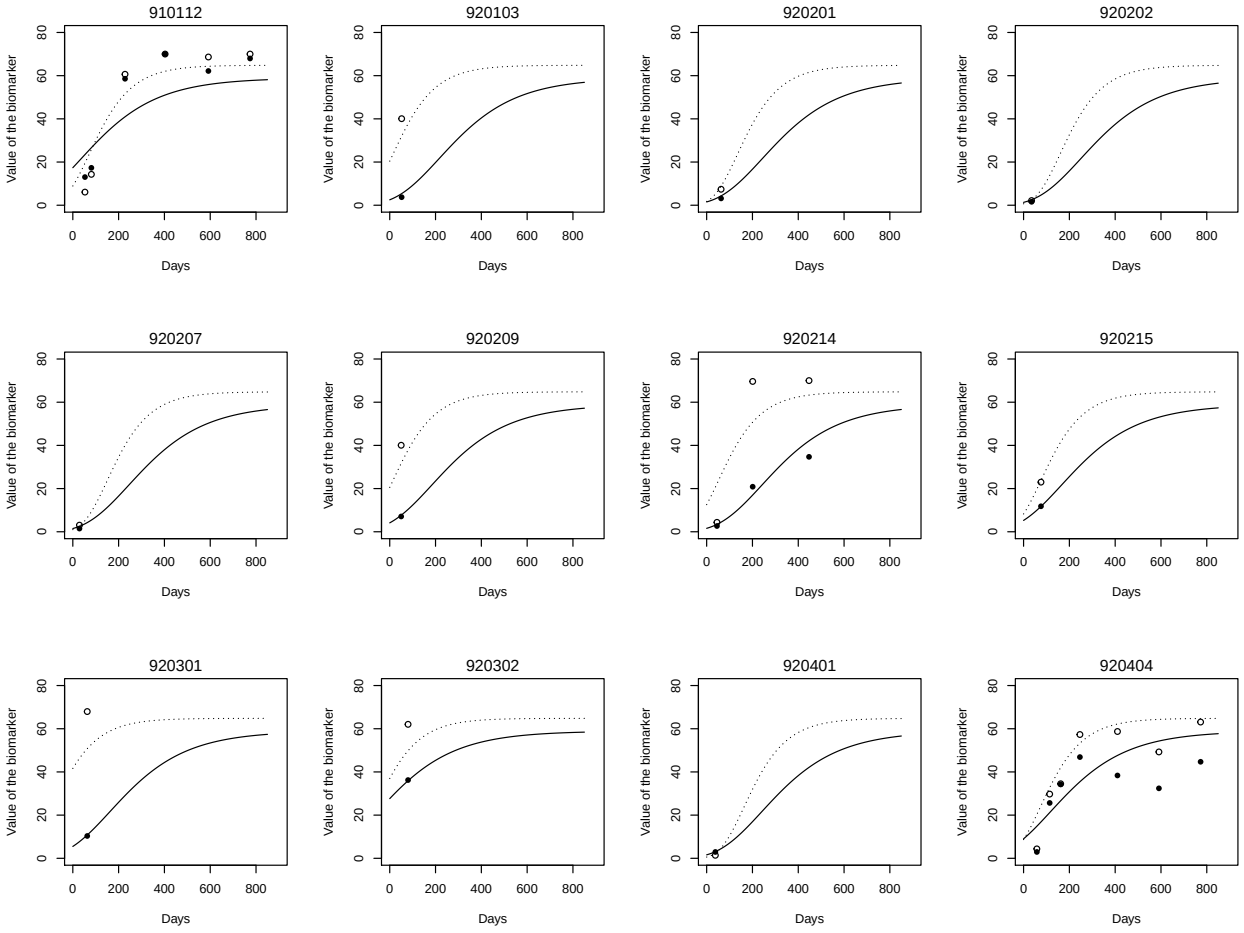
600
800


910112
920103
920201
920202
920207
920209
920214
920215
920301
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920401
920404
Value of the biomarker
Days
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600
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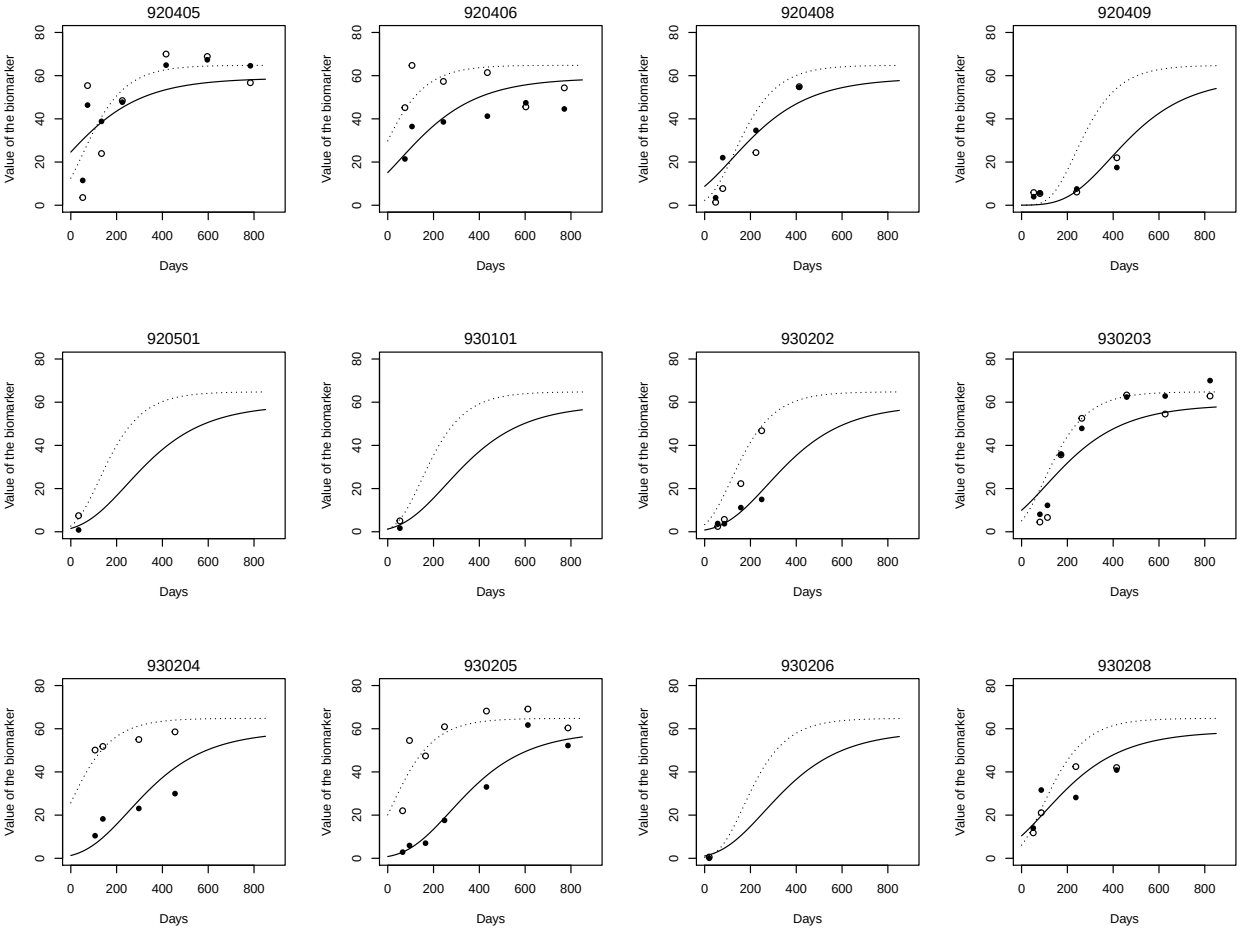
920405
920406
920408
920409
920501
930101
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930203
930204
930205
930206
930208
Value of the biomarker
Days
0
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40
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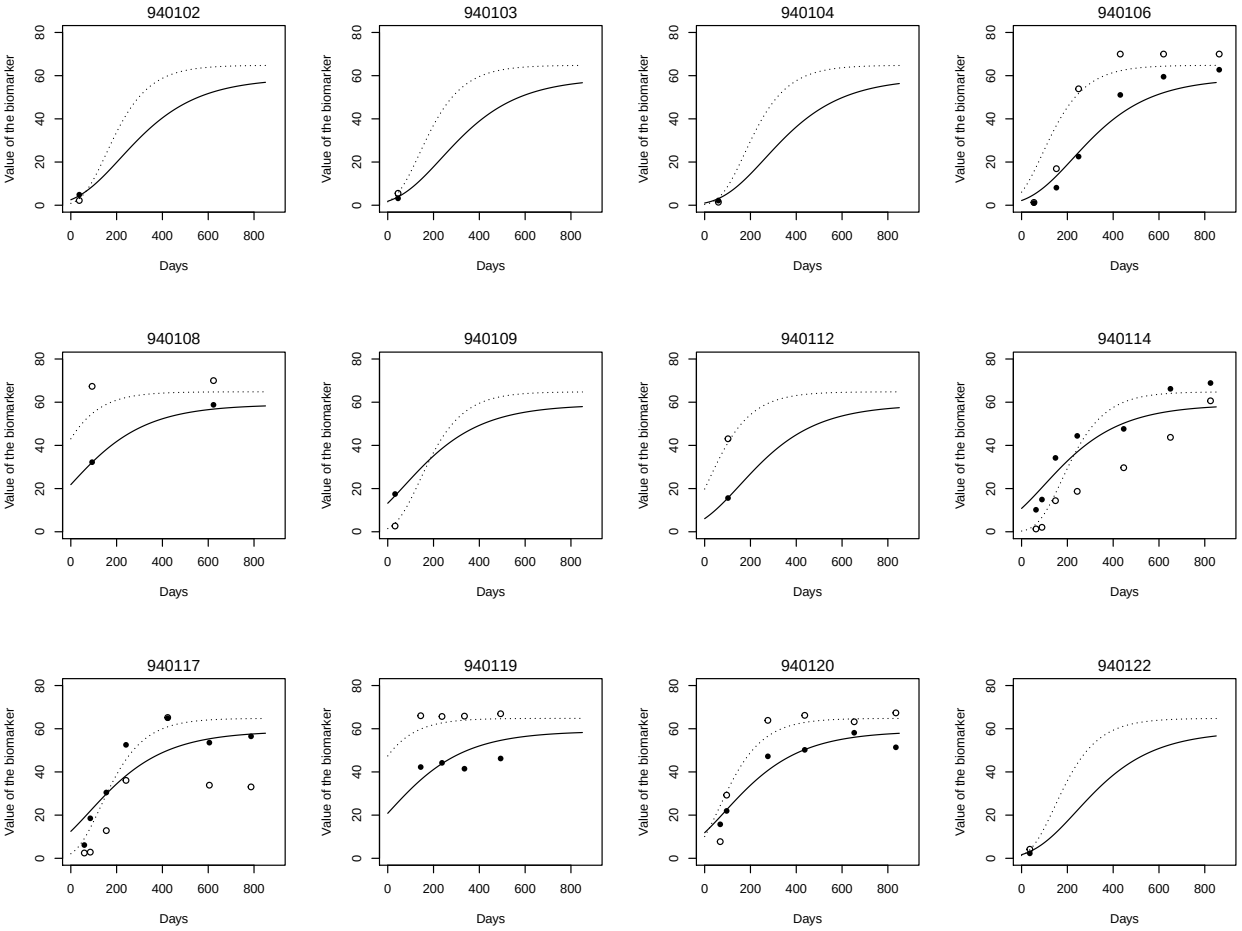
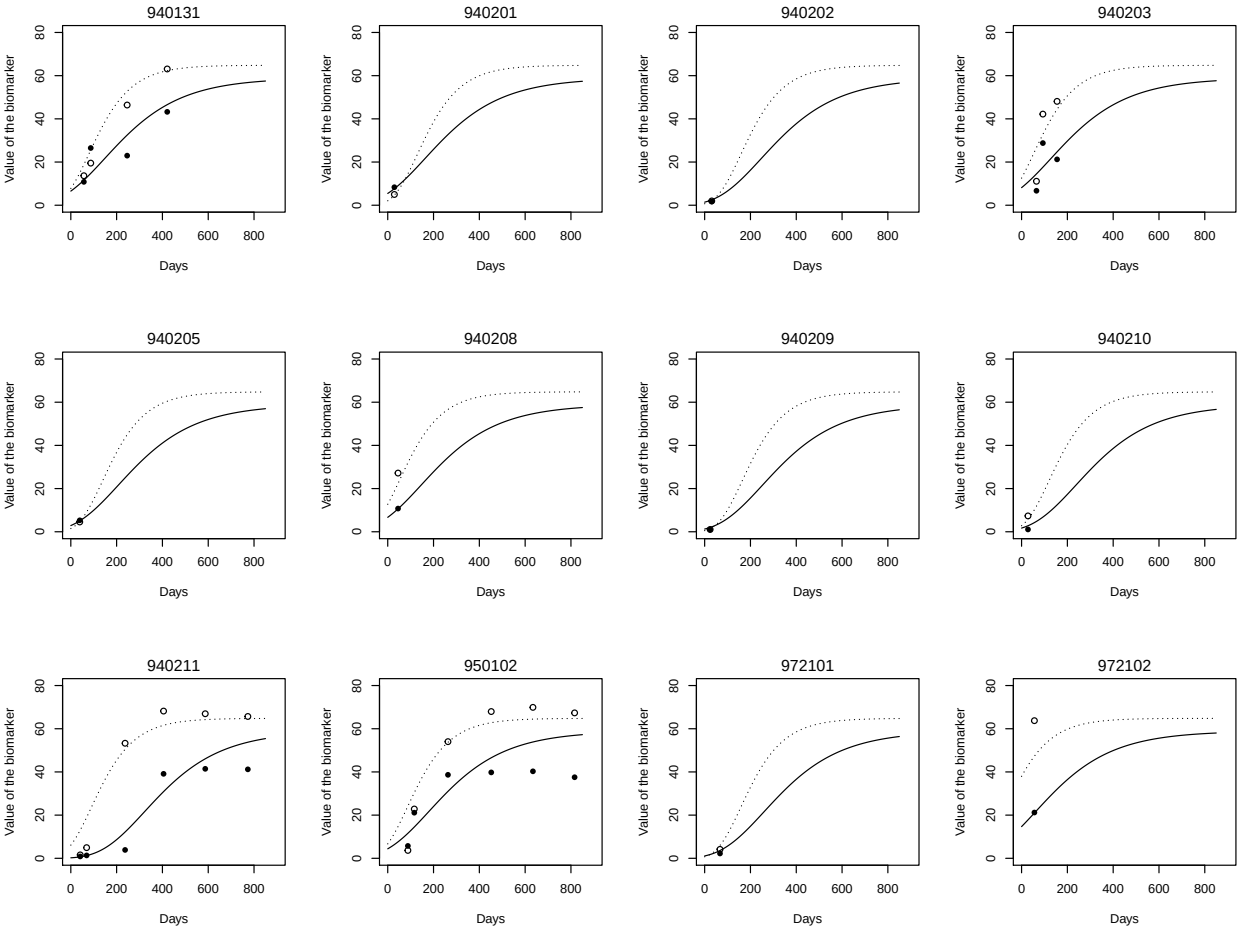
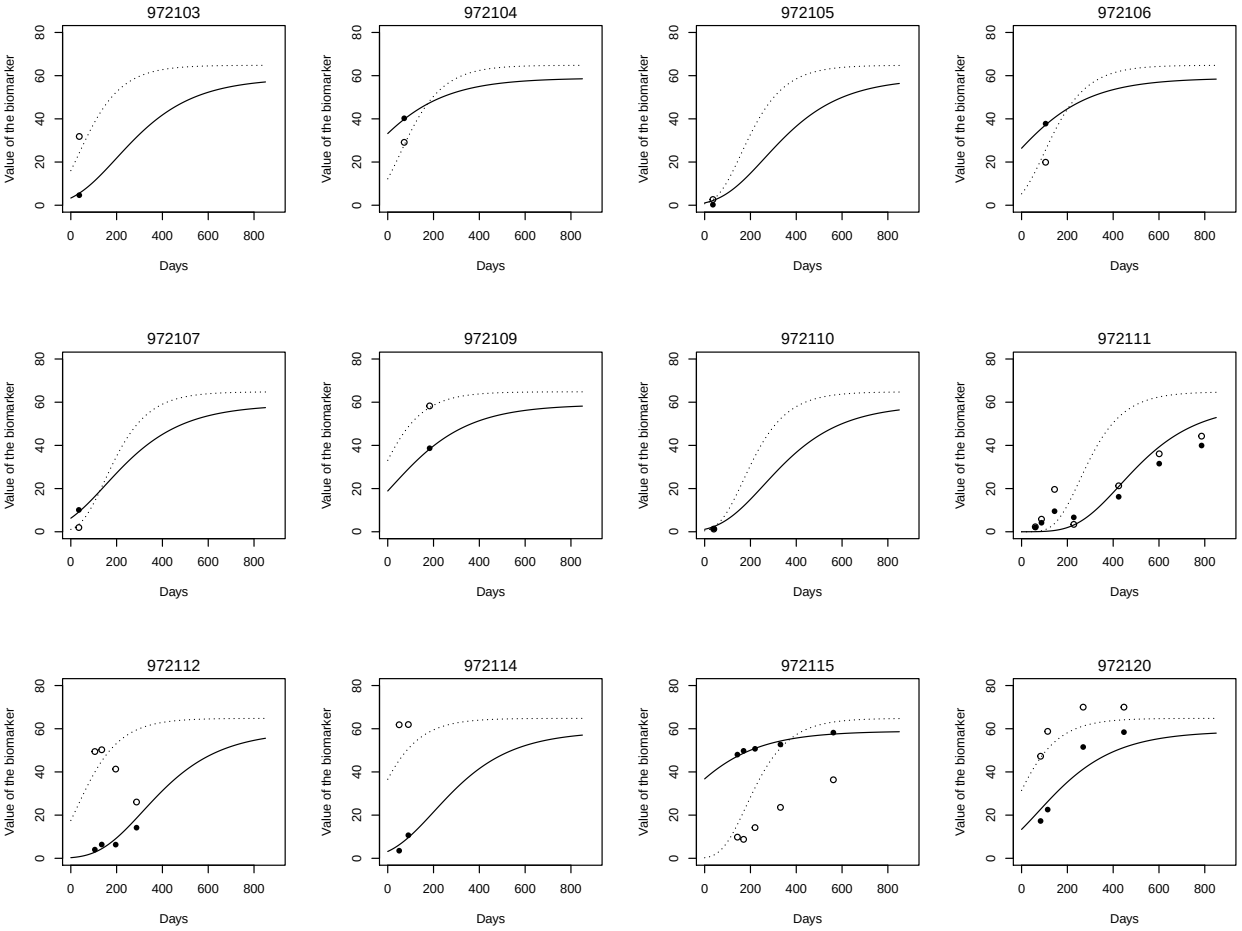
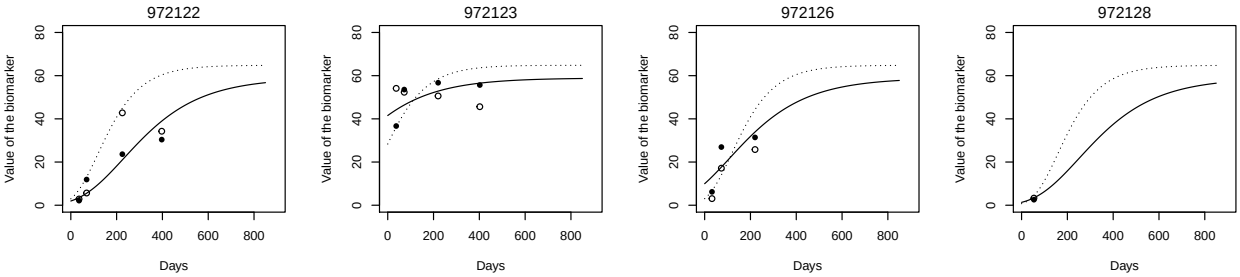
80
0
200
400
600
800


940102
940103
940104
940106
940108
940109
940112
940114
940117
940119
940120
940122
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


940131
940201
940202
940203
940205
940208
940209
940210
940211
950102
972101
972102
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


972103
972104
972105
972106
972107
972109
972110
972111
972112
972114
972115
972120
Value of the biomarker
Days
0
20
40
60
80
0
200
400
600
800


972122
Value of the biomarker
0
20
40
60
80
0
200
400
600
800
Days
972123
Value of the biomarker
0
20
40
60
80
0
200
400
600
800
Days
972126
Value of the biomarker
0
20
40
60
80
0
200
400
600
800
Days
972128
Value of the biomarker
0
20
40
60
80
0
200
400
600
800
Days

Values of the TM and V3 biomarkers for the four individuals who did not converge:

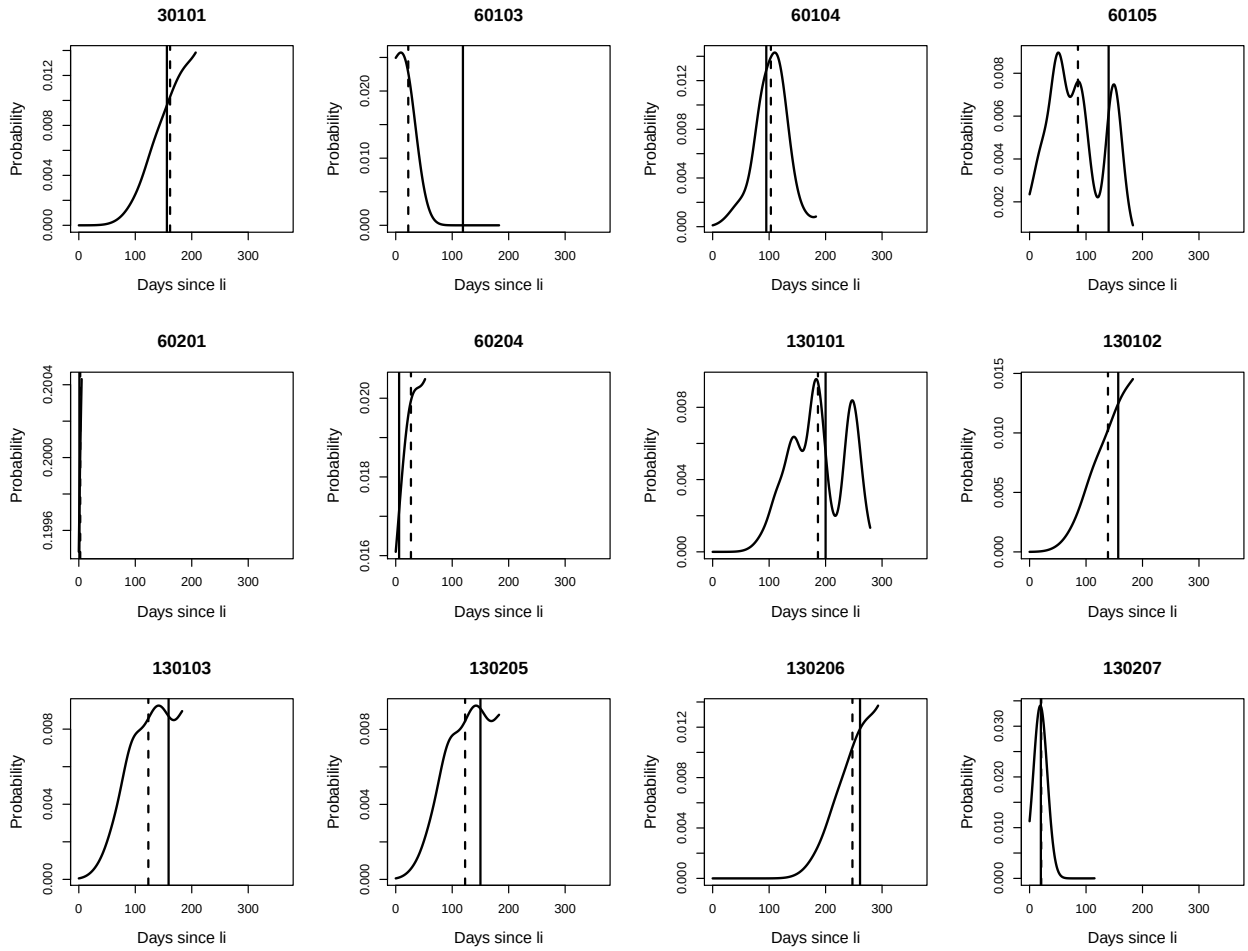
id	TM	V3	tps
220103	29.44	68.64	92
220103	36.20	69.38	126
220103	42.74	70.00	174
220103	41.26	70.00	266
220103	51.56	70.00	447
220103	51.64	58.48	629
220103	57.02	63.34	814

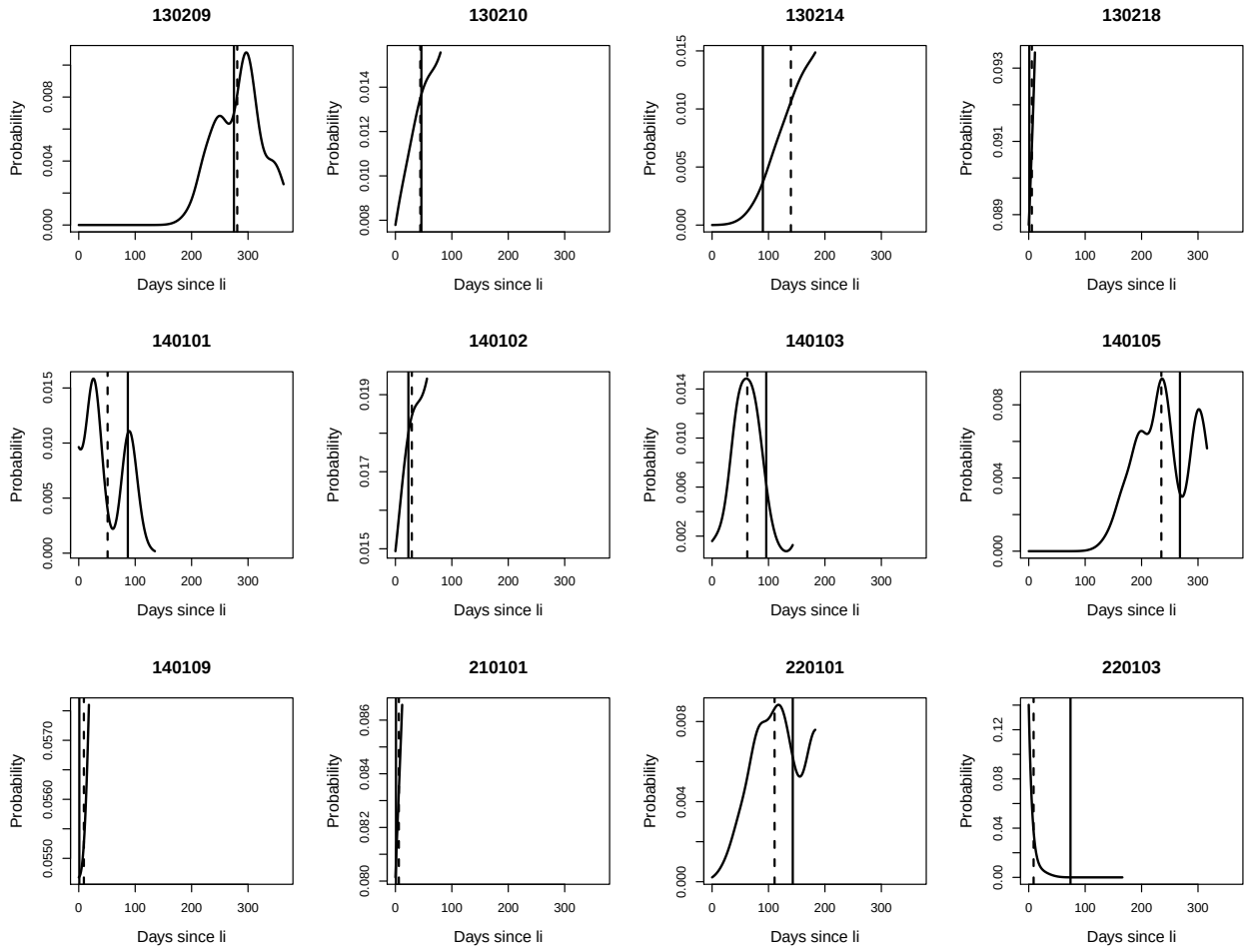
id	TM	V3	tps
751406	51.08	66.94	103
751406	54.24	70.00	133
751406	48.24	66.38	194
751406	53.32	70.00	271
751406	57.52	70.00	452
751406	63.74	70.00	634

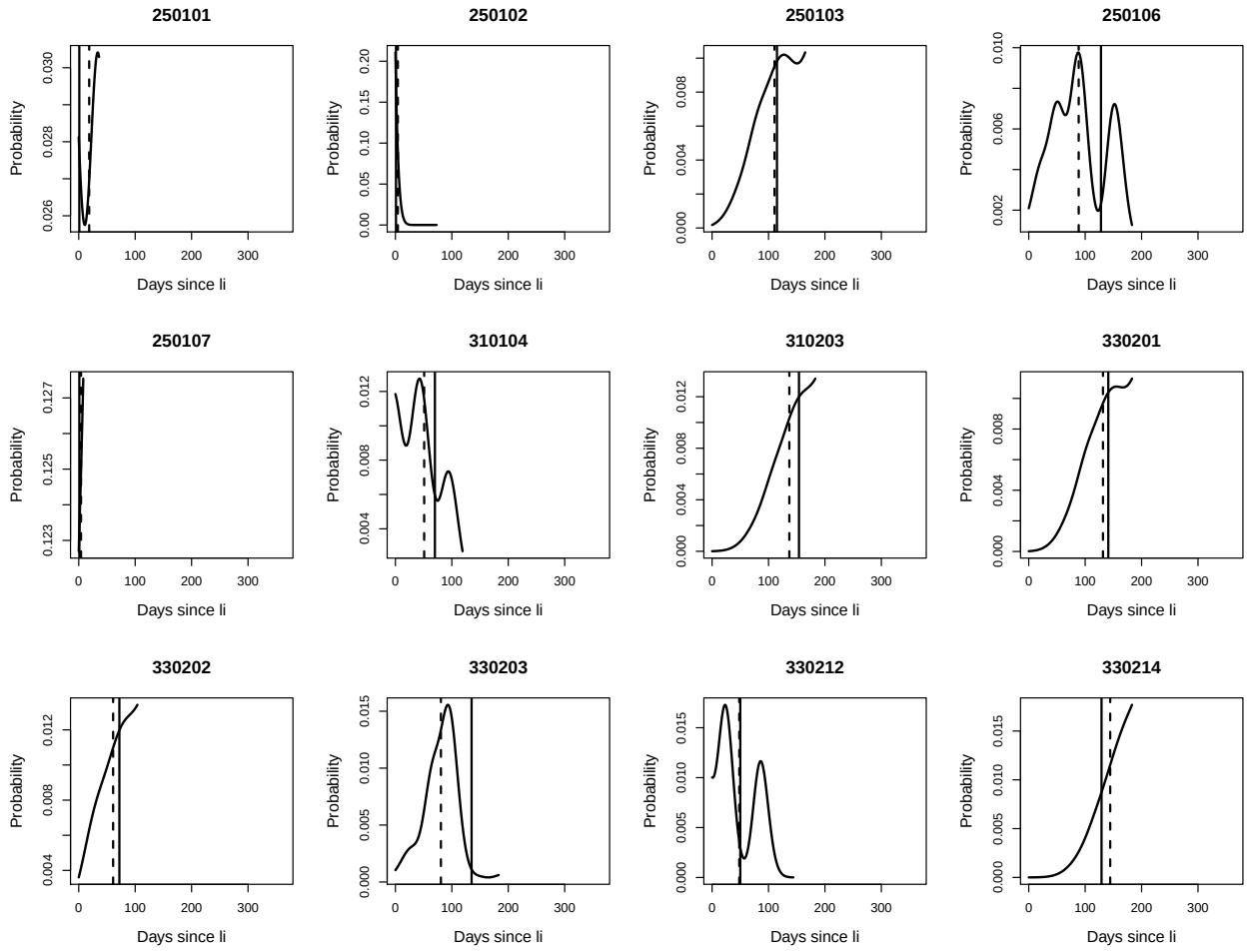
id	TM	V3	tps
751617	49.10	70.00	115
751617	54.42	68.40	150
751617	55.44	70.00	262
751617	62.04	69.62	416
751617	70.00	70.00	878

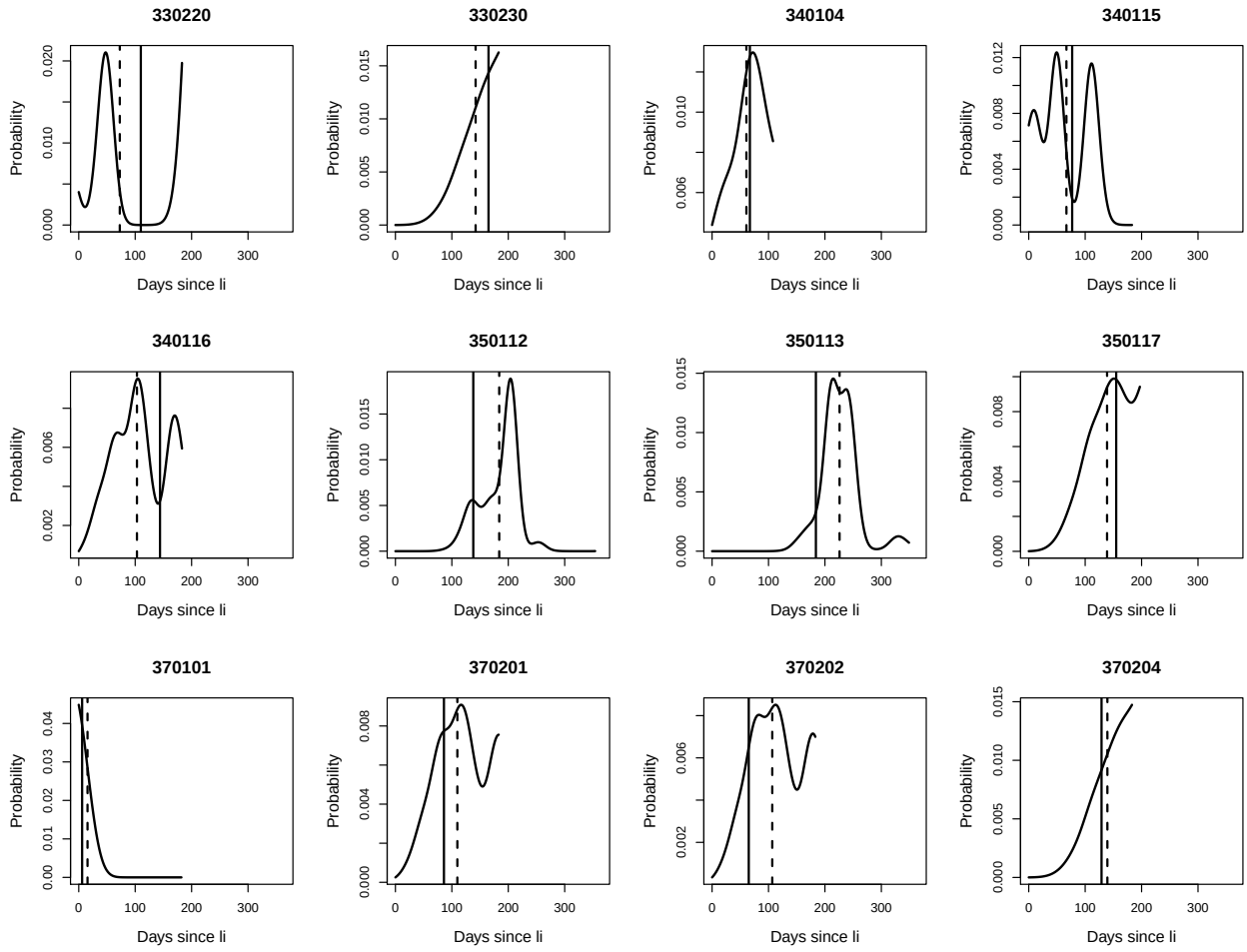
id	TM	V3	tps
751903	42.14	67.14	77
751903	50.14	61.72	99
751903	63.60	70.00	165
751903	67.96	70.00	250
751903	70.00	70.00	432

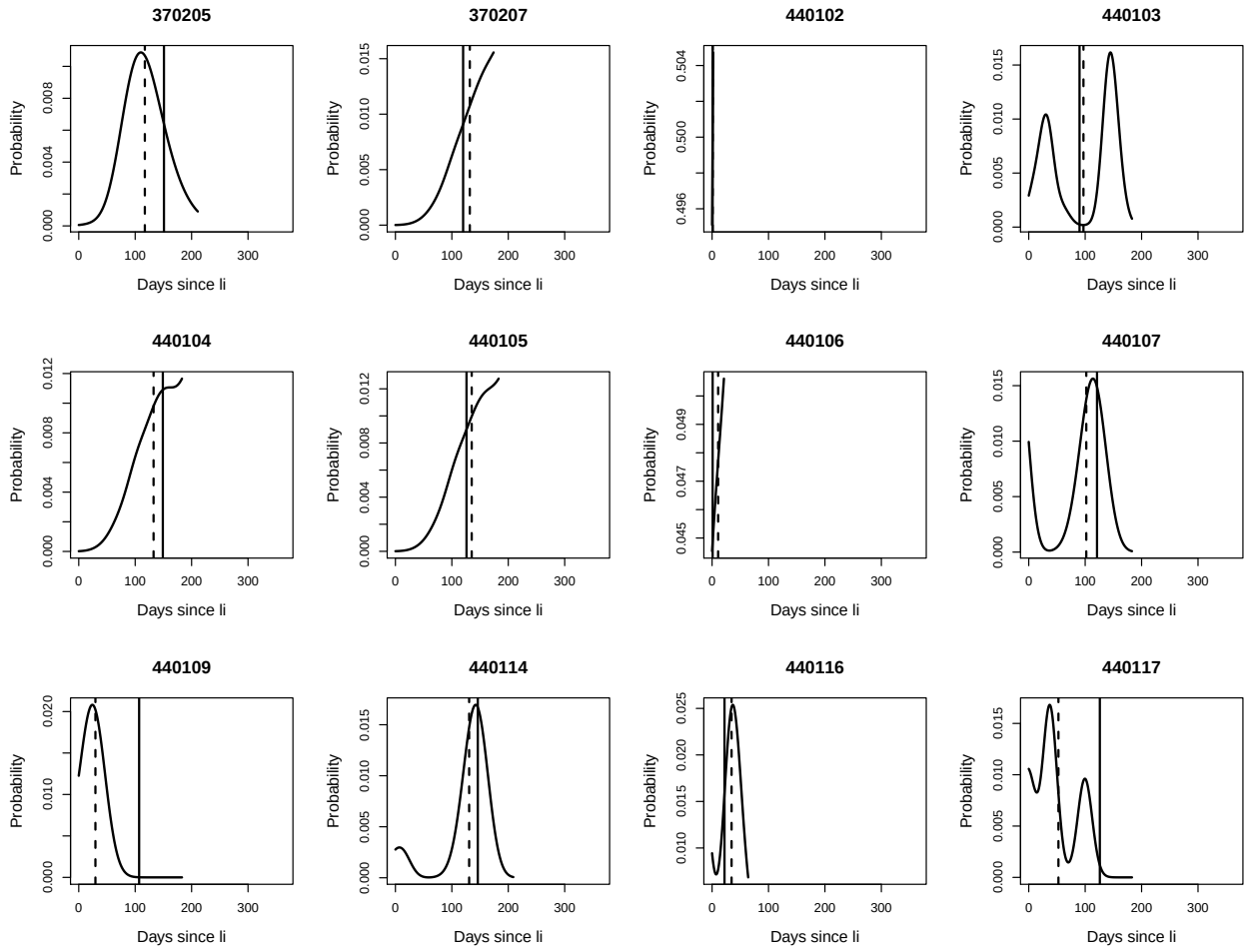
Posterior density and posterior expectation value (vertical dotted line) of the infection time for all the individuals of the PRIMO ANRS-C06 cohort. The vertical line represents the date of infection of subjects in the PRIMO ANRS-C06 cohort

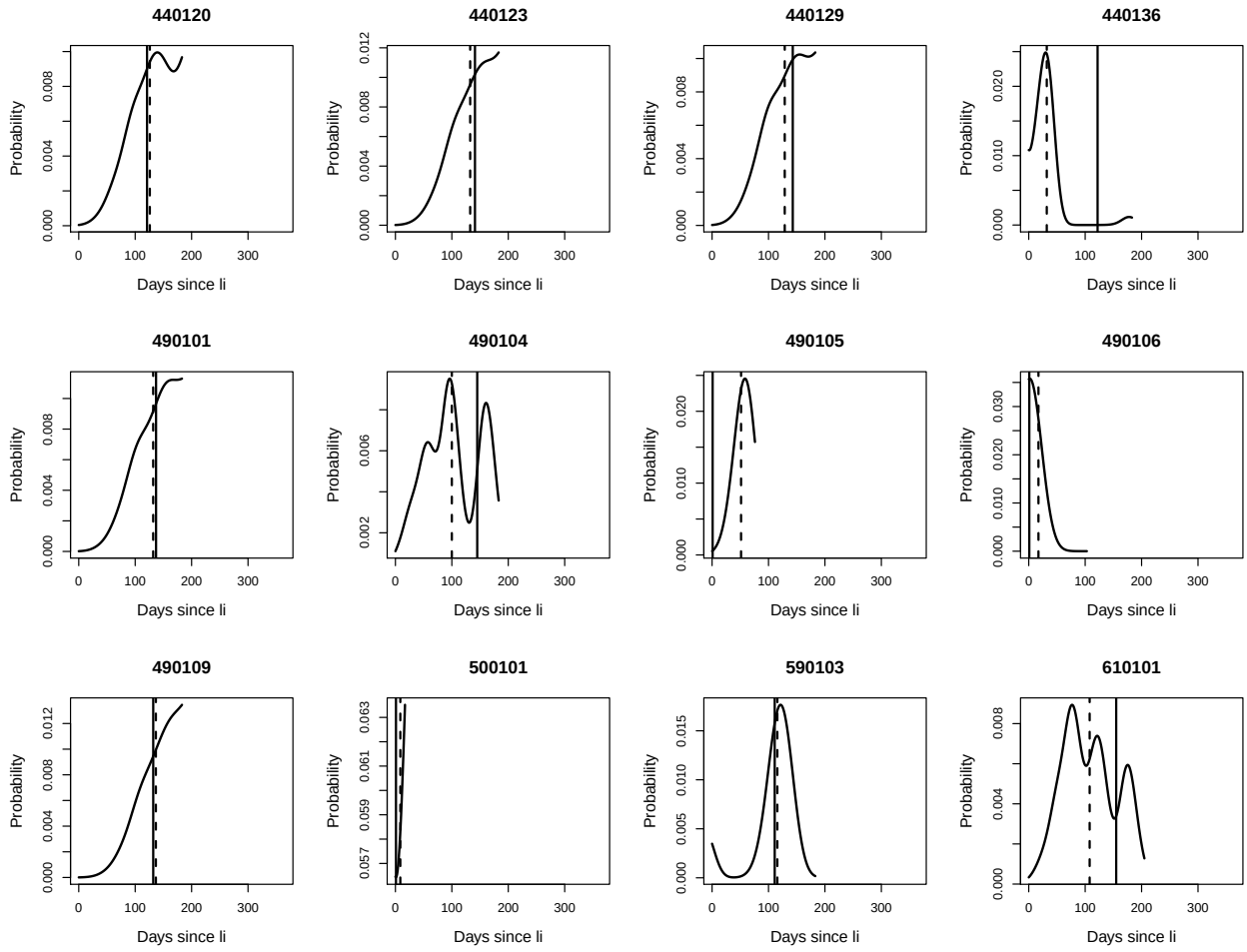


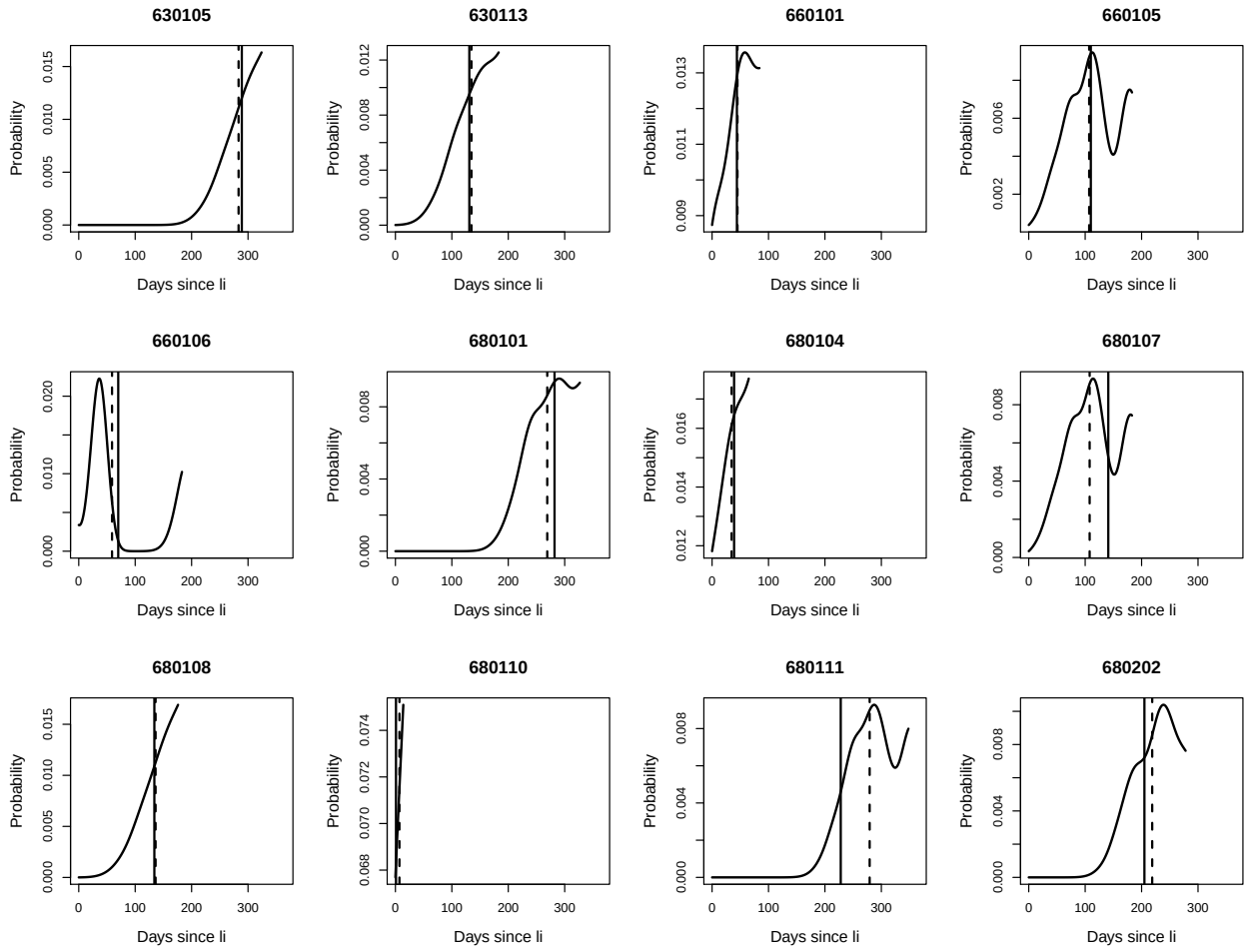

130209
130210
130214
130218
140101
140102
140103
140105
140109
210101
220101
220103
Probability
Days since li

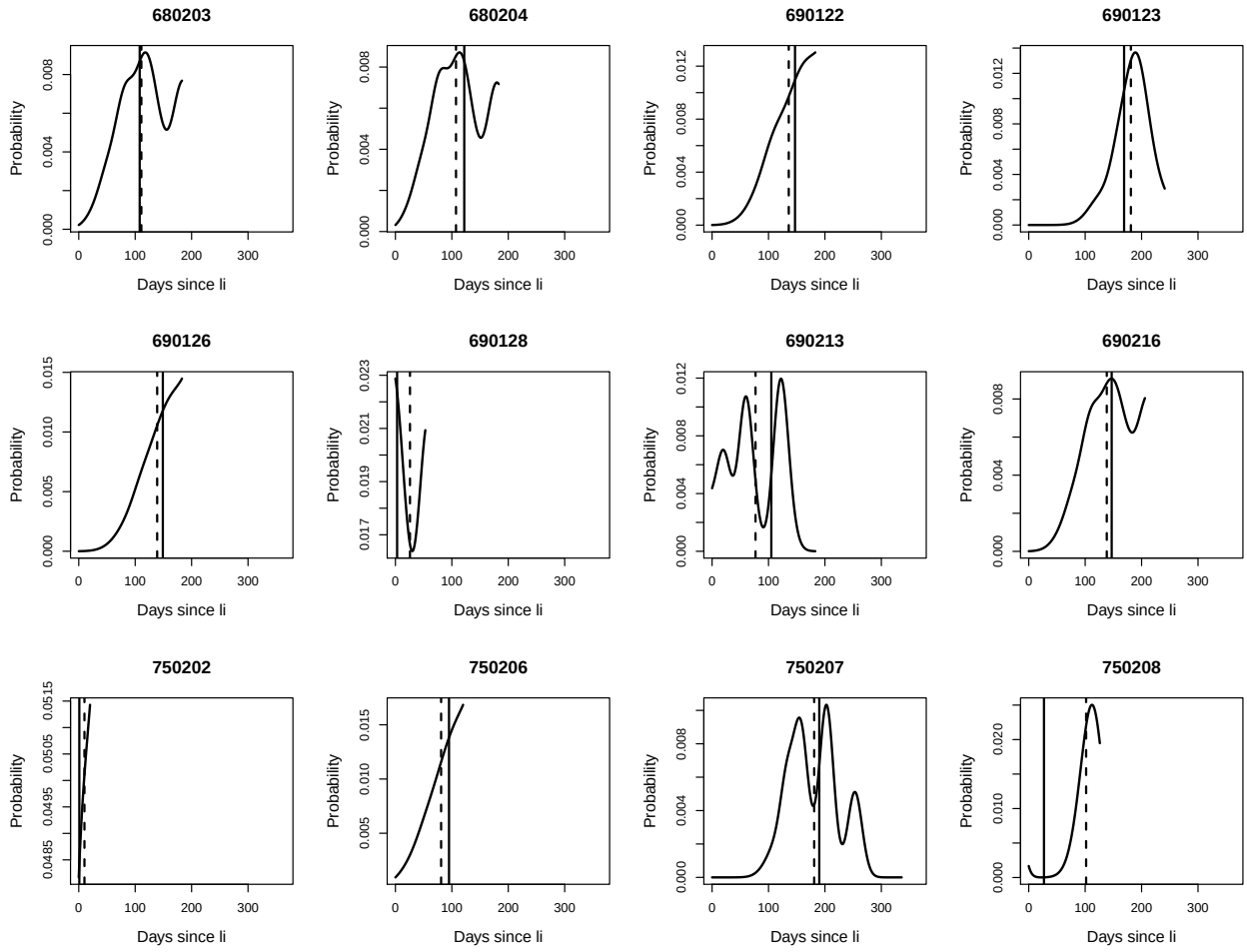

250101
250102
250103
250106
250107
310104
310203
330201
330202
330203
330212
330214
Probability
Days since li

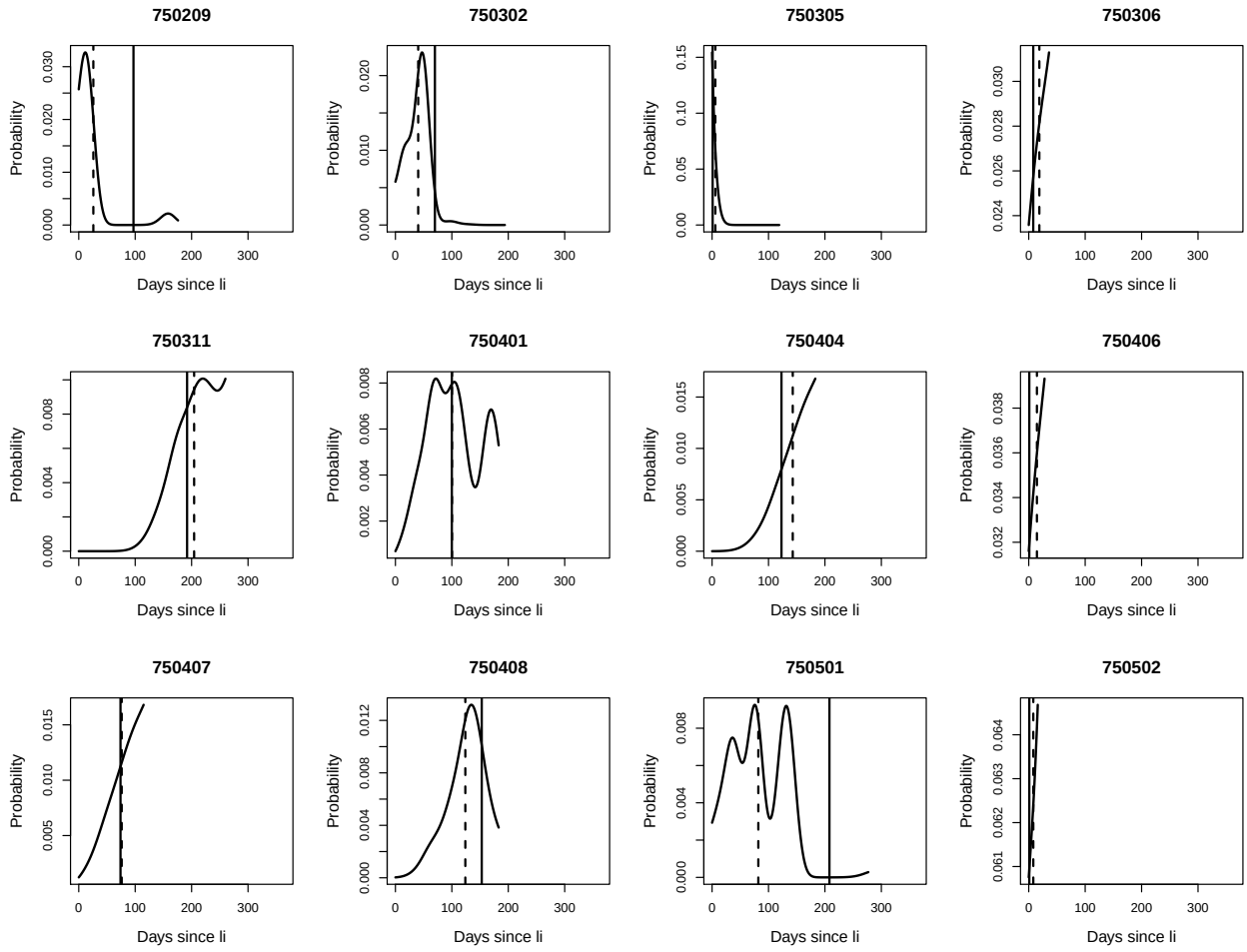

330220
330230
340104
340115
340116
350112
350113
350117
370101
370201
370202
370204
Probability
Days since li

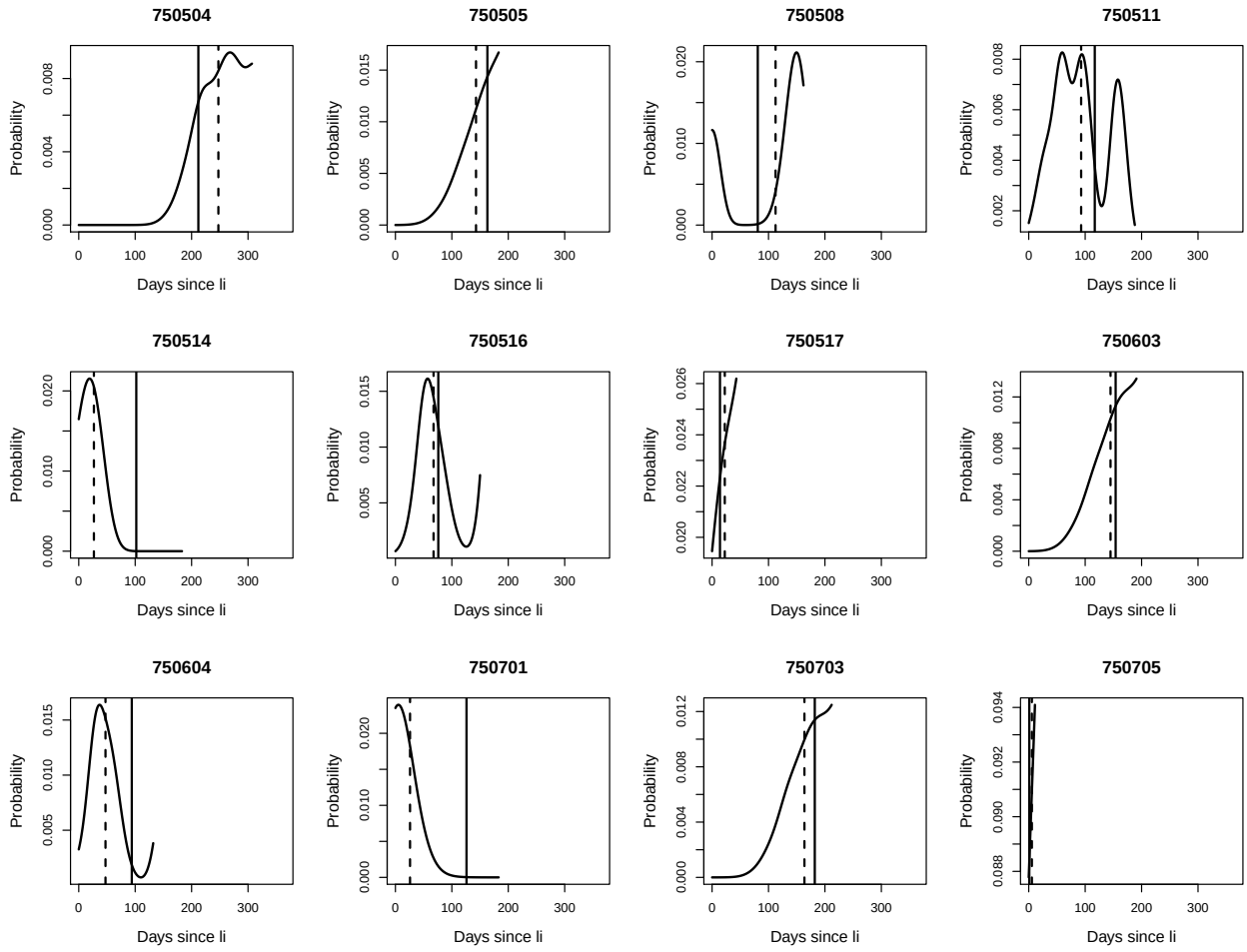

370205
370207
440102
440103
440104
440105
440106
440107
440109
440114
440116
440117
Probability
Days since li


440120
440123
440129
440136
490101
490104
490105
490106
490109
500101
590103
610101
Probability
Days since li


630105
630113
660101
660105
660106
680101
680104
680107
680108
680110
680111
680202
Probability
Days since li


680203
680204
690122
690123
690126
690128
690213
690216
750202
750206
750207
750208
Probability
Days since li


750209
750302
750305
750306
750311
750401
750404
750406
750407
750408
750501
750502
Probability
Days since li


750504
750505
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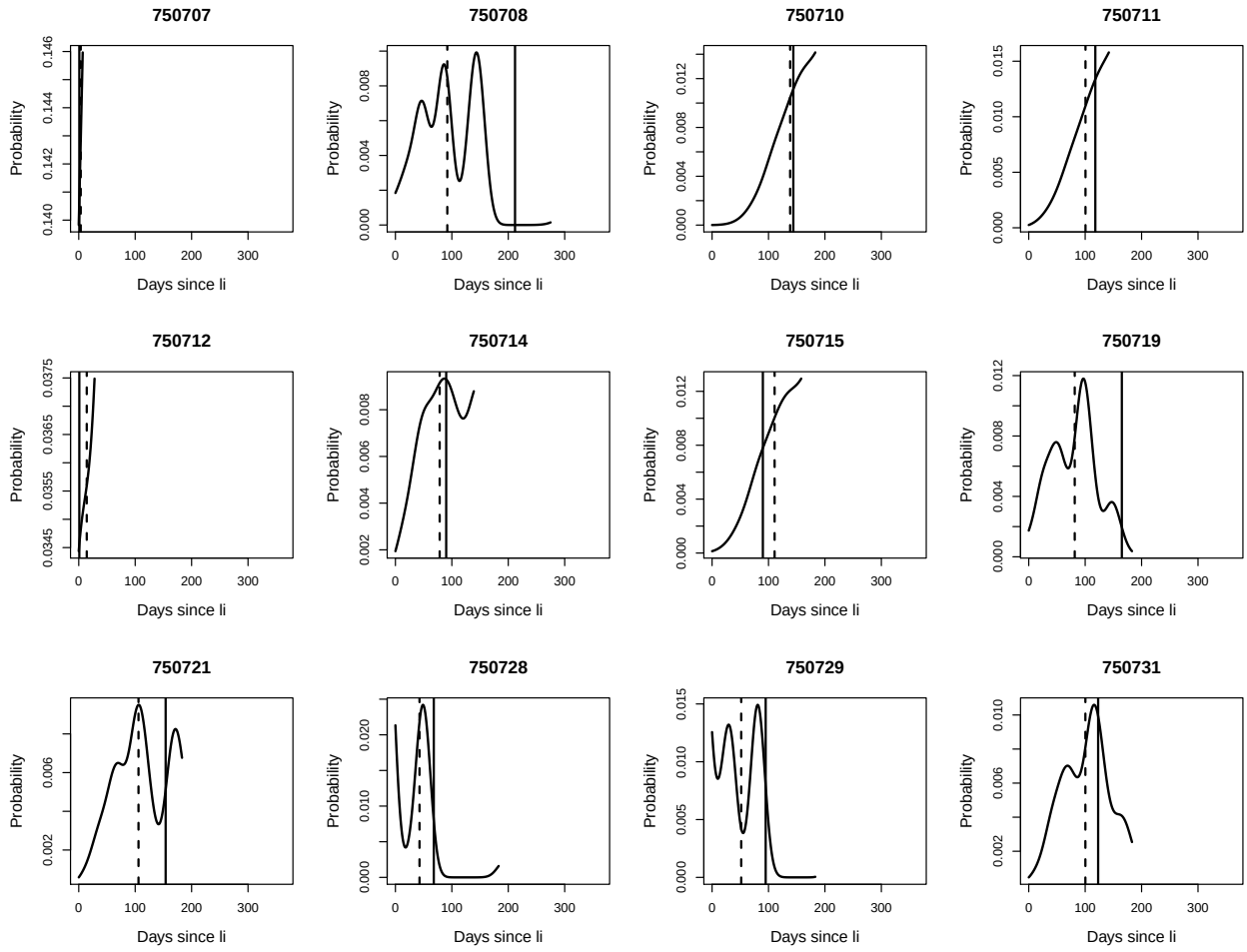
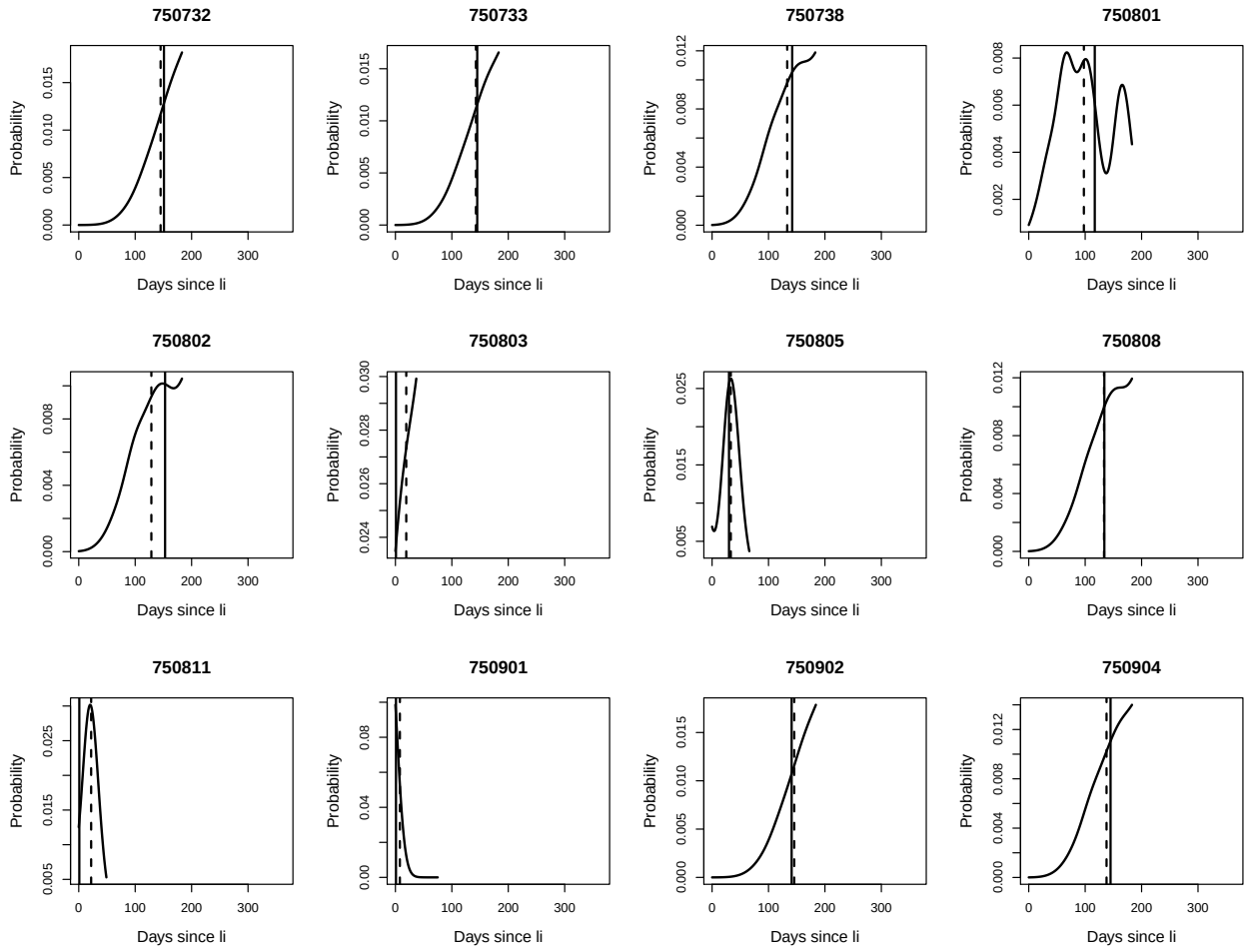
750511
750514
750516
750517
750603
750604
750701
750703
750705
Probability
Days since li


750707
750708
750710
750711
750712
750714
750715
750719
750721
750728
750729
750731
Probability
Days since li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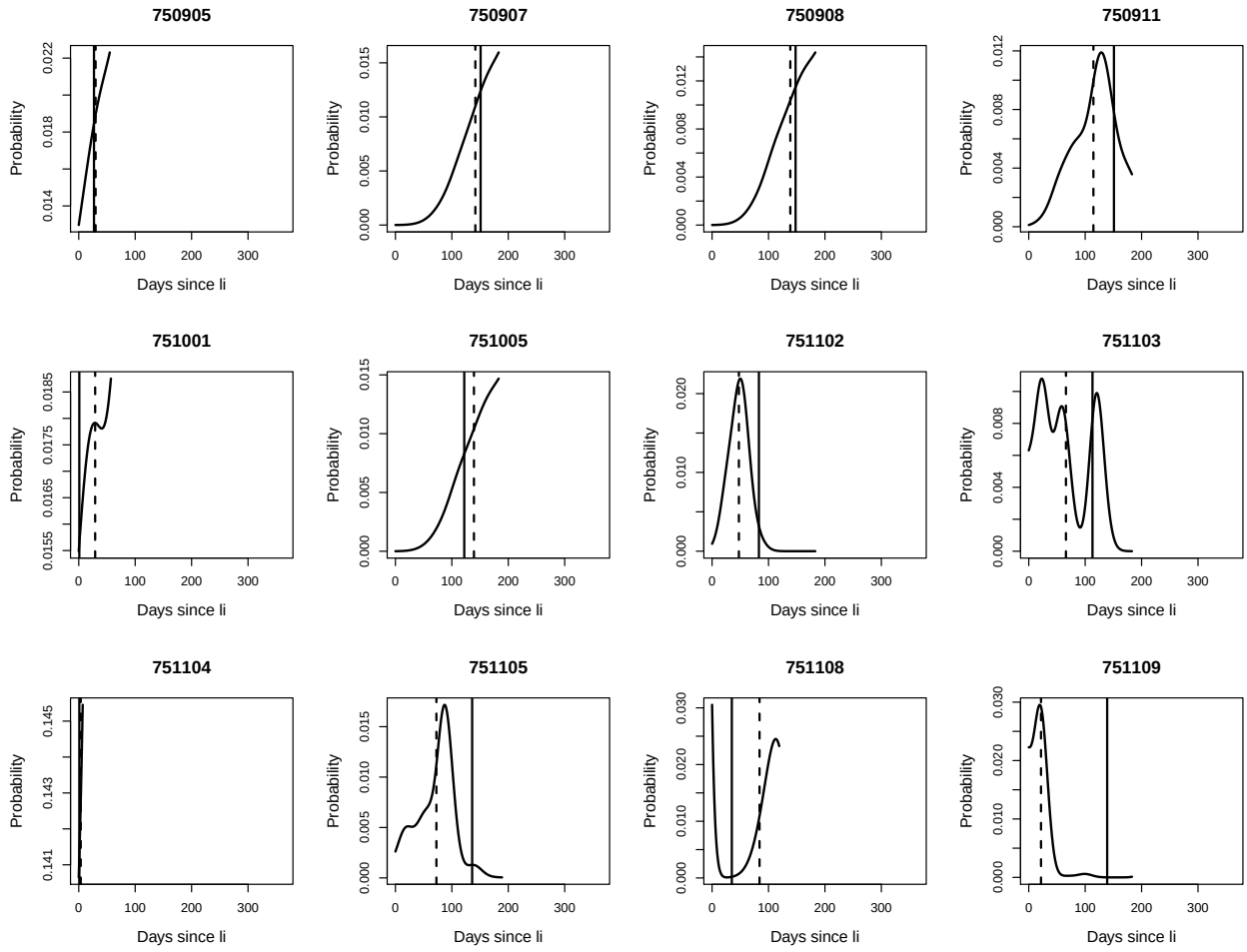
750801
750802
750803
750805
750808
750811
750901
750902
750904
Probability
Days since li


750905
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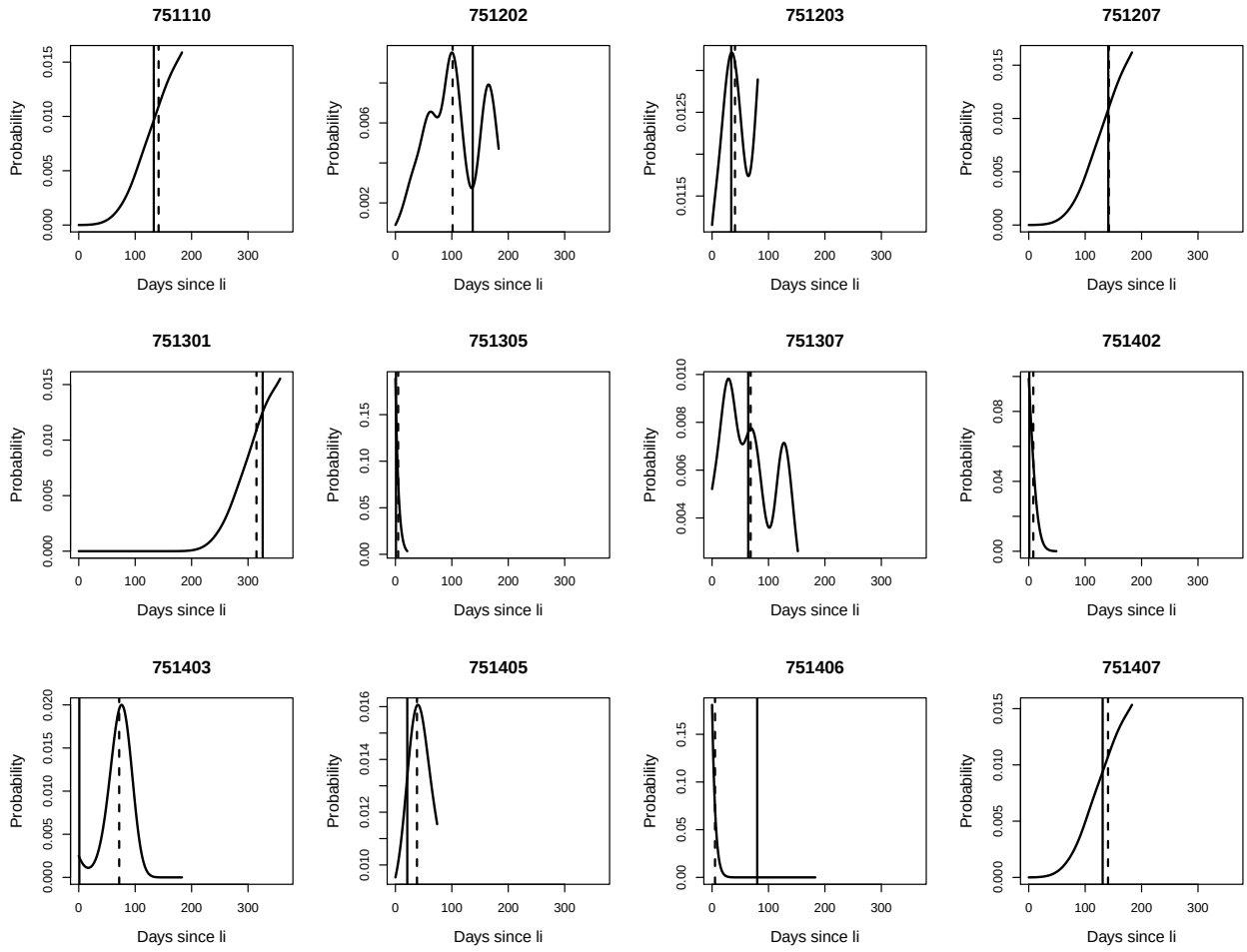
750908
750911
751001
751005
751102
751103
751104
751105
751108
751109
Probability
Days since li


751110
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751203
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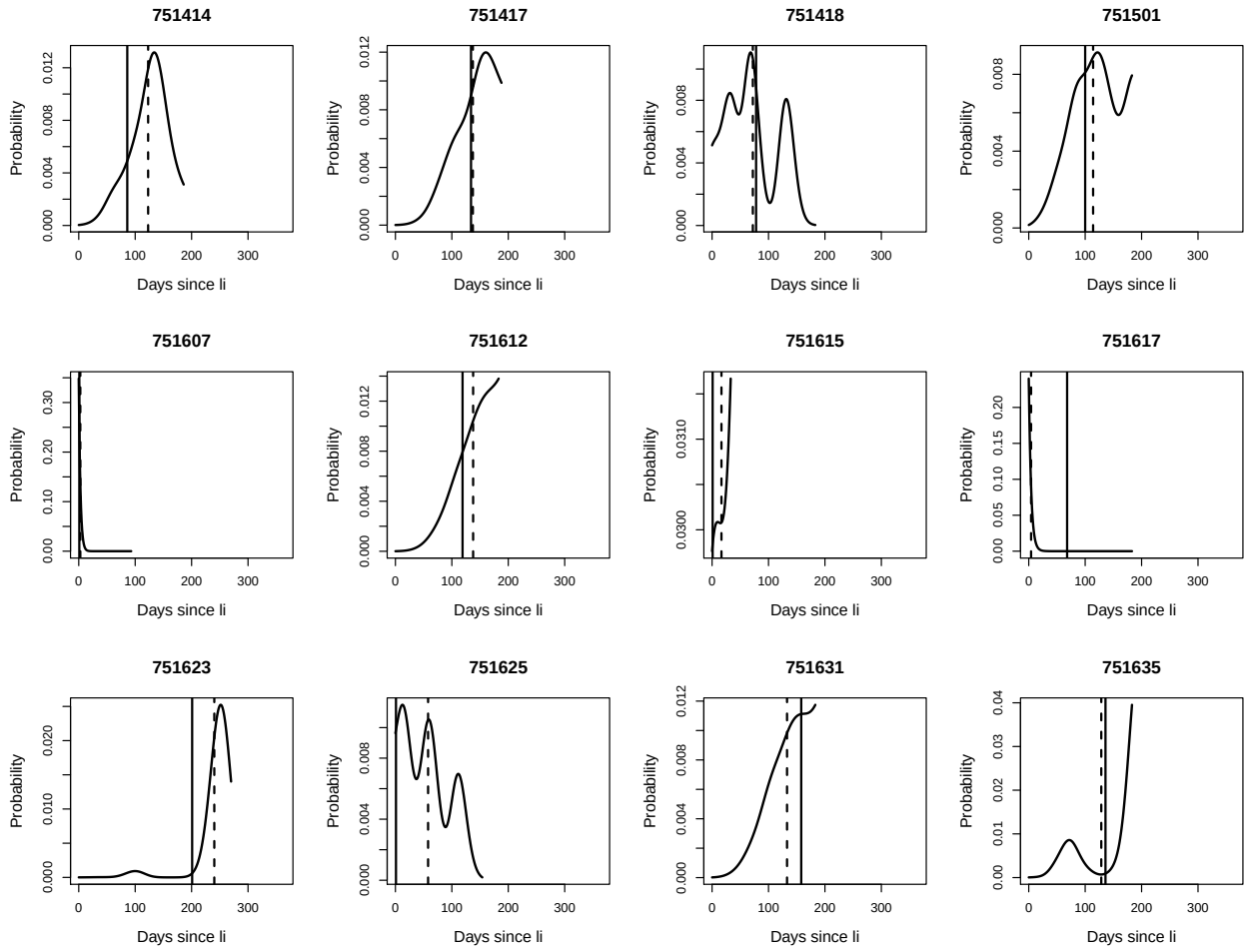
751305
751307
751402
751403
751405
751406
751407
Probability
Days since li


751414
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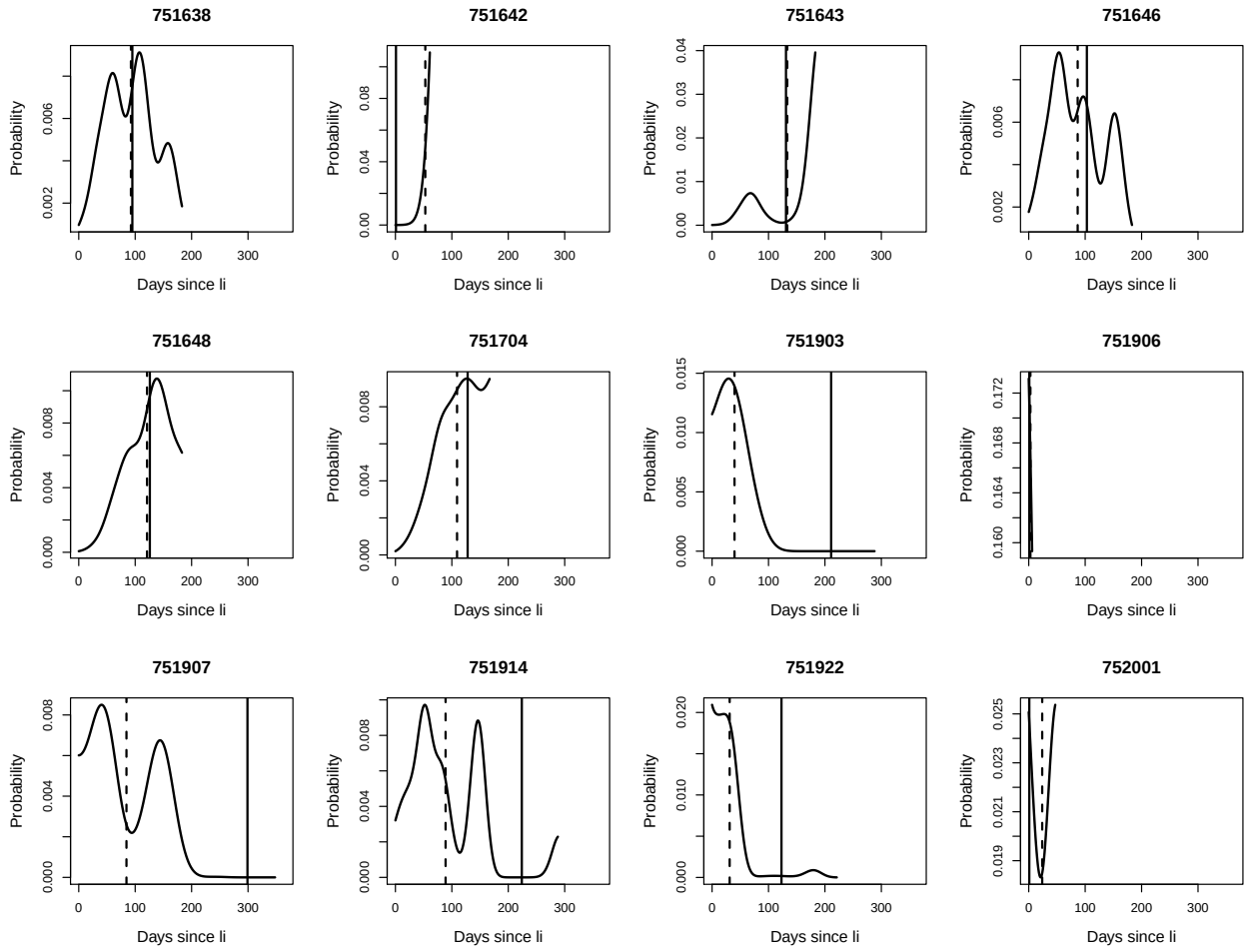
751607
751612
751615
751617
751623
751625
751631
751635
Probability
Days since li


751638
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751648
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751906
751907
751914
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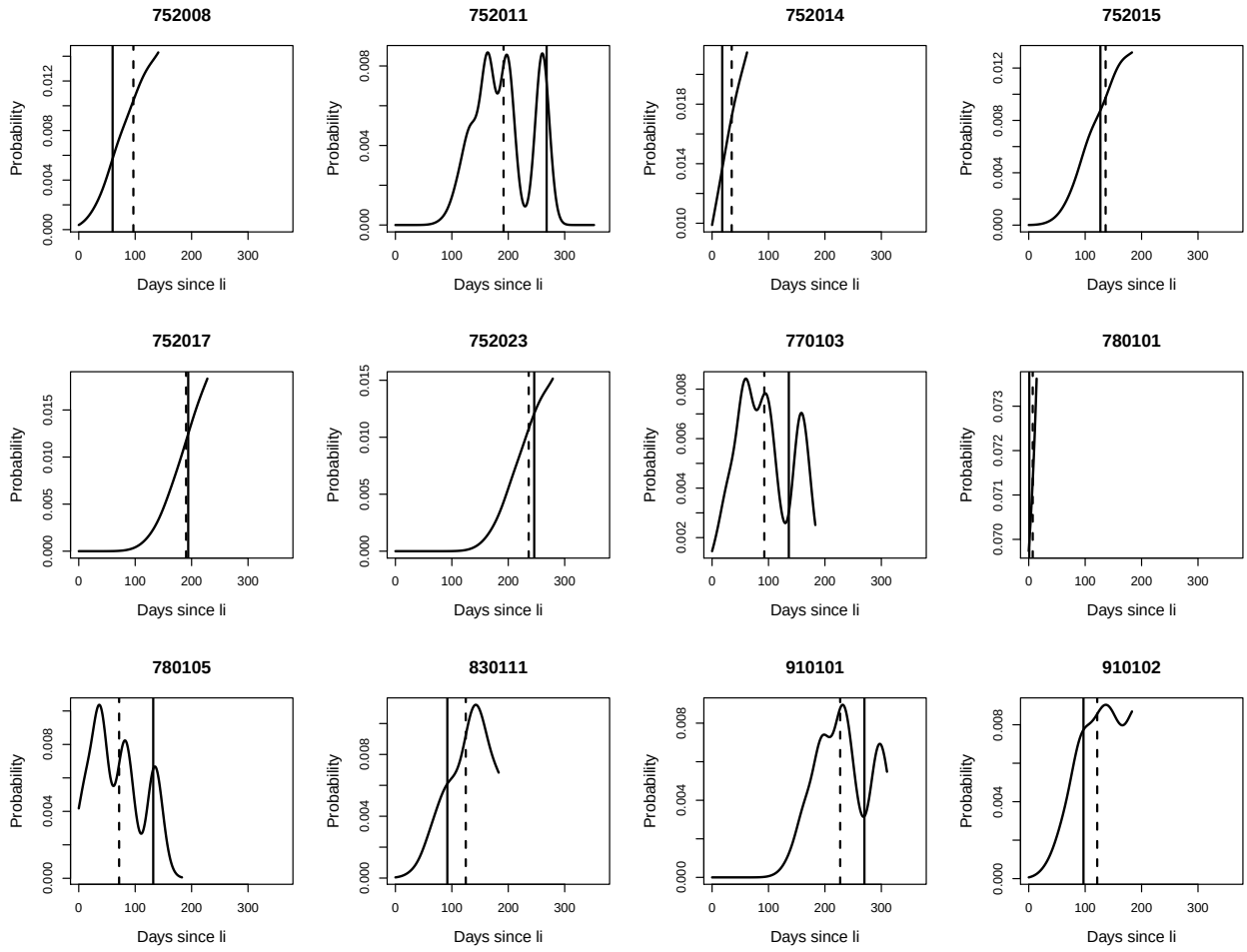
752001
Probability
Days since li


752008
752011
752014
752015
752017
752023
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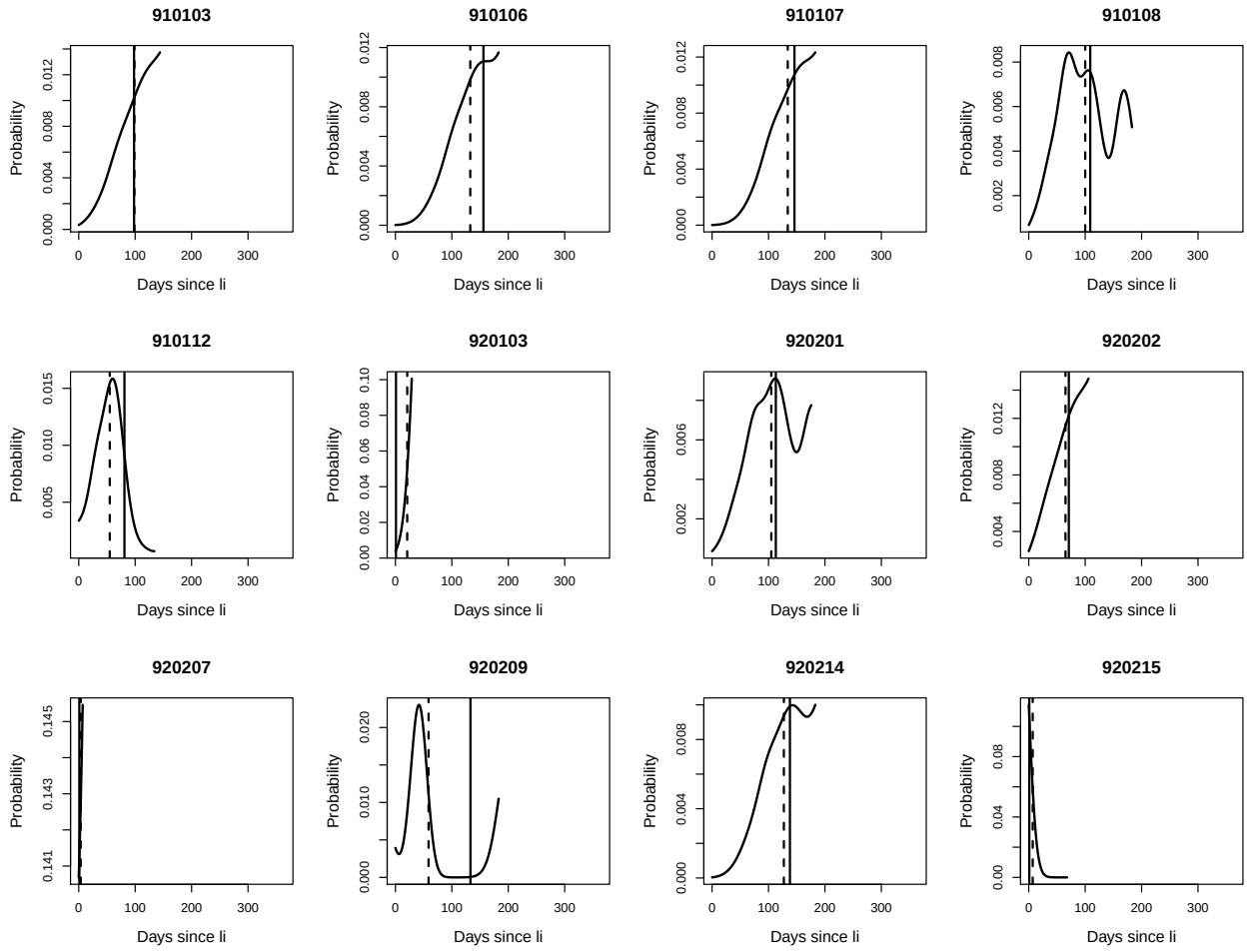
780101
780105
830111
910101
910102
Probability
Days since li


910103
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920209
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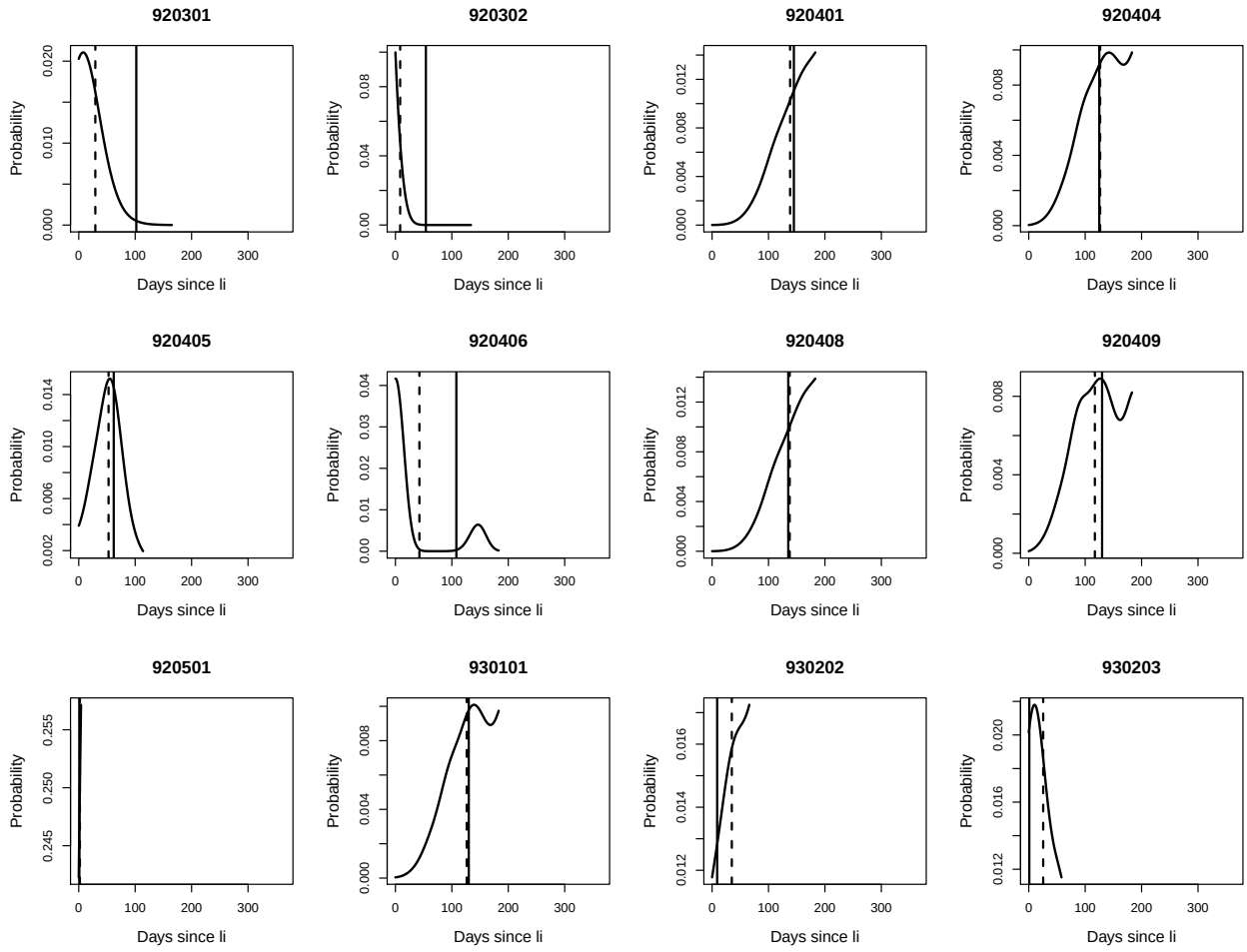
920215
Probability
Days since li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920406
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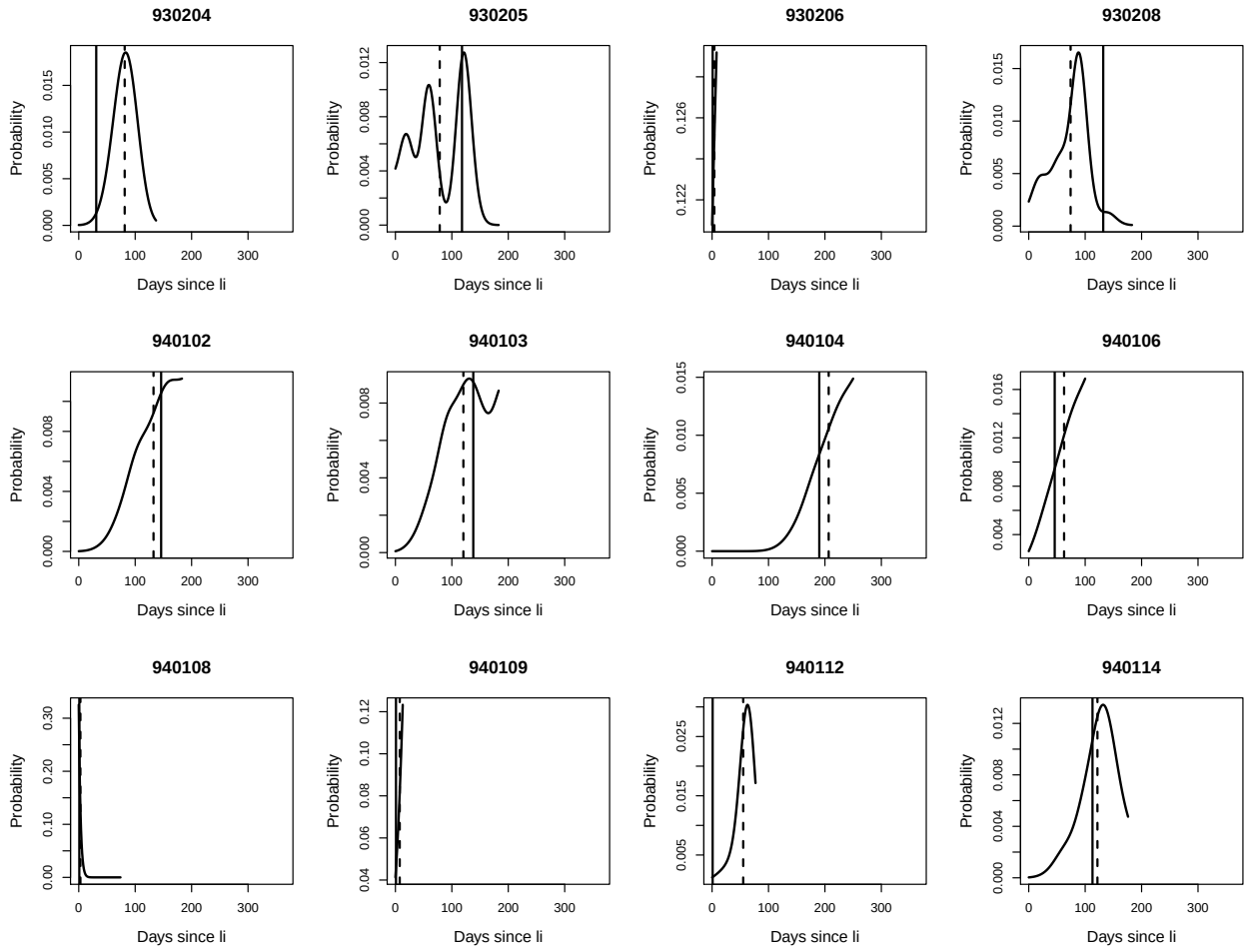
920501
930101
930202
930203
Probability
Days since li


930204
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940108
940109
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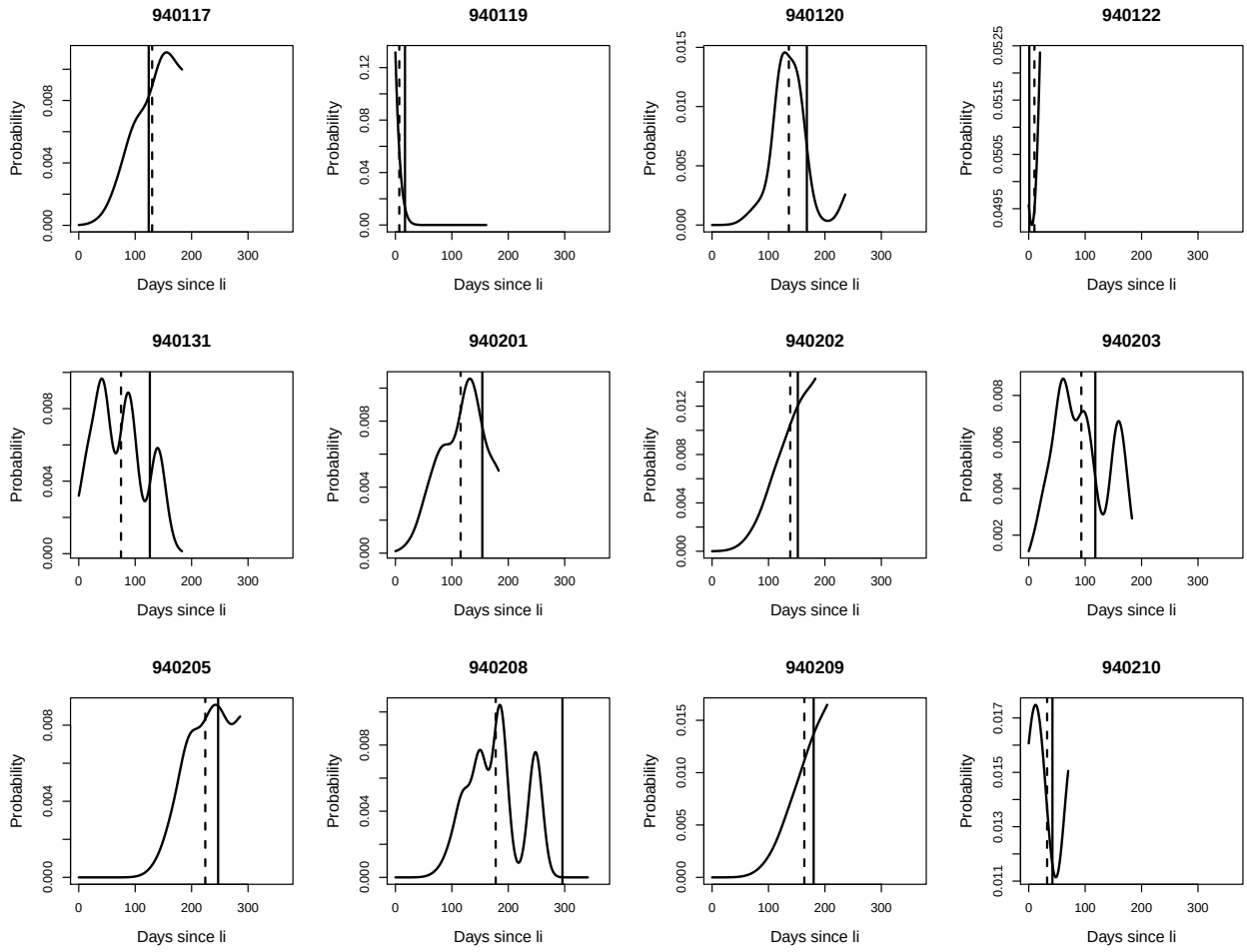
940114
Probability
Days since li


940117
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940122
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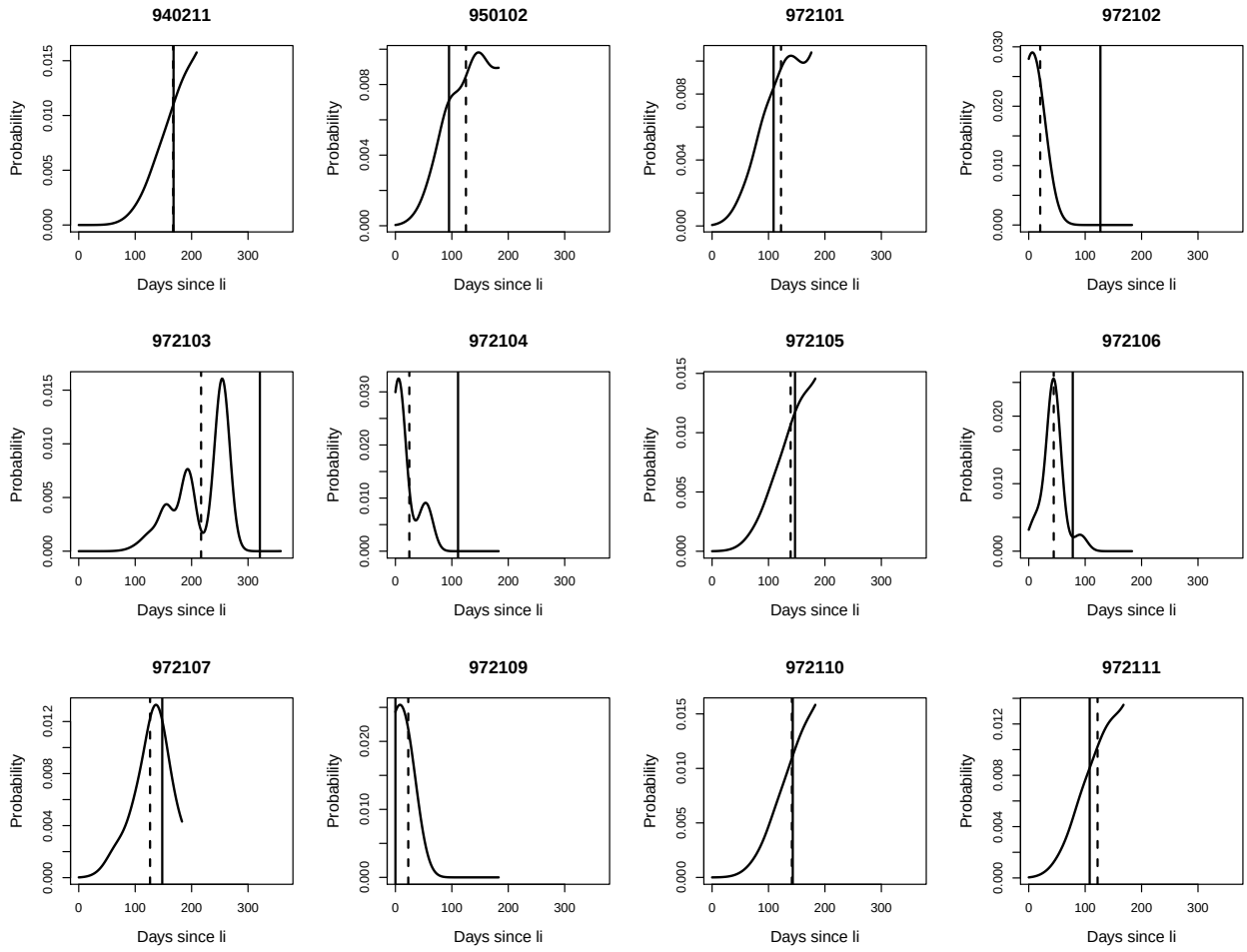
940202
940203
940205
940208
940209
940210
Probability
Days since li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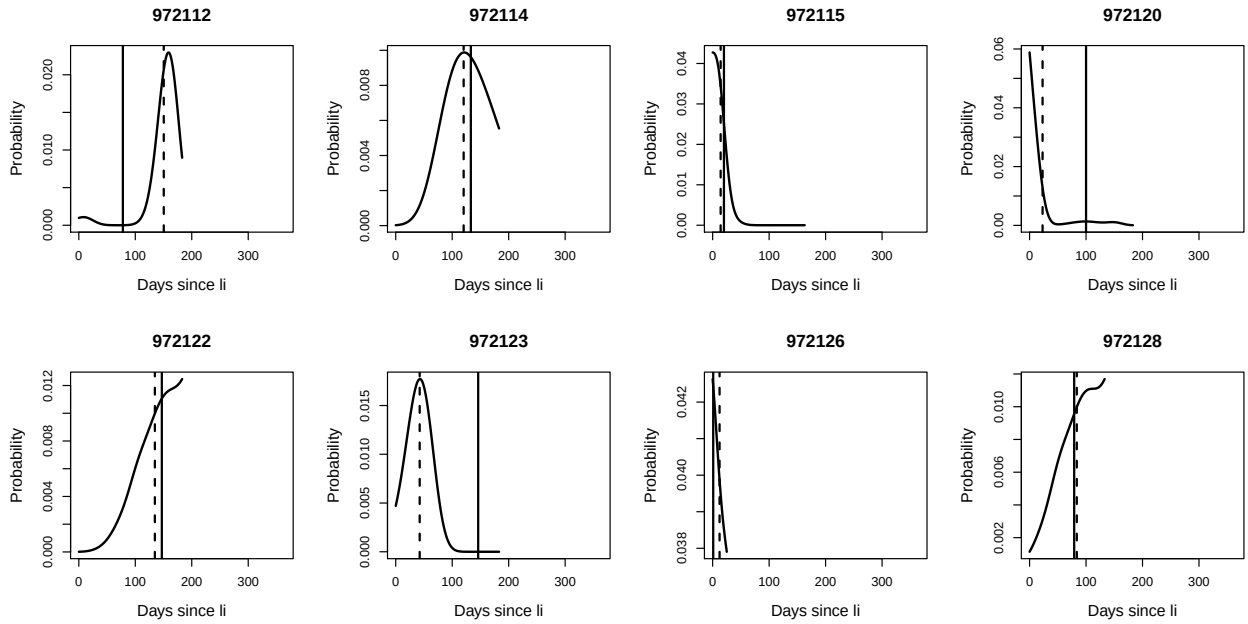
972106
972107
972109
972110
972111
Probability
Days since li


972112
Probability
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0.010
0.020
0
100
200
300
Days since li
972114
Probability
0.000
0.004
0.008
0
100
200
300
Days since li
972115
Probability
0.00
0.01
0.02
0.03
0.04
0
100
200
300
Days since li
972120
Probability
0.00
0.02
0.04
0.06
0
100
200
300
Days since li
972122
Probability
0.000
0.004
0.008
0.012
0
100
200
300
Days since li
972123
Probability
0.000
0.005
0.010
0.015
0
100
200
300
Days since li
972126
Probability
0.038
0.040
0.042
0
100
200
300
Days since li
972128
Probability
0.002
0.006
0.010
0
100
200
300
Days since li