

MOSAIC_{bioacc} REPORT

2021-04-14

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: Gammarus_4-nitrobenzyl-chloride_1d_Ashauer2012.csv

Exposure: 3897.655 $\mu\text{g.mL}^{-1}$

Accumulation phase duration: 1 days

Number of replicates: 2

Times: 0, 0.207, 0.208, 0.454, 0.455, 0.999, 1.207, 1.208, 1.52, 1.521, 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: 97396

Thin: 26

TK Model

The TK model used for these calculations was:

$$\frac{dC_p(t)}{dt} = k_{uw} \times c_w - (k_{ee} + k_{m1} + k_{m2} + k_{m3}) \times C_p(t) \quad \text{for } 0 \leq t \leq t_c$$

$$\frac{dC_p(t)}{dt} = - (k_{ee} + k_{m1} + k_{m2} + k_{m3}) \times C_p(t) \quad \text{for } t > t_c$$

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

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

$$\frac{dC_{m3}(t)}{dt} = k_{m3} \times C_p(t) - k_{em3} \times C_{m3}(t)$$

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

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

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

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

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

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

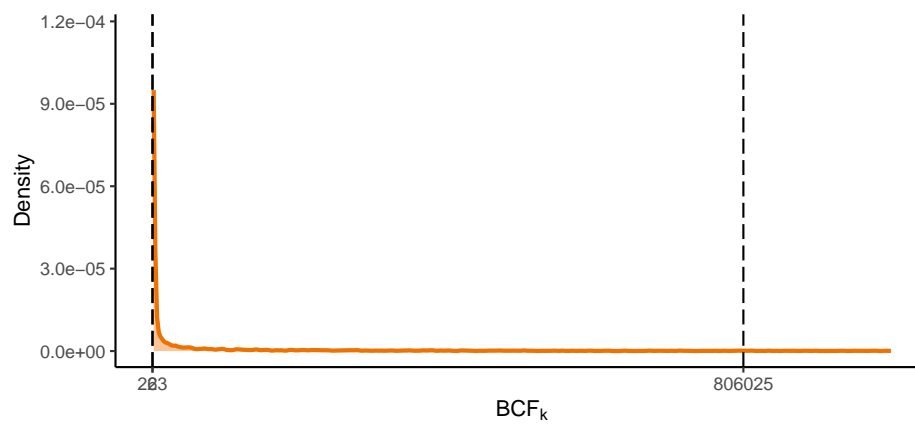
Calculations

$$BCF_k = \frac{k_{uw}}{k_{ee} + k_{m1} + k_{m2} + k_{m3}}$$

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

Bioconcentration factor (BCF)

BCF_k plot

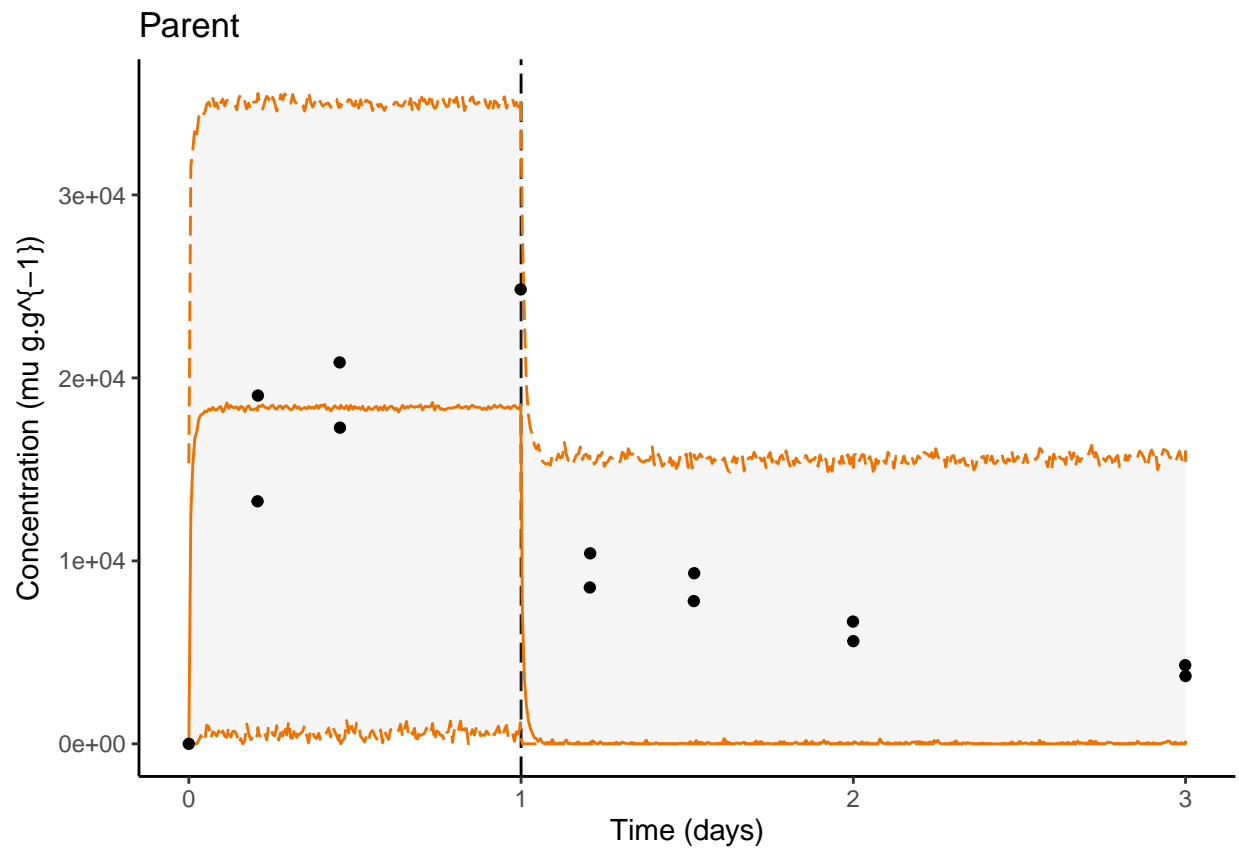


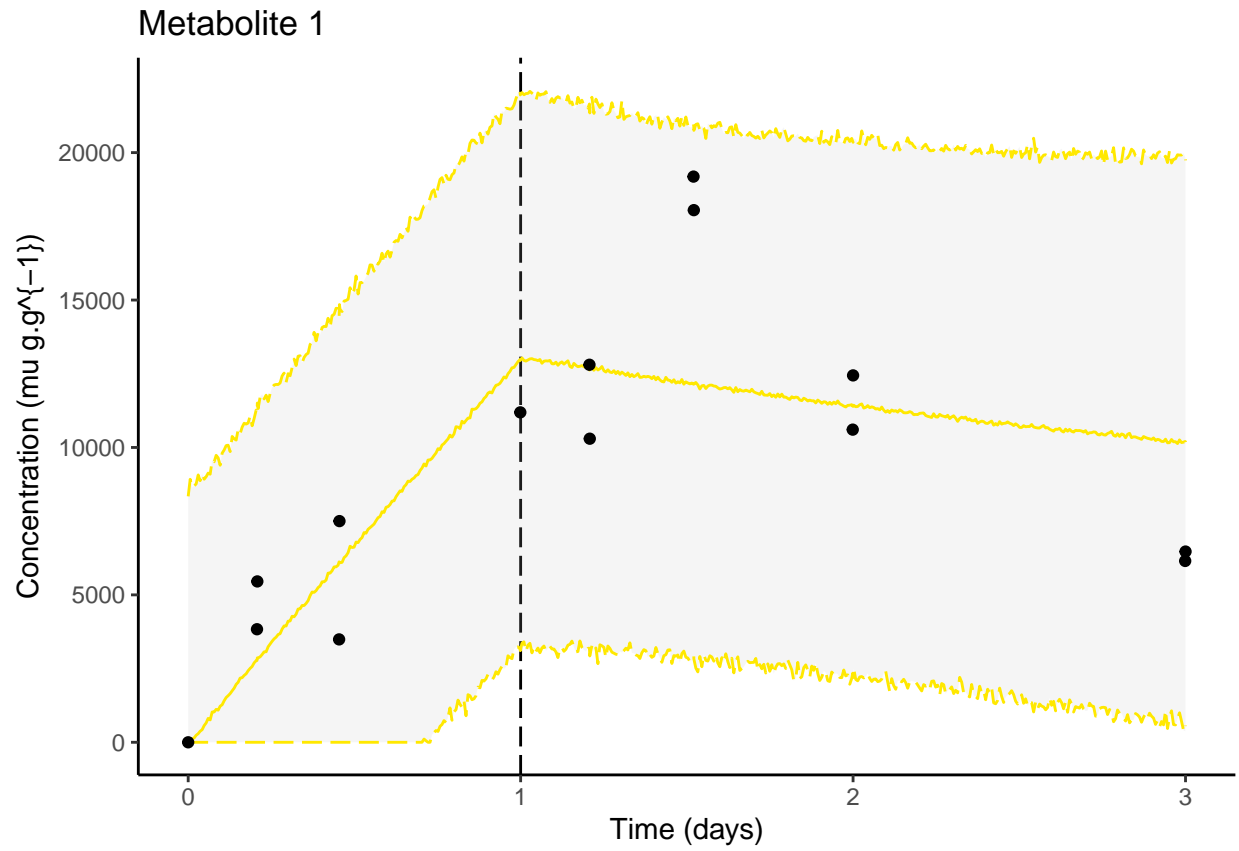
BCF summary

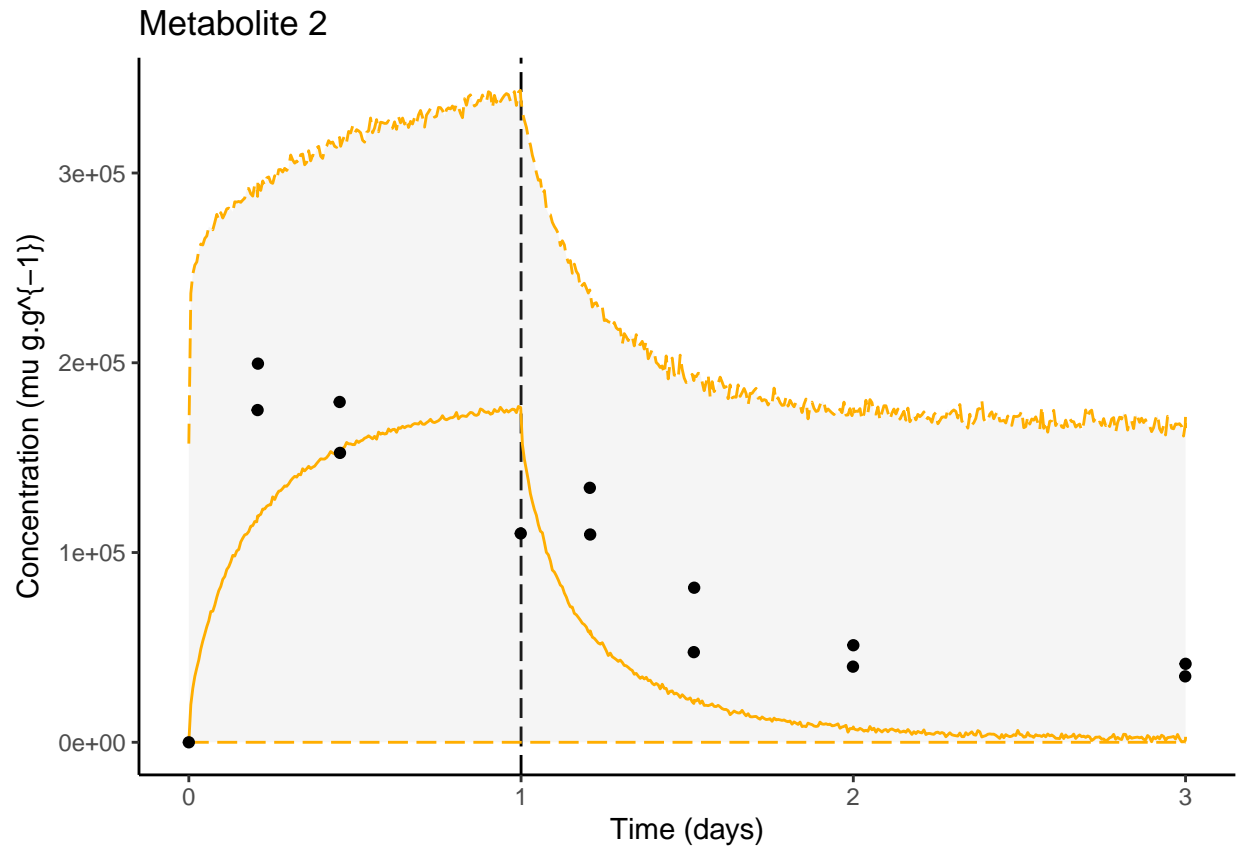
	2.5%	50%	97.5%	CV
BCF _k	6	223	806025	900

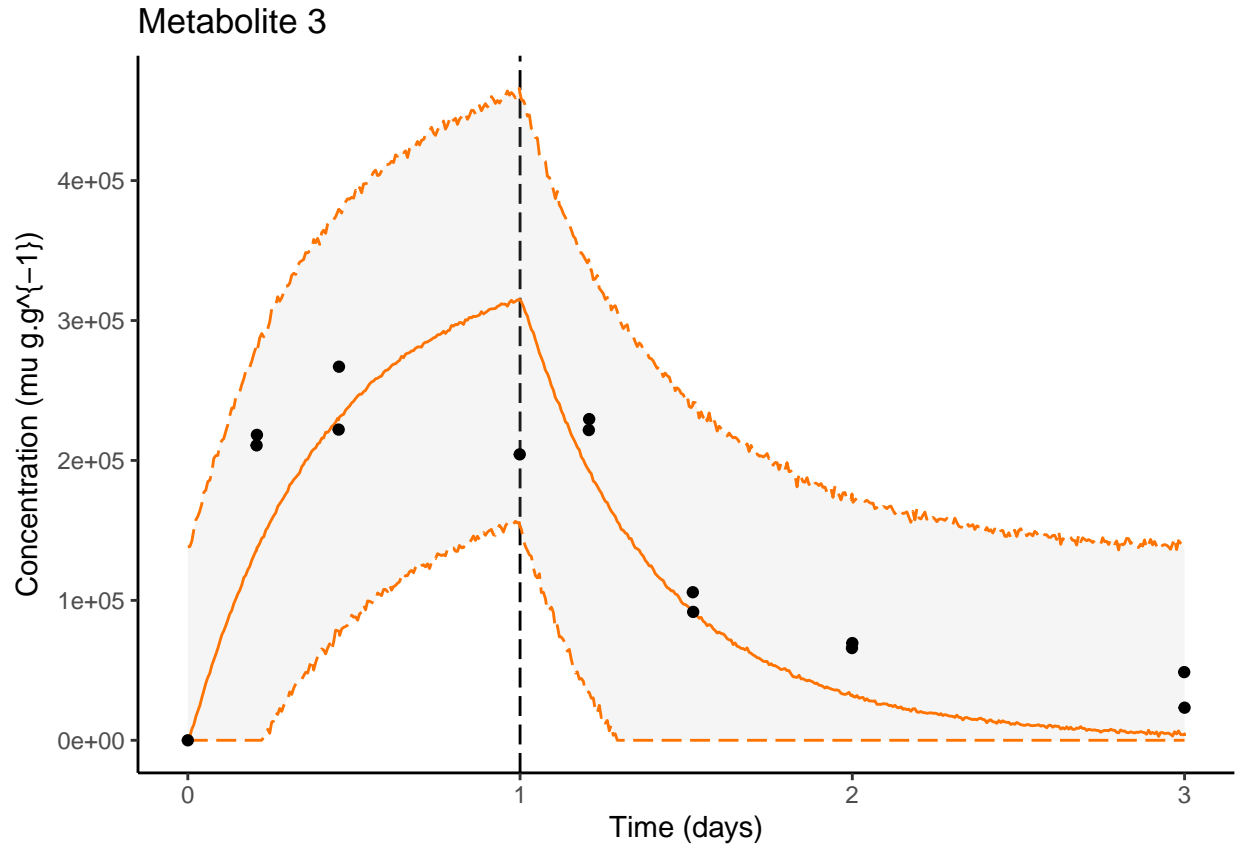
Fitting results

Fit plot









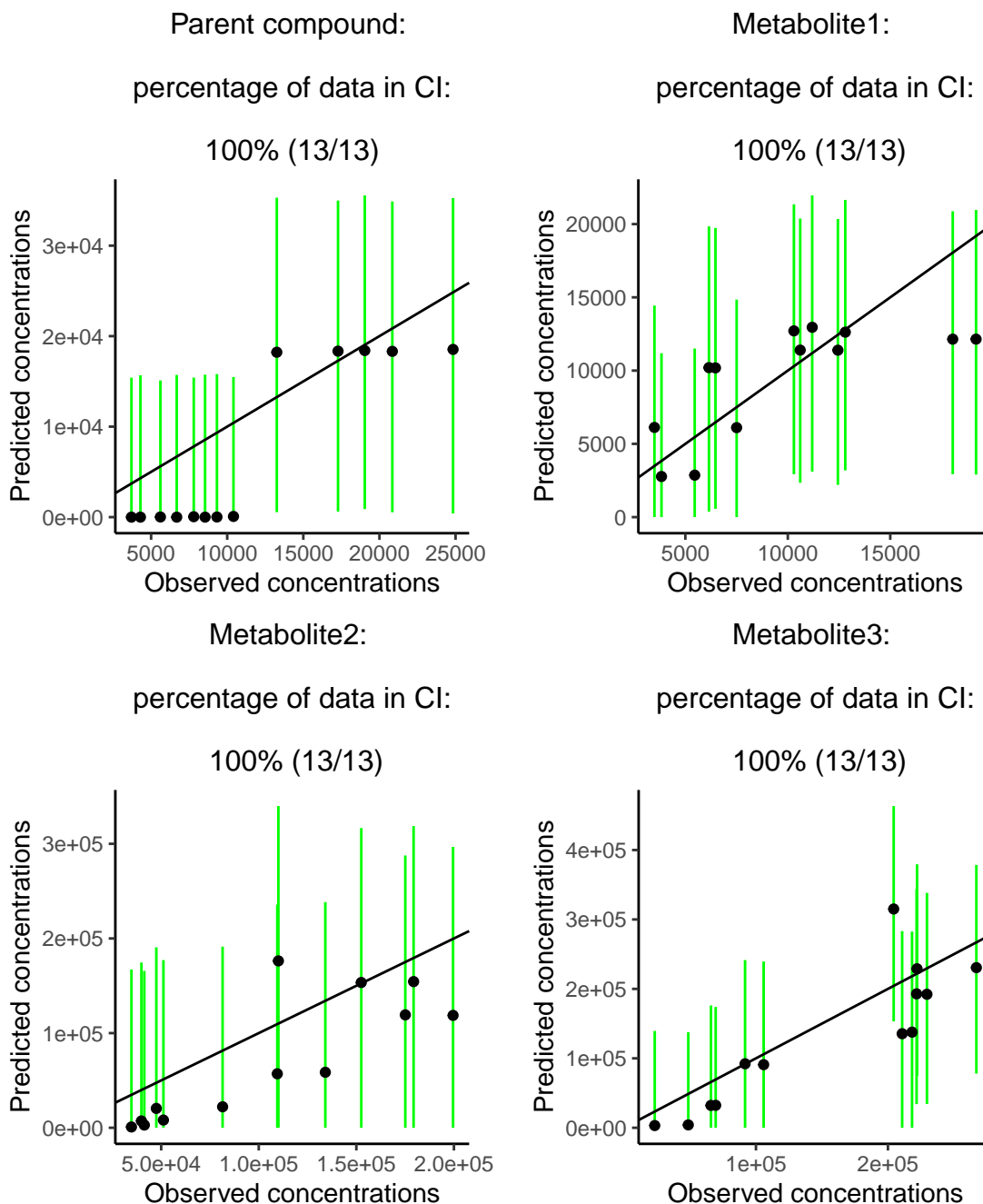
Quantiles of estimated parameters

	2.5%	50%	97.5%	
k_{uw}	252	854.6	76290	d^{-1}
k_{ee}	1.764e-05	0.5592	9874	d^{-1}
k_{m1}	0.4468	0.7453	1.55	d^{-1}
k_{m2}	0.1045	59.75	14980	d^{-1}
k_{m3}	24.35	46.74	114.4	d^{-1}
k_{em1}	1.623e-05	0.06575	0.4977	d^{-1}
k_{em2}	6.558e-03	5.587	1998	d^{-1}
k_{em3}	1.266	2.427	4.617	d^{-1}
σ_p	4862	7077	12590	$\mu g.g^{-1}$
σ_{met1}	2591	3882	6868	$\mu g.g^{-1}$
σ_{met2}	41600	68910	130400	$\mu g.g^{-1}$
σ_{met3}	40390	62960	103800	$\mu g.g^{-1}$

Goodness-of-fit criteria

Posterior Predictive Check

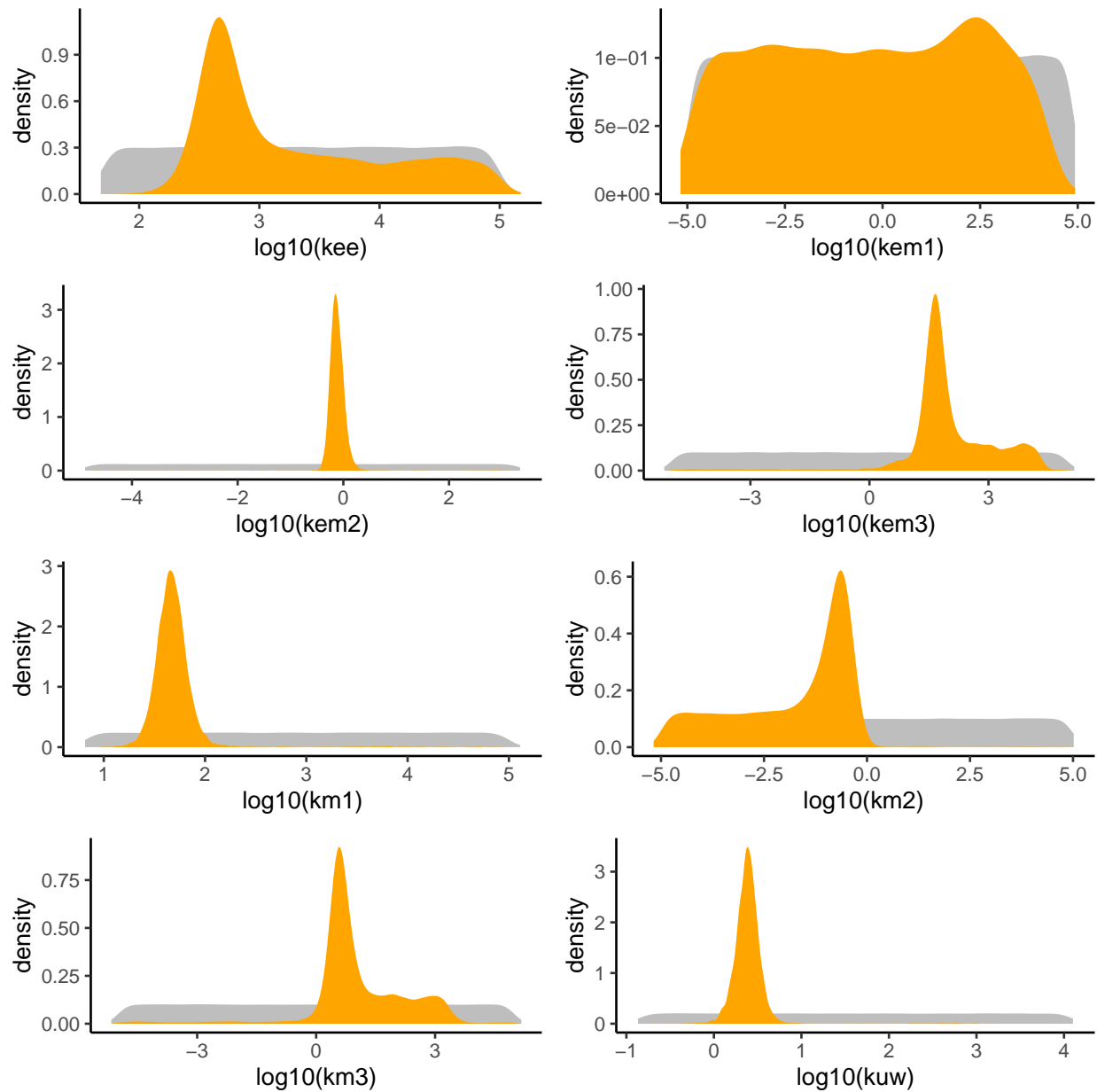
The PPC shows the observed values against their corresponding estimated predictions (black dots), along with their 95% credible interval (vertical segments). If the fit is correct, we expect to see 95% of the data within the intervals. Ideally observations and predictions should coincide, so we would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

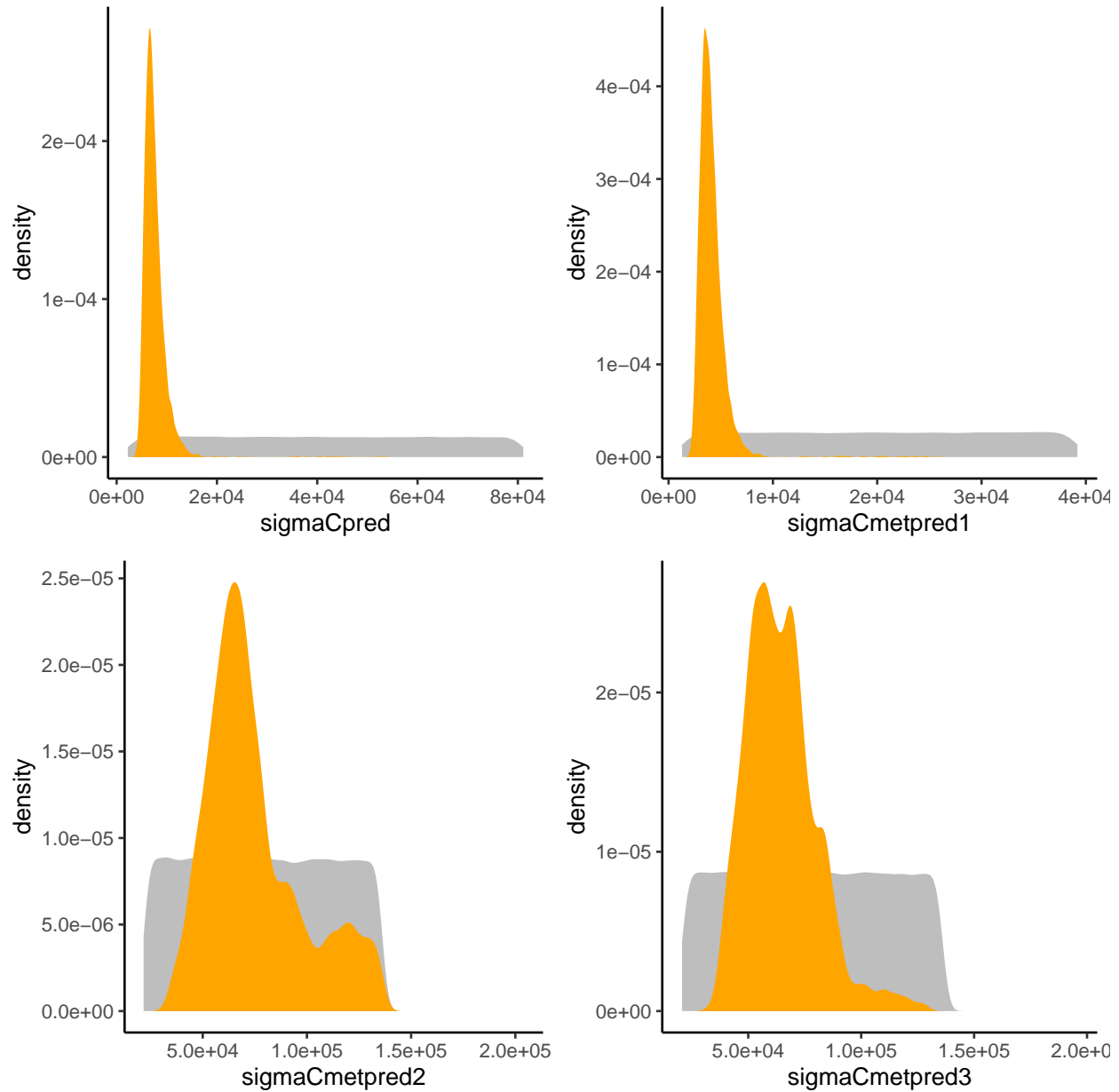


Priors and posteriors

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.

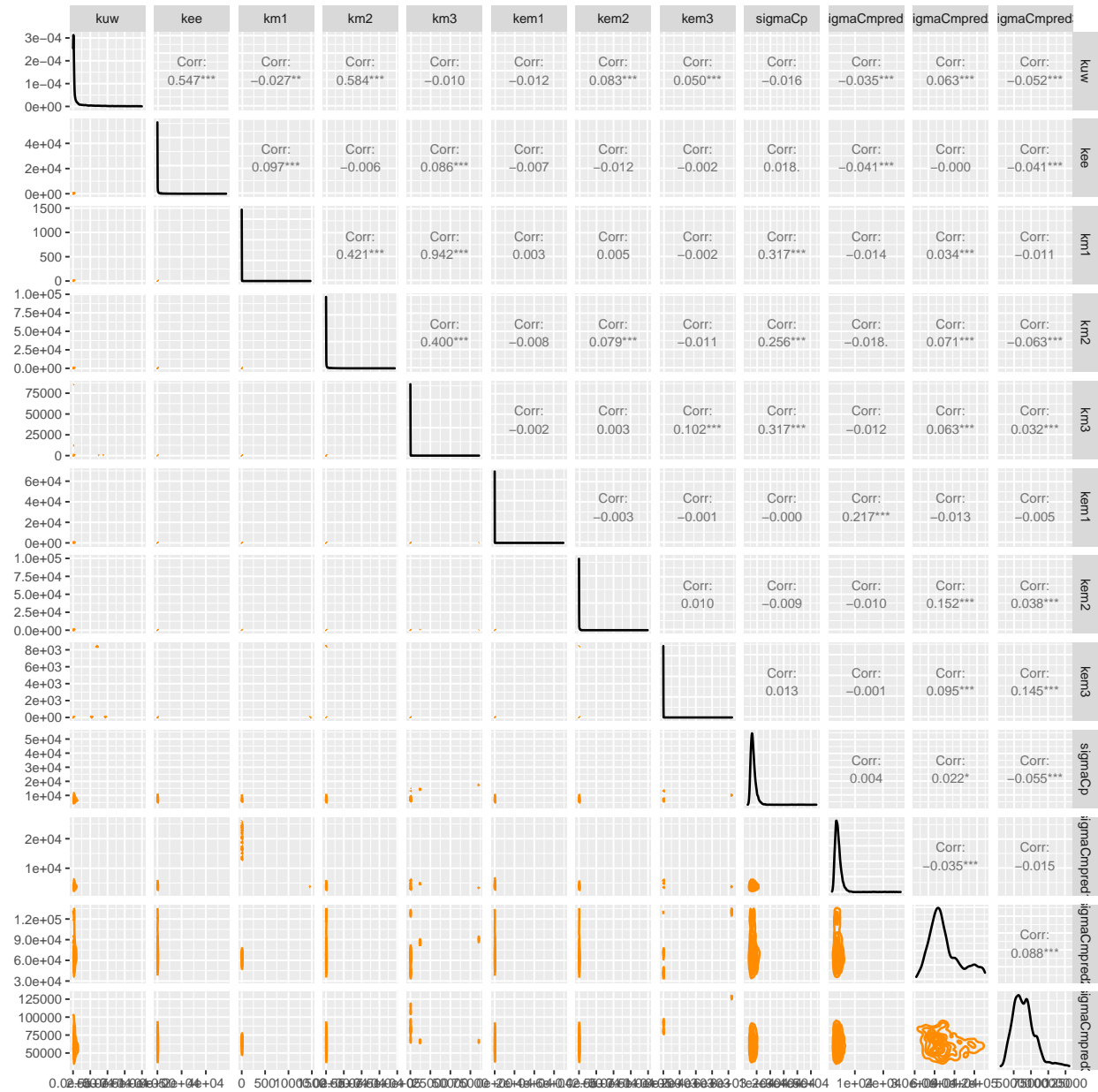




Correlation between parameters

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 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	1.002
kee	1.02
km1	1.296
km2	1.115
km3	1.277
kem1	1.29
kem2	1.115
kem3	1.293

	PSRF
sigmaCpred	1.159
sigmaCmetpred1	1.146
sigmaCmetpred2	1.255
sigmaCmetpred3	1.05

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.

$$\text{WAIC} = 1174$$

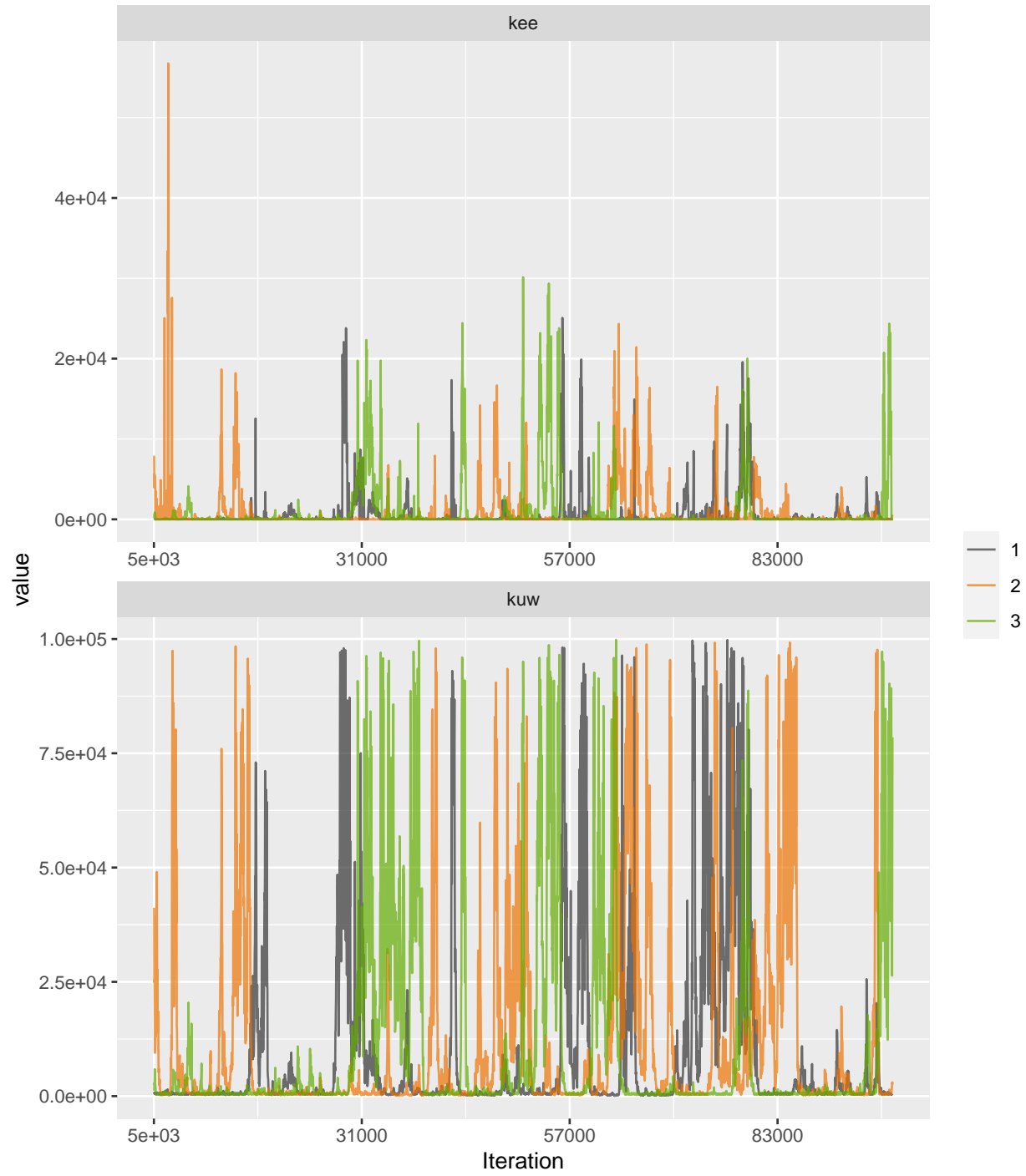
Deviance Information Criterion

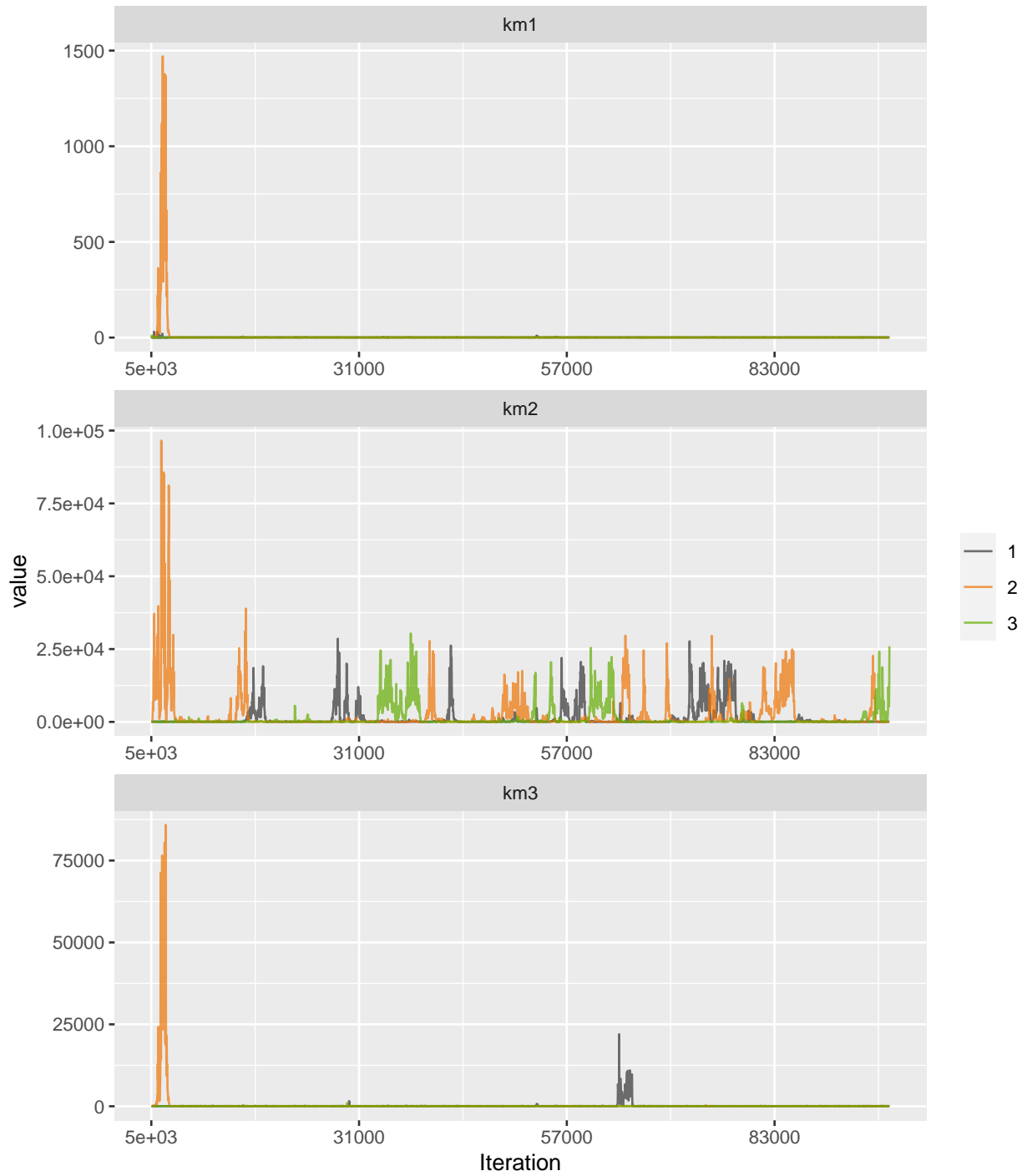
This criteria, denoted DIC, is a penalized deviance statistics accounting for the number of parameters for use in model comparison for a same dataset (e.g., with or without k_{ee}). Sub-models with lower DIC values will be preferred.

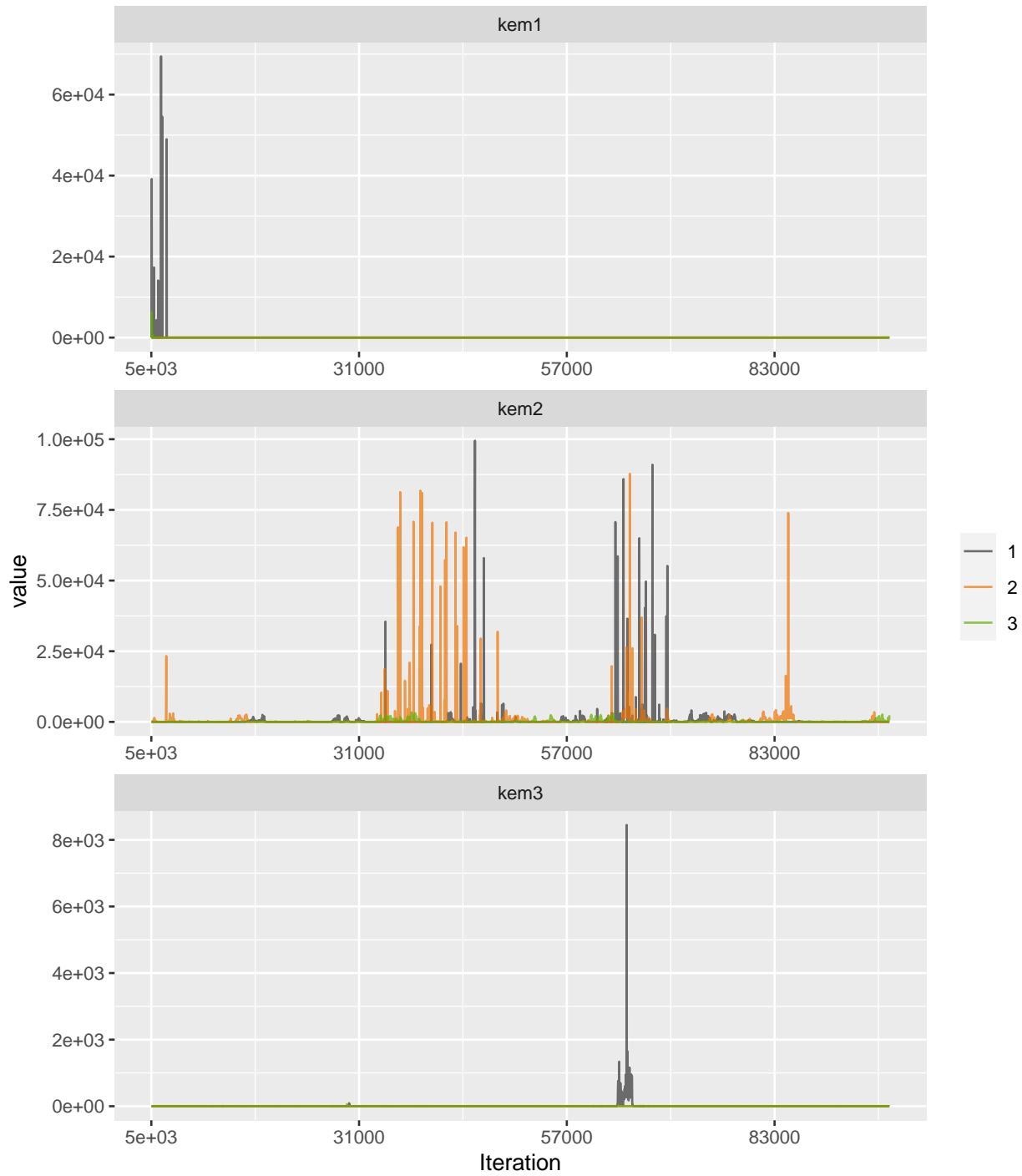
$$\text{DIC} = 1202$$

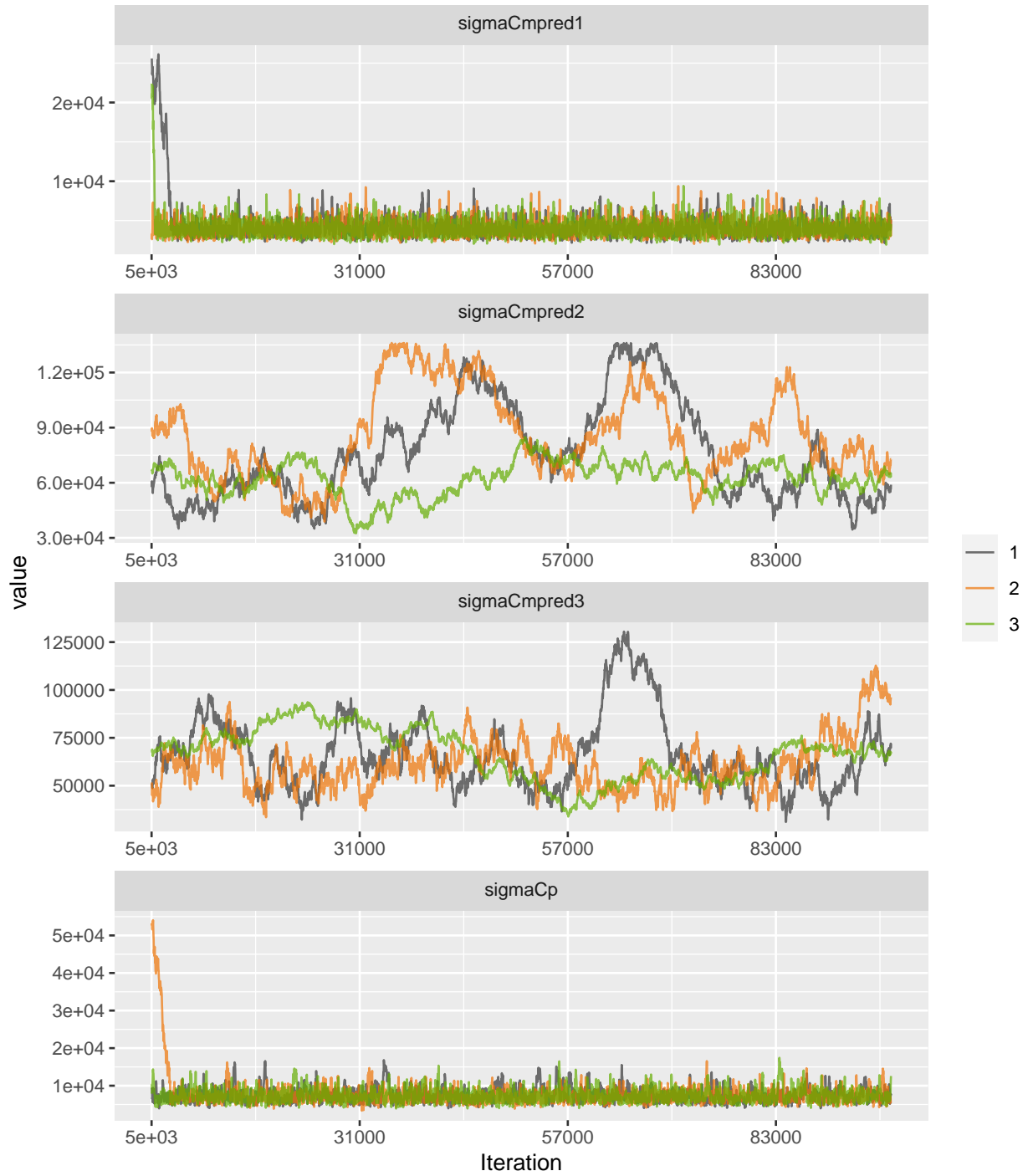
Traces of MCMC iterations

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	concm3	replicate
0.000	3898	0	0	0	0	1
0.207	3898	13257	3835	175088	210778	1
0.208	3898	19037	5456	199557	218273	2
0.454	3898	20847	3490	179337	222050	1
0.455	3898	17280	7503	152520	267001	2
0.999	3898	24837	11190	110057	204353	1
1.207	3898	8546	12805	134107	221725	1
1.208	3898	10412	10297	109496	229554	2
1.520	3898	7802	19187	47509	105828	1
1.521	3898	9325	18049	81469	91755	2
1.999	3898	6683	10605	39869	65930	1
2.000	3898	5612	12444	51148	69491	2
2.999	3898	4299	6151	34755	48725	1
3.000	3898	3708	6469	41355	23311	2