Testing hierarchical parent degradation kinetics with residue data on dimethenamid and dimethenamid-P

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Contents

Introduction **2**

Data **3**

Separate evaluations **10**

Hierarchichal model fits **11**
Parameter identifiability based on the Fisher Information Matrix 11
Alternative check of parameter identifiability 16

Conclusions **18**

Acknowledgements **18**

References **18**

Appendix **19**
Hierarchical model fit listings 19
Hierarchical model convergence plots 27
Session info 35
Hardware info 35

Introduction

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

It was assembled in the course of work package 1.1 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 1.2.2. 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()
if (Sys.info()["sysname"] == "Windows") {
  cl <- makePSOCKcluster(n_cores)
} else {
  cl <- makeForkCluster(n_cores)
}
```

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 still necessary:

- 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.
- The data for transformation products and 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$name == "DMTAP", "name"] <-  "DMTA"              # Rename DMTAP to DMTA
  ds_i <- subset(ds_i, name == "DMTA", c("name", "time", "value")) # Select data
  ds_i$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),
      label = paste0("tab:", ds_name), booktabs = TRUE))
    cat("\n\\clearpage\n")
}
```

Table 1: Dataset Calke

time	DMTA
0	95.8
0	98.7
14	60.5
30	39.1
59	15.2
120	4.8
120	4.6

Table 2: Dataset Borstel

time	DMTA
0.000000	100.5
0.000000	99.6
1.941295	91.9
1.941295	91.3
6.794534	81.8
6.794534	82.1
13.589067	69.1
13.589067	68.0
27.178135	51.4
27.178135	51.4
56.297565	27.6
56.297565	26.8
86.387643	15.7
86.387643	15.3
115.507073	7.9
115.507073	8.1

Table 3: Dataset Flaach

time	DMTA
0.0000000	96.5
0.0000000	96.8
0.0000000	97.0
0.6233856	82.9
0.6233856	86.7
0.6233856	87.4
1.8701567	72.8
1.8701567	69.9
1.8701567	71.9
4.3636989	51.4
4.3636989	52.9
4.3636989	48.6
8.7273979	28.5
8.7273979	27.3
8.7273979	27.5
13.0910968	14.8
13.0910968	13.4
13.0910968	14.4
17.4547957	7.7
17.4547957	7.3
17.4547957	8.1
26.1821936	2.0
26.1821936	1.5
26.1821936	1.9
34.9095915	1.3
34.9095915	1.0
34.9095915	1.1
43.6369893	0.9
43.6369893	0.7
43.6369893	0.7
52.3643872	0.6
52.3643872	0.4
52.3643872	0.5
74.8062674	0.4
74.8062674	0.3
74.8062674	0.3

Table 4: Dataset BBA 2.2

time	DMTA
0.0000000	98.09
0.0000000	98.77
0.7678922	93.52
0.7678922	92.03
2.3036765	88.39
2.3036765	87.18
5.3752452	69.38
5.3752452	71.06
10.7504904	45.21
10.7504904	46.81
16.1257355	30.54
16.1257355	30.07
21.5009807	21.60
21.5009807	20.41
32.2514711	9.10
32.2514711	9.70
43.0019614	6.58
43.0019614	6.31
53.7524518	3.47
53.7524518	3.52
64.5029421	3.40
64.5029421	3.67
91.3791680	1.62
91.3791680	1.62

Table 5: Dataset BBA 2.3

time	DMTA
0.0000000	99.33
0.0000000	97.44
0.6733938	93.73
0.6733938	93.77
2.0201814	87.84
2.0201814	89.82
4.7137565	71.61
4.7137565	71.42
9.4275131	45.60
9.4275131	45.42
14.1412696	31.12
14.1412696	31.68
18.8550262	23.20
18.8550262	24.13
28.2825393	9.43
28.2825393	9.82
37.7100523	7.08
37.7100523	8.64
47.1375654	4.41
47.1375654	4.78
56.5650785	4.92
56.5650785	5.08
80.1338612	2.13
80.1338612	2.23

Table 6: Dataset Elliot

time	DMTA
0.000000	97.5
0.000000	100.7
1.228478	86.4
1.228478	88.5
3.685435	69.8
3.685435	77.1
8.599349	59.0
8.599349	54.2
17.198697	31.3
17.198697	33.5
25.798046	19.6
25.798046	20.9
34.397395	13.3
34.397395	15.8
51.596092	6.7
51.596092	8.7
68.794789	8.8
68.794789	8.7
103.192184	6.0
103.192184	4.4
146.188928	3.3
146.188928	2.8
223.583066	1.4
223.583066	1.8
0.000000	93.4
0.000000	103.2
1.228478	89.2
1.228478	86.6
3.685435	78.2
3.685435	78.1
8.599349	55.6
8.599349	53.0
17.198697	33.7
17.198697	33.2
25.798046	20.9
25.798046	19.9
34.397395	18.2
34.397395	12.7
51.596092	7.8
51.596092	9.0
68.794789	11.4
68.794789	9.0
103.192184	3.9
103.192184	4.4
146.188928	2.6
146.188928	3.4
223.583066	2.0
223.583066	1.7

Separate evaluations

In order to obtain suitable starting parameters for the NLHM fits, separate fits of the four models to the data for each soil are generated using the `mmkin` function from the `mkin` package. In a first step, constant variance is assumed. Convergence is checked with the `status` function.

```
deg_mods <- c("SFO", "FOMC", "DFOP", "HS")
f_sep_const <- mmkin(
  deg_mods,
  dmta_ds,
  error_model = "const",
  quiet = TRUE)

status(f_sep_const) |> kable()
```

	Calke	Borstel	Flaach	BBA 2.2	BBA 2.3	Elliot
SFO	OK	OK	OK	OK	OK	OK
FOMC	OK	OK	OK	OK	OK	OK
DFOP	OK	OK	OK	OK	OK	OK
HS	OK	OK	OK	C	OK	OK

In the table above, OK indicates convergence, and C indicates failure to converge. All separate fits with constant variance converged, with the sole exception of the HS fit to the BBA 2.2 data. To prepare for fitting NLHM using the two-component error model, the separate fits are updated assuming two-component error.

```
f_sep_tc <- update(f_sep_const, error_model = "tc")
status(f_sep_tc) |> kable()
```

	Calke	Borstel	Flaach	BBA 2.2	BBA 2.3	Elliot
SFO	OK	OK	OK	OK	OK	OK
FOMC	OK	OK	OK	OK	C	OK
DFOP	OK	OK	C	OK	C	OK
HS	OK	C	OK	OK	OK	OK

Using the two-component error model, the one fit that did not converge with constant variance did converge, but other non-SFO fits failed to converge.

Hierarchichal model fits

The following code fits eight versions of hierarchical models to the data, using SFO, FOMC, DFOP and HS for the parent compound, and using either constant variance or two-component error for the error model. The default parameter distribution model in mkin allows for variation of all degradation parameters across the assumed population of soils. In other words, each degradation parameter is associated with a random effect as a first step. The `mhmkin` function makes it possible to fit all eight versions in parallel (given a sufficient number of computing cores being available) to save execution time.

Convergence plots and summaries for these fits are shown in the appendix.

```
f_saem <- mhmkin(list(f_sep_const, f_sep_tc), transformations = "saemix")
```

The output of the `status` function shows that all fits terminated successfully.

```
status(f_saem) |> kable()
```

	const	tc
SFO	OK	OK
FOMC	OK	OK
DFOP	OK	OK
HS	OK	OK

The AIC and BIC values show that the biphasic models DFOP and HS give the best fits.

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

	npar	AIC	BIC	Lik
SFO const	5	796.3	795.3	-393.2
SFO tc	6	798.3	797.1	-393.2
FOMC const	7	734.2	732.7	-360.1
FOMC tc	8	720.4	718.8	-352.2
DFOP const	9	711.8	710.0	-346.9
HS const	9	714.0	712.1	-348.0
DFOP tc	10	665.5	663.4	-322.8
HS tc	10	667.1	665.0	-323.6

The DFOP model is preferred here, as it has a better mechanistic basis for batch experiments with constant incubation conditions. Also, it shows the lowest AIC and BIC values in the first set of fits when combined with the two-component error model. Therefore, the DFOP model was selected for further refinements of the fits with the aim to make the model fully identifiable.

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(f_saem) |> kable()
```

	const	tc
SFO		b.1
FOMC		sd(DMTA_0)
DFOP	sd(k2)	sd(k2)
HS		sd(tb)

According to the `illparms` function, the fitted standard deviation of the second kinetic rate constant `k2` is ill-defined in both DFOP fits. This suggests that different values would be obtained for this standard deviation when using different starting values.

The thus identified overparameterisation is addressed by removing the random effect for `k2` from the parameter model.

```
f_saem_dfop_tc_no_ranef_k2 <- update(f_saem[["DFOP", "tc"]],
  no_random_effect = "k2")
```

For the resulting fit, it is checked whether there are still ill-defined parameters,

```
illparms(f_saem_dfop_tc_no_ranef_k2)
```

which is not the case. Below, the refined model is compared with the previous best model. The model without random effect for `k2` is a reduced version of the previous model. Therefore, the models are nested and can be compared using the likelihood ratio test. This is achieved with the argument `test = TRUE` to the `anova` function.

```
anova(f_saem[["DFOP", "tc"]], f_saem_dfop_tc_no_ranef_k2, test = TRUE) |>
  kable(format.args = list(digits = 4))
```

	npar	AIC	BIC	Lik	Chisq	Df	Pr(>Chisq)
f_saem_dfop_tc_no_ranef_k2	9	663.8	661.9	-322.9	NA	NA	NA
f_saem[[“DFOP”, “tc”]]	10	665.5	663.4	-322.8	0.2809	1	0.5961

The AIC and BIC criteria are lower after removal of the ill-defined random effect for `k2`. The p value of the likelihood ratio test is much greater than 0.05, indicating that the model with the higher likelihood (here the model with random effects for all degradation parameters `f_saem[["DFOP", "tc"]]`) does not fit significantly better than the model with the lower likelihood (the reduced model `f_saem_dfop_tc_no_ranef_k2`).

Therefore, AIC, BIC and likelihood ratio test suggest the use of the reduced model.

The convergence of the fit is checked visually.

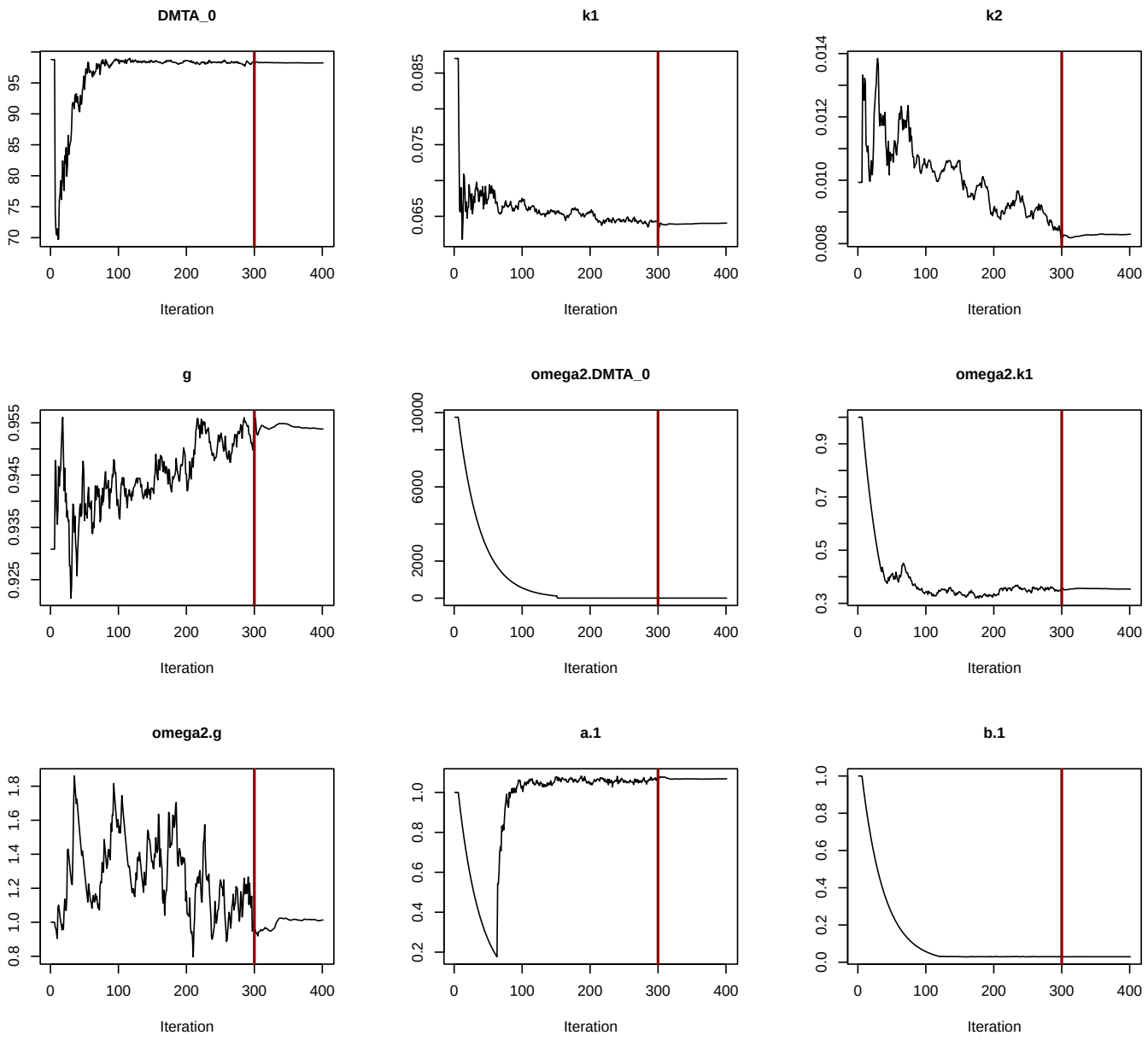

Figure 1: Convergence plot for the NLHM DFOP fit with two-component error and without a random effect on 'k2'

All parameters appear to have converged to a satisfactory degree. The final fit is plotted using the plot method from the mkin package.

```
plot(f_saem_dfop_tc_no_ranef_k2)
```

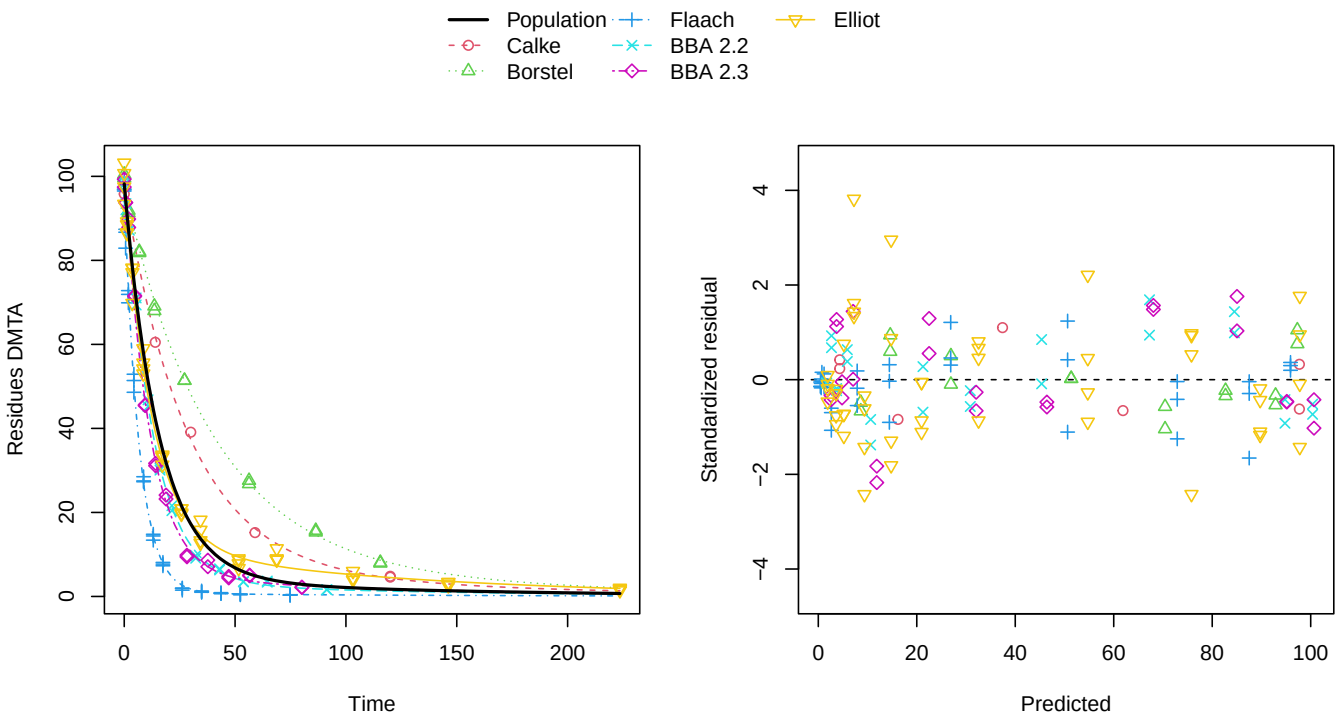

Figure 2: Plot of the final NLHM DFOP fit

Finally, a summary report of the fit is produced.

```
summary(f_saem_dfop_tc_no_ranef_k2)
```

```
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 22:38:36 2023
Date of summary: Thu Jan  5 22:38:36 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

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 4.065 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
   DMTA_0        k1        k2         g
98.759266  0.087034  0.009933  0.930827

Fixed degradation parameter values:
None
```

```
Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k1 k2 g
DMTA_0  98.76  0  0 0
k1       0.00  1  0 0
k2       0.00  0  1 0
g        0.00  0  0 1

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

Results:

Likelihood computed by importance sampling
    AIC   BIC logLik
  663.8 661.9 -322.9

Optimised parameters:
               est.     lower     upper
DMTA_0    98.228939 96.285869 100.17201
k1         0.064063  0.033477   0.09465
k2         0.008297  0.005824   0.01077
g          0.953821  0.914328   0.99331
a.1        1.068479  0.869538   1.26742
b.1        0.029424  0.022406   0.03644
SD.DMTA_0  2.030437  0.404824   3.65605
SD.k1      0.594692  0.256660   0.93272
SD.g       1.006754  0.361327   1.65218

Correlation:
   DMTA_0  k1      k2
k1  0.0218
k2  0.0556  0.0355
g  -0.0516 -0.0284 -0.2800

Random effects:
            est.  lower  upper
SD.DMTA_0 2.0304 0.4048 3.6560
SD.k1     0.5947 0.2567 0.9327
SD.g      1.0068 0.3613 1.6522

Variance model:
       est.   lower   upper
a.1 1.06848 0.86954 1.26742
b.1 0.02942 0.02241 0.03644

Estimated disappearance times:
      DT50 DT90 DT50back DT50_k1 DT50_k2
DMTA 11.45 41.4    12.46   10.82   83.54
```

Alternative check of parameter identifiability

The parameter check used in the `illparms` function is based on a quadratic approximation of the likelihood surface near its optimum, which is calculated using the Fisher Information Matrix (FIM). An alternative way to check parameter identifiability (Duchesne et al. 2021) based on a multistart approach has recently been implemented in mkin.

The graph below shows boxplots of the parameters obtained in 50 runs of the saem algorithm with different parameter combinations, sampled from the range of the parameters obtained for the individual datasets fitted separately using nonlinear regression.

```
f_saem_dfop_tc_multi <- multistart(f_saem[["DFOP", "tc"]], n = 50, cores = 15)
```

```
par(mar = c(6.1, 4.1, 2.1, 2.1))
parplot(f_saem_dfop_tc_multi, lpos = "bottomright", ylim = c(0.3, 10), las = 2)
```

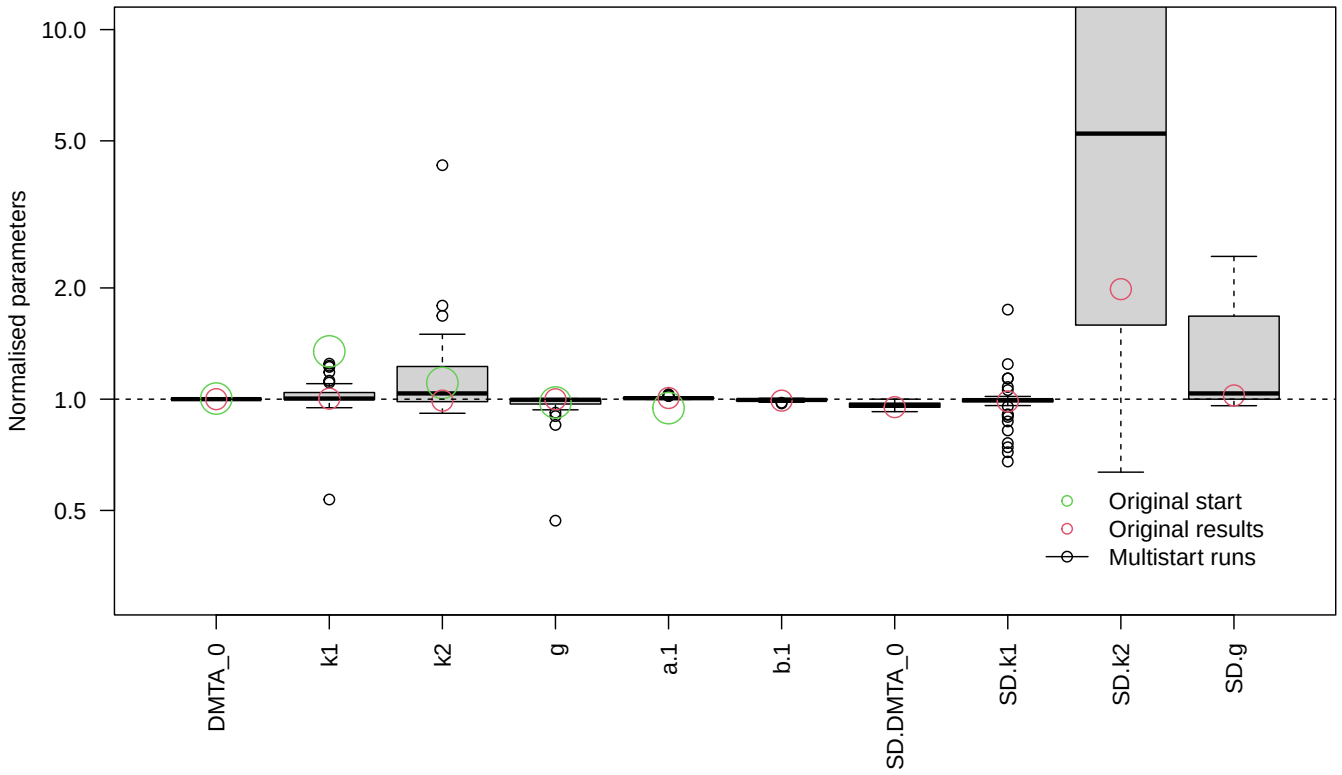

Figure 3: Scaled parameters from the multistart runs, full model

The graph clearly confirms the lack of identifiability of the variance of `k2` in the full model. The overparameterisation of the model also indicates a lack of identifiability of the variance of parameter `g`.

The parameter boxplots of the multistart runs with the reduced model shown below indicate that all runs give similar results, regardless of the starting parameters.

```
f_saem_dfop_tc_no_ranef_k2_multi <- multistart(f_saem_dfop_tc_no_ranef_k2,
  n = 50, cores = 15)
```

```
par(mar = c(6.1, 4.1, 2.1, 2.1))
parplot(f_saem_dfop_tc_no_ranef_k2_multi, ylim = c(0.5, 2), las = 2,
  lpos = "bottomright")
```

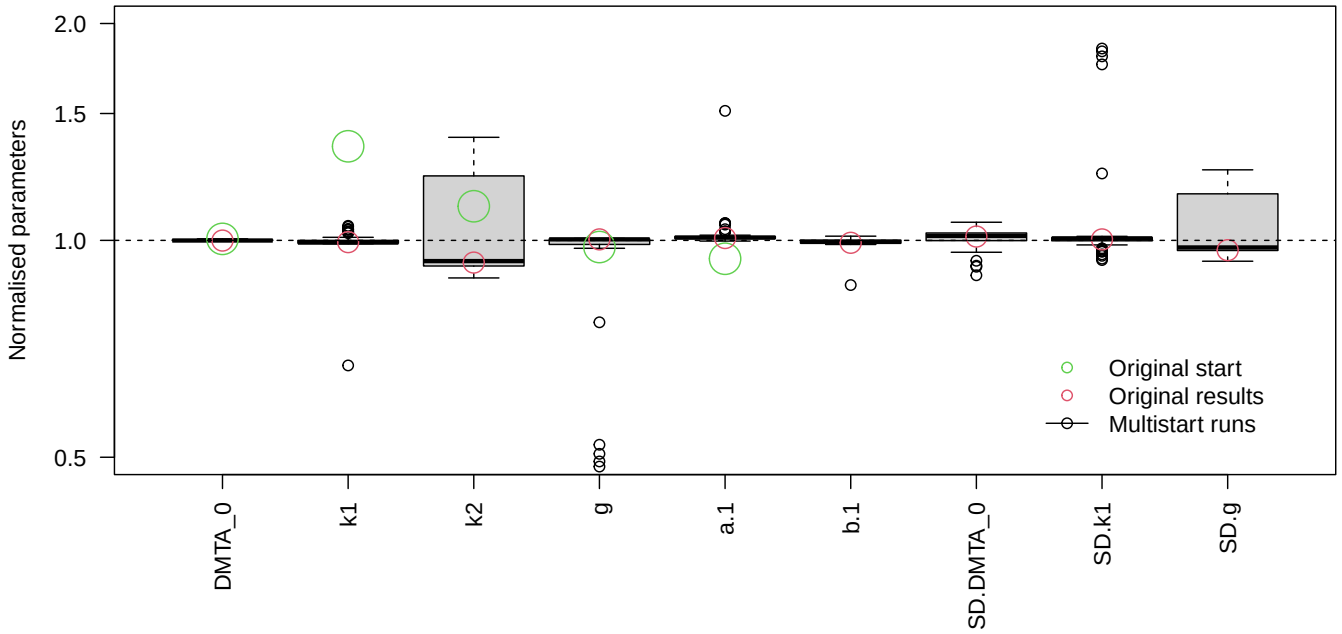

Figure 4: Scaled parameters from the multistart runs, reduced model

When only the parameters of the top 25% of the fits are shown (based on a feature introduced in mkin 1.2.2 currently under development), the scatter is even less as shown below.

```
par(mar = c(6.1, 4.1, 2.1, 2.1))
parplot(f_saem_dfop_tc_no_ranef_k2_multi, ylim = c(0.5, 2), las = 2, llquant = 0.25,
  lpos = "bottomright")
```

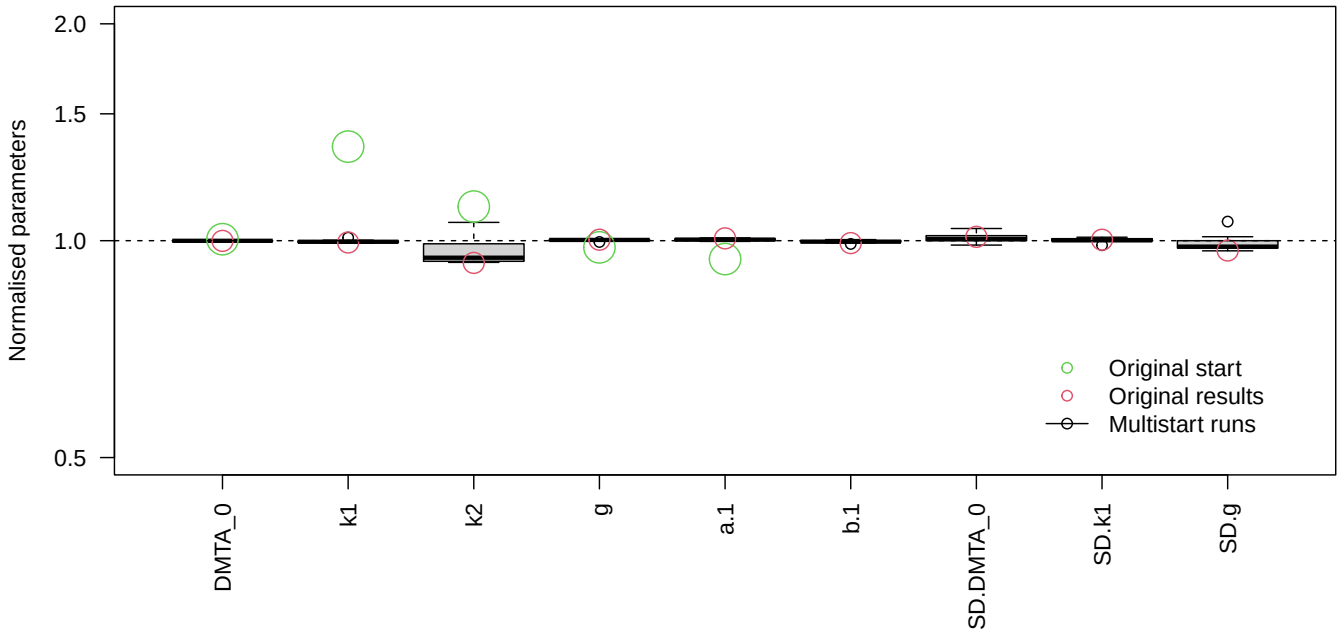

Figure 5: Scaled parameters from the multistart runs, reduced model, fits with the top 25% likelihood values

Conclusions

Fitting the four parent degradation models SFO, FOMC, DFOP and HS as part of hierarchical model fits with two different error models and normal distributions of the transformed degradation parameters works without technical problems. The biphasic models DFOP and HS gave the best fit to the data, but the default parameter distribution model was not fully identifiable. Removing the random effect for the second kinetic rate constant of the DFOP model resulted in a reduced model that was fully identifiable and showed the lowest values for the model selection criteria AIC and BIC. The reliability of the identification of all model parameters was confirmed using multiple starting values.

Acknowledgements

The helpful comments by Janina Wöltjen of the German Environment Agency 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.

Appendix

Hierarchical model fit listings

Listing 1: Hierarchical mkin fit of the SFO model with error model const

```
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 22:38:28 2023
Date of summary: Thu Jan  5 22:39:43 2023

Equations:
d_DMTA/dt = - k_DMTA * DMTA

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 0.837 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
 DMTA_0  k_DMTA
97.2953  0.0566

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k_DMTA
DMTA_0   97.3      0
k_DMTA    0.0      1

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
    AIC   BIC logLik
  796.3 795.3 -393.2

Optimised parameters:
             est.    lower   upper
DMTA_0    97.28130 95.71113 98.8515
k_DMTA     0.05665  0.02909  0.0842
a.1        2.66442  2.35579  2.9731
SD.DMTA_0  1.54776  0.15447  2.9411
SD.k_DMTA  0.60690  0.26248  0.9513

Correlation:
       DMTA_0
k_DMTA 0.0168

Random effects:
            est.  lower  upper
SD.DMTA_0 1.5478 0.1545 2.9411
SD.k_DMTA 0.6069 0.2625 0.9513

Variance model:
     est. lower upper
a.1 2.664 2.356 2.973

Estimated disappearance times:
      DT50  DT90
DMTA 12.24 40.65
```

Listing 2: Hierarchical mkin fit of the SFO model with error model tc

```
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 22:38:29 2023
Date of summary: Thu Jan  5 22:39:43 2023

Equations:
d_DMTA/dt = - k_DMTA * DMTA

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 2.19 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
  DMTA_0   k_DMTA
96.99175  0.05603

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k_DMTA
DMTA_0  96.99      0
k_DMTA   0.00      1

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

Results:

Likelihood computed by importance sampling
    AIC   BIC logLik
  798.3 797.1 -393.2

Optimised parameters:
               est.     lower    upper
DMTA_0    97.271822 95.703157 98.84049
k_DMTA     0.056638  0.029110  0.08417
a.1        2.660081  2.230398  3.08976
b.1        0.001665 -0.006911  0.01024
SD.DMTA_0  1.545520  0.145035  2.94601
SD.k_DMTA  0.606422  0.262274  0.95057

Correlation:
       DMTA_0
k_DMTA 0.0169

Random effects:
            est.  lower  upper
SD.DMTA_0 1.5455 0.1450 2.9460
SD.k_DMTA 0.6064 0.2623 0.9506

Variance model:
        est.     lower   upper
a.1 2.660081  2.230398 3.08976
b.1 0.001665 -0.006911 0.01024

Estimated disappearance times:
      DT50  DT90
DMTA 12.24 40.65
```

Listing 3: Hierarchical mkin fit of the FOMC model with error model const

```
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 22:38:28 2023
Date of summary: Thu Jan  5 22:39:43 2023

Equations:
d_DMTA/dt = - (alpha/beta) * 1/((time/beta) + 1) * DMTA

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 1.238 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
 DMTA_0   alpha    beta
 98.292   9.909 156.341

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 alpha beta
DMTA_0  98.29     0    0
alpha    0.00     1    0
beta     0.00     0    1

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
    AIC   BIC logLik
  734.2 732.7 -360.1

Optimised parameters:
             est.   lower   upper
DMTA_0     98.3435 96.9033  99.784
alpha       7.2007  2.5889  11.812
beta      112.8746 34.8816 190.868
a.1         2.0459  1.8054   2.286
SD.DMTA_0   1.4795  0.2717   2.687
SD.alpha    0.6396  0.1509   1.128
SD.beta     0.6874  0.1587   1.216

Correlation:
      DMTA_0  alpha
alpha -0.1125
beta  -0.1227  0.3632

Random effects:
            est.  lower upper
SD.DMTA_0 1.4795 0.2717 2.687
SD.alpha  0.6396 0.1509 1.128
SD.beta   0.6874 0.1587 1.216

Variance model:
     est. lower upper
a.1 2.046 1.805 2.286

Estimated disappearance times:
      DT50  DT90 DT50back
DMTA 11.41 42.53     12.8
```

Listing 4: Hierarchical mkin fit of the FOMC model with error model tc

```
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 22:38:30 2023
Date of summary: Thu Jan  5 22:39:43 2023

Equations:
d_DMTA/dt = - (alpha/beta) * 1/((time/beta) + 1) * DMTA

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 2.635 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
DMTA_0  alpha   beta
98.772  4.663 92.597

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 alpha beta
DMTA_0  98.77     0    0
alpha    0.00     1    0
beta     0.00     0    1

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

Results:

Likelihood computed by importance sampling
    AIC   BIC logLik
  720.4 718.8 -352.2

Optimised parameters:
             est.    lower     upper
DMTA_0    98.99136 97.26011 100.72261
alpha      5.86312  2.57485   9.15138
beta      88.55571 29.20889 147.90254
a.1        1.51063  1.24384   1.77741
b.1        0.02824  0.02040   0.03609
SD.DMTA_0  1.57436 -0.04867   3.19739
SD.alpha   0.59871  0.17132   1.02611
SD.beta    0.72994  0.22849   1.23139

Correlation:
      DMTA_0  alpha
alpha -0.1363
beta  -0.1414  0.2542

Random effects:
            est.    lower upper
SD.DMTA_0 1.5744 -0.04867 3.197
SD.alpha  0.5987  0.17132 1.026
SD.beta   0.7299  0.22849 1.231

Variance model:
       est.  lower   upper
a.1 1.51063 1.2438 1.77741
b.1 0.02824 0.0204 0.03609

Estimated disappearance times:
      DT50 DT90 DT50back
DMTA 11.11 42.6    12.82
```

Listing 5: Hierarchical mkin fit of the DFOP model with error model const

```
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 22:38:29 2023
Date of summary: Thu Jan  5 22:39:43 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

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 1.567 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
  DMTA_0       k1       k2        g
98.64383  0.09211  0.02999  0.76814

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k1 k2 g
DMTA_0  98.64  0  0 0
k1       0.00  1  0 0
k2       0.00  0  1 0
g        0.00  0  0 1

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
    AIC BIC logLik
  711.8 710 -346.9

Optimised parameters:
               est.     lower    upper
DMTA_0    98.092481 96.573898 99.61106
k1         0.062499  0.030336  0.09466
k2         0.009065 -0.005133  0.02326
g          0.948967  0.862079  1.03586
a.1        1.821671  1.604774  2.03857
SD.DMTA_0  1.677785  0.472066  2.88350
SD.k1      0.634962  0.270788  0.99914
SD.k2      1.033498 -0.205994  2.27299
SD.g       1.710046  0.428642  2.99145

Correlation:
   DMTA_0  k1      k2
k1  0.0246
k2  0.0491  0.0953
g  -0.0552 -0.0889 -0.4795

Random effects:
           est.   lower  upper
SD.DMTA_0 1.678  0.4721 2.8835
SD.k1     0.635  0.2708 0.9991
SD.k2     1.033 -0.2060 2.2730
SD.g      1.710  0.4286 2.9914

Variance model:
     est. lower upper
a.1 1.822 1.605 2.039

Estimated disappearance times:
      DT50 DT90 DT50back DT50_k1 DT50_k2
DMTA 11.79 42.8    12.88   11.09   76.46
```

Listing 6: Hierarchical mkin fit of the DFOP model with error model tc

```
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 22:38:30 2023
Date of summary: Thu Jan  5 22:39:43 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

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 3.04 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
   DMTA_0        k1        k2         g
98.759266  0.087034  0.009933  0.930827

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k1 k2 g
DMTA_0  98.76  0  0 0
k1       0.00  1  0 0
k2       0.00  0  1 0
g        0.00  0  0 1

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

Results:

Likelihood computed by importance sampling
    AIC   BIC logLik
  665.5 663.4 -322.8

Optimised parameters:
               est.     lower     upper
DMTA_0    98.377019 96.447952 100.30609
k1         0.064843  0.034607   0.09508
k2         0.008895  0.006368   0.01142
g          0.949696  0.903815   0.99558
a.1        1.065241  0.865754   1.26473
b.1        0.029340  0.022336   0.03634
SD.DMTA_0  2.007754  0.387982   3.62753
SD.k1      0.580473  0.250286   0.91066
SD.k2      0.006105 -4.920337   4.93255
SD.g       1.097149  0.412779   1.78152

Correlation:
   DMTA_0  k1      k2
k1  0.0235
k2  0.0595  0.0424
g  -0.0470 -0.0278 -0.2731

Random effects:
              est.   lower  upper
SD.DMTA_0 2.007754  0.3880 3.6275
SD.k1     0.580473  0.2503 0.9107
SD.k2     0.006105 -4.9203 4.9325
SD.g      1.097149  0.4128 1.7815

Variance model:
       est.   lower   upper
a.1 1.06524 0.86575 1.26473
b.1 0.02934 0.02234 0.03634

Estimated disappearance times:
      DT50  DT90 DT50back DT50_k1 DT50_k2
DMTA 11.36 41.32    12.44   10.69   77.92
```

Listing 7: Hierarchical mkin fit of the HS model with error model const

```
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 22:38:29 2023
Date of summary: Thu Jan  5 22:39:43 2023

Equations:
d_DMTA/dt = - ifelse(time <= tb, k1, k2) * DMTA

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 1.882 s
Using 300, 100 iterations and 9 chains

Variance model: Constant variance

Starting values for degradation parameters:
  DMTA_0       k1       k2       tb
97.82176  0.06931  0.02997 11.13945

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k1 k2 tb
DMTA_0  97.82  0  0  0
k1       0.00  1  0  0
k2       0.00  0  1  0
tb       0.00  0  0  1

Starting values for error model parameters:
a.1
  1

Results:

Likelihood computed by importance sampling
  AIC   BIC logLik
  714 712.1   -348

Optimised parameters:
              est.    lower    upper
DMTA_0    98.16102 96.47747 99.84456
k1         0.07876  0.05261  0.10491
k2         0.02227  0.01706  0.02747
tb        13.99089 -7.40049 35.38228
a.1        1.82305  1.60700  2.03910
SD.DMTA_0  1.88413  0.56204  3.20622
SD.k1      0.34292  0.10482  0.58102
SD.k2      0.19851  0.01718  0.37985
SD.tb      1.68168  0.58064  2.78272

Correlation:
   DMTA_0  k1      k2
k1  0.0142
k2  0.0001 -0.0025
tb  0.0165 -0.1256 -0.0301

Random effects:
           est.   lower  upper
SD.DMTA_0 1.8841 0.56204 3.2062
SD.k1     0.3429 0.10482 0.5810
SD.k2     0.1985 0.01718 0.3798
SD.tb     1.6817 0.58064 2.7827

Variance model:
     est. lower upper
a.1 1.823 1.607 2.039

Estimated disappearance times:
      DT50  DT90 DT50back DT50_k1 DT50_k2
DMTA 8.801 67.91    20.44   8.801   31.13
```

Listing 8: Hierarchical mkin fit of the HS model with error model tc

```
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 22:38:30 2023
Date of summary: Thu Jan  5 22:39:43 2023

Equations:
d_DMTA/dt = - ifelse(time <= tb, k1, k2) * DMTA

Data:
155 observations of 1 variable(s) grouped in 6 datasets

Model predictions using solution type analytical

Fitted in 3.293 s
Using 300, 100 iterations and 9 chains

Variance model: Two-component variance function

Starting values for degradation parameters:
  DMTA_0       k1       k2       tb
98.45190  0.07525  0.02576 19.19375

Fixed degradation parameter values:
None

Starting values for random effects (square root of initial entries in omega):
       DMTA_0 k1 k2 tb
DMTA_0  98.45  0  0  0
k1       0.00  1  0  0
k2       0.00  0  1  0
tb       0.00  0  0  1

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

Results:

Likelihood computed by importance sampling
    AIC BIC logLik
  667.1 665 -323.6

Optimised parameters:
              est.    lower    upper
DMTA_0    97.76570 95.81350 99.71791
k1         0.05855  0.03080  0.08630
k2         0.02337  0.01664  0.03010
tb        31.09638 29.38289 32.80987
a.1        1.08835  0.88590  1.29080
b.1        0.02964  0.02257  0.03671
SD.DMTA_0  2.04877  0.42607  3.67147
SD.k1      0.59166  0.25621  0.92711
SD.k2      0.30698  0.09561  0.51835
SD.tb      0.01274 -0.10914  0.13462

Correlation:
   DMTA_0  k1      k2
k1  0.0160
k2 -0.0070 -0.0024
tb -0.0668 -0.0103 -0.2013

Random effects:
             est.    lower  upper
SD.DMTA_0 2.04877  0.42607 3.6715
SD.k1     0.59166  0.25621 0.9271
SD.k2     0.30698  0.09561 0.5183
SD.tb     0.01274 -0.10914 0.1346

Variance model:
       est.   lower   upper
a.1 1.08835 0.88590 1.29080
b.1 0.02964 0.02257 0.03671

Estimated disappearance times:
      DT50  DT90 DT50back DT50_k1 DT50_k2
DMTA 11.84 51.71    15.57   11.84   29.66
```

Hierarchical model convergence plots

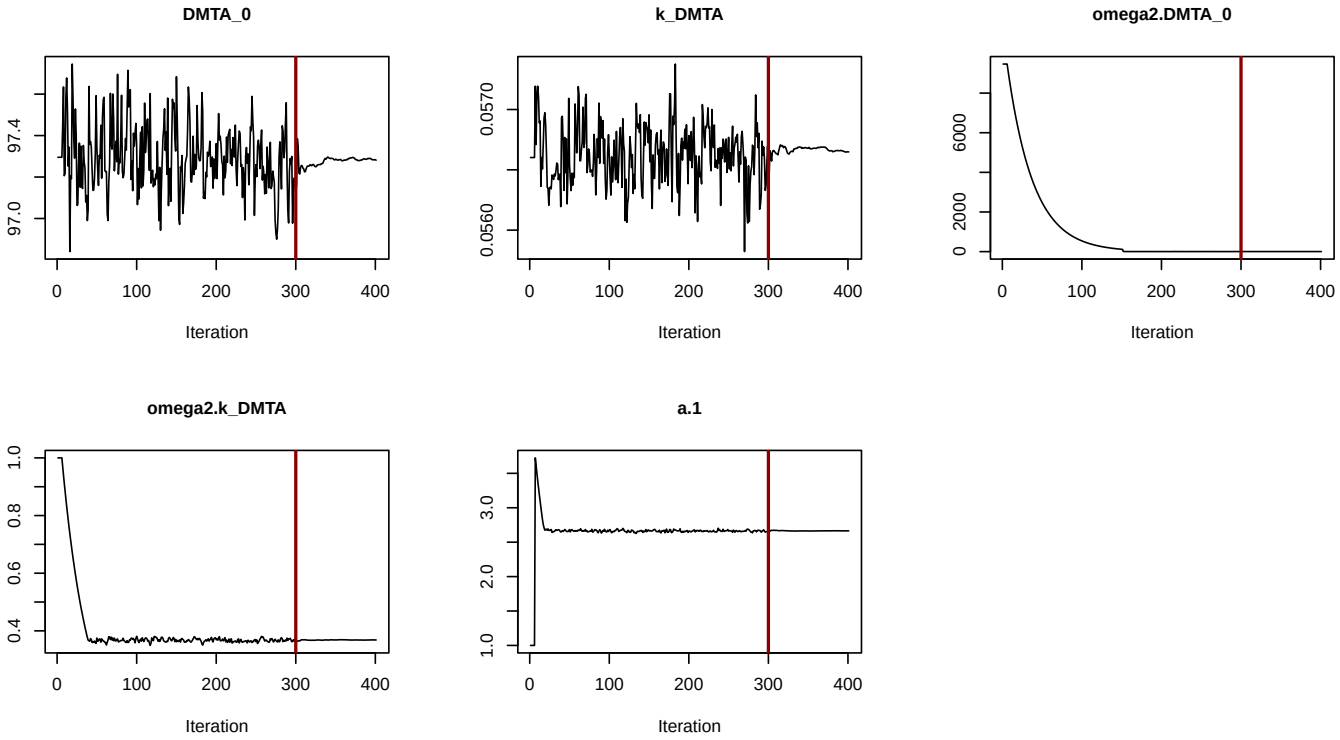

Figure 6: Convergence plot for the NLHM SFO fit with constant variance

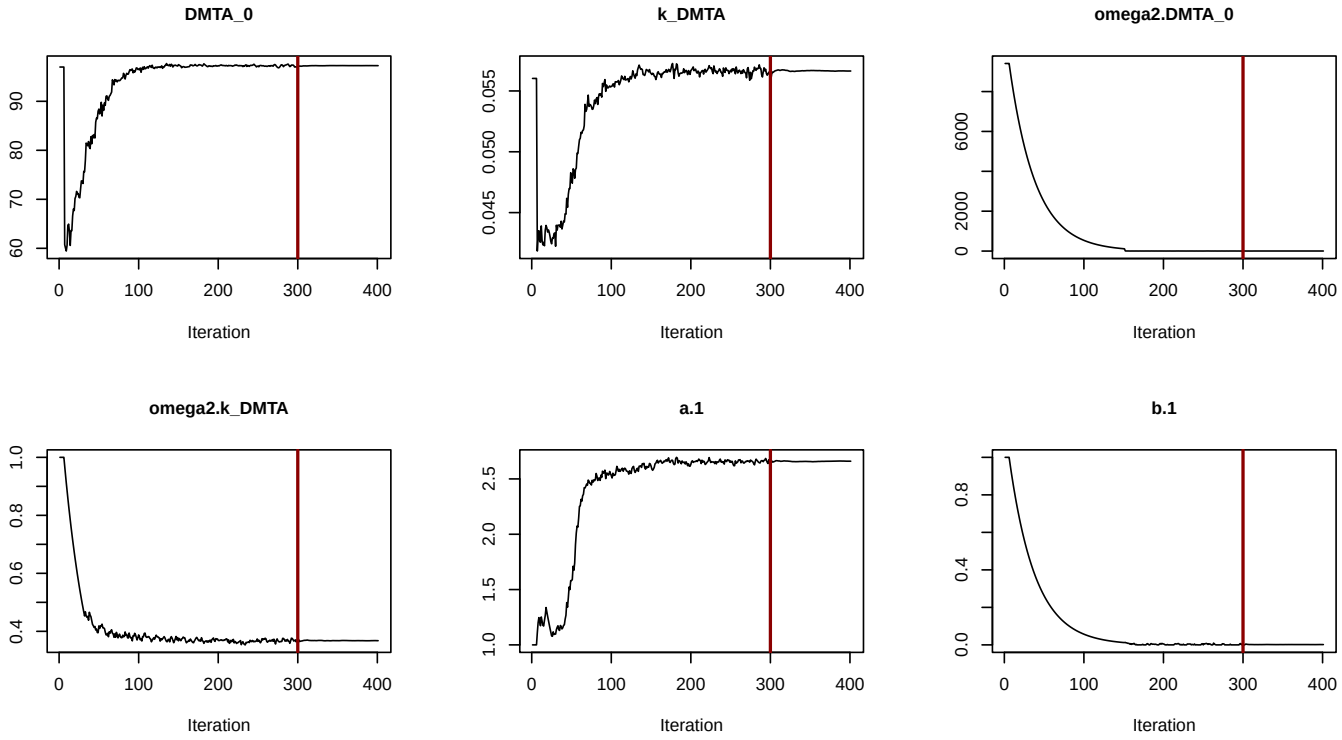

Figure 7: Convergence plot for the NLHM SFO fit with two-component error

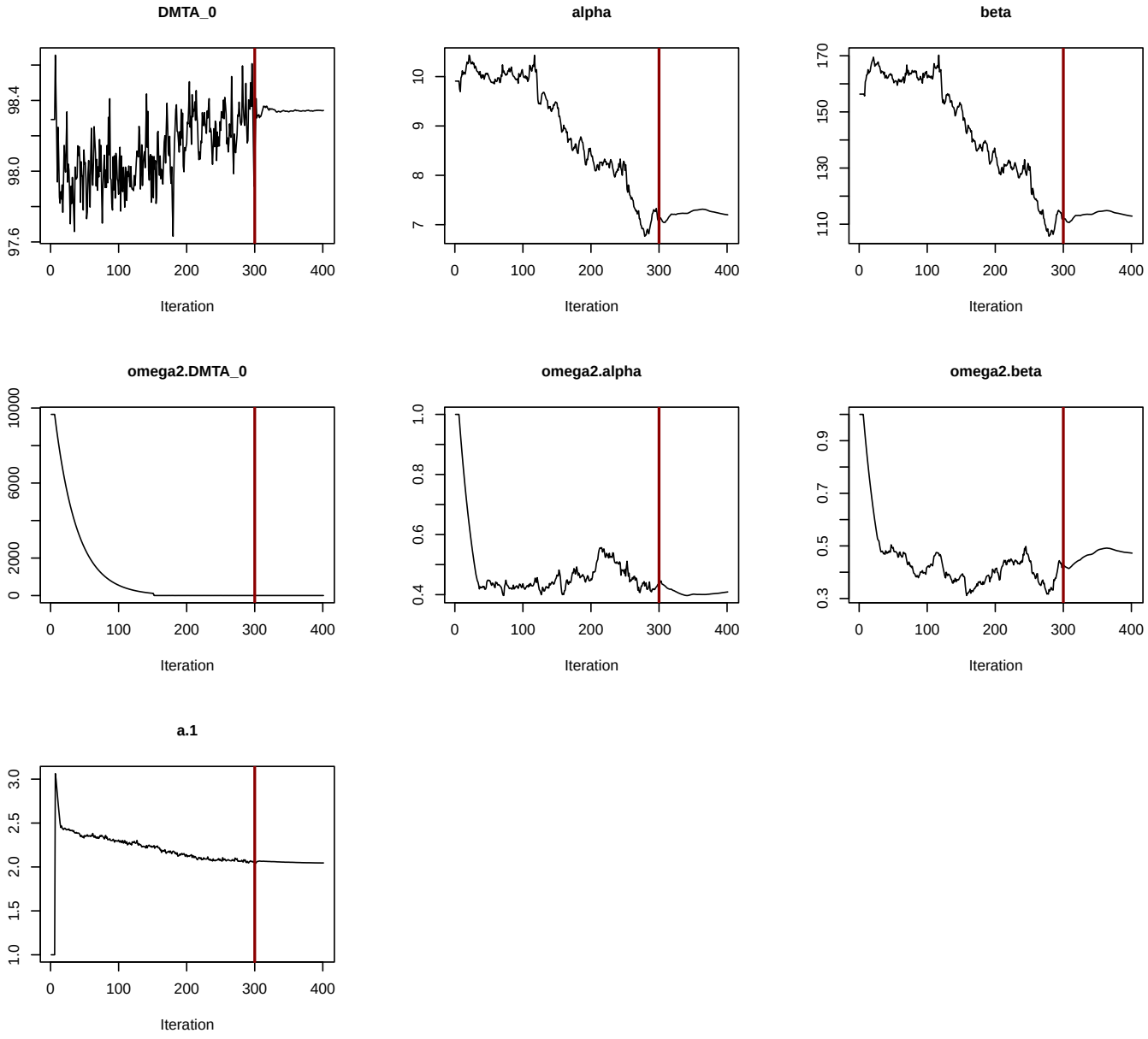

Figure 8: Convergence plot for the NLHM FOMC fit with constant variance

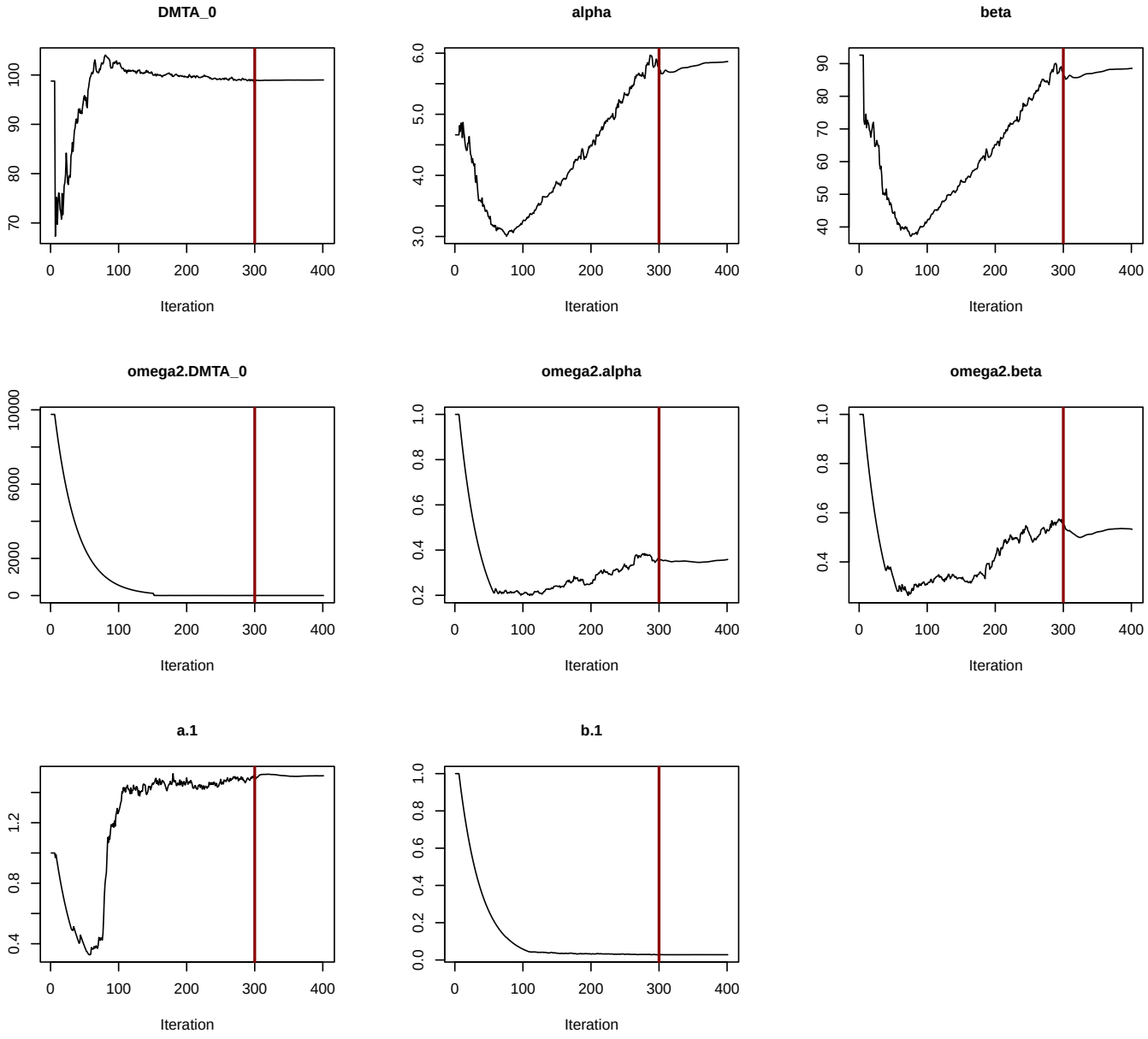

Figure 9: Convergence plot for the NLHM FOMC fit with two-component error

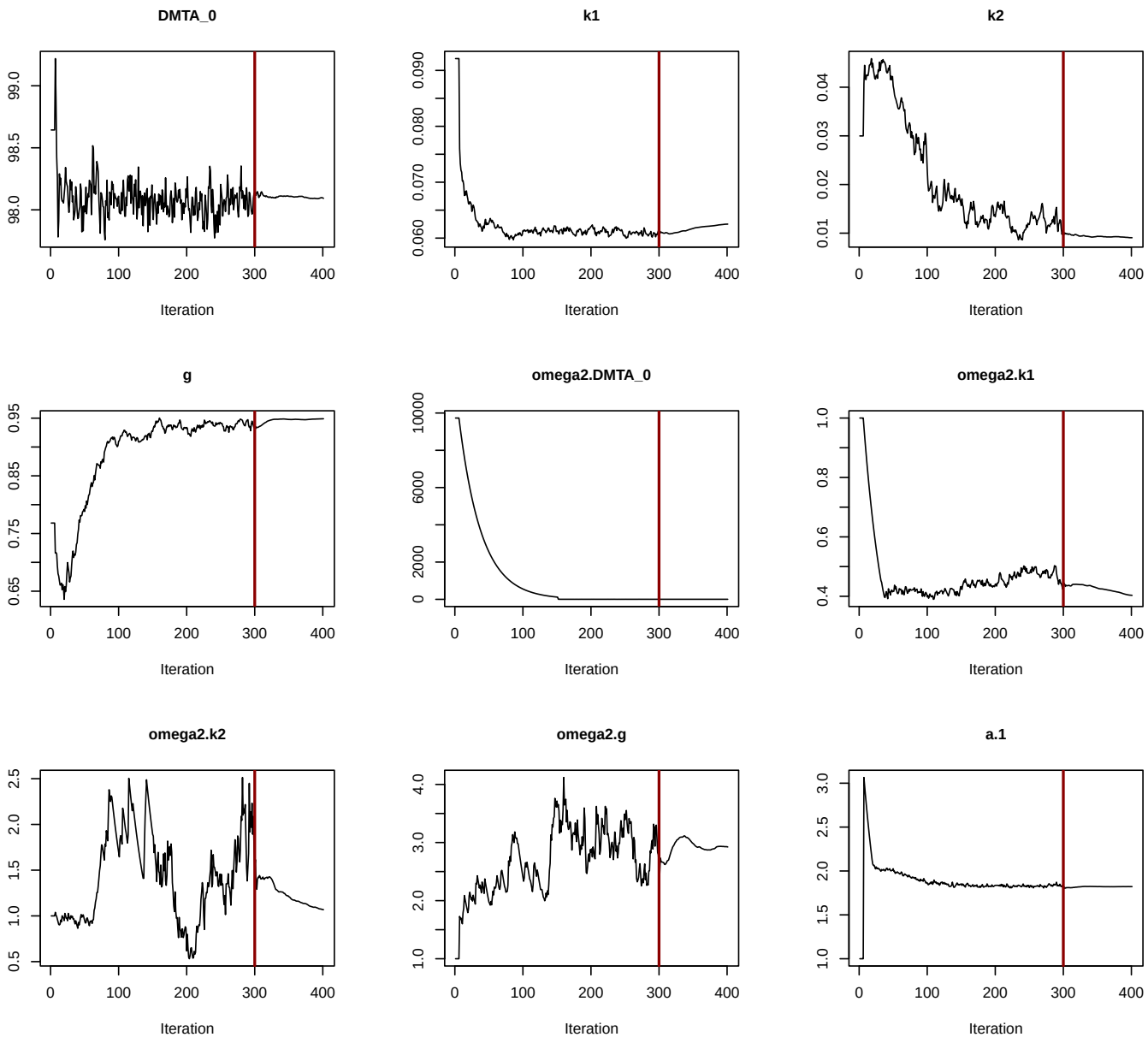

Figure 10: Convergence plot for the NLHM DFOP fit with constant variance

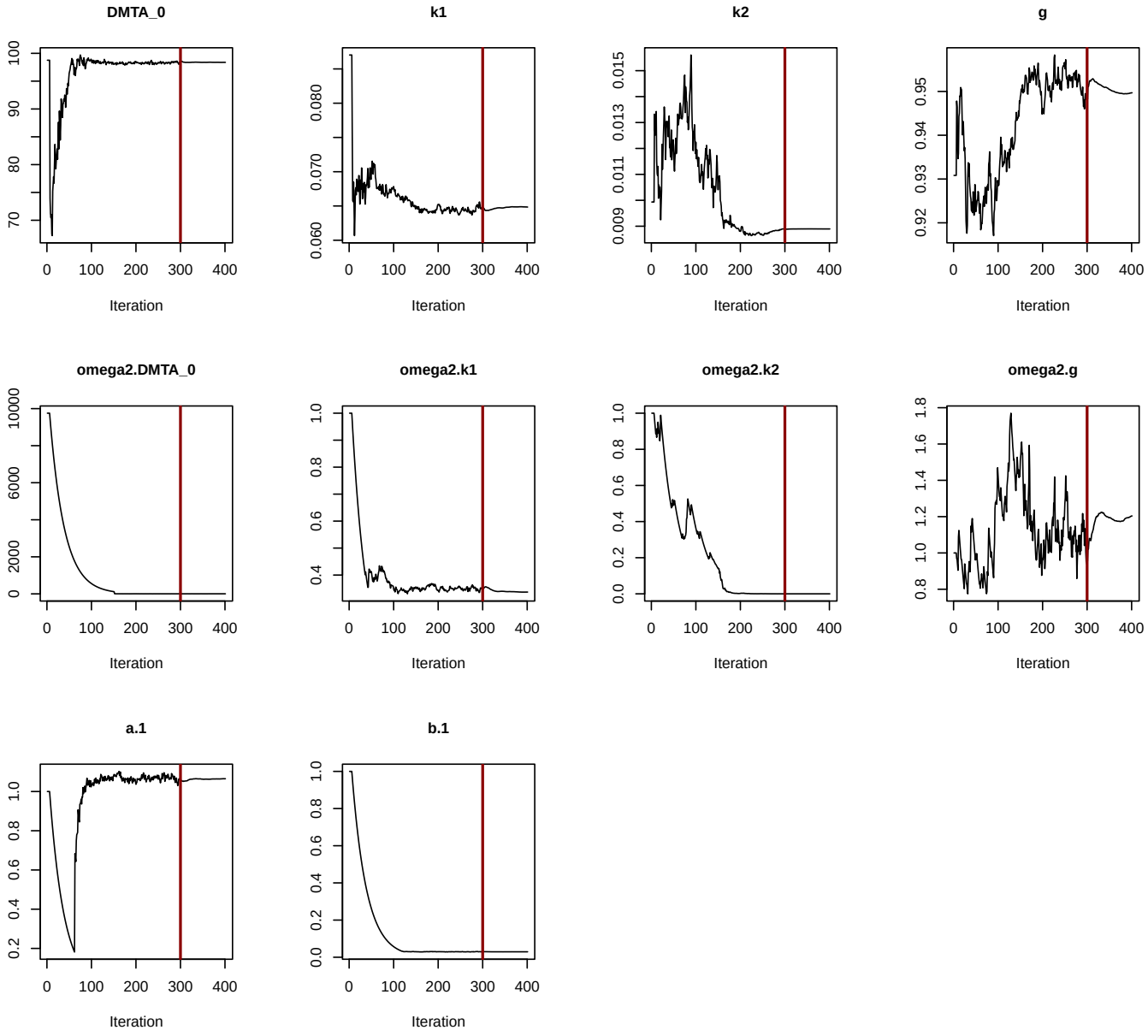

Figure 11: Convergence plot for the NLHM DFOP fit with two-component error

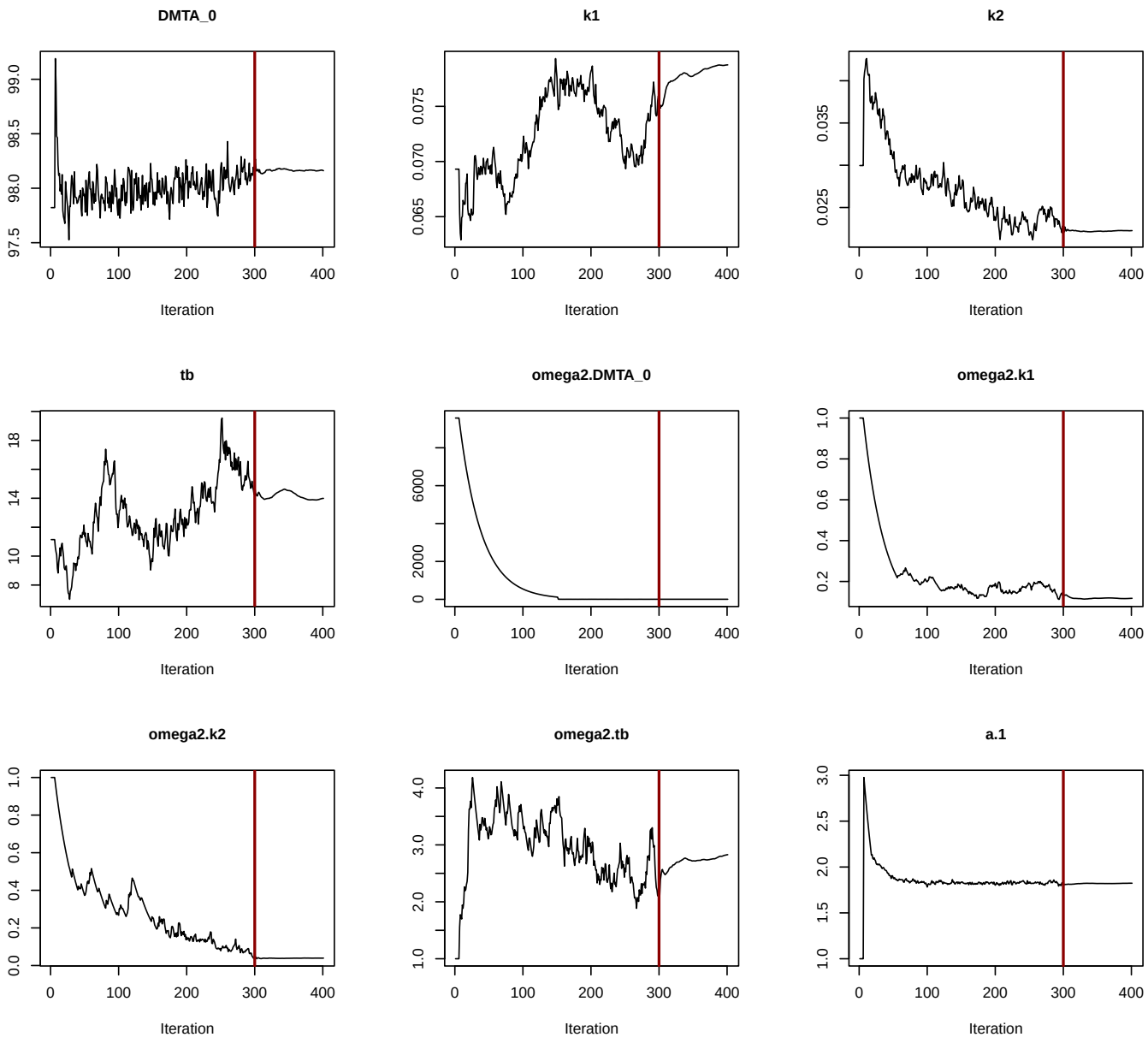

Figure 12: Convergence plot for the NLHM HS fit with constant variance

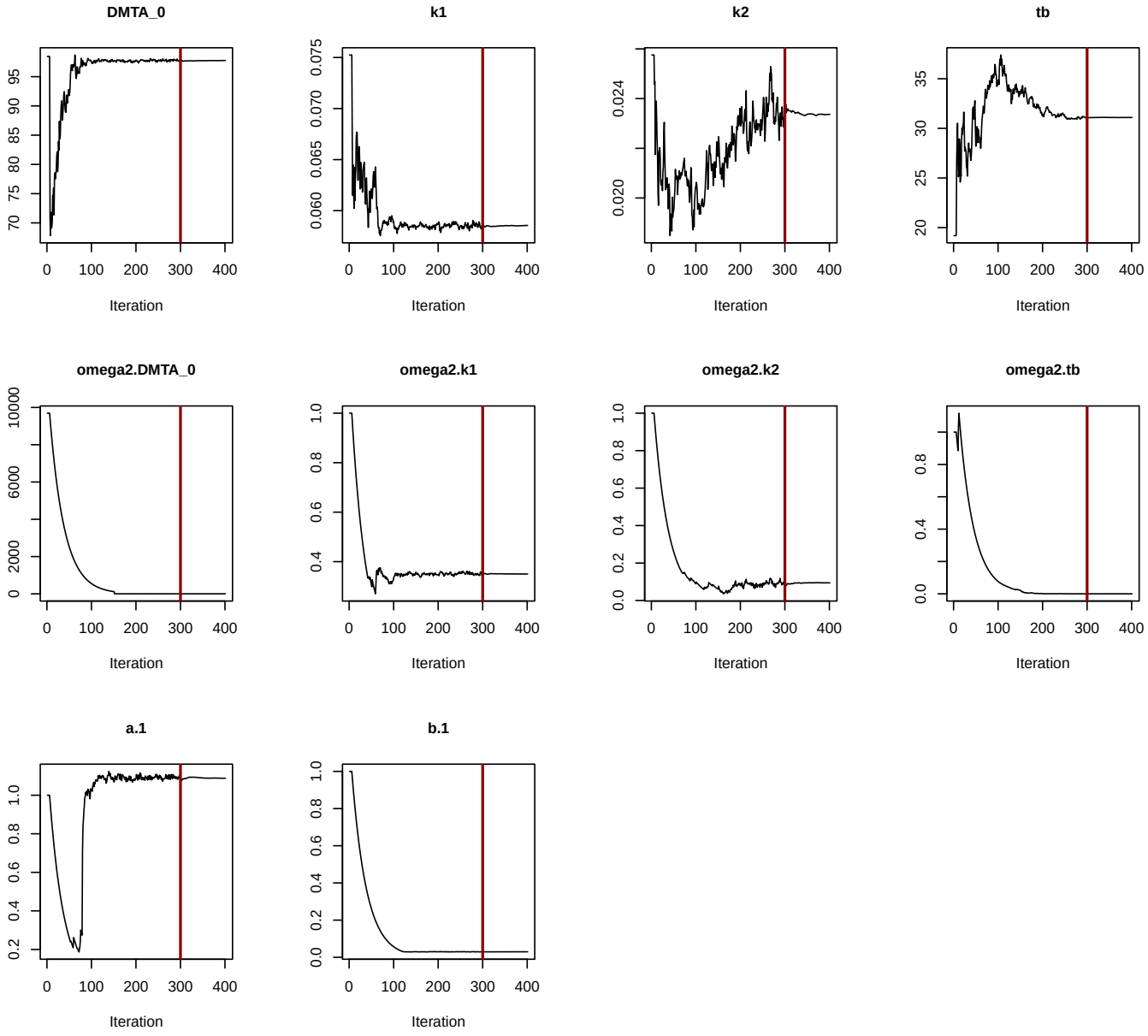

Figure 13: Convergence plot for the NLHM HS fit with two-component error

Session info

```
R version 4.2.2 Patched (2022-11-10 r83330)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Debian GNU/Linux bookworm/sid

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_1.41      mkin_1.2.2
[5] rmarkdown_2.19  nvimcom_0.9-133

loaded via a namespace (and not attached):
 [1] highr_0.9        compiler_4.2.2   pillar_1.8.1     tools_4.2.2
 [5] mclust_6.0.0     digest_0.6.31    evaluate_0.19    lifecycle_1.0.3
 [9] tibble_3.1.8     nlme_3.1-161     gtable_0.3.1     lattice_0.20-45
[13] pkgconfig_2.0.3  rlang_1.0.6      DBI_1.1.3        cli_3.5.0
[17] yaml_2.3.6       xfun_0.35        fastmap_1.1.0    gridExtra_2.3
[21] stringr_1.5.0    dplyr_1.0.10     generics_0.1.3   vctrs_0.5.1
[25] tidyselect_1.2.0 lmtest_0.9-40    grid_4.2.2       deSolve_1.34
[29] glue_1.6.2       R6_2.5.1         fansi_1.0.3      ggplot2_3.4.0
[33] magrittr_2.0.3   codetools_0.2-18 scales_1.2.1     htmltools_0.5.4
[37] assertthat_0.2.1 colorspace_2.0-3 utf8_1.2.2       stringi_1.7.8
[41] munsell_0.5.0    zoo_1.8-11
```

Hardware info

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

MemTotal:       64940452 kB
```