

# R-package **FME** : utilities for the application of models consisting of differential equations

Karline Soetaert  
NIOO-CEME  
The Netherlands

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## Abstract

Rpackage **FME** contains functions to perform complex applications of models, consisting of differential equations. This is a preliminary version.

*Keywords:* simulation models, differential equations, fitting, sensitivity, Monte Carlo, identifiability, R.

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## 1. Introduction

R-package **FME** contains part of the functions present in the software environment **FEMME** (Soetaert, deClippele, and Herman 2002), a *F*lexible *E*nvironment for *M*athematically *M*odeling the *E*nvironment. **FEMME** was written in FORTRAN. **FME** is – obviously – written in R.

Although **FME** can work with many types of functions, it is mainly meant to be used with models that are written as (a system of) differential equations (ordinary or partial), which are solved either with routines from package **deSolve** (Soetaert, Petzoldt, and Setzer 2008), which integrate the model in time, or from package **rootSolve** (Soetaert 2008) which estimate steady-state conditions. With **FME** it is possible to:

- perform local and global sensitivity analysis (Brun, Reichert, and Kunsch 2001; Soetaert and Herman 2009),
- perform parameter identifiability analysis (Brun *et al.* 2001),
- fit a model to data,
- run a Markov chain Monte Carlo (MCMC, Haario, Laine, Mira, and Saksman 2006).

Most of these functions have suitable methods for printing, visualising output etc. In addition, there are functions to generate parameter combinations corresponding to a certain distribution. In this document a – very quick – survey of the functionality is given, based on a simple model from (Soetaert and Herman 2009).

## 2. The example model

The example model describes growth of bacteria (**BACT**) on a substrate (**SUB**) in a closed vessel. The model equations are:

$$\begin{aligned}\frac{dBact}{dt} &= gmax \cdot eff \cdot \frac{Sub}{Sub + ks} \cdot Bact - d \cdot Bact - r_B \cdot Bact \\ \frac{dSub}{dt} &= -gmax \cdot \frac{Sub}{Sub + ks} \cdot Bact + d \cdot Bact\end{aligned}$$

where the first, second and third term of the rate of change of **Bact** is growth of bacteria, death and respiration respectively. In R, this model is implemented and solved as follows (see help pages of **deSolve** ). First the parameters are defined, as a list (a vector would also do)

```
> pars <- list(gmax =0.5,eff = 0.5,
+             ks =0.5, rB =0.01, dB =0.01)
```

The model function **solveBact** takes as input the parameters and the time sequence at which output is wanted. Within this function, **derivs** is defined, which is the *derivative* function, called at each time step by the solver. It takes as input the current time (**t**), the current values of the state variables (**state**) and the parameters (**pars**). It returns the rate of change of the state variables, packed as a list. Also within function **solveBact**, the state variables are given an initial condition (**state**) and the model is solved by integration, using function **ode** from package **deSolve**. The results of the integration are returned, packed as a data.frame.

```
> solveBact <- function(pars, times=seq(0,50,by=0.5)) {
+   derivs <- function(t,state,pars) { # returns rate of change
+     with(as.list(c(state,pars)), {
+
+       dBact = gmax*eff*Sub/(Sub+ks)*Bact - dB*Bact - rB*Bact
+       dSub  = -gmax      *Sub/(Sub+ks)*Bact + dB*Bact
+       return(list(c(dBact,dSub)))
+     })
+   }
+   state <- c(Bact=0.1,Sub = 100)
+   ## ode solves the model by integration...
+   return(as.data.frame(ode(y=state,times=times,func=derivs,parms=pars)))
+ }
```

The model is then solved by calling **solveBact** with the default parameters:

```
> out <- solveBact(pars)
```

and output plotted as:

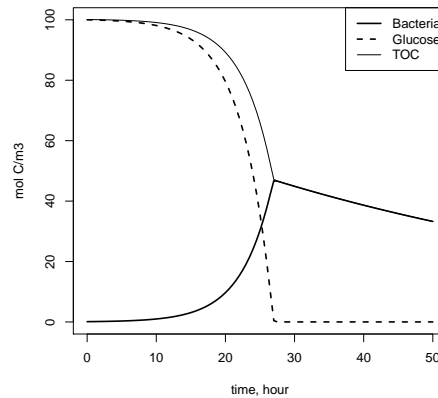


Figure 1: Solution of the simple bacterial growth model - see text for R-code

```
> plot(out$time,out$Bact,ylim=range(c(out$Bact,out$Sub)),
+       xlab="time, hour",ylab="mol C/m3",type="l",lwd=2)
> lines(out$time,out$Sub,lty=2,lwd=2)
> lines(out$time,out$Sub+out$Bact)
> legend("topright",c("Bacteria","Glucose","TOC"),
+       lty=c(1,2,1),lwd=c(2,2,1))
```

### 3. Global sensitivity

In global sensitivity analysis, certain parameters are changed over a large range, and the effect on certain model output variables assessed. In **FME** this is done via function `sensRange`.

First the sensitivity parameters are defined and a distribution is assigned; here we specify the minimum and maximum values of three parameters in a `data.frame`:

```
> parRanges <- data.frame(min=c(0.4,0.4,0.0),max=c(0.6,0.6,0.02))
> rownames(parRanges)<- c("gmax","eff","rB")
> parRanges
```

```
      min  max
gmax 0.4 0.60
eff   0.4 0.60
rB    0.0 0.02
```

Then we estimate the sensitivity to one parameter, `rB` (parameter 3), varying its values according to a regular grid (`dist=grid`). The effect of that on sensitivity variables `Bact` and `Sub` are estimated. To do this, the model is run 100 times (`num=100`). The `system.time` is printed (in seconds):

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```
> tout      <- 0:50
> print(system.time(
+ sR<-sensRange(func=solveBact,parms=pars,dist="grid",
+               sensvar=c("Bact","Sub"),parRange=parRanges[3,],num=50)
+ ))
```

```
      user system elapsed
2.01      0.00      2.02
```

```
> head(summary(sR))
```

|         | x         | Mean      | Sd            | Min       | Max       | q05       |
|---------|-----------|-----------|---------------|-----------|-----------|-----------|
| Bact0   | 0.0       | 0.1000000 | 0.00000000000 | 0.1000000 | 0.1000000 | 0.1000000 |
| Bact0.5 | 0.5       | 0.1121194 | 0.0003335405  | 0.1115597 | 0.1126809 | 0.1116155 |
| Bact1   | 1.0       | 0.1257062 | 0.0007479668  | 0.1244532 | 0.1269674 | 0.1245777 |
| Bact1.5 | 1.5       | 0.1409422 | 0.0012579439  | 0.1388384 | 0.1430668 | 0.1390468 |
| Bact2   | 2.0       | 0.1580263 | 0.0018805072  | 0.1548863 | 0.1612075 | 0.1551964 |
| Bact2.5 | 2.5       | 0.1771819 | 0.0026354918  | 0.1727886 | 0.1816476 | 0.1732211 |
|         | q25       | q50       | q75           | q95       |           |           |
| Bact0   | 0.1000000 | 0.1000000 | 0.1000000     | 0.1000000 |           |           |
| Bact0.5 | 0.1118390 | 0.1121189 | 0.1123996     | 0.1126246 |           |           |
| Bact1   | 0.1250770 | 0.1257040 | 0.1263341     | 0.1268405 |           |           |
| Bact1.5 | 0.1398836 | 0.1409367 | 0.1419978     | 0.1428524 |           |           |
| Bact2   | 0.1564430 | 0.1580153 | 0.1596034     | 0.1608854 |           |           |
| Bact2.5 | 0.1749620 | 0.1771627 | 0.1793911     | 0.1811941 |           |           |

The results are represented as a data.frame, containing summary information of the value of the sensitivity variable (`var`) at each time step (`x`). It is relatively simple to plot the ranges, either as  $\text{min} \pm \text{sd}$  or using quantiles:

```
> par(mfrow=c(2,2))
> plot(summary(sR),main="Sensitivity rB",xlab="time, hour",ylab="molC/m3",
+       legpos="topright")
> plot(summary(sR),main="Sensitivity rB",xlab="time, hour",ylab="molC/m3",
+       quant=TRUE,col=c("lightblue","darkblue"),legpos="topright")
> par(mfrow=c(1,1))
```

Sensitivity ranges can also be estimated for a combination of parameters. Here we use all 3 parameters, and select a latin hypercube distribution.

```
> Sens2 <- summary(sensRange(func=solveBact,parms=pars,
+                             dist="latin",sensvar="Bact",parRange=parRanges,num=100))

> plot(Sens2,main="Sensitivity gmax,eff,rB",xlab="time, hour",ylab="molC/m3")
```

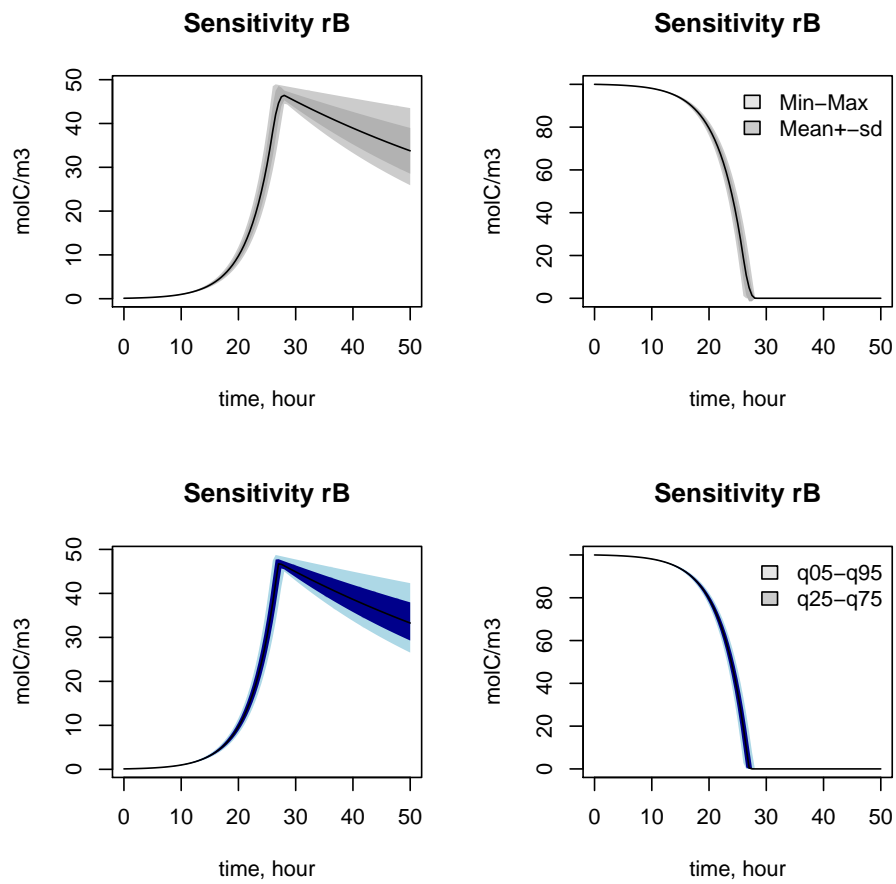


Figure 2: Sensitivity range for one parameter - see text for R-code

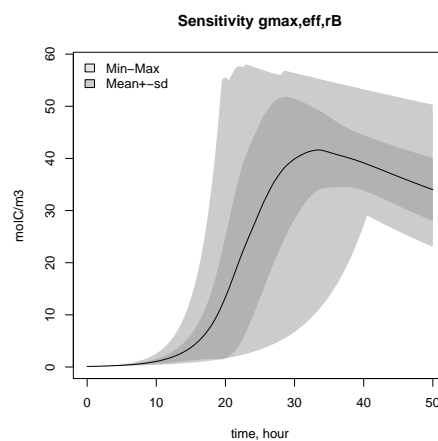


Figure 3: Sensitivity range for a combination of parameters - see text for R-code

## 4. Local sensitivity

In local sensitivity, the effect of a parameter value in a very small region near its nominal value is estimated. The methods implemented in **FME** are based on Brun *et al.* (2001) which should be consulted for details. They are based on so-called “sensitivity functions”.

### 4.1. Sensitivity functions

Sensitivity functions are generated with `sensFun`, and estimate the effect of a selection of parameters (here all parameters are selected) on a selection of variables (here only `Bact`).

```
> SnsBact<- sensFun(func=solveBact,parms=pars,
+                  sensvar="Bact",varscale=1)
> head(SnsBact)
```

|   | x   | var  | gmax       | eff        | ks            | rB           |
|---|-----|------|------------|------------|---------------|--------------|
| 1 | 0.0 | Bact | 0.00000000 | 0.00000000 | 0.0000000000  | 0.000000000  |
| 2 | 0.5 | Bact | 0.01394713 | 0.01394714 | -0.0000703354 | -0.000560559 |
| 3 | 1.0 | Bact | 0.03127214 | 0.03127218 | -0.0001562084 | -0.001257071 |
| 4 | 1.5 | Bact | 0.05259210 | 0.05259221 | -0.0002623735 | -0.002114135 |
| 5 | 2.0 | Bact | 0.07861787 | 0.07861810 | -0.0003921211 | -0.003160362 |
| 6 | 2.5 | Bact | 0.11017714 | 0.11017756 | -0.0005495271 | -0.004429033 |

```
      dB
1  0.0000000000
2 -0.0005605588
3 -0.0012570697
4 -0.0021141330
5 -0.0031603571
6 -0.0044290250
```

They can easily be plotted (Fig. 3):

```
> plot(SnsBact)
```

### 4.2. Univariate sensitivity

Based on the sensitivity functions, several summaries are generated, which allow to rank the parameters based on their influence on the selected variables.

```
> summary(SnsBact)
```

|      | value | scale | L1    | L2    | Mean | Min   | Max     | N   |
|------|-------|-------|-------|-------|------|-------|---------|-----|
| gmax | 0.50  | 0.50  | 29.51 | 5.859 | 16.2 | -17.1 | 266.361 | 101 |
| eff  | 0.50  | 0.50  | 37.12 | 6.212 | 37.1 | 0.0   | 268.408 | 101 |
| ks   | 0.50  | 0.50  | 0.17  | 0.037 | -0.1 | -1.8  | 0.097   | 101 |
| rB   | 0.01  | 0.01  | 3.47  | 0.463 | -3.5 | -10.8 | 0.000   | 101 |
| dB   | 0.01  | 0.01  | 2.06  | 0.297 | -2.1 | -10.8 | 0.000   | 101 |

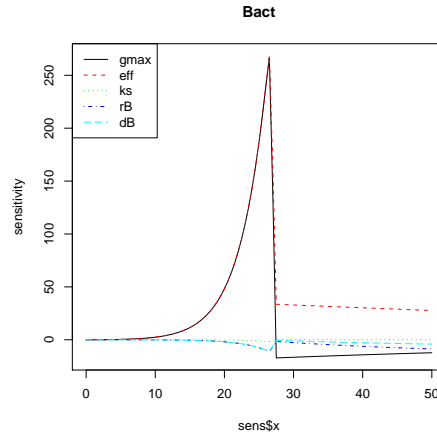


Figure 4: Sensitivity functions - see text for R-code

Sensitivity analysis can also be performed on several variables:

```
> summary(sensFun(solveBact,pars,varscale=1),var=TRUE)
```

|       | value | scale | L1    | L2     | Mean   | Min      | Max     | N   | var  |
|-------|-------|-------|-------|--------|--------|----------|---------|-----|------|
| gmax1 | 0.50  | 0.50  | 29.51 | 5.859  | 16.25  | -1.7e+01 | 2.7e+02 | 101 | Bact |
| gmax2 | 0.50  | 0.50  | 48.40 | 12.234 | -48.40 | -5.6e+02 | 0.0e+00 | 101 | Sub  |
| eff1  | 0.50  | 0.50  | 37.12 | 6.212  | 37.12  | 0.0e+00  | 2.7e+02 | 101 | Bact |
| eff2  | 0.50  | 0.50  | 39.64 | 10.200 | -39.64 | -4.8e+02 | 6.8e-06 | 101 | Sub  |
| ks1   | 0.50  | 0.50  | 0.17  | 0.037  | -0.10  | -1.8e+00 | 9.7e-02 | 101 | Bact |
| ks2   | 0.50  | 0.50  | 0.29  | 0.077  | 0.29   | 0.0e+00  | 3.8e+00 | 101 | Sub  |
| rB1   | 0.01  | 0.01  | 3.47  | 0.463  | -3.47  | -1.1e+01 | 0.0e+00 | 101 | Bact |
| rB2   | 0.01  | 0.01  | 1.59  | 0.410  | 1.59   | -2.8e-07 | 1.9e+01 | 101 | Sub  |
| dB1   | 0.01  | 0.01  | 2.06  | 0.297  | -2.06  | -1.1e+01 | 0.0e+00 | 101 | Bact |
| dB2   | 0.01  | 0.01  | 1.78  | 0.451  | 1.78   | 0.0e+00  | 2.1e+01 | 101 | Sub  |

#### 4.3. Bivariate sensitivity

The pairwise relationships in parameter sensitivity is easily assessed by plotting the sensitivity functions using R-function `pairs`, and by calculating the correlation.

```
> cor(SnsBact[,-(1:2)])
```

|      | gmax       | eff        | ks         | rB         | dB         |
|------|------------|------------|------------|------------|------------|
| gmax | 1.0000000  | 0.9184218  | -0.9879349 | -0.2602262 | -0.7165956 |
| eff  | 0.9184218  | 1.0000000  | -0.9265098 | -0.5575106 | -0.8883636 |
| ks   | -0.9879349 | -0.9265098 | 1.0000000  | 0.2878336  | 0.7302580  |
| rB   | -0.2602262 | -0.5575106 | 0.2878336  | 1.0000000  | 0.8599353  |
| dB   | -0.7165956 | -0.8883636 | 0.7302580  | 0.8599353  | 1.0000000  |

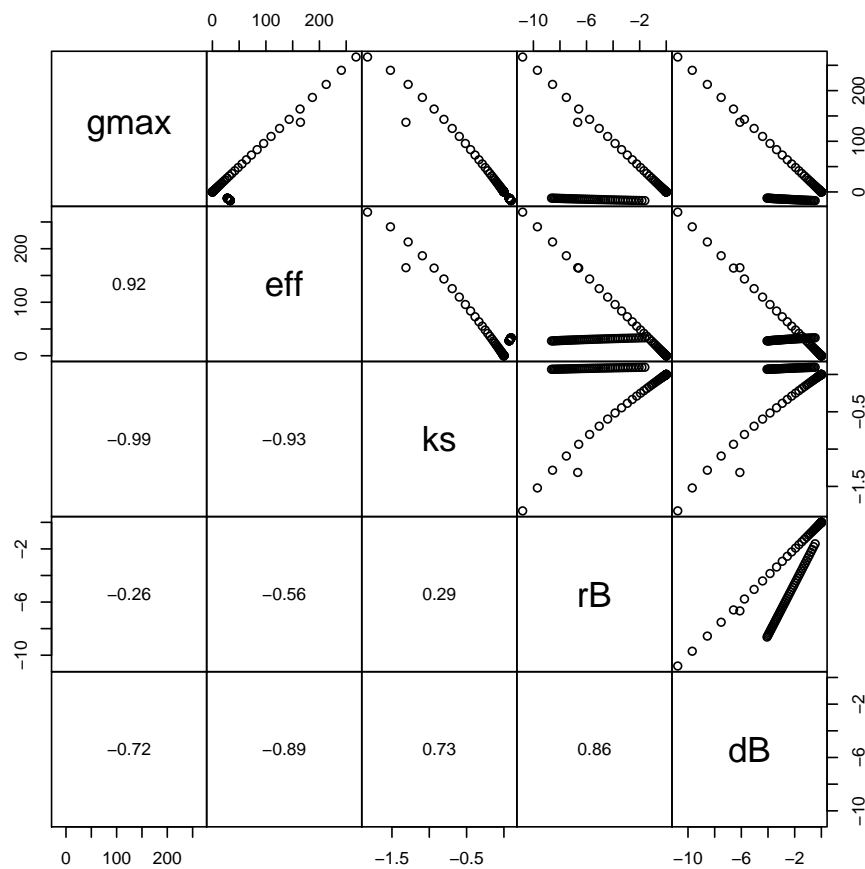


Figure 5: Pairs of sensitivity functions - see text for R-code

```
> pairs(SnsBact)
```

#### 4.4. Monte Carlo runs

Function `modCRL` runs a Monte Carlo simulation, outputting 0-D variables, (in contrast to `sensRange` which outputs 1-D variables).

```
> SF <- function (pars) {
+   out <- solveBact(pars)
+   return(out[nrow(out),2:3])
+ }
> CRL <- modCRL(func=SF,parms=pars,parRange=parRanges[1,])

> plot(CRL)
```



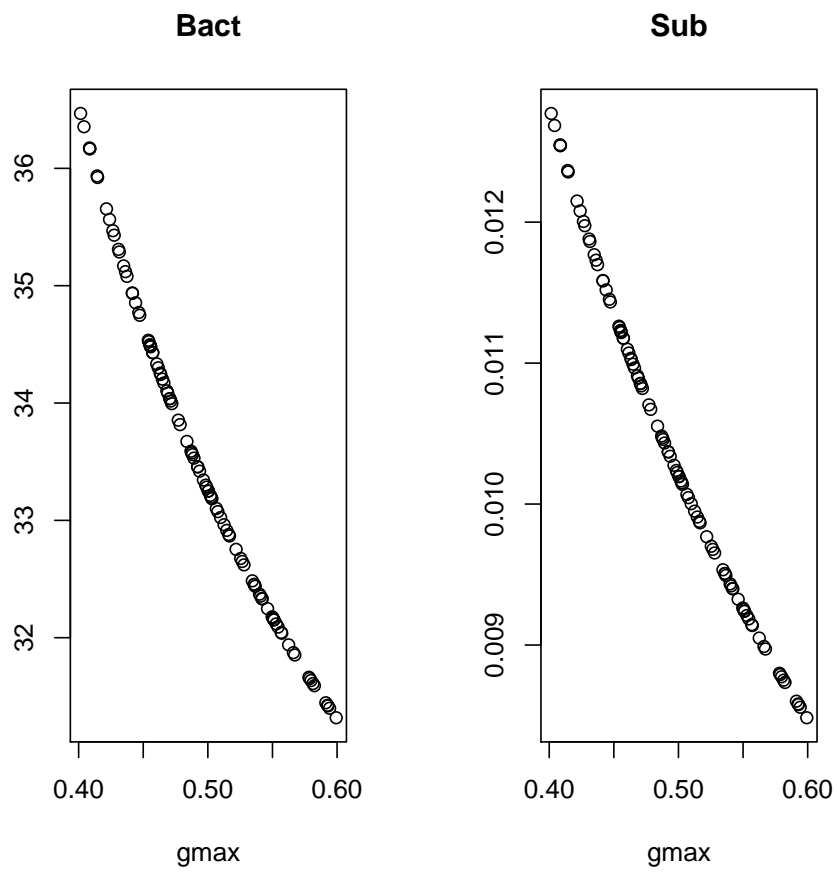


Figure 6: Monte carlo analysis - see text for R-code

## 5. Multivariate sensitivity analysis

Based on the sensitivity functions of model variables to selection of parameters, function `collin` calculates the *collinearity* or *identifiability* of sets of parameters.

```
> Coll <- collin(SnsBact)
> Coll
```

|    | gmax | eff | ks | rB | dB | N | collinearity |
|----|------|-----|----|----|----|---|--------------|
| 1  | 1    | 1   | 0  | 0  | 0  | 2 | 2.8          |
| 2  | 1    | 0   | 1  | 0  | 0  | 2 | 9.5          |
| 3  | 1    | 0   | 0  | 1  | 0  | 2 | 1.3          |
| 4  | 1    | 0   | 0  | 0  | 1  | 2 | 1.8          |
| 5  | 0    | 1   | 1  | 0  | 0  | 2 | 2.9          |
| 6  | 0    | 1   | 0  | 1  | 0  | 2 | 2.0          |
| 7  | 0    | 1   | 0  | 0  | 1  | 2 | 3.7          |
| 8  | 0    | 0   | 1  | 1  | 0  | 2 | 1.3          |
| 9  | 0    | 0   | 1  | 0  | 1  | 2 | 1.8          |
| 10 | 0    | 0   | 0  | 1  | 1  | 2 | 3.8          |
| 11 | 1    | 1   | 1  | 0  | 0  | 3 | 9.5          |
| 12 | 1    | 1   | 0  | 1  | 0  | 3 | 7.0          |
| 13 | 1    | 1   | 0  | 0  | 1  | 3 | 6.8          |
| 14 | 1    | 0   | 1  | 1  | 0  | 3 | 9.5          |
| 15 | 1    | 0   | 1  | 0  | 1  | 3 | 9.5          |
| 16 | 1    | 0   | 0  | 1  | 1  | 3 | 2261.4       |
| 17 | 0    | 1   | 1  | 1  | 0  | 3 | 6.7          |
| 18 | 0    | 1   | 1  | 0  | 1  | 3 | 6.8          |
| 19 | 0    | 1   | 0  | 1  | 1  | 3 | 12.2         |
| 20 | 0    | 0   | 1  | 1  | 1  | 3 | 22.6         |
| 21 | 1    | 1   | 1  | 1  | 0  | 4 | 9.6          |
| 22 | 1    | 1   | 1  | 0  | 1  | 4 | 9.5          |
| 23 | 1    | 1   | 0  | 1  | 1  | 4 | 3631.3       |
| 24 | 1    | 0   | 1  | 1  | 1  | 4 | 3451.1       |
| 25 | 0    | 1   | 1  | 1  | 1  | 4 | 23.5         |
| 26 | 1    | 1   | 1  | 1  | 1  | 5 | 2421318.6    |

```
> Coll [Coll[, "collinearity"] < 20 & Coll[, "N"] == 4, ]
```

|   | gmax | eff | ks | rB | dB | N | collinearity |
|---|------|-----|----|----|----|---|--------------|
| 1 | 1    | 1   | 1  | 1  | 0  | 4 | 9.6          |
| 2 | 1    | 1   | 1  | 0  | 1  | 4 | 9.5          |

```
> collin(SnsBact, parset=1:5)
```

|   | gmax | eff | ks | rB | dB | N | collinearity |
|---|------|-----|----|----|----|---|--------------|
| 1 | 1    | 1   | 1  | 1  | 1  | 5 | 2421319      |

The higher the value, the larger the (approximate) linear dependence. This function is mainly useful to derive suitable parameter sets that can be calibrated based on data (see next section).

## 6. Fitting the model to data

### 6.1. Data structures

There are two modes of data input:

- *data table (long) format*; this is a two to four column data.frame that contains the **name** of the observed variable (always the FIRST column), the (optional) **value of the independent variable** (default = "time"), the **value of the observation** and the (optional) **value of the error**.
- *crosstable format*; this is a matrix, where each column denotes one dependent (or independent) variable; the column name is the name of the observed variable.

As an example of both formats consider the data, called **Dat** consisting of two observed variables, called "Obs1" and "Obs2", both containing two observations, at time 1 and 2:

| name | time | val | err |
|------|------|-----|-----|
| Obs1 | 1    | 50  | 5   |
| Obs1 | 2    | 150 | 15  |
| Obs2 | 1    | 1   | 0.1 |
| Obs2 | 2    | 2   | 0.2 |

for the long format and

| time | Obs1 | Obs2 |
|------|------|------|
| 1    | 50   | 1    |
| 2    | 150  | 2    |

for the crosstable format. Note, that in the latter case it is not possible to provide separate errors per data point.

### 6.2. The model cost function

**FME** function **modCost** estimates the "model cost", which is the sum of (weighted) squared residuals of the model versus the data. This function is central to parameter identifiability analysis, model fitting or running a Markov chain Monte Carlo.

Assume the following model output (in a matrix or **data.frame** called **Mod**:

| time | Obs1 | Obs2 |
|------|------|------|
| 0    | 4    | 1    |
| 1    | 4    | 2    |
| 2    | 4    | 3    |
| 3    | 4    | 4    |

Then the modCost will give:

```
> Dat<- data.frame(name=c("Obs1","Obs1","Obs2","Obs2"),
+                  time=c(1,2,1,2),val=c(50,150,1,2),
+                  err=c(5,15,0.1,0.2))
> Mod <- Mod <- data.frame(time=0:3,Obs1=rep(4,4),Obs2=1:4)
> modCost(mod=Mod,obs=Dat,y="val")
```

```
$model
[1] 23434
```

```
$minlogp
[1] Inf
```

```
$var
  name scale N SSR.unweighted  SSR
1 Obs1     1 2          23432 23432
2 Obs2     1 2              2    2
```

```
$residuals
  name x obs mod weight res.unweighted  res
1 Obs1 1  50  4      1          -46  -46
2 Obs1 2 150  4      1         -146 -146
3 Obs2 1   1  2      1           1    1
4 Obs2 2   2  3      1           1    1
```

```
attr("class")
[1] "modCost"
```

in case the residuals are not weighed and

```
> modCost(mod=Mod,obs=Dat,y="val",err="err")
```

```
$model
[1] 304.3778
```

```
$minlogp
[1] Inf
```

```
$var
  name scale N SSR.unweighted  SSR
1 Obs1     1 2          23432 179.3778
2 Obs2     1 2              2 125.0000
```

```
$residuals
  name x obs mod      weight res.unweighted  res
```

```

1 Obs1 1 50 4 0.20000000 -46 -9.200000
2 Obs1 2 150 4 0.06666667 -146 -9.733333
3 Obs2 1 1 2 10.00000000 1 10.000000
4 Obs2 2 2 3 5.00000000 1 5.000000

```

```

attr(,"class")
[1] "modCost"

```

in case the residuals are weighed by 1/error.

### 6.3. Model fitting

Assume the following data set (in crosstable (wide) format):

```

> Data <- matrix (nc=2,byrow=2,data=
+ c( 2, 0.14, 4, 0.21, 6, 0.31, 8, 0.40,
+ 10, 0.69, 12, 0.97, 14, 1.42, 16, 2.0,
+ 18, 3.0, 20, 4.5, 22, 6.5, 24, 9.5,
+ 26, 13.5, 28, 20.5, 30, 29, 35, 65, 40, 61)
+ )
> colnames(Data) <- c("time","Bact")
> head(Data)

```

```

      time Bact
[1,]    2 0.14
[2,]    4 0.21
[3,]    6 0.31
[4,]    8 0.40
[5,]   10 0.69
[6,]   12 0.97

```

and assume that we want to fit the model parameters **gmax** and **eff** to these data.

We first define an objective function that returns the residuals of the model versus the data, as estimated by **modcost**. Input to the function are the current values of the parameters that need to be finetuned and their names (or position in **par**).

```

> Objective <- function(x,parset=names(x)) {
+   pars[parset]<- x
+   tout <- seq(0,50,by=0.5)
+   ## output times
+   out <- solveBact(pars,tout)
+   ## Model cost
+   return(modCost(obs=Data,model=out))
+ }

```

First it is instructive to establish which parameters are identifiable based on the data set. We assess that by means of the identifiability function **collin**, selecting only the output variables at the instances when there is an observation.

```
> Coll <- collin(sF<-sensFun(func=Objective,parms=pars,varscale=1))
> Coll
```

|    | gmax | eff | ks | rB | dB | N | collinearity |
|----|------|-----|----|----|----|---|--------------|
| 1  | 1    | 1   | 0  | 0  | 0  | 2 | 4.5          |
| 2  | 1    | 0   | 1  | 0  | 0  | 2 | 21.1         |
| 3  | 1    | 0   | 0  | 1  | 0  | 2 | 2.1          |
| 4  | 1    | 0   | 0  | 0  | 1  | 2 | 3.7          |
| 5  | 0    | 1   | 1  | 0  | 0  | 2 | 4.5          |
| 6  | 0    | 1   | 0  | 1  | 0  | 2 | 3.3          |
| 7  | 0    | 1   | 0  | 0  | 1  | 2 | 9.2          |
| 8  | 0    | 0   | 1  | 1  | 0  | 2 | 2.1          |
| 9  | 0    | 0   | 1  | 0  | 1  | 2 | 3.7          |
| 10 | 0    | 0   | 0  | 1  | 1  | 2 | 4.5          |
| 11 | 1    | 1   | 1  | 0  | 0  | 3 | 21.1         |
| 12 | 1    | 1   | 0  | 1  | 0  | 3 | 10.2         |
| 13 | 1    | 1   | 0  | 0  | 1  | 3 | 10.5         |
| 14 | 1    | 0   | 1  | 1  | 0  | 3 | 21.1         |
| 15 | 1    | 0   | 1  | 0  | 1  | 3 | 21.1         |
| 16 | 1    | 0   | 0  | 1  | 1  | 3 | 3442.4       |
| 17 | 0    | 1   | 1  | 1  | 0  | 3 | 9.9          |
| 18 | 0    | 1   | 1  | 0  | 1  | 3 | 10.5         |
| 19 | 0    | 1   | 0  | 1  | 1  | 3 | 13.8         |
| 20 | 0    | 0   | 1  | 1  | 1  | 3 | 39.2         |
| 21 | 1    | 1   | 1  | 1  | 0  | 4 | 21.3         |
| 22 | 1    | 1   | 1  | 0  | 1  | 4 | 21.1         |
| 23 | 1    | 1   | 0  | 1  | 1  | 4 | 6465.5       |
| 24 | 1    | 0   | 1  | 1  | 1  | 4 | 4198.5       |
| 25 | 0    | 1   | 1  | 1  | 1  | 4 | 40.1         |
| 26 | 1    | 1   | 1  | 1  | 1  | 5 | 16346953.1   |

The larger the collinearity value, the less identifiable the data set. In general a collinearity value less than about 20 is "identifiable". Below we plot the collinearity as a function of the number of parameters selected. We add a line at the height of 20, the critical value:

```
> plot(Coll,log="y")
> abline(h=20,col="red")
```

The collinearity index for parameters **gmax** and **eff** is small enough to enable estimating both parameters.

```
> collin(sF,parset=1:2)
```

|   | gmax | eff | ks | rB | dB | N | collinearity |
|---|------|-----|----|----|----|---|--------------|
| 1 | 1    | 1   | 0  | 0  | 0  | 2 | 4.5          |

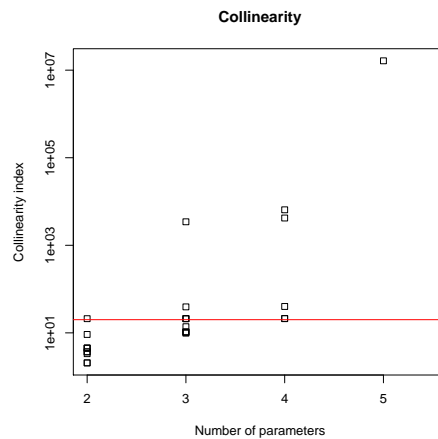


Figure 7: Collinearity analysis - see text for R-code

We now use function `modFit` to locate the minimum. It includes several fitting procedures; the default one is the Levenberg-Marquardt algorithm.

In the following example, parameters are constrained to be  $> 0$

```
> print(system.time(Fit <- modFit(p=c(gmax=0.5,eff=0.5),
+                                f=Objective,lower=c(0.0, 0.0))))
```

```
user  system elapsed
1.32   0.00   1.34
```

```
> summary(Fit)
```

Parameters:

|      | Estimate  | Std. Error | t value | Pr(> t )   |
|------|-----------|------------|---------|------------|
| gmax | 0.3003277 | 0.0004744  | 633.1   | <2e-16 *** |
| eff  | 0.7006292 | 0.0010819  | 647.6   | <2e-16 *** |

---

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.1531 on 15 degrees of freedom

Parameter correlation:

|      | gmax    | eff     |
|------|---------|---------|
| gmax | 1.0000  | -0.9151 |
| eff  | -0.9151 | 1.0000  |

The best-fit model is run, the model cost function estimated and the model outcome compared to data.

```

> pars[c("gmax","eff")]<- Fit$par
> out <- solveBact(pars)
> Cost <- modCost(obs=Data,model=out)
> Cost

$model
[1] 0.3514637

$minlogp
[1] 15.79769

$var
  name scale  N SSR.unweighted      SSR
1 Bact      1 17      0.3514637 0.3514637

$residuals
  name  x  obs      mod weight res.unweighted      res
1 Bact  2  0.14 0.1460459      1  0.0060458809 0.0060458809
2 Bact  4  0.21 0.2132921      1  0.0032921296 0.0032921296
3 Bact  6  0.31 0.3115005      1  0.0015004789 0.0015004789
4 Bact  8  0.40 0.4549261      1  0.0549260945 0.0549260945
5 Bact 10  0.69 0.6643861      1 -0.0256139211 -0.0256139211
6 Bact 12  0.97 0.9702790      1  0.0002789839 0.0002789839
7 Bact 14  1.42 1.4169922      1 -0.0030078325 -0.0030078325
8 Bact 16  2.00 2.0693334      1  0.0693333596 0.0693333596
9 Bact 18  3.00 3.0219120      1  0.0219119911 0.0219119911
10 Bact 20  4.50 4.4128138      1 -0.0871861894 -0.0871861894
11 Bact 22  6.50 6.4435104      1 -0.0564896371 -0.0564896371
12 Bact 24  9.50 9.4077851      1 -0.0922149224 -0.0922149224
13 Bact 26 13.50 13.7335832      1  0.2335831982 0.2335831982
14 Bact 28 20.50 20.0429739      1 -0.4570261141 -0.4570261141
15 Bact 30 29.00 29.2356342      1  0.2356342429 0.2356342429
16 Bact 35 65.00 65.0449095      1  0.0449094734 0.0449094734
17 Bact 40 61.00 60.9533707      1 -0.0466293436 -0.0466293436

attr(,"class")
[1] "modCost"

> plot(out$time,out$Bact,ylim=range(out$Bact),
+       xlab="time, hour",ylab="molC/m3",type="l",lwd=2)
> points(Data,cex=2,pch=18)

Finally, model residuals are plotted:

> plot(Cost, xlab="time",ylab="",main="residuals")

```



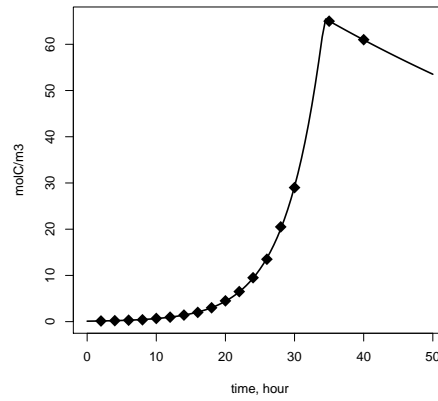


Figure 8: Fitting the model to data - see text for R-code

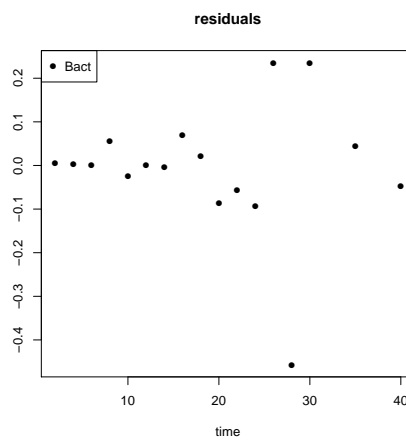


Figure 9: Model-data residuals - see text for R-code

## 7. Markov chain Monte Carlo

We can use the results of the fit to run a MCMC ([Gelman, Varlin, Stern, and Rubin 2004](#)). Function `modMCMC` implements the delayed rejection (DR) adaptive metropolis (AM) algorithm ([Haario \*et al.\* 2006](#)).

The `summary` method of the best fit returns several useful values:

- the model variance `modVarianc` is used as the initial model error variance (`var0`). In each MCMC step,  $1/\text{model variance}$  is drawn from a gamma function with parameters  $\text{shape}=0.5*N*(1+pvar0)$ , and the  $\text{rate}=0.5*(pvar0*N*var0+SS_{\text{new}})$  and where  $SS$  is the current sum of squared residuals,  $N$  is the number of data points and `pVar0` is a weighing parameter, input to `modMCMC`.
- The best-fit parameters are used as initial parameter values for the MCMC (`p`).
- The parameter covariance returned by the `summary` method, scaled with  $2.4^2/\text{length}(p)$ , gives a suitable covariance matrix, for generating new parameter values (`jump`).

```
> SF<-summary(Fit)
> SF
```

Parameters:

|      | Estimate  | Std. Error | t value | Pr(> t )   |
|------|-----------|------------|---------|------------|
| gmax | 0.3003277 | 0.0004744  | 633.1   | <2e-16 *** |
| eff  | 0.7006292 | 0.0010819  | 647.6   | <2e-16 *** |

---

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.1531 on 15 degrees of freedom

Parameter correlation:

|      | gmax    | eff     |
|------|---------|---------|
| gmax | 1.0000  | -0.9151 |
| eff  | -0.9151 | 1.0000  |

```
> SF[]
```

\$residuals

|               | Bact          | Bact         | Bact          | Bact          | Bact |
|---------------|---------------|--------------|---------------|---------------|------|
| 0.0060458809  | 0.0032921296  | 0.0015004789 | 0.0549260945  | -0.0256139211 |      |
|               | Bact          | Bact         | Bact          | Bact          | Bact |
| 0.0002789839  | -0.0030078325 | 0.0693333596 | 0.0219119911  | -0.0871861894 |      |
|               | Bact          | Bact         | Bact          | Bact          | Bact |
| -0.0564896371 | -0.0922149224 | 0.2335831982 | -0.4570261141 | 0.2356342429  |      |
|               | Bact          | Bact         |               |               |      |
| 0.0449094734  | -0.0466293436 |              |               |               |      |

```

$residualVariance
[1] 0.02343091

$sigma
[1] 0.1530716

$modVariance
[1] 0.02067434

$df
[1] 2 15

$cov.unscaled
      gmax      eff
gmax 9.604559e-06 -2.004615e-05
eff -2.004615e-05  4.995865e-05

$cov.scaled
      gmax      eff
gmax 2.250436e-07 -4.696997e-07
eff -4.696997e-07  1.170577e-06

$info
[1] 3

$niter
[1] 7

$stopmess
[1] "ok"

$par
      Estimate Std. Error t value    Pr(>|t|)
gmax 0.3003277 0.0004743876 633.0850 1.274385e-34
eff  0.7006292 0.0010819320 647.5723 9.076375e-35

> Var0<- SF$modVariance
> covIni <-SF$cov.scaled *2.4^2/2
> MCMC<-modMCMC(p=coef(Fit),f=Objective,jump=covIni,
+              var0=Var0,wvar0=1)

number of accepted runs: 340 out of 1000 (34%)

The plot method shows the trace of the parameters and, in Full is TRUE, also the model
function.

> plot(MCMC,Full=TRUE)

```

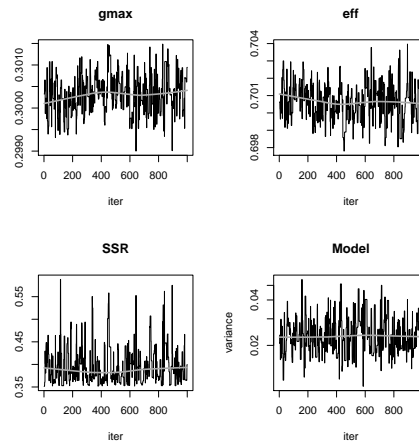


Figure 10: MCMC parameter values per iteration - see text for R-code

The `pairs` method plots both parameters as a function of one another:

```
> pairs(MCMC)
```

The MCMC output can be used in the functions from the **coda** package:

```
> MC <- as.mcmc(MCMC$pars)
```

```
> cumuplot(MC)
```

Finally, we compare the covariances based on generated parameters with the ones from the fit:

```
> cov(MCMC$pars)
```

|      | gmax          | eff           |
|------|---------------|---------------|
| gmax | 2.120390e-07  | -4.620131e-07 |
| eff  | -4.620131e-07 | 1.183012e-06  |

```
> covIni
```

|      | gmax          | eff           |
|------|---------------|---------------|
| gmax | 6.481255e-07  | -1.352735e-06 |
| eff  | -1.352735e-06 | 3.371261e-06  |

## 8. Distributions

Parameter values can be generated according to 4 different distributions:

Grid,Uniform,Normal,Latinhyper:

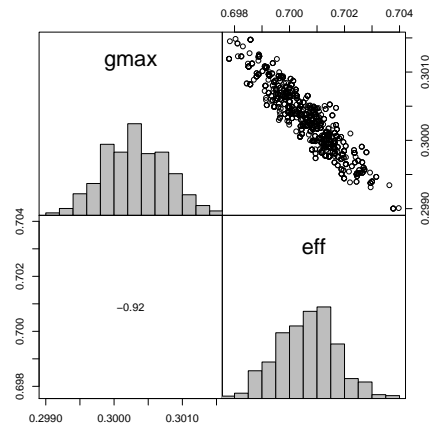


Figure 11: Pairs plot of MCMC results. See text for R-code

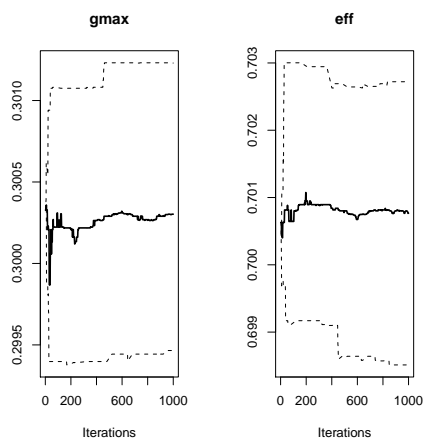


Figure 12: cumulative quantile plot from the MCMC run as from package **coda** - see text for R-code

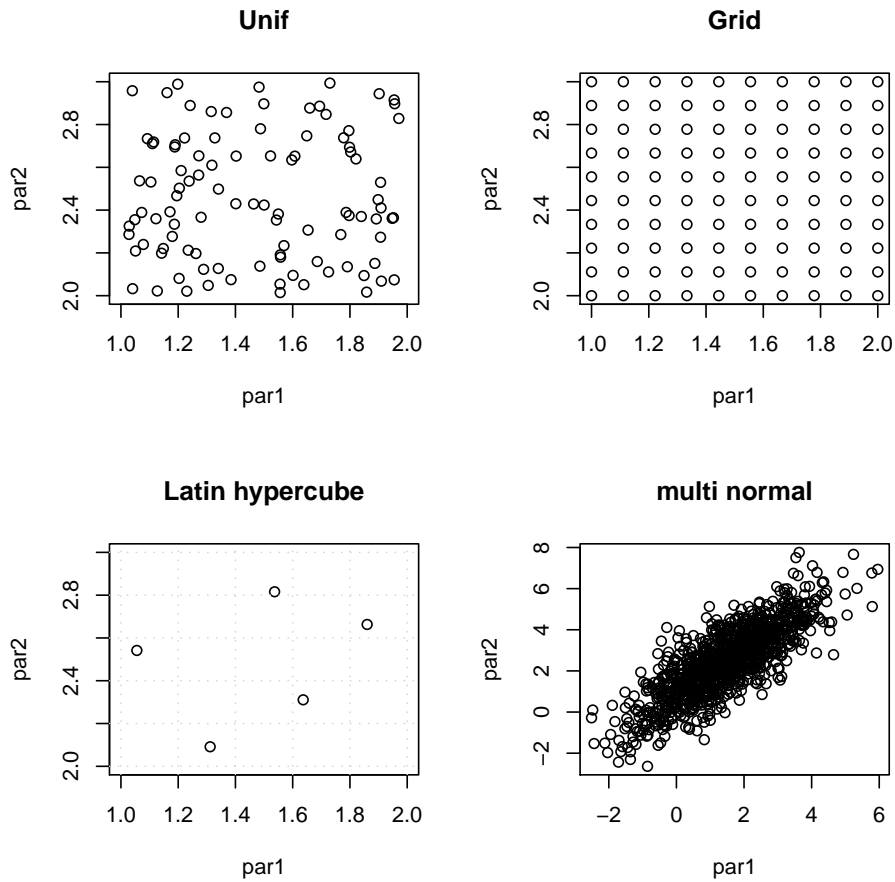


Figure 13: distributions

```
> par(mfrow=c(2,2))
> Minmax <- data.frame(min=c(1,2),max=c(2,3))
> rownames(Minmax) <-c("par1", "par2")
> Mean <- c(par1=1.5,par2=2.5)
> Covar <- matrix(nr=2,data=c(2,2,2,3))
> plot(Unif(Minmax,100),main="Unif",xlim=c(1,2),ylim=c(2,3))
> plot(Grid(Minmax,100),main="Grid",xlim=c(1,2),ylim=c(2,3))
> plot(Latinhyper(Minmax,5),main="Latin hypercube",xlim=c(1,2),ylim=c(2,3))
> grid()
> plot(Norm(parMean=Mean,parCovar=Covar,num=1000),main="multi normal")
```

## 9. Examples

Several examples are present in subdirectory examples of the package. They include:

- BODO2\_FME.R, a 1-D model of oxygen dynamics in a river. This model consists of

two coupled partial differential equations, which are solved to steady-state.

- `ccl4model_FME.R`. Here the functions are applied to "ccl4model", one of the models included in package **deSolve**. This is a model that has been written in FORTRAN.
- `Omexdia_FME.R`. Here the functions are applied to a model implemented in **simecol**, an object-oriented framework for ecological modeling (Petzoldt and Rinke 2007), more specifically in package **simecolModels** (Petzoldt and Soetaert 2008). The omexdia model is a 1-D diagenetic model.
- `O2profile_FME.R`. This contains a simple model of oxygen, diffusing along a spatial gradient, with imposed upper and lower boundary concentration

## 10. Finally

This vignette is mainly a Sweave (Leisch 2002) translation of part of the **FME** help files and examples.

Table 1: Summary of the functions in package FME

| Function                        | Description   |
|---------------------------------|---|
| sensFun                         | Sensitivity functions   |
| sensRange                       | Sensitivity ranges  |
| modCost                         | Estimates cost functions  |
| modFit                          | Fits a model to data  |
| modMCMC                         | Runs a Markov chain Monte Carlo   |
| collin                          | Estimates collinearity based on sensitivity functions                             |
| Grid, Norm,<br>Unif, Latinhyper | Generates parameter sets based on grid, normal, uniform or latin hypercube design |

Table 2: Summary of the methods in package FME

| Method        | Function | Description   |
|---------------|----------|---|
| summary       | modFit   | Summary statistics, including parameter std deviations, significance, parameter correlation |
| deviance      | modFit   | model deviance (sum of squared residuals)   |
| coef          | modFit   | values of fitted parameters   |
| residuals     | modFit   | residuals of model and data   |
| df.residual   | modFit   | degrees of freedom  |
| print.summary | modFit   | printout of model summary   |
| summary       | modMCMC  | Summary statistics of sampled parameters  |
| plot          | modMCMC  | Plots all sampled parameters  |
| pairs         | modMCMC  | Pairwise plots all sampled parameters   |

## References

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- Leisch F (2002). “Sweave: Dynamic Generation of Statistical Reports Using Literate Data Analysis.” In W Härdle, B Rönz (eds.), “Compstat 2002 - Proceedings in Computational Statistics,” pp. 575–580. Physica Verlag, Heidelberg. ISBN 3-7908-1517-9, URL <http://www.stat.uni-muenchen.de/~leisch/Sweave>.
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- Petzoldt T, Soetaert K (2008). *simecolModels: Model collection for the simecol package*. R package version 0.3, URL <http://www.simecol.de/>.
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- Soetaert K, Petzoldt T, Setzer RW (2008). *deSolve: General solvers for ordinary differential equations (ODE) and for differential algebraic equations (DAE)*. R package version 1.2.

**Affiliation:**

Karline Soetaert  
Centre for Estuarine and Marine Ecology (CEME)  
Netherlands Institute of Ecology (NIOO)  
4401 NT Yerseke, Netherlands  
E-mail: [k.soetaert@nioo.knaw.nl](mailto:k.soetaert@nioo.knaw.nl)  
URL: <http://www.nioo.knaw.nl/ppages/ksoetaert>