Testing hierarchical pathway kinetics with residue data on dimethenamid and dimethenamid-P

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Contents

Introduction

The purpose of this document is to test demonstrate how nonlinear hierarchical models (NLHM) based on the parent degradation models SFO, FOMC, DFOP and HS, with parallel formation of two or more metabolites can be fitted with the mkin package.

It was assembled in the course of work package 1.2 of Project Number 173340 (Application of nonlinear hierarchical models to the kinetic evaluation of chemical degradation data) of the German Environment Agency carried out in 2022 and 2023.

The mkin package is used in version 1.2.9, which is currently under development. It contains the test data, and the functions used in the evaluations. The `saemix` package is used as a backend for fitting the NLHM, but is also loaded to make the convergence plot function available.

This document is processed with the `knitr` package, which also provides the `kable` function that is used to improve the display of tabular data in R markdown documents. For parallel processing, the `parallel` package is used.

```
library(mkin)
library(knitr)
library(saemix)
library(parallel)
n_cores <- detectCores()

# We need to start a new cluster after defining a compiled model that is
# saved as a DLL to the user directory, therefore we define a function
# This is used again after defining the pathway model
start_cluster <- function(n_cores) {
  if (Sys.info()["sysname"] == "Windows") {
    ret <- makePSOCKcluster(n_cores)
  } else {
    ret <- makeForkCluster(n_cores)
  }
  return(ret)
}
```

Data

The test data are available in the mkin package as an object of class `mkindsg` (mkin dataset group) under the identifier `dimethenamid_2018`. The following preprocessing steps are done in this document.

- The data available for the enantiomer dimethenamid-P (DMTAP) are renamed to have the same substance name as the data for the racemic mixture dimethenamid (DMTA). The reason for this is that no difference between their degradation behaviour was identified in the EU risk assessment.
- Unnecessary columns are discarded
- The observation times of each dataset are multiplied with the corresponding normalisation factor also available in the dataset, in order to make it possible to describe all datasets with a single set of parameters that are independent of temperature
- Finally, datasets observed in the same soil (`Elliot 1` and `Elliot 2`) are combined, resulting in dimethenamid (DMTA) data from six soils.

The following commented R code performs this preprocessing.

```
# Apply a function to each of the seven datasets in the mkindsg object to create a list
dmta_ds <- lapply(1:7, function(i) {
  ds_i <- dimethenamid_2018$ds[[i]]$data                    # Get a dataset
  ds_i[ds_i$name == "DMTAP", "name"] <-  "DMTA"             # Rename DMTAP to DMTA
  ds_i <- subset(ds_i, select = c("name", "time", "value")) # Select data
  ds_i$time <- ds_i$time * dimethenamid_2018$f_time_norm[i]  # Normalise time
  ds_i                                                      # Return the dataset
})

# Use dataset titles as names for the list elements
names(dmta_ds) <- sapply(dimethenamid_2018$ds, function(ds) ds$title)

# Combine data for Elliot soil to obtain a named list with six elements
dmta_ds[["Elliot"]] <- rbind(dmta_ds[["Elliot 1"]], dmta_ds[["Elliot 2"]]) #
dmta_ds[["Elliot 1"]] <- NULL
dmta_ds[["Elliot 2"]] <- NULL
```

The following tables show the 6 datasets.

```
for (ds_name in names(dmta_ds)) {
  print(
    kable(mkin_long_to_wide(dmta_ds[[ds_name]]),
      caption = paste("Dataset", ds_name),
      booktabs = TRUE, row.names = FALSE))
    cat("\n\\clearpage\n")
}
```

Table 1: Dataset Calke

time	DMTA	M23	M27	M31
0	95.8	NA	NA	NA
0	98.7	NA	NA	NA
14	60.5	4.1	1.5	2.0
30	39.1	5.3	2.4	2.1
59	15.2	6.0	3.2	2.2
120	4.8	4.3	3.8	1.8
120	4.6	4.1	3.7	2.1

Table 2: Dataset Borstel

time	DMTA	M23	M27	M31
0.000000	100.5	NA	NA	NA
0.000000	99.6	NA	NA	NA
1.941295	91.9	0.4	NA	NA
1.941295	91.3	0.5	0.3	0.1
6.794534	81.8	1.2	0.8	1.0
6.794534	82.1	1.3	0.9	0.9
13.589067	69.1	2.8	1.4	2.0
13.589067	68.0	2.0	1.4	2.5
27.178135	51.4	2.9	2.7	4.3
27.178135	51.4	4.9	2.6	3.2
56.297565	27.6	12.2	4.4	4.3
56.297565	26.8	12.2	4.7	4.8
86.387643	15.7	12.2	5.4	5.0
86.387643	15.3	12.0	5.2	5.1
115.507073	7.9	10.4	5.4	4.3
115.507073	8.1	11.6	5.4	4.4

Table 3: Dataset Flaach

time	DMTA	M23	M27	M31
0.0000000	96.5	NA	NA	NA
0.0000000	96.8	NA	NA	NA
0.0000000	97.0	NA	NA	NA
0.6233856	82.9	0.7	1.1	0.3
0.6233856	86.7	0.7	1.1	0.3
0.6233856	87.4	0.2	0.3	0.1
1.8701567	72.8	2.2	2.6	0.7
1.8701567	69.9	1.8	2.4	0.6
1.8701567	71.9	1.6	2.3	0.7
4.3636989	51.4	4.1	5.0	1.3
4.3636989	52.9	4.2	5.9	1.2
4.3636989	48.6	4.2	4.8	1.4
8.7273979	28.5	7.5	8.5	2.4
8.7273979	27.3	7.1	8.5	2.1
8.7273979	27.5	7.5	8.3	2.3
13.0910968	14.8	8.4	9.3	3.3
13.0910968	13.4	6.8	8.7	2.4
13.0910968	14.4	8.0	9.1	2.6
17.4547957	7.7	7.2	8.6	4.0
17.4547957	7.3	7.2	8.5	3.6
17.4547957	8.1	6.9	8.9	3.3
26.1821936	2.0	4.9	8.1	2.1
26.1821936	1.5	4.3	7.7	1.7
26.1821936	1.9	4.5	7.4	1.8
34.9095915	1.3	3.8	5.9	1.6
34.9095915	1.0	3.1	6.0	1.6
34.9095915	1.1	3.1	5.9	1.4
43.6369893	0.9	2.7	5.6	1.8
43.6369893	0.7	2.3	5.2	1.5
43.6369893	0.7	2.1	5.6	1.3
52.3643872	0.6	1.6	4.3	1.2
52.3643872	0.4	1.1	3.7	0.9
52.3643872	0.5	1.3	3.9	1.1
74.8062674	0.4	0.4	2.5	0.5
74.8062674	0.3	0.4	2.4	0.5
74.8062674	0.3	0.3	2.2	0.3

Table 4: Dataset BBA 2.2

time	DMTA	M23	M27	M31
0.0000000	98.09	NA	NA	NA
0.0000000	98.77	NA	NA	NA
0.7678922	93.52	0.36	0.42	0.36
0.7678922	92.03	0.40	0.47	0.33
2.3036765	88.39	1.03	0.71	0.55
2.3036765	87.18	1.07	0.82	0.64
5.3752452	69.38	3.60	2.19	1.94
5.3752452	71.06	3.66	2.28	1.62
10.7504904	45.21	6.97	5.45	4.22
10.7504904	46.81	7.22	5.19	4.37
16.1257355	30.54	8.65	8.81	6.31
16.1257355	30.07	8.38	7.93	6.85
21.5009807	21.60	9.10	10.25	7.05
21.5009807	20.41	8.63	10.77	6.84
32.2514711	9.10	7.63	10.89	6.53
32.2514711	9.70	8.01	10.85	7.11
43.0019614	6.58	6.40	10.41	6.06
43.0019614	6.31	6.35	10.35	6.05
53.7524518	3.47	5.35	9.92	5.50
53.7524518	3.52	5.06	9.42	5.07
64.5029421	3.40	5.14	9.15	4.94
64.5029421	3.67	5.91	9.25	4.39
91.3791680	1.62	3.35	7.14	3.64
91.3791680	1.62	2.87	7.13	3.55

Table 5: Dataset BBA 2.3

time	DMTA	M23	M27	M31
0.0000000	99.33	NA	NA	NA
0.0000000	97.44	NA	NA	NA
0.6733938	93.73	0.18	0.50	0.47
0.6733938	93.77	0.18	0.83	0.34
2.0201814	87.84	0.52	1.25	1.00
2.0201814	89.82	0.43	1.09	0.89
4.7137565	71.61	1.19	3.28	3.58
4.7137565	71.42	1.11	3.24	3.41
9.4275131	45.60	2.26	7.17	8.74
9.4275131	45.42	1.99	7.91	8.28
14.1412696	31.12	2.81	10.15	9.67
14.1412696	31.68	2.83	9.55	8.95
18.8550262	23.20	3.39	12.09	10.34
18.8550262	24.13	3.56	11.89	10.00
28.2825393	9.43	3.49	13.32	7.89
28.2825393	9.82	3.28	12.05	8.13
37.7100523	7.08	2.80	10.04	5.06
37.7100523	8.64	2.97	10.78	5.54
47.1375654	4.41	2.42	9.32	3.79
47.1375654	4.78	2.51	9.62	4.11
56.5650785	4.92	2.22	8.00	3.11
56.5650785	5.08	1.95	8.45	2.98
80.1338612	2.13	1.28	5.71	1.78
80.1338612	2.23	0.99	3.33	1.55

Table 6: Dataset Elliot

time	DMTA	M23	M27	M31
0.000000	97.5	NA	NA	NA
0.000000	100.7	NA	NA	NA
1.228478	86.4	NA	NA	NA
1.228478	88.5	NA	NA	1.5
3.685435	69.8	2.8	2.3	5.0
3.685435	77.1	1.7	2.1	2.4
8.599349	59.0	4.3	4.0	4.3
8.599349	54.2	5.8	3.4	5.0
17.198697	31.3	8.2	6.6	8.0
17.198697	33.5	5.2	6.9	7.7
25.798046	19.6	5.1	8.2	7.8
25.798046	20.9	6.1	8.8	6.5
34.397395	13.3	6.0	9.7	8.0
34.397395	15.8	6.0	8.8	7.4
51.596092	6.7	5.0	8.3	6.9
51.596092	8.7	4.2	9.2	9.0
68.794789	8.8	3.9	9.3	5.5
68.794789	8.7	2.9	8.5	6.1
103.192184	6.0	1.9	8.6	6.1
103.192184	4.4	1.5	6.0	4.0
146.188928	3.3	2.0	5.6	3.1
146.188928	2.8	2.3	4.5	2.9
223.583066	1.4	1.2	4.1	1.8
223.583066	1.8	1.9	3.9	2.6
0.000000	93.4	NA	NA	NA
0.000000	103.2	NA	NA	NA
1.228478	89.2	NA	NA	1.3
1.228478	86.6	NA	NA	NA
3.685435	78.2	2.6	1.0	3.1
3.685435	78.1	2.4	2.6	2.3
8.599349	55.6	5.5	4.5	3.4
8.599349	53.0	5.6	4.6	4.3
17.198697	33.7	7.3	7.6	7.8
17.198697	33.2	6.5	6.7	8.7
25.798046	20.9	5.8	8.7	7.7
25.798046	19.9	7.7	7.6	6.5
34.397395	18.2	7.8	8.0	6.3
34.397395	12.7	7.3	8.6	8.7
51.596092	7.8	7.0	7.4	5.7
51.596092	9.0	6.3	7.2	4.2
68.794789	11.4	4.3	10.3	3.2
68.794789	9.0	3.8	9.4	4.2
103.192184	3.9	2.6	6.5	3.8
103.192184	4.4	2.8	6.9	4.0
146.188928	2.6	1.6	4.6	4.5
146.188928	3.4	1.1	4.5	4.5
223.583066	2.0	1.4	4.3	3.8
223.583066	1.7	1.3	4.2	2.3

Separate evaluations

As a first step to obtain suitable starting parameters for the NLHM fits, we do separate fits of several variants of the pathway model used previously (Ranke et al. 2021), varying the kinetic model for the parent compound. Because the SFORB model often provides faster convergence than the DFOP model, and can sometimes be fitted where the DFOP model results in errors, it is included in the set of parent models tested here.

```
if (!dir.exists("dmta_dlls")) dir.create("dmta_dlls")
m_sfo_path_1 <- mkinmod(
  DMTA = mkinsub("SFO", c("M23", "M27", "M31")),
  M23 = mkinsub("SFO"),
  M27 = mkinsub("SFO"),
  M31 = mkinsub("SFO", "M27", sink = FALSE),
  name = "m_sfo_path", dll_dir = "dmta_dlls",
  unload = TRUE, overwrite = TRUE,
  quiet = TRUE
)
m_fomc_path_1 <- mkinmod(
  DMTA = mkinsub("FOMC", c("M23", "M27", "M31")),
  M23 = mkinsub("SFO"),
  M27 = mkinsub("SFO"),
  M31 = mkinsub("SFO", "M27", sink = FALSE),
  name = "m_fomc_path", dll_dir = "dmta_dlls",
  unload = TRUE, overwrite = TRUE,
  quiet = TRUE
)
m_dfop_path_1 <- mkinmod(
  DMTA = mkinsub("DFOP", c("M23", "M27", "M31")),
  M23 = mkinsub("SFO"),
  M27 = mkinsub("SFO"),
  M31 = mkinsub("SFO", "M27", sink = FALSE),
  name = "m_dfop_path", dll_dir = "dmta_dlls",
  unload = TRUE, overwrite = TRUE,
  quiet = TRUE
)
m_sforb_path_1 <- mkinmod(
  DMTA = mkinsub("SFORB", c("M23", "M27", "M31")),
  M23 = mkinsub("SFO"),
  M27 = mkinsub("SFO"),
  M31 = mkinsub("SFO", "M27", sink = FALSE),
  name = "m_sforb_path", dll_dir = "dmta_dlls",
  unload = TRUE, overwrite = TRUE,
  quiet = TRUE
)
m_hs_path_1 <- mkinmod(
  DMTA = mkinsub("HS", c("M23", "M27", "M31")),
  M23 = mkinsub("SFO"),
  M27 = mkinsub("SFO"),
  M31 = mkinsub("SFO", "M27", sink = FALSE),
  name = "m_hs_path", dll_dir = "dmta_dlls",
  unload = TRUE, overwrite = TRUE,
  quiet = TRUE
)
cl <- start_cluster(n_cores)

deg_mods_1 <- list(
  sfo_path_1 = m_sfo_path_1,
```

```
  fomc_path_1 = m_fomc_path_1,
  dfop_path_1 = m_dfop_path_1,
  sforb_path_1 = m_sforb_path_1,
  hs_path_1 = m_hs_path_1)

sep_1_const <- mmkin(
  deg_mods_1,
  dmta_ds,
  error_model = "const",
  quiet = TRUE)

status(sep_1_const) |> kable()
```

	Calke	Borstel	Flaach	BBA 2.2	BBA 2.3	Elliot
sfo_path_1	OK	OK	OK	OK	OK	OK
fomc_path_1	OK	OK	OK	OK	OK	OK
dfop_path_1	OK	OK	C	OK	OK	OK
sforb_path_1	OK	OK	C	OK	OK	OK
hs_path_1	C	C	C	C	C	C

All separate pathway fits with SFO or FOMC for the parent and constant variance converged (status OK). Most fits with DFOP or SFORB for the parent converged as well. The fits with HS for the parent did not converge with default settings.

```
sep_1_tc <- update(sep_1_const, error_model = "tc")
status(sep_1_tc) |> kable()
```

	Calke	Borstel	Flaach	BBA 2.2	BBA 2.3	Elliot
sfo_path_1	OK	OK	OK	OK	OK	OK
fomc_path_1	OK	OK	C	OK	OK	C
dfop_path_1	OK	C	OK	OK	OK	OK
sforb_path_1	OK	C	OK	OK	OK	OK
hs_path_1	C	C	C	C	C	OK

With the two-component error model, the set of fits with convergence problems is slightly different, with convergence problems appearing for different data sets when applying the DFOP and SFORB model and some additional convergence problems when using the FOMC model for the parent.

Hierarchichal model fits

The following code fits two sets of the corresponding hierarchical models to the data, one assuming constant variance, and one assuming two-component error.

```
saem_1 <- mhmkin(list(sep_1_const, sep_1_tc))
```

The run time for these fits was around two hours on five year old hardware. After a recent hardware upgrade these fits complete in less than twenty minutes.

```
status(saem_1) |> kable()
```

	const	tc
sfo_path_1	OK	OK
fomc_path_1	OK	OK
dfop_path_1	OK	OK
sforb_path_1	OK	OK
hs_path_1	OK	OK

According to the `status` function, all fits terminated successfully.

```
anova(saem_1) |> kable(digits = 1)
```

```
Warning in FUN(X[[i]], ...): Could not obtain log likelihood with 'is' method
for sforb_path_1 const
```

	npar	AIC	BIC	Lik
sfo_path_1 const	17	2291.8	2288.3	-1128.9
sfo_path_1 tc	18	2276.3	2272.5	-1120.1
fomc_path_1 const	19	2099.0	2095.0	-1030.5
fomc_path_1 tc	20	1939.6	1935.5	-949.8
dfop_path_1 const	21	2038.8	2034.4	-998.4
hs_path_1 const	21	2024.2	2019.8	-991.1
dfop_path_1 tc	22	1879.8	1875.2	-917.9
sforb_path_1 tc	22	1832.9	1828.3	-894.4
hs_path_1 tc	22	1831.4	1826.8	-893.7

When the goodness-of-fit of the models is compared, a warning is obtained, indicating that the likelihood of the pathway fit with SFORB for the parent compound and constant variance could not be calculated with importance sampling (method 'is'). As this is the default method on which all AIC and BIC comparisons are based, this variant is not included in the model comparison table. Comparing the goodness-of-fit of the remaining models, HS model model with two-component error provides the best fit. However, for batch experiments performed with constant conditions such as the experiments evaluated here, there is no reason to assume a discontinuity, so the SFORB model is preferable from a mechanistic viewpoint. In addition, the information criteria AIC and BIC are very similar for HS and SFORB. Therefore, the SFORB model is selected here for further refinements.

Parameter identifiability based on the Fisher Information Matrix

Using the `illparms` function, ill-defined statistical model parameters such as standard deviations of the degradation parameters in the population and error model parameters can be found.

```
illparms(saem_1) |> kable()
```

	const	tc
sfo_path_1		sd(DMTA_0)
fomc_path_1		sd(DMTA_0)
dfop_path_1		
sforb_path_1		sd(log_k_DMTA_bound_free)
hs_path_1		sd(log_tb)

When using constant variance, no ill-defined variance parameters are identified with the `illparms` function in any of the degradation models. When using the two-component error model, there is one ill-defined variance parameter in all variants except for the variant using DFOP for the parent compound.

For the selected combination of the SFORB pathway model with two-component error, the random effect for the rate constant from reversibly bound DMTA to the free DMTA (`k_DMTA_bound_free`) is not well-defined. Therefore, the fit is updated without assuming a random effect for this parameter.

```
saem_sforb_path_1_tc_reduced <- update(saem_1[["sforb_path_1", "tc"]],
  no_random_effect = "log_k_DMTA_bound_free")
illparms(saem_sforb_path_1_tc_reduced)
```

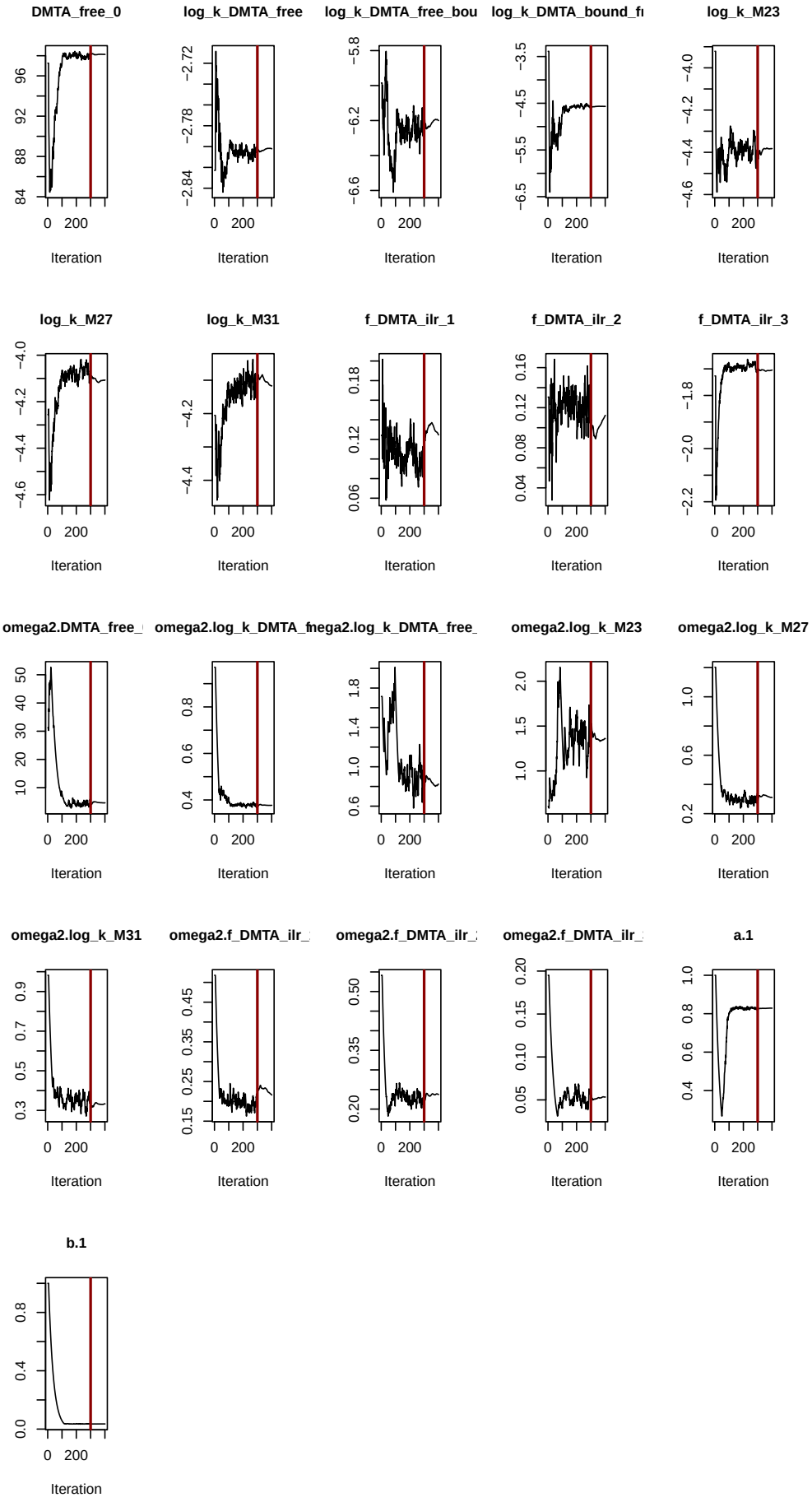
As expected, no ill-defined parameters remain. The model comparison below shows that the reduced model is preferable.

```
anova(saem_1[["sforb_path_1", "tc"]], saem_sforb_path_1_tc_reduced) |> kable(digits = 1)
```

	npar	AIC	BIC	Lik
saem_sforb_path_1_tc_reduced	21	1830.3	1825.9	-894.2
saem_1[[“sforb_path_1”, “tc”]]	22	1832.9	1828.3	-894.4

The convergence plot of the refined fit is shown below.

```
plot(saem_sforb_path_1_tc_reduced$so, plot.type = "convergence")
```


DMTA_free_0
log_k_DMTA_free
log_k_DMTA_free_bou
log_k_DMTA_bound_fi
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
omega2.DMTA_free_
omega2.log_k_DMTA_fr
ega2.log_k_DMTA_free_
omega2.log_k_M23
omega2.log_k_M27
omega2.log_k_M31
omega2.f_DMTA_ilr_
omega2.f_DMTA_ilr_
omega2.f_DMTA_ilr_
a.1
b.1
Iteration

For some parameters, for example for `f_DMTA_ilr_1` and `f_DMTA_ilr_2`, i.e. for two of the parameters determining the formation fractions of the parallel formation of the three metabolites, some movement of the parameters is still visible in the second phase of the algorithm. However, the amplitude of this movement is in the range of the amplitude towards the end of the first phase. Therefore, it is likely that an increase in iterations would not improve the parameter estimates very much, and it is proposed that the fit is acceptable. No numeric convergence criterion is implemented in saemix.

Alternative check of parameter identifiability

As an alternative check of parameter identifiability (Duchesne et al. 2021), multistart runs were performed on the basis of the refined fit shown above.

```
saem_sforb_path_1_tc_reduced_multi <- multistart(saem_sforb_path_1_tc_reduced,
  n = 32, cores = 10)
```

```
print(saem_sforb_path_1_tc_reduced_multi)
```

```
<multistart> object with 32 fits:
 E OK
15 17
OK: Fit terminated successfully
E: Error
```

Out of the 32 fits that were initiated, only 17 terminated without an error. The reason for this is that the wide variation of starting parameters in combination with the parameter variation that is used in the SAEM algorithm leads to parameter combinations for the degradation model that the numerical integration routine cannot cope with. Because of this variation of initial parameters, some of the model fits take up to two times more time than the original fit.

```
par(mar = c(12.1, 4.1, 2.1, 2.1))
parplot(saem_sforb_path_1_tc_reduced_multi, ylim = c(0.5, 2), las = 2)
```

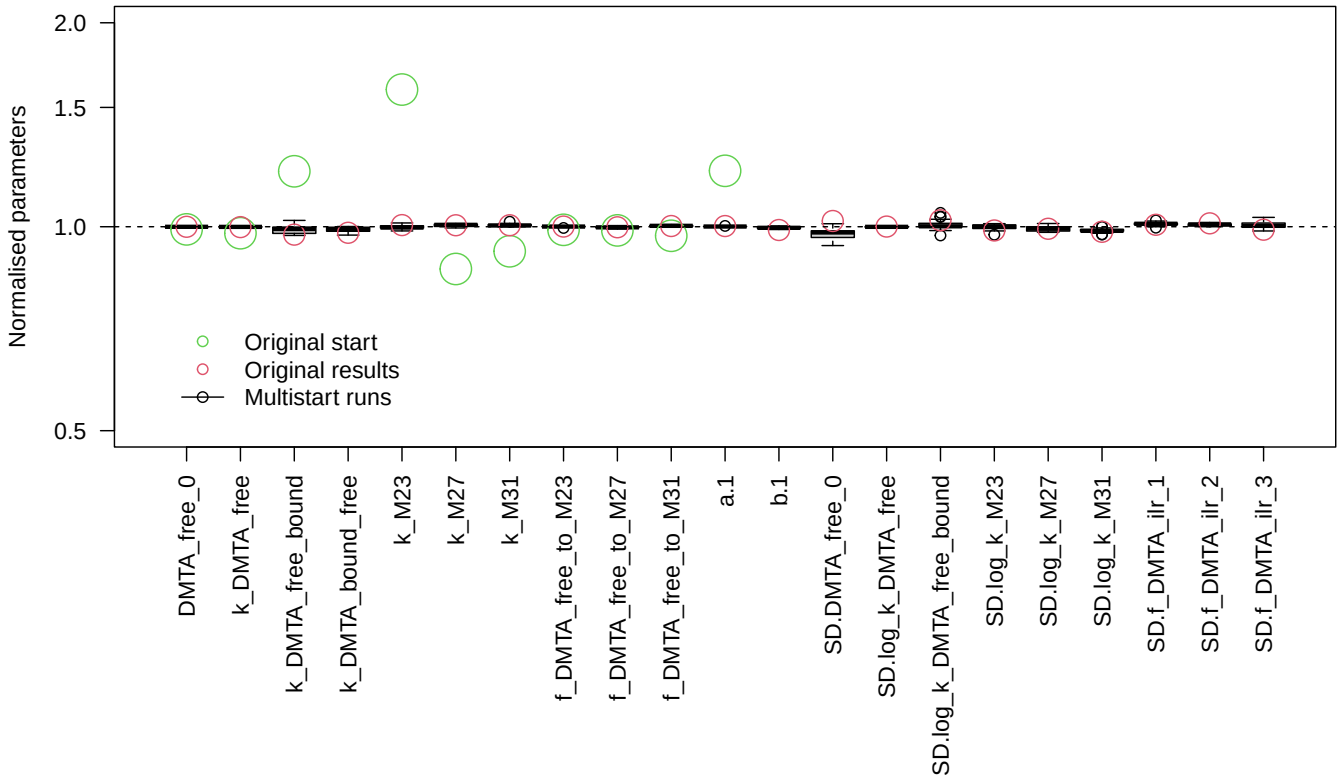


Figure 1: Parameter boxplots for the multistart runs that succeeded

However, visual analysis of the boxplot of the parameters obtained in the successful fits confirms that the results are sufficiently independent of the starting parameters, and there are no remaining ill-defined parameters.

Plots of selected fits

The SFORB pathway fits with full and reduced parameter distribution model are shown below.

```
plot(saem_1[["sforb_path_1", "tc"]])
```

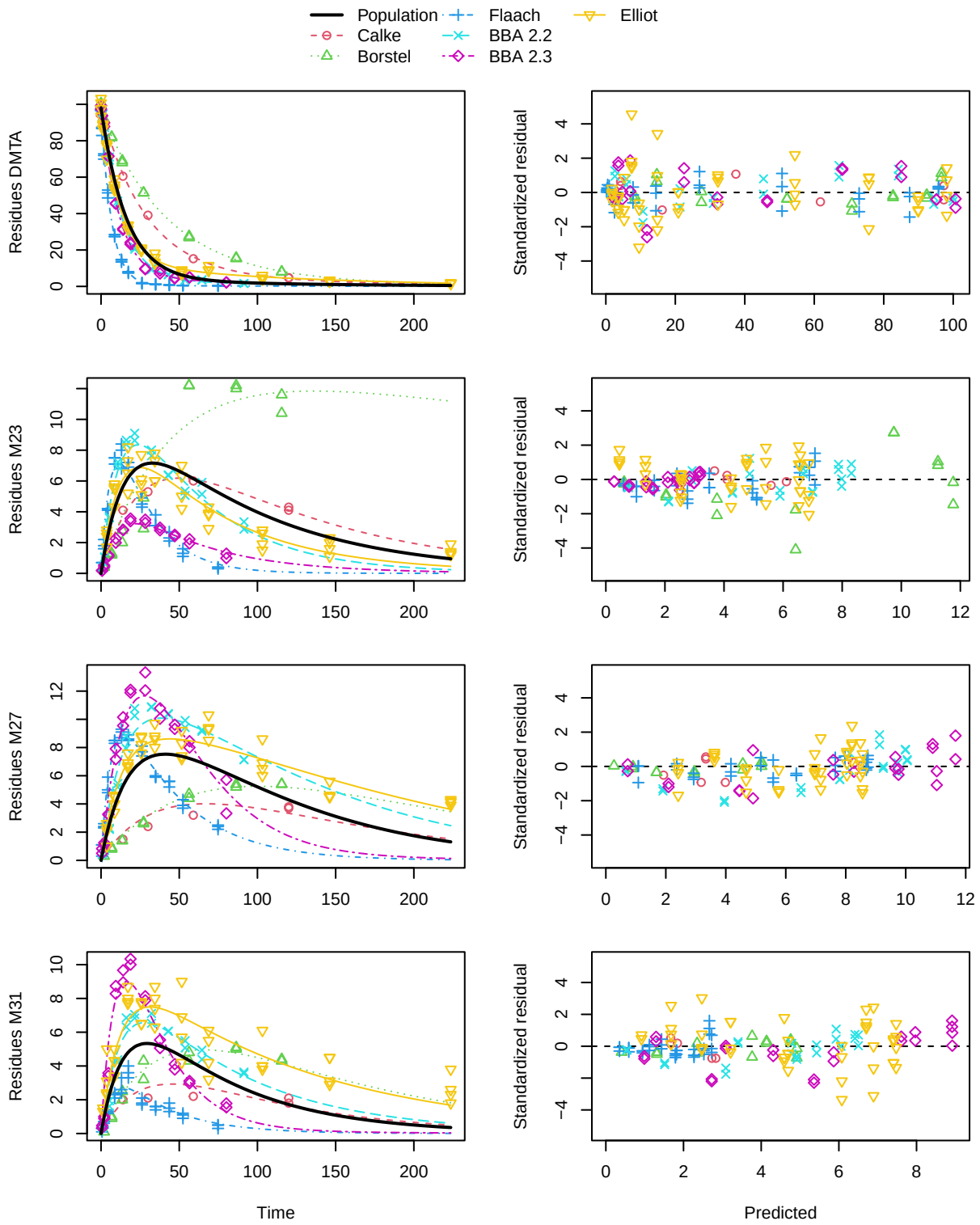


Figure 2: SFORB pathway fit with two-component error

```
plot(saem_sforb_path_1_tc_reduced)
```

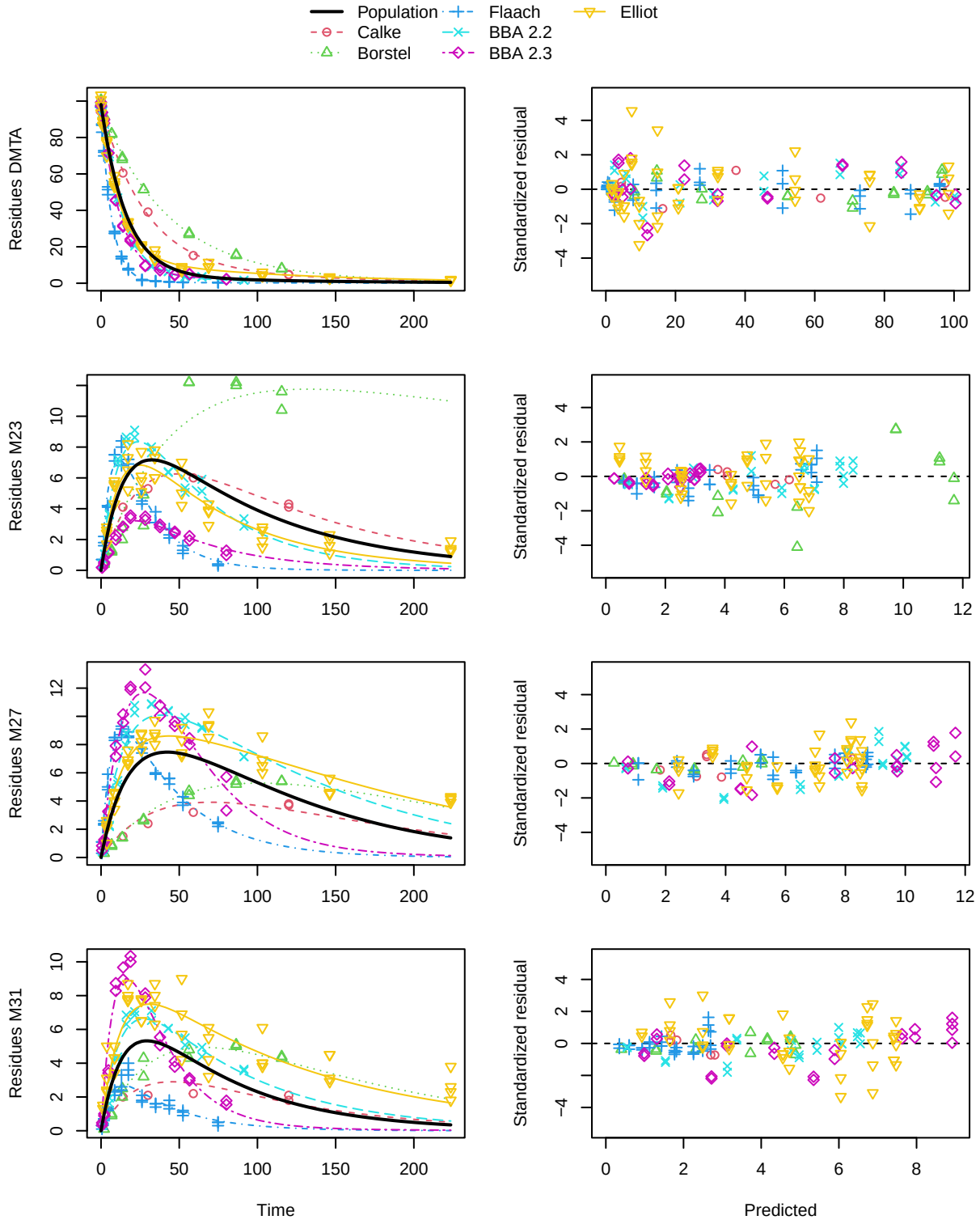


Figure 3: SFORB pathway fit with two-component error, reduced parameter model

Plots of the remaining fits and listings for all successful fits are shown in the Appendix.

```
stopCluster(cl)
```

Conclusions

Pathway fits with SFO, FOMC, DFOP, SFORB and HS models for the parent compound could be successfully performed.

Acknowledgements

The helpful comments by Janina Wöltjen of the German Environment Agency on earlier versions of this document are gratefully acknowledged.

References

Duchesne, Ronan, Anissa Guillemin, Olivier Gandrillon, and Fabien Crauste. 2021. "Practical Identifiability in the Frame of Nonlinear Mixed Effects Models: The Example of the in Vitro Erythropoiesis." *BMC Bioinformatics* 22 (478). https://doi.org/10.1186/s12859-021-04373-4.

Ranke, Johannes, Janina Wöltjen, Jana Schmidt, and Emmanuelle Comets. 2021. "Taking Kinetic Evaluations of Degradation Data to the Next Level with Nonlinear Mixed-Effects Models." *Environments* 8 (8). https://doi.org/10.3390/environments8080071.

Appendix

Plots of hierarchical fits not selected for refinement

```
plot(saem_1[["sfo_path_1", "tc"]])
```

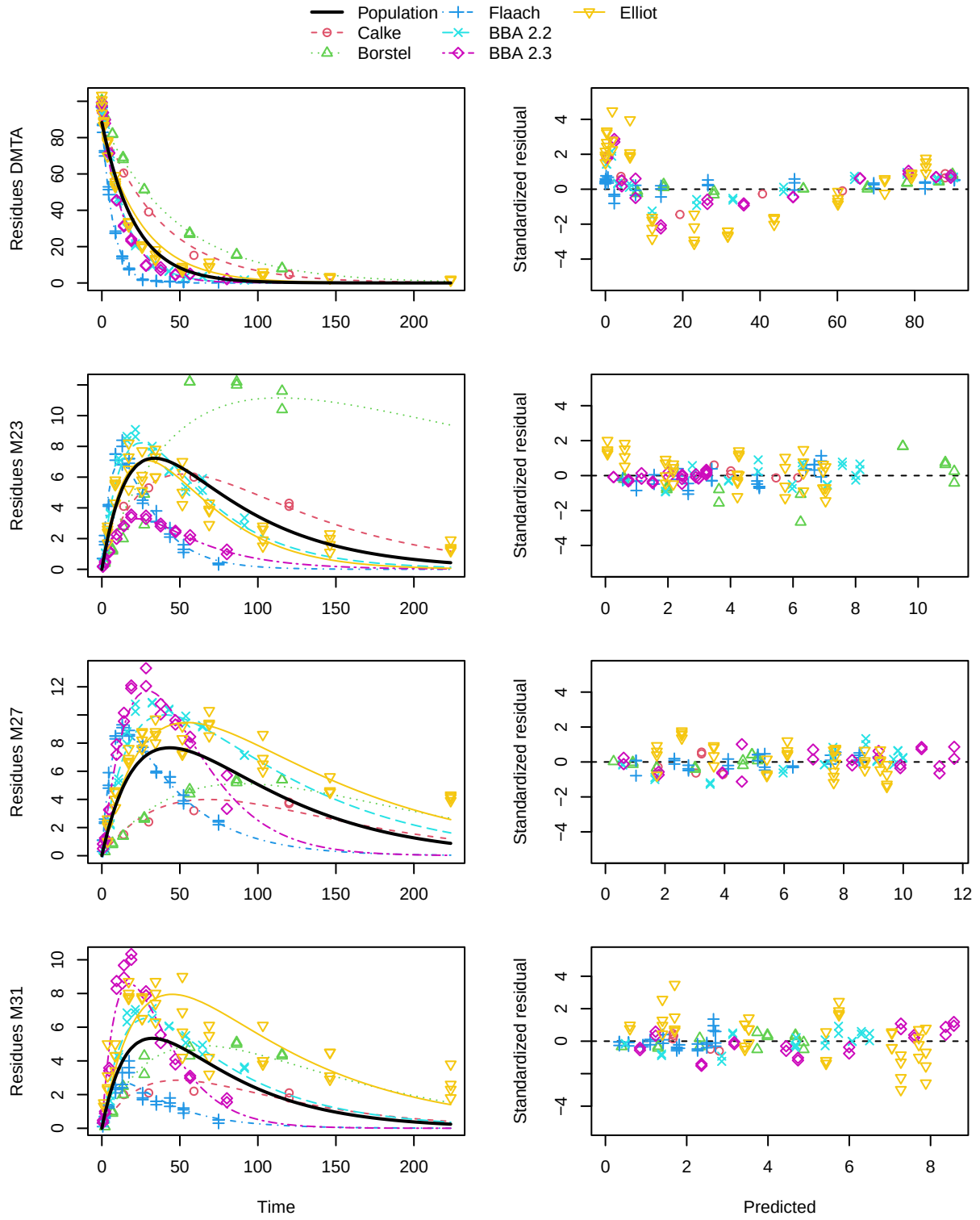


Figure 4: SFO pathway fit with two-component error

```
plot(saem_1[["fomc_path_1", "tc"]])
```

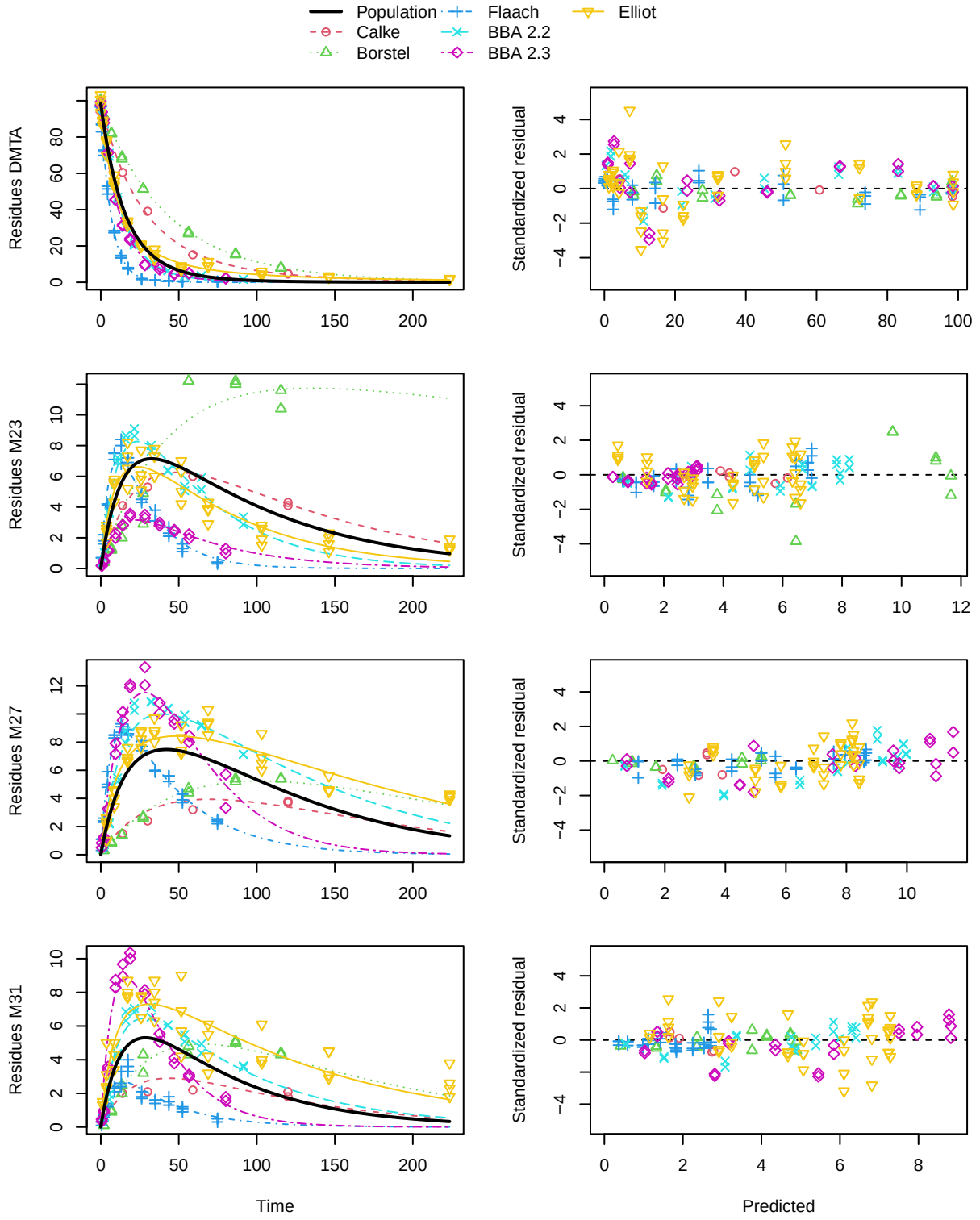


Figure 5: FOMC pathway fit with two-component error

```
plot(saem_1[["sforb_path_1", "tc"]])
```

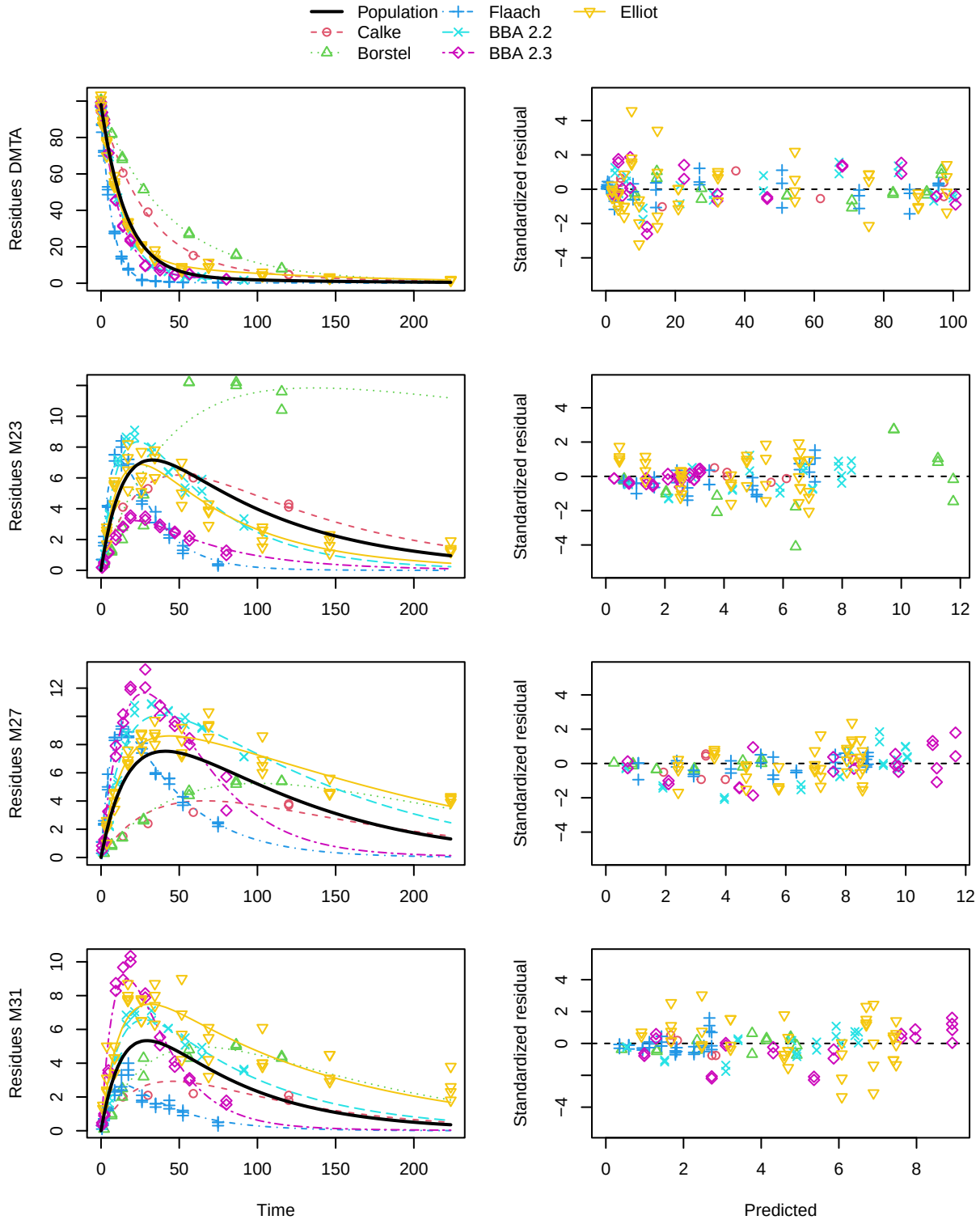


Figure 6: HS pathway fit with two-component error

Hierarchical model fit listings

Fits with random effects for all degradation parameters

Listing 1: Hierarchical SFO path 1 fit with constant variance

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:07:58 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - k_DMTA * DMTA
d_M23/dt = + f_DMTA_to_M23 * k_DMTA * DMTA - k_M23 * M23
d_M27/dt = + f_DMTA_to_M27 * k_DMTA * DMTA - k_M27 * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * k_DMTA * DMTA - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 756.354 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
      DMTA_0   log_k_DMTA    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1
     97.2914      -2.8719      -4.4799      -4.1939      -4.1675       0.1423
f_DMTA_ilr_2 f_DMTA_ilr_3
      0.1429      -1.7035

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_DMTA log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1
DMTA_0        2.947     0.0000     0.000     0.000     0.000       0.0000
log_k_DMTA    0.000     0.9413     0.000     0.000     0.000       0.0000
log_k_M23     0.000     0.0000     2.331     0.000     0.000       0.0000
log_k_M27     0.000     0.0000     0.000     1.076     0.000       0.0000
log_k_M31     0.000     0.0000     0.000     0.000     1.004       0.0000
f_DMTA_ilr_1  0.000     0.0000     0.000     0.000     0.000       0.7349
f_DMTA_ilr_2  0.000     0.0000     0.000     0.000     0.000       0.0000
f_DMTA_ilr_3  0.000     0.0000     0.000     0.000     0.000       0.0000
             f_DMTA_ilr_2 f_DMTA_ilr_3
DMTA_0             0.0000       0.0000
log_k_DMTA         0.0000       0.0000
log_k_M23          0.0000       0.0000
log_k_M27          0.0000       0.0000
log_k_M31          0.0000       0.0000
f_DMTA_ilr_1       0.0000       0.0000
f_DMTA_ilr_2       0.7365       0.0000
f_DMTA_ilr_3       0.0000       0.4565

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  2292 2288  -1129

Optimised parameters:
                    est.    lower   upper
DMTA_0          97.26786 95.67823 98.8575
log_k_DMTA      -2.87273 -3.36023 -2.3852
log_k_M23       -4.18506 -5.00826 -3.3619
log_k_M27       -3.87596 -4.29723 -3.4547
log_k_M31       -4.02059 -4.57377 -3.4674
f_DMTA_ilr_1     0.05974 -0.27557  0.3950
f_DMTA_ilr_2     0.14183 -0.26810  0.5518
f_DMTA_ilr_3    -1.60231 -1.75871 -1.4459
a.1              1.57902  1.49964  1.6584
SD.DMTA_0        1.84675  0.64110  3.0524
SD.log_k_DMTA    0.60889  0.26400  0.9538
SD.log_k_M23     0.94708  0.33329  1.5609
SD.log_k_M27     0.46988  0.15182  0.7879
SD.log_k_M31     0.59868  0.17038  1.0270
```

```
SD.f_DMTA_ilr_1  0.38216  0.12846  0.6359
SD.f_DMTA_ilr_2  0.46970  0.16345  0.7760
SD.f_DMTA_ilr_3  0.16279  0.03761  0.2880

Correlation:
             DMTA_0  l__DMTA lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2
log_k_DMTA    0.0060
log_k_M23    -0.0037 -0.0007
log_k_M27    -0.0049 -0.0009 -0.0033
log_k_M31    -0.0032 -0.0006 -0.0011  0.1030
f_DMTA_ilr_1 -0.0011 -0.0002  0.0731 -0.0517  0.0483
f_DMTA_ilr_2 -0.0003 -0.0001  0.0340 -0.0415 -0.1324 -0.0457
f_DMTA_ilr_3 -0.0303 -0.0032  0.0888  0.1419  0.0769 -0.0052   -0.0019

Random effects:
                  est.   lower  upper
SD.DMTA_0       1.8467 0.64110 3.0524
SD.log_k_DMTA   0.6089 0.26400 0.9538
SD.log_k_M23    0.9471 0.33329 1.5609
SD.log_k_M27    0.4699 0.15182 0.7879
SD.log_k_M31    0.5987 0.17038 1.0270
SD.f_DMTA_ilr_1 0.3822 0.12846 0.6359
SD.f_DMTA_ilr_2 0.4697 0.16345 0.7760
SD.f_DMTA_ilr_3 0.1628 0.03761 0.2880

Variance model:
     est. lower upper
a.1 1.579   1.5 1.658

Backtransformed parameters:
                   est.     lower    upper
DMTA_0        97.26786 95.678234 98.85749
k_DMTA         0.05654  0.034727  0.09207
k_M23          0.01522  0.006683  0.03467
k_M27          0.02073  0.013606  0.03160
k_M31          0.01794  0.010319  0.03120
f_DMTA_to_M23  0.11793        NA       NA
f_DMTA_to_M27  0.10838        NA       NA
f_DMTA_to_M31  0.09503        NA       NA

Resulting formation fractions:
               ff
DMTA_M23  0.11793
DMTA_M27  0.10838
DMTA_M31  0.09503
DMTA_sink 0.67867

Estimated disappearance times:
      DT50   DT90
DMTA 12.26  40.72
M23  45.54 151.27
M27  33.43 111.05
M31  38.63 128.33
```

Listing 2: Hierarchical SFO path 1 fit with two-component error

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:08:15 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - k_DMTA * DMTA
d_M23/dt = + f_DMTA_to_M23 * k_DMTA * DMTA - k_M23 * M23
d_M27/dt = + f_DMTA_to_M27 * k_DMTA * DMTA - k_M27 * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * k_DMTA * DMTA - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 773.377 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
      DMTA_0   log_k_DMTA    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1
     95.5662      -2.9048      -3.8130      -4.1600      -4.1486       0.1341
f_DMTA_ilr_2 f_DMTA_ilr_3
      0.1385      -1.6700

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_DMTA log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1
DMTA_0        4.802     0.0000    0.0000     0.000    0.0000       0.0000
log_k_DMTA    0.000     0.9834    0.0000     0.000    0.0000       0.0000
log_k_M23     0.000     0.0000    0.6983     0.000    0.0000       0.0000
log_k_M27     0.000     0.0000    0.0000     1.028    0.0000       0.0000
log_k_M31     0.000     0.0000    0.0000     0.000    0.9841       0.0000
f_DMTA_ilr_1  0.000     0.0000    0.0000     0.000    0.0000       0.7185
f_DMTA_ilr_2  0.000     0.0000    0.0000     0.000    0.0000       0.0000
f_DMTA_ilr_3  0.000     0.0000    0.0000     0.000    0.0000       0.0000
             f_DMTA_ilr_2 f_DMTA_ilr_3
DMTA_0             0.0000       0.0000
log_k_DMTA         0.0000       0.0000
log_k_M23          0.0000       0.0000
log_k_M27          0.0000       0.0000
log_k_M31          0.0000       0.0000
f_DMTA_ilr_1       0.0000       0.0000
f_DMTA_ilr_2       0.7378       0.0000
f_DMTA_ilr_3       0.0000       0.4451

Starting values for error model parameters:
a.1 b.1
  1   1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  2276 2273  -1120

Optimised parameters:
                  est.   lower   upper
DMTA_0         88.3192 83.8656 92.7729
log_k_DMTA     -3.0530 -3.5686 -2.5373
log_k_M23      -4.0620 -4.9202 -3.2038
log_k_M27      -3.8633 -4.2668 -3.4598
log_k_M31      -3.9731 -4.4763 -3.4699
f_DMTA_ilr_1    0.1346 -0.2150  0.4841
f_DMTA_ilr_2    0.1449 -0.2593  0.5491
f_DMTA_ilr_3   -1.3882 -1.7011 -1.0753
a.1             0.9156  0.8217  1.0095
b.1             0.1383  0.1216  0.1550
SD.DMTA_0       3.7280 -0.6949  8.1508
SD.log_k_DMTA   0.6431  0.2781  1.0080
SD.log_k_M23    1.0096  0.3782  1.6409
SD.log_k_M27    0.4583  0.1541  0.7625
SD.log_k_M31    0.5738  0.1942  0.9533
SD.f_DMTA_ilr_1 0.4119  0.1528  0.6709
SD.f_DMTA_ilr_2 0.4780  0.1806  0.7754
SD.f_DMTA_ilr_3 0.3657  0.1383  0.5931
```

```
Correlation:
             DMTA_0  l__DMTA lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2
log_k_DMTA    0.0303
log_k_M23    -0.0229 -0.0032
log_k_M27    -0.0372 -0.0049  0.0041
log_k_M31    -0.0245 -0.0032  0.0022  0.0815
f_DMTA_ilr_1 -0.0046 -0.0006  0.0415 -0.0433  0.0324
f_DMTA_ilr_2 -0.0008 -0.0002  0.0214 -0.0267 -0.0893 -0.0361
f_DMTA_ilr_3 -0.1755 -0.0135  0.0423  0.0775  0.0377 -0.0066    0.0060

Random effects:
                  est.   lower  upper
SD.DMTA_0       3.7280 -0.6949 8.1508
SD.log_k_DMTA   0.6431  0.2781 1.0080
SD.log_k_M23    1.0096  0.3782 1.6409
SD.log_k_M27    0.4583  0.1541 0.7625
SD.log_k_M31    0.5738  0.1942 0.9533
SD.f_DMTA_ilr_1 0.4119  0.1528 0.6709
SD.f_DMTA_ilr_2 0.4780  0.1806 0.7754
SD.f_DMTA_ilr_3 0.3657  0.1383 0.5931

Variance model:
      est.  lower upper
a.1 0.9156 0.8217 1.009
b.1 0.1383 0.1216 0.155

Backtransformed parameters:
                  est.     lower    upper
DMTA_0        88.31924 83.865625 92.77286
k_DMTA         0.04722  0.028196  0.07908
k_M23          0.01721  0.007298  0.04061
k_M27          0.02100  0.014027  0.03144
k_M31          0.01882  0.011375  0.03112
f_DMTA_to_M23  0.14608        NA       NA
f_DMTA_to_M27  0.12077        NA       NA
f_DMTA_to_M31  0.11123        NA       NA

Resulting formation fractions:
              ff
DMTA_M23  0.1461
DMTA_M27  0.1208
DMTA_M31  0.1112
DMTA_sink 0.6219

Estimated disappearance times:
      DT50   DT90
DMTA 14.68  48.76
M23  40.27 133.76
M27  33.01 109.65
M31  36.84 122.38
```

Listing 3: Hierarchical FOMC path 1 fit with constant variance

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:09:48 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - (alpha/beta) * 1/((time/beta) + 1) * DMTA
d_M23/dt = + f_DMTA_to_M23 * (alpha/beta) * 1/((time/beta) + 1) * DMTA
           - k_M23 * M23
d_M27/dt = + f_DMTA_to_M27 * (alpha/beta) * 1/((time/beta) + 1) * DMTA
           - k_M27 * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * (alpha/beta) * 1/((time/beta) + 1) * DMTA
           - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 866.372 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
      DMTA_0    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
     98.1960      -3.8778      -4.2808      -4.2073       0.1409       0.1369
f_DMTA_ilr_3    log_alpha     log_beta
     -1.7285       2.1896       4.9809

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
DMTA_0        2.663    0.0000     0.000     0.000       0.0000       0.0000
log_k_M23     0.000    0.7521     0.000     0.000       0.0000       0.0000
log_k_M27     0.000    0.0000     1.205     0.000       0.0000       0.0000
log_k_M31     0.000    0.0000     0.000     1.063       0.0000       0.0000
f_DMTA_ilr_1  0.000    0.0000     0.000     0.000       0.7374       0.0000
f_DMTA_ilr_2  0.000    0.0000     0.000     0.000       0.0000       0.7375
f_DMTA_ilr_3  0.000    0.0000     0.000     0.000       0.0000       0.0000
log_alpha     0.000    0.0000     0.000     0.000       0.0000       0.0000
log_beta      0.000    0.0000     0.000     0.000       0.0000       0.0000
             f_DMTA_ilr_3 log_alpha log_beta
DMTA_0             0.0000     0.000    0.000
log_k_M23          0.0000     0.000    0.000
log_k_M27          0.0000     0.000    0.000
log_k_M31          0.0000     0.000    0.000
f_DMTA_ilr_1       0.0000     0.000    0.000
f_DMTA_ilr_2       0.0000     0.000    0.000
f_DMTA_ilr_3       0.4598     0.000    0.000
log_alpha          0.0000     1.762    0.000
log_beta           0.0000     0.000    1.463

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  2099 2095  -1030

Optimised parameters:
                   est.    lower   upper
DMTA_0          98.2099 96.82991 99.5898
log_k_M23       -4.3443 -5.33209 -3.3565
log_k_M27       -3.9589 -4.39124 -3.5265
log_k_M31       -4.0469 -4.56847 -3.5253
f_DMTA_ilr_1     0.0782 -0.28002  0.4364
f_DMTA_ilr_2     0.1123 -0.30050  0.5250
f_DMTA_ilr_3    -1.6557 -1.82793 -1.4836
log_alpha        2.2802  1.47312  3.0873
log_beta         5.0466  4.19543  5.8978
a.1              1.2813  1.20298  1.3596
SD.DMTA_0        1.5989  0.55414  2.6436
SD.log_k_M23     1.1470  0.41798  1.8760
SD.log_k_M27     0.4919  0.16775  0.8160
SD.log_k_M31     0.5796  0.18013  0.9791
```

```
SD.f_DMTA_ilr_1  0.4202  0.15421  0.6862
SD.f_DMTA_ilr_2  0.4838  0.17898  0.7885
SD.f_DMTA_ilr_3  0.1940  0.06269  0.3252
SD.log_alpha     0.8910  0.28062  1.5014
SD.log_beta      0.9401  0.29616  1.5839

Correlation:
             DMTA_0  lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2 f_DMTA__3
log_k_M23    -0.0060
log_k_M27    -0.0072 -0.0008
log_k_M31    -0.0045  0.0002  0.0897
f_DMTA_ilr_1 -0.0009  0.0468 -0.0396  0.0397
f_DMTA_ilr_2 -0.0004  0.0230 -0.0336 -0.1056 -0.0404
f_DMTA_ilr_3 -0.0259  0.0567  0.1049  0.0523 -0.0142    0.0028
log_alpha    -0.0556  0.0088  0.0096  0.0048  0.0004    0.0013    0.0132
log_beta     -0.0588  0.0092  0.0101  0.0051  0.0005    0.0013    0.0145
             log_lph
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
log_alpha
log_beta      0.2191

Random effects:
                  est.   lower  upper
SD.DMTA_0       1.5989 0.55414 2.6436
SD.log_k_M23    1.1470 0.41798 1.8760
SD.log_k_M27    0.4919 0.16775 0.8160
SD.log_k_M31    0.5796 0.18013 0.9791
SD.f_DMTA_ilr_1 0.4202 0.15421 0.6862
SD.f_DMTA_ilr_2 0.4838 0.17898 0.7885
SD.f_DMTA_ilr_3 0.1940 0.06269 0.3252
SD.log_alpha    0.8910 0.28062 1.5014
SD.log_beta     0.9401 0.29616 1.5839

Variance model:
     est. lower upper
a.1 1.281 1.203  1.36

Backtransformed parameters:
                   est.     lower     upper
DMTA_0         98.20985 96.829913  99.58980
k_M23           0.01298  0.004834   0.03486
k_M27           0.01908  0.012385   0.02941
k_M31           0.01748  0.010374   0.02944
f_DMTA_to_M23   0.11318        NA        NA
f_DMTA_to_M27   0.10134        NA        NA
f_DMTA_to_M31   0.09334        NA        NA
alpha           9.77858  4.362842  21.91707
beta          155.49513 66.381971 364.23646

Resulting formation fractions:
               ff
DMTA_M23  0.11318
DMTA_M27  0.10134
DMTA_M31  0.09334
DMTA_sink 0.69214

Estimated disappearance times:
      DT50   DT90 DT50back
DMTA 11.42  41.28    12.43
M23  53.40 177.39       NA
M27  36.32 120.65       NA
M31  39.66 131.75       NA
```

Listing 4: Hierarchical FOMC path 1 fit with two-component error

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:09:53 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - (alpha/beta) * 1/((time/beta) + 1) * DMTA
d_M23/dt = + f_DMTA_to_M23 * (alpha/beta) * 1/((time/beta) + 1) * DMTA
           - k_M23 * M23
d_M27/dt = + f_DMTA_to_M27 * (alpha/beta) * 1/((time/beta) + 1) * DMTA
           - k_M27 * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * (alpha/beta) * 1/((time/beta) + 1) * DMTA
           - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 871.866 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
      DMTA_0    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
     97.9192      -3.9376      -4.1632      -4.0881       0.1262       0.1219
f_DMTA_ilr_3    log_alpha     log_beta
     -1.7445       2.0049       4.4962

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
DMTA_0        5.883    0.0000     0.000     0.000       0.0000       0.0000
log_k_M23     0.000    0.7991     0.000     0.000       0.0000       0.0000
log_k_M27     0.000    0.0000     1.196     0.000       0.0000       0.0000
log_k_M31     0.000    0.0000     0.000     1.033       0.0000       0.0000
f_DMTA_ilr_1  0.000    0.0000     0.000     0.000       0.7173       0.0000
f_DMTA_ilr_2  0.000    0.0000     0.000     0.000       0.0000       0.7387
f_DMTA_ilr_3  0.000    0.0000     0.000     0.000       0.0000       0.0000
log_alpha     0.000    0.0000     0.000     0.000       0.0000       0.0000
log_beta      0.000    0.0000     0.000     0.000       0.0000       0.0000
             f_DMTA_ilr_3 log_alpha log_beta
DMTA_0             0.0000     0.000    0.000
log_k_M23          0.0000     0.000    0.000
log_k_M27          0.0000     0.000    0.000
log_k_M31          0.0000     0.000    0.000
f_DMTA_ilr_1       0.0000     0.000    0.000
f_DMTA_ilr_2       0.0000     0.000    0.000
f_DMTA_ilr_3       0.4557     0.000    0.000
log_alpha          0.0000     1.973    0.000
log_beta           0.0000     0.000    1.736

Starting values for error model parameters:
a.1 b.1
  1   1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  1940 1935 -949.8

Optimised parameters:
                    est.    lower    upper
DMTA_0          98.40215 96.54263 100.2617
log_k_M23       -4.42549 -5.47959  -3.3714
log_k_M27       -4.09561 -4.57796  -3.6133
log_k_M31       -4.11539 -4.63602  -3.5948
f_DMTA_ilr_1     0.10845 -0.26103   0.4779
f_DMTA_ilr_2     0.11247 -0.28749   0.5124
f_DMTA_ilr_3    -1.70891 -1.91873  -1.4991
log_alpha        1.97268  1.23049   2.7149
log_beta         4.69673  3.77267   5.6208
a.1              0.84402  0.76903   0.9190
b.1              0.05663  0.04736   0.0659
SD.DMTA_0        0.50302 -5.02389   6.0299
SD.log_k_M23     1.23709  0.46698   2.0072
SD.log_k_M27     0.56292  0.20599   0.9198
```

```
SD.log_k_M31     0.60563  0.21756   0.9937
SD.f_DMTA_ilr_1  0.44620  0.17729   0.7151
SD.f_DMTA_ilr_2  0.48080  0.18949   0.7721
SD.f_DMTA_ilr_3  0.24795  0.09702   0.3989
SD.log_alpha     0.82800  0.27453   1.3815
SD.log_beta      1.05702  0.38076   1.7333

Correlation:
             DMTA_0  lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2 f_DMTA__3
log_k_M23    -0.0339
log_k_M27    -0.0462  0.0042
log_k_M31    -0.0294  0.0028  0.0680
f_DMTA_ilr_1 -0.0033  0.0256 -0.0272  0.0245
f_DMTA_ilr_2 -0.0014  0.0135 -0.0222 -0.0680 -0.0269
f_DMTA_ilr_3 -0.1744  0.0355  0.0692  0.0334 -0.0105    0.0024
log_alpha    -0.1556  0.0235  0.0261  0.0156  0.0017    0.0014    0.0463
log_beta     -0.1544  0.0217  0.0245  0.0147  0.0016    0.0013    0.0451
             log_lph
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
log_alpha
log_beta      0.1810

Random effects:
                  est.    lower  upper
SD.DMTA_0       0.5030 -5.02389 6.0299
SD.log_k_M23    1.2371  0.46698 2.0072
SD.log_k_M27    0.5629  0.20599 0.9198
SD.log_k_M31    0.6056  0.21756 0.9937
SD.f_DMTA_ilr_1 0.4462  0.17729 0.7151
SD.f_DMTA_ilr_2 0.4808  0.18949 0.7721
SD.f_DMTA_ilr_3 0.2480  0.09702 0.3989
SD.log_alpha    0.8280  0.27453 1.3815
SD.log_beta     1.0570  0.38076 1.7333

Variance model:
       est.   lower  upper
a.1 0.84402 0.76903 0.9190
b.1 0.05663 0.04736 0.0659

Backtransformed parameters:
                   est.     lower     upper
DMTA_0         98.40215 96.542632 100.26166
k_M23           0.01197  0.004171   0.03434
k_M27           0.01665  0.010276   0.02696
k_M31           0.01632  0.009696   0.02747
f_DMTA_to_M23   0.11076        NA        NA
f_DMTA_to_M27   0.09501        NA        NA
f_DMTA_to_M31   0.08938        NA        NA
alpha           7.18989  3.422914  15.10247
beta          109.58857 43.495928 276.10984

Resulting formation fractions:
               ff
DMTA_M23  0.11076
DMTA_M27  0.09501
DMTA_M31  0.08938
DMTA_sink 0.70486

Estimated disappearance times:
      DT50   DT90 DT50back
DMTA 11.09  41.37    12.45
M23  57.92 192.39       NA
M27  41.64 138.33       NA
M31  42.47 141.09       NA
```

Listing 5: Hierarchical DFOP path 1 fit with constant variance

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:10:48 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - ((k1 * g * exp(-k1 * time) + k2 * (1 - g) * exp(-k2 *
           time)) / (g * exp(-k1 * time) + (1 - g) * exp(-k2 * time)))
           * DMTA
d_M23/dt = + f_DMTA_to_M23 * ((k1 * g * exp(-k1 * time) + k2 * (1 - g)
           * exp(-k2 * time)) / (g * exp(-k1 * time) + (1 - g) *
           exp(-k2 * time))) * DMTA - k_M23 * M23
d_M27/dt = + f_DMTA_to_M27 * ((k1 * g * exp(-k1 * time) + k2 * (1 - g)
           * exp(-k2 * time)) / (g * exp(-k1 * time) + (1 - g) *
           exp(-k2 * time))) * DMTA - k_M27 * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * ((k1 * g * exp(-k1 * time) + k2 * (1 - g)
           * exp(-k2 * time)) / (g * exp(-k1 * time) + (1 - g) *
           exp(-k2 * time))) * DMTA - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 926.756 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
      DMTA_0    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
     98.5020      -4.1092      -4.4920      -4.3713       0.1367       0.1385
f_DMTA_ilr_3       log_k1       log_k2     g_qlogis
     -1.7427      -2.3315      -3.7194      -0.2508

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
DMTA_0        2.422    0.0000     0.000     0.000       0.0000       0.0000
log_k_M23     0.000    0.4611     0.000     0.000       0.0000       0.0000
log_k_M27     0.000    0.0000     1.152     0.000       0.0000       0.0000
log_k_M31     0.000    0.0000     0.000     1.047       0.0000       0.0000
f_DMTA_ilr_1  0.000    0.0000     0.000     0.000       0.7396       0.0000
f_DMTA_ilr_2  0.000    0.0000     0.000     0.000       0.0000       0.7319
f_DMTA_ilr_3  0.000    0.0000     0.000     0.000       0.0000       0.0000
log_k1        0.000    0.0000     0.000     0.000       0.0000       0.0000
log_k2        0.000    0.0000     0.000     0.000       0.0000       0.0000
g_qlogis      0.000    0.0000     0.000     0.000       0.0000       0.0000
             f_DMTA_ilr_3 log_k1 log_k2 g_qlogis
DMTA_0             0.0000  0.000  0.000    0.000
log_k_M23          0.0000  0.000  0.000    0.000
log_k_M27          0.0000  0.000  0.000    0.000
log_k_M31          0.0000  0.000  0.000    0.000
f_DMTA_ilr_1       0.0000  0.000  0.000    0.000
f_DMTA_ilr_2       0.0000  0.000  0.000    0.000
f_DMTA_ilr_3       0.4627  0.000  0.000    0.000
log_k1             0.0000  1.464  0.000    0.000
log_k2             0.0000  0.000  1.491    0.000
g_qlogis           0.0000  0.000  0.000    5.149

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  2039 2034 -998.4

Optimised parameters:
                  est.    lower   upper
DMTA_0         98.10945 96.63826 99.5806
log_k_M23      -4.32896 -5.27027 -3.3876
log_k_M27      -4.01882 -4.47638 -3.5613
log_k_M31      -4.09749 -4.63229 -3.5627
f_DMTA_ilr_1    0.09446 -0.27614  0.4651
f_DMTA_ilr_2    0.12385 -0.29707  0.5448
f_DMTA_ilr_3   -1.67130 -1.85702 -1.4856
```

```
log_k1          -2.89772 -3.83174 -1.9637
log_k2          -3.58026 -4.50361 -2.6569
g_qlogis         0.20649 -3.37843  3.7914
a.1              1.17980  1.11928  1.2403
SD.DMTA_0        1.74178  0.64708  2.8365
SD.log_k_M23     1.09824  0.39902  1.7975
SD.log_k_M27     0.52185  0.17817  0.8655
SD.log_k_M31     0.59267  0.18116  1.0042
SD.f_DMTA_ilr_1  0.43199  0.15538  0.7086
SD.f_DMTA_ilr_2  0.49162  0.17972  0.8035
SD.f_DMTA_ilr_3  0.20921  0.06744  0.3510
SD.log_k1        1.10830  0.43293  1.7837
SD.log_k2        1.09078  0.42140  1.7602
SD.g_qlogis      3.34706  0.62689  6.0672

Correlation:
             DMTA_0  lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2 f_DMTA__3
log_k_M23    -0.0048
log_k_M27    -0.0063  0.0002
log_k_M31    -0.0039  0.0005  0.0962
f_DMTA_ilr_1 -0.0008  0.0600 -0.0378  0.0406
f_DMTA_ilr_2 -0.0002  0.0303 -0.0373 -0.1124 -0.0333
f_DMTA_ilr_3 -0.0209  0.0680  0.1038  0.0560  0.0032    0.0087
log_k1        0.0294  0.0006 -0.0010 -0.0003  0.0004    0.0001   -0.0062
log_k2        0.0083  0.0028  0.0070  0.0056  0.0000   -0.0015    0.0044
g_qlogis     -0.0287 -0.0035 -0.0050 -0.0044 -0.0007    0.0008    0.0007
             log_k1  log_k2
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
log_k1
log_k2        0.0542
g_qlogis     -0.1621 -0.1702

Random effects:
                 est.   lower  upper
SD.DMTA_0       1.7418 0.64708 2.8365
SD.log_k_M23    1.0982 0.39902 1.7975
SD.log_k_M27    0.5218 0.17817 0.8655
SD.log_k_M31    0.5927 0.18116 1.0042
SD.f_DMTA_ilr_1 0.4320 0.15538 0.7086
SD.f_DMTA_ilr_2 0.4916 0.17972 0.8035
SD.f_DMTA_ilr_3 0.2092 0.06744 0.3510
SD.log_k1       1.1083 0.43293 1.7837
SD.log_k2       1.0908 0.42140 1.7602
SD.g_qlogis     3.3471 0.62689 6.0672

Variance model:
    est. lower upper
a.1 1.18 1.119  1.24

Backtransformed parameters:
                   est.     lower    upper
DMTA_0        98.10945 96.638257 99.58064
k_M23          0.01318  0.005142  0.03379
k_M27          0.01797  0.011375  0.02840
k_M31          0.01661  0.009732  0.02836
f_DMTA_to_M23  0.11358        NA       NA
f_DMTA_to_M27  0.09938        NA       NA
f_DMTA_to_M31  0.09129        NA       NA
k1             0.05515  0.021672  0.14034
k2             0.02787  0.011069  0.07016
g              0.55144  0.032976  0.97793

Resulting formation fractions:
               ff
DMTA_M23  0.11358
DMTA_M27  0.09938
DMTA_M31  0.09129
DMTA_sink 0.69576

Estimated disappearance times:
      DT50   DT90 DT50back DT50_k1 DT50_k2
DMTA 16.76  61.31    18.46   12.57   24.87
M23  52.59 174.69       NA      NA      NA
M27  38.56 128.10       NA      NA      NA
M31  41.72 138.59       NA      NA      NA
```

Listing 6: Hierarchical DFOP path 1 fit with two-component error

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:11:03 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - ((k1 * g * exp(-k1 * time) + k2 * (1 - g) * exp(-k2 *
           time)) / (g * exp(-k1 * time) + (1 - g) * exp(-k2 * time)))
           * DMTA
d_M23/dt = + f_DMTA_to_M23 * ((k1 * g * exp(-k1 * time) + k2 * (1 - g)
           * exp(-k2 * time)) / (g * exp(-k1 * time) + (1 - g) *
           exp(-k2 * time))) * DMTA - k_M23 * M23
d_M27/dt = + f_DMTA_to_M27 * ((k1 * g * exp(-k1 * time) + k2 * (1 - g)
           * exp(-k2 * time)) / (g * exp(-k1 * time) + (1 - g) *
           exp(-k2 * time))) * DMTA - k_M27 * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * ((k1 * g * exp(-k1 * time) + k2 * (1 - g)
           * exp(-k2 * time)) / (g * exp(-k1 * time) + (1 - g) *
           exp(-k2 * time))) * DMTA - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 941.485 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
      DMTA_0    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
     98.7132      -3.9216      -4.3306      -4.2442       0.1376       0.1388
f_DMTA_ilr_3       log_k1       log_k2     g_qlogis
     -1.7554      -2.2352      -3.7758       0.4363

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
DMTA_0        3.291    0.0000     0.000     0.000       0.0000       0.0000
log_k_M23     0.000    0.7768     0.000     0.000       0.0000       0.0000
log_k_M27     0.000    0.0000     1.209     0.000       0.0000       0.0000
log_k_M31     0.000    0.0000     0.000     1.055       0.0000       0.0000
f_DMTA_ilr_1  0.000    0.0000     0.000     0.000       0.7396       0.0000
f_DMTA_ilr_2  0.000    0.0000     0.000     0.000       0.0000       0.7324
f_DMTA_ilr_3  0.000    0.0000     0.000     0.000       0.0000       0.0000
log_k1        0.000    0.0000     0.000     0.000       0.0000       0.0000
log_k2        0.000    0.0000     0.000     0.000       0.0000       0.0000
g_qlogis      0.000    0.0000     0.000     0.000       0.0000       0.0000
             f_DMTA_ilr_3 log_k1 log_k2 g_qlogis
DMTA_0             0.0000  0.000   0.00    0.000
log_k_M23          0.0000  0.000   0.00    0.000
log_k_M27          0.0000  0.000   0.00    0.000
log_k_M31          0.0000  0.000   0.00    0.000
f_DMTA_ilr_1       0.0000  0.000   0.00    0.000
f_DMTA_ilr_2       0.0000  0.000   0.00    0.000
f_DMTA_ilr_3       0.4505  0.000   0.00    0.000
log_k1             0.0000  1.274   0.00    0.000
log_k2             0.0000  0.000   2.23    0.000
g_qlogis           0.0000  0.000   0.00    4.387

Starting values for error model parameters:
a.1 b.1
  1   1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  1880 1875 -917.9

Optimised parameters:
                   est.    lower     upper
DMTA_0          97.87025 95.66344 100.07706
log_k_M23       -4.34365 -5.25761  -3.42969
log_k_M27       -4.09030 -4.56320  -3.61739
log_k_M31       -4.12995 -4.64427  -3.61563
f_DMTA_ilr_1     0.11371 -0.25718   0.48459
f_DMTA_ilr_2     0.12477 -0.27937   0.52891
f_DMTA_ilr_3    -1.69151 -1.88761  -1.49541
```

```
log_k1          -2.98891 -3.67142  -2.30639
log_k2          -4.52624 -5.99605  -3.05644
g_qlogis         2.49480 -0.34432   5.33392
a.1              0.82333  0.75859   0.88807
b.1              0.03652  0.03040   0.04264
SD.DMTA_0        2.32169  0.49719   4.14619
SD.log_k_M23     1.08750  0.41815   1.75686
SD.log_k_M27     0.54747  0.19530   0.89965
SD.log_k_M31     0.59008  0.20283   0.97733
SD.f_DMTA_ilr_1  0.44731  0.17709   0.71753
SD.f_DMTA_ilr_2  0.48496  0.19043   0.77950
SD.f_DMTA_ilr_3  0.23105  0.08645   0.37564
SD.log_k1        0.83930  0.35424   1.32436
SD.log_k2        1.23217  0.05037   2.41397
SD.g_qlogis      2.70695  0.66629   4.74762

Correlation:
             DMTA_0  lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2 f_DMTA__3
log_k_M23    -0.0154
log_k_M27    -0.0211  0.0035
log_k_M31    -0.0139  0.0025  0.0811
f_DMTA_ilr_1 -0.0026  0.0281 -0.0295  0.0265
f_DMTA_ilr_2 -0.0008  0.0146 -0.0261 -0.0777 -0.0272
f_DMTA_ilr_3 -0.0743  0.0384  0.0794  0.0411 -0.0098    0.0015
log_k1        0.0256 -0.0040 -0.0058 -0.0032 -0.0005   -0.0006   -0.0113
log_k2        0.0169  0.0142  0.0089  0.0091  0.0014   -0.0029    0.0019
g_qlogis     -0.0382  0.0028  0.0052  0.0010  0.0002    0.0021    0.0137
             log_k1  log_k2
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
log_k1
log_k2        0.0659
g_qlogis     -0.0926 -0.3433

Random effects:
                   est.   lower  upper
SD.DMTA_0       2.3217 0.49719 4.1462
SD.log_k_M23    1.0875 0.41815 1.7569
SD.log_k_M27    0.5475 0.19530 0.8996
SD.log_k_M31    0.5901 0.20283 0.9773
SD.f_DMTA_ilr_1 0.4473 0.17709 0.7175
SD.f_DMTA_ilr_2 0.4850 0.19043 0.7795
SD.f_DMTA_ilr_3 0.2310 0.08645 0.3756
SD.log_k1       0.8393 0.35424 1.3244
SD.log_k2       1.2322 0.05037 2.4140
SD.g_qlogis     2.7070 0.66629 4.7476

Variance model:
       est.  lower   upper
a.1 0.82333 0.7586 0.88807
b.1 0.03652 0.0304 0.04264

Backtransformed parameters:
                   est.     lower     upper
DMTA_0        97.87025 95.663437 100.07706
k_M23          0.01299  0.005208   0.03240
k_M27          0.01673  0.010429   0.02685
k_M31          0.01608  0.009617   0.02690
f_DMTA_to_M23  0.11329        NA        NA
f_DMTA_to_M27  0.09646        NA        NA
f_DMTA_to_M31  0.08973        NA        NA
k1             0.05034  0.025440   0.09962
k2             0.01082  0.002489   0.04706
g              0.92378  0.414760   0.99520

Resulting formation fractions:
               ff
DMTA_M23  0.11329
DMTA_M27  0.09646
DMTA_M31  0.08973
DMTA_sink 0.70052

Estimated disappearance times:
      DT50  DT90 DT50back DT50_k1 DT50_k2
DMTA 14.95  55.0    16.56   13.77   64.05
M23  53.36 177.3       NA      NA      NA
M27  41.42 137.6       NA      NA      NA
M31  43.10 143.2       NA      NA      NA
```

Listing 7: Hierarchical SFORB path 1 fit with constant variance

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:10:47 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA_free/dt = - k_DMTA_free * DMTA_free - k_DMTA_free_bound *
          DMTA_free + k_DMTA_bound_free * DMTA_bound
d_DMTA_bound/dt = + k_DMTA_free_bound * DMTA_free - k_DMTA_bound_free *
          DMTA_bound
d_M23/dt = + f_DMTA_free_to_M23 * k_DMTA_free * DMTA_free - k_M23 * M23
d_M27/dt = + f_DMTA_free_to_M27 * k_DMTA_free * DMTA_free - k_M27 * M27
           + k_M31 * M31
d_M31/dt = + f_DMTA_free_to_M31 * k_DMTA_free * DMTA_free - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 925.232 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
          DMTA_free_0       log_k_DMTA_free log_k_DMTA_free_bound
              98.5280               -2.5260               -3.7382
log_k_DMTA_bound_free             log_k_M23             log_k_M27
              -1.7548               -3.8933               -4.2881
            log_k_M31          f_DMTA_ilr_1          f_DMTA_ilr_2
              -4.2144                0.1393                0.1359
         f_DMTA_ilr_3
              -1.7391

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
                     DMTA_free_0 log_k_DMTA_free log_k_DMTA_free_bound
DMTA_free_0                2.391          0.0000                 0.000
log_k_DMTA_free            0.000          0.8891                 0.000
log_k_DMTA_free_bound      0.000          0.0000                 4.519
log_k_DMTA_bound_free      0.000          0.0000                 0.000
log_k_M23                  0.000          0.0000                 0.000
log_k_M27                  0.000          0.0000                 0.000
log_k_M31                  0.000          0.0000                 0.000
f_DMTA_ilr_1               0.000          0.0000                 0.000
f_DMTA_ilr_2               0.000          0.0000                 0.000
f_DMTA_ilr_3               0.000          0.0000                 0.000
                     log_k_DMTA_bound_free log_k_M23 log_k_M27 log_k_M31
DMTA_free_0                          0.000    0.0000     0.000     0.000
log_k_DMTA_free                      0.000    0.0000     0.000     0.000
log_k_DMTA_free_bound                0.000    0.0000     0.000     0.000
log_k_DMTA_bound_free                3.192    0.0000     0.000     0.000
log_k_M23                            0.000    0.7268     0.000     0.000
log_k_M27                            0.000    0.0000     1.167     0.000
log_k_M31                            0.000    0.0000     0.000     1.041
f_DMTA_ilr_1                         0.000    0.0000     0.000     0.000
f_DMTA_ilr_2                         0.000    0.0000     0.000     0.000
f_DMTA_ilr_3                         0.000    0.0000     0.000     0.000
                     f_DMTA_ilr_1 f_DMTA_ilr_2 f_DMTA_ilr_3
DMTA_free_0                0.0000       0.0000       0.0000
log_k_DMTA_free            0.0000       0.0000       0.0000
log_k_DMTA_free_bound      0.0000       0.0000       0.0000
log_k_DMTA_bound_free      0.0000       0.0000       0.0000
log_k_M23                  0.0000       0.0000       0.0000
log_k_M27                  0.0000       0.0000       0.0000
log_k_M31                  0.0000       0.0000       0.0000
f_DMTA_ilr_1               0.7452       0.0000       0.0000
f_DMTA_ilr_2               0.0000       0.7306       0.0000
f_DMTA_ilr_3               0.0000       0.0000       0.4521

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
  AIC BIC logLik
```

```
   NA  NA     NA

Optimised parameters:
                           est.    lower   upper
DMTA_free_0              98.27188 96.80788 99.7359
log_k_DMTA_free          -2.69691 -3.13017 -2.2636
log_k_DMTA_free_bound    -4.82084 -6.64366 -2.9980
log_k_DMTA_bound_free    -3.97953 -6.52678 -1.4323
log_k_M23                -4.35772 -5.32473 -3.3907
log_k_M27                -3.99549 -4.42448 -3.5665
log_k_M31                -4.09809 -4.61809 -3.5781
f_DMTA_ilr_1              0.07078 -0.27912  0.4207
f_DMTA_ilr_2              0.13180 -0.28124  0.5448
f_DMTA_ilr_3             -1.66881 -1.83891 -1.4987
a.1                       1.17123  1.12495  1.2175
SD.DMTA_free_0            1.72001  0.62279  2.8172
SD.log_k_DMTA_free        0.53476  0.22553  0.8440
SD.log_k_DMTA_free_bound  2.12596  0.78120  3.4707
SD.log_k_DMTA_bound_free  2.58759  0.70645  4.4687
SD.log_k_M23              1.13179  0.41916  1.8444
SD.log_k_M27              0.49159  0.17088  0.8123
SD.log_k_M31              0.58329  0.18688  0.9797
SD.f_DMTA_ilr_1           0.41413  0.15577  0.6725
SD.f_DMTA_ilr_2           0.48909  0.18581  0.7924
SD.f_DMTA_ilr_3           0.19445  0.06599  0.3229

Correlation:
                       DMTA__0 lg__DMTA_ lg_k_DMTA_f_ lg_k_DMTA_b_ lg__M23
log_k_DMTA_free         0.0227
log_k_DMTA_free_bound   0.0337  0.0390
log_k_DMTA_bound_free   0.0204  0.0226    0.1104
log_k_M23              -0.0054 -0.0016   -0.0002       0.0017
log_k_M27              -0.0057 -0.0013   -0.0006       0.0030      -0.0005
log_k_M31              -0.0034 -0.0007    0.0002       0.0028       0.0001
f_DMTA_ilr_1           -0.0008 -0.0002    0.0002       0.0008       0.0416
f_DMTA_ilr_2           -0.0004 -0.0002   -0.0004      -0.0007       0.0202
f_DMTA_ilr_3           -0.0224 -0.0052   -0.0052      -0.0006       0.0503
                       lg__M27 lg__M31 f_DMTA__1 f_DMTA__2
log_k_DMTA_free
log_k_DMTA_free_bound
log_k_DMTA_bound_free
log_k_M23
log_k_M27
log_k_M31               0.0850
f_DMTA_ilr_1           -0.0372  0.0339
f_DMTA_ilr_2           -0.0298 -0.0941 -0.0331
f_DMTA_ilr_3            0.0958  0.0500 -0.0117   -0.0004

Random effects:
                          est.   lower  upper
SD.DMTA_free_0          1.7200 0.62279 2.8172
SD.log_k_DMTA_free      0.5348 0.22553 0.8440
SD.log_k_DMTA_free_bound 2.1260 0.78120 3.4707
SD.log_k_DMTA_bound_free 2.5876 0.70645 4.4687
SD.log_k_M23            1.1318 0.41916 1.8444
SD.log_k_M27            0.4916 0.17088 0.8123
SD.log_k_M31            0.5833 0.18688 0.9797
SD.f_DMTA_ilr_1         0.4141 0.15577 0.6725
SD.f_DMTA_ilr_2         0.4891 0.18581 0.7924
SD.f_DMTA_ilr_3         0.1945 0.06599 0.3229

Variance model:
     est. lower upper
a.1 1.171 1.125 1.218

Backtransformed parameters:
                        est.     lower    upper
DMTA_free_0        98.27188 96.807877 99.73588
k_DMTA_free         0.06741  0.043710  0.10397
k_DMTA_free_bound   0.00806  0.001302  0.04989
k_DMTA_bound_free   0.01869  0.001464  0.23876
k_M23               0.01281  0.004870  0.03368
k_M27               0.01840  0.011980  0.02825
k_M31               0.01660  0.009872  0.02793
f_DMTA_free_to_M23  0.11229  0.069099  0.10722
f_DMTA_free_to_M27  0.10160  0.069099  0.10722
f_DMTA_free_to_M31  0.09089  0.069099  0.10722

Estimated Eigenvalues of SFORB model(s):
DMTA_b1 DMTA_b2  DMTA_g
0.07801 0.01615 0.82864

Resulting formation fractions:
                    ff
```

```
DMTA_free_M23  0.11229
DMTA_free_M27  0.10160
DMTA_free_M31  0.09089
DMTA_free_sink 0.69522
DMTA_free      1.00000

Estimated disappearance times:
      DT50   DT90 DT50back DT50_DMTA_b1 DT50_DMTA_b2
DMTA 10.82  47.47    14.29        8.885        42.91
M23  54.12 179.78       NA           NA           NA
M27  37.67 125.15       NA           NA           NA
M31  41.74 138.67       NA           NA           NA
```

Listing 8: Hierarchical SFORB path 1 fit with two-component error

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:10:44 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA_free/dt = - k_DMTA_free * DMTA_free - k_DMTA_free_bound *
          DMTA_free + k_DMTA_bound_free * DMTA_bound
d_DMTA_bound/dt = + k_DMTA_free_bound * DMTA_free - k_DMTA_bound_free *
          DMTA_bound
d_M23/dt = + f_DMTA_free_to_M23 * k_DMTA_free * DMTA_free - k_M23 * M23
d_M27/dt = + f_DMTA_free_to_M27 * k_DMTA_free * DMTA_free - k_M27 * M27
           + k_M31 * M31
d_M31/dt = + f_DMTA_free_to_M31 * k_DMTA_free * DMTA_free - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 922.452 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
          DMTA_free_0       log_k_DMTA_free log_k_DMTA_free_bound
              97.2597               -2.8229               -5.9851
log_k_DMTA_bound_free             log_k_M23             log_k_M27
              -3.3880               -3.9216               -4.2555
            log_k_M31          f_DMTA_ilr_1          f_DMTA_ilr_2
              -4.2054                0.1243                0.1306
         f_DMTA_ilr_3
              -1.7266

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
                     DMTA_free_0 log_k_DMTA_free log_k_DMTA_free_bound
DMTA_free_0                5.586          0.0000                 0.000
log_k_DMTA_free            0.000          0.9851                 0.000
log_k_DMTA_free_bound      0.000          0.0000                 1.309
log_k_DMTA_bound_free      0.000          0.0000                 0.000
log_k_M23                  0.000          0.0000                 0.000
log_k_M27                  0.000          0.0000                 0.000
log_k_M31                  0.000          0.0000                 0.000
f_DMTA_ilr_1               0.000          0.0000                 0.000
f_DMTA_ilr_2               0.000          0.0000                 0.000
f_DMTA_ilr_3               0.000          0.0000                 0.000
                     log_k_DMTA_bound_free log_k_M23 log_k_M27 log_k_M31
DMTA_free_0                          0.000    0.0000     0.000    0.0000
log_k_DMTA_free                      0.000    0.0000     0.000    0.0000
log_k_DMTA_free_bound                0.000    0.0000     0.000    0.0000
log_k_DMTA_bound_free                4.482    0.0000     0.000    0.0000
log_k_M23                            0.000    0.7768     0.000    0.0000
log_k_M27                            0.000    0.0000     1.096    0.0000
log_k_M31                            0.000    0.0000     0.000    0.9909
f_DMTA_ilr_1                         0.000    0.0000     0.000    0.0000
f_DMTA_ilr_2                         0.000    0.0000     0.000    0.0000
f_DMTA_ilr_3                         0.000    0.0000     0.000    0.0000
                     f_DMTA_ilr_1 f_DMTA_ilr_2 f_DMTA_ilr_3
DMTA_free_0                0.0000       0.0000       0.0000
log_k_DMTA_free            0.0000       0.0000       0.0000
log_k_DMTA_free_bound      0.0000       0.0000       0.0000
log_k_DMTA_bound_free      0.0000       0.0000       0.0000
log_k_M23                  0.0000       0.0000       0.0000
log_k_M27                  0.0000       0.0000       0.0000
log_k_M31                  0.0000       0.0000       0.0000
f_DMTA_ilr_1               0.7196       0.0000       0.0000
f_DMTA_ilr_2               0.0000       0.7359       0.0000
f_DMTA_ilr_3               0.0000       0.0000       0.4417

Starting values for error model parameters:
a.1 b.1
  1   1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
```

```
  1833 1828 -894.4

Optimised parameters:
                            est.    lower     upper
DMTA_free_0              98.131566 95.97820 100.28493
log_k_DMTA_free          -2.803276 -3.29545  -2.31110
log_k_DMTA_free_bound    -6.220056 -7.02080  -5.41932
log_k_DMTA_bound_free    -4.601324 -4.84240  -4.36025
log_k_M23                -4.409080 -5.42254  -3.39562
log_k_M27                -4.073777 -4.52470  -3.62285
log_k_M31                -4.123967 -4.63101  -3.61693
f_DMTA_ilr_1              0.096016 -0.26295   0.45498
f_DMTA_ilr_2              0.122320 -0.27368   0.51832
f_DMTA_ilr_3             -1.694475 -1.88172  -1.50723
a.1                       0.829893  0.76551   0.89428
b.1                       0.035087  0.02892   0.04125
SD.DMTA_free_0            2.251174  0.46307   4.03928
SD.log_k_DMTA_free        0.614338  0.26609   0.96258
SD.log_k_DMTA_free_bound  0.904557  0.30542   1.50370
SD.log_k_DMTA_bound_free  0.005574 -3.83190   3.84305
SD.log_k_M23              1.199822  0.45907   1.94058
SD.log_k_M27              0.528851  0.19554   0.86216
SD.log_k_M31              0.590868  0.21289   0.96885
SD.f_DMTA_ilr_1           0.434070  0.17309   0.69505
SD.f_DMTA_ilr_2           0.477091  0.18914   0.76505
SD.f_DMTA_ilr_3           0.222161  0.08468   0.35964

Correlation:
                         DMTA__0 lg__DMTA_ lg_k_DMTA_f_ lg_k_DMTA_b_ lg__M23
log_k_DMTA_free           0.0162
log_k_DMTA_free_bound     0.0582  0.0141
log_k_DMTA_bound_free     0.0518  0.0139    0.1538
log_k_M23                -0.0136 -0.0023   -0.0170      -0.0020
log_k_M27                -0.0166 -0.0025   -0.0154       0.0002       0.0023
log_k_M31                -0.0109 -0.0016   -0.0095       0.0021       0.0017
f_DMTA_ilr_1             -0.0019 -0.0003   -0.0012       0.0001       0.0247
f_DMTA_ilr_2             -0.0004 -0.0001   -0.0006      -0.0018       0.0127
f_DMTA_ilr_3             -0.0694 -0.0058   -0.0242      -0.0119       0.0329
                         lg__M27 lg__M31 f_DMTA__1 f_DMTA__2
log_k_DMTA_free
log_k_DMTA_free_bound
log_k_DMTA_bound_free
log_k_M23
log_k_M27
log_k_M31                 0.0650
f_DMTA_ilr_1             -0.0258  0.0237
f_DMTA_ilr_2             -0.0221 -0.0660 -0.0257
f_DMTA_ilr_3              0.0664  0.0322 -0.0111    0.0013

Random effects:
                              est.    lower  upper
SD.DMTA_free_0            2.251174  0.46307 4.0393
SD.log_k_DMTA_free        0.614338  0.26609 0.9626
SD.log_k_DMTA_free_bound  0.904557  0.30542 1.5037
SD.log_k_DMTA_bound_free  0.005574 -3.83190 3.8431
SD.log_k_M23              1.199822  0.45907 1.9406
SD.log_k_M27              0.528851  0.19554 0.8622
SD.log_k_M31              0.590868  0.21289 0.9688
SD.f_DMTA_ilr_1           0.434070  0.17309 0.6950
SD.f_DMTA_ilr_2           0.477091  0.18914 0.7650
SD.f_DMTA_ilr_3           0.222161  0.08468 0.3596

Variance model:
       est.   lower   upper
a.1 0.82989 0.76551 0.89428
b.1 0.03509 0.02892 0.04125

Backtransformed parameters:
                         est.     lower     upper
DMTA_free_0         98.131566 9.598e+01 100.28493
k_DMTA_free          0.060611 3.705e-02   0.09915
k_DMTA_free_bound    0.001989 8.931e-04   0.00443
k_DMTA_bound_free    0.010039 7.888e-03   0.01278
k_M23                0.012166 4.416e-03   0.03352
k_M27                0.017013 1.084e-02   0.02671
k_M31                0.016180 9.745e-03   0.02687
f_DMTA_free_to_M23   0.111529 6.530e-02   0.10607
f_DMTA_free_to_M27   0.097368 6.530e-02   0.10607
f_DMTA_free_to_M31   0.089710 6.530e-02   0.10607

Estimated Eigenvalues of SFORB model(s):
 DMTA_b1  DMTA_b2   DMTA_g
0.062977 0.009661 0.955617
```

```
Resulting formation fractions:
                    ff
DMTA_free_M23  0.11153
DMTA_free_M27  0.09737
DMTA_free_M31  0.08971
DMTA_free_sink 0.70139
DMTA_free      1.00000

Estimated disappearance times:
      DT50   DT90 DT50back DT50_DMTA_b1 DT50_DMTA_b2
DMTA 11.60  41.45    12.48        11.01        71.74
M23  56.97 189.26       NA           NA           NA
M27  40.74 135.34       NA           NA           NA
M31  42.84 142.31       NA           NA           NA
```

Listing 9: Hierarchical HS path 1 fit with constant variance

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:10:37 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - ifelse(time <= tb, k1, k2) * DMTA
d_M23/dt = + f_DMTA_to_M23 * ifelse(time <= tb, k1, k2) * DMTA - k_M23
           * M23
d_M27/dt = + f_DMTA_to_M27 * ifelse(time <= tb, k1, k2) * DMTA - k_M27
           * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * ifelse(time <= tb, k1, k2) * DMTA - k_M31
           * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 915.146 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
      DMTA_0    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
     98.1794      -3.8929      -4.2833      -4.2120       0.1387       0.1359
f_DMTA_ilr_3       log_k1       log_k2       log_tb
     -1.7320      -2.6017      -3.5984       2.9221

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
DMTA_0        2.953    0.0000     0.000      0.00       0.0000       0.0000
log_k_M23     0.000    0.7318     0.000      0.00       0.0000       0.0000
log_k_M27     0.000    0.0000     1.161      0.00       0.0000       0.0000
log_k_M31     0.000    0.0000     0.000      1.03       0.0000       0.0000
f_DMTA_ilr_1  0.000    0.0000     0.000      0.00       0.7464       0.0000
f_DMTA_ilr_2  0.000    0.0000     0.000      0.00       0.0000       0.7316
f_DMTA_ilr_3  0.000    0.0000     0.000      0.00       0.0000       0.0000
log_k1        0.000    0.0000     0.000      0.00       0.0000       0.0000
log_k2        0.000    0.0000     0.000      0.00       0.0000       0.0000
log_tb        0.000    0.0000     0.000      0.00       0.0000       0.0000
             f_DMTA_ilr_3 log_k1 log_k2 log_tb
DMTA_0             0.0000 0.0000 0.0000  0.000
log_k_M23          0.0000 0.0000 0.0000  0.000
log_k_M27          0.0000 0.0000 0.0000  0.000
log_k_M31          0.0000 0.0000 0.0000  0.000
f_DMTA_ilr_1       0.0000 0.0000 0.0000  0.000
f_DMTA_ilr_2       0.0000 0.0000 0.0000  0.000
f_DMTA_ilr_3       0.4555 0.0000 0.0000  0.000
log_k1             0.0000 0.6228 0.0000  0.000
log_k2             0.0000 0.0000 0.3525  0.000
log_tb             0.0000 0.0000 0.0000  1.511

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  2024 2020 -991.1

Optimised parameters:
                   est.    lower   upper
DMTA_0          98.01978 96.44819 99.5914
log_k_M23       -4.34266 -5.30344 -3.3819
log_k_M27       -4.01771 -4.46462 -3.5708
log_k_M31       -4.10032 -4.62327 -3.5774
f_DMTA_ilr_1     0.08931 -0.27364  0.4523
f_DMTA_ilr_2     0.12507 -0.28841  0.5385
f_DMTA_ilr_3    -1.67136 -1.85691 -1.4858
log_k1          -2.66051 -3.01910 -2.3019
log_k2          -3.78451 -4.03983 -3.5292
log_tb           2.82494  1.58415  4.0657
a.1              1.17672  1.13019  1.2232
SD.DMTA_0        1.86733  0.70082  3.0338
```

```
SD.log_k_M23     1.12459  0.41614  1.8330
SD.log_k_M27     0.51049  0.17612  0.8449
SD.log_k_M31     0.58520  0.18634  0.9841
SD.f_DMTA_ilr_1  0.42928  0.16136  0.6972
SD.f_DMTA_ilr_2  0.48811  0.18409  0.7921
SD.f_DMTA_ilr_3  0.21445  0.07543  0.3535
SD.log_k1        0.41452  0.15450  0.6745
SD.log_k2        0.24919  0.05181  0.4466
SD.log_tb        1.35920  0.45938  2.2590

Correlation:
             DMTA_0  lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2 f_DMTA__3
log_k_M23    -0.0053
log_k_M27    -0.0051 -0.0004
log_k_M31    -0.0034  0.0001  0.0884
f_DMTA_ilr_1 -0.0008  0.0414 -0.0386  0.0353
f_DMTA_ilr_2 -0.0002  0.0208 -0.0308 -0.0982 -0.0365
f_DMTA_ilr_3 -0.0186  0.0479  0.0925  0.0464 -0.0140    0.0021
log_k1        0.0190 -0.0024 -0.0020 -0.0012  0.0003   -0.0003   -0.0037
log_k2       -0.0003  0.0022  0.0062  0.0051  0.0006   -0.0012    0.0035
log_tb       -0.0007 -0.0007 -0.0003 -0.0001 -0.0005    0.0000   -0.0009
             log_k1  log_k2
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
log_k1
log_k2       -0.0008
log_tb       -0.0984 -0.0179

Random effects:
                  est.   lower  upper
SD.DMTA_0       1.8673 0.70082 3.0338
SD.log_k_M23    1.1246 0.41614 1.8330
SD.log_k_M27    0.5105 0.17612 0.8449
SD.log_k_M31    0.5852 0.18634 0.9841
SD.f_DMTA_ilr_1 0.4293 0.16136 0.6972
SD.f_DMTA_ilr_2 0.4881 0.18409 0.7921
SD.f_DMTA_ilr_3 0.2145 0.07543 0.3535
SD.log_k1       0.4145 0.15450 0.6745
SD.log_k2       0.2492 0.05181 0.4466
SD.log_tb       1.3592 0.45938 2.2590

Variance model:
     est. lower upper
a.1 1.177  1.13 1.223

Backtransformed parameters:
                  est.     lower    upper
DMTA_0        98.01978 96.448195 99.59136
k_M23          0.01300  0.004974  0.03398
k_M27          0.01799  0.011509  0.02813
k_M31          0.01657  0.009821  0.02795
f_DMTA_to_M23  0.11322        NA       NA
f_DMTA_to_M27  0.09979        NA       NA
f_DMTA_to_M31  0.09120        NA       NA
k1             0.06991  0.048845  0.10007
k2             0.02272  0.017600  0.02933
tb            16.85989  4.875122 58.30747

Resulting formation fractions:
                ff
DMTA_M23  0.11322
DMTA_M27  0.09979
DMTA_M31  0.09120
DMTA_sink 0.69579

Estimated disappearance times:
       DT50   DT90 DT50back DT50_k1 DT50_k2
DMTA  9.914  66.33    19.97   9.914   30.51
M23  53.311 177.10       NA      NA      NA
M27  38.521 127.96       NA      NA      NA
M31  41.838 138.98       NA      NA      NA
```

Listing 10: Hierarchical HS path 1 fit with two-component error

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:11:14 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA/dt = - ifelse(time <= tb, k1, k2) * DMTA
d_M23/dt = + f_DMTA_to_M23 * ifelse(time <= tb, k1, k2) * DMTA - k_M23
           * M23
d_M27/dt = + f_DMTA_to_M27 * ifelse(time <= tb, k1, k2) * DMTA - k_M27
           * M27 + k_M31 * M31
d_M31/dt = + f_DMTA_to_M31 * ifelse(time <= tb, k1, k2) * DMTA - k_M31
           * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 952.309 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
      DMTA_0    log_k_M23    log_k_M27    log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
     96.0836      -3.8918      -4.1230      -4.1315       0.1151       0.1232
f_DMTA_ilr_3       log_k1       log_k2       log_tb
     -1.6682      -2.8580      -3.4085       2.7034

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
             DMTA_0 log_k_M23 log_k_M27 log_k_M31 f_DMTA_ilr_1 f_DMTA_ilr_2
DMTA_0        6.474     0.000     0.000     0.000       0.0000       0.0000
log_k_M23     0.000     0.786     0.000     0.000       0.0000       0.0000
log_k_M27     0.000     0.000     0.985     0.000       0.0000       0.0000
log_k_M31     0.000     0.000     0.000     0.913       0.0000       0.0000
f_DMTA_ilr_1  0.000     0.000     0.000     0.000       0.7081       0.0000
f_DMTA_ilr_2  0.000     0.000     0.000     0.000       0.0000       0.7444
f_DMTA_ilr_3  0.000     0.000     0.000     0.000       0.0000       0.0000
log_k1        0.000     0.000     0.000     0.000       0.0000       0.0000
log_k2        0.000     0.000     0.000     0.000       0.0000       0.0000
log_tb        0.000     0.000     0.000     0.000       0.0000       0.0000
             f_DMTA_ilr_3 log_k1 log_k2 log_tb
DMTA_0             0.0000  0.000  0.000  0.000
log_k_M23          0.0000  0.000  0.000  0.000
log_k_M27          0.0000  0.000  0.000  0.000
log_k_M31          0.0000  0.000  0.000  0.000
f_DMTA_ilr_1       0.0000  0.000  0.000  0.000
f_DMTA_ilr_2       0.0000  0.000  0.000  0.000
f_DMTA_ilr_3       0.4377  0.000  0.000  0.000
log_k1             0.0000  1.081  0.000  0.000
log_k2             0.0000  0.000  1.097  0.000
log_tb             0.0000  0.000  0.000  1.524

Starting values for error model parameters:
a.1 b.1
  1   1

Results:

Likelihood computed by importance sampling
   AIC  BIC logLik
  1831 1827 -893.7

Optimised parameters:
                    est.    lower    upper
DMTA_0          97.127306 94.96753 99.28708
log_k_M23       -4.340939 -5.27262 -3.40926
log_k_M27       -4.079298 -4.54430 -3.61429
log_k_M31       -4.125264 -4.63566 -3.61487
f_DMTA_ilr_1     0.108318 -0.25702  0.47366
f_DMTA_ilr_2     0.128873 -0.27187  0.52962
f_DMTA_ilr_3    -1.672627 -1.86802 -1.47723
log_k1          -2.858335 -3.35349 -2.36318
log_k2          -3.749355 -4.02909 -3.46962
log_tb           3.442549  3.39860  3.48650
a.1              0.808860  0.74423  0.87349
b.1              0.040018  0.03339  0.04665
```

```
SD.DMTA_0        2.163341  0.30906  4.01762
SD.log_k_M23     1.108478  0.42756  1.78940
SD.log_k_M27     0.545110  0.20147  0.88875
SD.log_k_M31     0.594829  0.21460  0.97506
SD.f_DMTA_ilr_1  0.442524  0.17725  0.70780
SD.f_DMTA_ilr_2  0.483605  0.19250  0.77471
SD.f_DMTA_ilr_3  0.232158  0.08913  0.37518
SD.log_k1        0.618000  0.26758  0.96842
SD.log_k2        0.307633  0.10361  0.51165
SD.log_tb        0.006502 -0.14501  0.15802

Correlation:
             DMTA_0  lg__M23 lg__M27 lg__M31 f_DMTA__1 f_DMTA__2 f_DMTA__3
log_k_M23    -0.0199
log_k_M27    -0.0209  0.0042
log_k_M31    -0.0138  0.0030  0.0661
f_DMTA_ilr_1 -0.0025  0.0243 -0.0261  0.0227
f_DMTA_ilr_2 -0.0006  0.0125 -0.0212 -0.0648 -0.0244
f_DMTA_ilr_3 -0.0822  0.0349  0.0664  0.0329 -0.0104    0.0013
log_k1        0.0186 -0.0034 -0.0031 -0.0020 -0.0004   -0.0001   -0.0068
log_k2       -0.0077  0.0050  0.0069  0.0050  0.0007   -0.0004    0.0070
log_tb       -0.0804  0.0054  0.0079  0.0035  0.0004    0.0017    0.0249
             log_k1  log_k2
log_k_M23
log_k_M27
log_k_M31
f_DMTA_ilr_1
f_DMTA_ilr_2
f_DMTA_ilr_3
log_k1
log_k2       -0.0026
log_tb       -0.0111 -0.1647

Random effects:
                    est.    lower  upper
SD.DMTA_0       2.163341  0.30906 4.0176
SD.log_k_M23    1.108478  0.42756 1.7894
SD.log_k_M27    0.545110  0.20147 0.8888
SD.log_k_M31    0.594829  0.21460 0.9751
SD.f_DMTA_ilr_1 0.442524  0.17725 0.7078
SD.f_DMTA_ilr_2 0.483605  0.19250 0.7747
SD.f_DMTA_ilr_3 0.232158  0.08913 0.3752
SD.log_k1       0.618000  0.26758 0.9684
SD.log_k2       0.307633  0.10361 0.5117
SD.log_tb       0.006502 -0.14501 0.1580

Variance model:
       est.   lower   upper
a.1 0.80886 0.74423 0.87349
b.1 0.04002 0.03339 0.04665

Backtransformed parameters:
                   est.    lower    upper
DMTA_0        97.12731 94.96753 99.28708
k_M23          0.01302  0.00513  0.03307
k_M27          0.01692  0.01063  0.02694
k_M31          0.01616  0.00970  0.02692
f_DMTA_to_M23  0.11479       NA       NA
f_DMTA_to_M27  0.09848       NA       NA
f_DMTA_to_M31  0.09080       NA       NA
k1             0.05736  0.03496  0.09412
k2             0.02353  0.01779  0.03113
tb            31.26657 29.92214 32.67141

Resulting formation fractions:
              ff
DMTA_M23  0.11479
DMTA_M27  0.09848
DMTA_M31  0.09080
DMTA_sink 0.69593

Estimated disappearance times:
      DT50  DT90 DT50back DT50_k1 DT50_k2
DMTA 12.08  52.9    15.92   12.08   29.45
M23  53.22 176.8       NA      NA      NA
M27  40.97 136.1       NA      NA      NA
M31  42.89 142.5       NA      NA      NA
```

Improved fit of the SFORB pathway model with two-component error

Listing 11: Hierarchical SFORB pathway fit with two-component error

```
saemix version used for fitting:      3.2
mkin version used for pre-fitting:  1.2.2
R version used for fitting:         4.2.2
Date of fit:     Thu Jan  5 15:32:42 2023
Date of summary: Thu Jan  5 16:42:52 2023

Equations:
d_DMTA_free/dt = - k_DMTA_free * DMTA_free - k_DMTA_free_bound *
           DMTA_free + k_DMTA_bound_free * DMTA_bound
d_DMTA_bound/dt = + k_DMTA_free_bound * DMTA_free - k_DMTA_bound_free *
           DMTA_bound
d_M23/dt = + f_DMTA_free_to_M23 * k_DMTA_free * DMTA_free - k_M23 * M23
d_M27/dt = + f_DMTA_free_to_M27 * k_DMTA_free * DMTA_free - k_M27 * M27
           + k_M31 * M31
d_M31/dt = + f_DMTA_free_to_M31 * k_DMTA_free * DMTA_free - k_M31 * M31

Data:
563 observations of 4 variable(s) grouped in 6 datasets

Model predictions using solution type deSolve

Fitted in 1286.938 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
          DMTA_free_0       log_k_DMTA_free log_k_DMTA_free_bound
              97.2597               -2.8229               -5.9851
log_k_DMTA_bound_free             log_k_M23             log_k_M27
              -3.3880               -3.9216               -4.2555
            log_k_M31          f_DMTA_ilr_1          f_DMTA_ilr_2
              -4.2054                0.1243                0.1306
         f_DMTA_ilr_3
              -1.7266

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
                     DMTA_free_0 log_k_DMTA_free log_k_DMTA_free_bound
DMTA_free_0                5.586          0.0000                 0.000
log_k_DMTA_free            0.000          0.9851                 0.000
log_k_DMTA_free_bound      0.000          0.0000                 1.309
log_k_DMTA_bound_free      0.000          0.0000                 0.000
log_k_M23                  0.000          0.0000                 0.000
log_k_M27                  0.000          0.0000                 0.000
log_k_M31                  0.000          0.0000                 0.000
f_DMTA_ilr_1               0.000          0.0000                 0.000
f_DMTA_ilr_2               0.000          0.0000                 0.000
f_DMTA_ilr_3               0.000          0.0000                 0.000
                     log_k_DMTA_bound_free log_k_M23 log_k_M27 log_k_M31
DMTA_free_0                          0.000    0.0000     0.000    0.0000
log_k_DMTA_free                      0.000    0.0000     0.000    0.0000
log_k_DMTA_free_bound                0.000    0.0000     0.000    0.0000
log_k_DMTA_bound_free                4.482    0.0000     0.000    0.0000
log_k_M23                            0.000    0.7768     0.000    0.0000
log_k_M27                            0.000    0.0000     1.096    0.0000
log_k_M31                            0.000    0.0000     0.000    0.9909
f_DMTA_ilr_1                         0.000    0.0000     0.000    0.0000
f_DMTA_ilr_2                         0.000    0.0000     0.000    0.0000
f_DMTA_ilr_3                         0.000    0.0000     0.000    0.0000
                     f_DMTA_ilr_1 f_DMTA_ilr_2 f_DMTA_ilr_3
DMTA_free_0                0.0000       0.0000       0.0000
log_k_DMTA_free            0.0000       0.0000       0.0000
log_k_DMTA_free_bound      0.0000       0.0000       0.0000
log_k_DMTA_bound_free      0.0000       0.0000       0.0000
log_k_M23                  0.0000       0.0000       0.0000
log_k_M27                  0.0000       0.0000       0.0000
log_k_M31                  0.0000       0.0000       0.0000
f_DMTA_ilr_1               0.7196       0.0000       0.0000
f_DMTA_ilr_2               0.0000       0.7359       0.0000
f_DMTA_ilr_3               0.0000       0.0000       0.4417

Starting values for error model parameters:
a.1 b.1
  1   1

Results:
```

```
Likelihood computed by importance sampling
   AIC  BIC logLik
  1830 1826 -894.2

Optimised parameters:
                           est.    lower     upper
DMTA_free_0              98.12951 96.04142 100.21760
log_k_DMTA_free          -2.80215 -3.29420  -2.31011
log_k_DMTA_free_bound    -6.20032 -7.00324  -5.39740
log_k_DMTA_bound_free    -4.56658 -4.80300  -4.33015
log_k_M23                -4.38232 -5.36504  -3.39961
log_k_M27                -4.10689 -4.58275  -3.63102
log_k_M31                -4.11686 -4.61305  -3.62067
f_DMTA_ilr_1              0.12460 -0.25920   0.50840
f_DMTA_ilr_2              0.11236 -0.29215   0.51686
f_DMTA_ilr_3             -1.70444 -1.89852  -1.51037
a.1                       0.82880  0.76216   0.89543
b.1                       0.03539  0.02900   0.04178
SD.DMTA_free_0            2.14737  0.38706   3.90767
SD.log_k_DMTA_free        0.61415  0.26600   0.96230
SD.log_k_DMTA_free_bound  0.90747  0.30720   1.50774
SD.log_k_M23              1.16637  0.44805   1.88469
SD.log_k_M27              0.55720  0.20526   0.90915
SD.log_k_M31              0.57721  0.20682   0.94760
SD.f_DMTA_ilr_1           0.46475  0.18610   0.74340
SD.f_DMTA_ilr_2           0.48722  0.19310   0.78135
SD.f_DMTA_ilr_3           0.23092  0.08873   0.37312

Correlation:
                       DMTA__0 lg__DMTA_ lg_k_DMTA_f_ lg_k_DMTA_b_ lg__M23
log_k_DMTA_free         0.0170
log_k_DMTA_free_bound   0.0607  0.0143
log_k_DMTA_bound_free   0.0544  0.0142    0.1550
log_k_M23              -0.0143 -0.0023   -0.0172      -0.0021
log_k_M27              -0.0169 -0.0025   -0.0153       0.0001       0.0023
log_k_M31              -0.0115 -0.0016   -0.0096       0.0021       0.0018
f_DMTA_ilr_1           -0.0022 -0.0003   -0.0015       0.0001       0.0232
f_DMTA_ilr_2           -0.0003 -0.0001   -0.0005      -0.0018       0.0123
f_DMTA_ilr_3           -0.0697 -0.0056   -0.0234      -0.0118       0.0317
                       lg__M27 lg__M31 f_DMTA__1 f_DMTA__2
log_k_DMTA_free
log_k_DMTA_free_bound
log_k_DMTA_bound_free
log_k_M23
log_k_M27
log_k_M31               0.0658
f_DMTA_ilr_1           -0.0244  0.0253
f_DMTA_ilr_2           -0.0220 -0.0667 -0.0279
f_DMTA_ilr_3            0.0643  0.0290 -0.0130    0.0039

Random effects:
                            est.   lower  upper
SD.DMTA_free_0            2.1474 0.38706 3.9077
SD.log_k_DMTA_free        0.6142 0.26600 0.9623
SD.log_k_DMTA_free_bound 0.9075 0.30720 1.5077
SD.log_k_M23              1.1664 0.44805 1.8847
SD.log_k_M27              0.5572 0.20526 0.9091
SD.log_k_M31              0.5772 0.20682 0.9476
SD.f_DMTA_ilr_1           0.4648 0.18610 0.7434
SD.f_DMTA_ilr_2           0.4872 0.19310 0.7813
SD.f_DMTA_ilr_3           0.2309 0.08873 0.3731

Variance model:
       est.  lower   upper
a.1 0.82880 0.7622 0.89543
b.1 0.03539 0.0290 0.04178

Backtransformed parameters:
                         est.     lower     upper
DMTA_free_0         98.129511 9.604e+01 1.002e+02
k_DMTA_free          0.060679 3.710e-02 9.925e-02
k_DMTA_free_bound    0.002029 9.089e-04 4.528e-03
k_DMTA_bound_free    0.010393 8.205e-03 1.317e-02
k_M23                0.012496 4.677e-03 3.339e-02
k_M27                0.016459 1.023e-02 2.649e-02
k_M31                0.016296 9.922e-03 2.676e-02
f_DMTA_free_to_M23   0.112408 6.387e-02 1.056e-01
f_DMTA_free_to_M27   0.094247 6.387e-02 1.056e-01
f_DMTA_free_to_M31   0.089695 6.387e-02 1.056e-01

Estimated Eigenvalues of SFORB model(s):
 DMTA_b1  DMTA_b2   DMTA_g
0.063108 0.009993 0.954272
```

```
Resulting formation fractions:
                    ff
DMTA_free_M23  0.11241
DMTA_free_M27  0.09425
DMTA_free_M31  0.08970
DMTA_free_sink 0.70365
DMTA_free      1.00000

Estimated disappearance times:
      DT50   DT90 DT50back DT50_DMTA_b1 DT50_DMTA_b2
DMTA 11.59  41.45    12.48        10.98        69.36
M23  55.47 184.26       NA           NA           NA
M27  42.11 139.90       NA           NA           NA
M31  42.54 141.30       NA           NA           NA
```

Session info

```
R version 4.2.3 (2023-03-15)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Debian GNU/Linux 12 (bookworm)

Matrix products: default
BLAS:   /usr/lib/x86_64-linux-gnu/openblas-serial/libblas.so.3
LAPACK: /usr/lib/x86_64-linux-gnu/openblas-serial/libopenblas-r0.3.21.so

locale:
 [1] LC_CTYPE=de_DE.UTF-8       LC_NUMERIC=C
 [3] LC_TIME=de_DE.UTF-8        LC_COLLATE=de_DE.UTF-8
 [5] LC_MONETARY=de_DE.UTF-8    LC_MESSAGES=de_DE.UTF-8
 [7] LC_PAPER=de_DE.UTF-8       LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C
[11] LC_MEASUREMENT=de_DE.UTF-8 LC_IDENTIFICATION=C

attached base packages:
[1] parallel  stats     graphics  grDevices utils     datasets  methods
[8] base

other attached packages:
[1] saemix_3.2        npde_3.3          knitr_1.42        mkin_1.2.3
[5] rmarkdown_2.21    nvimcom_0.9-133.1

loaded via a namespace (and not attached):
 [1] compiler_4.2.3    pillar_1.9.0      prettyunits_1.1.1 tools_4.2.3
 [5] pkgbuild_1.4.0    digest_0.6.31     mclust_6.0.0      evaluate_0.20
 [9] lifecycle_1.0.3   tibble_3.2.1      gtable_0.3.3      nlme_3.1-162
[13] lattice_0.21-8    pkgconfig_2.0.3   rlang_1.1.0       cli_3.6.1
[17] DBI_1.1.3         yaml_2.3.7        xfun_0.38         fastmap_1.1.1
[21] gridExtra_2.3     dplyr_1.1.1       generics_0.1.3    vctrs_0.6.1
[25] lmtest_0.9-40     grid_4.2.3        tidyselect_1.2.0  deSolve_1.35
[29] inline_0.3.19     glue_1.6.2        R6_2.5.1          processx_3.8.0
[33] fansi_1.0.4       callr_3.7.3       ggplot2_3.4.2     magrittr_2.0.3
[37] codetools_0.2-19  ps_1.7.4          scales_1.2.1      htmltools_0.5.5
[41] colorspace_2.1-0  utf8_1.2.3        munsell_0.5.0     crayon_1.5.2
[45] zoo_1.8-12
```

Hardware info

```
CPU model: AMD Ryzen 9 7950X 16-Core Processor

MemTotal:       64936316 kB
```