$\text{MOSAIC}_{\text{bioacc}}$ REPORT

2021-06-09

This report is provided by the $\text{MOSAIC}_{\text{bioacc}}$ application available here:
https://mosaic.univ-lyon1.fr/bioacc

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$\text{MOSAIC}_{\text{bioacc}}$ uses the JAGS (version 4.3.0) and R (version 4.0.2) software, and in particular packages RJags (version 4.10), jagsUI (version 1.5.1) and Shiny (version 1.6.0).

The $\text{MOSAIC}_{\text{bioacc}}$ application is a turn-key web tool providing bioaccumulation factors (BCF/BSAF/BMF) from a toxicokinetic (TK) model fitted to accumulation-depuration data. It is designed to fulfil the requirements of regulators when examining applications for market authorization of active substances.

Data summary

File used: Hyalella_diclofenac_1d_Fu2021_Cext-constant.txt

Exposure: 3.557 $\mu g.mL^{-1}$

Accumulation phase duration: 1 days

Number of replicates: 2

Times: 0, 0.02, 0.06, 0.1, 0.23, 0.4, 0.73, 1, 2, 3, 4, 5, 10

Exposure routes: water

Elimination routes: excretion biotransformation

Bayesian inference

Three MCMC chains were used to estimate model parameters.

Number of iterations: 142348

Thin: 38

TK Model

The TK model used for these calculations was:

$$\frac{dC_p(t)}{dt} = k_{uw} \times c_w - (k_{ee} + k_{m1}) \times C_p(t) \quad for\ 0 \leq t \leq t_c$$

$$\frac{dC_p(t)}{dt} = -(k_{ee} + k_{m1}) \times C_p(t) \quad for\ t > t_c$$

$$\frac{dC_{m1}(t)}{dt} = k_{m1} \times C_p(t) - k_{em1} \times C_{m1}(t)$$

with:

t: time (expressed in days)

t_c: duration of the accumulation phase (expressed in days)

$C_p(t)$: internal concentration of the parent compound at time (expressed in $\mu g.g^{-1}$)

k_{ee}: elimination rates of excretion (expressed per days $^{-1}$)

c_w: exposure concentration of water route (expressed in $\mu g.mL^{-1}$)

k_{uw}: uptake rate of water exposure (expressed per days $^{-1}$)

$C_{m\ell}(t)$: internal concentration of metabolite ℓ (expressed in $\mu g.g^{-1}$)

ℓ: index of metabolites, $\ell = 1 \ldots L$ with L total number of metabolites

$k_{m\ell}$: metabolization rate of metabolite ℓ (expressed per days $^{-1}$)

$k_{em\ell}$: elimination rates of metabolite ℓ (expressed per days $^{-1}$)

Bioaccumulation factor calculation

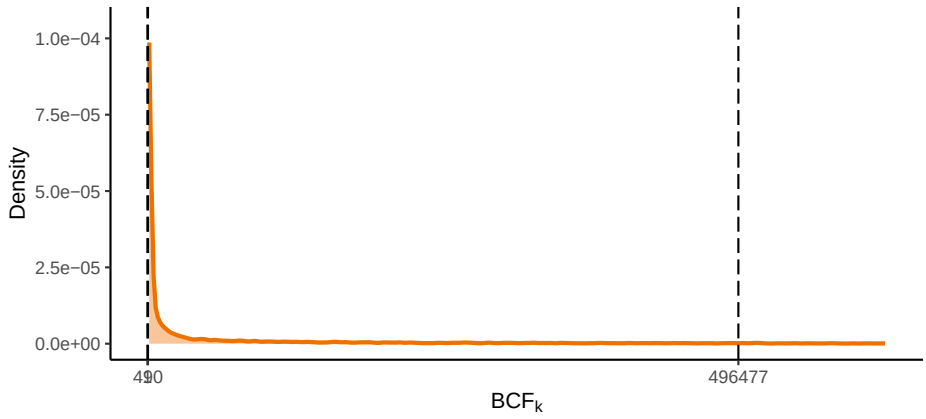
Calculations

$$BCF_k = \frac{k_{uw}}{k_{ee} + k_{m1}}$$

$$BCF_{ss} = \frac{C_p(t_c)}{c_w}$$

Bioconcentration factor (BCF)

BCF_k plot

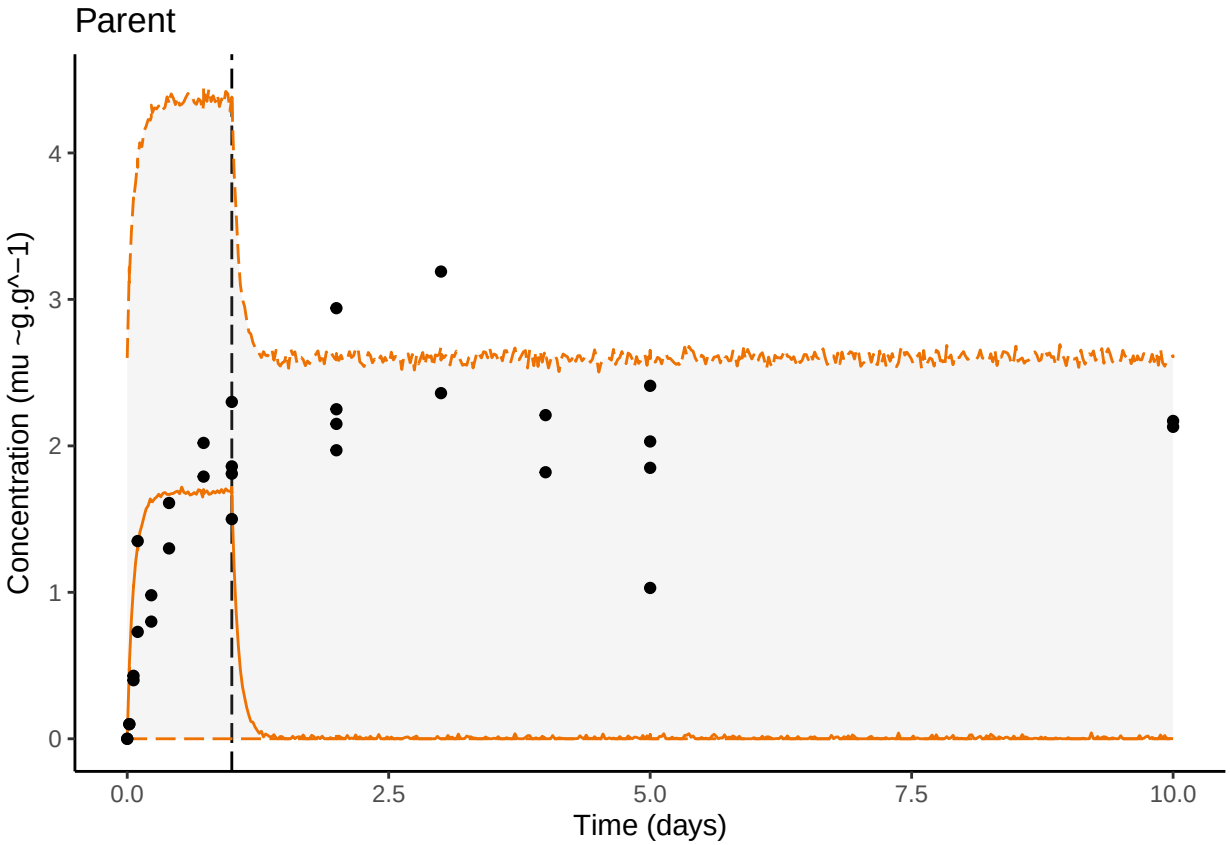


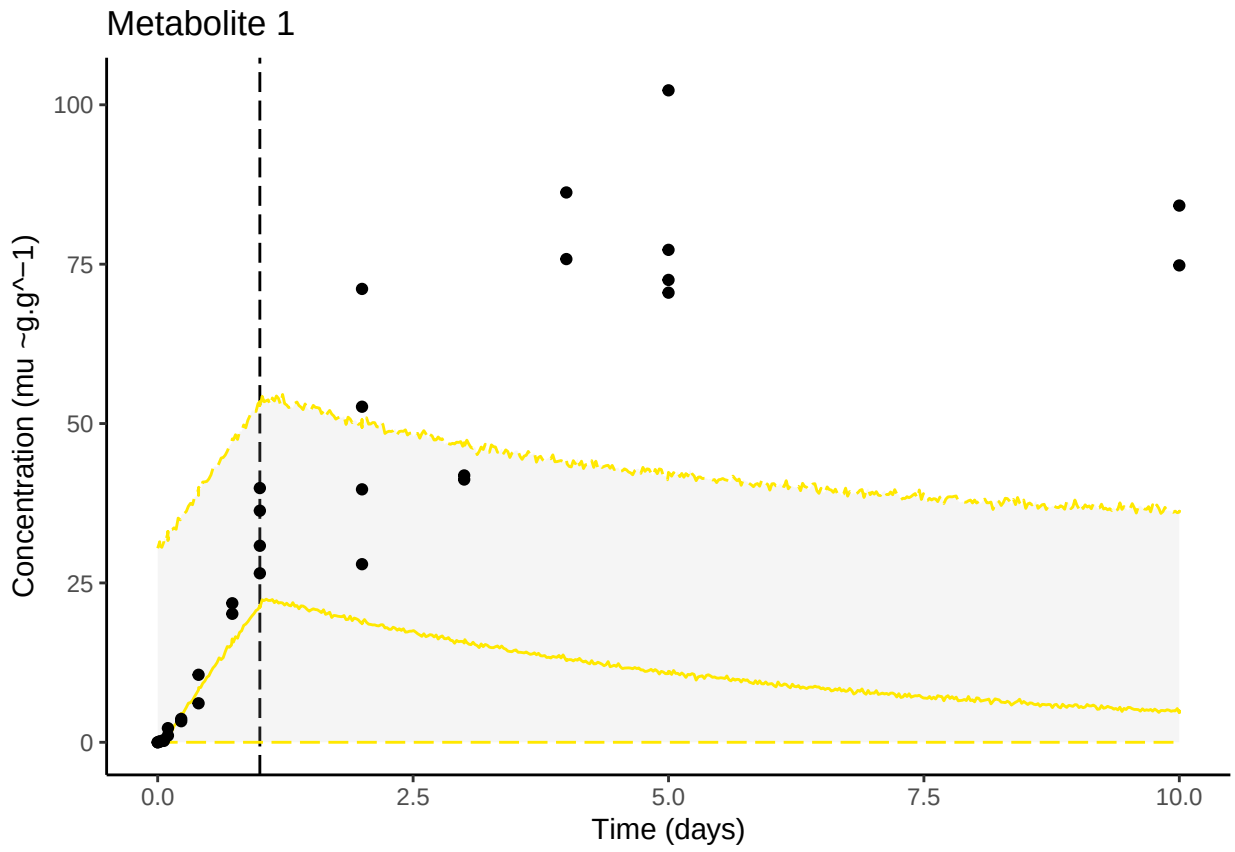
BCF summary

	2.5%	50%	97.5%	CV
BCFk	1	490	496477	250

Fitting results

Fit plot





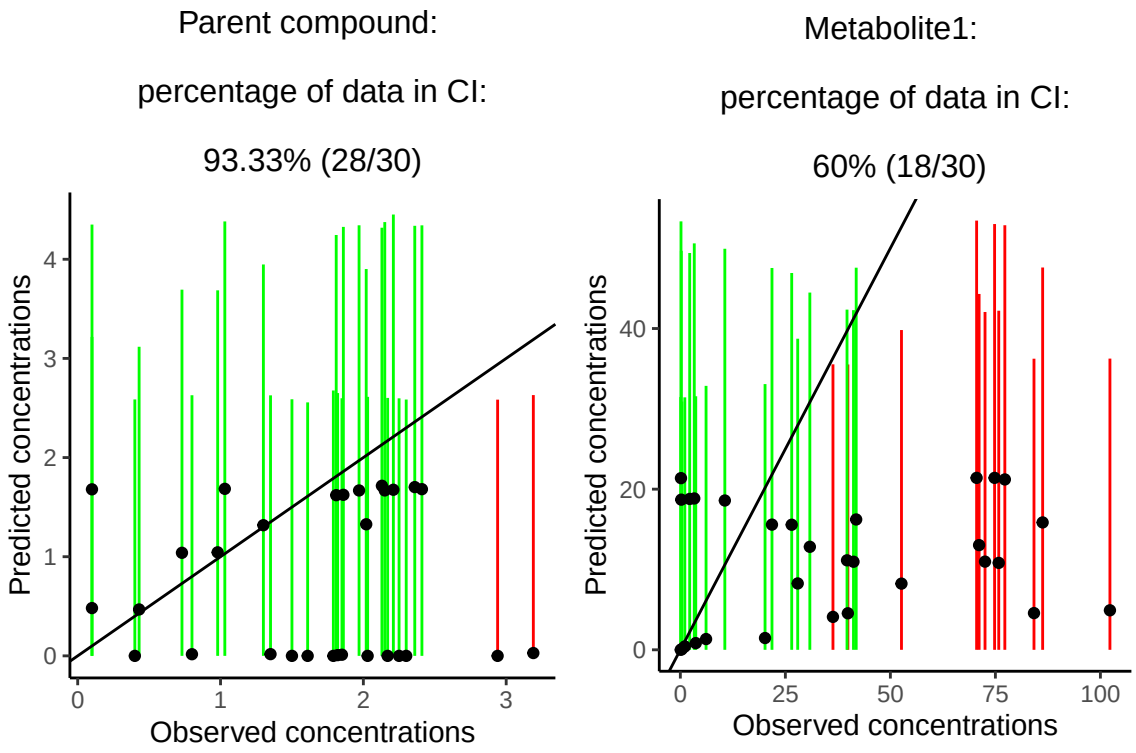
Quantiles of estimated parameters

	2.5%	50%	97.5%	
k_{uw}	4.766	7.353	95.24	d^{-1}
k_{ee}	1.408e-05	0.01399	226.5	d^{-1}
k_{m1}	8.49	14.76	27.2	d^{-1}
k_{em1}	0.03884	0.1823	0.3581	d^{-1}
σ_p	1.006	1.284	1.725	$\mu g.g^{-1}$
σ_{met1}	15.34	15.83	15.95	$\mu g.g^{-1}$

Goodness-of-fit criteria

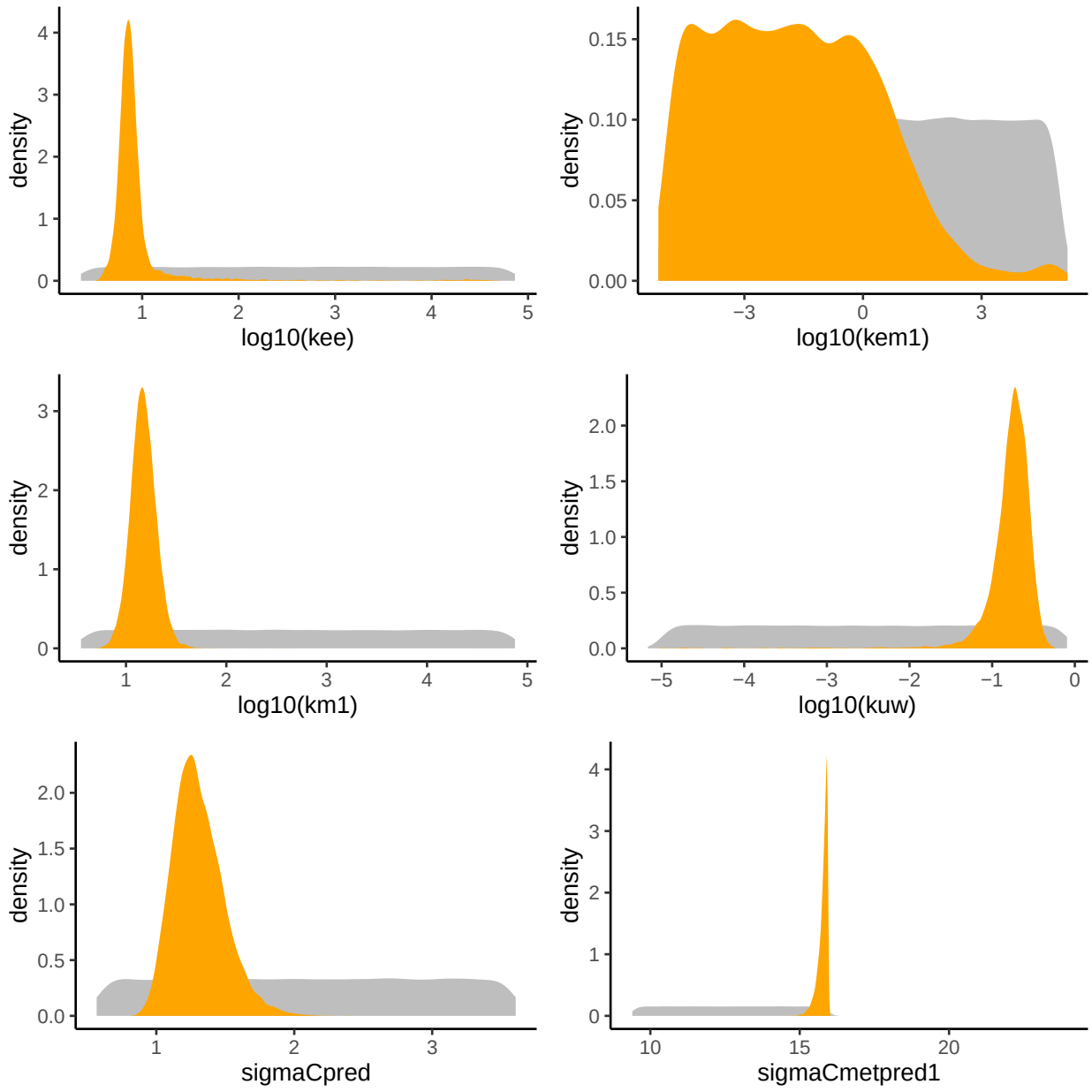
Posterior Predictive Check

The PPC shows the observed values against their corresponding estimated predictions (black dots), along with their 95% credible interval (vertical segments). If the fit is correct, we expect to see 95% of the data within the intervals. Ideally observations and predictions should coincide, so we would expect to see black dots along the first bisector y = x (plain black line). The 95% credible intervals are colored in green if they overlap this line, in red otherwise.



Priors and posteriors

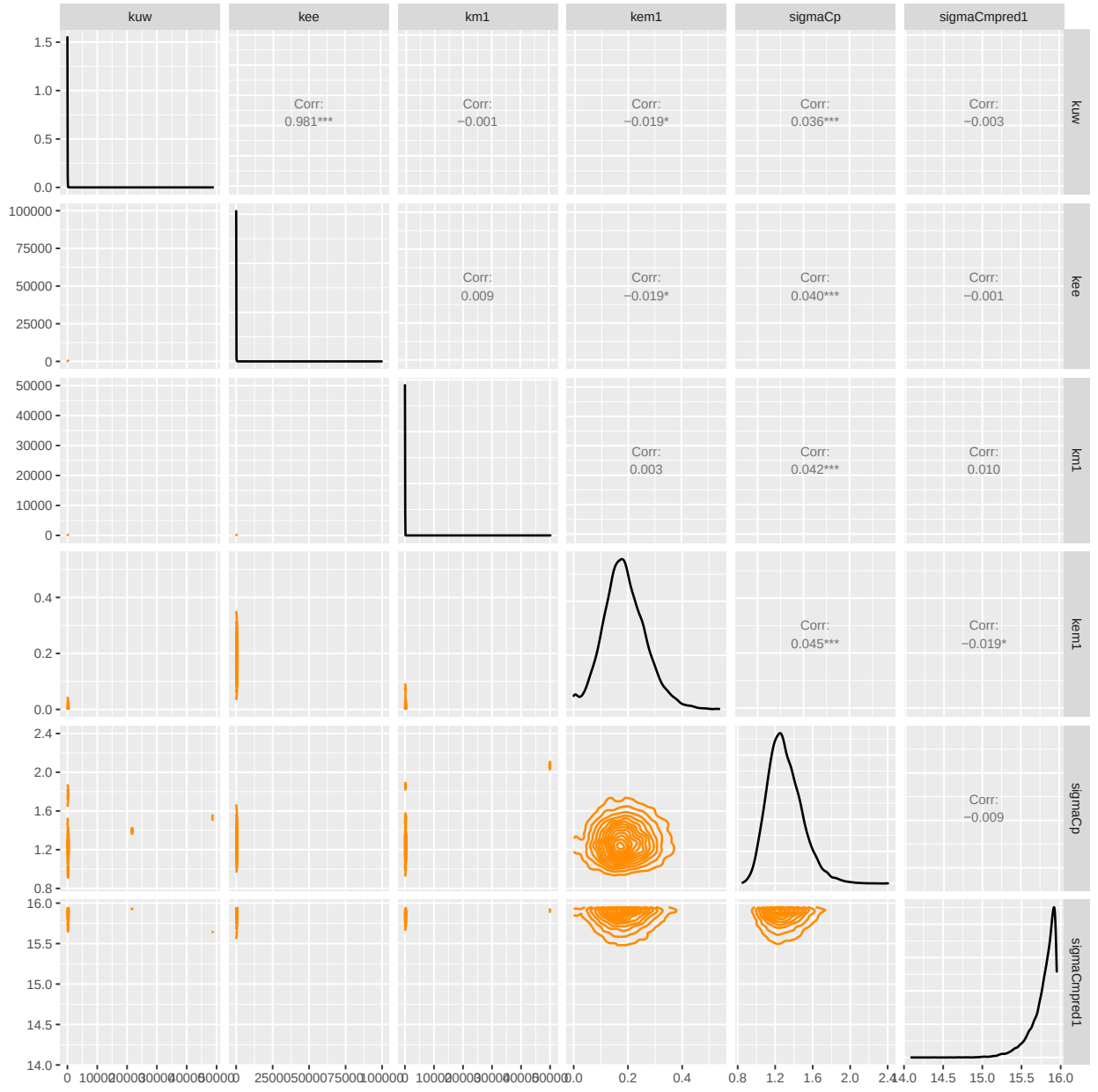
The prior distribution is represented by the gray area and the posterior distribution by the orange area. The accuracy of the model parameter estimation can be visualized by comparing prior and posterior distributions: the overall expectation is to get a narrower posterior distribution compared to the prior one, what reflects that data contributed enough to precisely estimate parameters.



Correlation between parameters

If you want to see the coloured matrix giving a summary of parameter correlations, you need to import the corresponding figure directly from the application, page bottom, section "Downloads", then choose Download an output and select "GOF" then "parameter correlation". You can select the output format you prefer.

Correlations between parameters are visualized by projecting the joint posterior distribution in a plot matrix with planes of parameter pairs (lower triangular elements), marginal posterior distribution of each model parameter (diagonal), and Pearson correlation coefficients (upper triangular elements). Correlations are expected to be low (reflected by "potatoid" shapes of density lines in orange); a leaning elliptical shape translates high correlations (positive if leaning to the right, negative if leaning to the left).



Potential Scale Reduction Factors

Convergence of the MCMC chains can be check with the Gelman-Rubin diagnostic expressed with the potential scale reduction factor (PSRF). Approximate convergence is diagnosed when the PSRF is below 1.01.

	PSRF
kuw	1.303157
kee	1.302443
km1	1.29104
kem1	1.000161
sigmaCpred	1.000805
sigmaCmetpred1	1.000006

Watanabe–Akaike information criterion

Information criteria offer a computationally appealing way of estimating the generalization performance of the model. A fully Bayesian criterion is the widely applicable information criterion (WAIC) by Watanabe a penalized deviance statistics accounting for the uncertainty in the parameters and can be used also for singular models. WAIC is widely used in model comparison for a same dataset (e.g., with or without k_{ee}). Sub-models with lower WAIC values will be preferred.

WAIC = 450.8

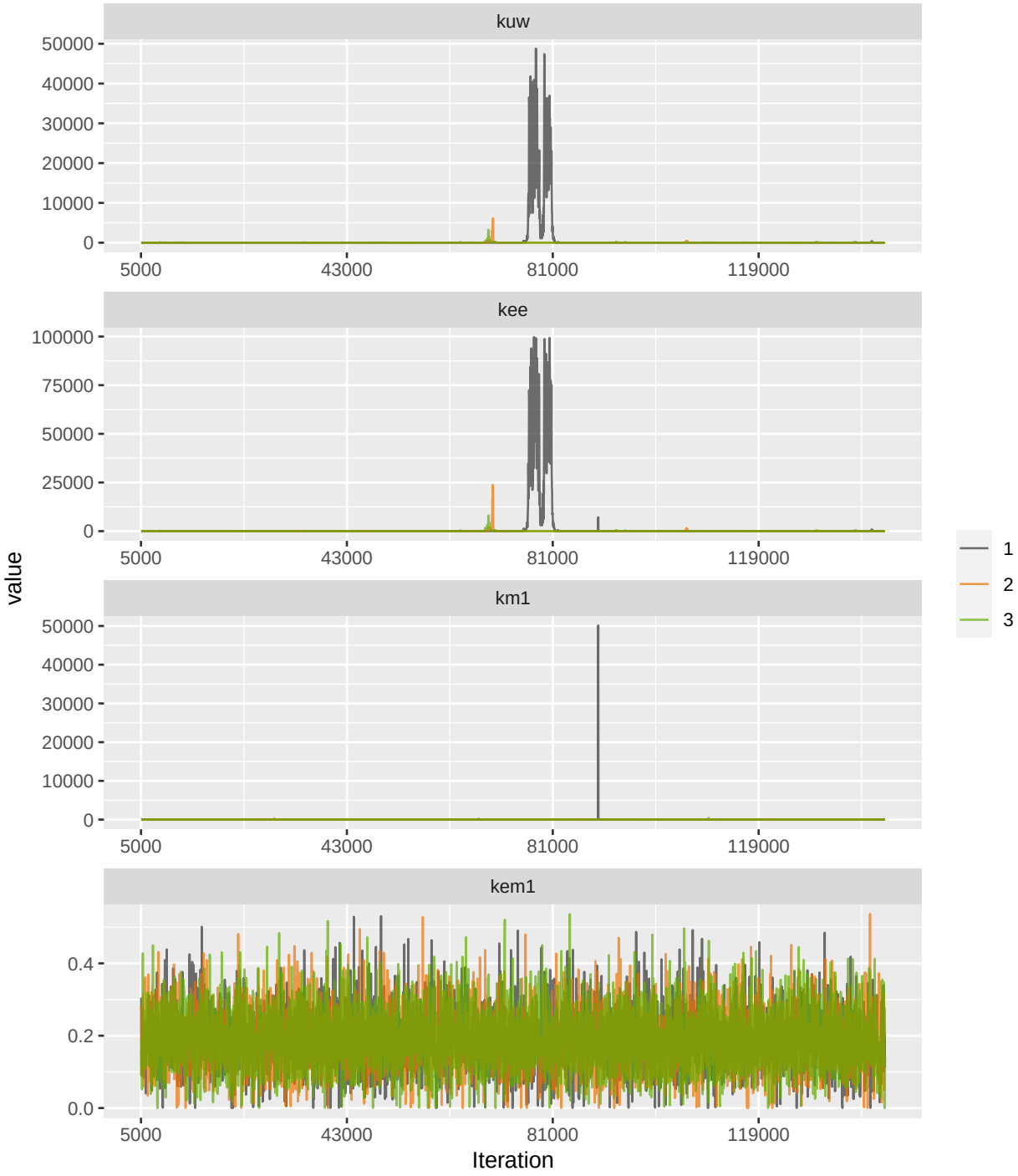
Deviance Information Criterion

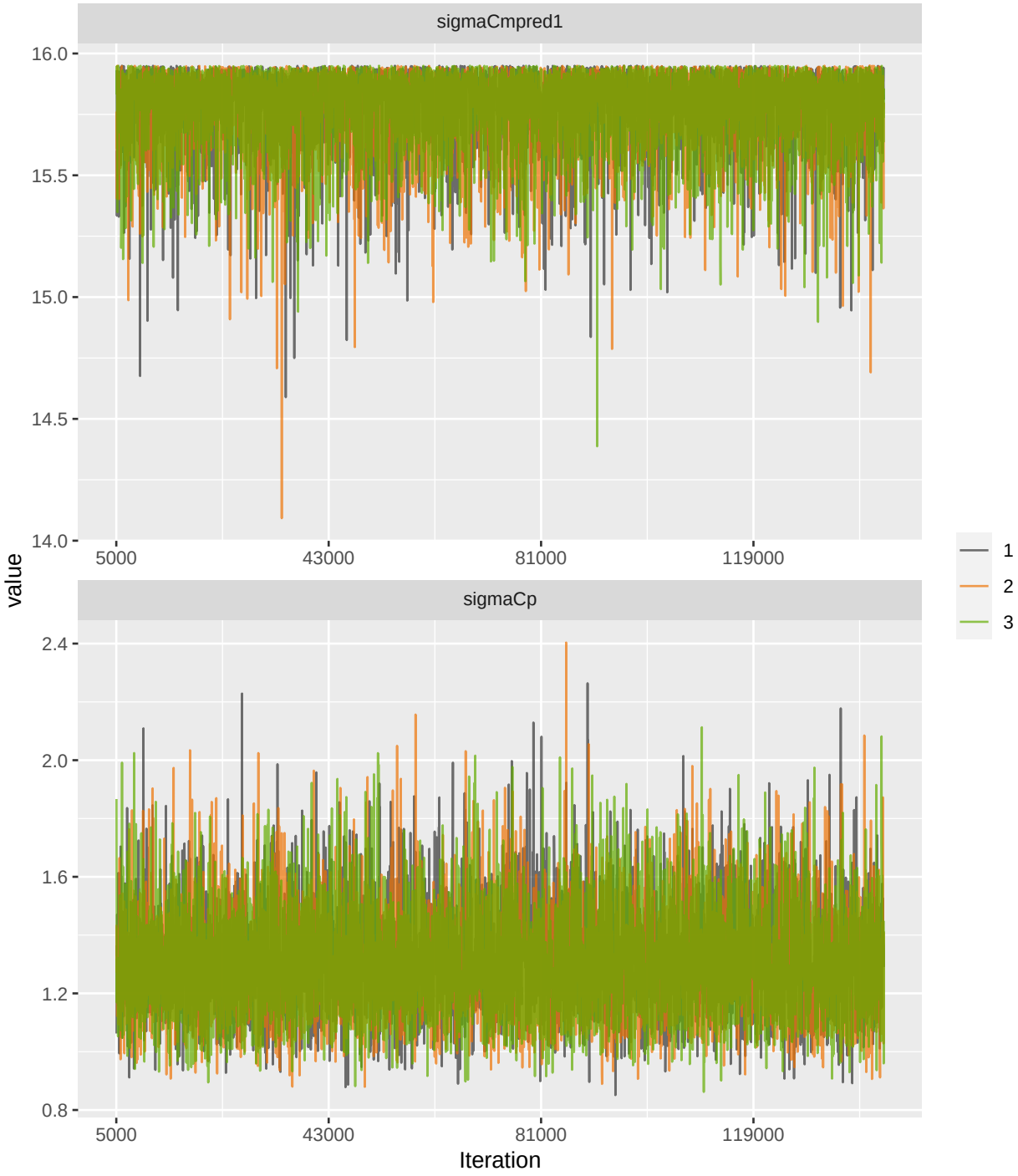
This criteria, denoted DIC, is a penalized deviance statistics accounting for the number of parameters for use in model comparison for a same dataset (e.g., with or without k_{ee}). Sub-models with lower DIC values will be preferred.

DIC = 448.3663

Traces of MCMC iterations

A traceplot is an essential plot for assessing convergence and diagnosing of MCMC chains. It shows the time series of the sampling process leading to the posterior distribution. Different colors are used for each of the chains (here 3) to assess within-chain convergence.


kuw
kee
km1
kem1
value
Iteration
1
2
3
5000
43000
81000
119000


sigmaCmpred1
16.0
15.5
15.0
14.5
14.0
5000
43000
81000
119000
sigmaCp
2.4
2.0
1.6
1.2
0.8
value
Iteration
1
2
3

Data Table

time	expw	conc	replicate	concm1
0.00	3.557	0.00	1	0.00
0.02	3.557	0.10	1	0.09
0.06	3.557	0.43	1	0.36
0.10	3.557	0.73	1	1.06
0.23	3.557	0.98	1	3.67
0.40	3.557	1.30	1	6.12
0.73	3.557	2.02	1	20.16
1.00	3.557	1.81	1	39.88
1.00	3.557	1.86	1	36.33
2.00	3.557	1.97	1	52.64
2.00	3.557	2.15	1	27.94
3.00	3.557	2.36	1	41.86
4.00	3.557	2.21	1	86.25
5.00	3.557	1.03	1	70.53
5.00	3.557	2.41	1	77.25
10.00	3.557	2.13	1	74.81
0.00	3.557	0.00	2	0.00
0.02	3.557	0.10	2	0.15
0.06	3.557	0.40	2	0.22
0.10	3.557	1.35	2	2.22
0.23	3.557	0.80	2	3.31
0.40	3.557	1.61	2	10.59
0.73	3.557	1.79	2	21.81
1.00	3.557	2.30	2	26.51
1.00	3.557	1.50	2	30.83
2.00	3.557	2.94	2	71.12
2.00	3.557	2.25	2	39.68
3.00	3.557	3.19	2	41.22
4.00	3.557	1.82	2	75.80
5.00	3.557	1.85	2	72.53
5.00	3.557	2.03	2	102.27
10.00	3.557	2.17	2	84.19