

# MOSAIC<sub>bioacc</sub> REPORT

2021-05-12

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

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MOSAIC<sub>bioacc</sub> 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<sub>bioacc</sub> 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.

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## Data summary

File used: Gammarus\_azoxistrobine\_1d\_Rosch2017.txt

Exposure:  $0.5 \mu\text{g.mL}^{-1}$

Accumulation phase duration: 1 days

Number of replicates: 2

Times: 0, 0.02, 0.06, 0.1, 0.23, 0.4, 0.73, 1, 1.04, 1.08, 1.17, 1.29, 1.46, 1.75, 2.08, 2.71, 3.13, 3.96, 4.96, 6

Exposure routes: water

Elimination routes: excretion biotransformation

## Bayesian inference

Three MCMC chains were used to estimate model parameters.

Number of iterations: 1333576

Thin: 356

## TK Model

The TK model used for these calculations was:

$$\frac{dC_p(t)}{dt} = k_{uw} \times c_w - (k_{ee} + k_{m1} + k_{m2} + k_{m3} + k_{m4} + k_{m5} + k_{m6} + k_{m7} + k_{m8}) \times C_p(t) \quad \text{for } 0 \leq t \leq t_c$$

$$\frac{dC_p(t)}{dt} = -(k_{ee} + k_{m1} + k_{m2} + k_{m3} + k_{m4} + k_{m5} + k_{m6} + k_{m7} + k_{m8}) \times C_p(t) \quad \text{for } t > t_c$$

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

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

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

$$\frac{dC_{m4}(t)}{dt} = k_{m4} \times C_p(t) - k_{em4} \times C_{m4}(t)$$

$$\frac{dC_{m5}(t)}{dt} = k_{m5} \times C_p(t) - k_{em5} \times C_{m5}(t)$$

$$\frac{dC_{m6}(t)}{dt} = k_{m6} \times C_p(t) - k_{em6} \times C_{m6}(t)$$

$$\frac{dC_{m7}(t)}{dt} = k_{m7} \times C_p(t) - k_{em7} \times C_{m7}(t)$$

$$\frac{dC_{m8}(t)}{dt} = k_{m8} \times C_p(t) - k_{em8} \times C_{m8}(t)$$

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

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

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

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

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

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

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

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

## Bioaccumulation factor calculation

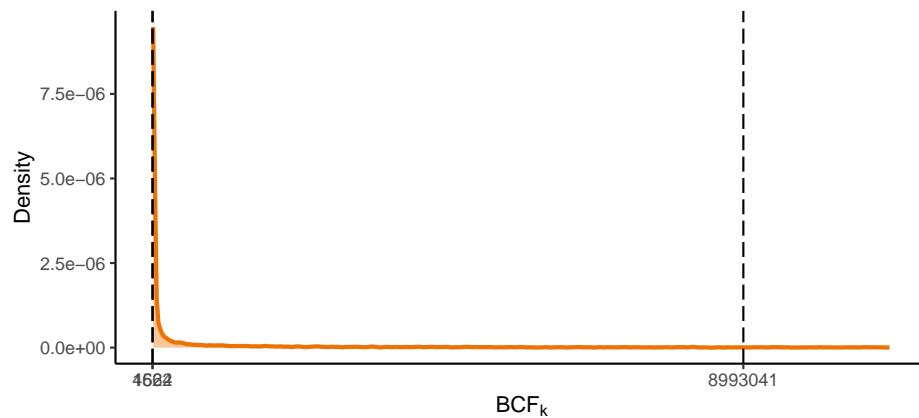
### Calculations

$$BCF_k = \frac{k_{uw}}{k_{ee} + k_{m1} + k_{m2} + k_{m3} + k_{m4} + k_{m5} + k_{m6} + k_{m7} + k_{m8}}$$

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

### Bioconcentration factor (BCF)

#### $BCF_k$ plot

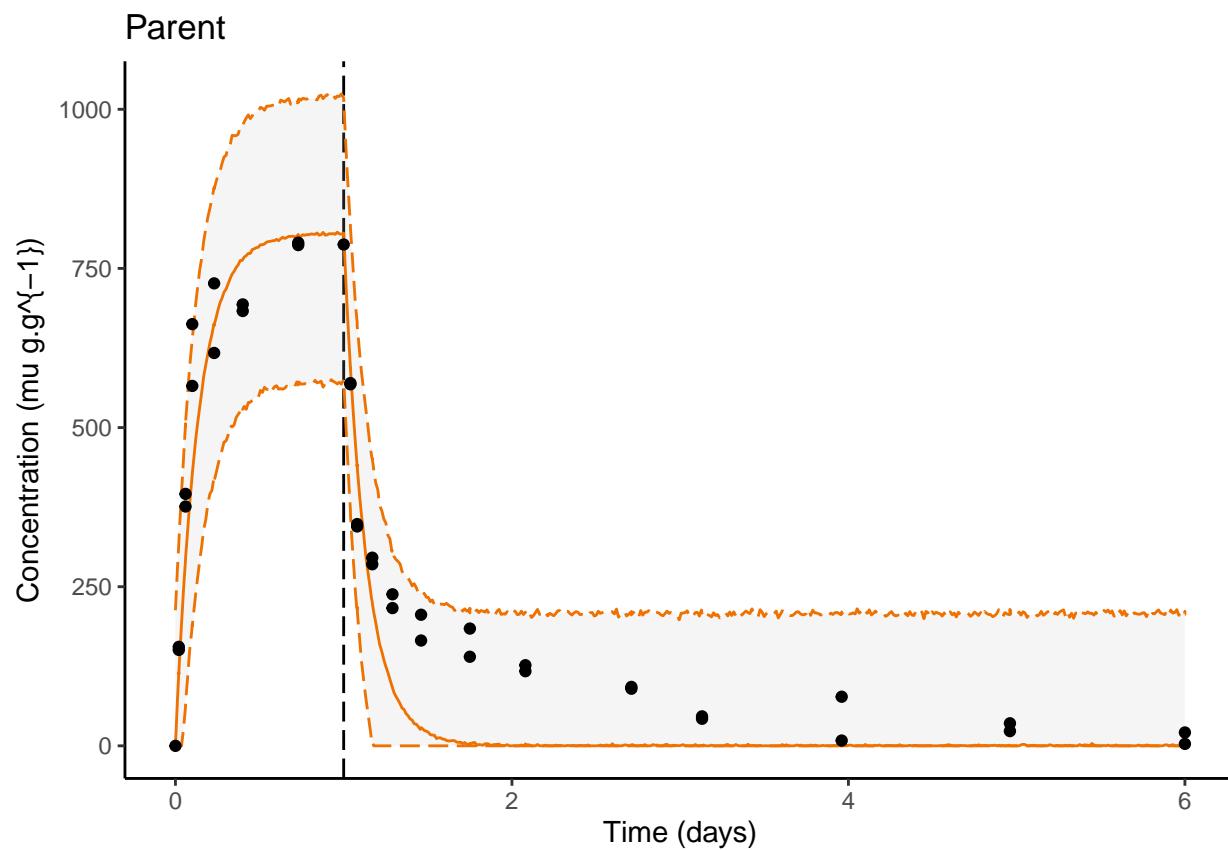


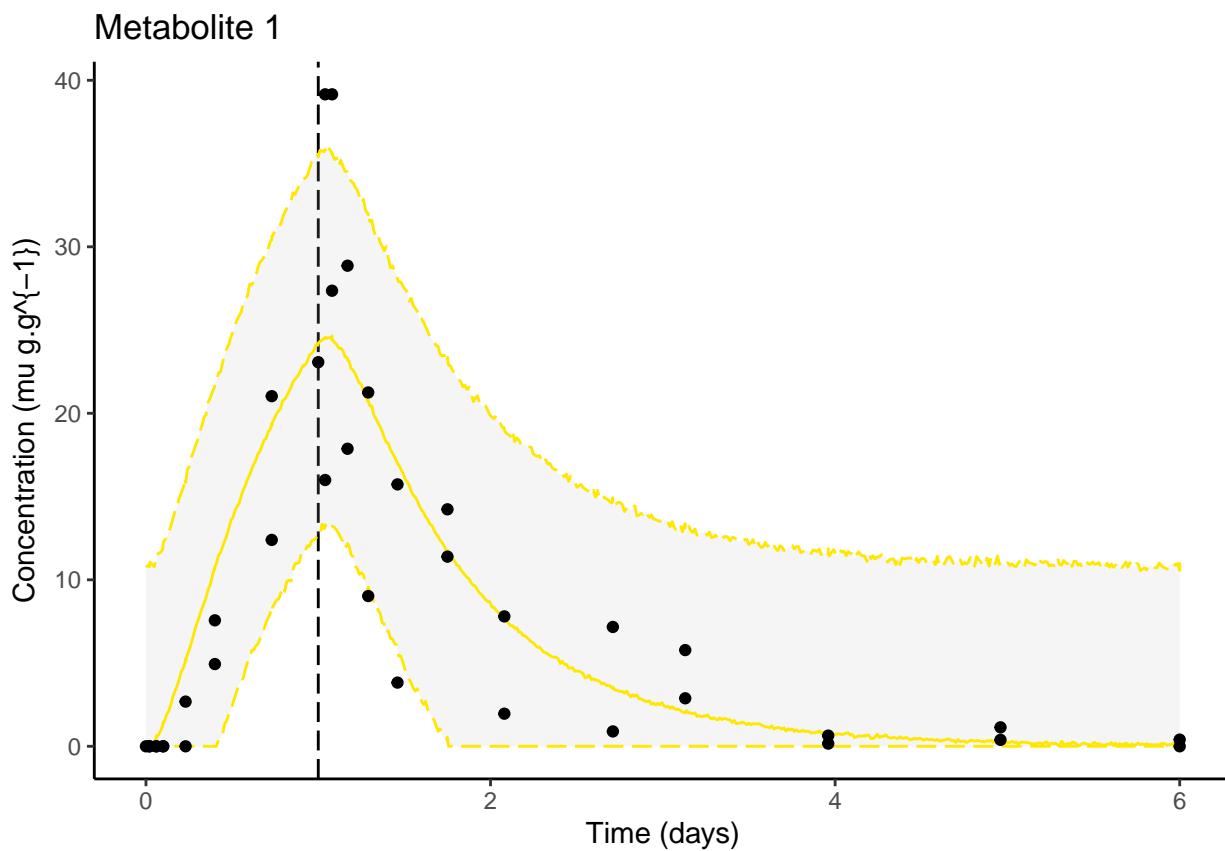
#### BCF summary

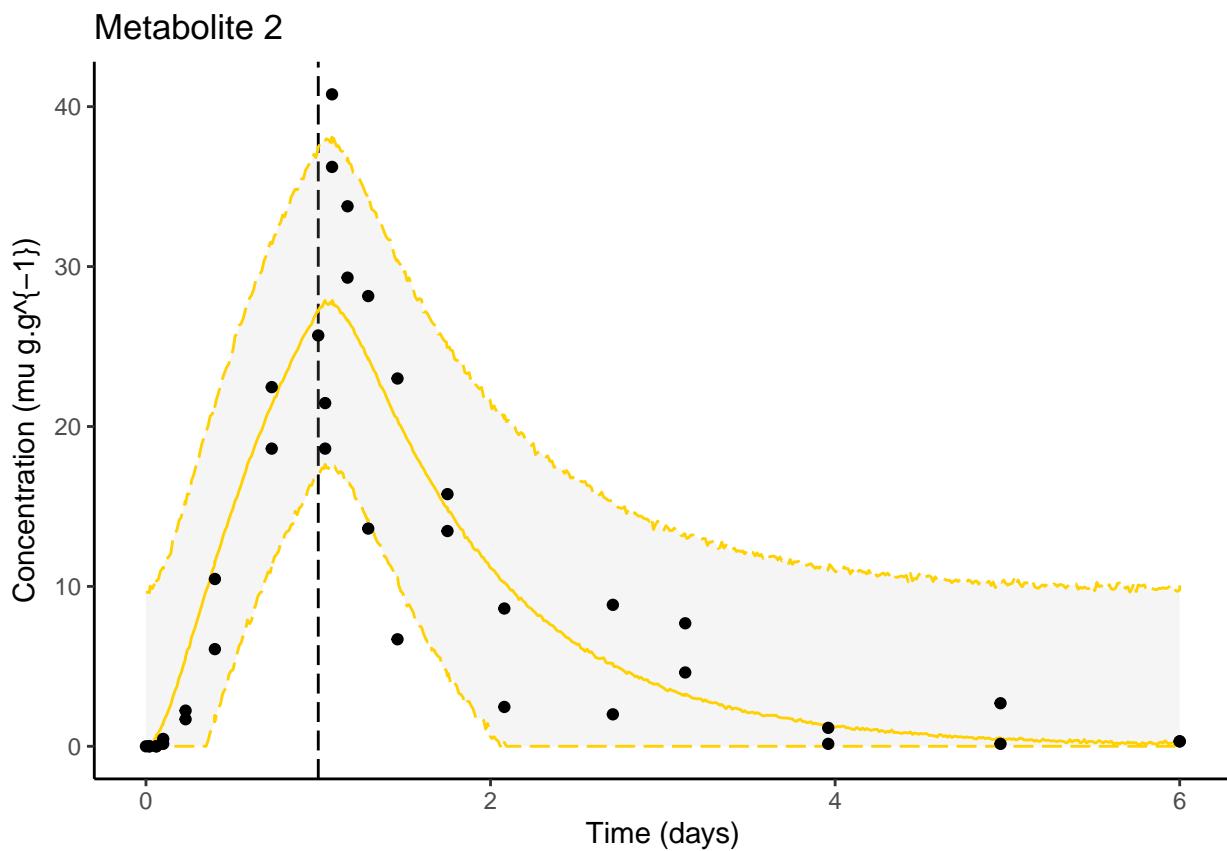
	2.5%	50%	97.5%	CV
BCFk	1662	4524	8993041	500

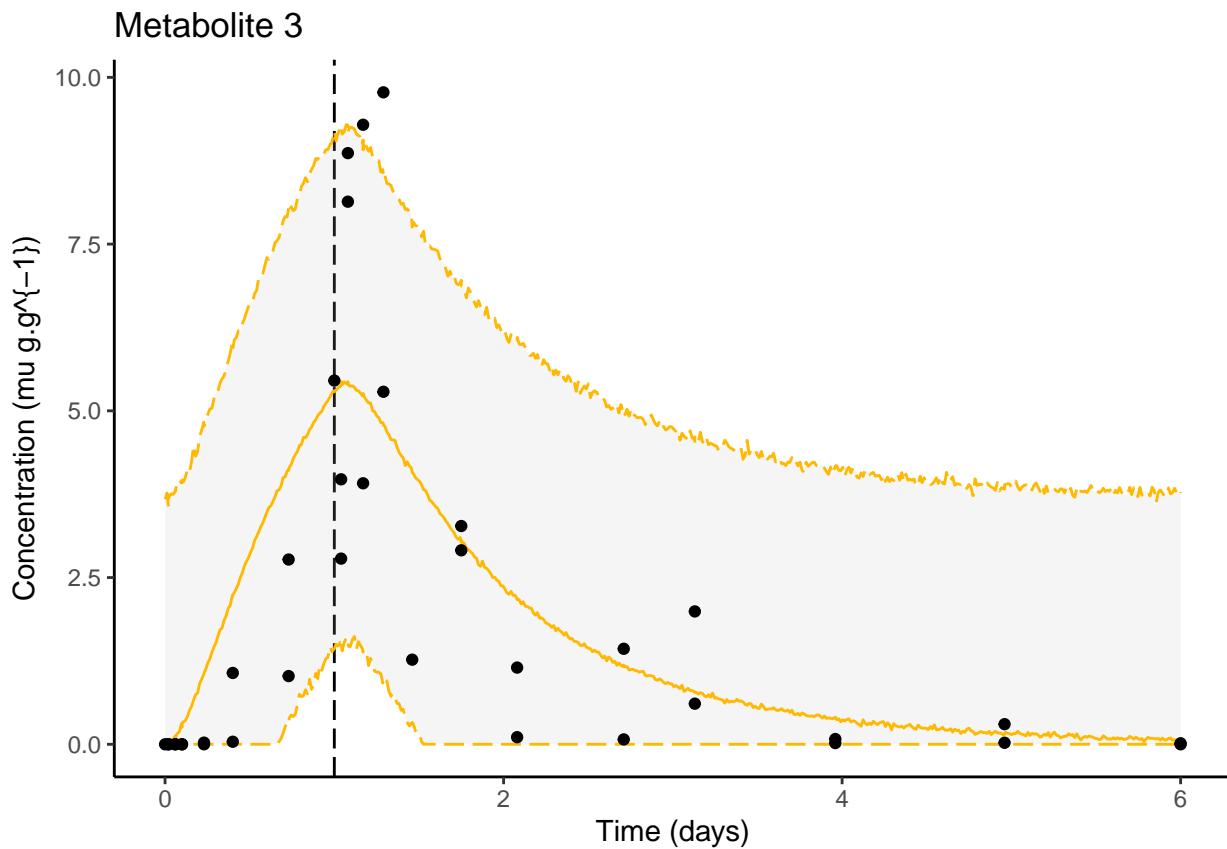
#### Fitting results

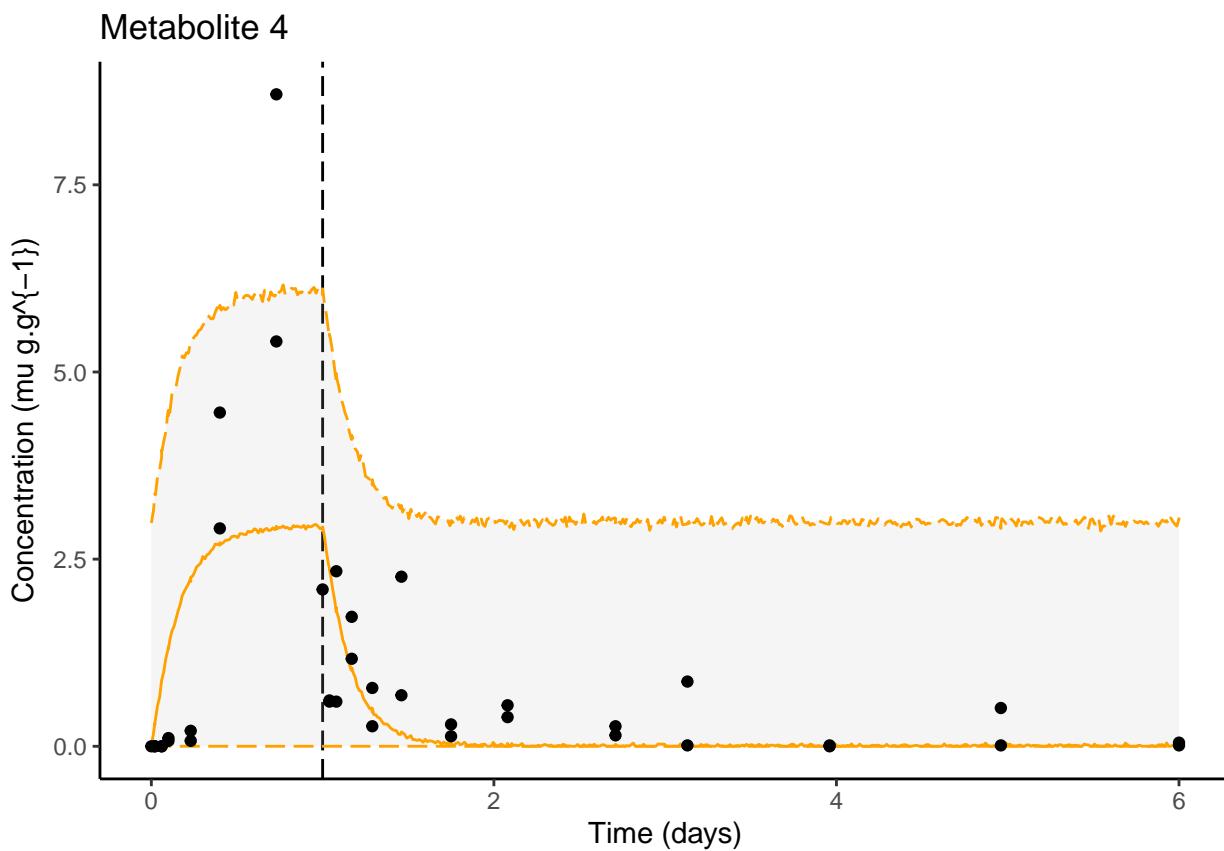
Fit plot

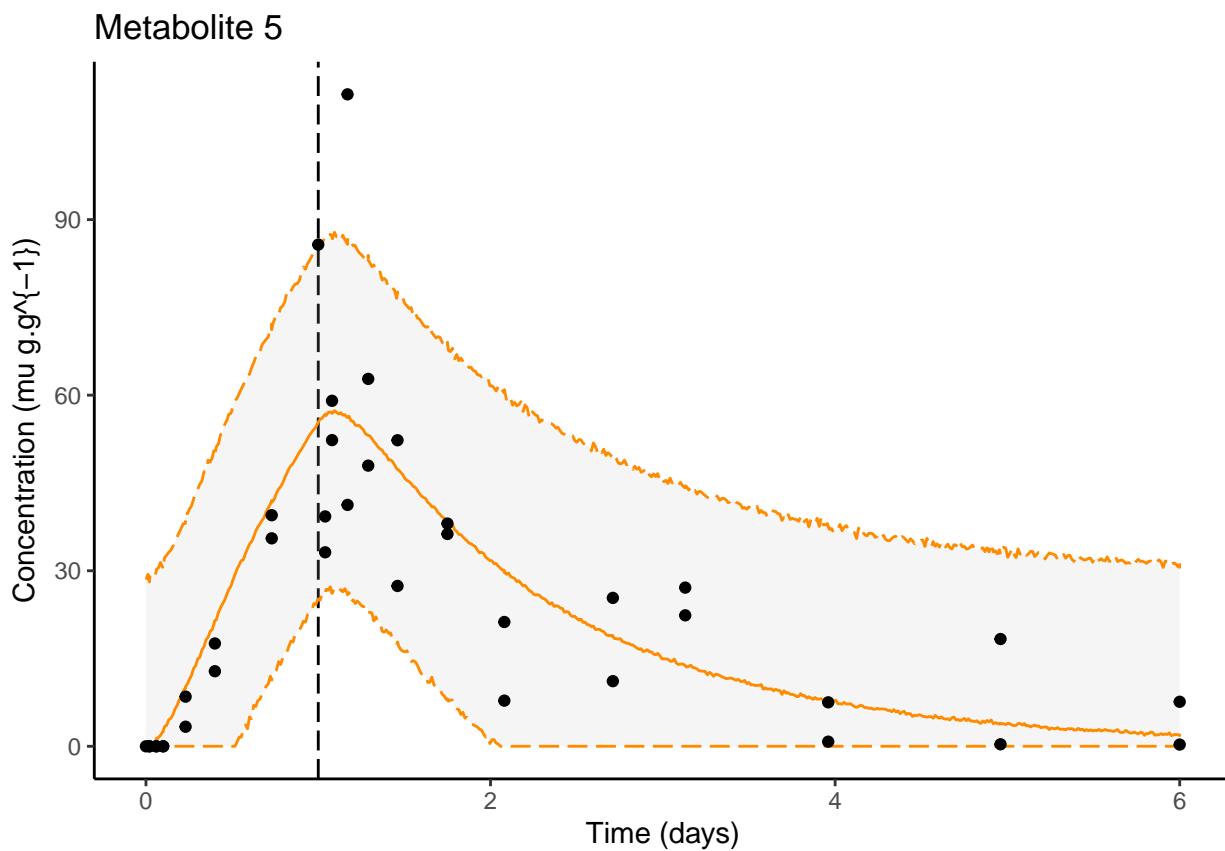


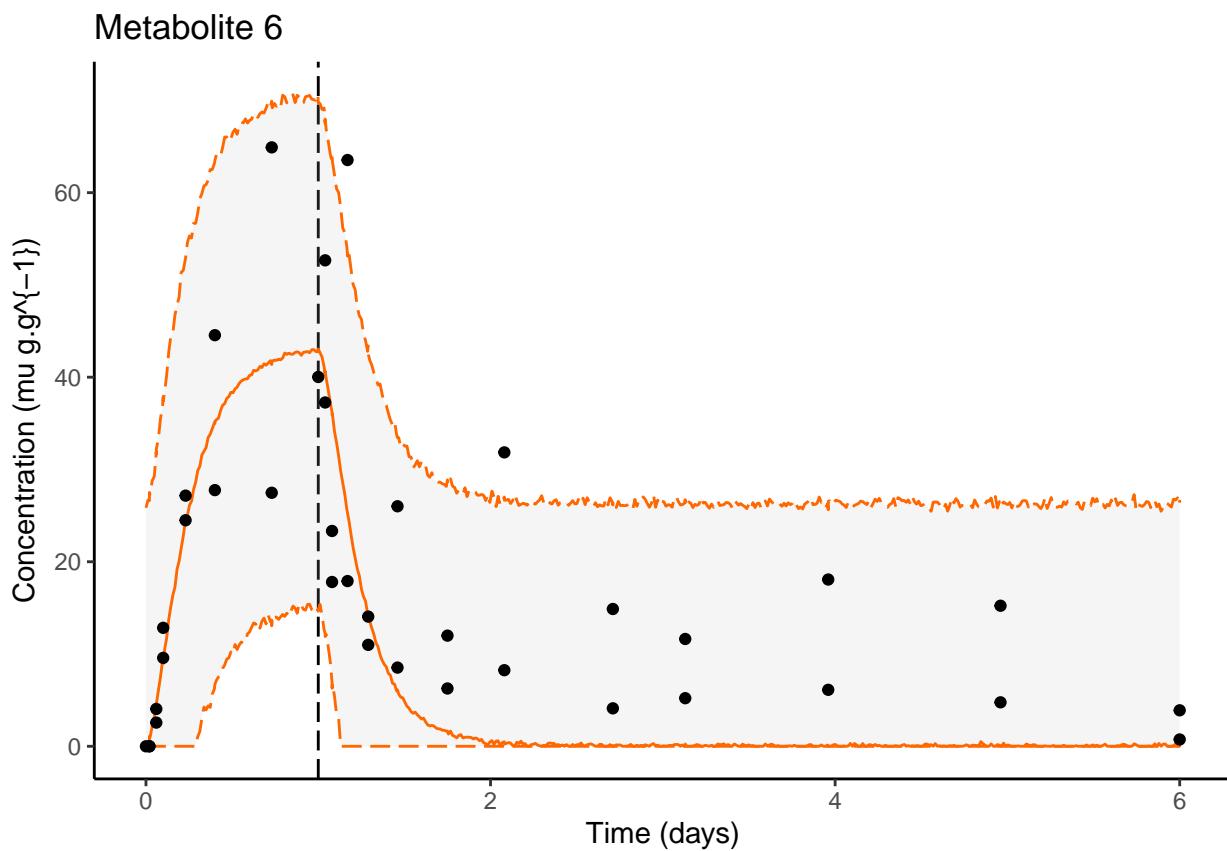


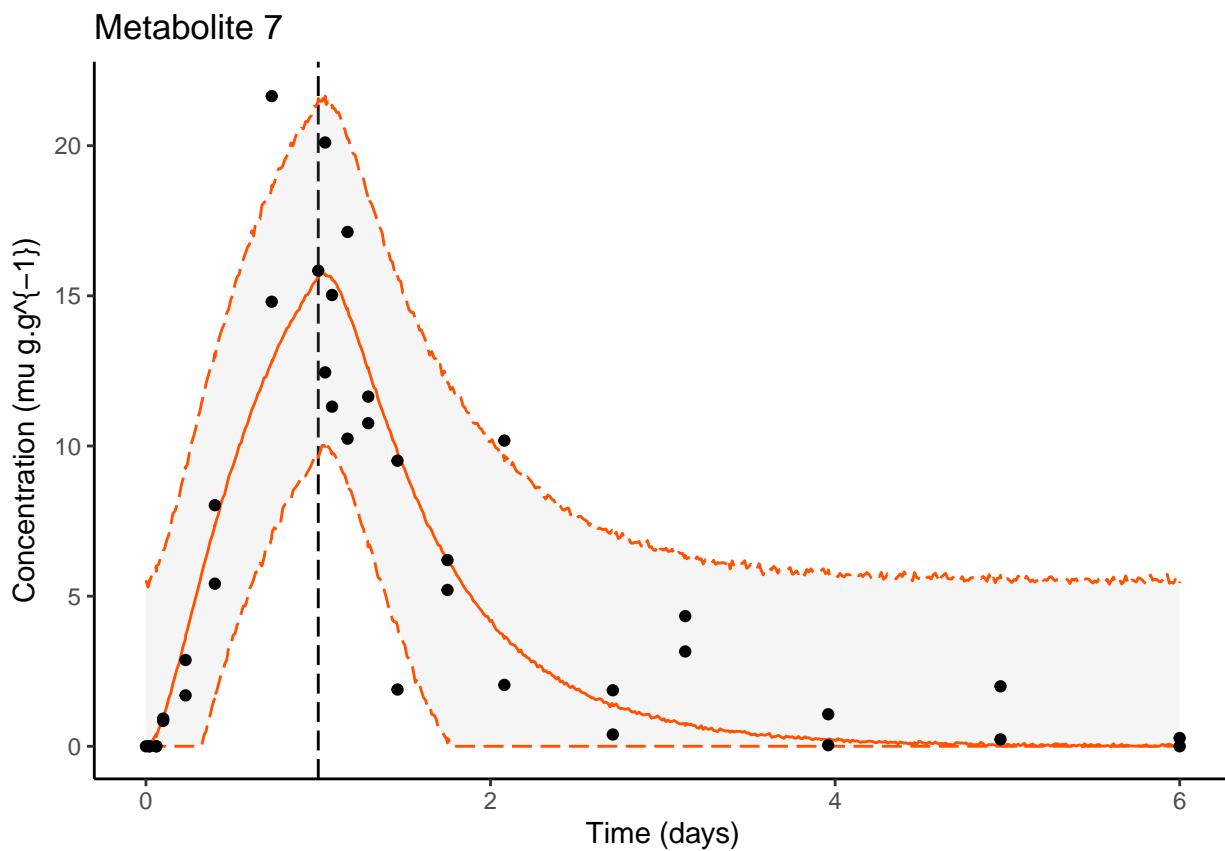




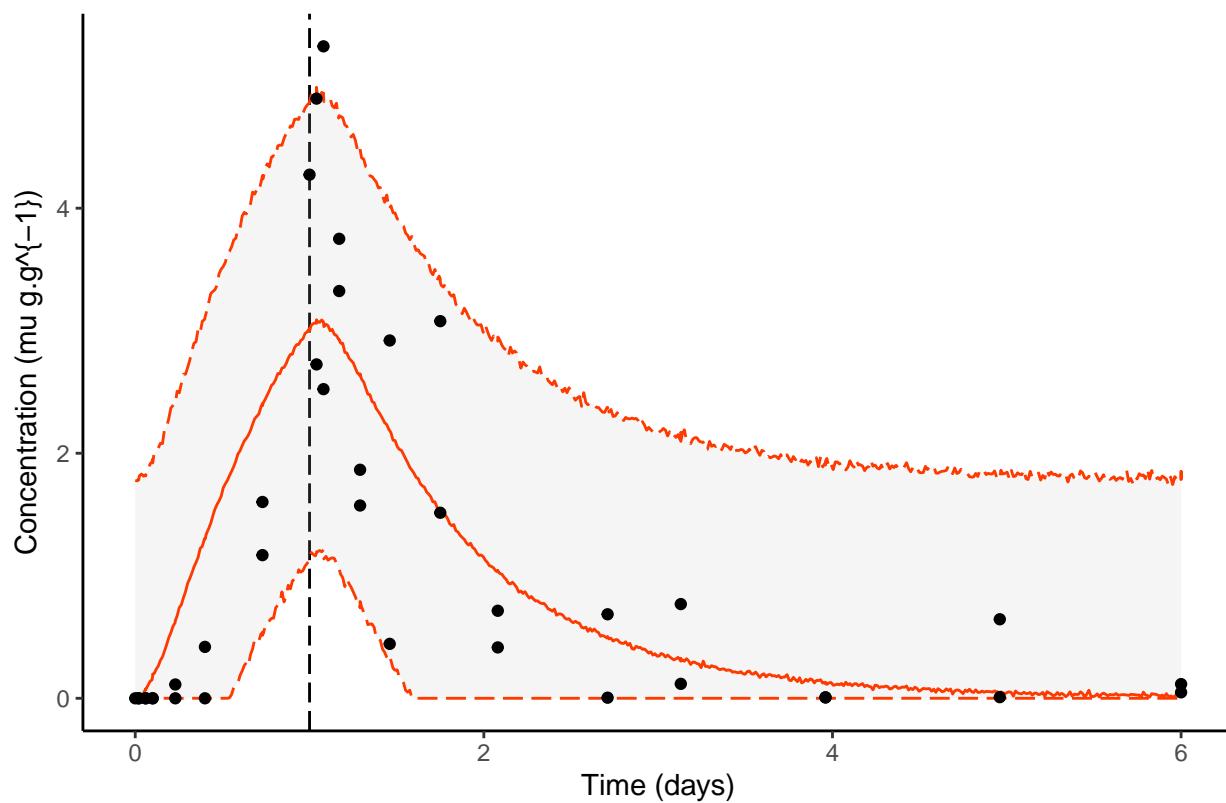








## Metabolite 8



### Quantiles of estimated parameters

	2.5%	50%	97.5%	
$k_{uw}$	8916	12120	15580	$d^{-1}$
$k_{ee}$	1.678e-05	0.4469	8.482	$d^{-1}$
$k_{m1}$	0.04356	0.059	0.08499	$d^{-1}$
$k_{m2}$	0.04948	0.06215	0.08168	$d^{-1}$
$k_{m3}$	0.007943	0.0117	0.01841	$d^{-1}$
$k_{m4}$	0.01791	4.545	8.663	$d^{-1}$
$k_{m5}$	0.08201	0.1093	0.152	$d^{-1}$
$k_{m6}$	0.1648	0.4726	6.51	$d^{-1}$
$k_{m7}$	0.03155	0.04267	0.06327	$d^{-1}$
$k_{m8}$	0.004952	0.007159	0.01133	$d^{-1}$
$k_{em1}$	0.8239	1.322	2.065	$d^{-1}$
$k_{em2}$	0.786	1.141	1.631	$d^{-1}$
$k_{em3}$	0.5502	1.041	1.905	$d^{-1}$
$k_{em4}$	4.624	1130	2824	$d^{-1}$

	2.5%	50%	97.5%	
$k_{em5}$	0.4481	0.755	1.241	$d^{-1}$
$k_{em6}$	2.846	8.719	110.6	$d^{-1}$
$k_{em7}$	1.058	1.65	2.58	$d^{-1}$
$k_{em8}$	0.6918	1.237	2.181	$d^{-1}$
$\sigma_p$	79.5	100.3	136.9	$\mu g.g^{-1}$
$\sigma_{met1}$	4.25	5.338	6.972	$\mu g.g^{-1}$
$\sigma_{met2}$	3.829	4.81	6.313	$\mu g.g^{-1}$
$\sigma_{met3}$	1.453	1.822	2.381	$\mu g.g^{-1}$
$\sigma_{met4}$	1.193	1.487	1.939	$\mu g.g^{-1}$
$\sigma_{met5}$	11.44	14.34	18.68	$\mu g.g^{-1}$
$\sigma_{met6}$	10.38	13.03	16.96	$\mu g.g^{-1}$
$\sigma_{met7}$	2.178	2.736	3.559	$\mu g.g^{-1}$
$\sigma_{met8}$	0.7027	0.8806	1.154	$\mu g.g^{-1}$

## Goodness-of-fit criteria

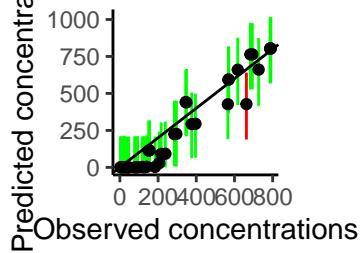
### Posterior Predictive Check

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:

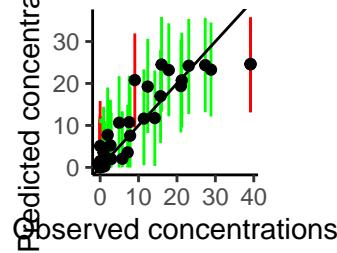
97.22% (35/36)



## Metabolite1:

percentage of data in CI:

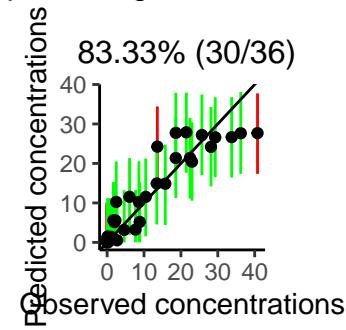
69.44% (25/36)



## Metabolite2:

percentage of data in CI:

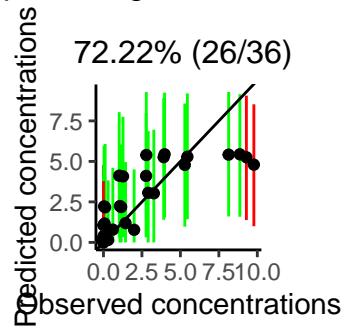
83.33% (30/36)



## Metabolite3:

percentage of data in CI:

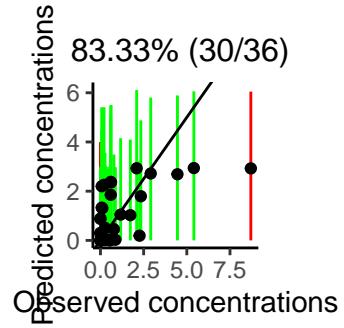
72.22% (26/36)



## Metabolite4:

percentage of data in CI:

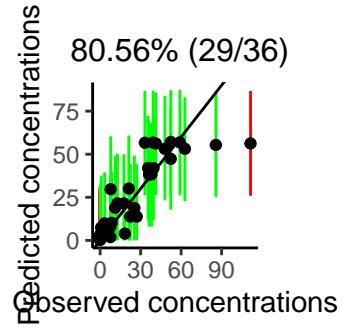
83.33% (30/36)



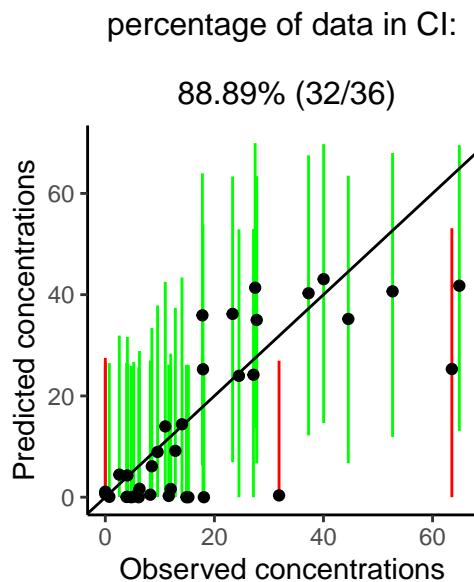
## Metabolite5:

percentage of data in CI:

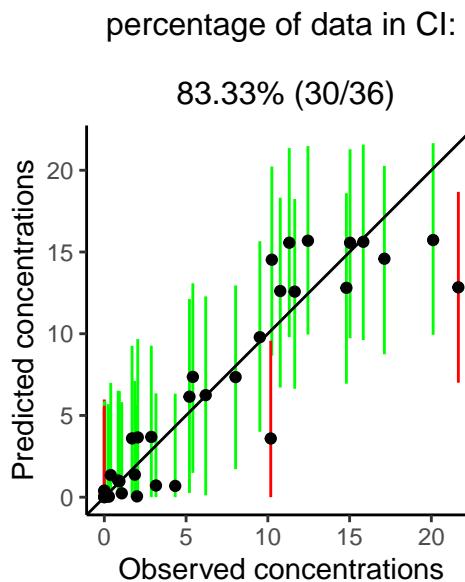
80.56% (29/36)



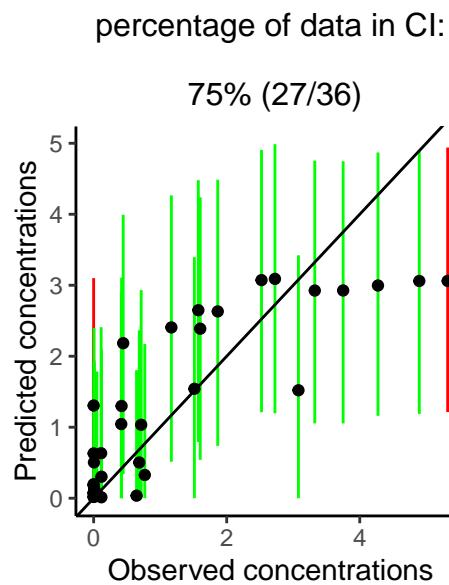
Metabolite6:



Metabolite7:

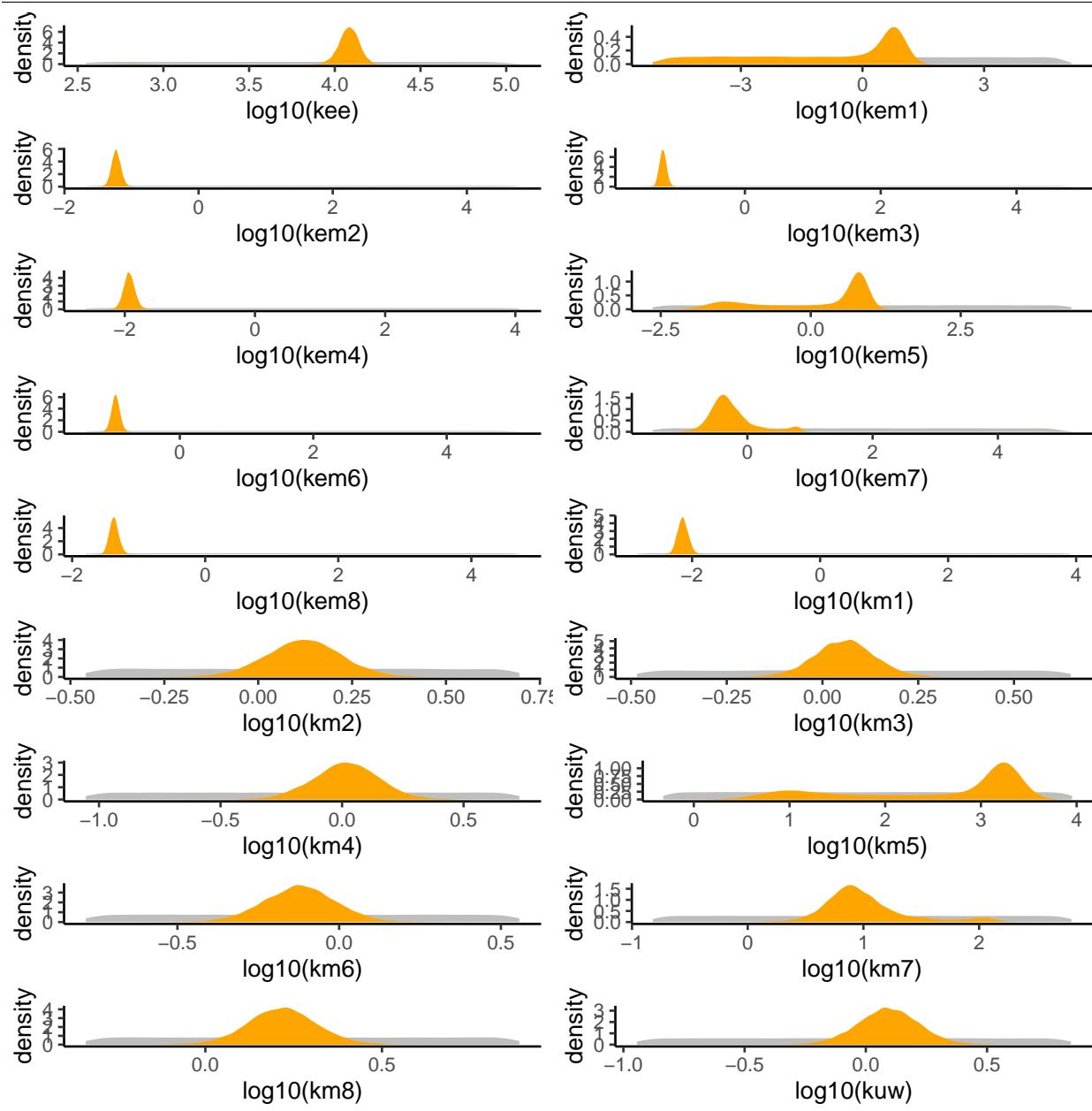


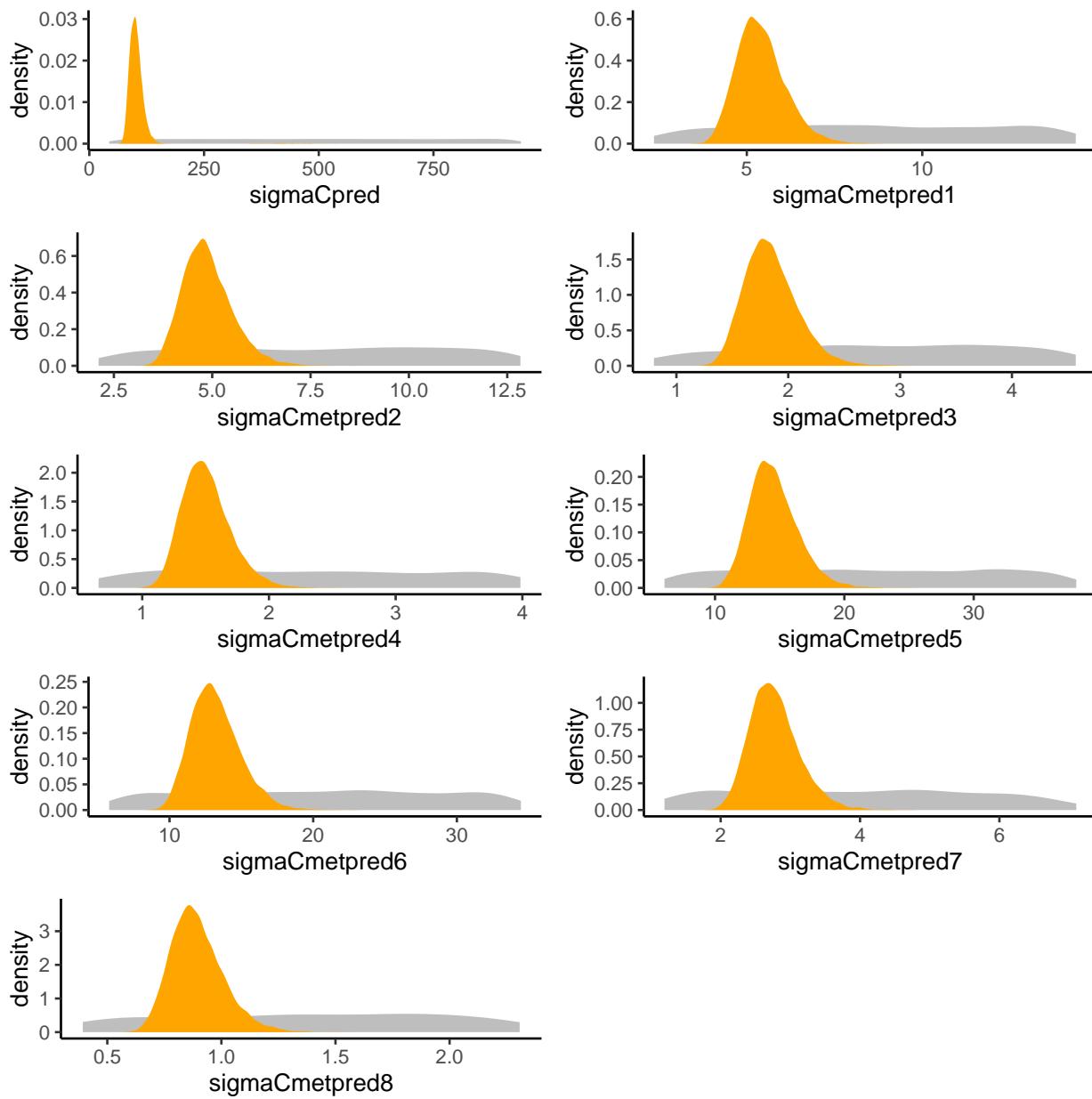
Metabolite8:



### 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.

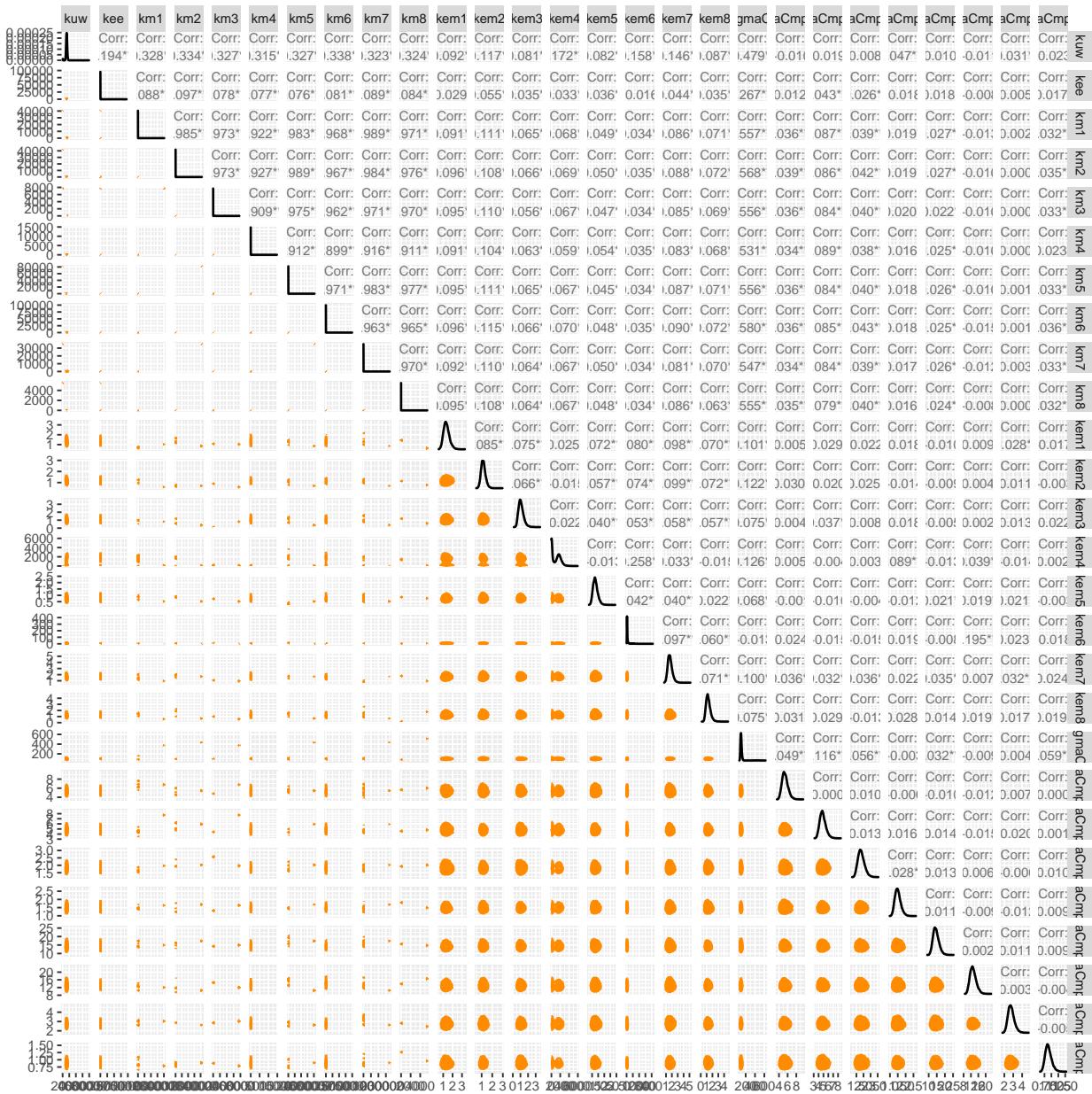




### Correlation between parameters

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	1.00209
kee	1.204458
km1	1.120141
km2	1.120423
km3	1.111766
km4	1.117392
km5	1.120168
km6	1.108546

	PSRF
km7	1.131213
km8	1.107067
kem1	1.000338
kem2	1.000003
kem3	1.000011
kem4	1.000012
kem5	1.000161
kem6	1.00836
kem7	1.000101
kem8	1.000093
sigmaCpred	1.017666
sigmaCmetpred1	1.000248
sigmaCmetpred2	1.000054
sigmaCmetpred3	1.000005
sigmaCmetpred4	1.000253
sigmaCmetpred5	1.000061
sigmaCmetpred6	1.00049
sigmaCmetpred7	1.000439
sigmaCmetpred8	1.000002

### 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 = 2035

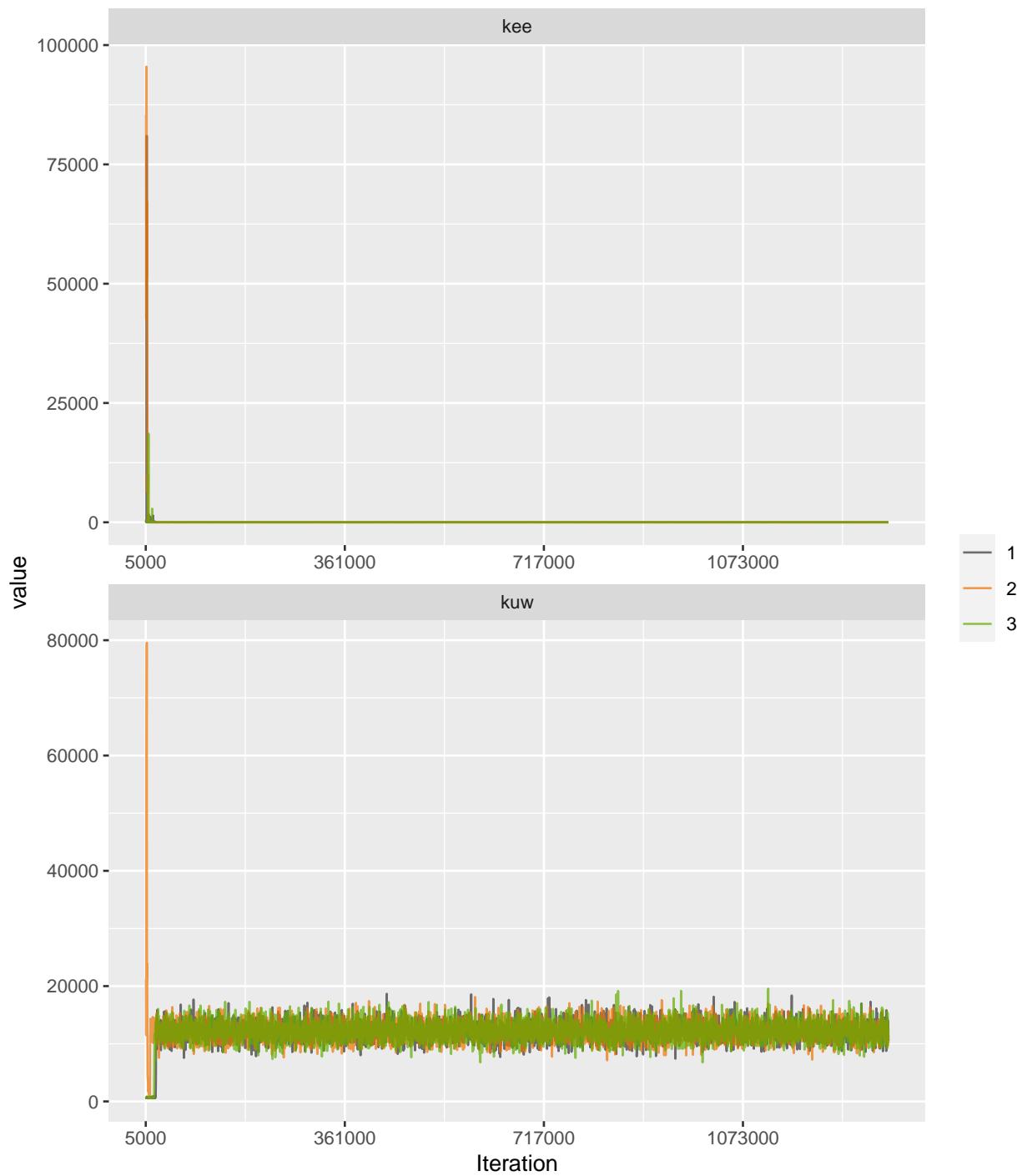
### Deviance Information Criterion

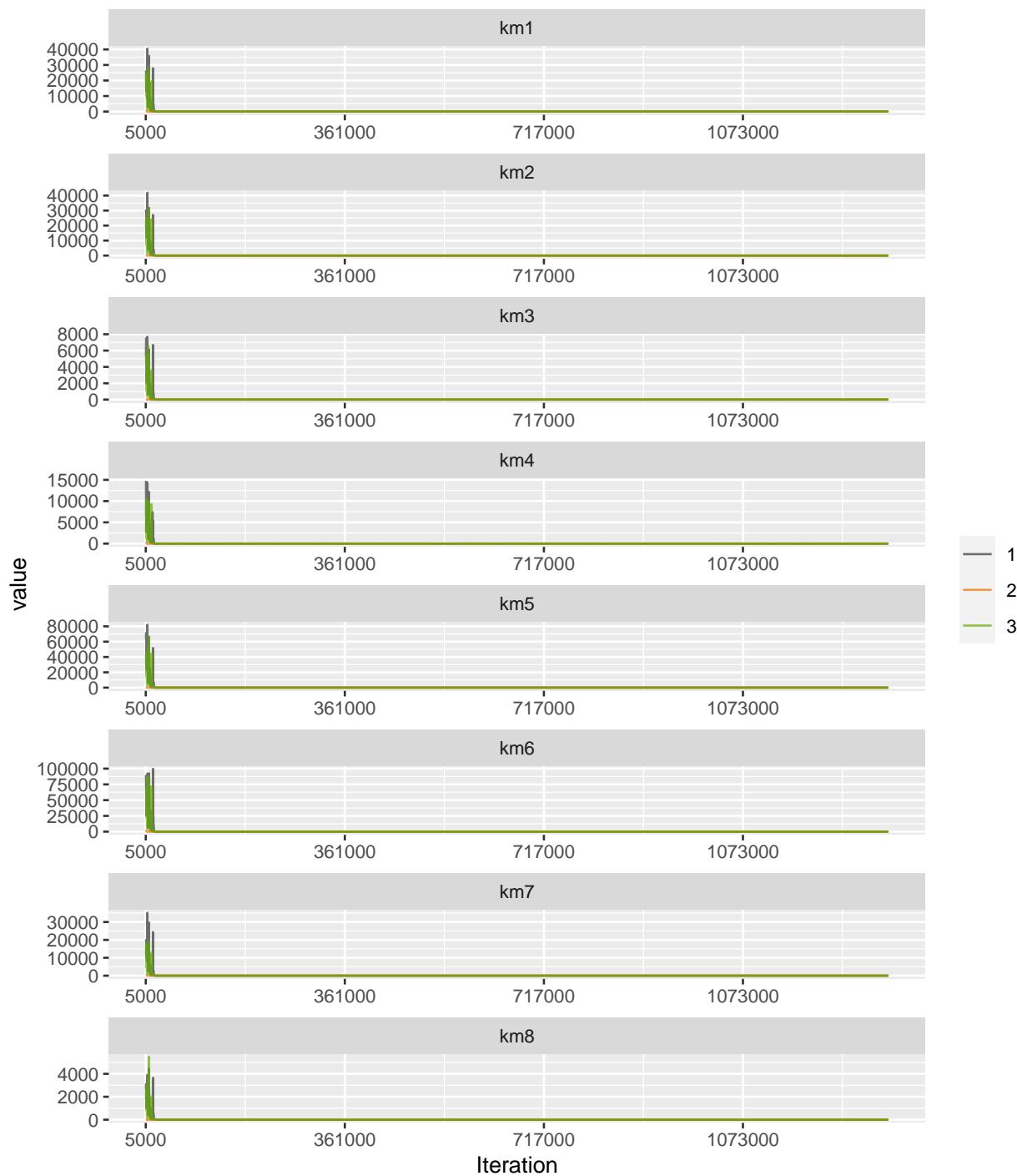
This criteria, denoted DIC, is a penalized deviance statistics accounting for the number of parameters for use in model comparison for a same dataset (e.g., with or without  $k_{ee}$ ). Sub-models with lower DIC values will be preferred.

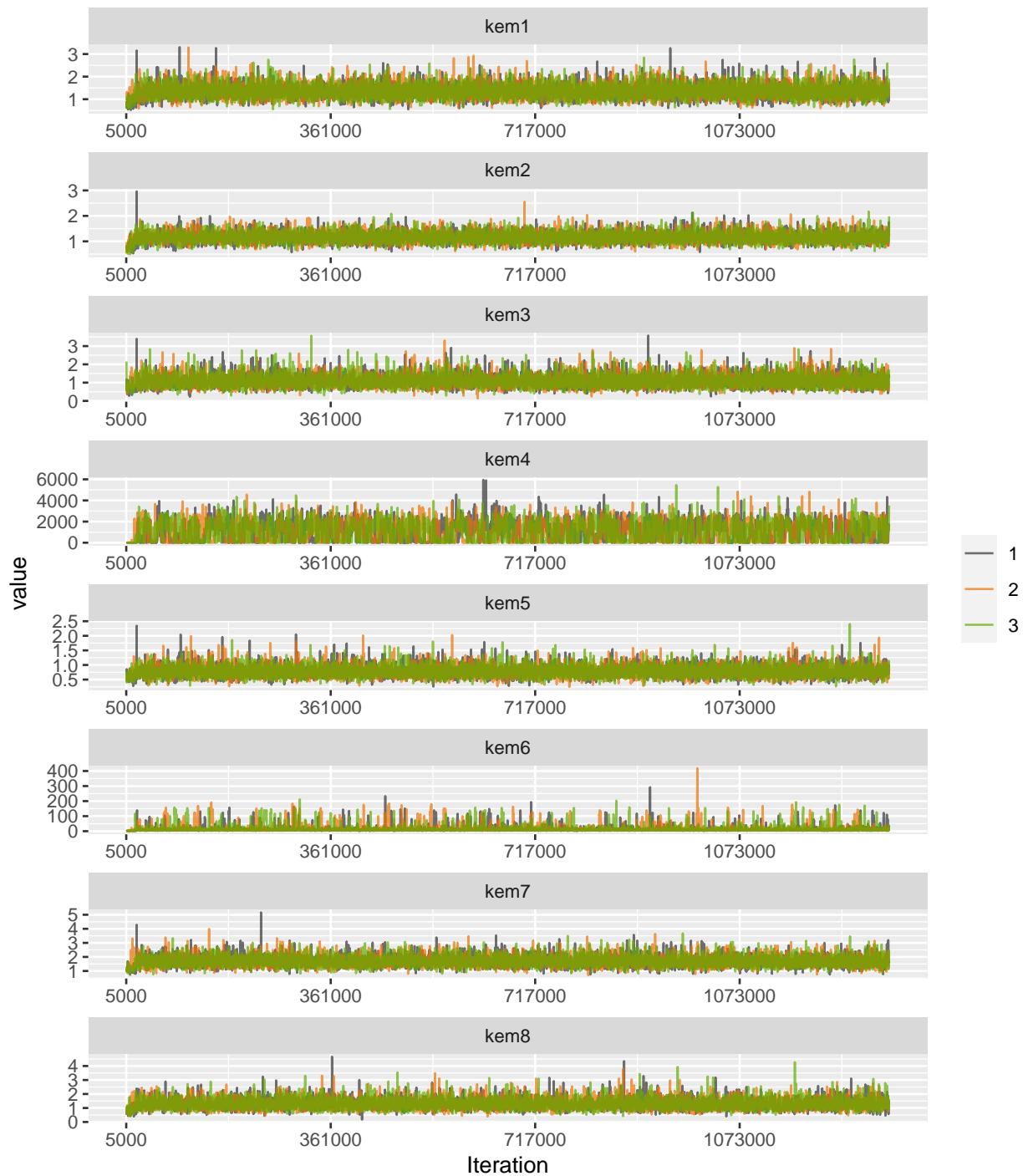
DIC = 2115.476

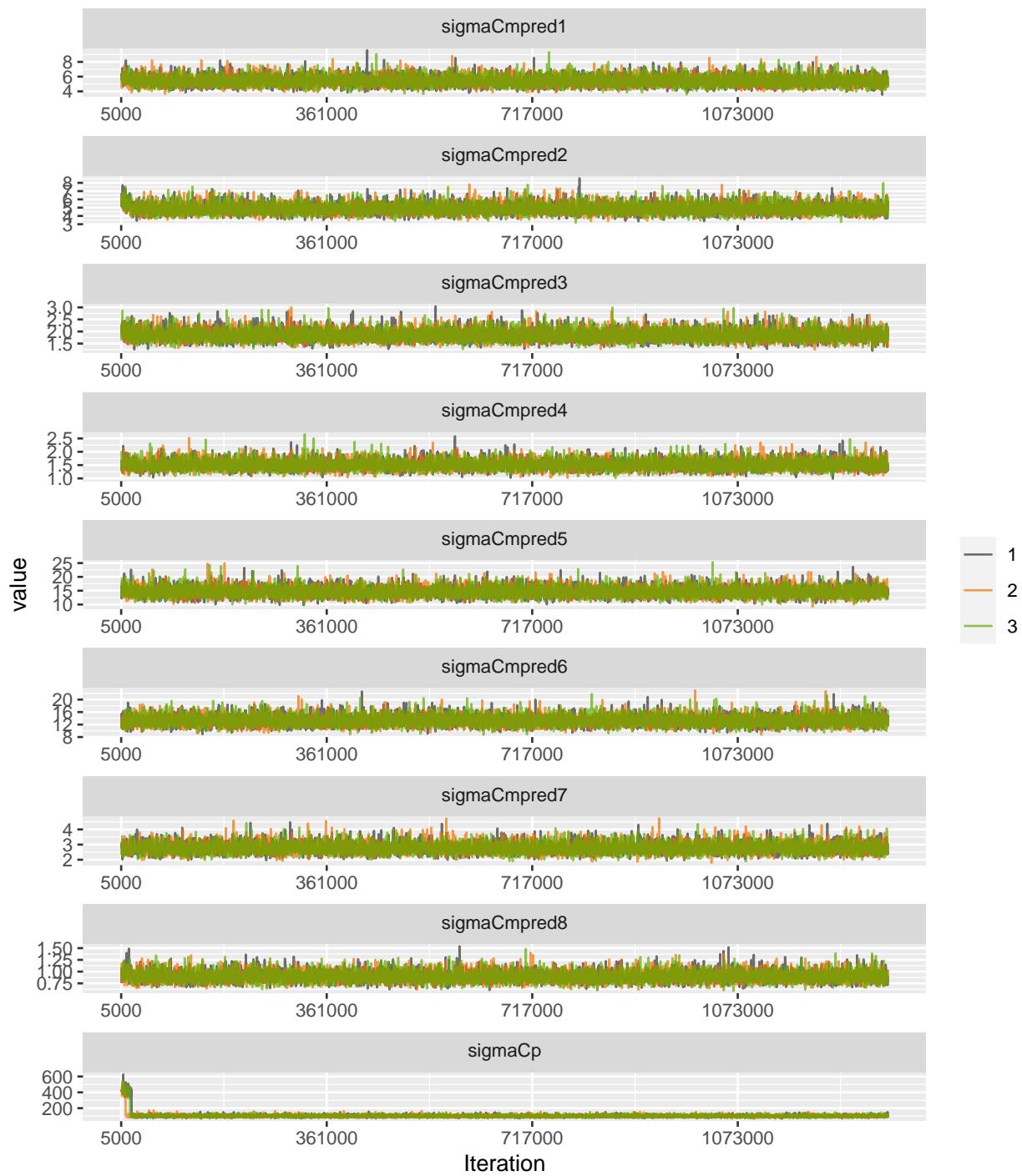
### Traces of MCMC iterations

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	replicate	concm1	concm2	concm3	concm4	concm5	concm6	concm7	concm8
0.00	0.5	0.0000	1	0.0000	0.0000000	0.0000	0.0000	0.0000	0.0000000	0.0000	0.0000
0.02	0.5	155.4897	1	0.0000	0.0000000	0.0000	0.0000	0.0000	0.0000000	0.0000	0.0000
0.02	0.5	150.7777	2	0.0000	0.0000000	0.0000	0.0000	0.0000	0.0000000	0.0000	0.0000
0.06	0.5	376.0054	1	0.0000	0.0000000	0.0000	0.0000	0.0000	2.5677764	0.0000	0.0000
0.06	0.5	395.7959	2	0.0000	0.0000000	0.0000	0.0000	0.0000	4.0492751	0.0013	0.0000
0.10	0.5	565.4192	1	0.0000	0.4615385	0.0000	0.0731	0.0000	9.5819036	0.9216	0.0000
0.10	0.5	662.4798	2	0.0000	0.1538462	0.0000	0.1096	0.0000	12.841046	10.8466	0.0000
0.23	0.5	617.2152	1	2.6841	1.6923077	0.0000	0.0731	3.3466	24.4987480	1.6955	0.0000
0.23	0.5	726.5367	2	0.0000	2.2307692	0.0254	0.2071	8.4859	27.165291	21.8733	0.1126
0.40	0.5	683.1399	1	4.9385	6.0769231	0.0384	2.9111	12.8252	27.763145	7.54148	0.0000
0.40	0.5	693.5064	2	7.5658	10.4615385	1.0699	4.4580	17.5683	44.552691	10.80282	0.4197
0.73	0.5	790.4844	1	21.0286	18.6153846	1.0229	8.7089	35.5365	27.4741105	14.8043	1.1685
0.73	0.5	786.7148	2	12.3962	22.4615385	2.7703	5.4080	39.4897	64.906797	21.6509	1.6024
1.00	0.5	787.5820	2	23.0692	25.6923075	7.4536	2.0950	85.7217	40.0242666	15.8374	4.2737
1.04	0.5	569.8766	1	15.9928	21.4615385	2.7839	0.5968	33.1496	37.2601935	12.4510	4.8947
1.04	0.5	567.9918	2	39.1565	18.6153846	3.9733	0.6128	39.2780	52.667315	20.1077	2.7251
1.08	0.5	348.3991	1	39.1565	36.2307692	8.1360	2.3386	52.3185	23.3350335	15.0285	2.5233
1.08	0.5	344.6294	2	27.3605	40.7692308	8.8642	0.5968	59.0379	17.8034870	11.3104	5.3212
1.17	0.5	295.6001	1	28.8636	29.3076923	9.2895	1.7296	41.2464	63.5353489	10.2437	3.3239
1.17	0.5	285.2360	2	17.8709	33.7692308	9.9136	1.1693	111.4042	17.905963	117.1275	3.7503
1.29	0.5	238.0866	1	9.0255	28.1538462	9.7755	0.7795	47.9599	14.0566942	11.6439	1.8653
1.29	0.5	216.4113	2	21.2508	13.6153846	5.2859	0.2680	62.7807	10.9946212	10.7603	1.5735
1.46	0.5	205.9915	1	15.7300	23.0000000	1.2689	2.2655	52.2986	8.5299391	9.5105	0.4441
1.46	0.5	165.4729	2	3.8266	6.6923077	NA	0.6821	27.3987	26.0111595	1.8907	2.9204
1.75	0.5	184.2385	1	14.2327	15.7692308	3.2727	0.2923	38.0562	6.2647995	6.2004	3.0781
1.75	0.5	139.9479	2	11.3908	13.4615385	2.9087	0.1340	36.2776	11.9932610	5.2065	1.5145
2.08	0.5	126.6669	1	7.8026	8.6153846	1.1503	0.5481	21.2408	8.2484775	10.1790	0.7146
2.08	0.5	117.2428	2	1.9581	2.4615385	0.1067	0.3898	7.8021	31.8536894	2.0439	0.4154
2.71	0.5	89.7408	1	7.1679	8.8461538	1.4323	0.2680	11.1310	14.8812946	1.8655	0.6859
2.71	0.5	92.5680	2	0.8942	2.0000000	0.0731	0.1462	25.3606	4.1157377	0.3932	0.0051
3.13	0.5	46.2810	1	5.7790	7.6923077	0.6090	0.8648	27.1183	5.2128350	4.3355	0.7689
3.13	0.5	42.5114	2	2.8836	4.6153846	1.9924	0.0122	22.3759	11.6328173	13.1576	0.1181
3.96	0.5	77.1548	1	0.6428	0.1538462	0.0788	0.0122	7.5122	6.1222913	1.0671	0.0075
3.96	0.5	8.3494	2	0.1604	1.1538462	0.0181	0.0000	0.7908	18.0733562	0.0364	0.0075
4.96	0.5	35.4221	1	1.1388	2.6923077	0.3018	0.5116	18.3294	15.2341649	1.9968	0.6452
4.96	0.5	23.1684	2	0.3882	0.1538462	0.0227	0.0122	0.3481	4.7645986	0.2300	0.0093
6.00	0.5	20.9973	1	0.4024	0.3076923	0.0152	0.0122	7.6097	3.9008934	0.0000	0.1160
6.00	0.5	3.0916	2	0.0000	0.3076923	0.0000	0.0487	0.2961	0.7408266	0.2761	0.0487