DEBtox Research

Ring test results for BYOM

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Contents

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1 Background

Full details of the GUTS ring test are provided in the e-book [1]. Here, I will only present the results for the BYOM platform, including both likelihood-based and Bayesian intervals. The data sets and the exposure profiles are provided in an Excel file that can be downloaded from http://www.debtox.info/book_guts.html.

These calculations have been updated, so they may differ slightly from the ones used in the book chapter. Most profound difference is in the confidence intervals for the likelihood-based predictions (LCx and LPx). The joint confidence region was calculated using the critical value from the χ^2 distribution with as degrees of freedom the number of free parameters. While this is a correct way to make such a confidence region, this is not the set that needs to be propagated to obtain the 95% confidence interval on model predictions. It turns out that we need to use a smaller set (using the χ^2 distribution with $v = 1$). In this document, the corrected results are given, which are also more in line with the Bayesian CIs. This issue will be explained in an update of the GUTS e-book.

Smaller differences will occur as I decided to use linear interpolation for time-varying exposures (for calibration in data set B, and for the LP10 calculations) as this allows the use of analytical solutions for scaled damage. In the first ring test, BYOM was using cubic-hermite splining for the time-varying exposures (along with the ODE version of the model).

Note that also for data set A an LP10 calculation is made, as data set C is a bit peculiar (no background mortality and fast kinetics for SD). The LP10 calculations for data set A may therefore provide a better test for software performance.

Likelihood-based intervals. Profile likelihood for individual parameters (automated procedure with variable step size), 10 sub-optimisations used at each evaluation point (plus a 'detailed' run). Likelihood-region for joint intervals. Sampling (LHS) continued in bursts until at least 5000 samples were found within the joint region within the cut-off for $\chi^2_{v=1,\alpha=0.05}$. For forward predictions, this region needs to be propagated, and the min-max of all the curves is used for the CI on the predictions. Because the sample consists of a limited number of points, I decided to take this region a little bit wider to build in some safety (0.4 extra on top of the $\chi^2_{v=1,\alpha=0.05}$). For the LC50 predictions, the full propagation sample was used. For the LP10 predictions (which are more time consuming), a sub sample was used (all sets within plus or minus 0.4 from the $\chi^2_{v=1,\alpha=0.05}$).

Bayesian intervals. MCMC sampling using the Matlab slice sampler. 10000 samples kept, after 200 burn-in samples and thinning of 20 (keeping one in every 20 samples). Slice sampling was done on log scale (but priors were uniform on normal scale). Thinning and log-scale were needed to keep auto-correlation in the sample within reasonable bounds. For forward predictions, the 0.025 and 0.975 quantiles of all curves resulting from propagating the sample were used for the CIs.

Calculations. All calculations were done with BYOM (version 4.2b, with a small update that will go into the next version) using the package for GUTS (version 2.2, with

updates that will go into v. 2.3), using the reduced model from the 'standard' directory. This calculates scaled damage analytically for constant and time-varying exposure. Time varying exposure profiles (for calibration in data set B, and predictions in data sets A and C) are interpolated linearly, which allows analytical solutions for scaled damage for all ring-test cases. For IT, survival follows analytically from damage, but for SD a numerical integration over time was used.

2 Data set A

2.1 Data set A: constant exposure SD

LP10 calculation was added for this data set, using the same exposure profiles as for data set C.

Table 1: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

Param.	Optimum	byom guts A SD Likelihood CI	minloglik = 96.45 Bayes CI
k_d	0.711	0.497 - 0.981	0.466 - 0.967
m_w	2.89	2.29 - 3.36	2.17 - 3.30
h_b	0.00802	0.00132 - 0.0253	0.00104 - 0.0229
b_w	0.619	0.414 - 1.09	0.396 - 1.02
F_s	1.00	fixed	fixed
β	Inf	fixed	fixed
4-d LC50	3.95	3.60 - 4.27	3.56 - 4.23
30-d LC50	2.93	2.32 - 3.41	2.23 - 3.34
LP10 FOCUS	2.69e+03	2.25e+03 - 3.04e+03	2.15e+03 - 2.98e+03
LP10 Monitor	2.48e+04	2.19e+04 - 2.75e+04	2.13e+04 - 2.71e+04

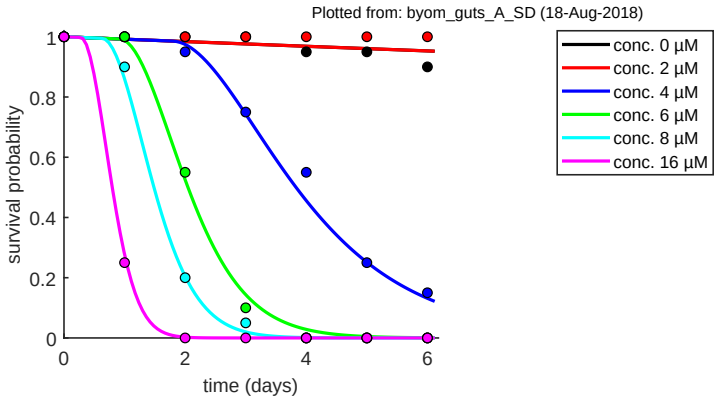

Figure 1: Fit for data set byom guts A SD.

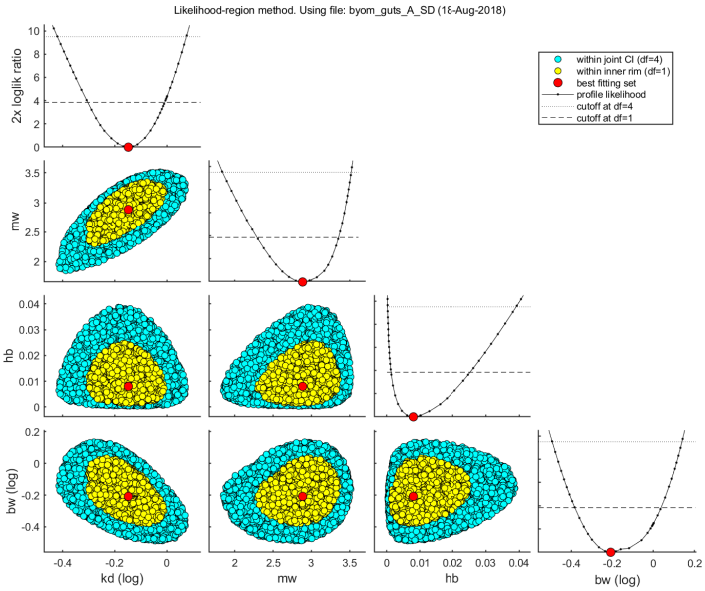

Figure 2: Likelihood region for data set byom guts A SD.

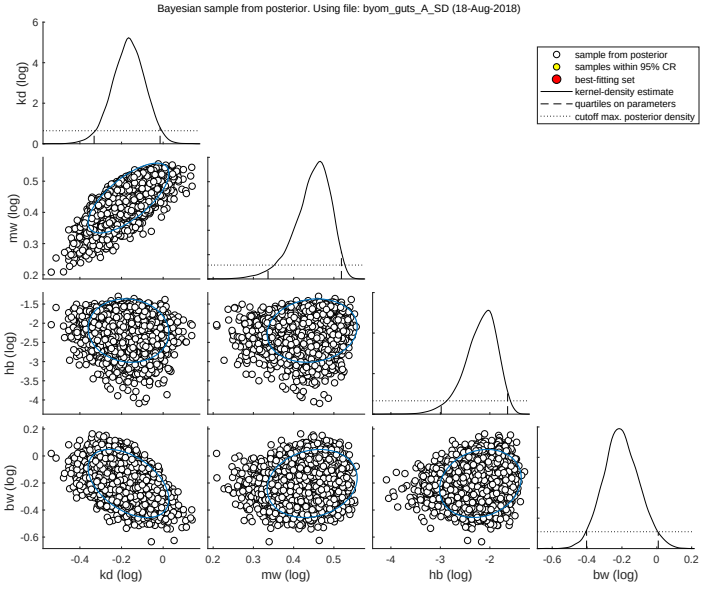

Figure 3: Bayesian sample from posterior for data set byom guts A SD.

2.2 Data set A: constant exposure IT

LP10 calculation was added for this data set, using the same exposure profiles as for data set C. Note that for the spread of the threshold distribution two parameters are provided (F_s and β). Only one parameter was fitted (F_s) and the other can simply be calculated from it.

Table 2: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

		byom guts A IT	minloglik = 116.02
Param.	Optimum	Likelihood CI	Bayes CI
k_d	0.793	0.558 - 1.11	0.525 - 1.08
m_w	5.42	4.48 - 6.41	4.36 - 6.40
h_b	0.0262	0.0102 - 0.0518	0.00884 - 0.0500
b_w	1.00	fixed	fixed
F_s	2.03	1.64 - 2.69	1.69 - 2.91
β	5.19	3.70 - 7.38	3.43 - 6.98
4-d LC50	5.66	4.91 - 6.55	4.85 - 6.52
30-d LC50	5.42	4.46 - 6.44	4.38 - 6.38
LP10 FOCUS	3.08e+03	2.32e+03 - 3.83e+03	2.21e+03 - 3.69e+03
LP10 Monitor	2.68e+04	2.13e+04 - 3.24e+04	2.05e+04 - 3.14e+04

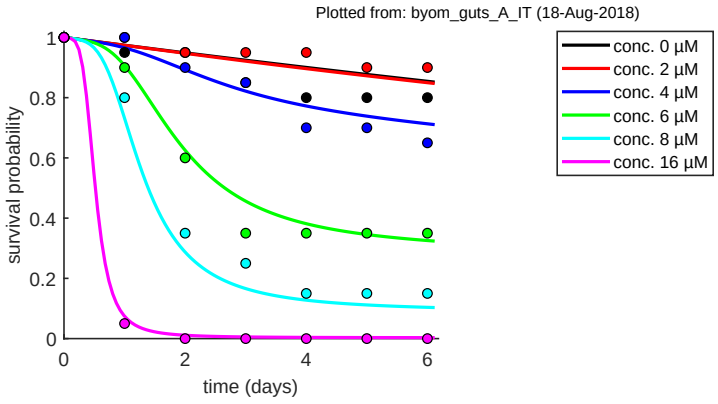

Figure 4: Fit for data set byom guts A IT.

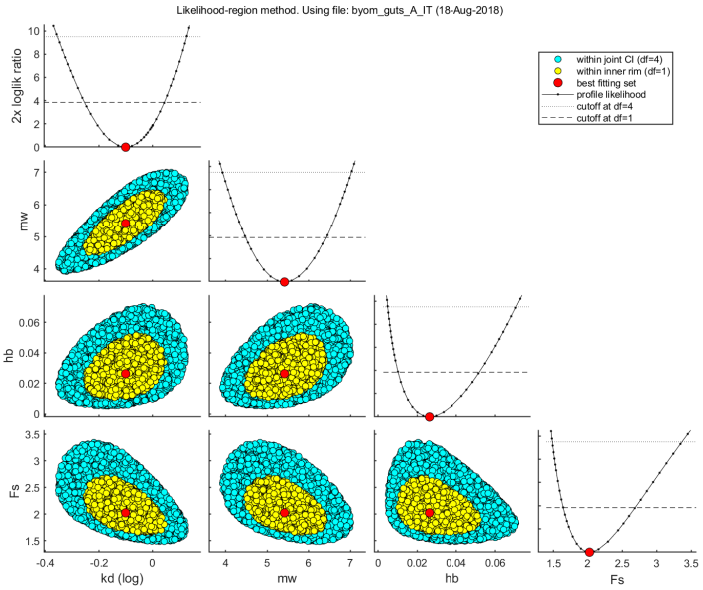

Figure 5: Likelihood region for data set byom guts A IT.

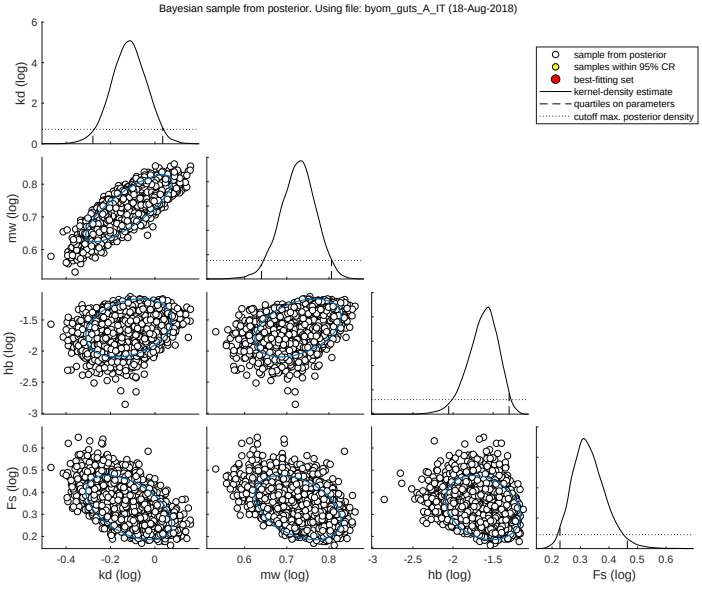

Figure 6: Bayesian sample from posterior for data set byom guts A IT.

3 Data set B

3.1 Data set B: Constant exposure SD

Table 3: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

Param.	Optimum	byom guts B const SD Likelihood CI	minloglik = 123.83 Bayes CI
k_d	2.16	1.60 - 3.33	1.59 - 3.69
m_w	17.1	15.9 - 17.7	15.5 - 18.9
h_b	0.0275	0.0133 - 0.0495	0.0128 - 0.0508
b_w	0.132	0.0863 - 0.196	0.0776 - 0.191
F_s	1.00	fixed	fixed
β	Inf	fixed	fixed
4-d LC50	19.1	18.2 - 20.0	18.1 - 20.8
30-d LC50	17.2	16.0 - 17.9	15.7 - 19.1

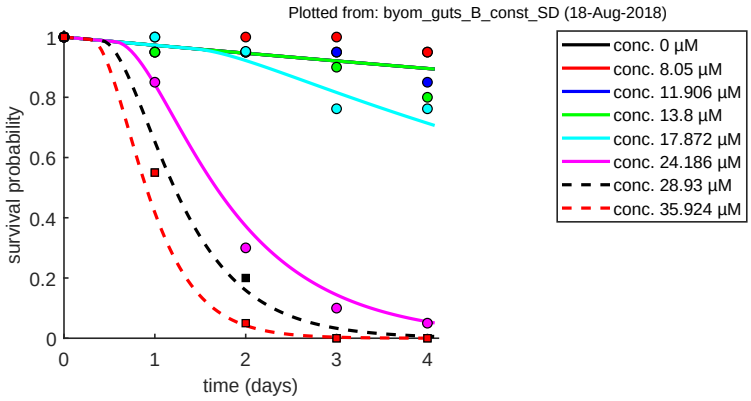

Figure 7: Fit for data set byom guts B const SD.

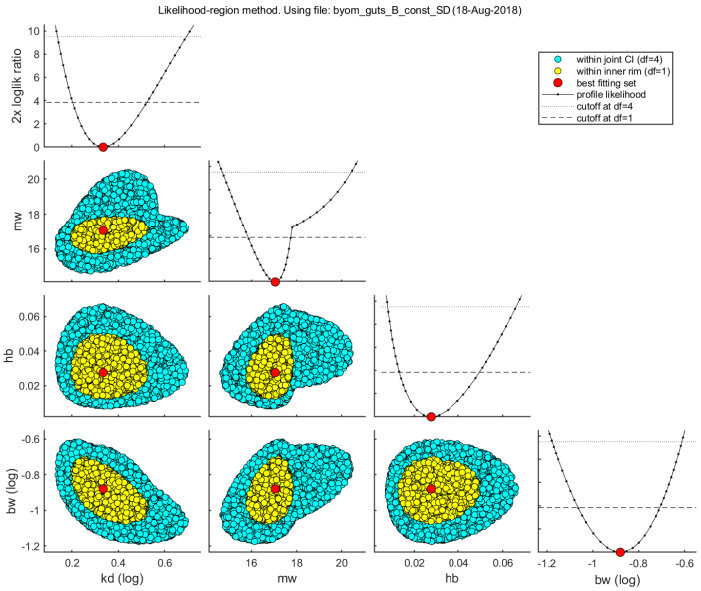

Figure 8: Likelihood region for data set byom guts B const SD.

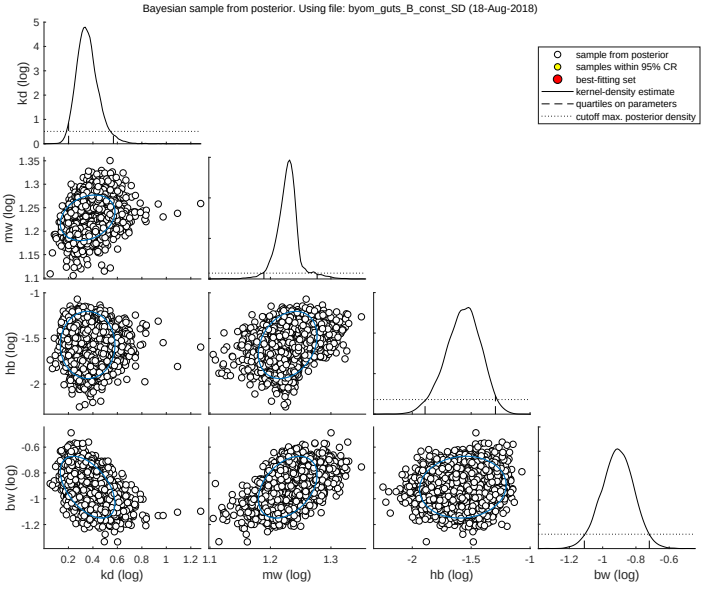

Figure 9: Bayesian sample from posterior for data set byom guts B const SD.

3.2 Data set B: Constant exposure IT

Bayesian analysis still showed too much autocorrelation, so thinning was increased to 25. Note that for the spread of the threshold distribution two parameters are provided (F_s and β). Only one parameter was fitted (F_s) and the other can simply be calculated from it.

Table 4: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

Param.	Optimum	byom guts B const IT Likelihood CI	minloglik = 127.75 Bayes CI
k_d	0.750	0.555 - 0.977	0.517 - 0.948
m_w	18.1	15.4 - 20.6	14.9 - 20.3
h_b	0.0186	0.00489 - 0.0415	0.00238 - 0.0391
b_w	1.00	fixed	fixed
F_s	1.68	1.48 - 2.02	1.51 - 2.18
β	7.04	5.20 - 9.42	4.71 - 8.95
4-d LC50	19.0	17.1 - 21.2	16.9 - 20.9
30-d LC50	18.1	15.4 - 20.6	14.9 - 20.3

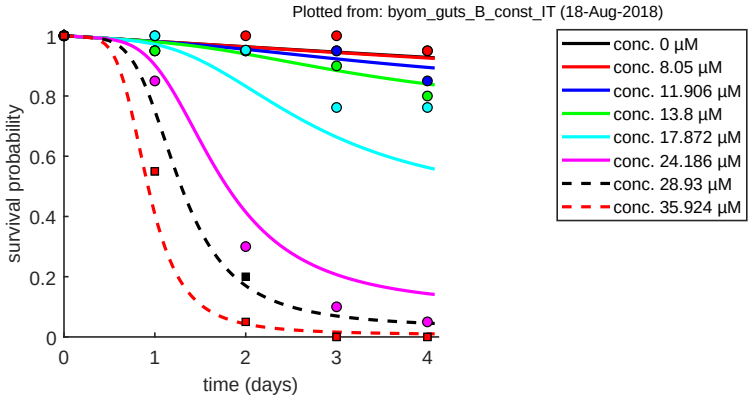

Figure 10: Fit for data set byom guts B const IT.

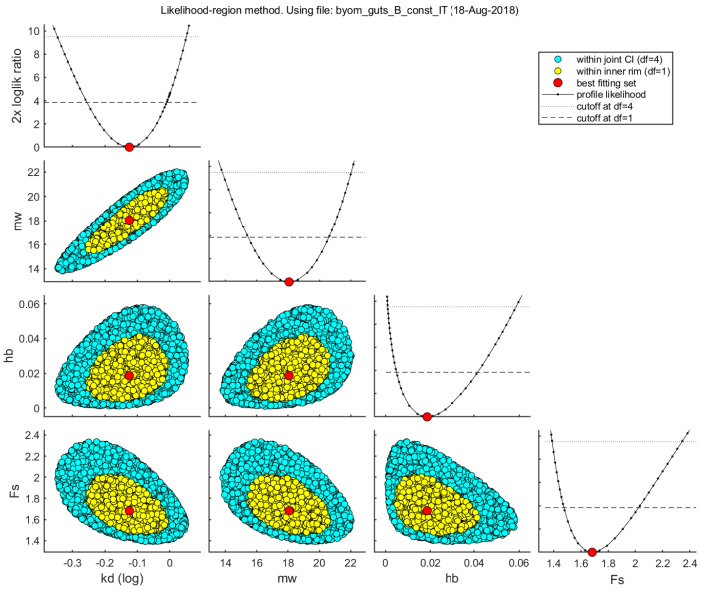

Figure 11: Likelihood region for data set byom guts B const IT.

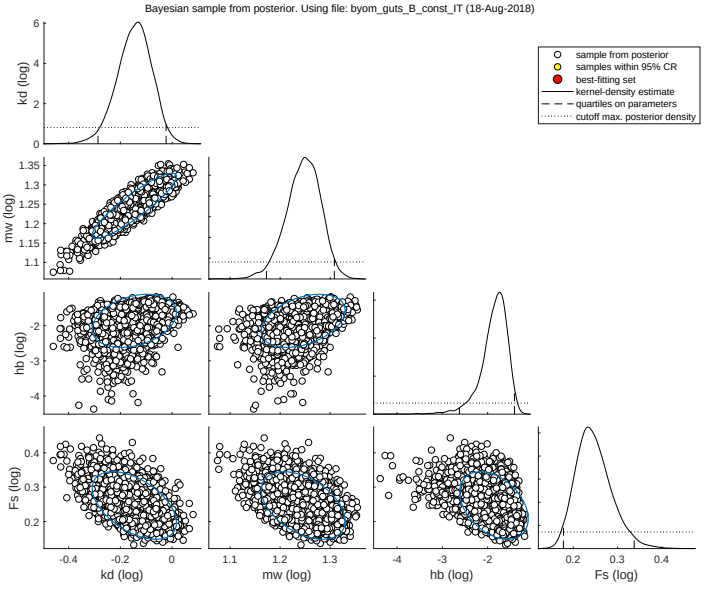

Figure 12: Bayesian sample from posterior for data set byom guts B const IT.

3.3 Data set B: Pulsed exposure SD

Only likelihood-region method used as the slice sample for the Bayesian calculations ran into problems (extreme autocorrelation and poor sampling). Note that the CI for k_d runs into the maximum value allowed in this analysis (20). This indicates that this analysis runs into 'fast kinetics' (the CI may well extend all the way up to infinity). For a different maximum value, CIs may turn out different (especially for Bayesian analyses). Also note that in the plot for the likelihood region, the light blue points do not indicate the 95% joint confidence region but a smaller region (this was done to decrease calculation time). The exposure scenario is also shown in plot below.

Table 5: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

		byom guts B timevar SD	minloglik = 328.15
Param.	Optimum	Likelihood CI	Bayes CI
k_d	2.17	1.38 - 20.0	NaN - NaN
m_w	22.3	18.8 - 26.6	NaN - NaN
h_b	0.0239	0.0175 - 0.0320	NaN - NaN
b_w	0.469	0.0520 - 1.46	NaN - NaN
F_s	1.00	fixed	fixed
β	Inf	fixed	fixed
4-d LC50	23.0	19.7 - 28.3	NaN - NaN
30-d LC50	22.3	18.7 - 26.8	NaN - NaN

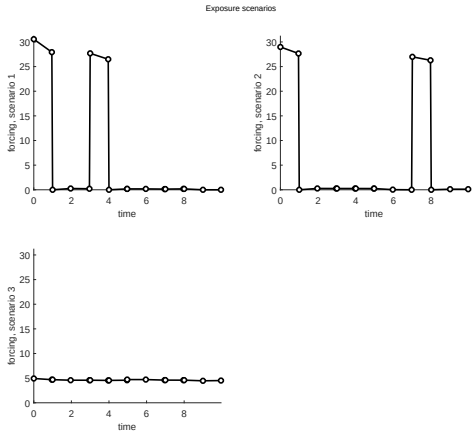

Figure 13: Exposure scenario for data set byom guts B timevar SD, with linear interpolation.

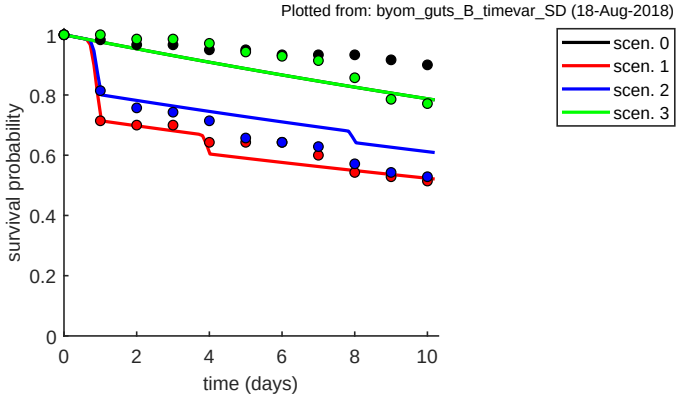

Figure 14: Fit for data set byom guts B timevar SD.

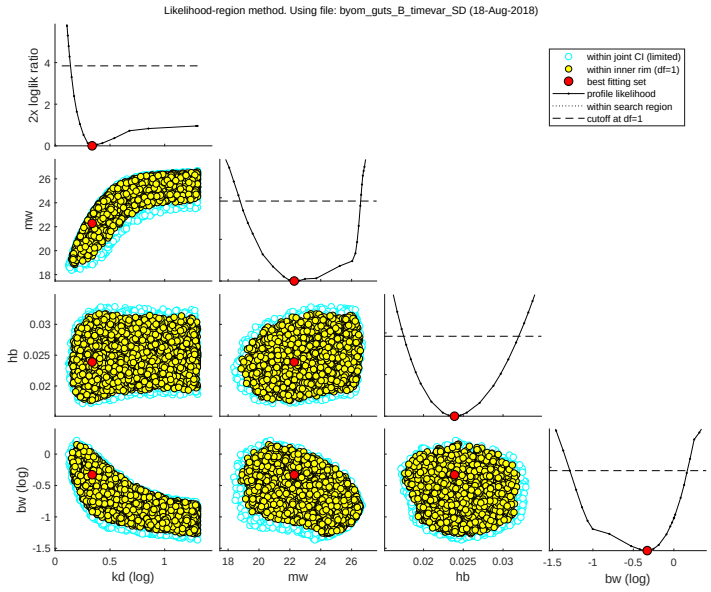

Figure 15: Likelihood region for data set byom guts B timevar SD.

3.4 Data set B: Pulsed exposure IT

Only likelihood-region method used as the slice sample for the Bayesian calculations ran into problems (extreme autocorrelation and poor sampling), likely related to the oddly-shaped parameter space. Note that for the spread of the threshold distribution two parameters are provided (F_s and β). Only one parameter was fitted (F_s) and the other can simply be calculated from it. Note that the CI for k_d runs into the maximum value allowed in this analysis (20). This indicates that this analysis runs into 'fast kinetics' (the CI may well extend all the way up to infinity). For a different maximum value, CIs may turn out different (especially for Bayesian analyses). Also note that in the plot for the likelihood region, the light blue points do not indicate the 95% joint confidence region but a smaller region (this was done to decrease calculation time). The exposure scenario is the same as shown in Section 3.3.

Table 6: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

		byom guts B timevar IT	minloglik = 330.54
Param.	Optimum	Likelihood CI	Bayes CI
k_d	0.923	0.516 - 20.0	NaN - NaN
m_w	18.0	16.5 - 31.7	NaN - NaN
h_b	0.0263	0.0198 - 0.0341	NaN - NaN
b_w	1.00	fixed	fixed
F_s	1.18	1.07 - 5.08	NaN - NaN
β	21.6	2.25 - 54.4	NaN - NaN
4-d LC50	18.4	17.6 - 34.6	NaN - NaN
30-d LC50	18.0	16.3 - 34.6	NaN - NaN

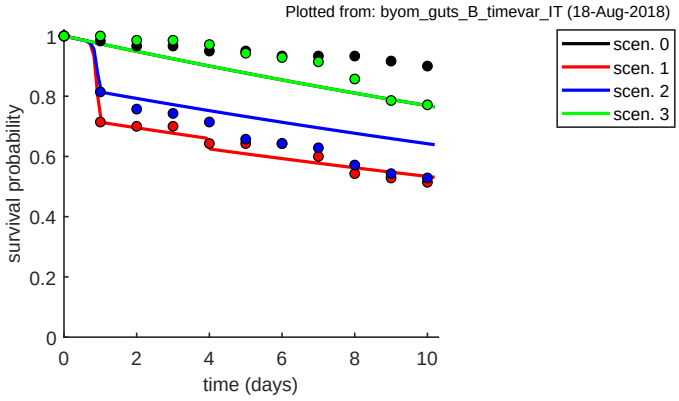

Figure 16: Fit for data set byom guts B timevar IT.

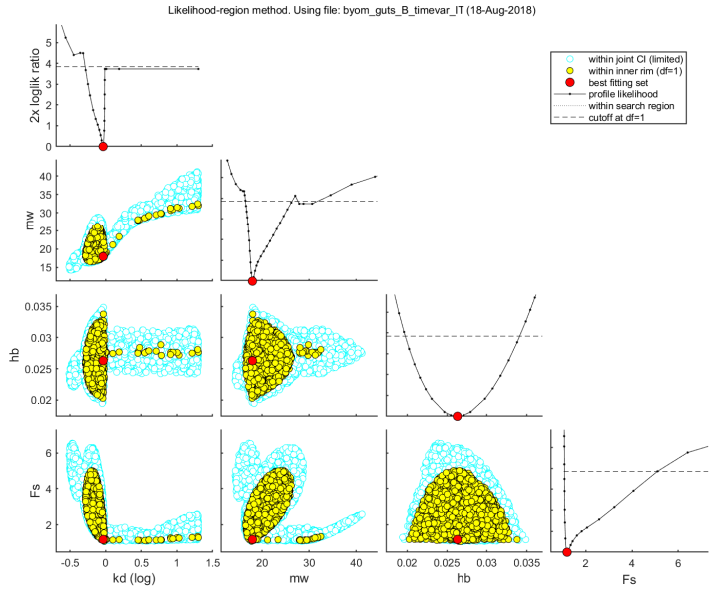

Figure 17: Likelihood region for data set byom guts B timevar IT.

3.5 Data set B: both sets SD

Both data sets are fitted simultaneously with the same set of parameters. The exposure scenario is the same as shown in Section 3.3.

Table 7: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

		byom guts B both SD	minloglik = 459.62
Param.	Optimum	Likelihood CI	Bayes CI
k_d	1.67	1.40 - 2.15	1.41 - 2.36
m_w	17.0	15.9 - 20.0	15.8 - 20.5
h_b	0.0235	0.0176 - 0.0305	0.0176 - 0.0315
b_w	0.136	0.0861 - 0.217	0.0811 - 0.238
F_s	1.00	fixed	fixed
β	Inf	fixed	fixed
4-d LC50	19.4	18.5 - 21.8	18.6 - 22.1
30-d LC50	17.2	16.2 - 20.4	16.1 - 20.6

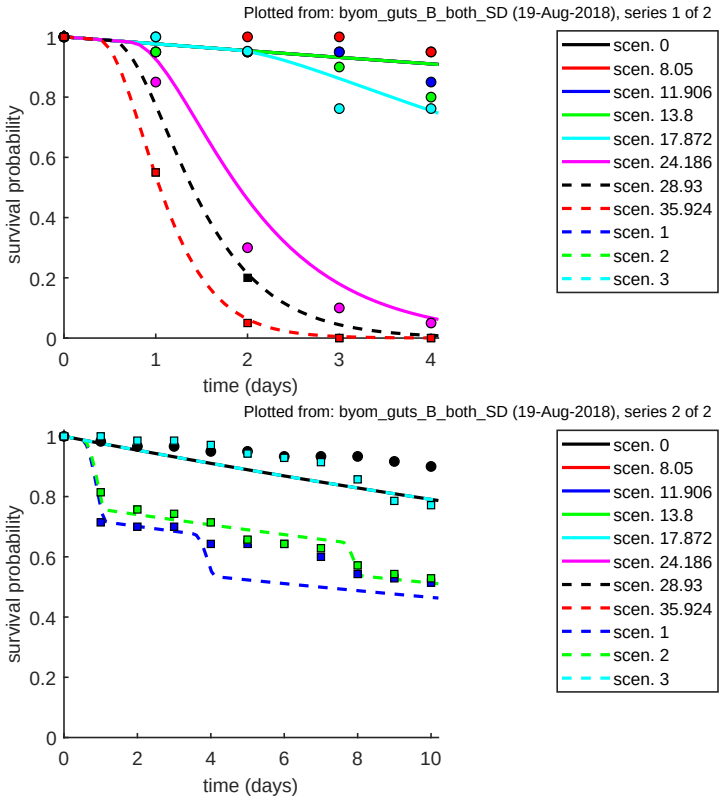

Figure 18: Fit for data set byom guts B both SD.

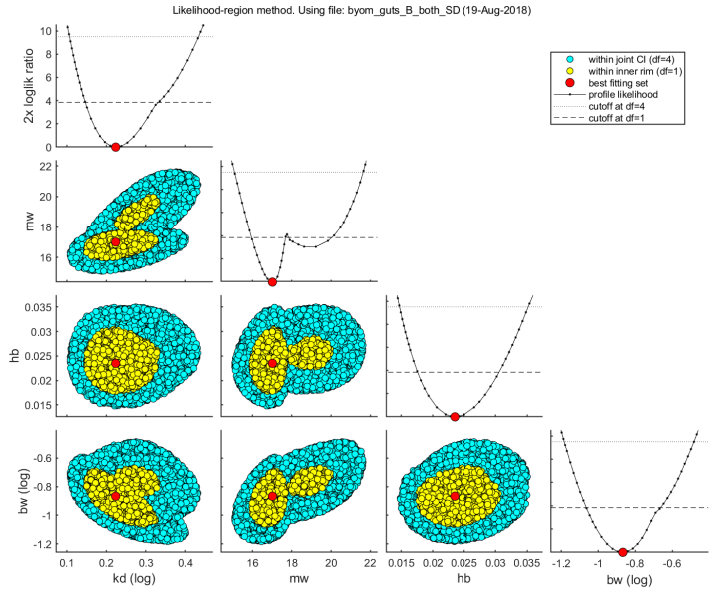

Figure 19: Likelihood region for data set byom guts B both SD.

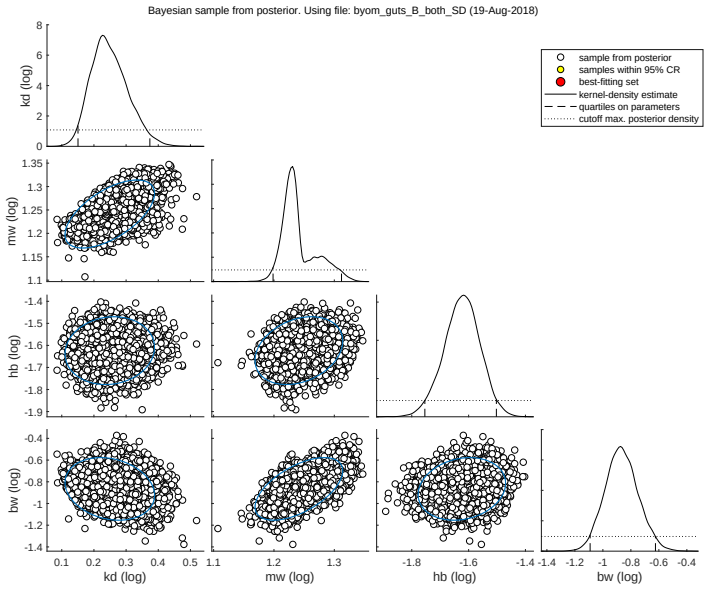

Figure 20: Bayesian sample from posterior for data set byom guts B both SD.

3.6 Data set B: both sets IT

Both data sets are fitted simultaneously with the same set of parameters. The exposure scenario is the same as shown in Section 3.3. Note that for the spread of the threshold distribution two parameters are provided (F_s and β). Only one parameter was fitted (F_s) and the other can simply be calculated from it.

Table 8: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

		byom guts B both IT	minloglik = 459.07
Param.	Optimum	Likelihood CI	Bayes CI
k_d	0.804	0.659 - 0.937	0.635 - 0.928
m_w	18.6	16.8 - 20.3	16.6 - 20.3
h_b	0.0255	0.0194 - 0.0327	0.0190 - 0.0326
b_w	1.00	fixed	fixed
F_s	1.65	1.48 - 1.93	1.50 - 2.02
β	7.29	5.57 - 9.34	5.23 - 8.97
4-d LC50	19.4	18.0 - 20.9	18.0 - 20.9
30-d LC50	18.6	16.8 - 20.4	16.7 - 20.3

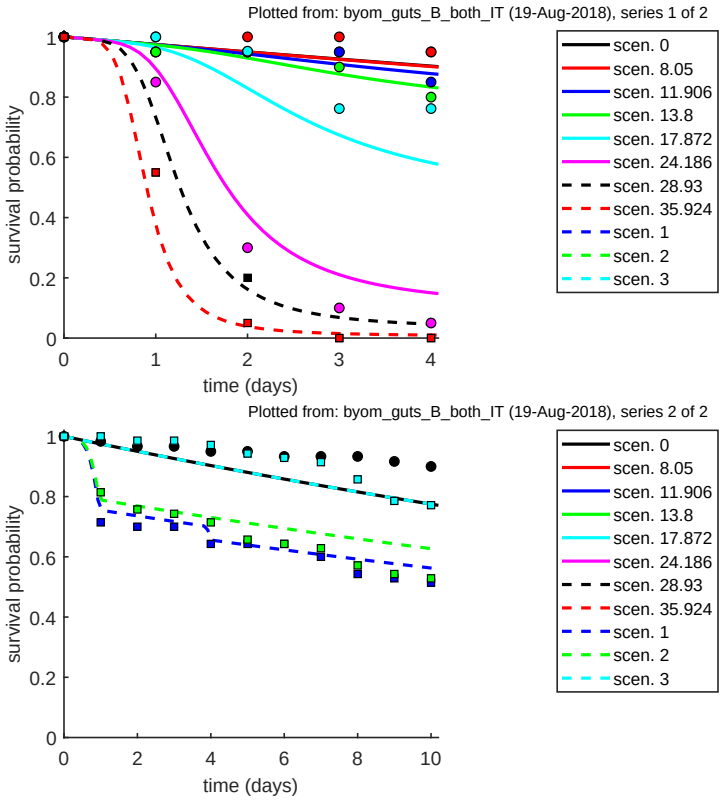

Figure 21: Fit for data set byom guts B both IT.

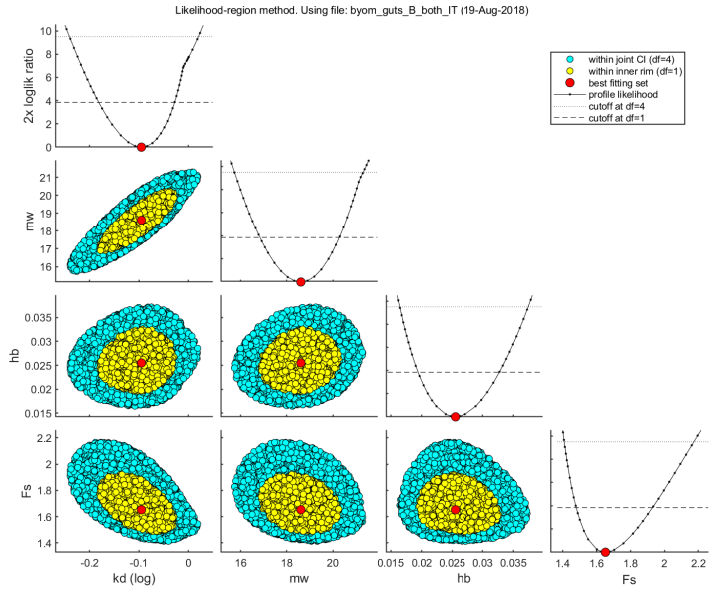

Figure 22: Likelihood region for data set byom guts B both IT.

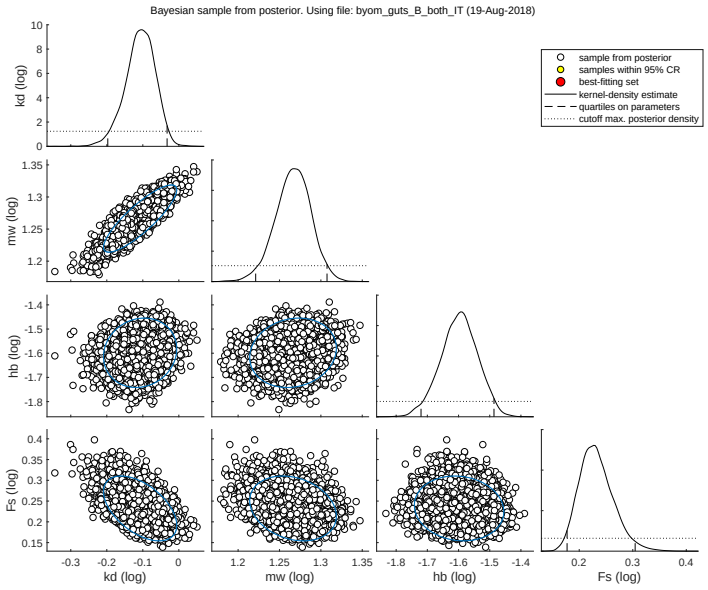

Figure 23: Bayesian sample from posterior for data set byom guts B both IT.

4 Data set C

4.1 Data set C: Constant exposure SD

Note that not only the CI for k_d, but also its optimum value runs into the maximum value allowed in this analysis (20). This indicates that this analysis runs into 'fast kinetics' (the CI may well extend all the way up to infinity). The choice for where to cut off k_d will influence the CIs (especially for Bayesian analyses).

Table 9: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

Param.	Optimum	byom guts C SD Likelihood CI	minloglik = 63.64 Bayes CI
k_d	20.0	6.47 - 20.0	5.38 - 20.0
m_w	6.14	4.87 - 6.61	4.51 - 6.54
h_b	0.000	fixed	fixed
b_w	0.0846	0.0530 - 0.124	0.0480 - 0.119
F_s	1.00	fixed	fixed
β	Inf	fixed	fixed
4-d LC50	8.25	7.44 - 9.18	7.31 - 9.13
30-d LC50	6.41	5.19 - 6.87	4.93 - 6.76
LP10 FOCUS	4.61e+03	3.74e+03 - 4.93e+03	3.57e+03 - 4.89e+03
LP10 Monitor	4.27e+04	3.66e+04 - 4.59e+04	3.52e+04 - 4.52e+04

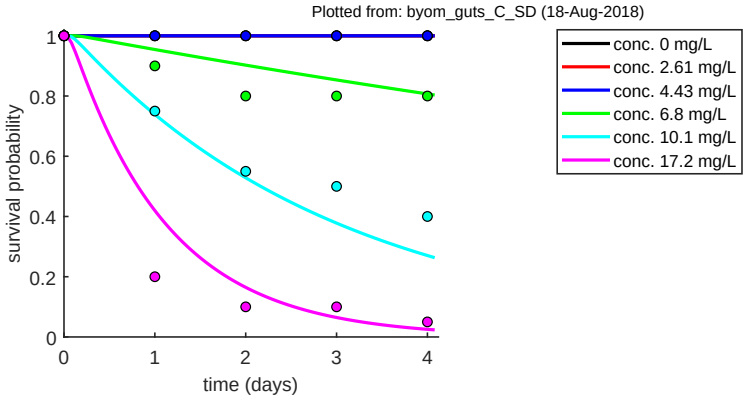

Figure 24: Fit for data set byom guts C SD.

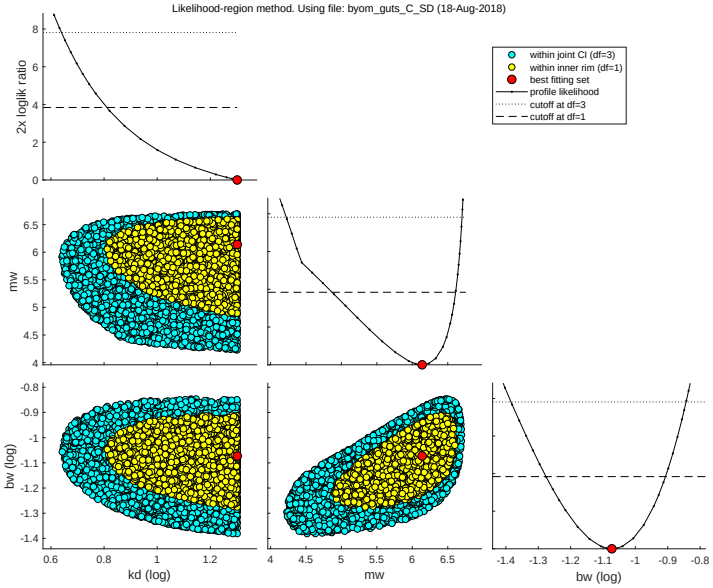

Figure 25: Likelihood region for data set byom guts C SD.

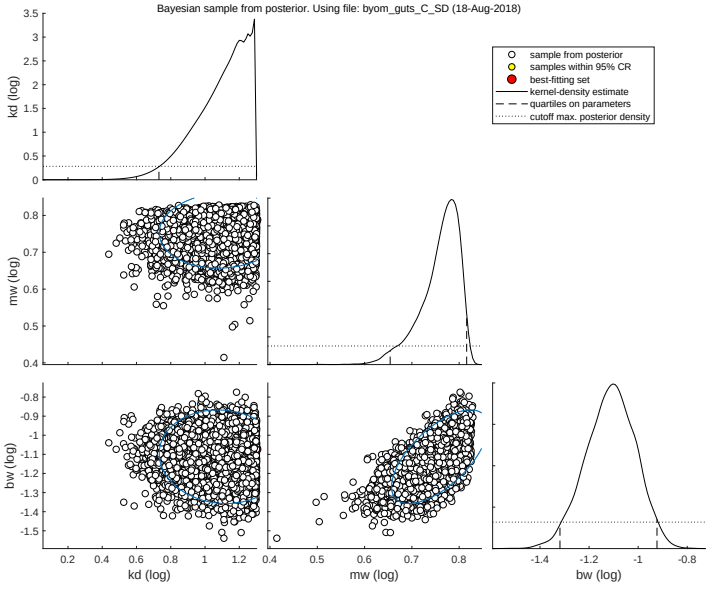

Figure 26: Bayesian sample from posterior for data set byom guts C SD.

4.2 Data set C: Constant exposure IT

Note that for the spread of the threshold distribution two parameters are provided (F_s and β). Only one parameter was fitted (F_s) and the other can simply be calculated from it.

Table 10: Parameter fits with likelihood-based and Bayesian CIs. Predictions for 4-day and 30-day LC50 also shown with CIs.

Param.	Optimum	byom guts C IT Likelihood CI	minloglik = 61.29 Bayes CI
k_d	1.26	0.907 - 1.68	0.859 - 1.67
m_w	9.34	8.08 - 10.7	7.96 - 10.9
h_b	0.000	fixed	fixed
b_w	1.00	fixed	fixed
F_s	2.25	1.80 - 3.23	1.86 - 3.71
β	4.51	3.12 - 6.25	2.79 - 5.92
4-d LC50	9.40	8.17 - 10.8	8.13 - 10.9
30-d LC50	9.34	8.04 - 10.8	7.98 - 10.8
LP10 FOCUS	4.56e+03	3.58e+03 - 5.44e+03	3.37e+03 - 5.30e+03
LP10 Monitor	3.78e+04	2.99e+04 - 4.47e+04	2.83e+04 - 4.37e+04

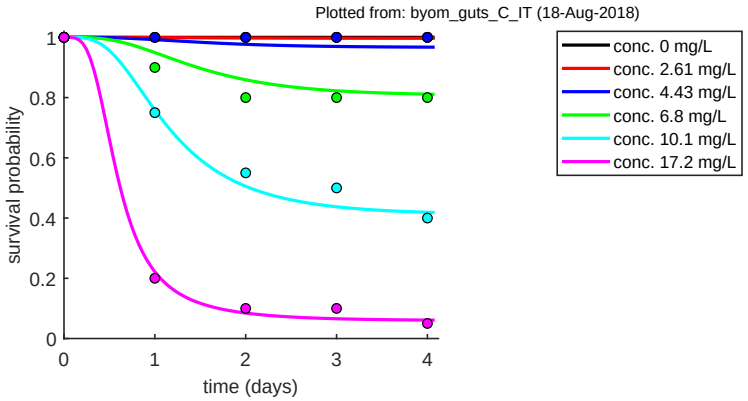

Figure 27: Fit for data set byom guts C IT.

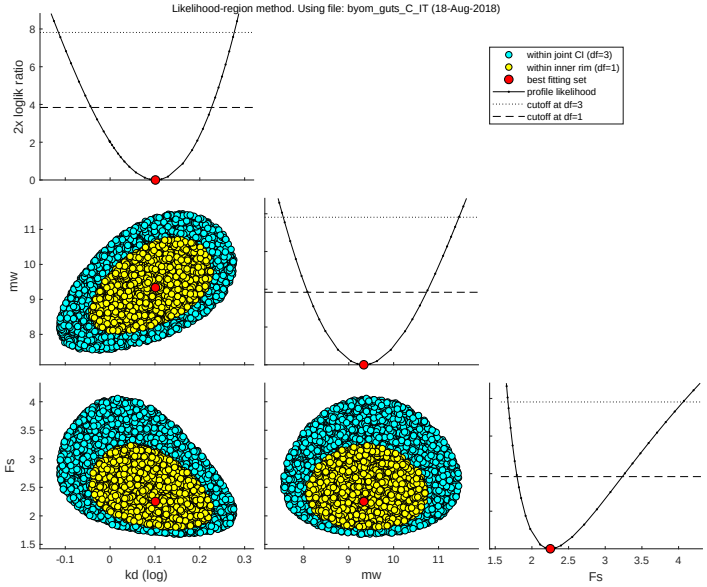

Figure 28: Likelihood region for data set byom guts C IT.

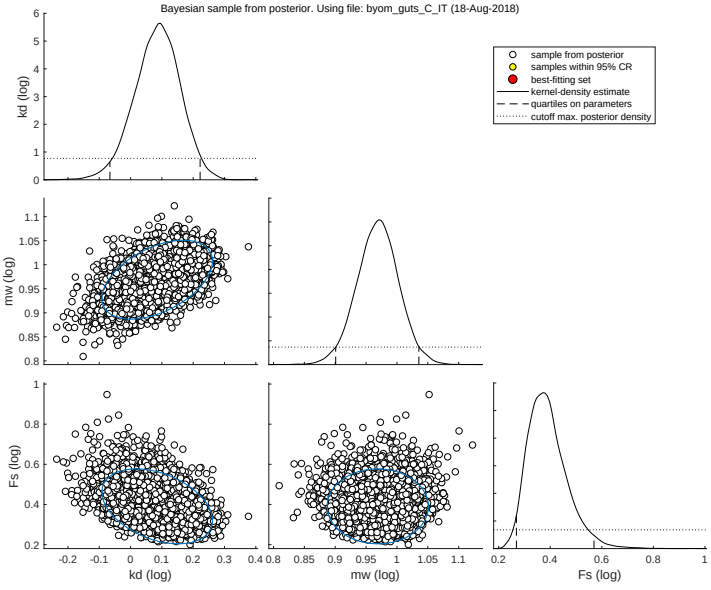

Figure 29: Bayesian sample from posterior for data set byom guts C IT.

References

[1] T. Jager and R. Ashauer. *Modelling survival under chemical stress. A comprehensive guide to the GUTS framework*. Toxicodynamics Ltd., York, UK. Available from Leanpub, https://leanpub.com/guts_book, Version 1.0, 18 January 2018, 2018.