Individual parameter estimation and prediction interval through conditional distributions in saemix

Emmanuelle

11/04/2020

Context

Recurrent question: how to estimate individual parameters with limited data or to do therapeutic drug monitoring.

Objective

- Show how to estimate individual parameters in saemix
  - for subjects in the estimation dataset
  - for new subjects
- Provide a prediction interval based on the conditional distribution for each individual

Estimating individual parameters

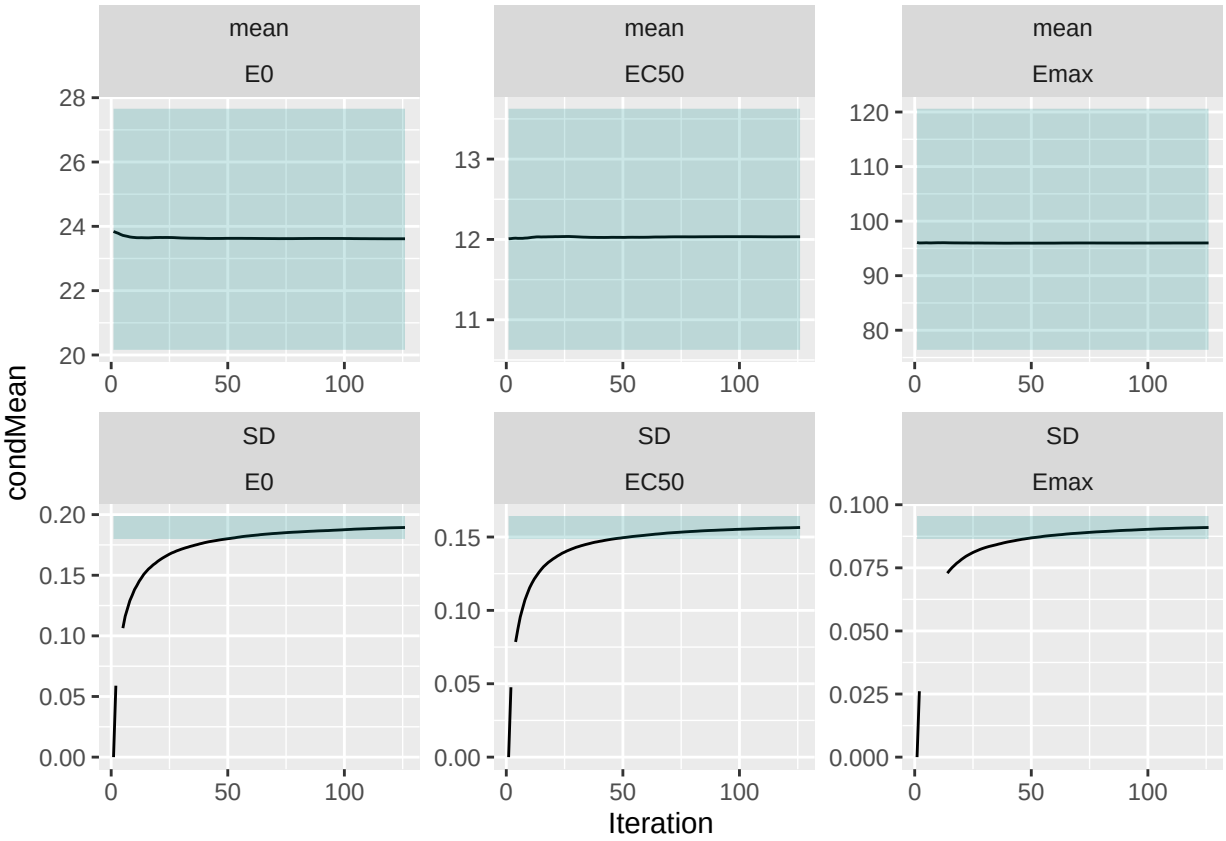
We use the Emax model from the saemix help, for the dataset without a covariate effect.

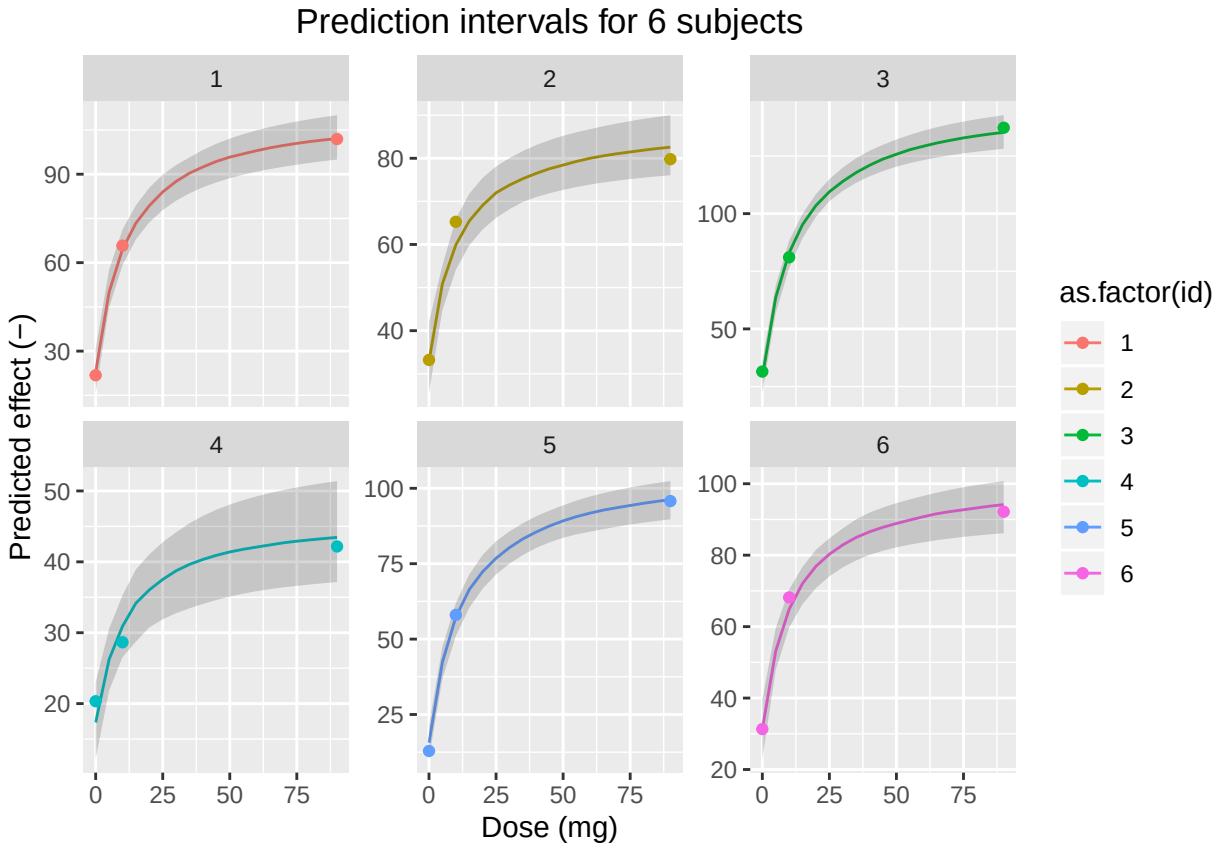
For subjects in the estimation dataset

If the subject is in the dataset, we just need to run the **conddist.saemix()** function to obtain samples from the conditional distribution, and use these to plot the median of the predictions (solid line) and the prediction band. We overlay the observed data.

```
## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN
```

```
## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN
```





For new subjects

For additional subjects, we create a dataset with the same predictors and response as in the original dataset, and use the function **predict.newdata()** to estimate the conditional distributions for the new data.

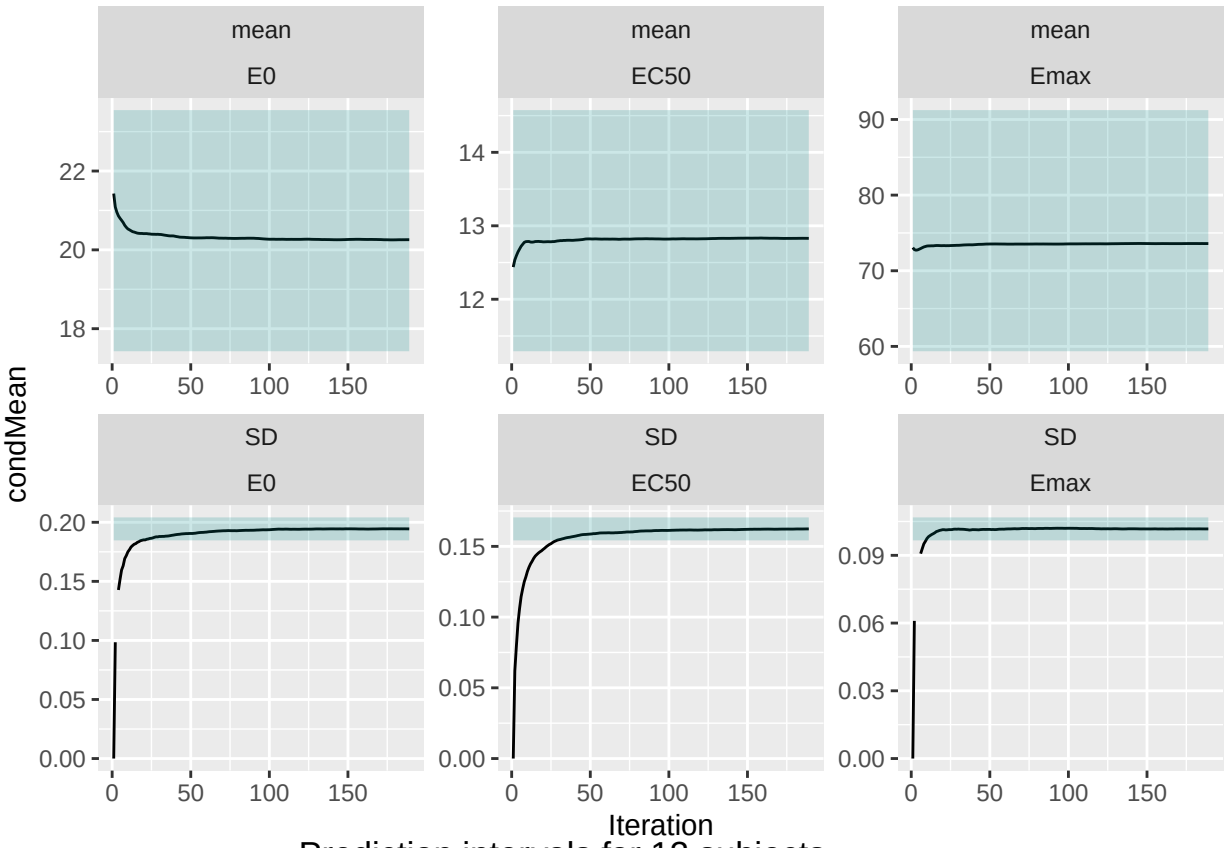
The data was originally simulated with fixed effects set to $(\ln(E_O), \ln(E_{\max}), \ln(ED_{50})) = (24, 100, 12)$, a diagonal covariance matrix for the random effects was a diagonal matrix with variances (0.12 , 0.26 , 0.05), and a constant variance $a^2 = 20$.

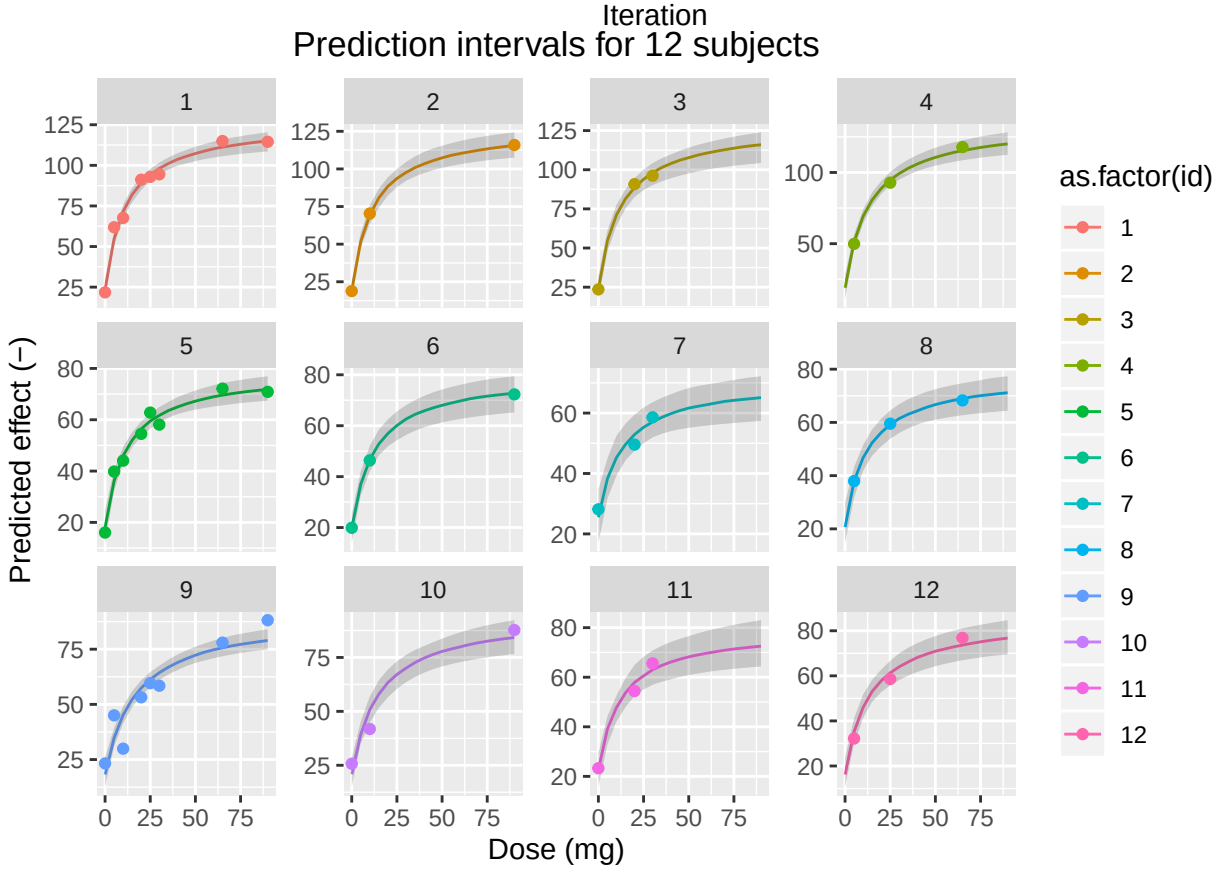
In the dataset, three different sampling schedules were used. In the following we simulate one subject with each design and one subject with the complete set of doses. With these four subjects, we create predictions under three settings:

- original parameters
- Emax reduced by 50%
- EC50 multiplied by 4

In this simulation we don't add variability so all subjects in one setting have the same value of the parameters, but it would be very easy to add variability.

```
## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN

## Warning in sqrt(varik): production de NaN
```






```
## Estimated individual parameters
```

```
##           [,1]      [,2]     [,3]
##  [1,] 23.42264 103.31252 11.59060
##  [2,] 19.67640 108.22524 11.80207
##  [3,] 23.23818 103.49879 11.80656
##  [4,] 18.86053 114.82413 13.10575
##  [5,] 17.86230  61.10361 12.08893
##  [6,] 19.50638  59.57720 12.22262
##  [7,] 24.85364  45.07597 12.66326
##  [8,] 20.42732  56.49078 12.17795
##  [9,] 18.96985  70.24963 16.85865
## [10,] 20.83259  72.42530 14.64005
## [11,] 21.60006  58.31335 12.56856
## [12,] 15.65424  69.05656 13.28480
```

```
## Simulated parameters (4 of each)
```

```
##        [,1] [,2] [,3]
## param    24  100   12
## param1   24   50   12
## param2   24  100   48
```

We note that in the last setting we cannot recover the simulated value of the EC50, even for the subject with a rich design (although there is a stronger signal for this subject). This is due to the low value of the estimated variabiliy on EC50 (only about 18%), since the conditional distribution depends both on the observed data and on the prior distribution represented by the population estimates.