Three perspectives on modelling for ecological risk assessment

A toy example with a simple one-compartment toxicokinetic model

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Abstract

We provide here a toy example based on the use of a simple one-compartment toxicokinetic model to describe the bioaccumulation of chemical substances within the whole body of living organisms. From a simple ODE model, we will illustrate : (P1) how to simulate both accumulation and depuration phases under constant exposure and to compare model outputs to observed data; (P2) how to fit such a model on data without using any prior information on the model (Frequentist point of view); (3) how to benefit of prior information in combination with knowledge in data to update the calibration results (Bayesian point of view).

Introduction

Perform calculations under the three perspectives as described within the main document

Case study

Based on (Ashauer et al. 2010). Data set on *Gammarus pulex* exposed to Malathion.

A toxicokinetic (TK) model simply describing bioaccumulation of chemical substances within the whole body of living organisms is based on a set of two differential equations standing for the deterministic part (Charles, Ratier, and Lopes 2021):

$$\begin{cases} \dfrac{dC}{dt}(t) = k_u \times C_w - k_e \times C(t) \quad \forall\, 0 \leq t \leq t_c & \text{(1a)} \\ \dfrac{dC}{dt}(t) = -k_e \times C(t) \quad \forall\, t > t_c & \text{(1b)} \end{cases}$$

where t_c stands for the duration of the accumulation phase (namely the end of the exposure period, before organisms are transferred into a clean medium). Quantity C_w stands for the exposure concentration in water, while variable $C(t)$ corresponds to the internal concentration within the whole body of organisms over time t. Parameters k_u and k_e are the uptake and the elimination rates, respectively.

Given that state variables are concentrations, an appropriate stochastic part to describe the variability of the data around the mean tendency is the Gaussian distribution, so that:

$$C_{obs}(t_i) \simeq \mathcal{N}(C(t_i), \sigma) \tag{2}$$

where $C_{obs}(t_i)$ are the measured internal concentrations at time point t_i, $\forall\, i \in 1, n$, with n the total number of time points. Parameter σ stands for the standard deviation of the normal distribution.

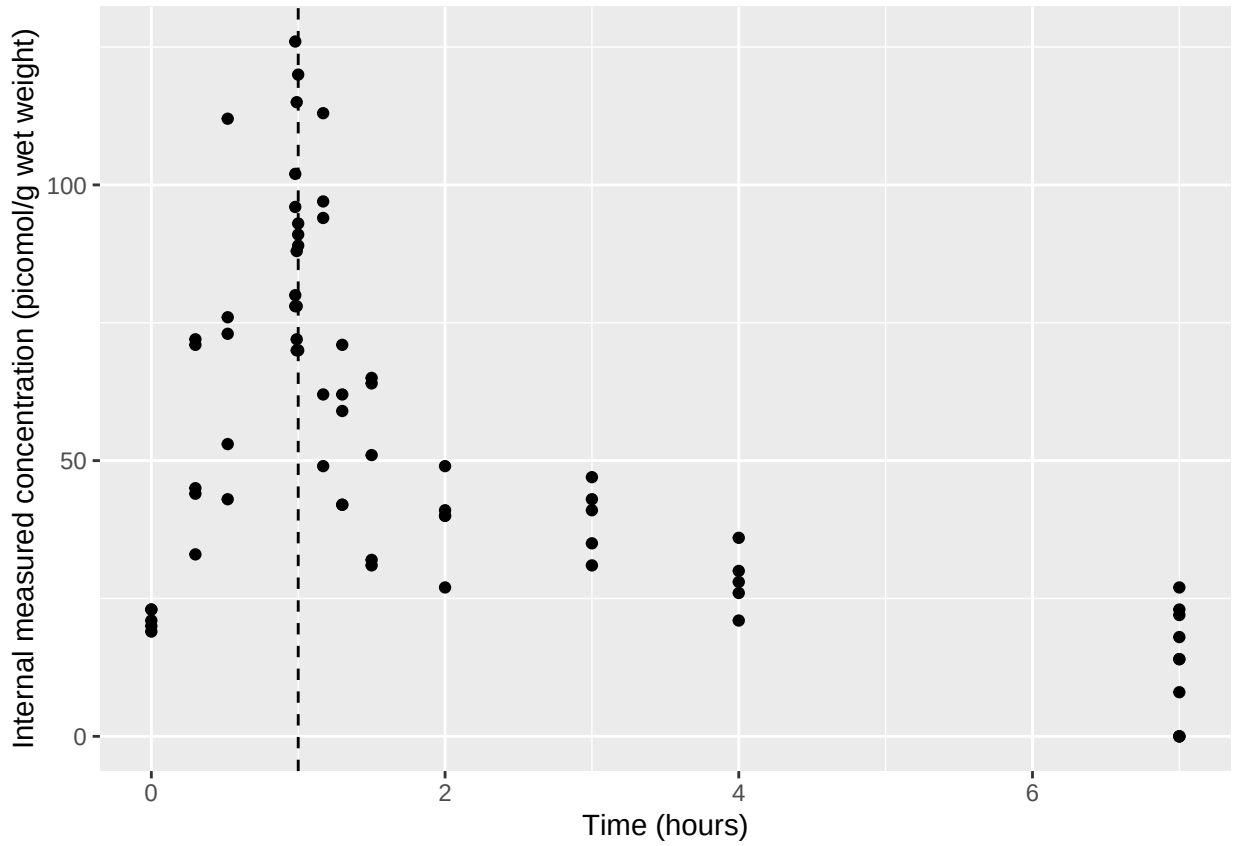


Figure 1: Raw data vizualisation (black dots). the vertical dashed line stands for the end of the accumulation phase ($t_c = 1$ day. Exposure concentration equals 1.485 picomol/ml.

Perspective 1 -

Under perspective 1, the idea is to simulate under the model equations (1) and to compare with observed data. In this perspective, we used the k_u and k_e parameter estimates as provided in Table 1 of (Ashauer et al. 2010). However, the estimation of parameter σ is missing. In addition, two options can be considered, accounting for the uncertainty or not.

Persp.1 - option 1

Persp.1 - option 2

Perspective 2

Perspective 3

In the section, we fit the one compartment model (equations (1)) under a Bayesian framework with the R-package `rbioacc` (Ratier and Charles 2022). The same calculation can be easily reproduced on-line with the MOSAIC web platform and its `bioacc` module: https://mosaic.univ-lyon1.fr/bioacc.

Model fitting

```
# Prepare the data to be use in the `rbioacc` package
mdf <- modelData(df, time_accumulation = 1, )
# fit the TK model built by default from the data
fit <- fitTK(mdf, refresh = 0)
```

Model equations

```
# Below is the code line allowing to get
# the used model equations
equations(fit, df)
```

Fitting results

```
# Get parameter estimates
# medians and 95% credible intervals
quantile_table(fit)
```

```
               2.5%        50%      97.5% parameter
ku        53.0360997 65.7125384 85.0232805        ku
kee        0.3697629  0.5654089  0.8964173       kee
sigmaConc 15.3725873 18.1702794 21.6028211 sigmaConc
```

```
# Fitting plot
plot(fit)
```

Bioaccumulation metric

```
# Calculation of the posterior probability distribution
# of the kinetic bioconcentration factor
bm <- bioacc_metric(fit)
# Display median and 95% credible interval of the BCF_k
quantile(bm$BCFk, probs = c(0.025, 0.5, 0.975))
```

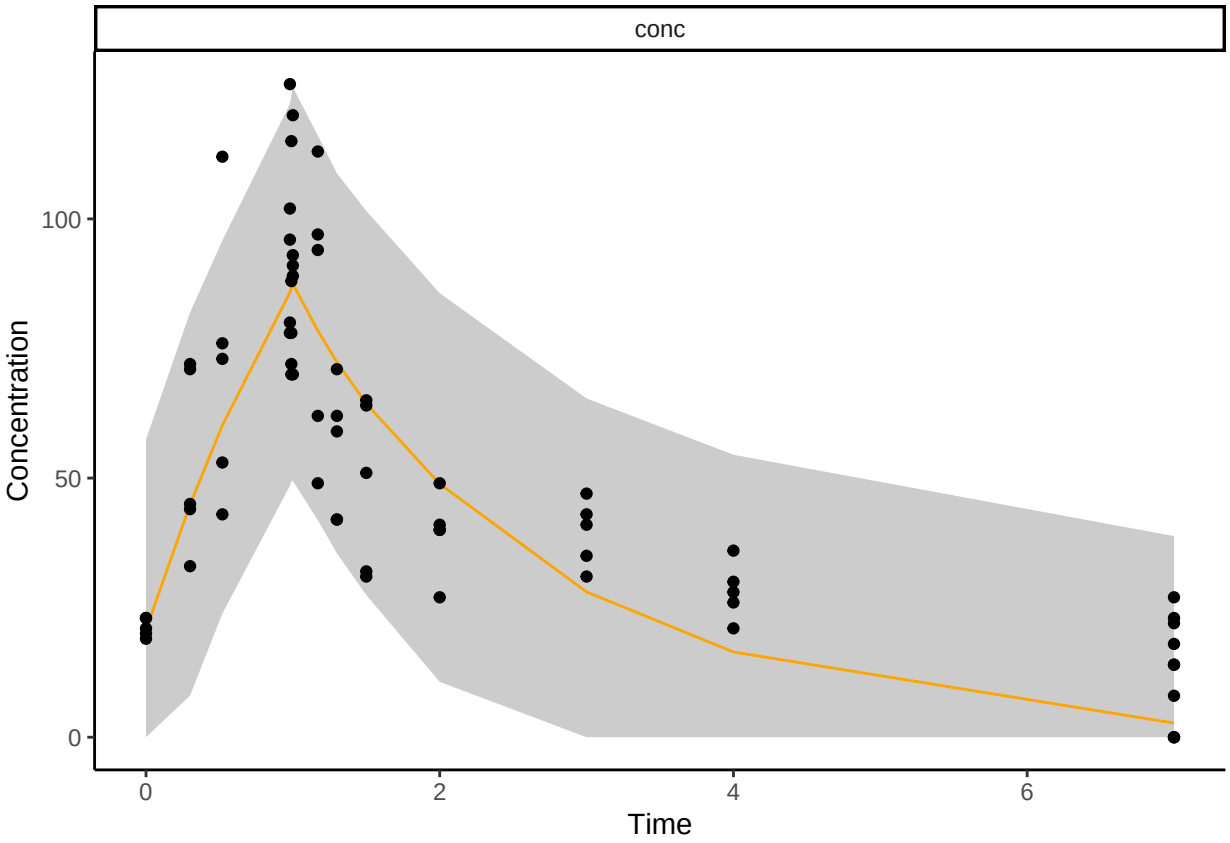


Figure 2: Fitting plot with black dots representing the observed data, the solid orange line the median predictive model and the grey area the 95% uncertainty band including the uncertainty on the model parameter estimates as well as the stochastic part of the model.

```
     2.5%       50%     97.5%
 92.53494 116.49525 149.60447
```

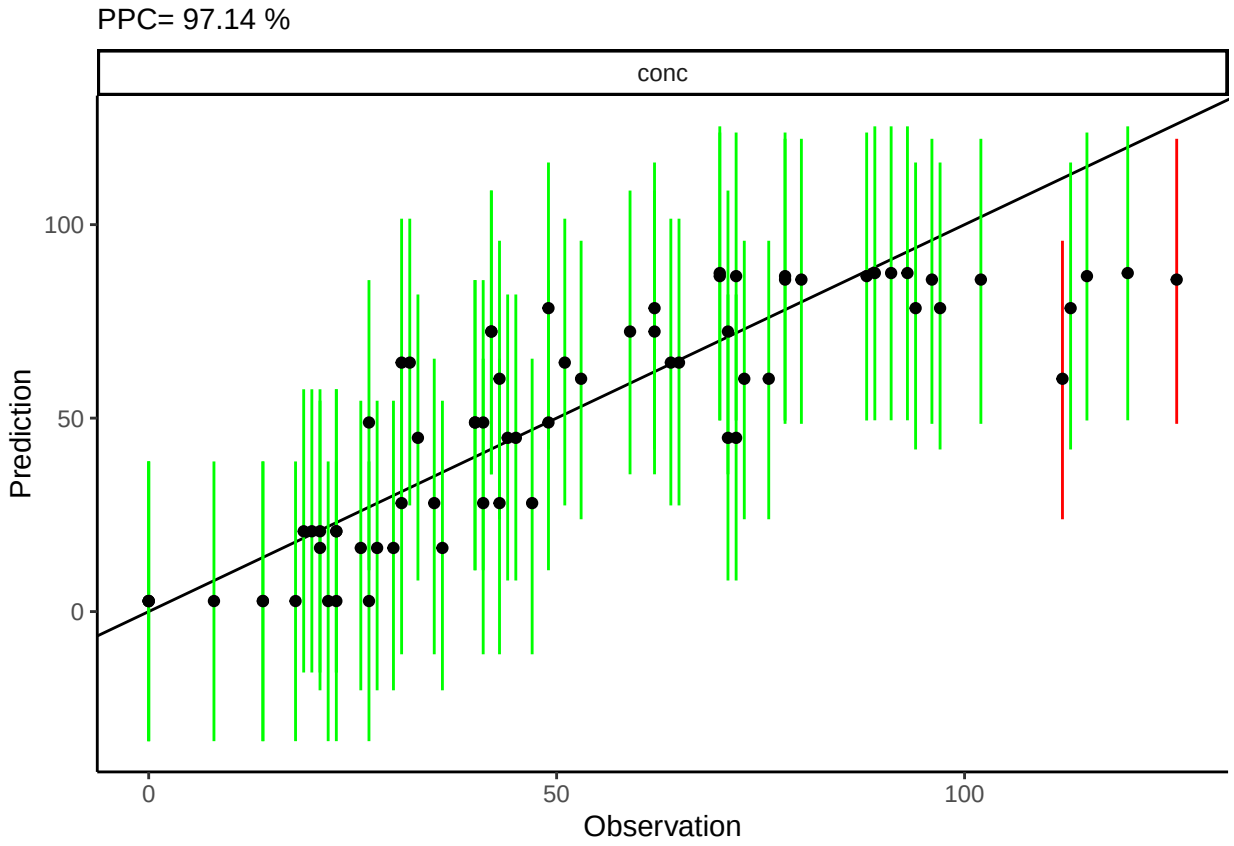
The 95% elimination time can also be easily calulated.

```
signif(t95(fit), digits = 3)
```

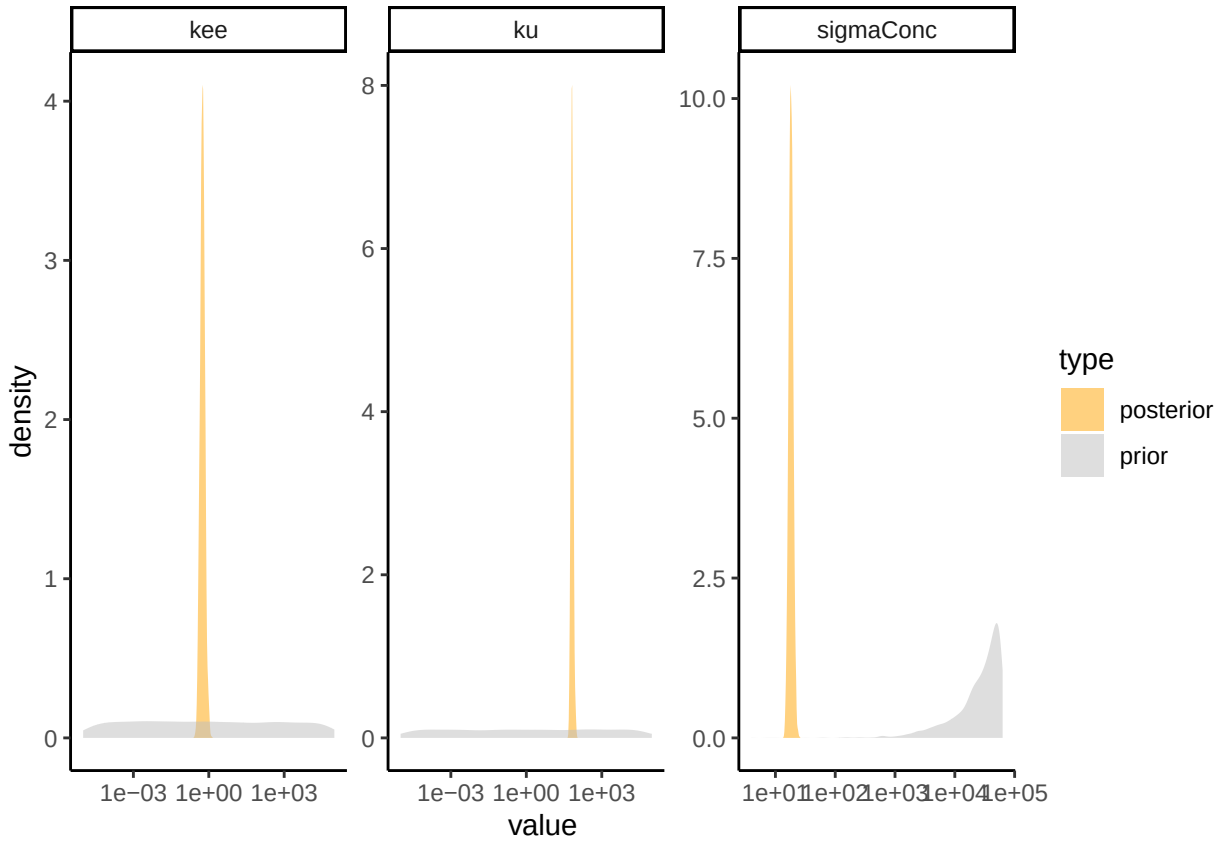
```
[1] 5.3
```

Goodness-of-fit criteria

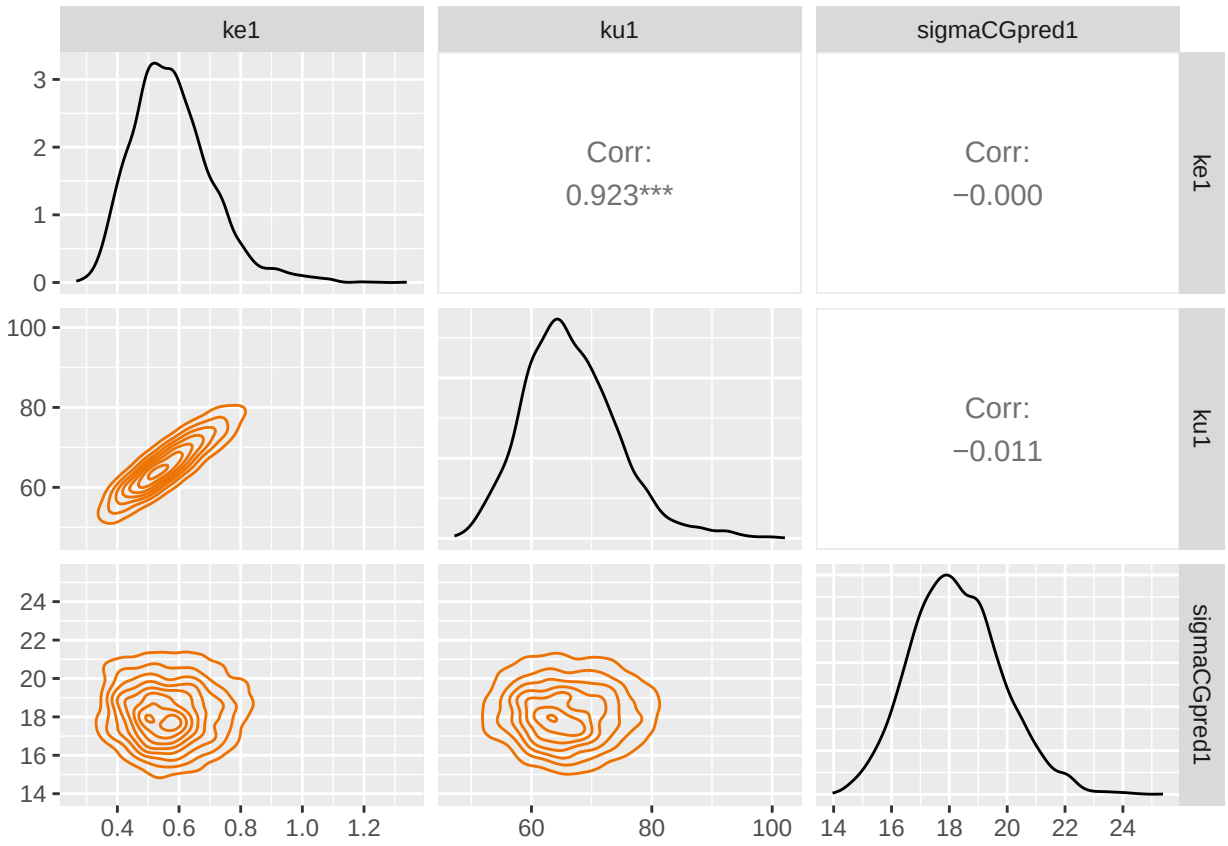
```
# Posterior Predictive Check (PPC)
# The expectation is to get ~95% of data
# within their prediction interval
ppc(fit)
```




```
# Compare priors and posteriors
plot_PriorPost(fit)
```



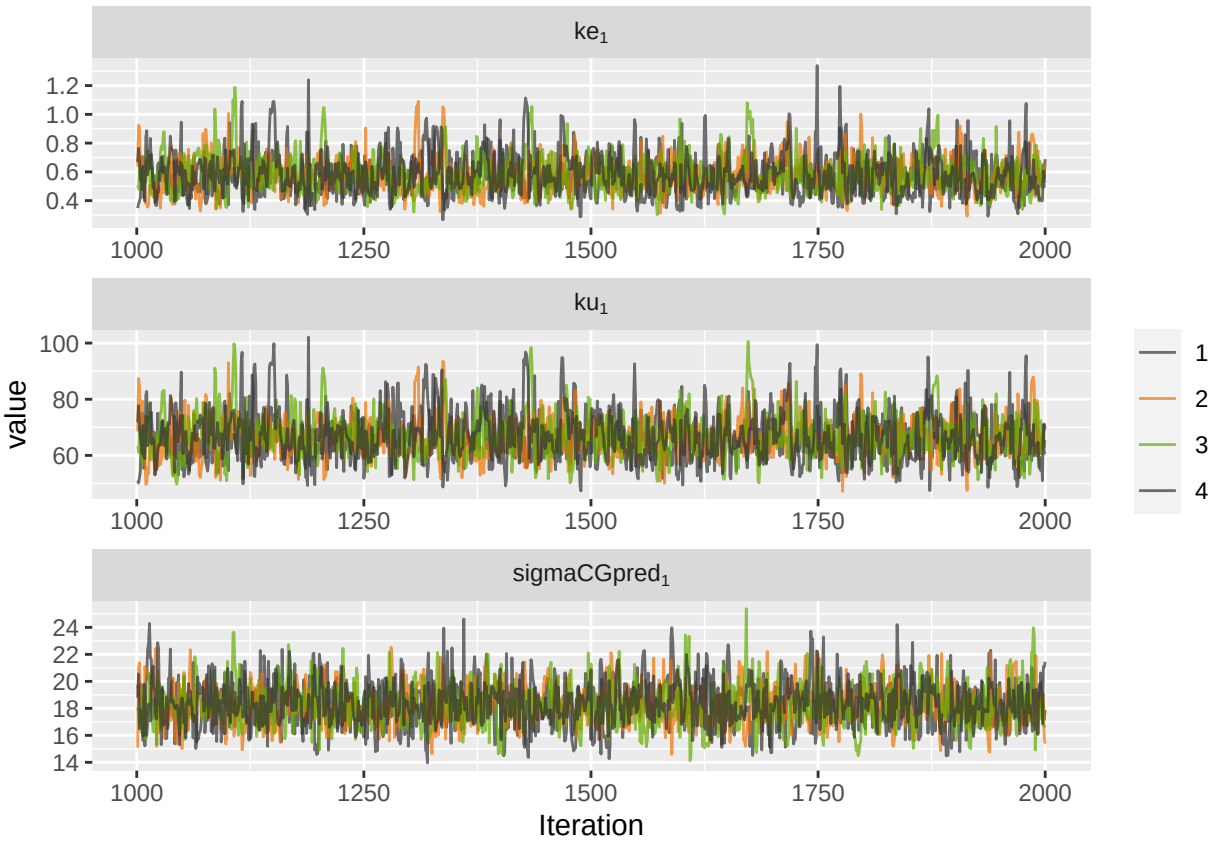

```
# Check for correlations between parameters
corrPlot(fit)
```




```
# Check  for non-signigicantly different traces
# of the four MCMC chains run in paralell
psrf(fit)
```

```
           PSRF parameter
ku         1.005        ku
kee        1.007       kee
sigmaConc 1.000 sigmaConc
```

```
# Look at the traces of the 4 MCMC chains
mcmcTraces(fit)
```



References

Ashauer, Roman, Ivo Caravatti, Anita Hintermeister, and Beate Escher. 2010. "Bioaccumulation kinetics of organic xenobiotic pollutants in the freshwater invertebrate Gammarus pulex modeled with prediction intervals." *Environmental Toxicology and Chemistry* 29 (7): 1625–36. https://doi.org/10.1002/etc.175.

Charles, Sandrine, Aude Ratier, and Christelle Lopes. 2021. "Generic Solving of One-compartment Toxicokinetic Models." *Journal of Exploratory Research in Pharmacology* 6 (4): 158–67. https://doi.org/10.14218/jerp.2021.00024.

Ratier, Aude, and Sandrine Charles. 2022. "Accumulation-depuration data collection in support of toxicokinetic modelling." *Nature, Scientific Data* 9 (1): 130. https://doi.org/10.1038/s41597-022-01248-y.

APPENDIX

Table of raw data

```
df <- read.table("data.txt", header = TRUE, sep = "")
kable(df[1:25,], format="latex")
```

time	conc	replicate	expw
0.00	23	1	1.485
0.00	19	2	1.485
0.00	20	3	1.485
0.00	21	4	1.485
0.00	23	5	1.485
0.30	44	1	1.485
0.30	72	2	1.485
0.30	33	3	1.485
0.30	71	4	1.485
0.30	45	5	1.485
0.52	43	1	1.485
0.52	76	2	1.485
0.52	53	3	1.485
0.52	112	4	1.485
0.52	73	5	1.485
0.98	102	1	1.485
0.98	78	2	1.485
0.98	96	3	1.485
0.98	126	4	1.485
0.98	80	5	1.485
0.99	72	1	1.485
0.99	115	2	1.485
0.99	70	3	1.485
0.99	88	4	1.485
0.99	78	5	1.485

One more thing

This will be Appendix B.