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

2021-04-14

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: Gammarus_2,4-dichloro-aniline_0.999d_Ashauer2012.txt

Exposure: 5760.092 $\mu g.mL^{-1}$

Accumulation phase duration: 0.999 days

Number of replicates: 2

Times: 0, 0.207, 0.208, 0.478, 0.999, 1, 1.207, 1.208, 1.537, 1.538, 1.999, 2, 2.999, 3

Exposure routes: water

Elimination routes: excretion biotransformation

Bayesian inference

Three MCMC chains were used to estimate model parameters.

Number of iterations: 149840

Thin: 40

TK Model

The TK model used for these calculations was:

$$\frac{dC_p(t)}{dt} = k_{uw} \times c_w - (k_{ee} + k_{m1} + k_{m2}) \times C_p(t) \quad for\ 0 \leq t \leq t_c$$

$$\frac{dC_p(t)}{dt} = -(k_{ee} + k_{m1} + k_{m2}) \times C_p(t) \quad for\ t > t_c$$

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

$$\frac{dC_{m2}(t)}{dt} = k_{m2} \times C_p(t) - k_{em2} \times C_{m2}(t)$$

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

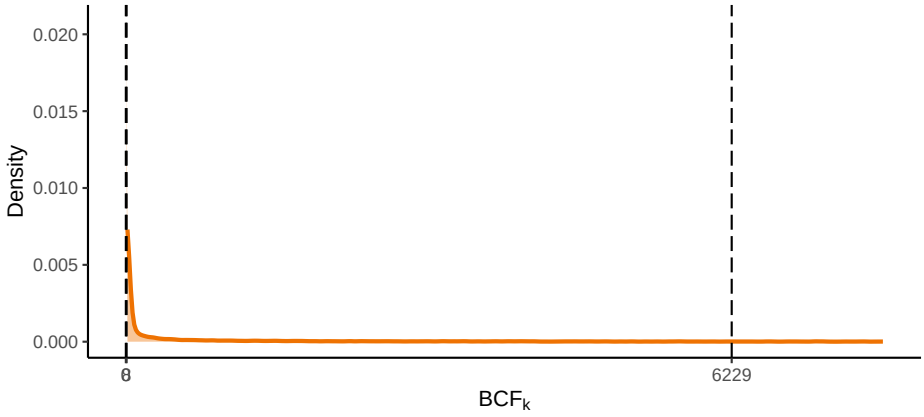
Calculations

$$BCF_k = \frac{k_{uw}}{k_{ee} + k_{m1} + k_{m2}}$$

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

Bioconcentration factor (BCF)

BCF_k plot

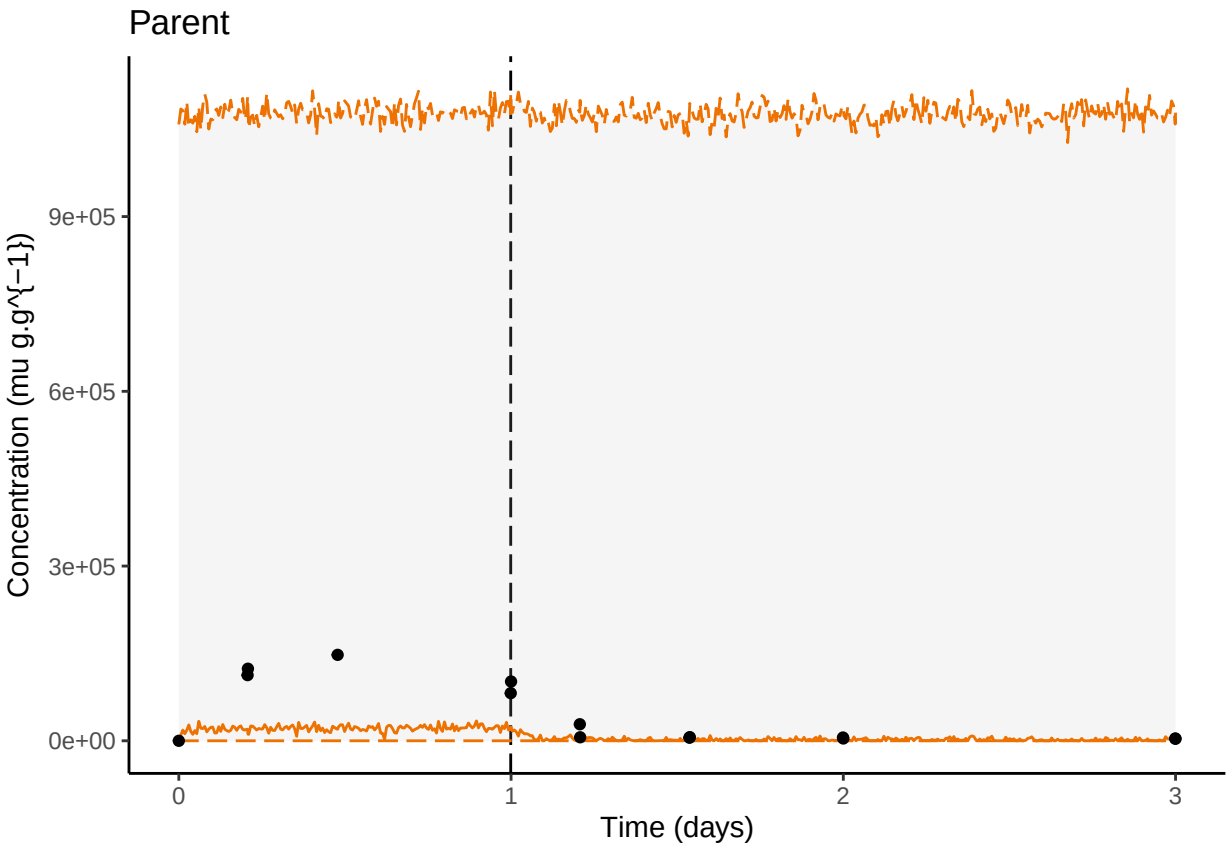


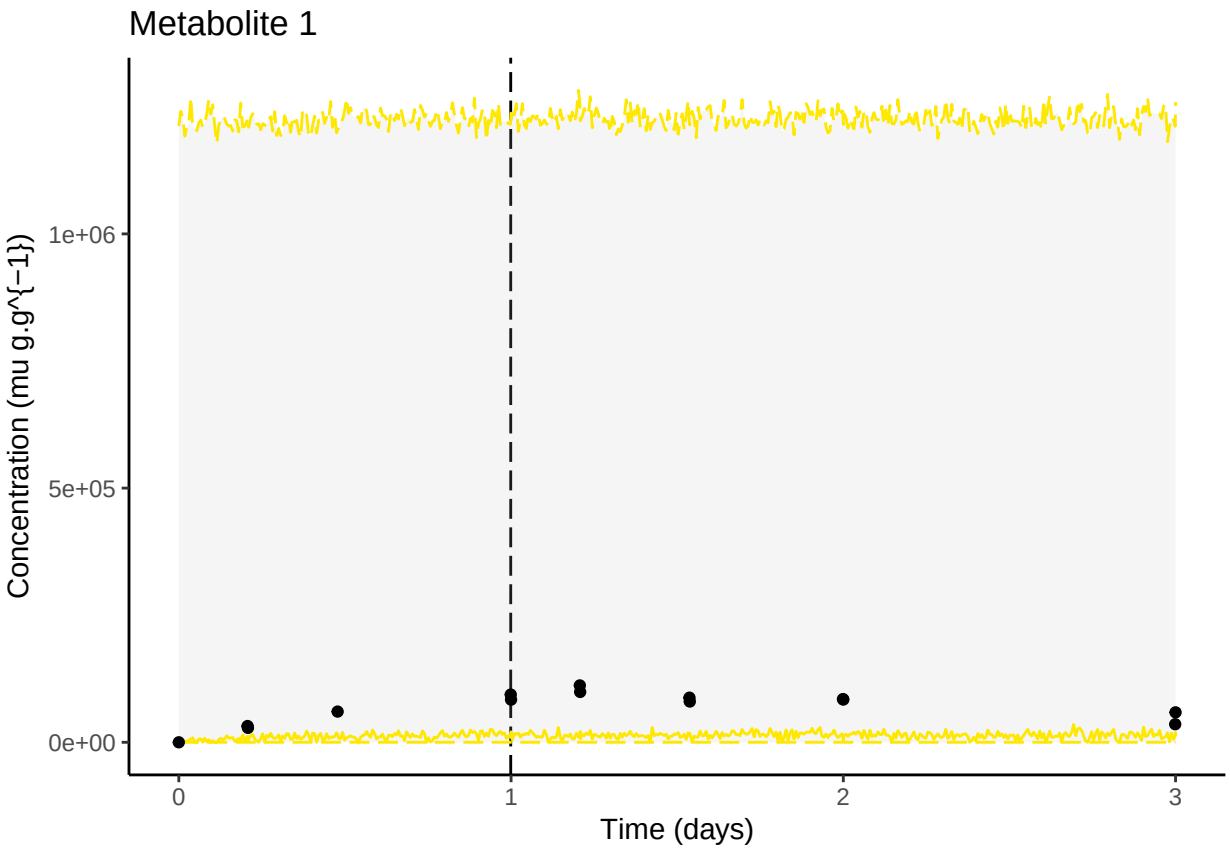
BCF summary

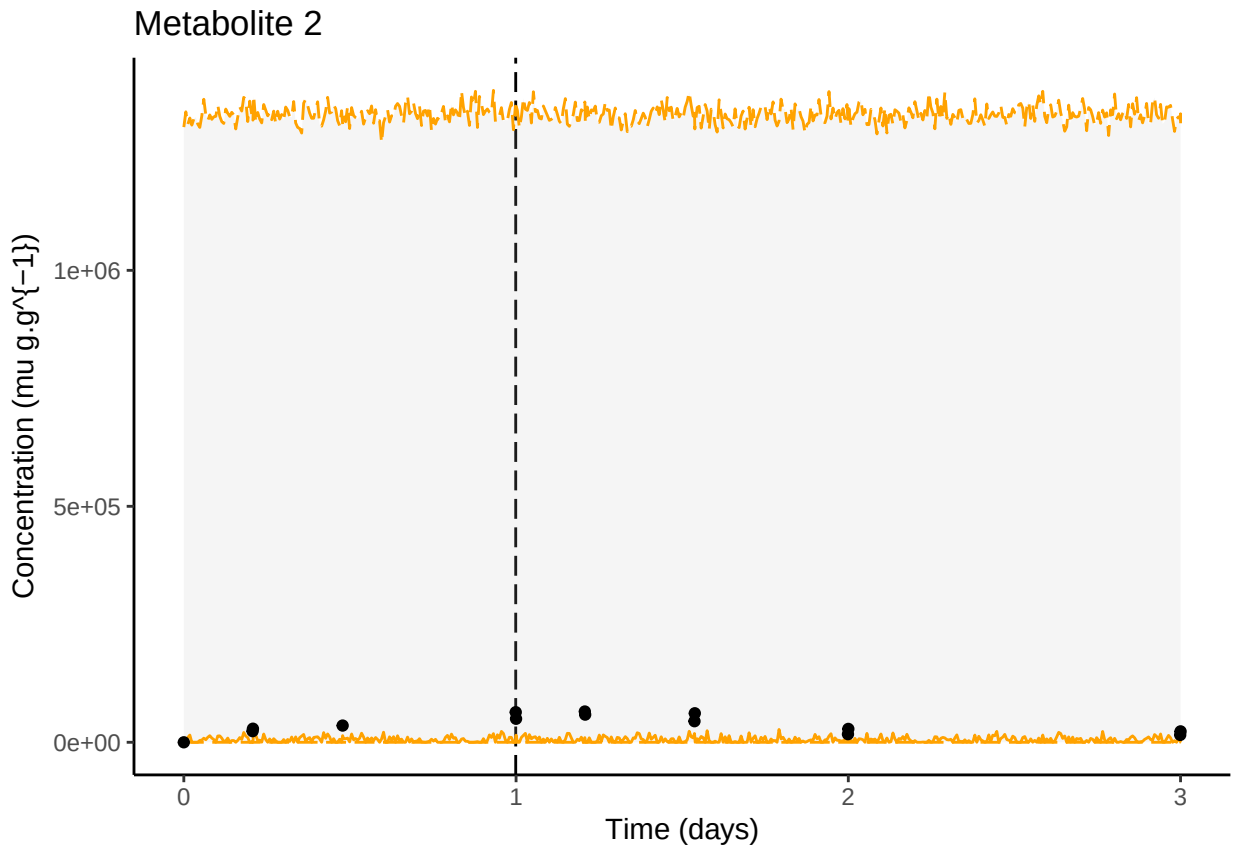
	2.5%	50%	97.5%	CV
BCFk	0	8	6229	190

Fitting results

Fit plot




Metabolite 1
Concentration (mu g.g^{−1})
1e+06
5e+05
0e+00
0
1
2
3
Time (days)



Quantiles of estimated parameters

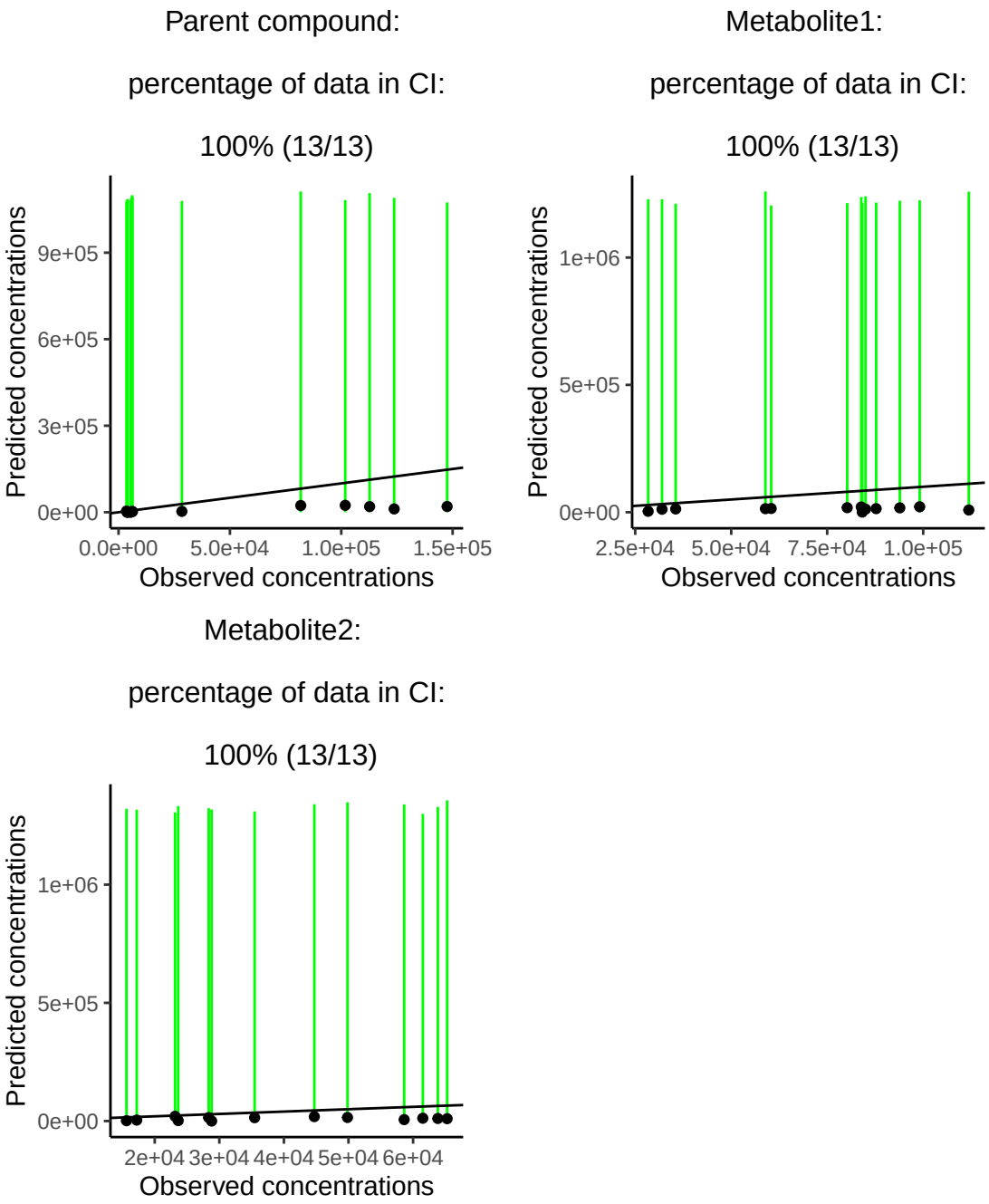
	2.5%	50%	97.5%	
k_{uw}	1.682e-05	0.1613	11130	d^{-1}
k_{ee}	1.86e-05	2.841	62830	d^{-1}
k_{m1}	1.87e-05	1.216	58600	d^{-1}
k_{m2}	1.805e-05	0.9297	51880	d^{-1}
k_{em1}	1.842e-05	1.542	58550	d^{-1}
k_{em2}	1.894e-05	2.032	60840	d^{-1}
σ_p	50270	563400	647900	$\mu g.g^{-1}$
σ_{met1}	105500	642500	715700	$\mu g.g^{-1}$
σ_{met2}	533400	689000	770500	$\mu g.g^{-1}$

Goodness-of-fit criteria

Posterior Predictive Check

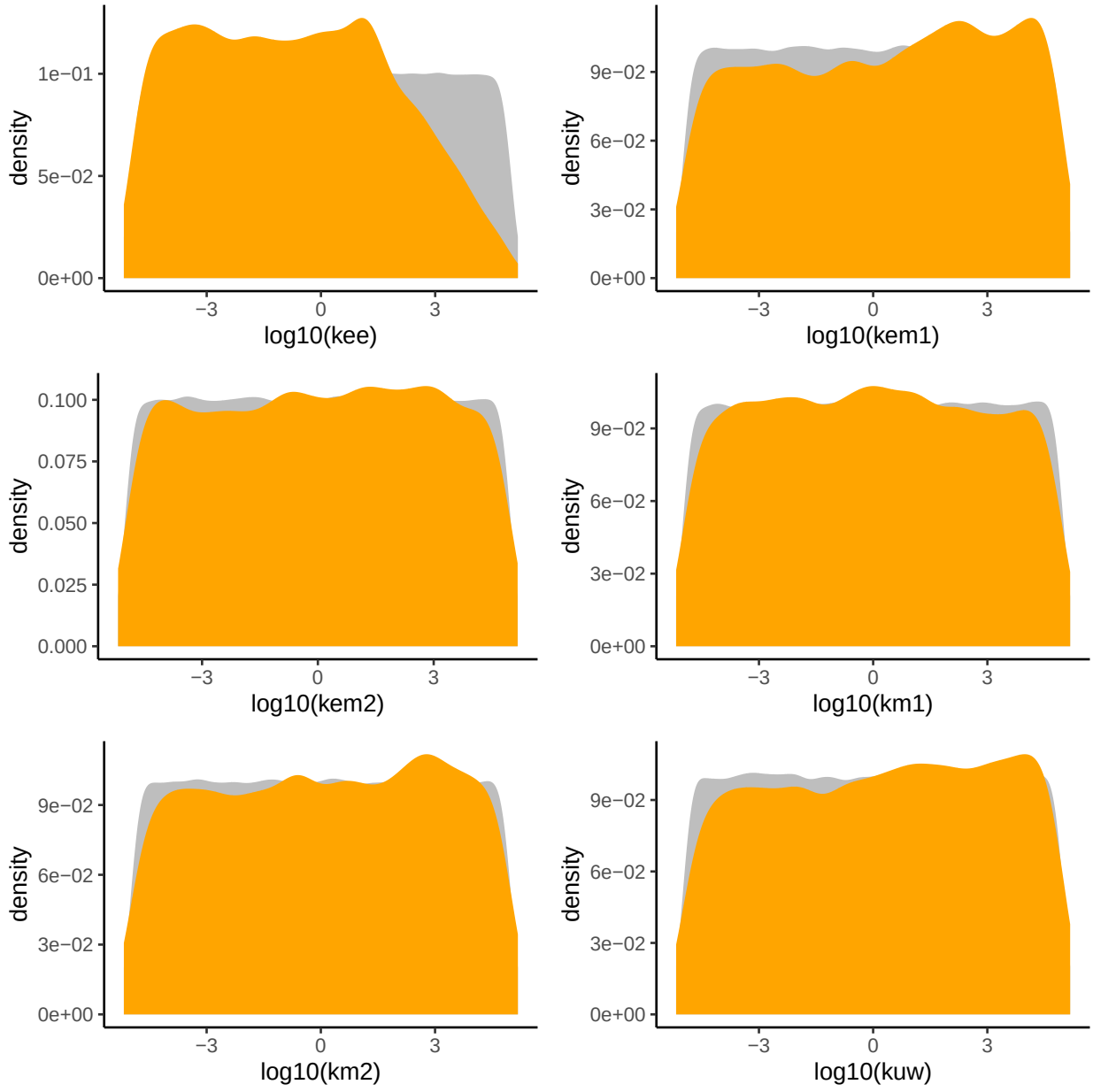
The PPC shows the observed values against their corresponding estimated predictions (black dots), along with their 95% credible interval (vertical segments). If the fit is correct, we expect to see 95% of the data within the intervals. Ideally observations and predictions should coincide, so we would expect to see black

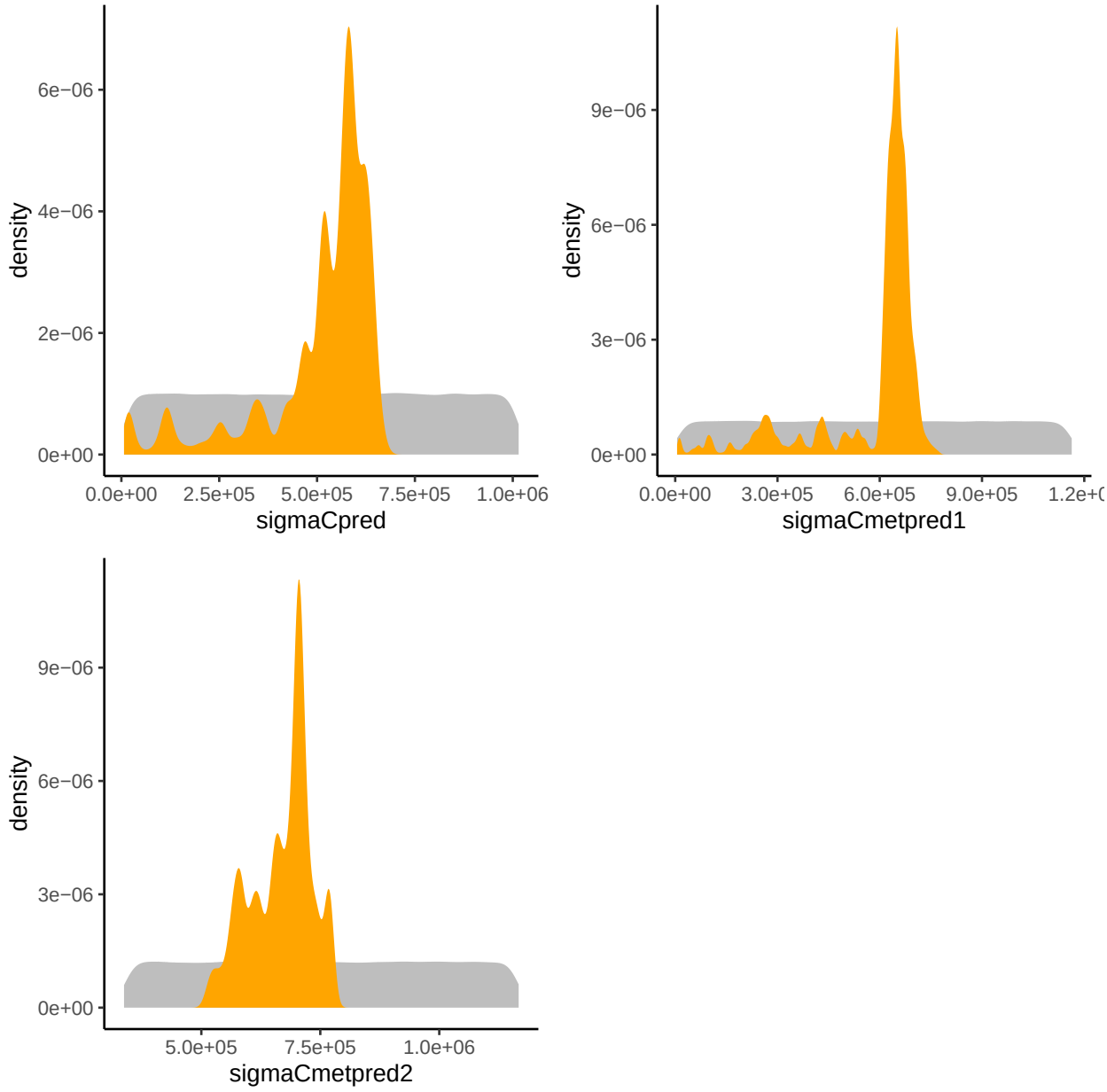
dots along the first bisector y = x (plain black line). The 95% credible intervals are colored in green if they overlap this line, in red otherwise.



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.

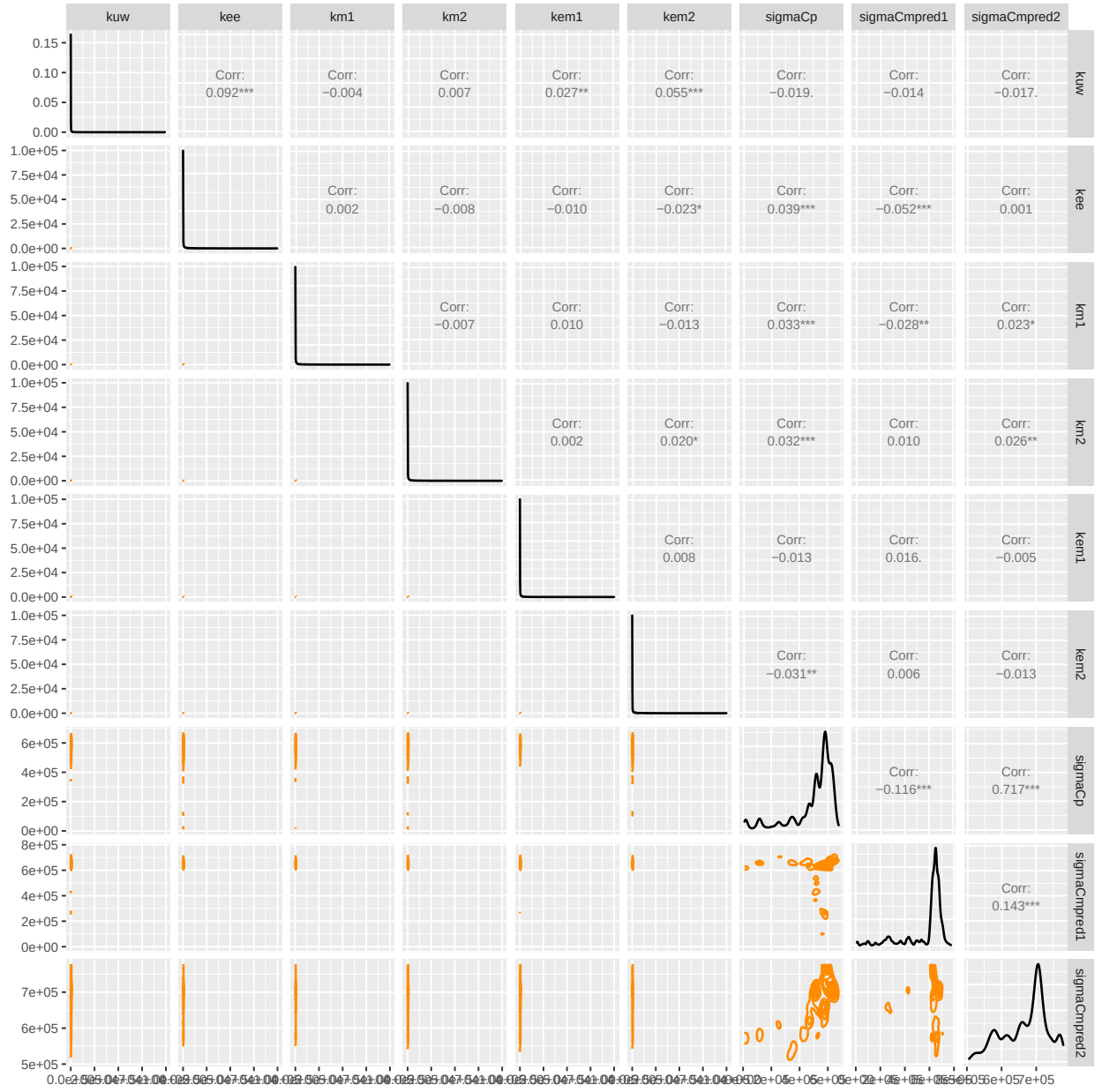

density
1e−01
5e−02
0e+00
−3
0
3
log10(kee)
density
9e−02
6e−02
3e−02
0e+00
−3
0
3
log10(kem1)
density
0.100
0.075
0.050
0.025
0.000
−3
0
3
log10(kem2)
density
9e−02
6e−02
3e−02
0e+00
−3
0
3
log10(km1)
density
9e−02
6e−02
3e−02
0e+00
−3
0
3
log10(km2)
density
9e−02
6e−02
3e−02
0e+00
−3
0
3
log10(kuw)



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	1.007
kee	1.007
km1	1.003
km2	1.002
kem1	1
kem2	1.001
sigmaCpred	2.146
sigmaCmetpred1	1.884

	PSRF
sigmaCmetpred2	2.38

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 = 1110

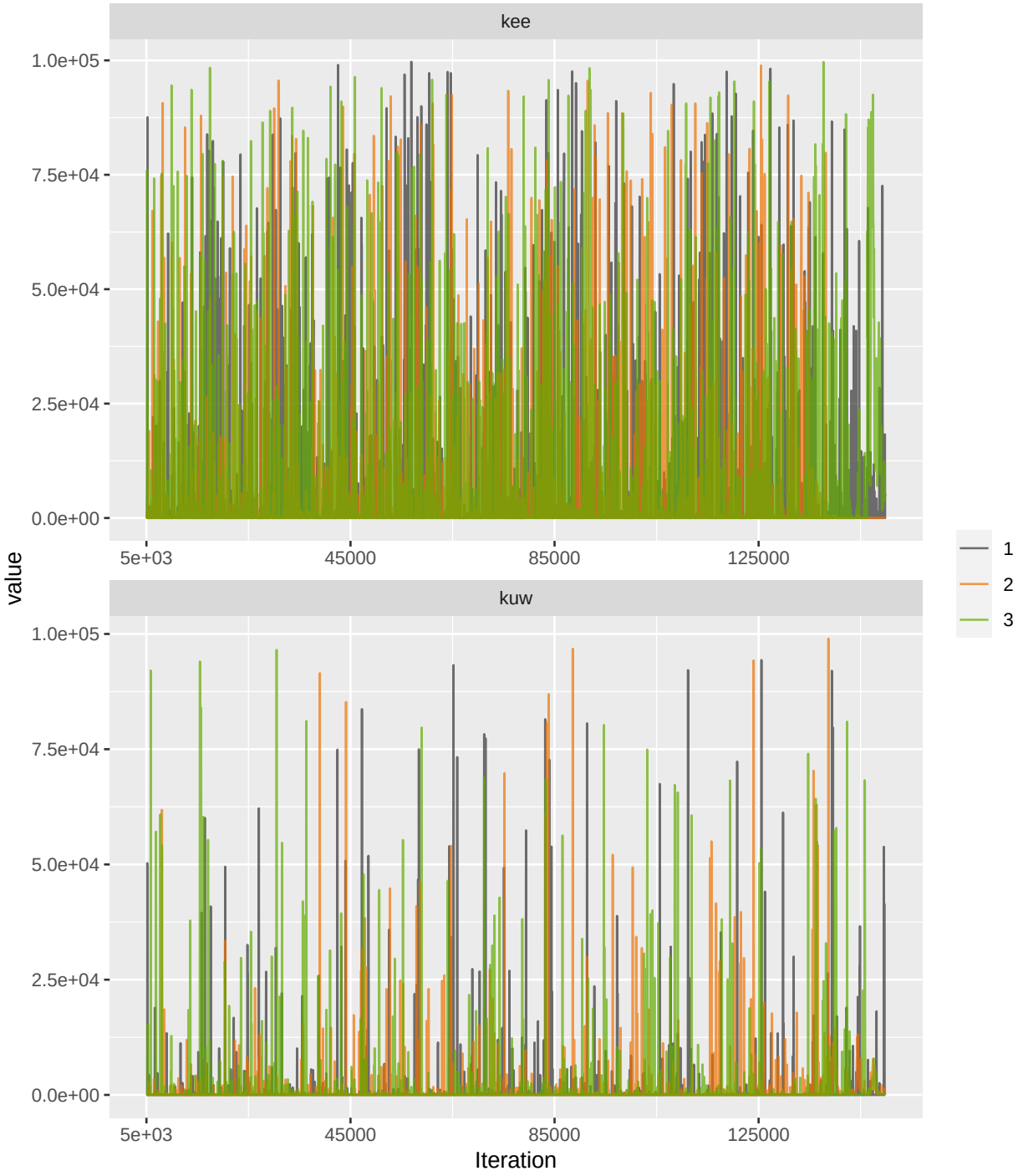
Deviance Information Criterion

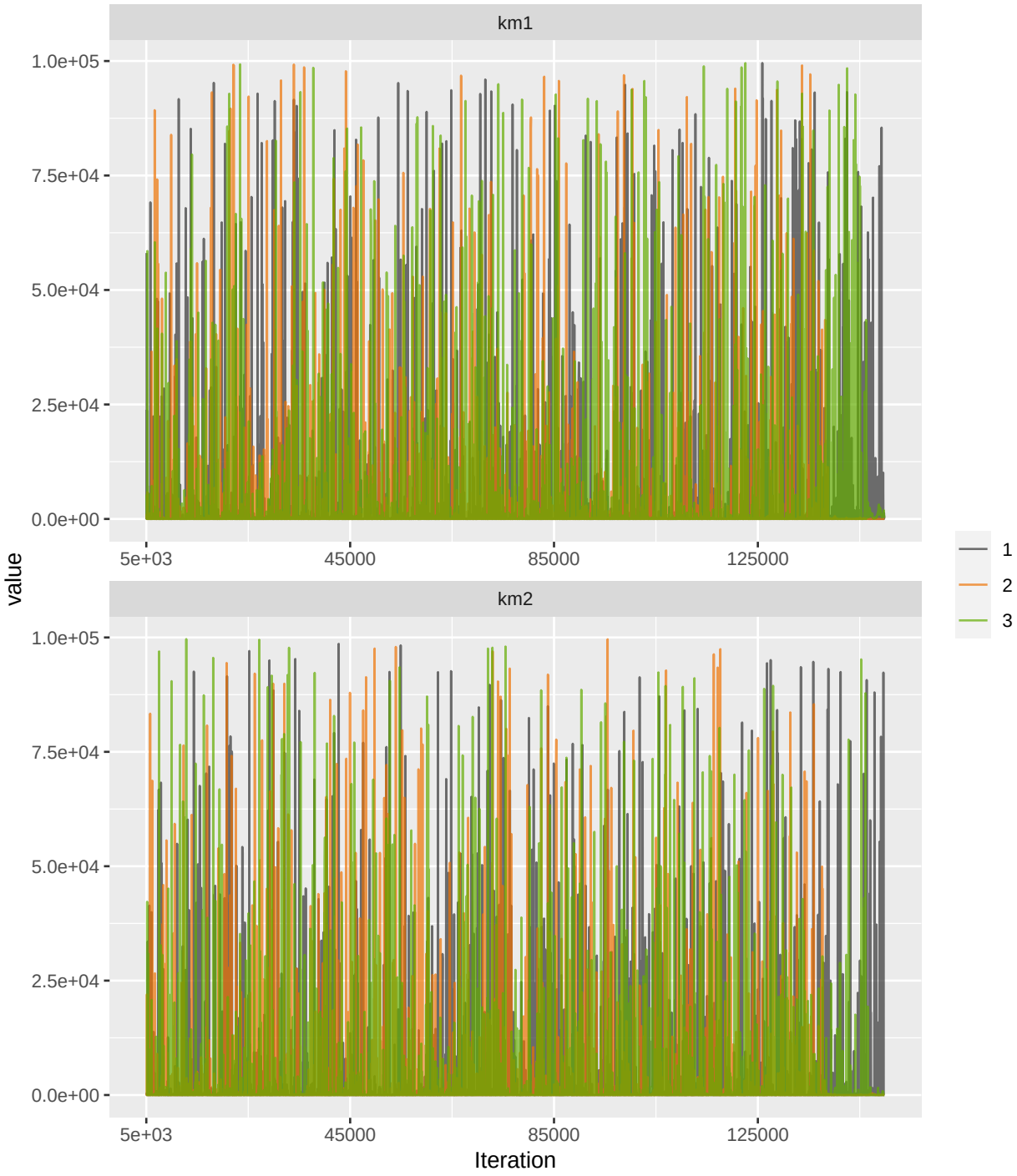
This criteria, denoted DIC, is a penalized deviance statistics accounting for the number of parameters for use in model comparison for a same dataset (e.g., with or without k_{ee}). Sub-models with lower DIC values will be preferred.

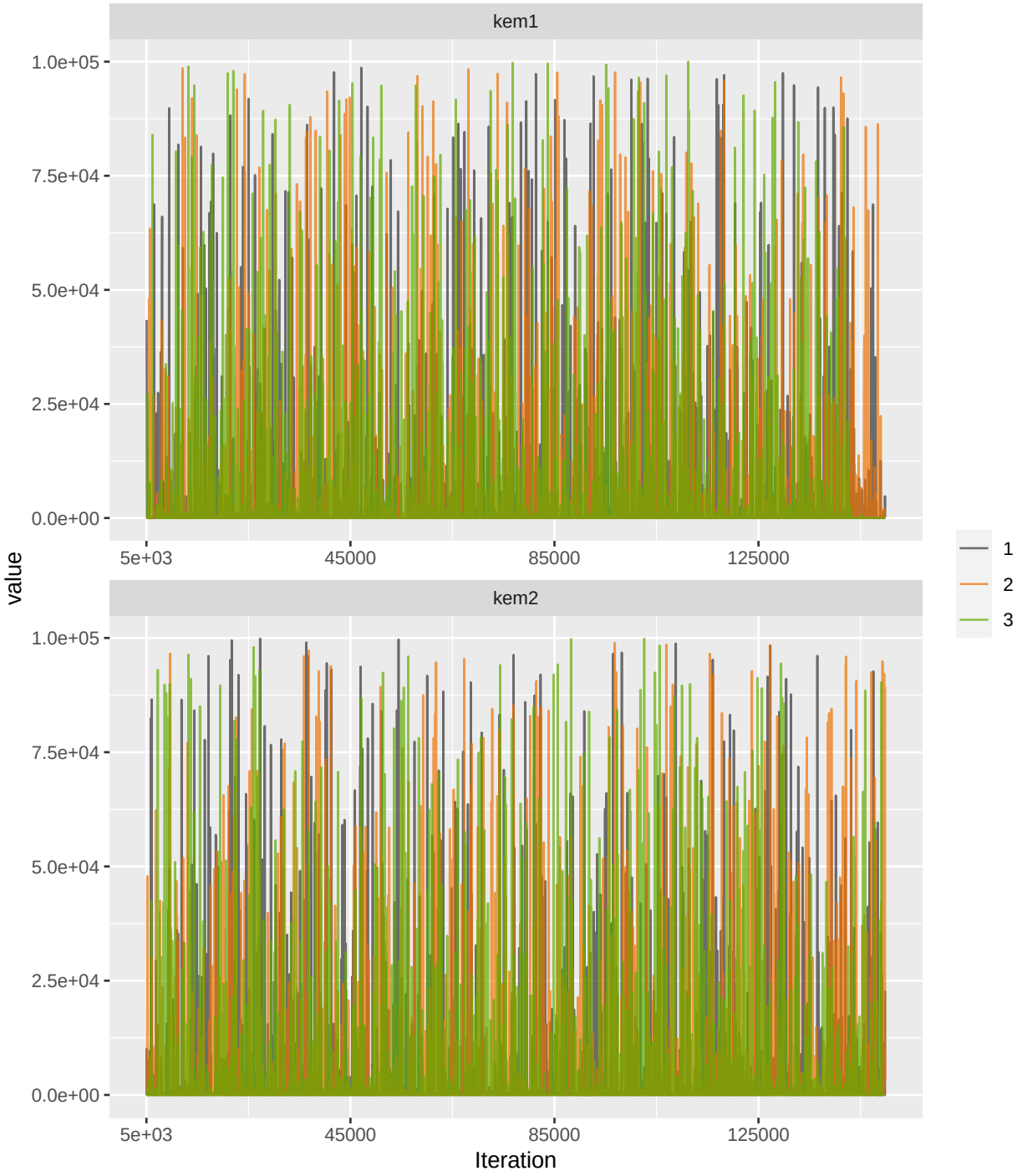
DIC = 1250

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.


kee
kuw
value
Iteration
1.0e+05
7.5e+04
5.0e+04
2.5e+04
0.0e+00
5e+03
45000
85000
125000
1
2
3


km1
km2
1.0e+05
7.5e+04
5.0e+04
2.5e+04
0.0e+00
5e+03
45000
85000
125000
value
Iteration
1
2
3


kem1
kem2
value
Iteration
1.0e+05
7.5e+04
5.0e+04
2.5e+04
0.0e+00
5e+03
45000
85000
125000
1
2
3


sigmaCmpred1
8e+05
6e+05
4e+05
2e+05
0e+00
5e+03
45000
85000
125000
sigmaCmpred2
7e+05
6e+05
5e+05
sigmaCp
value
Iteration
1
2
3

Data Table

time	conc	concm1	expw	replicate	concm2
0.000	0	0	5760	1	0
0.207	112736	31981	5760	1	23635
0.208	123750	28377	5760	2	28811
0.478	147531	60408	5760	2	35465
0.999	81808	93916	5760	1	63835
1.000	101785	83874	5760	2	49843
1.207	28429	111882	5760	1	65270
1.208	6033	99091	5760	2	58620
1.537	5276	87748	5760	1	44710
1.538	6254	80215	5760	2	61507
1.999	5626	84984	5760	1	17211
2.000	3968	84126	5760	2	28358
2.999	3856	35542	5760	1	15626
3.000	3554	58915	5760	2	23146