Tools on R for Dose-Response curves analysis

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ENV Nantes France

Background: experimental pharmacology

- Drug - receptor interactions studies commonly establish Dose – response curves
  - Applied agonist concentrations on isolated tissues
  - Physiological effect observed
- Design : repeated measurements with cumulative concentrations

Background : data analysis

Data analysis of Dose – Response experiments should model:

- Experimental design of repeated measurements
- Physiological response : Empirical equations commonly used :
  - Hill equation
  - Richards function
  - Gompertz model
  - Hill modified equation

Mixed effects models : the best way to analyse such data sets

DRC data analysis with R by nlme models

- Statistical modeling
  - Choice of predictive function

```
Hill1<-function(x, Em, n, D){Em/(1 + 10^(n * (D - x)))}

Richard<-function(x,Em,n,b,s){Em/((1+10^(n*(b-x)))^s)}

Gompertz<-function (x,Em,n,i){Em*(exp(-exp(ln(10)*n*(i-x))))}

HillModif<-function(x,Em,b,p){Em/((1+10^(b-x))^p)}
```

  - Est.Pop function

```
EstH.Pop<-function(DataSet)
                {InitVal<-function(DataSet){
                   xy<-
sortedXyData(DataSet$LogC,DataSet$Response,DataSet)
                   Em<-max(xy[c(2)])
                   D<-NLSstClosestX(xy,Em/2)
                   n<-1
                value<-c(Em,n,D)
                value}
DataSet.nlme<-
nlme(Response~Hill1(LogC,Em,n,D),DataSet,fixed=Em+n+D~1,ra
ndom=Em+D+n~1,groups=~Identity,weights=varPower(),cor=co
rAR1(),start=c(Em=InitVal(DataSet)[c(1)],n=InitVal(DataSet)[c(2)],
D=InitVal(DataSet)[c(3)]))}
```

DRC data analysis with R by nlme models

- Estimation of parameters
  - Summary(Est.Pop)

```
summary(EstH.Pop(Your Data))
```

  - CI.par function provides the 95% Confidence interval for each parameter:

```
CI.par<-function(DataSet){intervals(EstH.Pop(DataSet))}
CI.par(Your Data)
```

- Diagnosis curves

Q-Q Normal plot:

```
Diag1H.Graph<-function(DataSet){qqnorm(resid(EstH.Pop(DataSet)))}
```

Residuals vs Fitted values plot

```
Diag2H.Graph<-function(DataSet){plot(EstH.Pop(DataSet))}
```

Parameters plot

```
Diag3H.Graph<-function(DataSet){pairs(EstH.Pop(DataSet))}
```

```
Diag1H.Graph(Your Data)
Diag2H.Graph(Your Data)
Diag3H.Graph(Your Data)
```

DRC data analysis with R

- Model comparison
  - Comp.Mod function
- More additionnal graph

```
Comp.Mod<-function (Mod1,Mod2){anova(Mod1,Mod2)}
```

  - Graph.Curves display fixed and individual curves
  - Observed Curves

```
plot(augPred(Iso.nlme,~LogC,level=0:1))
```

```
CCRCgraph<-function (Data,n) {
                    x<-matrix(Data[,2],nrow=nrow(Data)/n,ncol=n,byrow=T)
                    y<-matrix(Data[,3],nrow=nrow(Data)/n,ncol=n,byrow=T)
                    matplot(x,y,type="b",lty=1:n,pch=1:n,col=1,main="CCRC ",xlab="Log C",
ylab="Response (%)",cex=1)}

      CCRCgraph(Your Data, number of curves)
```

- Est.Boot function

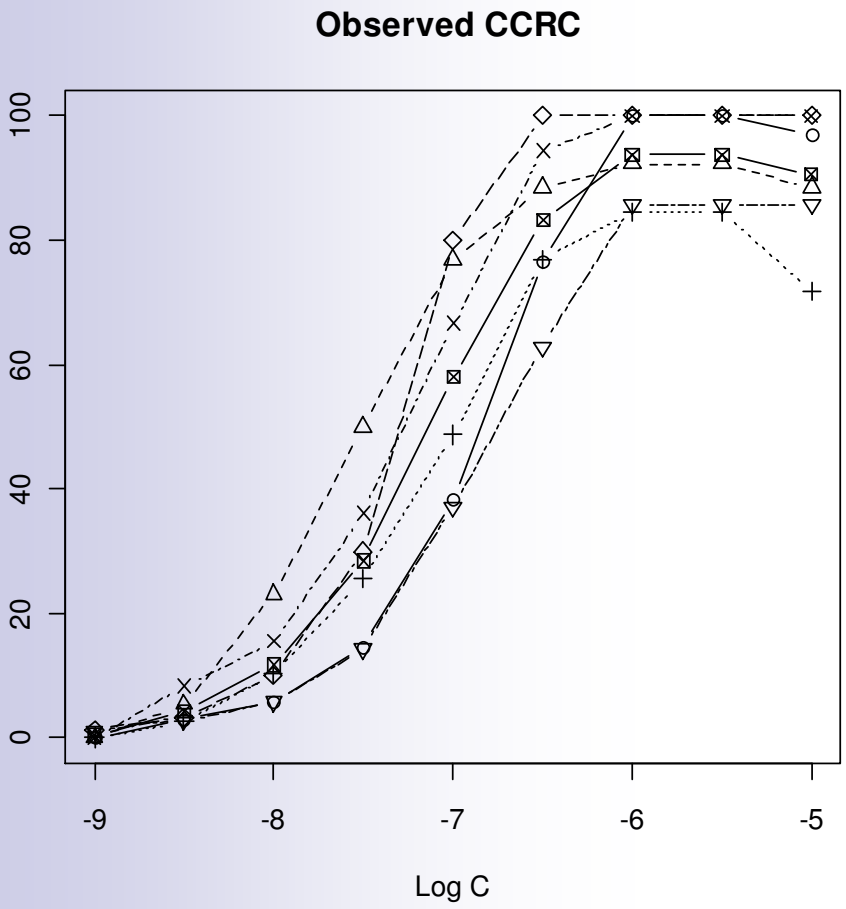
DRC data analysis with R

Full Script :

```
Hill1<-function(x, Em, n, D){Em/(1 + 10^(n * (D - x)))}
EstH.Pop<-function(DataSet)
                    {InitVal<-function(DataSet){
                       xy<-sortedXyData(DataSet$LogC,DataSet$Response,DataSet)
                       Em<-max(xy[c(2)])
                       D<-NLSstClosestX(xy,Em/2)
                       n<-1
                    value<-c(Em,n,D)
                    value}
DataSet.nlme<-
nlme(Response~Hill1(LogC,Em,n,D),DataSet,fixed=Em+n+D~1,random=Em+D+n
~1,groups=~Identity,weights=varPower(),cor=corAR1(),start=c(Em=InitVal(DataSe
t)[c(1)],n=InitVal(DataSet)[c(2)],D=InitVal(DataSet)[c(3)]))}

      summary(EstH.Pop(Your Data))

CI.par<-function(DataSet){intervals(EstH.Pop(DataSet))}
     CI.par(Your Data)

Diag1H.Graph<-function(DataSet){qqnorm(resid(EstH.Pop(DataSet)))}
Diag2H.Graph<-function(DataSet){plot(EstH.Pop(DataSet))}
Diag3H.Graph<-function(DataSet){pairs(EstH.Pop(DataSet))}
       Diag1H.Graph(Your Data)
       Diag2H.Graph(Your Data)
       Diag3H.Graph(Your Data)
```

An example:
Analysis of Cumulative Concentration Response Curves

Experiment on β-adrenoceptors-mediated blood vessels relaxation



Results with Hill function

Model: Response ~ Hill1(LogC, Em, n, d)

AIC	BIC	logLik
332.7532	356.621	-154.3766

Fixed effects: Em + n + d ~ 1

	Value	Std.Error	DF
Em	94.80339	3.526444	46
n	1.20706	0.075529	46
d	-7.16770	0.110319	46

Results with Richards Function

Model: Response ~ Richard(LogC, Em, n, b, s)

AIC	BIC	logLik
334.519	368.3318	-150.2595

Fixed effects: Em + n + b + s ~ 1

	Value	Std.Error	DF
Em	92.94116	3.451870	45
n	1.97127	0.280346	45
b	-6.85007	0.133057	45
s	0.43023	0.084348	45

An example : CCRC data analysis

- Model Comparison

Comp.Mod(EstH.Pop(Iso),EstR.Pop(Iso))

	Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
Mod1	1	12	332.75	356.62	-154.3766			
Mod2	2	17	334.51	368.33	-150.2595	1 vs 2	8.234197	0.1438

Approximate 95% confidence intervals

Fixed effects:

	lower	est.	upper
Em	87.90	94.803	101.701
n	1.059	1.207	1.354
d	-7.383	-7.167	-6.951

Correlation structure:

	lower	est.	upper
Phi	-0.142	0.466	0.818

Random Effects:

Level: Identity

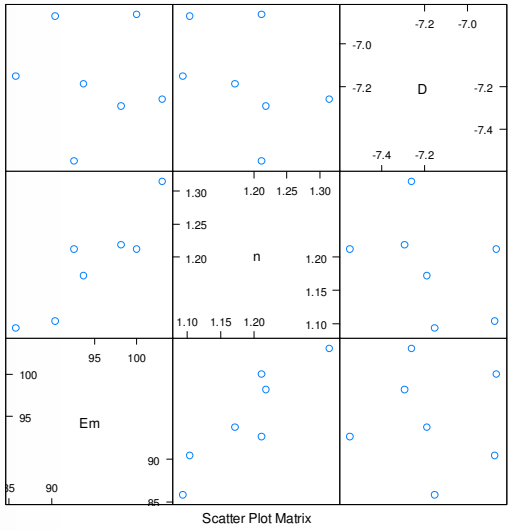
	lower	est.	upper
sd(Em)	2.9020	6.9413	16.6025
sd(d)	0.1351	0.2508	0.465
sd(n)	0.0098	0.0957	0.934
cor(Em,d)	-0.7318	0.0212	0.751
cor(Em,n)	-0.999	0.7562	0.999
cor(d,n)	-0.9735	-0.3189	0.904

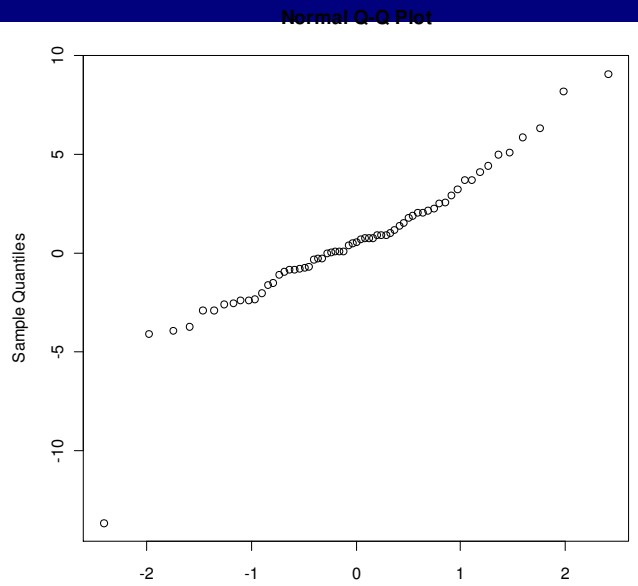
Variance function:

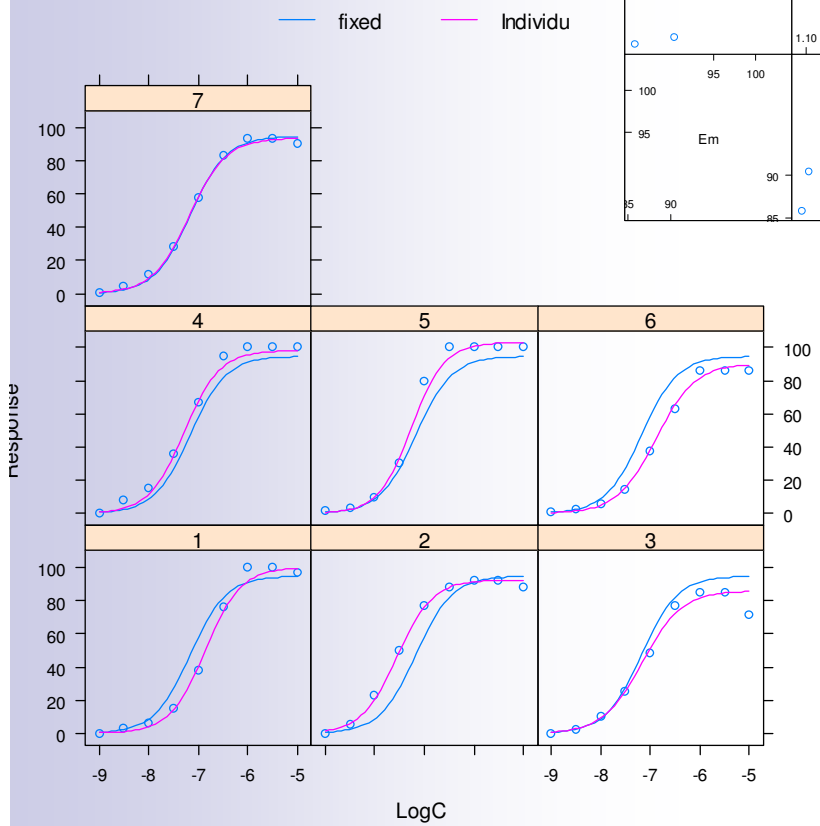
	lower	est.	upper
power	0.1621966	0.2988498	0.4355029

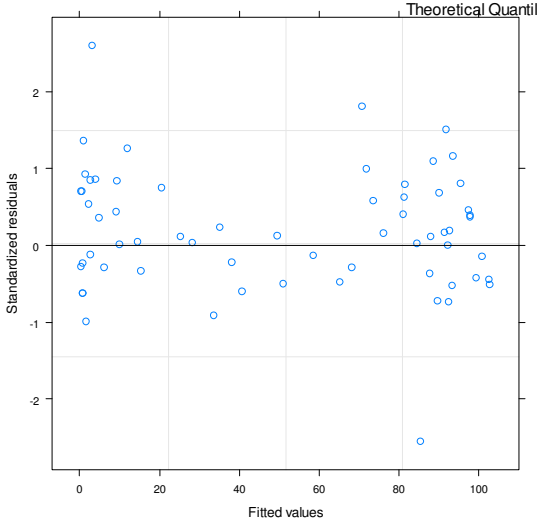
An example : CCRC data analysis

- Graphes









DRC data analysis with R : Limits and conditions

- Complete curves : no missing data
- DataSet organised in a specific way
- Script « closed » : no interactivity to choose and modify one function component

DRC data analysis with R : Conclusion

- Script easy to use for non informatician and non statistician scientists
- Evolution in a more interactive form

Thank you

for

your attention !