

MOSAIC_{bioacc} REPORT

2021-04-15

This report is provided by the MOSAIC_{bioacc} application available here:
<https://mosaic.univ-lyon1.fr/bioacc>

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MOSAIC_{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 MOSAIC_{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_AZ_1d_Fu2018.txt

Exposure: 80 $\mu\text{g.mL}^{-1}$

Accumulation phase duration: 1 days

Number of replicates: 2

Times: 0, 0.021, 0.063, 0.104, 0.229, 0.396, 0.729, 1, 1.042, 1.083, 1.167, 1.292, 1.458, 1.75, 2.083, 2.708, 3.958, 4.958, 6

Exposure routes: water

Elimination routes: excretion biotransformation

Bayesian inference

Three MCMC chains were used to estimate model parameters.

Number of iterations: 157332

Thin: 42

TK Model

The TK model used for these calculations was:

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

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

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

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

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 $\mu g \cdot g^{-1}$)

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

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

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

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

ℓ : index of metabolites, $\ell = 1 \dots L$ 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

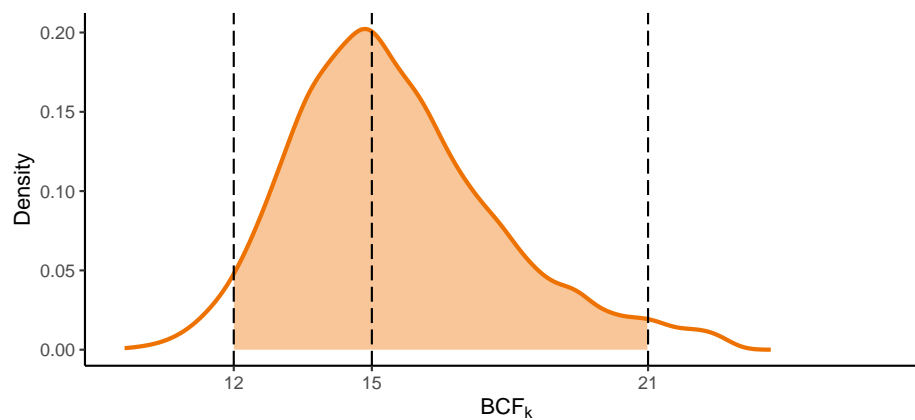
Calculations

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

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

Bioconcentration factor (BCF)

BCF_k plot

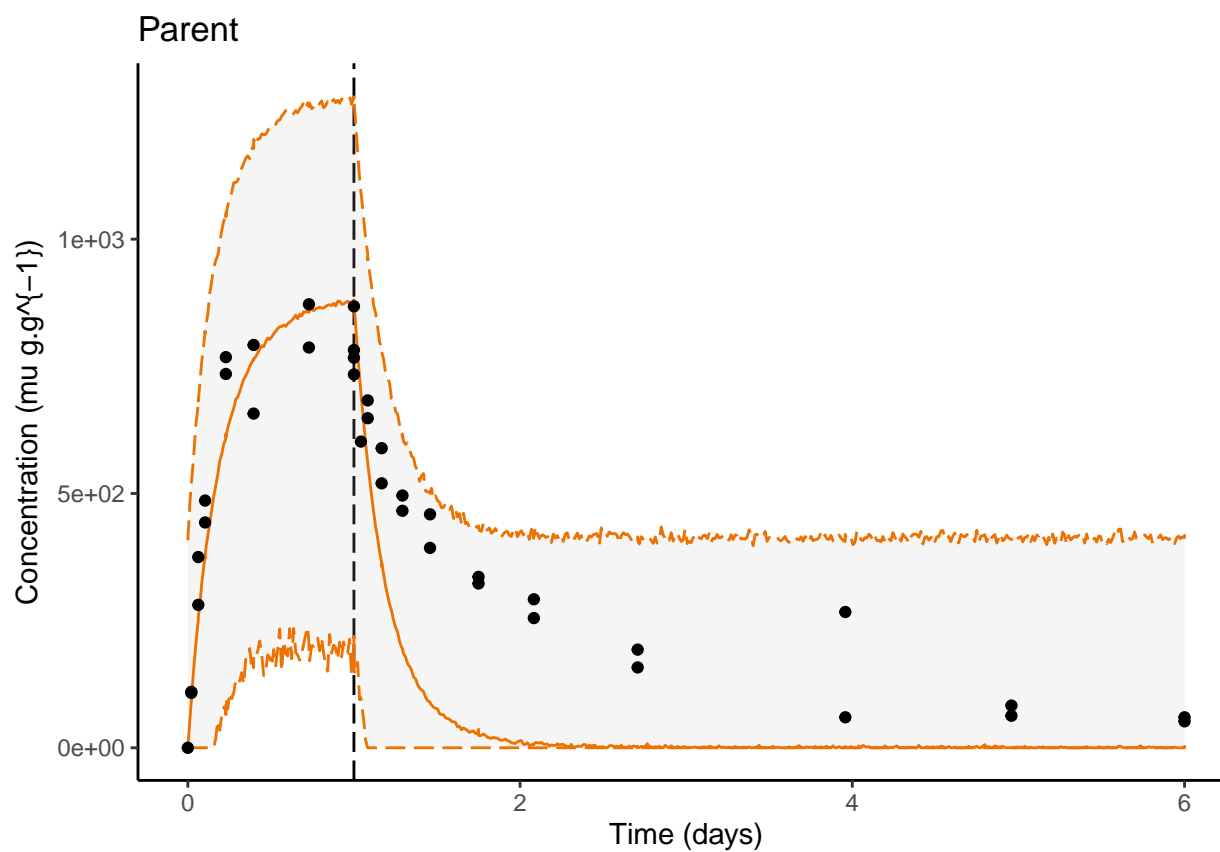


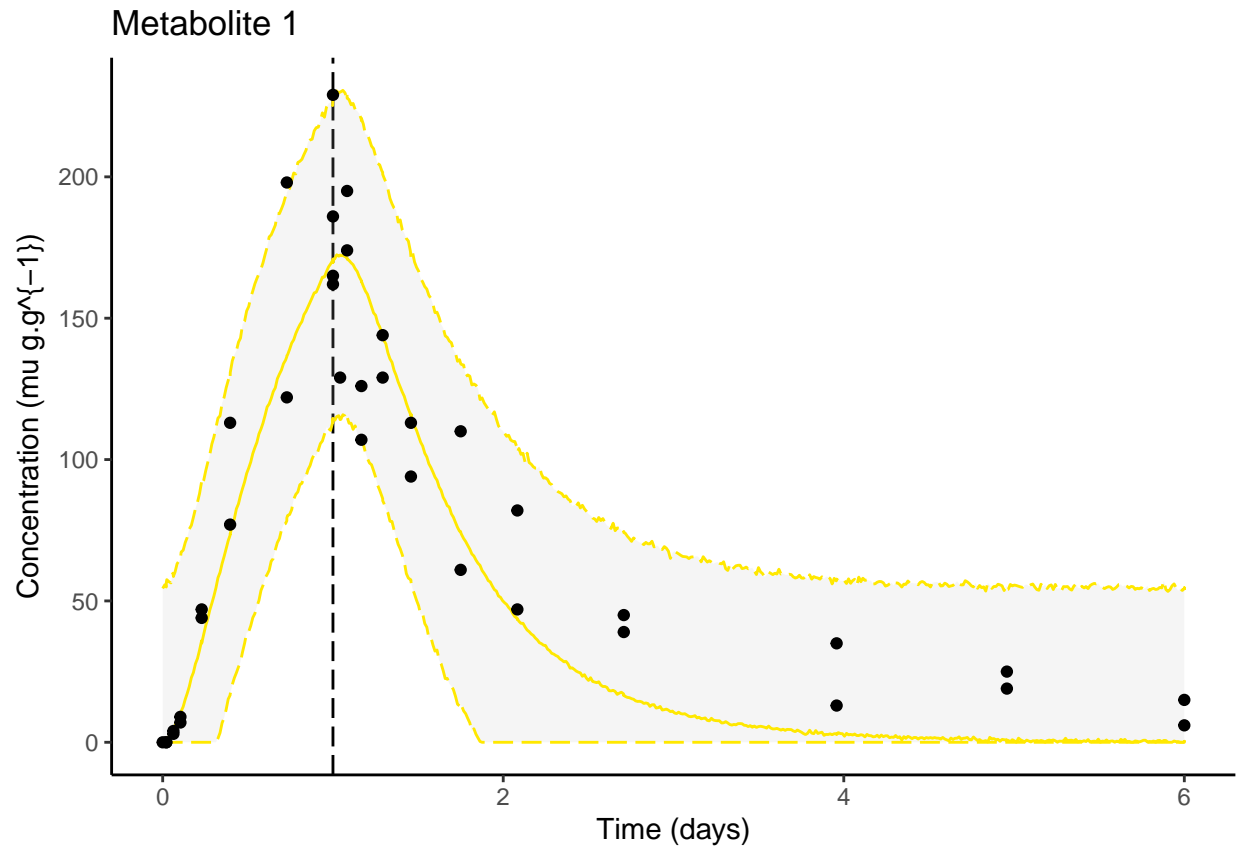
BCF summary

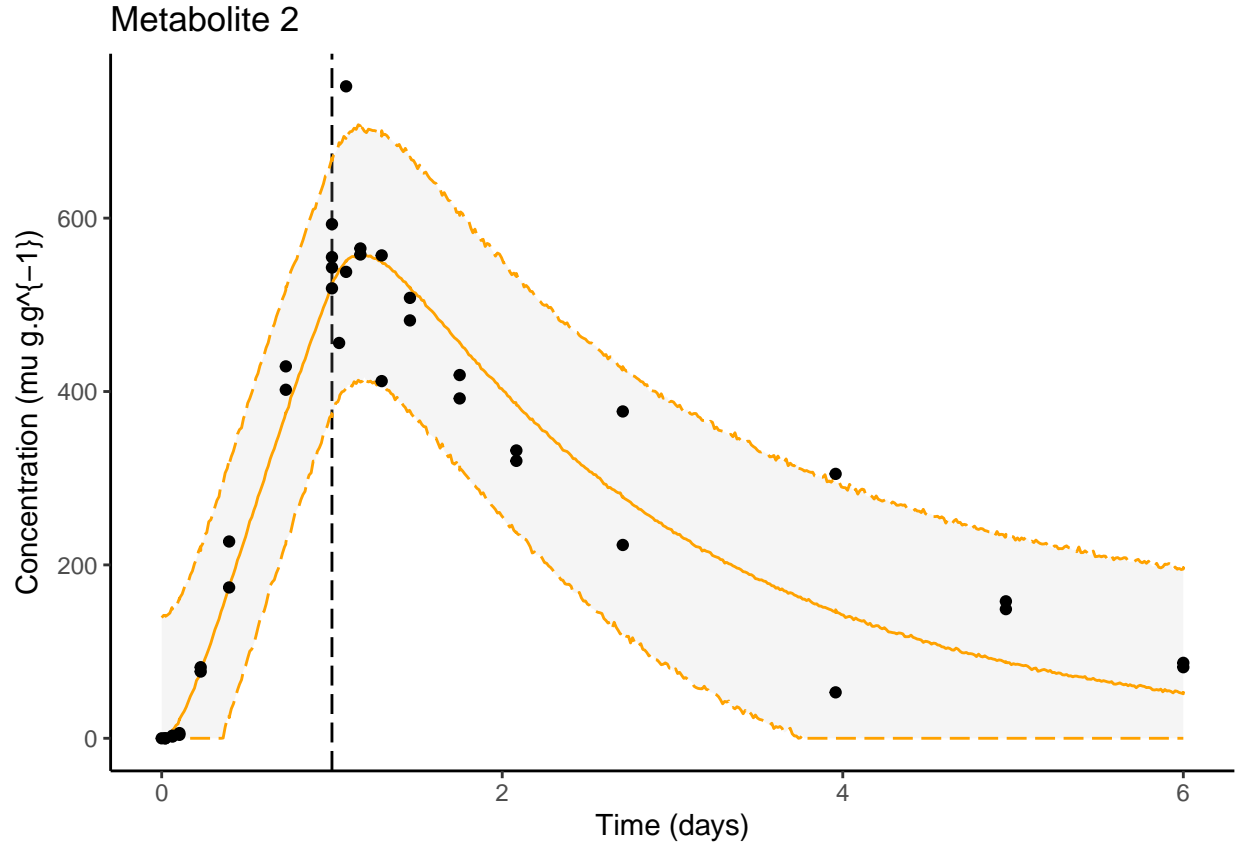
	2.5%	50%	97.5%	CV
BCF _k	12	15	21	0.15

Fitting results

Fit plot







Quantiles of estimated parameters

	2.5%	50%	97.5%	
k_{uw}	12.15	59.67	100.4	d^{-1}
k_{ee}	1.648e-03	4.069	8.828	d^{-1}
k_{m1}	0.3231	0.4543	79.53	d^{-1}
k_{m2}	0.7542	0.9027	187.4	d^{-1}
k_{em1}	0.9325	1.699	4.676	d^{-1}
k_{em2}	0.3643	0.5177	0.8929	d^{-1}
σ_p	142.3	188.3	504.1	$\mu g.g^{-1}$
σ_{met1}	21.19	27.13	35.42	$\mu g.g^{-1}$
σ_{met2}	53.12	68.82	93.68	$\mu g.g^{-1}$

Goodness-of-fit criteria

Posterior Predictive Check

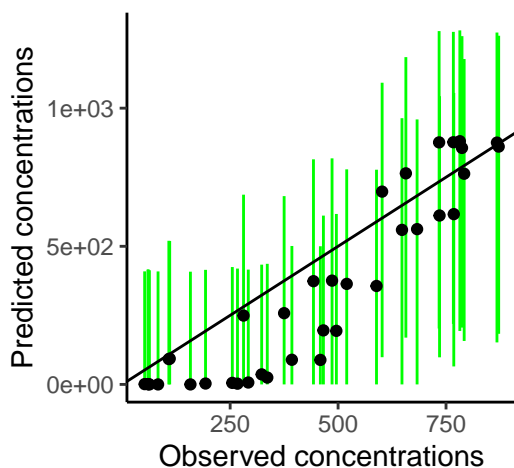
The PPC shows the observed values against their corresponding estimated predictions (black dots), along with their 95% credible interval (vertical segments). If the fit is correct, we expect to see 95% of the data within the intervals. Ideally observations and predictions should coincide, so we would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

Parent compound:

percentage of data in CI:

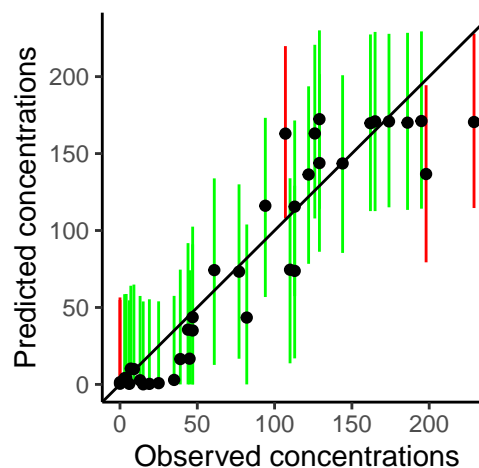
100% (37/37)



Metabolite1:

percentage of data in CI:

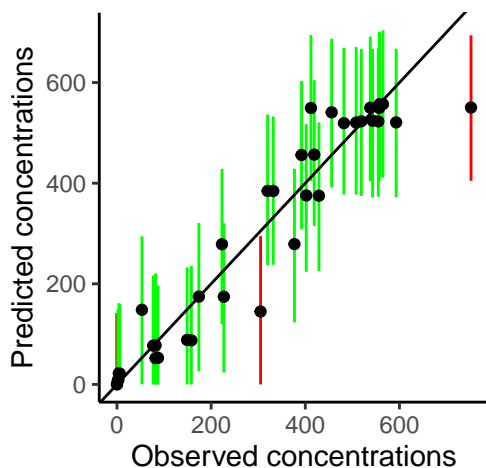
86.49% (32/37)



Metabolite2:

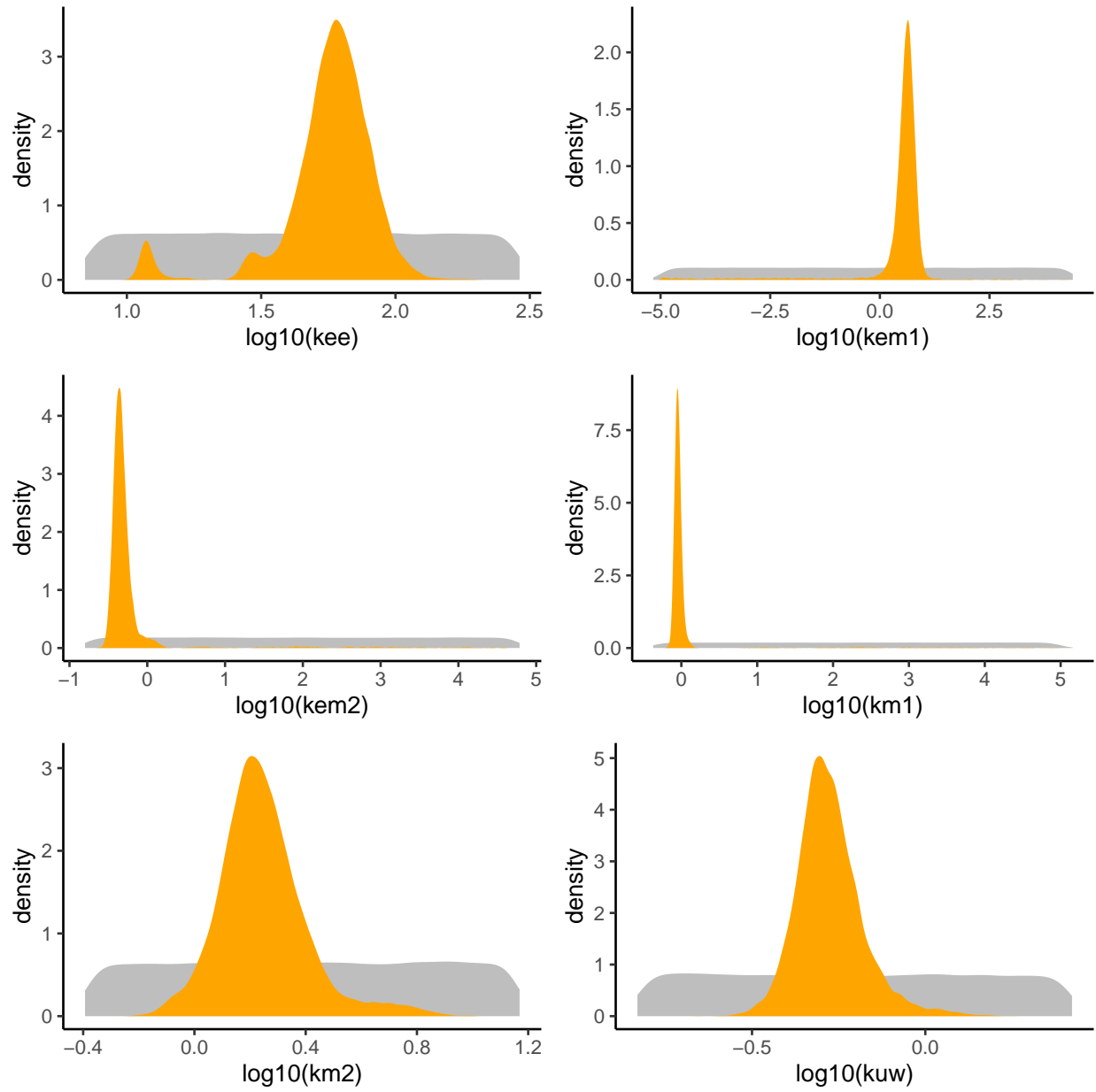
percentage of data in CI:

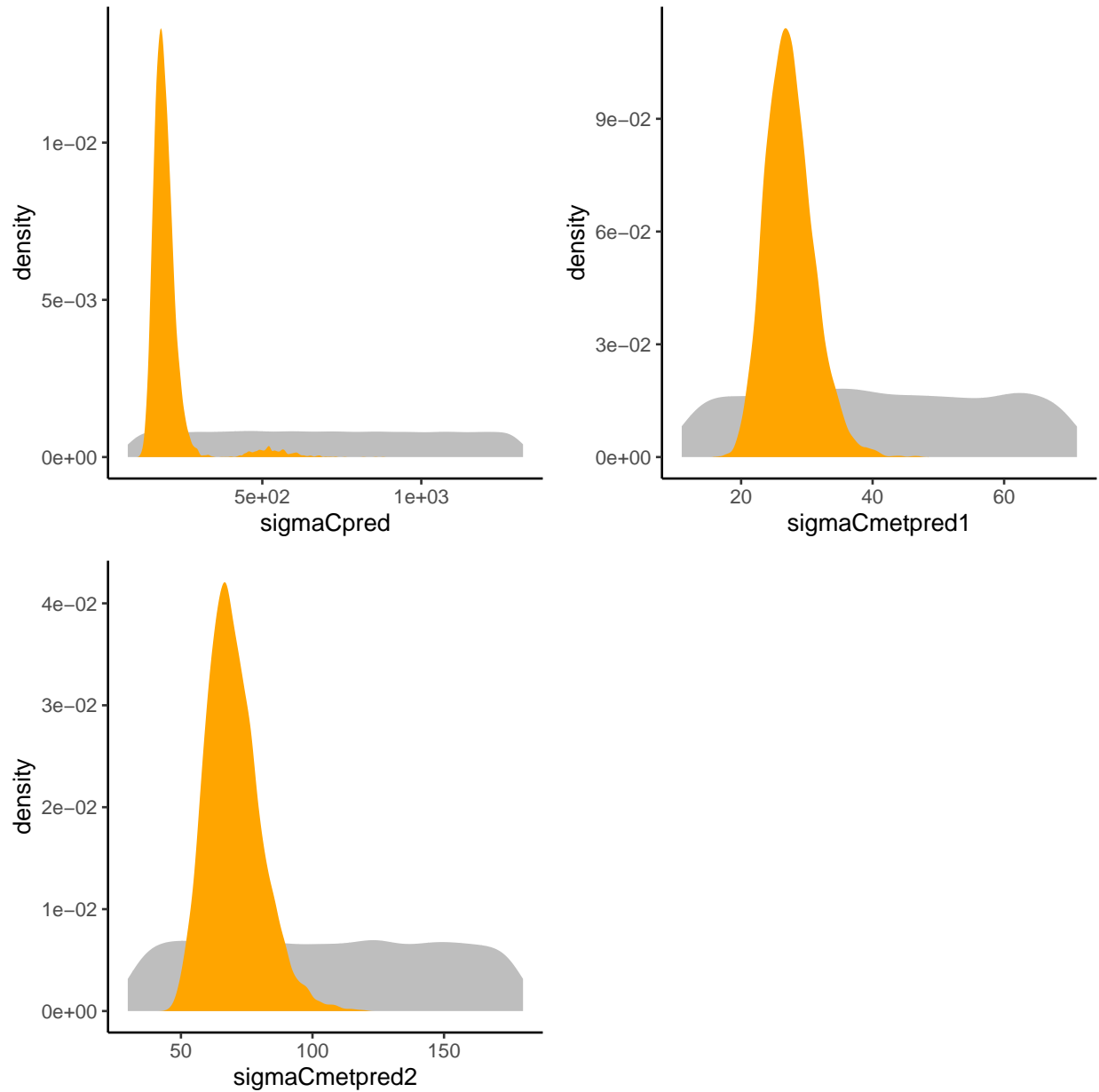
89.19% (33/37)



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.

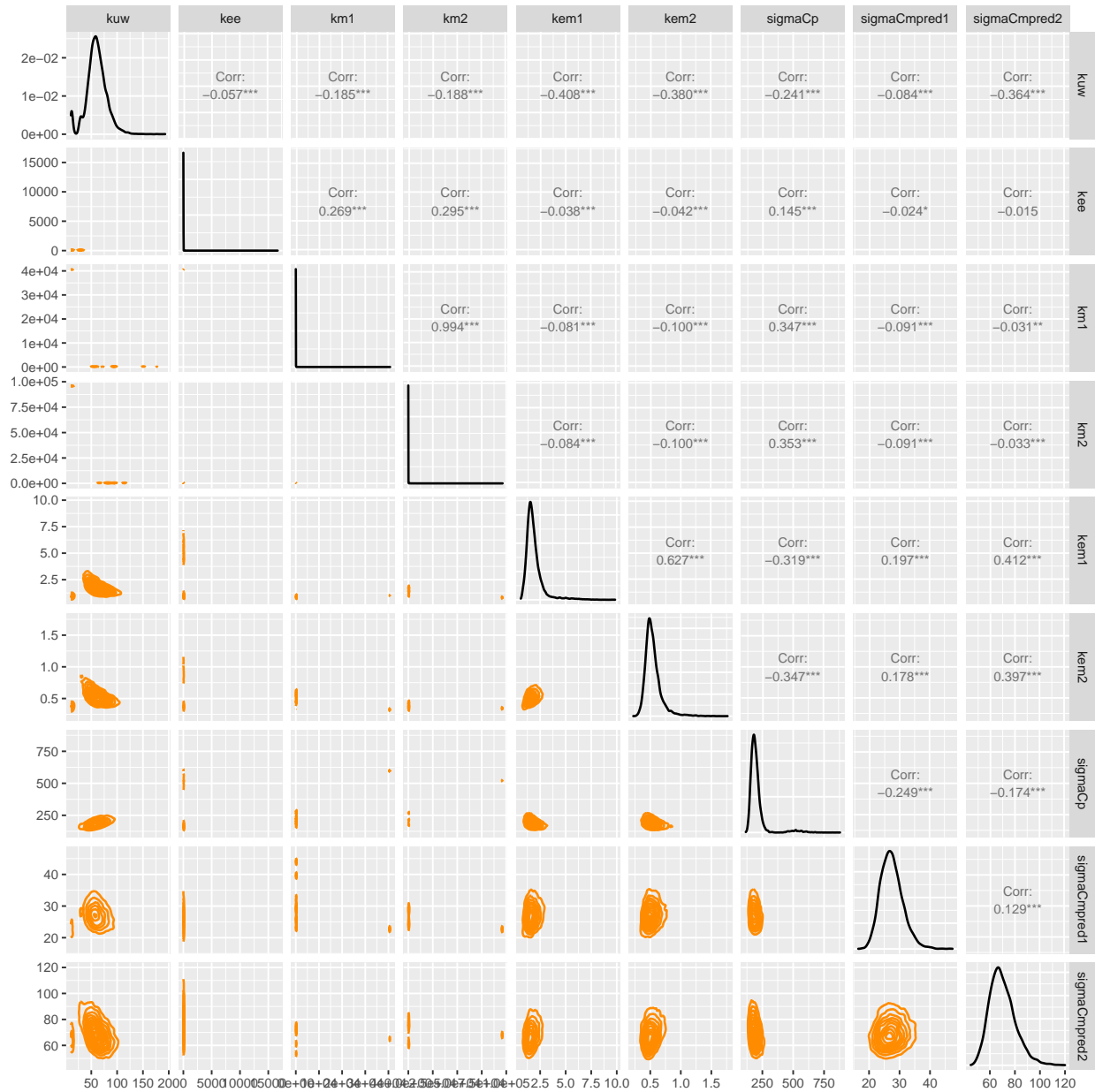




Correlation between parameters

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 checked 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	1.046
kee	1.292
km1	1.3
km2	1.301
kem1	1.004
kem2	1.007
sigmaCpred	1.283
sigmaCmetpred1	1.002

PSRF	
sigmaCmetpred2	1

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.

$$\text{WAIC} = 1273$$

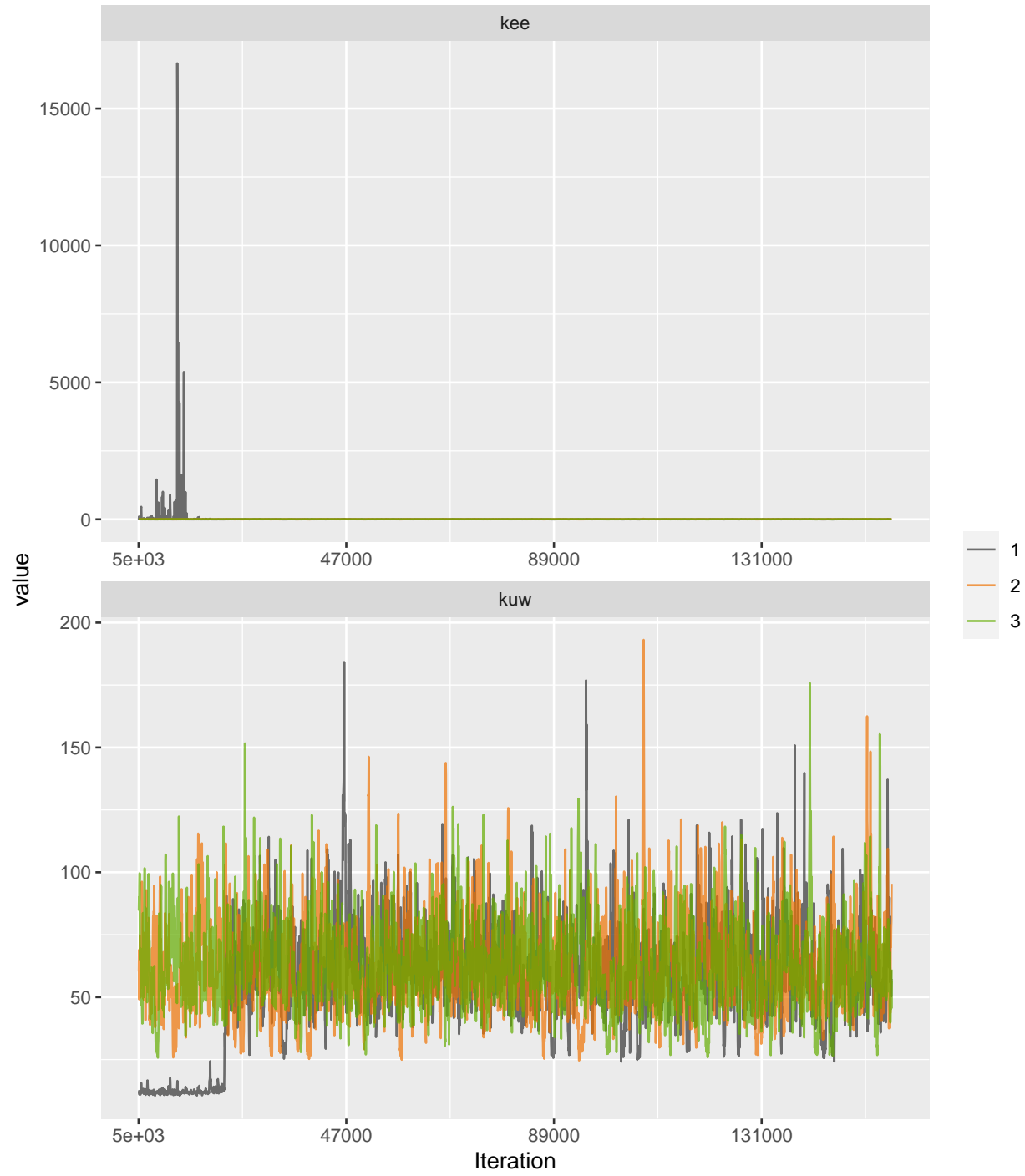
Deviance Information Criterion

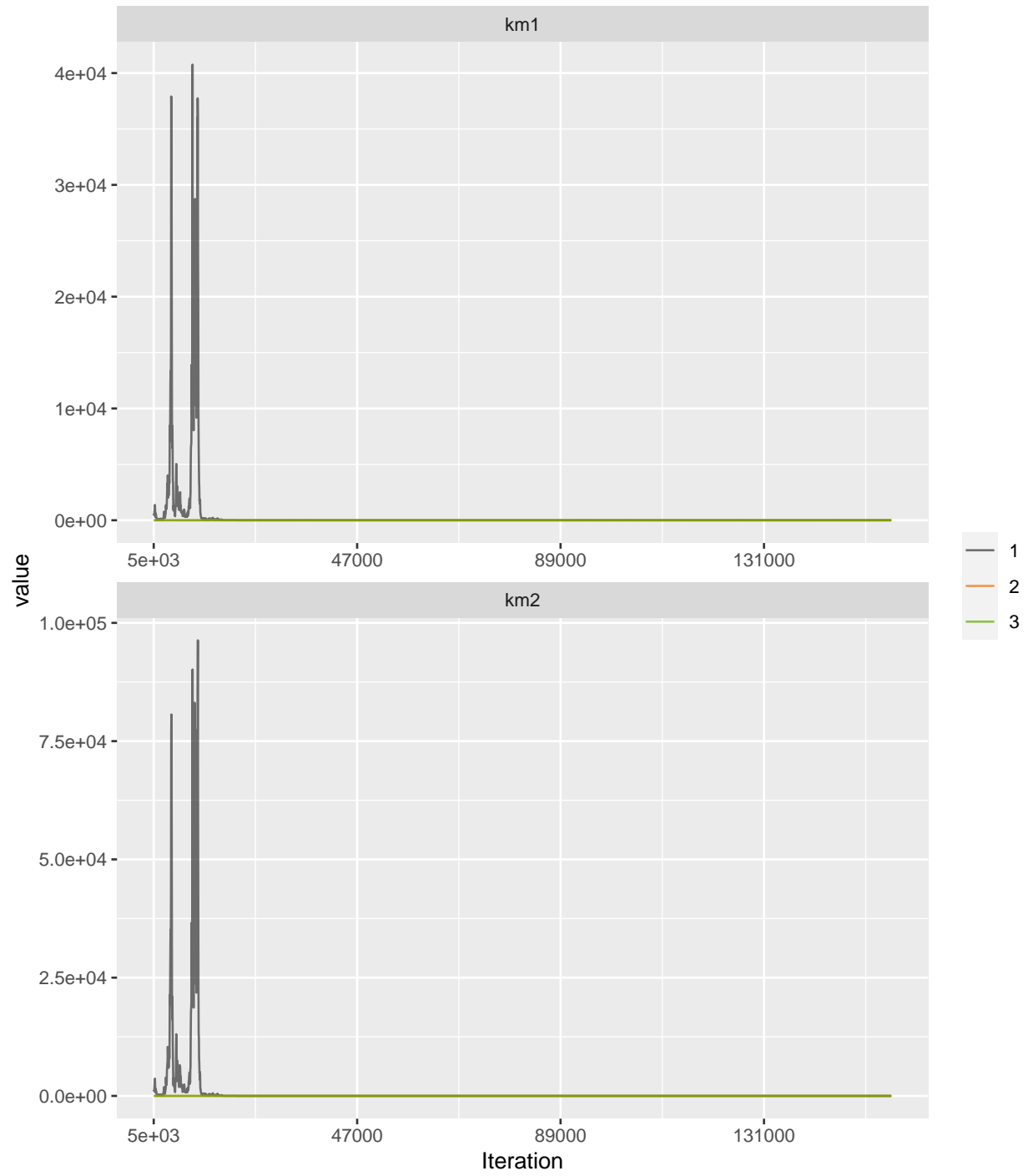
This criteria, denoted DIC, is a penalized deviance statistics accounting for the number of parameters for use in model comparison for a same dataset (e.g., with or without k_{ee}). Sub-models with lower DIC values will be preferred.

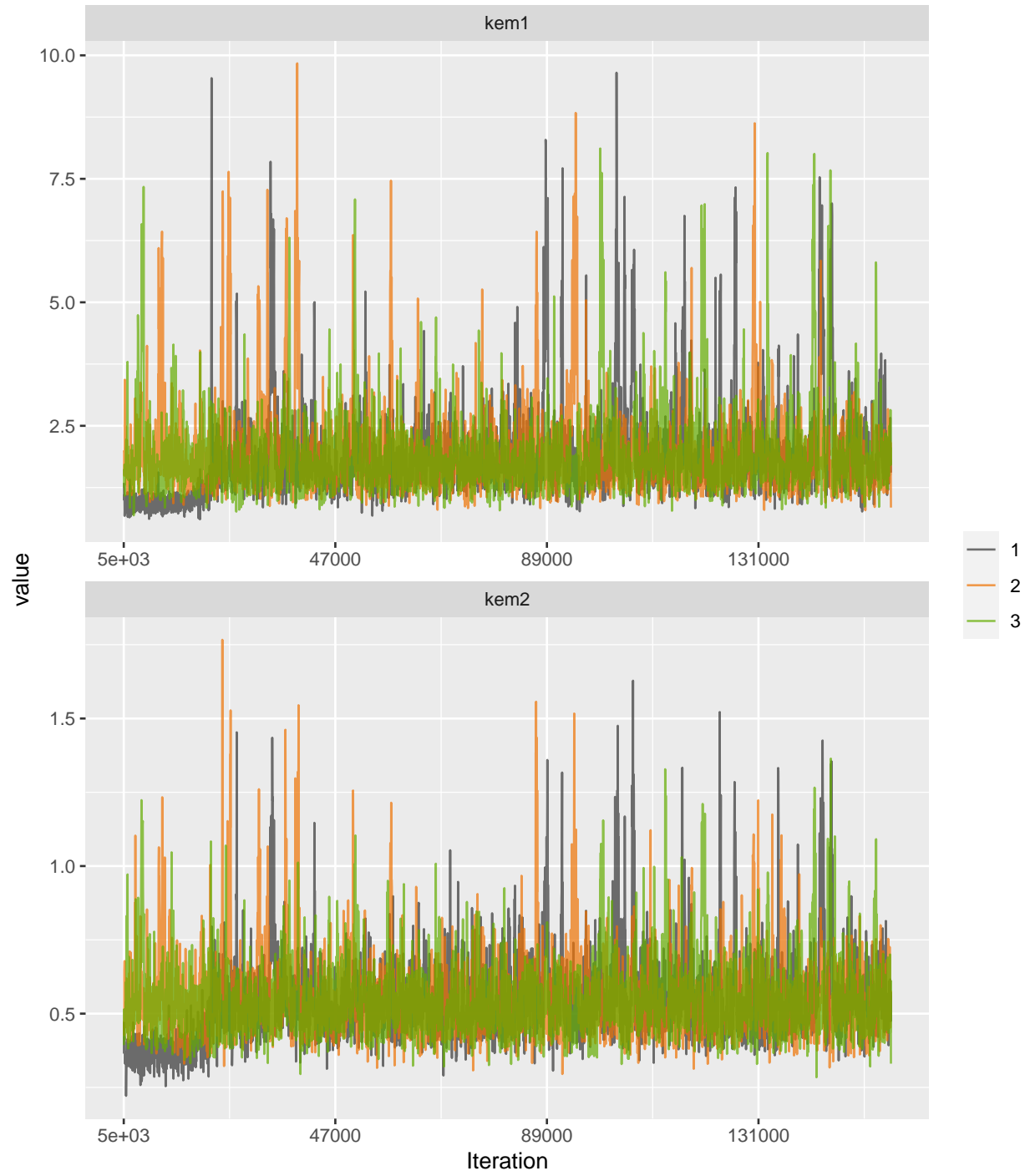
$$\text{DIC} = 1336$$

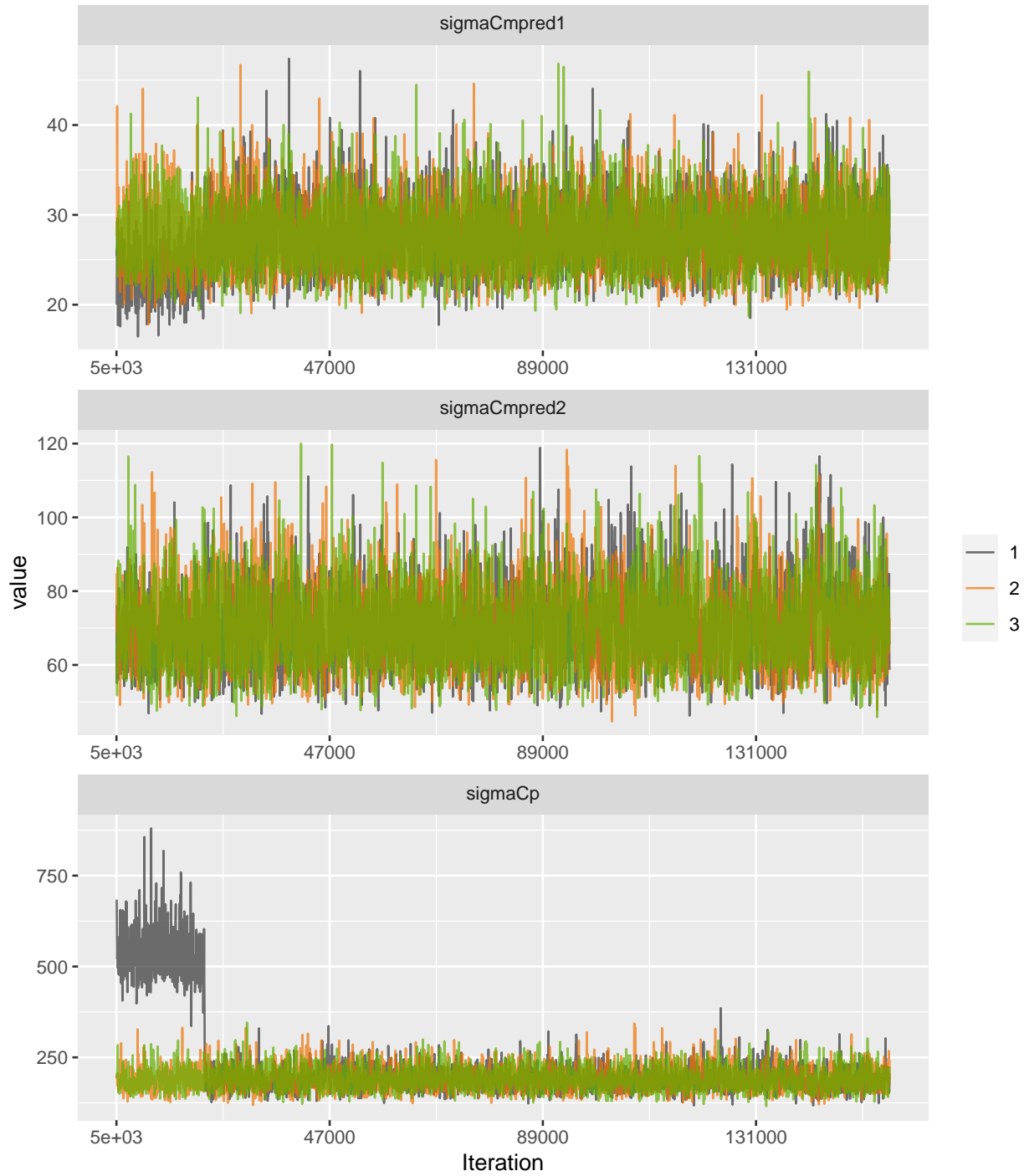
Traces of MCMC iterations

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.









Data Table

time	expw	conc	concm1	concm2	replicate
0.000	80	0	0	0	1
0.021	80	110	0	0	1
0.021	80	108	0	0	2
0.063	80	281	3	2	1
0.063	80	375	4	3	2
0.104	80	486	7	4	1
0.104	80	443	9	6	2
0.229	80	768	44	77	1
0.229	80	735	47	82	2
0.396	80	657	77	174	1
0.396	80	792	113	227	2
0.729	80	787	122	402	1
0.729	80	872	198	429	2
1.000	80	767	229	555	1
1.000	80	782	162	543	2
1.000	80	734	186	593	1
1.000	80	868	165	519	2
1.042	80	602	129	456	1
1.083	80	683	195	752	1
1.083	80	648	174	538	2
1.167	80	589	107	565	1
1.167	80	520	126	558	2
1.292	80	466	129	412	1
1.292	80	496	144	557	2
1.458	80	393	113	482	1
1.458	80	459	94	508	2
1.750	80	323	110	419	1
1.750	80	336	61	392	2
2.083	80	255	82	332	1
2.083	80	292	47	320	2
2.708	80	193	39	377	1
2.708	80	158	45	223	2
3.958	80	267	35	305	1
3.958	80	60	13	53	2
4.958	80	83	19	149	1
4.958	80	63	25	158	2
6.000	80	60	6	87	1
6.000	80	52	15	82	2