

Examples for kinetic evaluations using mkin

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Key words: Kinetics, FOCUS, nonlinear optimisation

1 Kinetic evaluations for parent compounds

These examples are also evaluated in a parallel vignette of the **kinfit** package ([Ranke, 2012](#)). The datasets are from Appendix 3, of the FOCUS kinetics report ([FOCUS Work Group on Degradation Kinetics, 2006, 2011](#)).

1.1 Laboratory Data L1

The following code defines example dataset L1 from the FOCUS kinetics report, p. 284

```
R> library("mkin")
R> FOCUS_2006_L1 = data.frame(
+   t = rep(c(0, 1, 2, 3, 5, 7, 14, 21, 30), each = 2),
+   parent = c(88.3, 91.4, 85.6, 84.5, 78.9, 77.6,
+              72.0, 71.9, 50.3, 59.4, 47.0, 45.1,
+              27.7, 27.3, 10.0, 10.4, 2.9, 4.0))
R> FOCUS_2006_L1_mkin <- mkin_wide_to_long(FOCUS_2006_L1)
```

The next step is to set up the models used for the kinetic analysis. Note that the model definitions contain the names of the observed variables in the data. In this case, there is only one variable called **parent**.

```
R> SFO <- mkinmod(parent = list(type = "SFO"))
R> FOMC <- mkinmod(parent = list(type = "FOMC"))
R> DFOP <- mkinmod(parent = list(type = "DFOP"))
```

The three models cover the first assumption of simple first order (SFO), the case of declining rate constant over time (FOMC) and the case of two different phases of the kinetics

(DFOP). For a more detailed discussion of the models, please see the FOCUS kinetics report.

The following two lines fit the model and produce the summary report of the model fit. This covers the numerical analysis given in the FOCUS report.

```
R> m.L1.SF0 <- mkinfit(SF0, FOCUS_2006_L1_mkin, quiet=TRUE)
R> summary(m.L1.SF0)
```

```
mkim version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:30 2013
Date of summary:   Tue Mar  5 01:40:30 2013
```

```
Equations:
[1] d_parent = - k_parent_sink * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100.0	state	100.000000
k_parent_sink	0.1	deparm	-2.302585

Fixed parameter values:
None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	92.470	1.36800	89.570	95.370
k_parent_sink	-2.347	0.04057	-2.433	-2.261

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	92.47000	89.57000	95.3700
k_parent_sink	0.09561	0.08773	0.1042

Residual standard error: 2.948 on 16 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	3.424	2	7
parent	3.424	2	7

Estimated disappearance times:

	DT50	DT90
parent	7.249	24.08

Estimated formation fractions:

	ff
parent_sink	1

Parameter correlation:

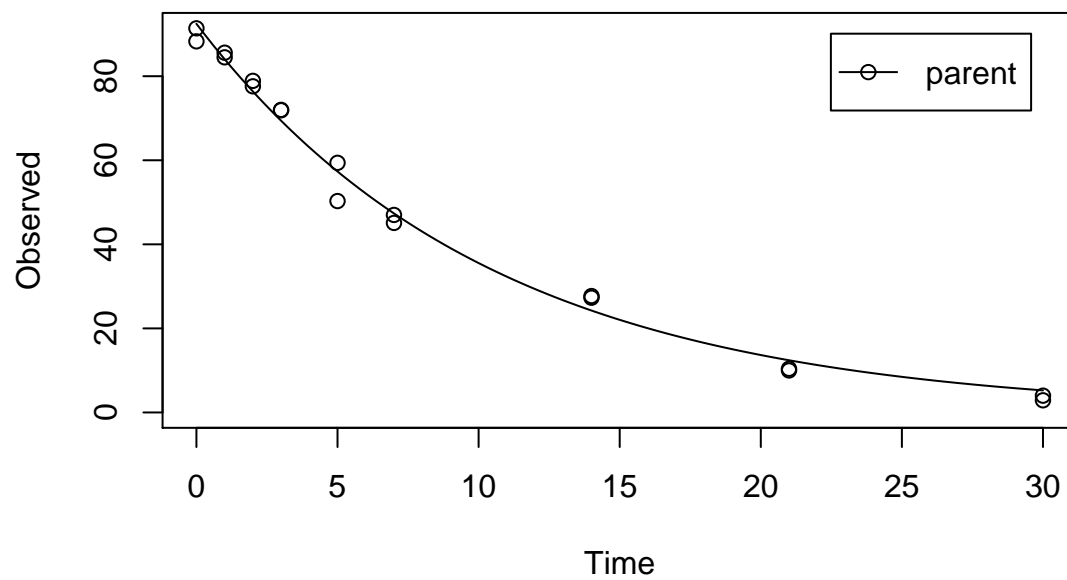
	parent_0	k_parent_sink
parent_0	1.0000	0.6248
k_parent_sink	0.6248	1.0000

Data:

time	variable	observed	predicted	residual
0	parent	88.3	92.471	-4.1710
0	parent	91.4	92.471	-1.0710
1	parent	85.6	84.039	1.5610
1	parent	84.5	84.039	0.4610
2	parent	78.9	76.376	2.5241
2	parent	77.6	76.376	1.2241
3	parent	72.0	69.412	2.5884
3	parent	71.9	69.412	2.4884
5	parent	50.3	57.330	-7.0301
5	parent	59.4	57.330	2.0699
7	parent	47.0	47.352	-0.3515
7	parent	45.1	47.352	-2.2515
14	parent	27.7	24.247	3.4527
14	parent	27.3	24.247	3.0527
21	parent	10.0	12.416	-2.4163
21	parent	10.4	12.416	-2.0163
30	parent	2.9	5.251	-2.3513
30	parent	4.0	5.251	-1.2513

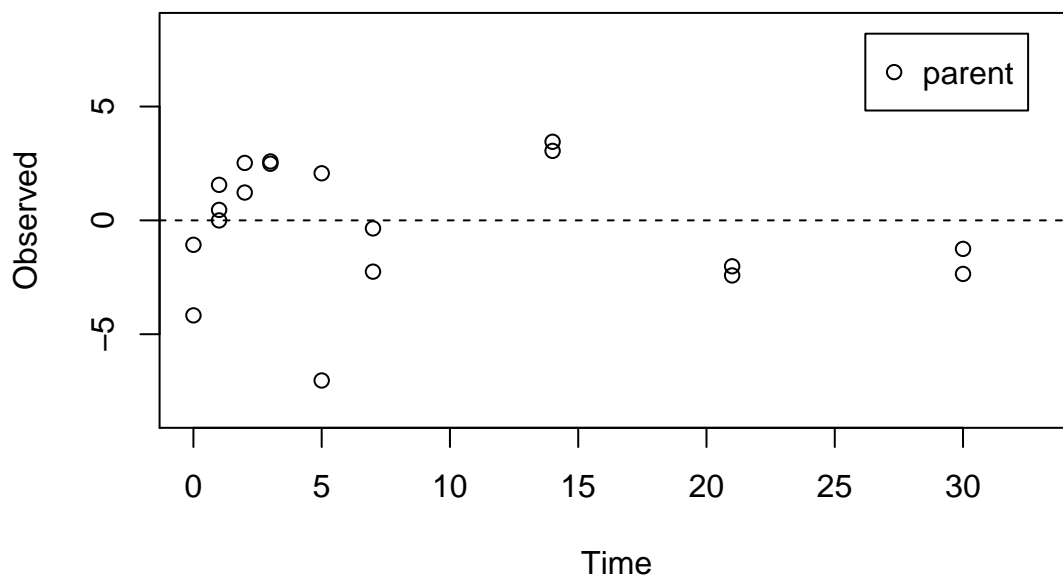
A plot of the fit is obtained with the plot function for mkinfit objects.

```
R> plot(m.L1.SF0)
```



The residual plot can be easily obtained by

```
R> mkinresplot(m.L1.SF0, ylab = "Observed", xlab = "Time")
```



For comparison, the FOMC model is fitted as well, and the χ^2 error level is checked.

```
R> m.L1.FOMC <- mkinfit(FOMC, FOCUS_2006_L1_mkin, quiet=TRUE)
```

```
R> summary(m.L1.FOMC)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:      Tue Mar  5 01:40:30 2013
Date of summary:  Tue Mar  5 01:40:30 2013
```

Equations:

```
[1] d_parent = - (alpha/beta) * ((time/beta) + 1)^-1 * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100	state	100.000000
alpha	1	deparm	0.000000
beta	10	deparm	2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	92.47	NA	NA	NA
alpha	25.63	NA	NA	NA

beta	27.98	NA	NA	NA
------	-------	----	----	----

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	9.247e+01	NA	NA
alpha	1.350e+11	NA	NA
beta	1.412e+12	NA	NA

Residual standard error: 3.045 on 15 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	3.619	3	6
parent	3.619	3	6

Estimated disappearance times:

	DT50	DT90
parent	7.249	24.08

Parameter correlation:

Could not estimate covariance matrix; singular system:

Data:

time	variable	observed	predicted	residual
0	parent	88.3	92.471	-4.1711
0	parent	91.4	92.471	-1.0711
1	parent	85.6	84.038	1.5618
1	parent	84.5	84.038	0.4618
2	parent	78.9	76.377	2.5233
2	parent	77.6	76.377	1.2233
3	parent	72.0	69.412	2.5884
3	parent	71.9	69.412	2.4884
5	parent	50.3	57.331	-7.0306
5	parent	59.4	57.331	2.0694
7	parent	47.0	47.351	-0.3510
7	parent	45.1	47.351	-2.2510
14	parent	27.7	24.247	3.4526
14	parent	27.3	24.247	3.0526
21	parent	10.0	12.416	-2.4162
21	parent	10.4	12.416	-2.0162
30	parent	2.9	5.251	-2.3513
30	parent	4.0	5.251	-1.2513

Due to the higher number of parameters, and the lower number of degrees of freedom of the fit, the χ^2 error level is actually higher for the FOMC model (3.6%) than for the SFO model (3.4%). Additionally, the covariance matrix can not be obtained, indicating overparameterisation of the model.

The χ^2 error levels reported in Appendix 3 and Appendix 7 to the FOCUS kinetics report are rounded to integer percentages and partly deviate by one percentage point from the results calculated by **mk**. The reason for this is not known. However, **mk** gives the same χ^2 error levels as the **kinfit** package. Furthermore, the calculation routines of the **kinfit** package have been extensively compared to the results obtained by the KinGUI software, as documented in the **kinfit** package vignette. KinGUI is a widely used standard package in this field. Therefore, the reason for the difference was not investigated further.

1.2 Laboratory Data L2

The following code defines example dataset L2 from the FOCUS kinetics report, p. 287

```
R> FOCUS_2006_L2 = data.frame(
+   t = rep(c(0, 1, 3, 7, 14, 28), each = 2),
+   parent = c(96.1, 91.8, 41.4, 38.7,
+             19.3, 22.3, 4.6, 4.6,
+             2.6, 1.2, 0.3, 0.6))
R> FOCUS_2006_L2_mkin <- mkin_wide_to_long(FOCUS_2006_L2)
```

Again, the SFO model is fitted and a summary is obtained.

```
R> m.L2.SFO <- mkinfit(SFO, FOCUS_2006_L2_mkin, quiet=TRUE)
R> summary(m.L2.SFO)
```

```
mk version:      0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:30 2013
Date of summary: Tue Mar  5 01:40:30 2013
```

```
Equations:
[1] d_parent = - k_parent_sink * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100.0	state	100.000000
k_parent_sink	0.1	deparm	-2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	91.4700	3.8070	82.9800	99.9500
k_parent_sink	-0.4112	0.1074	-0.6505	-0.1719

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	91.4700	82.9800	99.9500
k_parent_sink	0.6629	0.5218	0.8421

Residual standard error: 5.51 on 10 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	14.38	2	4
parent	14.38	2	4

Estimated disappearance times:

	DT50	DT90
parent	1.046	3.474

Estimated formation fractions:

	ff
parent_sink	1

Parameter correlation:

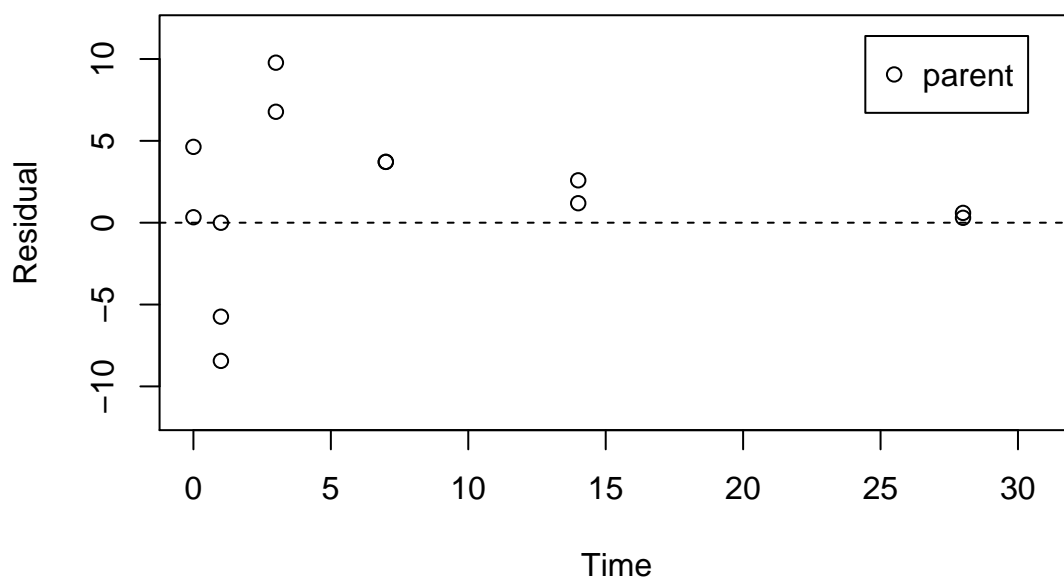
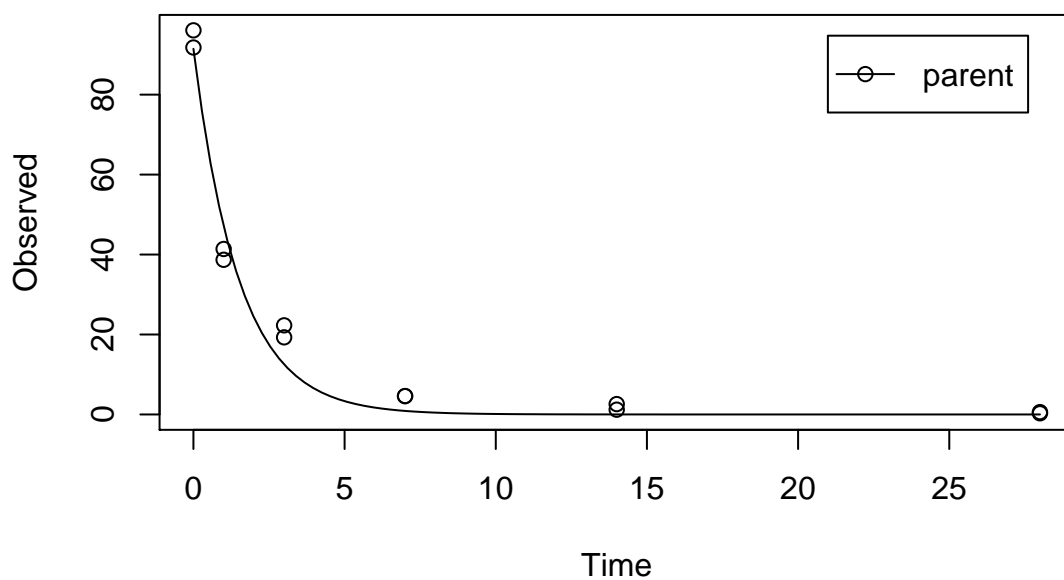
	parent_0	k_parent_sink
parent_0	1.0000	0.4295
k_parent_sink	0.4295	1.0000

Data:

time	variable	observed	predicted	residual
0	parent	96.1	91.4656079103	4.6344
0	parent	91.8	91.4656079103	0.3344
1	parent	41.4	47.1395280371	-5.7395
1	parent	38.7	47.1395280371	-8.4395
3	parent	19.3	12.5210295280	6.7790
3	parent	22.3	12.5210295280	9.7790
7	parent	4.6	0.8833842647	3.7166
7	parent	4.6	0.8833842647	3.7166
14	parent	2.6	0.0085318162	2.5915
14	parent	1.2	0.0085318162	1.1915
28	parent	0.3	0.0000007958	0.3000
28	parent	0.6	0.0000007958	0.6000

The χ^2 error level of 14% suggests that the model does not fit very well. This is also obvious from the plots of the fit and the residuals.

```
R> par(mfrow = c(2, 1))
R> plot(m.L2.SF0)
R> mkinresplot(m.L2.SF0)
```



In the FOCUS kinetics report, it is stated that there is no apparent systematic error observed from the residual plot up to the measured DT90 (approximately at day 5), and

there is an underestimation beyond that point.

We may add that it is difficult to judge the random nature of the residuals just from the three samplings at days 0, 1 and 3. Also, it is not clear *a priori* why a consistent underestimation after the approximate DT90 should be irrelevant. However, this can be rationalised by the fact that the FOCUS fate models generally only implement SFO kinetics.

For comparison, the FOMC model is fitted as well, and the χ^2 error level is checked.

```
R> m.L2.FOMC <- mkinfit(FOMC, FOCUS_2006_L2_mkin, quiet = TRUE)
R> par(mfrow = c(2, 1))
R> plot(m.L2.FOMC)
R> mkinresplot(m.L2.FOMC)
R> summary(m.L2.FOMC, data = FALSE)
```

```
mkim version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:31 2013
Date of summary:   Tue Mar  5 01:40:31 2013
```

Equations:

```
[1] d_parent = - (alpha/beta) * ((time/beta) + 1)^-1 * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100	state	100.000000
alpha	1	deparm	0.000000
beta	10	deparm	2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	93.7700	1.8560	89.5700	97.9700
alpha	0.3180	0.1867	-0.1044	0.7405
beta	0.2102	0.2943	-0.4556	0.8759

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	93.770	89.5700	97.970
alpha	1.374	0.9009	2.097
beta	1.234	0.6341	2.401

Residual standard error: 2.628 on 9 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	6.204	3	3

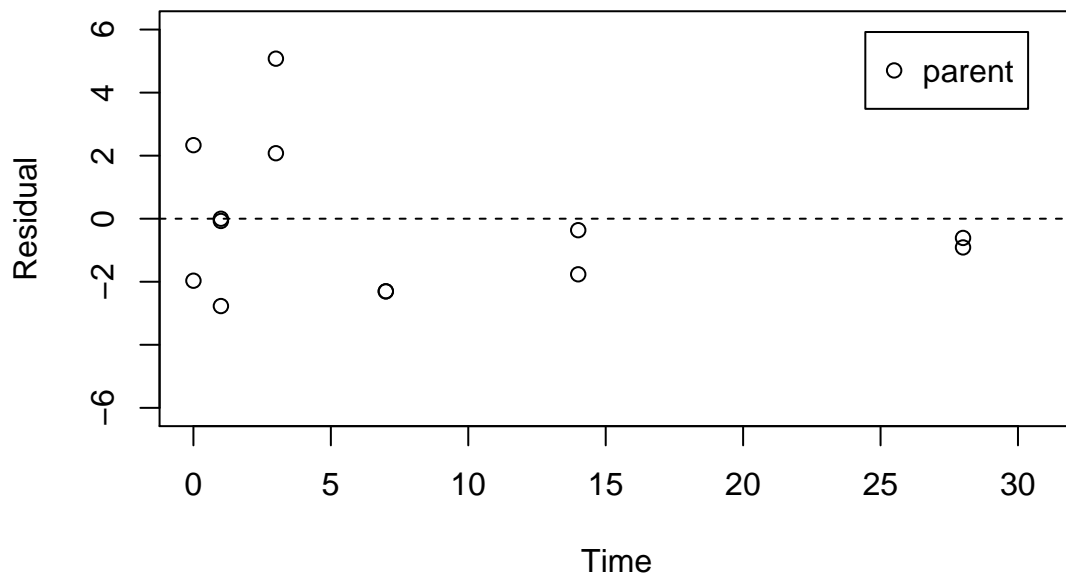
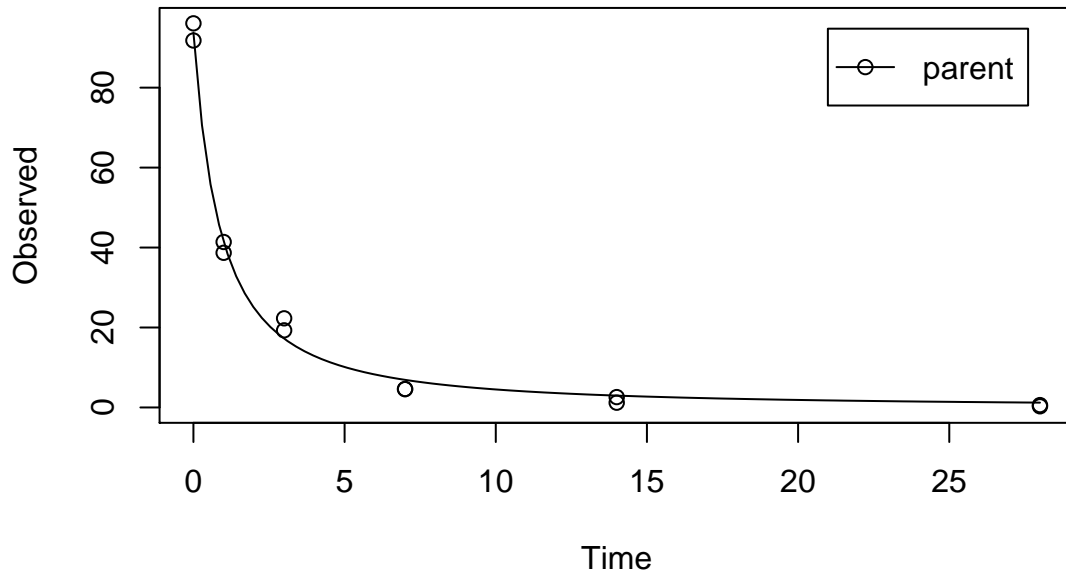
parent 6.204 3 3

Estimated disappearance times:

DT50 DT90
parent 0.8092 5.356

Parameter correlation:

	parent_0	alpha	beta
parent_0	1.00000	-0.09553	-0.1863
alpha	-0.09553	1.00000	0.9757
beta	-0.18628	0.97568	1.0000

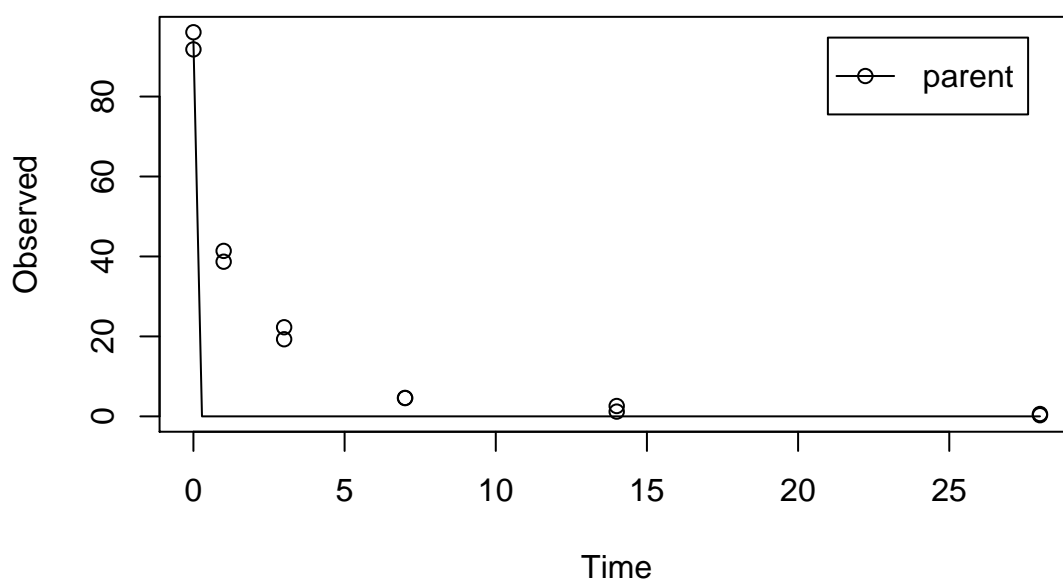


The error level at which the χ^2 test passes is much lower in this case. Therefore, the FOMC model provides a better description of the data, as less experimental error has to

be assumed in order to explain the data.

Fitting the four parameter DFOP model further reduces the χ^2 error level.

```
R> m.L2.DFOP <- mkinfit(DFOP, FOCUS_2006_L2_mkin, quiet = TRUE)
R> plot(m.L2.DFOP)
```



Here, the default starting parameters for the DFOP model obviously do not lead to a reasonable solution. Therefore the fit is repeated with different starting parameters.

```
R> m.L2.DFOP <- mkinfit(DFOP, FOCUS_2006_L2_mkin,
+   parms.ini = c(k1 = 1, k2 = 0.01, g = 0.8),
+   quiet=TRUE)
R> plot(m.L2.DFOP)
R> summary(m.L2.DFOP, data = FALSE)
```

```
mkim version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:31 2013
Date of summary: Tue Mar  5 01:40:31 2013
```

Equations:

```
[1] d_parent = - ((k1 * g * exp(-k1 * time) + k2 * (1 - g) * exp(-k2 * time)) / (g * exp
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	1e+02	state	100.0000000
k1	1e+00	deparm	0.0000000
k2	1e-02	deparm	-4.6051702
g	8e-01	deparm	0.9802581

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	93.9500	NA	NA	NA
k1	4.9590	NA	NA	NA
k2	-1.0880	NA	NA	NA
g	-0.2821	NA	NA	NA

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	93.9500	NA	NA
k1	142.4000	NA	NA
k2	0.3369	NA	NA
g	0.4016	NA	NA

Residual standard error: 1.732 on 8 degrees of freedom

Chi2 error levels in percent:

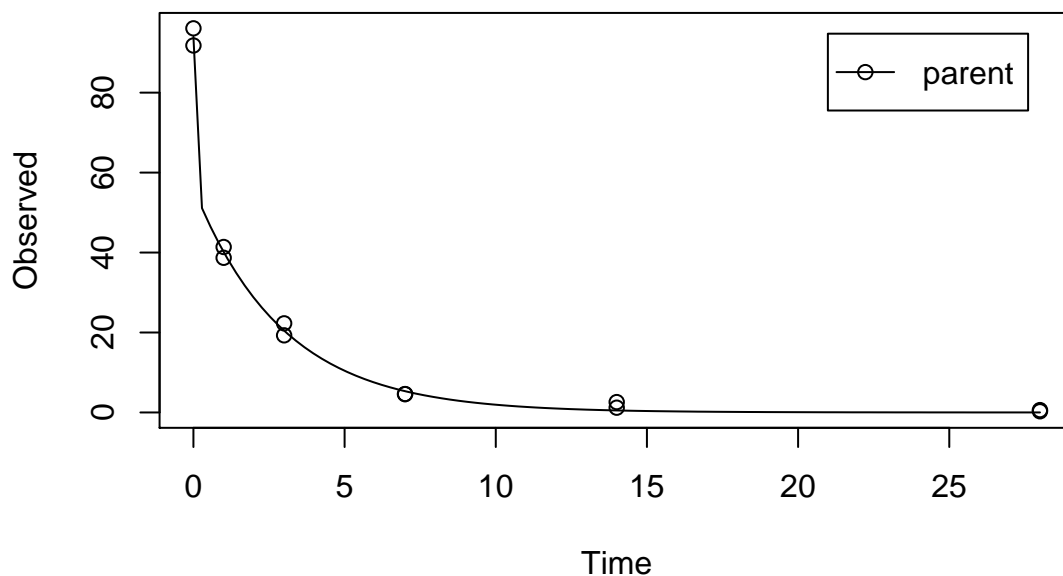
	err.min	n.optim	df
All data	2.529	4	2
parent	2.529	4	2

Estimated disappearance times:

	DT50	DT90
parent	NA	NA

Parameter correlation:

Could not estimate covariance matrix; singular system:



Here, the DFOP model is clearly the best-fit model for dataset L2 based on the χ^2 error level criterion. However, the failure to calculate the covariance matrix indicates that the parameter estimates correlate excessively. Therefore, the FOMC model may be preferred for this dataset.

1.3 Laboratory Data L3

The following code defines example dataset L3 from the FOCUS kinetics report, p. 290.

```
R> FOCUS_2006_L3 = data.frame(
+   t = c(0, 3, 7, 14, 30, 60, 91, 120),
+   parent = c(97.8, 60, 51, 43, 35, 22, 15, 12))
R> FOCUS_2006_L3_mkin <- mkin_wide_to_long(FOCUS_2006_L3)
```

SFO model, summary and plot:

```
R> m.L3.SFO <- mkinfit(SFO, FOCUS_2006_L3_mkin, quiet = TRUE)
R> plot(m.L3.SFO)
R> summary(m.L3.SFO)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:31 2013
```


Date of summary: Tue Mar 5 01:40:31 2013

Equations:

```
[1] d_parent = - k_parent_sink * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100.0	state	100.000000
k_parent_sink	0.1	deparm	-2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	74.870	8.4580	54.180	95.57
k_parent_sink	-3.678	0.3261	-4.476	-2.88

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	74.87000	54.18000	95.57000
k_parent_sink	0.02527	0.01138	0.05612

Residual standard error: 12.91 on 6 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	21.24	2	6
parent	21.24	2	6

Estimated disappearance times:

	DT50	DT90
parent	27.43	91.12

Estimated formation fractions:

	ff
parent_sink	1

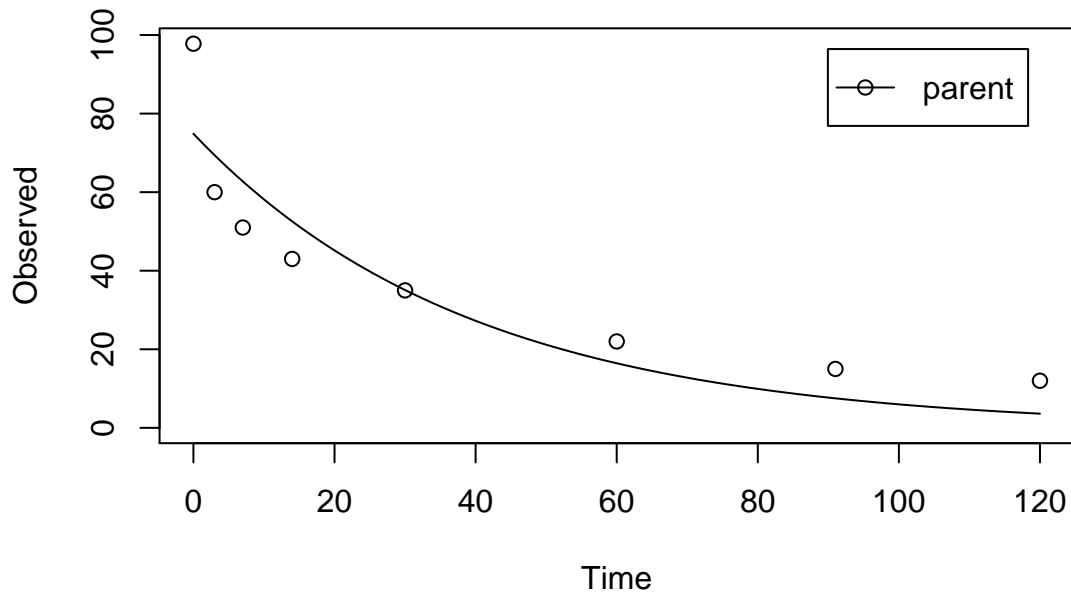
Parameter correlation:

	parent_0	k_parent_sink
parent_0	1.0000	0.5484
k_parent_sink	0.5484	1.0000

Data:

time	variable	observed	predicted	residual
0	parent	97.8	74.873	22.92734
3	parent	60.0	69.407	-9.40654
7	parent	51.0	62.734	-11.73403
14	parent	43.0	52.563	-9.56336

30	parent	35.0	35.083	-0.08281
60	parent	22.0	16.439	5.56137
91	parent	15.0	7.510	7.48961
120	parent	12.0	3.609	8.39083



The χ^2 error level of 22% as well as the plot suggest that the model does not fit very well.

The FOMC model performs better:

```
R> m.L3.FOMC <- mkinfit(FOMC, FOCUS_2006_L3_mkin, quiet = TRUE)
R> plot(m.L3.FOMC)
R> summary(m.L3.FOMC, data = FALSE)
```

```
mkim version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:32 2013
Date of summary:   Tue Mar  5 01:40:32 2013
```

Equations:

```
[1] d_parent = - (alpha/beta) * ((time/beta) + 1)^-1 * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100	state	100.000000
alpha	1	deparm	0.000000
beta	10	deparm	2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	96.9700	4.5500	85.2800	108.7000
alpha	-0.8619	0.1704	-1.3000	-0.4237
beta	0.6193	0.4744	-0.6003	1.8390

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	96.9700	85.2800	108.7000
alpha	0.4224	0.2725	0.6546
beta	1.8580	0.5487	6.2890

Residual standard error: 4.572 on 5 degrees of freedom

Chi2 error levels in percent:

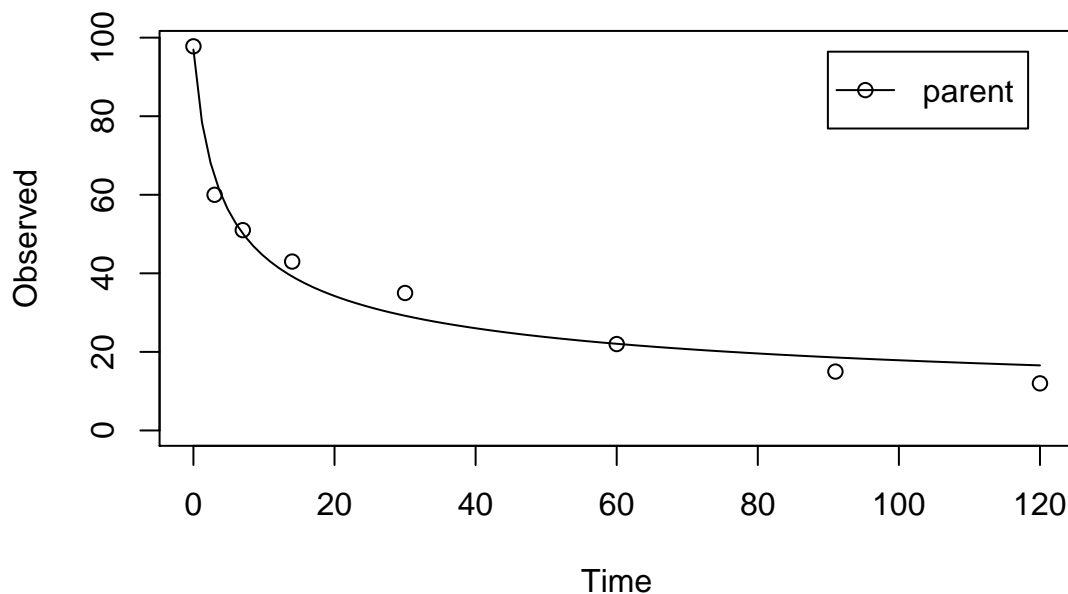
	err.min	n.optim	df
All data	7.322	3	5
parent	7.322	3	5

Estimated disappearance times:

	DT50	DT90
parent	7.729	431.2

Parameter correlation:

	parent_0	alpha	beta
parent_0	1.0000	-0.1512	-0.4271
alpha	-0.1512	1.0000	0.9110
beta	-0.4271	0.9110	1.0000



The error level at which the χ^2 test passes is 7% in this case.

Fitting the four parameter DFOP model further reduces the χ^2 error level considerably:

```
R> m.L3.DFOP <- mkinfit(DFOP, FOCUS_2006_L3_mkin, quiet = TRUE)
```

```
R> plot(m.L3.DFOP)
```

```
R> summary(m.L3.DFOP, data = FALSE)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:32 2013
Date of summary: Tue Mar  5 01:40:32 2013
```

Equations:

```
[1] d_parent = - ((k1 * g * exp(-k1 * time) + k2 * (1 - g) * exp(-k2 * time)) / (g * exp
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	1e+02	state	100.000000
k1	1e-01	deparm	-2.302585
k2	1e-02	deparm	-4.605170
g	5e-01	deparm	0.000000

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	97.7500	1.43800	93.7500	101.70000
k1	-0.6612	0.13340	-1.0310	-0.29100
k2	-4.2860	0.05902	-4.4500	-4.12200
g	-0.1229	0.05121	-0.2651	0.01925

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	97.75000	93.75000	101.70000
k1	0.51620	0.35650	0.74750
k2	0.01376	0.01168	0.01621
g	0.45660	0.40730	0.50680

Residual standard error: 1.439 on 4 degrees of freedom

Chi2 error levels in percent:

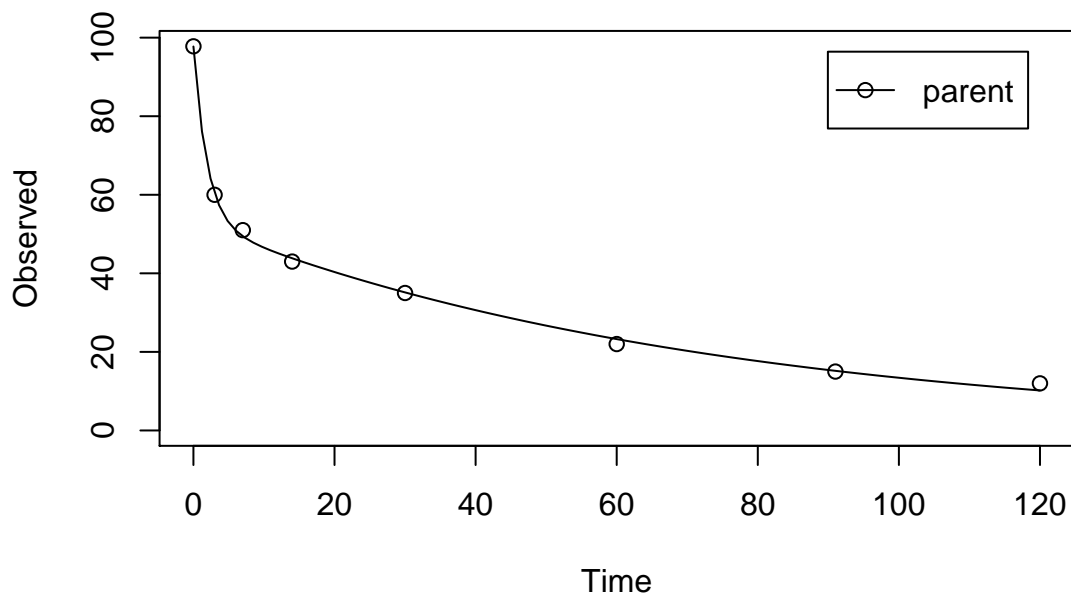
	err.min	n.optim	df
All data	2.224	4	4
parent	2.224	4	4

Estimated disappearance times:

	DT50	DT90
parent	7.464	123

Parameter correlation:

	parent_0	k1	k2	g
parent_0	1.00000	0.1640	0.01315	0.4253
k1	0.16399	1.0000	0.46477	-0.5526
k2	0.01315	0.4648	1.00000	-0.6631
g	0.42526	-0.5526	-0.66310	1.0000



Here, a look to the model plot, the confidence intervals of the parameters and the correlation matrix suggest that the parameter estimates are reliable, and the DFOP model can be used as the best-fit model based on the χ^2 error level criterion for laboratory data L3.

1.4 Laboratory Data L4

The following code defines example dataset L4 from the FOCUS kinetics report, p. 293

```
R> FOCUS_2006_L4 = data.frame(
+   t = c(0, 3, 7, 14, 30, 60, 91, 120),
+   parent = c(96.6, 96.3, 94.3, 88.8, 74.9, 59.9, 53.5, 49.0))
R> FOCUS_2006_L4_mkin <- mkin_wide_to_long(FOCUS_2006_L4)
```

SFO model, summary and plot:

```
R> m.L4.SFO <- mkinfit(SFO, FOCUS_2006_L4_mkin, quiet = TRUE)
R> plot(m.L4.SFO)
R> summary(m.L4.SFO, data = FALSE)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:32 2013
Date of summary: Tue Mar  5 01:40:32 2013
```

Equations:

```
[1] d_parent = - k_parent_sink * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100.0	state	100.000000
k_parent_sink	0.1	deparm	-2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	96.44	1.94900	91.670	101.200
k_parent_sink	-5.03	0.07999	-5.225	-4.834

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	96.440000	91.670000	1.012e+02
k_parent_sink	0.006541	0.005378	7.955e-03

Residual standard error: 3.651 on 6 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	3.288	2	6
parent	3.288	2	6

Estimated disappearance times:

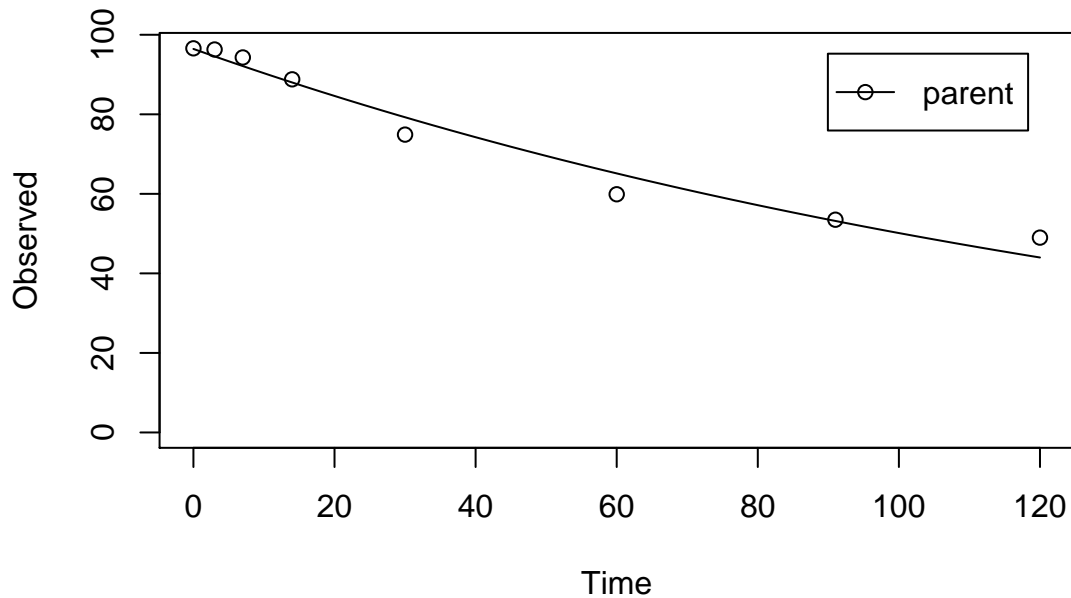
	DT50	DT90
parent	106	352

Estimated formation fractions:

	ff
parent_sink	1

Parameter correlation:

	parent_0	k_parent_sink
parent_0	1.0000	0.5865
k_parent_sink	0.5865	1.0000



The χ^2 error level of 3.3% as well as the plot suggest that the model fits very well.

The FOMC model for comparison

```
R> m.L4.FOMC <- mkinfit(FOMC, FOCUS_2006_L4_mkin, quiet = TRUE)
```

```
R> plot(m.L4.FOMC)
```

```
R> summary(m.L4.FOMC, data = FALSE)
```

```

mkin version:    0.9.16
R version:       2.15.2
Date of fit:      Tue Mar  5 01:40:32 2013
Date of summary:  Tue Mar  5 01:40:32 2013

```

Equations:

```
[1] d_parent = - (alpha/beta) * ((time/beta) + 1)^-1 * parent
```

Starting values for optimised parameters:

	initial	type	transformed
parent_0	100	state	100.000000
alpha	1	deparm	0.000000
beta	10	deparm	2.302585

Fixed parameter values:

None

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
parent_0	99.1400	1.6800	94.820	103.5000
alpha	-0.3506	0.3725	-1.308	0.6068
beta	4.1740	0.5635	2.725	5.6230

Backtransformed parameters:

	Estimate	Lower	Upper
parent_0	99.1400	94.8200	103.500
alpha	0.7042	0.2703	1.835
beta	64.9800	15.2600	276.600

Residual standard error: 2.315 on 5 degrees of freedom

Chi2 error levels in percent:

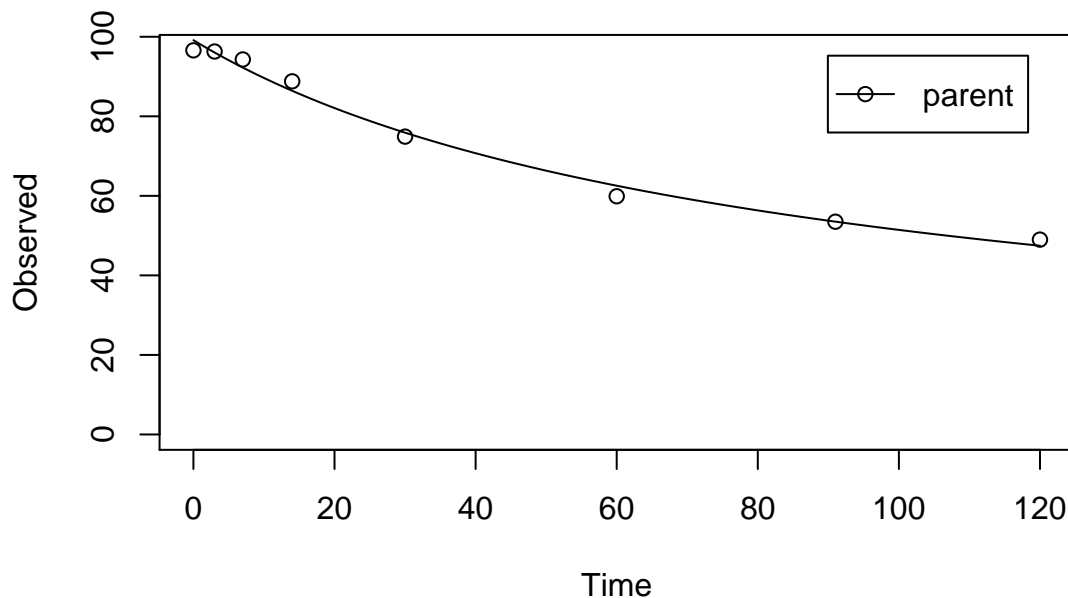
	err.min	n.optim	df
All data	2.028	3	5
parent	2.028	3	5

Estimated disappearance times:

	DT50	DT90
parent	108.9	1644

Parameter correlation:

	parent_0	alpha	beta
parent_0	1.0000	-0.5365	-0.6083
alpha	-0.5365	1.0000	0.9913
beta	-0.6083	0.9913	1.0000



The error level at which the χ^2 test passes is slightly lower for the FOMC model. However, the difference appears negligible.

2 Kinetic evaluations for parent and metabolites

2.1 Laboratory Data for example compound Z

The following code defines the example dataset from Appendix 7 to the FOCUS kinetics report, p.350

```
R> LOD = 0.5
R> FOCUS_2006_Z = data.frame(
+   t = c(0, 0.04, 0.125, 0.29, 0.54, 1, 2, 3, 4, 7, 10, 14, 21,
+         42, 61, 96, 124),
+   Z0 = c(100, 81.7, 70.4, 51.1, 41.2, 6.6, 4.6, 3.9, 4.6, 4.3, 6.8,
+         2.9, 3.5, 5.3, 4.4, 1.2, 0.7),
+   Z1 = c(0, 18.3, 29.6, 46.3, 55.1, 65.7, 39.1, 36, 15.3, 5.6, 1.1,
+         1.6, 0.6, 0.5 * LOD, NA, NA, NA),
+   Z2 = c(0, NA, 0.5 * LOD, 2.6, 3.8, 15.3, 37.2, 31.7, 35.6, 14.5,
+         0.8, 2.1, 1.9, 0.5 * LOD, NA, NA, NA),
```

```
+ Z3 = c(0, NA, NA, NA, NA, 0.5 * LOD, 9.2, 13.1, 22.3, 28.4, 32.5,
+       25.2, 17.2, 4.8, 4.5, 2.8, 4.4))
R> FOCUS_2006_Z_mkin <- mkin_wide_to_long(FOCUS_2006_Z)
```

The next step is to set up the models used for the kinetic analysis. As the simultaneous fit of parent and the first metabolite is usually straightforward, Step 1 (SFO for parent only) is skipped here. We start with the model 2a, with formation and decline of metabolite Z1 and the pathway from parent directly to sink included (default in mkin).

```
R> Z.2a <- mkinmod(Z0 = list(type = "SFO", to = "Z1"),
+               Z1 = list(type = "SFO"))
R> m.Z.2a <- mkinfit(Z.2a, FOCUS_2006_Z_mkin, quiet = TRUE)
R> plot(m.Z.2a)
R> summary(m.Z.2a, data = FALSE)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:33 2013
Date of summary: Tue Mar  5 01:40:33 2013
```

Equations:

```
[1] d_Z0 = - k_Z0_sink * Z0 - k_Z0_Z1 * Z0
[2] d_Z1 = + k_Z0_Z1 * Z0 - k_Z1_sink * Z1
```

Starting values for optimised parameters:

	initial	type	transformed
Z0_0	100.0	state	100.000000
k_Z0_sink	0.1	deparm	-2.302585
k_Z0_Z1	0.1	deparm	-2.302585
k_Z1_sink	0.1	deparm	-2.302585

Fixed parameter values:

	value	type
Z1	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_0	97.0100	NA	NA	NA
k_Z0_sink	-36.2900	NA	NA	NA
k_Z0_Z1	0.8047	NA	NA	NA
k_Z1_sink	-0.7296	NA	NA	NA

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_0	9.701e+01	NA	NA
k_Z0_sink	1.733e-16	NA	NA
k_Z0_Z1	2.236e+00	NA	NA
k_Z1_sink	4.821e-01	NA	NA

Residual standard error: 5.064 on 27 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	18.20	4	27
Z0	18.04	3	14
Z1	15.75	1	13

Estimated disappearance times:

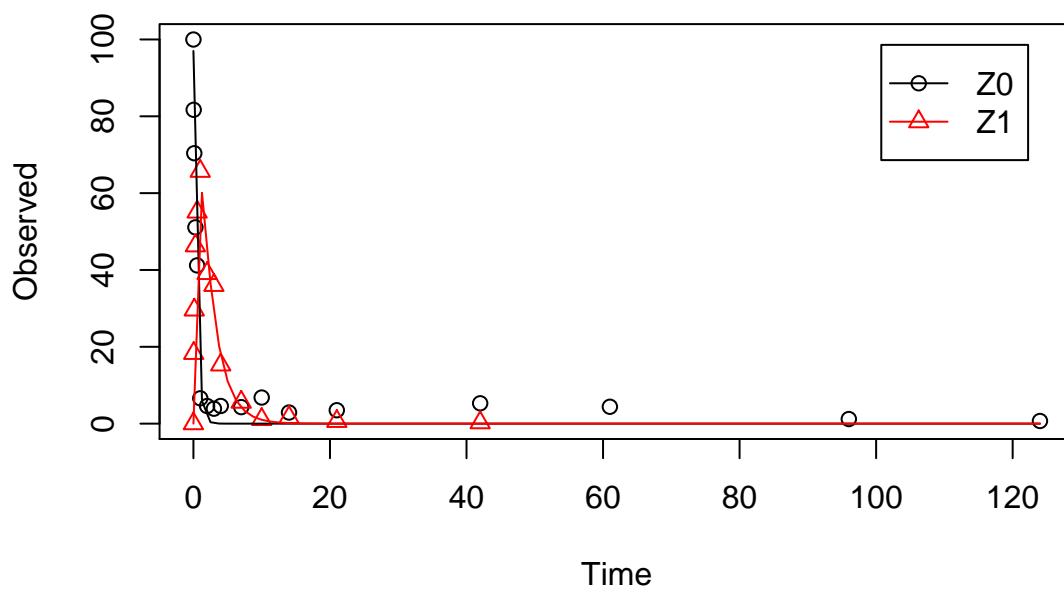
	DT50	DT90
Z0	0.310	1.030
Z1	1.438	4.776

Estimated formation fractions:

	ff
Z0_sink	7.75e-17
Z0_Z1	1.00e+00
Z1_sink	1.00e+00

Parameter correlation:

Could not estimate covariance matrix; singular system:



As obvious from the summary, the kinetic rate constant from parent compound Z to sink is negligible. Accordingly, the exact magnitude of the fitted parameter $\log k_{Z_sink}$ is

ill-defined and the covariance matrix is not returned. This suggests, in agreement with the analysis in the FOCUS kinetics report, to simplify the model by removing the pathway to sink.

A similar result can be obtained when formation fractions are used in the model formulation:

```
R> Z.2a.ff <- mkinmod(Z0 = list(type = "SF0", to = "Z1"),
+                    Z1 = list(type = "SF0"), use_of_ff = "max")
R> m.Z.2a.ff <- mkinfit(Z.2a.ff, FOCUS_2006_Z_mkin, quiet = TRUE)
R> plot(m.Z.2a.ff)
R> summary(m.Z.2a.ff, data = FALSE)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:34 2013
Date of summary: Tue Mar  5 01:40:34 2013
```

```
Equations:
[1] d_Z0 = - k_Z0 * Z0
[2] d_Z1 = + f_Z0_to_Z1 * k_Z0 * Z0 - k_Z1 * Z1
```

Starting values for optimised parameters:

	initial	type	transformed
Z0_0	100.0	state	100.0000000
k_Z0	0.1	deparm	-2.3025851
f_Z0_to_Z1	0.2	deparm	-0.9802581
k_Z1	0.1	deparm	-2.3025851

Fixed parameter values:

	value	type
Z1	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_0	9.701e+01	NA	NA	NA
k_Z0	8.047e-01	NA	NA	NA
f_Z0_to_Z1	8.862e+06	NA	NA	NA
k_Z1	-7.296e-01	NA	NA	NA

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_0	97.0100	NA	NA
k_Z0	2.2360	NA	NA
f_Z0_to_Z1	1.0000	NA	NA
k_Z1	0.4821	NA	NA

Residual standard error: 5.064 on 27 degrees of freedom

Chi2 error levels in percent:

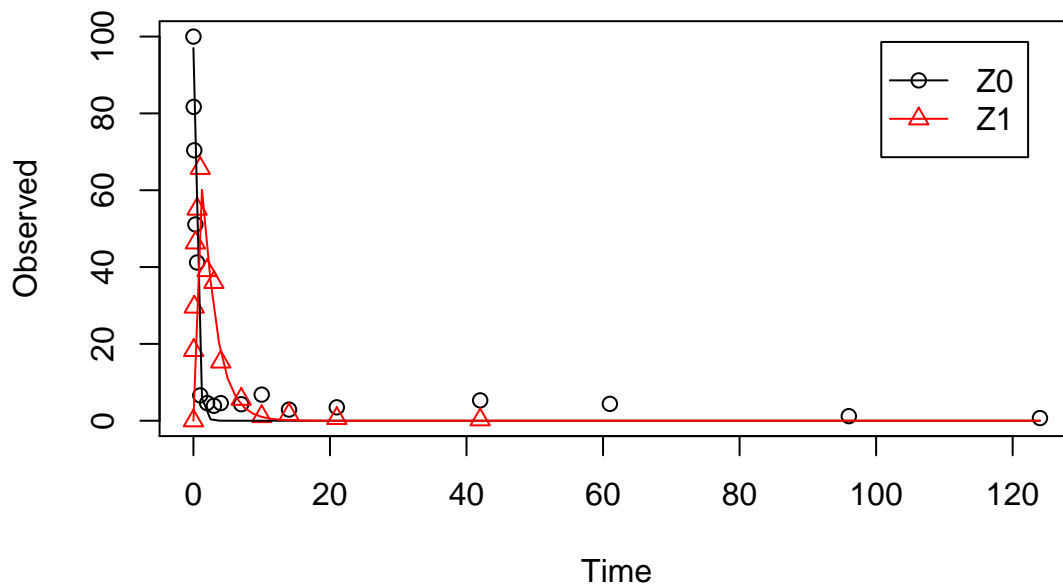
	err.min	n.optim	df
All data	18.20	4	27
Z0	17.56	2	15
Z1	16.25	2	12

Estimated disappearance times:

	DT50	DT90
Z0	0.310	1.030
Z1	1.438	4.776

Parameter correlation:

Could not estimate covariance matrix; singular system:



Here, the `ilr` transformed formation fraction fitted in the model takes a very large value, and the backtransformed formation fraction from parent Z to Z1 is practically unity. Again, the covariance matrix is not returned as the model is overparameterised.

The simplified model is obtained by setting the list component `sink` to `FALSE`. This model definition is not supported when formation fractions are used.

```
R> Z.3 <- mkinmod(Z0 = list(type = "SF0", to = "Z1", sink = FALSE),
+               Z1 = list(type = "SF0"))
R> m.Z.3 <- mkinfit(Z.3, FOCUS_2006_Z_mkin, parms.ini = c(k_Z0_Z1 = 0.5),
```

```

+               quiet = TRUE)
R> #m.Z.3 <- mkinfit(Z.3, FOCUS_2006_Z_mkin, solution_type = "deSolve")
R> plot(m.Z.3)
R> summary(m.Z.3, data = FALSE)

mkin version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:34 2013
Date of summary:   Tue Mar  5 01:40:34 2013

Equations:
[1] d_Z0 = - 0 - k_Z0_Z1 * Z0
[2] d_Z1 = + k_Z0_Z1 * Z0 - k_Z1_sink * Z1

Starting values for optimised parameters:
      initial   type transformed
Z0_0      100.0  state 100.0000000
k_Z0_Z1     0.5 deparm -0.6931472
k_Z1_sink   0.1 deparm -2.3025851

Fixed parameter values:
      value type
Z1       0 state

Optimised, transformed parameters:
      Estimate Std. Error  Lower  Upper
Z0_0      97.0100    2.68200 91.5200 102.5000
k_Z0_Z1    0.8047    0.06568  0.6702  0.9392
k_Z1_sink -0.7296    0.08854 -0.9109 -0.5482

Backtransformed parameters:
      Estimate  Lower  Upper
Z0_0      97.0100 91.5200 102.500
k_Z0_Z1    2.2360  1.9550  2.558
k_Z1_sink   0.4821  0.4022  0.578

Residual standard error: 4.973 on 28 degrees of freedom

Chi2 error levels in percent:
      err.min n.optim df
All data  17.93      3 28
Z0        17.56      2 15
Z1        15.75      1 13

Estimated disappearance times:
      DT50  DT90
Z0 0.310 1.030
Z1 1.438 4.776

```

Estimated formation fractions:

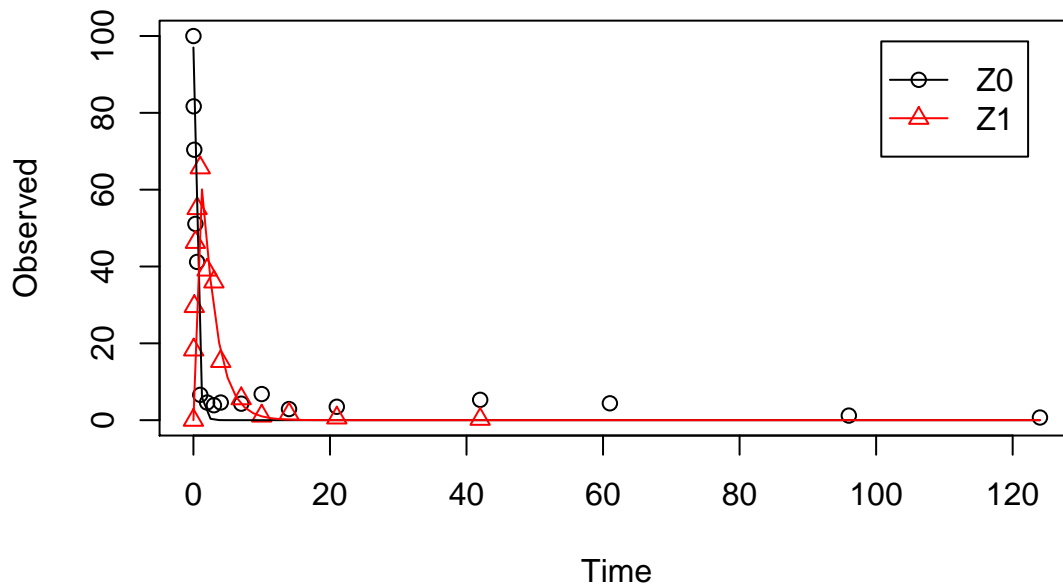
```

      ff
Z0_Z1  1
Z1_sink 1

```

Parameter correlation:

	Z0_0	k_Z0_Z1	k_Z1_sink
Z0_0	1.0000	0.10629	0.41038
k_Z0_Z1	0.1063	1.00000	0.04345
k_Z1_sink	0.4104	0.04345	1.00000



The first attempt to fit the model failed, as the default solution type chosen by `mkinf` is based on eigenvalues, and the system defined by the starting parameters is identified as being singular to the solver. This is caused by the fact that the rate constants for both state variables are the same using the default starting parameters. Setting a different starting value for one of the parameters overcomes this. Alternatively, the **deSolve** based model solution can be chosen, at the cost of a bit more computing time.

```

R> Z.4a <- mkinmod(Z0 = list(type = "SF0", to = "Z1", sink = FALSE),
+                 Z1 = list(type = "SF0", to = "Z2"),
+                 Z2 = list(type = "SF0"))
R> m.Z.4a <- mkinfit(Z.4a, FOCUS_2006_Z_mkin, parms.ini = c(k_Z0_Z1 = 0.5),
+                  quiet = TRUE)
R> plot(m.Z.4a)

```



```
R> summary(m.Z.4a, data = FALSE)
```

```

mkin version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:36 2013
Date of summary:   Tue Mar  5 01:40:36 2013

```

Equations:

```

[1] d_Z0 = - 0 - k_Z0_Z1 * Z0
[2] d_Z1 = + k_Z0_Z1 * Z0 - k_Z1_sink * Z1 - k_Z1_Z2 * Z1
[3] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2

```

Starting values for optimised parameters:

	initial	type	transformed
Z0_0	100.0	state	100.0000000
k_Z0_Z1	0.5	deparm	-0.6931472
k_Z1_sink	0.1	deparm	-2.3025851
k_Z1_Z2	0.1	deparm	-2.3025851
k_Z2_sink	0.1	deparm	-2.3025851

Fixed parameter values:

	value	type
Z1	0	state
Z2	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_0	96.9600	2.44700	92.0100	101.9000
k_Z0_Z1	0.7970	0.05974	0.6762	0.9179
k_Z1_sink	-4.1040	4.84700	-13.9100	5.7000
k_Z1_Z2	-0.7667	0.14630	-1.0630	-0.4707
k_Z2_sink	-0.8410	0.22860	-1.3030	-0.3787

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_0	96.9600	9.201e+01	101.9000
k_Z0_Z1	2.2190	1.966e+00	2.5040
k_Z1_sink	0.0165	9.112e-07	298.8000
k_Z1_Z2	0.4645	3.455e-01	0.6245
k_Z2_sink	0.4313	2.716e-01	0.6848

Residual standard error: 4.54 on 39 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	19.78	5	39
Z0	17.47	2	15
Z1	16.37	2	12
Z2	20.47	1	12

Estimated disappearance times:

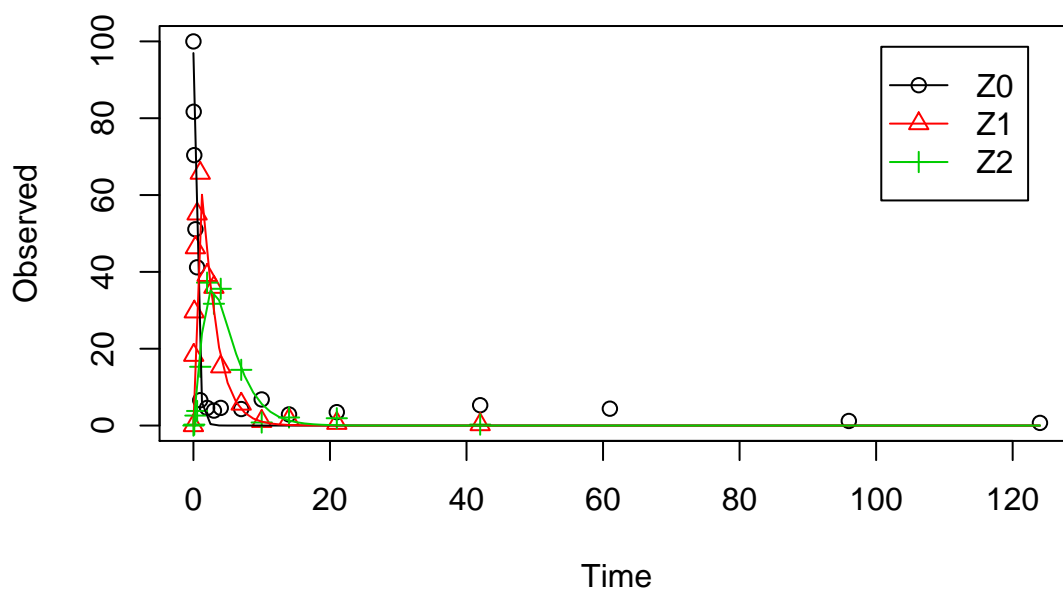
	DT50	DT90
Z0	0.3124	1.038
Z1	1.4410	4.787
Z2	1.6072	5.339

Estimated formation fractions:

	ff
Z0_Z1	1.0000
Z1_sink	0.0343
Z1_Z2	0.9657
Z2_sink	1.0000

Parameter correlation:

	Z0_0	k_Z0_Z1	k_Z1_sink	k_Z1_Z2	k_Z2_sink
Z0_0	1.0000	0.1064	0.3492	-0.1769	-0.1534
k_Z0_Z1	0.1064	1.0000	0.1479	-0.1501	-0.1226
k_Z1_sink	0.3492	0.1479	1.0000	-0.8745	-0.8656
k_Z1_Z2	-0.1769	-0.1501	-0.8745	1.0000	0.8190
k_Z2_sink	-0.1534	-0.1226	-0.8656	0.8190	1.0000



As suggested in the FOCUS report, the pathway to sink was removed for metabolite Z1 as well in the next step. While this step appears questionable on the basis of the above results, it is followed here for the purpose of comparison. Also, in the FOCUS report,

it is assumed that there is additional empirical evidence that Z1 quickly and exclusively hydrolyses to Z2. Again, in order to avoid a singular system when using default starting parameters, the starting parameter for the pathway without sink term has to be adapted.

```
R> Z.5 <- mkinmod(Z0 = list(type = "SF0", to = "Z1", sink = FALSE),
+               Z1 = list(type = "SF0", to = "Z2", sink = FALSE),
+               Z2 = list(type = "SF0"))
R> m.Z.5 <- mkinfit(Z.5, FOCUS_2006_Z_mkin,
+               parms.ini = c(k_Z0_Z1 = 0.5, k_Z1_Z2 = 0.2), quiet = TRUE)
R> plot(m.Z.5)
R> summary(m.Z.5, data = FALSE)
```

```
mkim version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:36 2013
Date of summary:   Tue Mar  5 01:40:36 2013
```

Equations:

```
[1] d_Z0 = - 0 - k_Z0_Z1 * Z0
[2] d_Z1 = + k_Z0_Z1 * Z0 - 0 - k_Z1_Z2 * Z1
[3] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2
```

Starting values for optimised parameters:

	initial	type	transformed
Z0_0	100.0	state	100.0000000
k_Z0_Z1	0.5	deparm	-0.6931472
k_Z1_Z2	0.2	deparm	-1.6094379
k_Z2_sink	0.1	deparm	-2.3025851

Fixed parameter values:

	value	type
Z1	0	state
Z2	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_0	96.7700	2.26600	92.1900	101.3000
k_Z0_Z1	0.7948	0.05843	0.6767	0.9129
k_Z1_Z2	-0.7410	0.06821	-0.8789	-0.6032
k_Z2_sink	-0.8027	0.11090	-1.0270	-0.5785

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_0	96.7700	92.1900	101.3000
k_Z0_Z1	2.2140	1.9670	2.4920
k_Z1_Z2	0.4766	0.4152	0.5471
k_Z2_sink	0.4481	0.3581	0.5607

Residual standard error: 4.486 on 40 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	19.58	4	40
Z0	17.43	2	15
Z1	15.94	1	13
Z2	20.51	1	12

Estimated disappearance times:

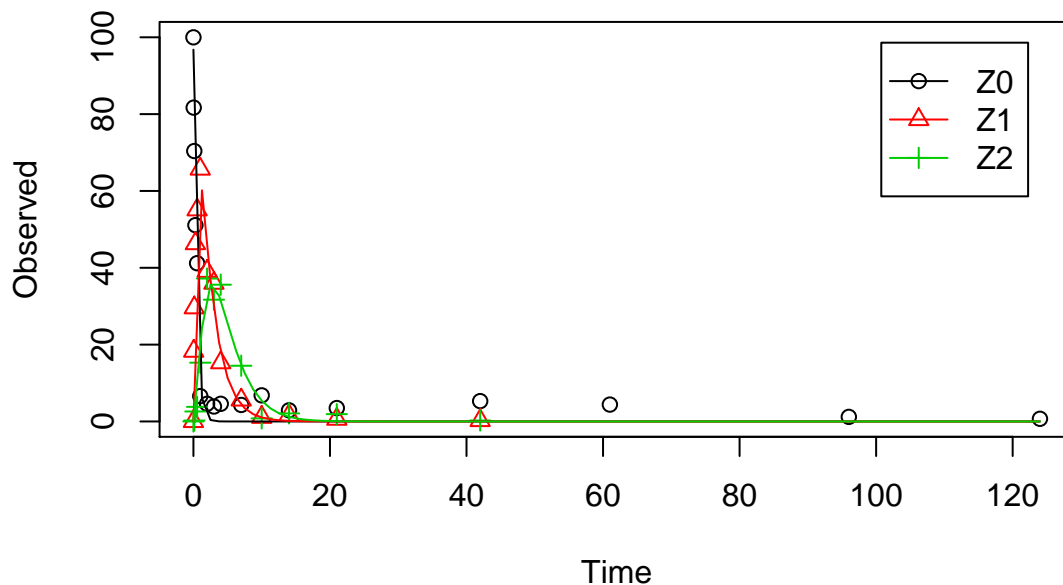
	DT50	DT90
Z0	0.3131	1.040
Z1	1.4543	4.831
Z2	1.5468	5.138

Estimated formation fractions:

	ff
Z0_Z1	1
Z1_Z2	1
Z2_sink	1

Parameter correlation:

	Z0_0	k_Z0_Z1	k_Z1_Z2	k_Z2_sink
Z0_0	1.00000	0.05781	0.28747	0.31786
k_Z0_Z1	0.05781	1.00000	-0.04361	0.01212
k_Z1_Z2	0.28747	-0.04361	1.00000	0.24018
k_Z2_sink	0.31786	0.01212	0.24018	1.00000



Finally, metabolite Z3 is added to the model.

```
R> Z.FOCUS <- mkinmod(Z0 = list(type = "SF0", to = "Z1", sink = FALSE),
+                    Z1 = list(type = "SF0", to = "Z2", sink = FALSE),
+                    Z2 = list(type = "SF0", to = "Z3"),
+                    Z3 = list(type = "SF0"))
R> m.Z.FOCUS <- mkinfit(Z.FOCUS, FOCUS_2006_Z_mkin,
+                      parms.ini = c(k_Z0_Z1 = 0.5, k_Z1_Z2 = 0.2, k_Z2_Z3 = 0.3),
+                      quiet = TRUE)
R> plot(m.Z.FOCUS)
R> summary(m.Z.FOCUS, data = FALSE)
```

```
mkim version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:38 2013
Date of summary:   Tue Mar  5 01:40:38 2013
```

Equations:

```
[1] d_Z0 = - 0 - k_Z0_Z1 * Z0
[2] d_Z1 = + k_Z0_Z1 * Z0 - 0 - k_Z1_Z2 * Z1
[3] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2 - k_Z2_Z3 * Z2
[4] d_Z3 = + k_Z2_Z3 * Z2 - k_Z3_sink * Z3
```

Starting values for optimised parameters:

	initial	type	transformed
Z0_0	100.0	state	100.0000000
k_Z0_Z1	0.5	deparm	-0.6931472
k_Z1_Z2	0.2	deparm	-1.6094379
k_Z2_Z3	0.3	deparm	-1.2039728
k_Z2_sink	0.1	deparm	-2.3025851
k_Z3_sink	0.1	deparm	-2.3025851

Fixed parameter values:

	value	type
Z1	0	state
Z2	0	state
Z3	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_0	96.8400	2.05900	92.7100	101.0000
k_Z0_Z1	0.7954	0.05332	0.6884	0.9025
k_Z1_Z2	-0.7375	0.06123	-0.8604	-0.6146
k_Z2_Z3	-1.5470	0.12250	-1.7930	-1.3010
k_Z2_sink	-1.4330	0.17160	-1.7770	-1.0880
k_Z3_sink	-2.8350	0.24360	-3.3240	-2.3470

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_0	96.84000	92.71000	101.0000
k_Z0_Z1	2.21500	1.99100	2.4660
k_Z1_Z2	0.47830	0.42300	0.5409
k_Z2_Z3	0.21290	0.16650	0.2723
k_Z2_sink	0.23870	0.16910	0.3368
k_Z3_sink	0.05869	0.03599	0.0957

Residual standard error: 4.1 on 51 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	19.78	6	51
Z0	17.45	2	15
Z1	15.92	1	13
Z2	21.24	2	11
Z3	12.46	1	12

Estimated disappearance times:

	DT50	DT90
Z0	0.3129	1.039
Z1	1.4492	4.814
Z2	1.5348	5.099
Z3	11.8100	39.232

Estimated formation fractions:

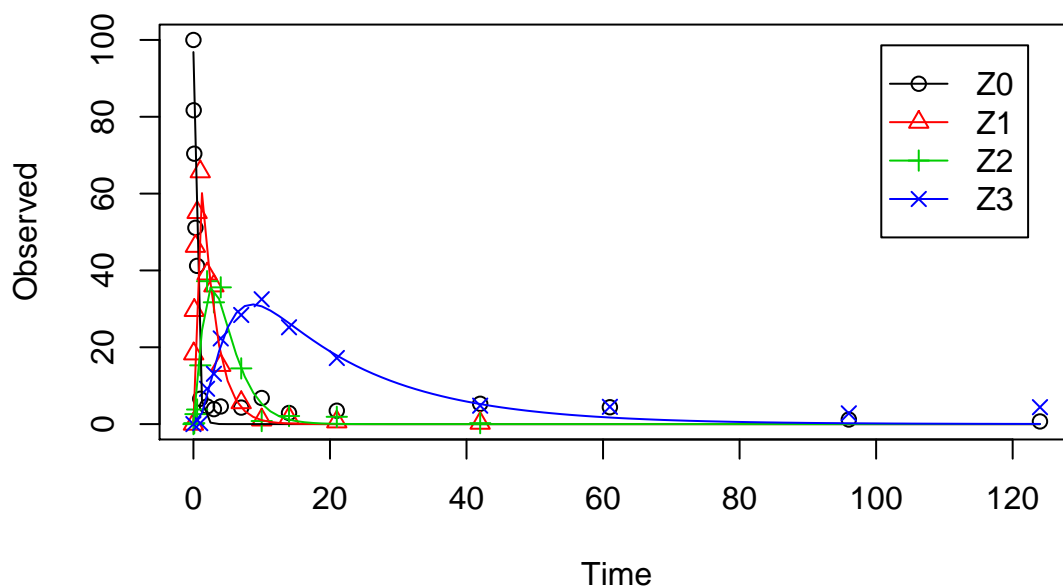
```

ff
Z0_Z1  1.0000
Z1_Z2  1.0000
Z2_sink 0.5285
Z2_Z3  0.4715
Z3_sink 1.0000

```

Parameter correlation:

	Z0_0	k_Z0_Z1	k_Z1_Z2	k_Z2_Z3	k_Z2_sink	k_Z3_sink
Z0_0	1.00000	0.05387	0.2727	-0.07295	0.37006	-0.11348
k_Z0_Z1	0.05387	1.00000	-0.0521	-0.03581	0.02442	-0.02521
k_Z1_Z2	0.27275	-0.05210	1.0000	-0.12132	0.29384	-0.19144
k_Z2_Z3	-0.07295	-0.03581	-0.1213	1.00000	-0.18887	0.55154
k_Z2_sink	0.37006	0.02442	0.2938	-0.18887	1.00000	-0.64293
k_Z3_sink	-0.11348	-0.02521	-0.1914	0.55154	-0.64293	1.00000

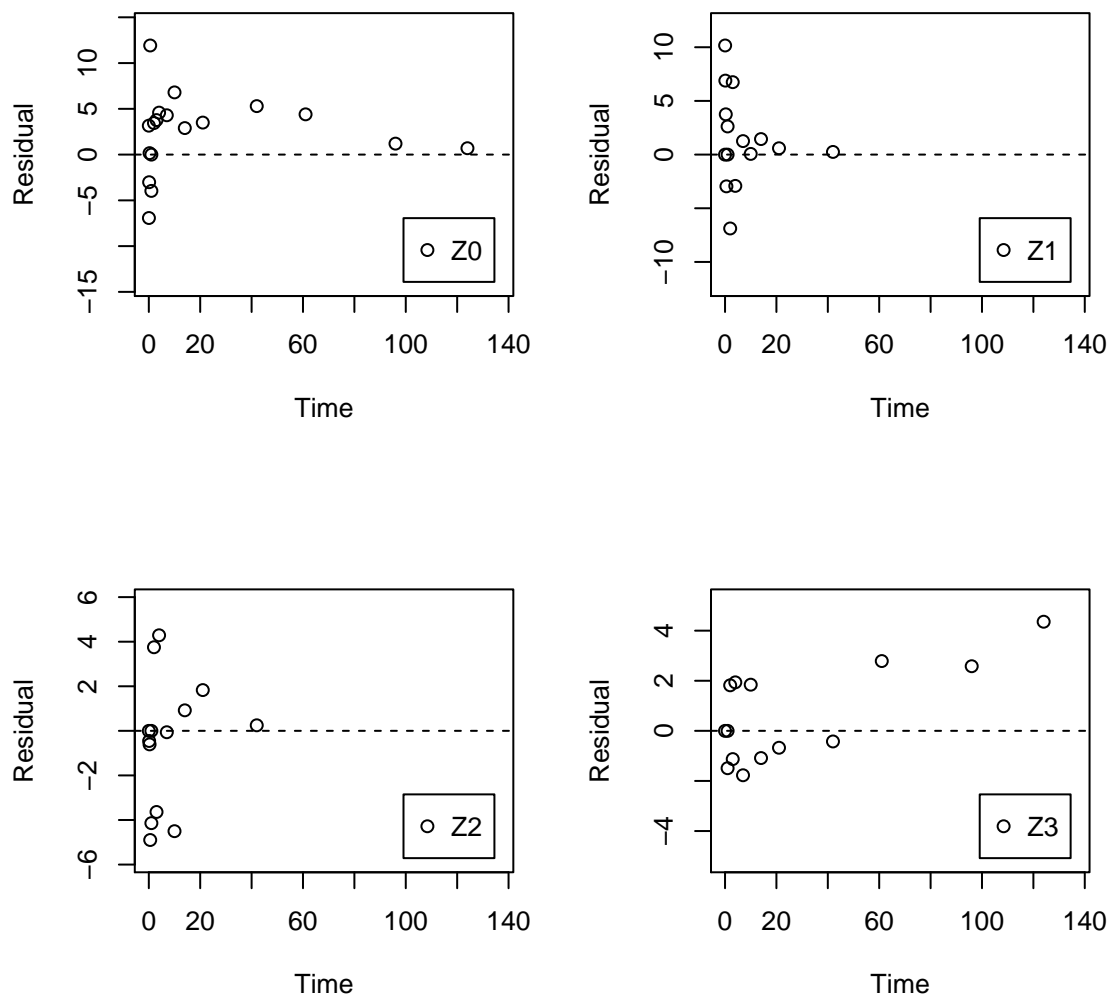


This is the fit corresponding to the final result chosen in Appendix 7 of the FOCUS report. The residual plots can be obtained by

```

R> par(mfrow = c(2, 2))
R> mkinresplot(m.Z.FOCUS, "Z0", lpos = "bottomright")
R> mkinresplot(m.Z.FOCUS, "Z1", lpos = "bottomright")
R> mkinresplot(m.Z.FOCUS, "Z2", lpos = "bottomright")
R> mkinresplot(m.Z.FOCUS, "Z3", lpos = "bottomright")

```



As the FOCUS report states, there is a certain tailing of the time course of metabolite Z3. Also, the time course of the parent compound is not fitted very well using the SFO model, as residues at a certain low level remain.

Therefore, an additional model is offered here, using the single first-order reversible binding (SFORB) model for metabolite Z3. As expected, the χ^2 error level is lower for metabolite Z3 using this model and the graphical fit for Z3 is improved. However, the covariance matrix is not returned.

```
R> Z.mkin.1 <- mkinmod(Z0 = list(type = "SFO", to = "Z1", sink = FALSE),
+                       Z1 = list(type = "SFO", to = "Z2", sink = FALSE),
+                       Z2 = list(type = "SFO", to = "Z3"),
+                       Z3 = list(type = "SFORB"))
```



```

R> m.Z.mkin.1 <- mkinfit(Z.mkin.1, FOCUS_2006_Z_mkin,
+                          parms.ini = c(k_Z0_Z1 = 0.5, k_Z1_Z2 = 0.3, k_Z2_Z3 = 0.2),
+                          quiet = TRUE)
R> plot(m.Z.mkin.1)
R> summary(m.Z.mkin.1, data = FALSE)

mkin version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:43 2013
Date of summary:   Tue Mar  5 01:40:43 2013

Equations:
[1] d_Z0 = - 0 - k_Z0_Z1 * Z0
[2] d_Z1 = + k_Z0_Z1 * Z0 - 0 - k_Z1_Z2 * Z1
[3] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2 - k_Z2_Z3_free * Z2
[4] d_Z3_free = + k_Z2_Z3_free * Z2 - k_Z3_free_sink * Z3_free - k_Z3_free_bound * Z3_free
[5] d_Z3_bound = + k_Z3_free_bound * Z3_free - k_Z3_bound_free * Z3_bound

Starting values for optimised parameters:
              initial   type transformed
Z0_0          1e+02  state 100.0000000
k_Z0_Z1       5e-01 deparm -0.6931472
k_Z1_Z2       3e-01 deparm -1.2039728
k_Z2_Z3       2e-01 deparm -1.6094379
k_Z2_sink     1e-01 deparm -2.3025851
k_Z2_Z3_free  1e-01 deparm -2.3025851
k_Z3_free_sink 1e-01 deparm -2.3025851
k_Z3_free_bound 1e-01 deparm -2.3025851
k_Z3_bound_free 2e-02 deparm -3.9120230

Fixed parameter values:
              value type
Z1              0 state
Z2              0 state
Z3_free         0 state
Z3_bound        0 state

Optimised, transformed parameters:
              Estimate Std. Error Lower Upper
Z0_0          96.7400          NA      NA      NA
k_Z0_Z1        0.7947          NA      NA      NA
k_Z1_Z2       -0.7426          NA      NA      NA
k_Z2_Z3       -1.6090          NA      NA      NA
k_Z2_sink     -1.4950          NA      NA      NA
k_Z2_Z3_free  -1.5040          NA      NA      NA
k_Z3_free_sink -2.6540          NA      NA      NA
k_Z3_free_bound -5.2440          NA      NA      NA
k_Z3_bound_free -19.8400          NA      NA      NA

```

Backtransformed parameters:

	<i>Estimate</i>	<i>Lower</i>	<i>Upper</i>
<i>Z0_0</i>	9.674e+01	NA	NA
<i>k_Z0_Z1</i>	2.214e+00	NA	NA
<i>k_Z1_Z2</i>	4.759e-01	NA	NA
<i>k_Z2_Z3</i>	2.000e-01	NA	NA
<i>k_Z2_sink</i>	2.243e-01	NA	NA
<i>k_Z2_Z3_free</i>	2.222e-01	NA	NA
<i>k_Z3_free_sink</i>	7.034e-02	NA	NA
<i>k_Z3_free_bound</i>	5.279e-03	NA	NA
<i>k_Z3_bound_free</i>	2.412e-09	NA	NA

Residual standard error: 4.149 on 48 degrees of freedom

Chi2 error levels in percent:

	<i>err.min</i>	<i>n.optim</i>	<i>df</i>
<i>All data</i>	19.931	9	48
<i>Z0</i>	17.429	2	15
<i>Z1</i>	15.949	1	13
<i>Z2</i>	21.967	3	10
<i>Z3</i>	8.561	3	10

Estimated disappearance times:

	<i>DT50</i>	<i>DT90</i>
<i>Z0</i>	0.3131	1.040
<i>Z1</i>	1.4566	4.839
<i>Z2</i>	1.5523	5.157
<i>Z3</i>	10.1977	45.329

Estimated formation fractions:

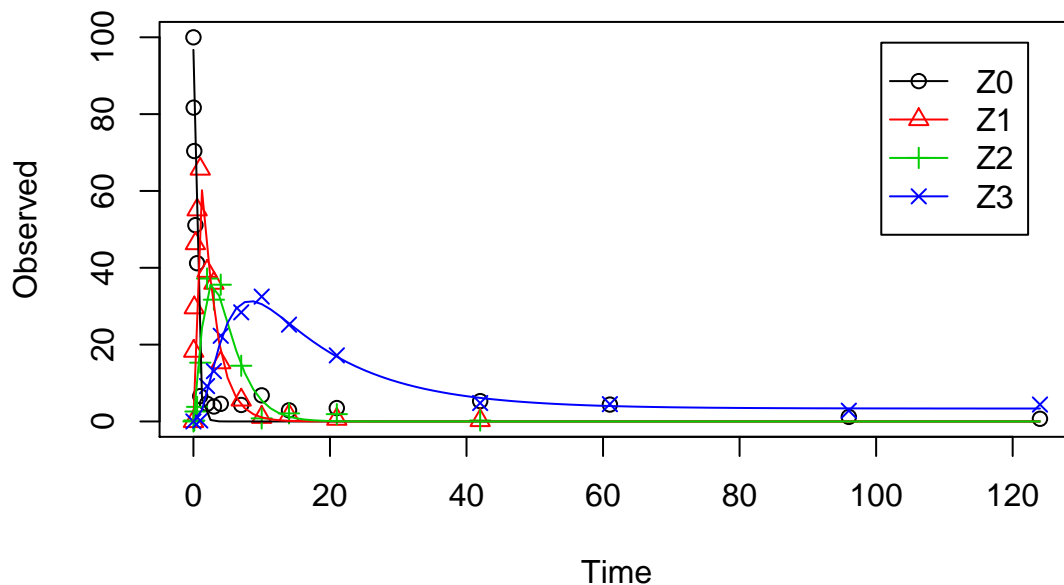
	<i>ff</i>
<i>Z0_Z1</i>	1.0000
<i>Z1_Z2</i>	1.0000
<i>Z2_sink</i>	0.5024
<i>Z2_Z3_free</i>	0.4976
<i>Z3_free_sink</i>	1.0000

Estimated Eigenvalues of SFORB model(s):

<i>Z3_b1</i>	<i>Z3_b2</i>
7.562e-02	2.244e-09

Parameter correlation:

Could not estimate covariance matrix; singular system:



Therefore, a further stepwise model building is performed starting from the stage of parent and one metabolite, starting from the assumption that the model fit for the parent compound can be improved by using the SFORB model.

```
R> Z.mkin.2 <- mkinmod(Z0 = list(type = "SFORB", to = "Z1", sink = FALSE),
+                      Z1 = list(type = "SFO"))
R> m.Z.mkin.2 <- mkinfit(Z.mkin.2, FOCUS_2006_Z_mkin, quiet = TRUE)
R> plot(m.Z.mkin.2)
R> summary(m.Z.mkin.2, data = FALSE)
```

```
mkim version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:43 2013
Date of summary:   Tue Mar  5 01:40:43 2013
```

Equations:

```
[1] d_Z0_free = - 0 - k_Z0_free_bound * Z0_free + k_Z0_bound_free * Z0_bound - k_Z0_free
[2] d_Z0_bound = + k_Z0_free_bound * Z0_free - k_Z0_bound_free * Z0_bound
[3] d_Z1 = + k_Z0_free_Z1 * Z0_free - k_Z1_sink * Z1
```

Starting values for optimised parameters:

	initial	type	transformed
Z0_free_0	1e+02	state	100.000000
k_Z0_free_bound	1e-01	deparm	-2.302585
k_Z0_bound_free	2e-02	deparm	-3.912023

<i>k_Z0_free_Z1</i>	1e-01	deparm	-2.302585
<i>k_Z1_sink</i>	1e-01	deparm	-2.302585

Fixed parameter values:

	value	type
<i>Z0_bound</i>	0	state
<i>Z1</i>	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
<i>Z0_free_0</i>	97.2900	2.39500	92.3600	102.2000
<i>k_Z0_free_bound</i>	-2.0820	0.43220	-2.9710	-1.1940
<i>k_Z0_bound_free</i>	-4.7200	1.60500	-8.0190	-1.4220
<i>k_Z0_free_Z1</i>	0.8549	0.06430	0.7227	0.9871
<i>k_Z1_sink</i>	-0.7934	0.08506	-0.9682	-0.6185

Backtransformed parameters:

	Estimate	Lower	Upper
<i>Z0_free_0</i>	97.290000	9.236e+01	102.2000
<i>k_Z0_free_bound</i>	0.124700	5.128e-02	0.3031
<i>k_Z0_bound_free</i>	0.008911	3.291e-04	0.2413
<i>k_Z0_free_Z1</i>	2.351000	2.060e+00	2.6830
<i>k_Z1_sink</i>	0.452300	3.798e-01	0.5387

Residual standard error: 4.438 on 26 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	15.89	5	26
<i>Z0</i>	14.74	4	13
<i>Z1</i>	14.94	1	13

Estimated disappearance times:

	DT50	DT90
<i>Z0</i>	0.302	1.190
<i>Z1</i>	1.532	5.091

Estimated formation fractions:

	ff
<i>Z0_free_Z1</i>	1
<i>Z1_sink</i>	1

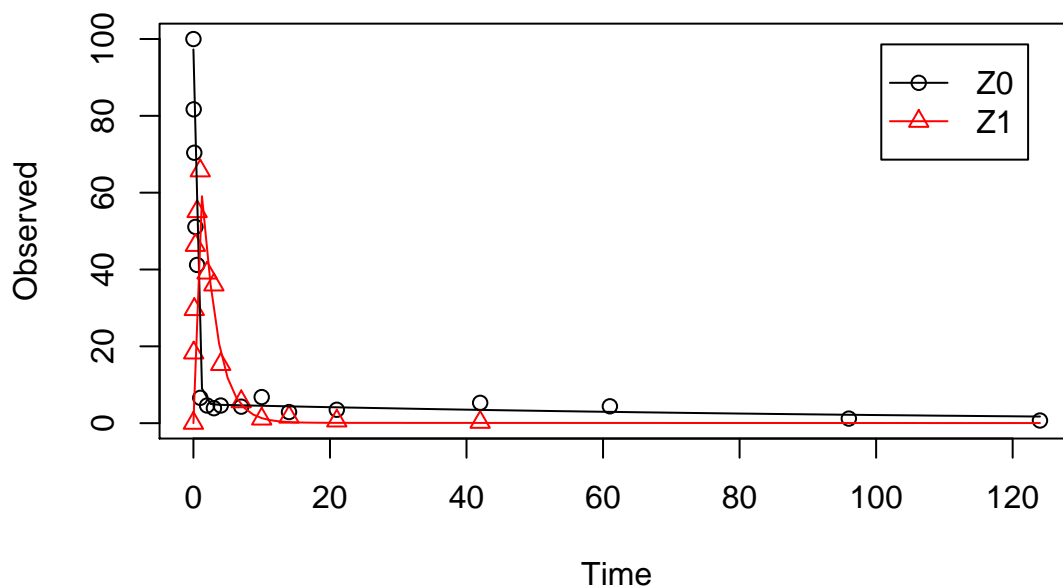
Estimated Eigenvalues of SFORB model(s):

	<i>Z0_b1</i>	<i>Z0_b2</i>
	2.476313	0.008461

Parameter correlation:

	<i>Z0_free_0</i>	<i>k_Z0_free_bound</i>	<i>k_Z0_bound_free</i>	<i>k_Z0_free_Z1</i>
<i>Z0_free_0</i>	1.000000	0.006494	0.03324	0.11182

<i>k_Z0_free_bound</i>	0.006494	1.000000	0.54646	0.41393
<i>k_Z0_bound_free</i>	0.033238	0.546465	1.00000	0.15837
<i>k_Z0_free_Z1</i>	0.111819	0.413926	0.15837	1.00000
<i>k_Z1_sink</i>	0.391553	-0.291912	-0.12597	-0.04188
	<i>k_Z1_sink</i>			
<i>Z0_free_0</i>	0.39155			
<i>k_Z0_free_bound</i>	-0.29191			
<i>k_Z0_bound_free</i>	-0.12597			
<i>k_Z0_free_Z1</i>	-0.04188			
<i>k_Z1_sink</i>	1.00000			



When metabolite Z2 is added, the additional sink for Z1 is turned off again, for the same reasons as in the original analysis.

```
R> Z.mkin.3 <- mkinmod(Z0 = list(type = "SFORB", to = "Z1", sink = FALSE),
+                      Z1 = list(type = "SFO", to = "Z2"),
+                      Z2 = list(type = "SFO"))
R> m.Z.mkin.3 <- mkinfit(Z.mkin.3, FOCUS_2006_Z_mkin, quiet = TRUE)
R> plot(m.Z.mkin.3)
R> summary(m.Z.mkin.3, data = FALSE)
```

```
mkin version:    0.9.16
R version:       2.15.2
Date of fit:     Tue Mar  5 01:40:47 2013
Date of summary: Tue Mar  5 01:40:47 2013
```

Equations:

```
[1] d_Z0_free = - 0 - k_Z0_free_bound * Z0_free + k_Z0_bound_free * Z0_bound - k_Z0_free_bound * Z0_bound
[2] d_Z0_bound = + k_Z0_free_bound * Z0_free - k_Z0_bound_free * Z0_bound
[3] d_Z1 = + k_Z0_free_Z1 * Z0_free - k_Z1_sink * Z1 - k_Z1_Z2 * Z1
[4] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2
```

Starting values for optimised parameters:

	initial	type	transformed
Z0_free_0	1e+02	state	100.000000
k_Z0_free_bound	1e-01	deparm	-2.302585
k_Z0_bound_free	2e-02	deparm	-3.912023
k_Z0_free_Z1	1e-01	deparm	-2.302585
k_Z1_sink	1e-01	deparm	-2.302585
k_Z1_Z2	1e-01	deparm	-2.302585
k_Z2_sink	1e-01	deparm	-2.302585

Fixed parameter values:

	value	type
Z0_bound	0	state
Z1	0	state
Z2	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_free_0	97.4400	2.124e+00	9.313e+01	1.017e+02
k_Z0_free_bound	-2.1490	4.121e-01	-2.984e+00	-1.314e+00
k_Z0_bound_free	-4.8380	1.636e+00	-8.153e+00	-1.524e+00
k_Z0_free_Z1	0.8457	5.911e-02	7.259e-01	9.655e-01
k_Z1_sink	-19.3800	1.751e+06	-3.547e+06	3.547e+06
k_Z1_Z2	-0.7812	8.755e-02	-9.586e-01	-6.038e-01
k_Z2_sink	-0.8606	1.439e-01	-1.152e+00	-5.691e-01

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_free_0	9.744e+01	93.130000	101.7000
k_Z0_free_bound	1.166e-01	0.050600	0.2688
k_Z0_bound_free	7.920e-03	0.000288	0.2178
k_Z0_free_Z1	2.330e+00	2.067000	2.6260
k_Z1_sink	3.834e-09	0.000000	Inf
k_Z1_Z2	4.579e-01	0.383400	0.5467
k_Z2_sink	4.229e-01	0.316000	0.5660

Residual standard error: 4.136 on 37 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	17.95	7	37
Z0	14.67	4	13

Z1	15.52	2 12
Z2	21.27	1 12

Estimated disappearance times:

	DT50	DT90
Z0	0.3043	1.185
Z1	1.5138	5.029
Z2	1.6391	5.445

Estimated formation fractions:

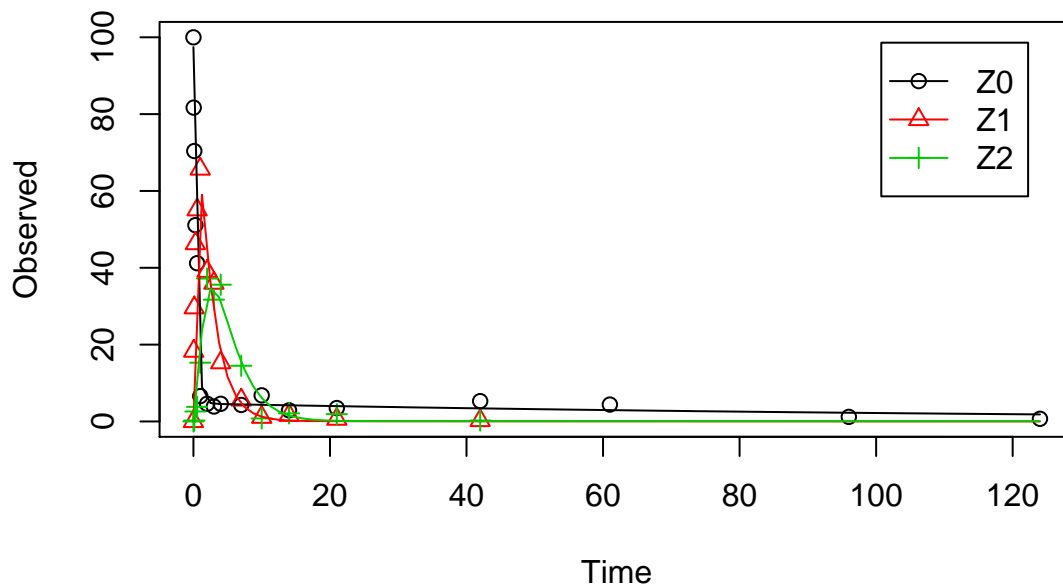
	ff
Z0_free_Z1	1.000e+00
Z1_sink	8.373e-09
Z1_Z2	1.000e+00
Z2_sink	1.000e+00

Estimated Eigenvalues of SFORB model(s):

	Z0_b1	Z0_b2
	2.446638	0.007542

Parameter correlation:

	Z0_free_0	k_Z0_free_bound	k_Z0_bound_free	k_Z0_free_Z1
Z0_free_0	1.00000	0.05615	0.06063	0.09324
k_Z0_free_bound	0.05615	1.00000	0.54490	0.41896
k_Z0_bound_free	0.06063	0.54490	1.00000	0.16141
k_Z0_free_Z1	0.09324	0.41896	0.16141	1.00000
k_Z1_sink	0.15262	-0.11467	-0.06038	0.02314
k_Z1_Z2	0.08997	-0.09395	-0.02475	-0.09097
k_Z2_sink	0.11068	-0.07920	-0.01859	-0.05193
	k_Z1_sink	k_Z1_Z2	k_Z2_sink	
Z0_free_0	0.15262	0.08997	0.11068	
k_Z0_free_bound	-0.11467	-0.09395	-0.07920	
k_Z0_bound_free	-0.06038	-0.02475	-0.01859	
k_Z0_free_Z1	0.02314	-0.09097	-0.05193	
k_Z1_sink	1.00000	-0.66065	-0.66738	
k_Z1_Z2	-0.66065	1.00000	0.59341	
k_Z2_sink	-0.66738	0.59341	1.00000	



This results in a much better representation of the behaviour of the parent compound Z0.

Finally, Z3 is added as well. This model appears overparameterised (no covariance matrix returned) if the sink for Z1 is left in the model.

```
R> Z.mkin.4 <- mkinmod(Z0 = list(type = "SFORB", to = "Z1", sink = FALSE),
+                     Z1 = list(type = "SF0", to = "Z2", sink = FALSE),
+                     Z2 = list(type = "SF0", to = "Z3"),
+                     Z3 = list(type = "SF0"))
R> m.Z.mkin.4 <- mkinfit(Z.mkin.4, FOCUS_2006_Z_mkin,
+   parms.ini = c(k_Z1_Z2 = 0.05), quiet = TRUE)
R> plot(m.Z.mkin.4)
R> summary(m.Z.mkin.4, data = FALSE)
```

```
mkin version:      0.9.16
R version:         2.15.2
Date of fit:       Tue Mar  5 01:40:51 2013
Date of summary:   Tue Mar  5 01:40:51 2013
```

Equations:

```
[1] d_Z0_free = - 0 - k_Z0_free_bound * Z0_free + k_Z0_bound_free * Z0_bound - k_Z0_free_bound * Z0_free
[2] d_Z0_bound = + k_Z0_free_bound * Z0_free - k_Z0_bound_free * Z0_bound
[3] d_Z1 = + k_Z0_free_Z1 * Z0_free - 0 - k_Z1_Z2 * Z1
[4] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2 - k_Z2_Z3 * Z2
```


[5] $d_{Z3} = + k_{Z2_Z3} * Z2 - k_{Z3_sink} * Z3$

Starting values for optimised parameters:

	initial	type	transformed
Z0_free_0	1e+02	state	100.000000
k_Z1_Z2	5e-02	deparm	-2.995732
k_Z0_free_bound	1e-01	deparm	-2.302585
k_Z0_bound_free	2e-02	deparm	-3.912023
k_Z0_free_Z1	1e-01	deparm	-2.302585
k_Z2_sink	1e-01	deparm	-2.302585
k_Z2_Z3	1e-01	deparm	-2.302585
k_Z3_sink	1e-01	deparm	-2.302585

Fixed parameter values:

	value	type
Z0_bound	0	state
Z1	0	state
Z2	0	state
Z3	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_free_0	97.5300	1.88700	93.7400	101.3000
k_Z1_Z2	-0.7769	0.05834	-0.8942	-0.6597
k_Z0_free_bound	-2.1360	0.36810	-2.8760	-1.3960
k_Z0_bound_free	-4.7650	1.41700	-7.6130	-1.9170
k_Z0_free_Z1	0.8470	0.05339	0.7398	0.9543
k_Z2_sink	-1.5610	0.18260	-1.9280	-1.1940
k_Z2_Z3	-1.5280	0.11350	-1.7560	-1.2990
k_Z3_sink	-2.7690	0.22460	-3.2200	-2.3180

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_free_0	97.53000	9.374e+01	101.3000
k_Z1_Z2	0.45980	4.089e-01	0.5170
k_Z0_free_bound	0.11810	5.636e-02	0.2475
k_Z0_bound_free	0.00852	4.938e-04	0.1470
k_Z0_free_Z1	2.33300	2.095e+00	2.5970
k_Z2_sink	0.20990	1.455e-01	0.3030
k_Z2_Z3	0.21700	1.728e-01	0.2727
k_Z3_sink	0.06272	3.994e-02	0.0985

Residual standard error: 3.737 on 49 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	17.98	8	49
Z0	14.69	4	13
Z1	15.03	1	13

Z2	21.99	2 11
Z3	12.32	1 12

Estimated disappearance times:

	DT50	DT90
Z0	0.304	1.186
Z1	1.507	5.008
Z2	1.623	5.393
Z3	11.051	36.712

Estimated formation fractions:

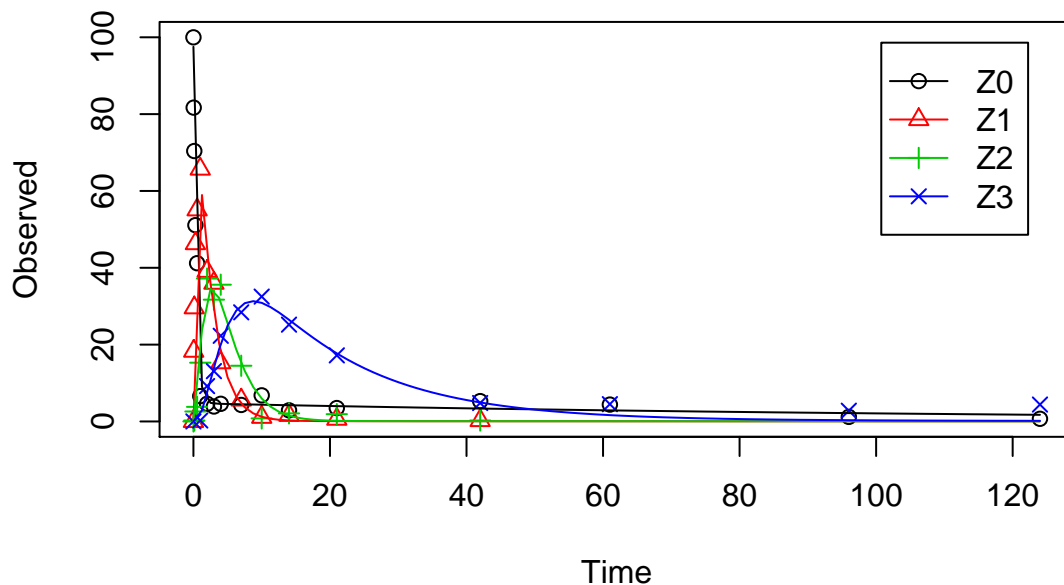
	ff
Z0_free_Z1	1.0000
Z1_Z2	1.0000
Z2_sink	0.4917
Z2_Z3	0.5083
Z3_sink	1.0000

Estimated Eigenvalues of SFORB model(s):

Z0_b1	Z0_b2
2.451259	0.008108

Parameter correlation:

	Z0_free_0	k_Z1_Z2	k_Z0_free_bound	k_Z0_bound_free	k_Z0_free_Z1
Z0_free_0	1.00000	0.24238	0.07823	0.06921	0.08883
k_Z1_Z2	0.24238	1.00000	-0.22742	-0.08934	-0.10841
k_Z0_free_bound	0.07823	-0.22742	1.00000	0.53976	0.42766
k_Z0_bound_free	0.06921	-0.08934	0.53976	1.00000	0.16281
k_Z0_free_Z1	0.08883	-0.10841	0.42766	0.16281	1.00000
k_Z2_sink	0.32993	0.34052	-0.26331	-0.12743	-0.05310
k_Z2_Z3	-0.07494	-0.14885	0.06698	0.06082	-0.01281
k_Z3_sink	-0.10456	-0.22486	0.13845	0.12526	0.01858
	k_Z2_sink	k_Z2_Z3	k_Z3_sink		
Z0_free_0	0.3299	-0.07494	-0.10456		
k_Z1_Z2	0.3405	-0.14885	-0.22486		
k_Z0_free_bound	-0.2633	0.06698	0.13845		
k_Z0_bound_free	-0.1274	0.06082	0.12526		
k_Z0_free_Z1	-0.0531	-0.01281	0.01858		
k_Z2_sink	1.0000	-0.25473	-0.68320		
k_Z2_Z3	-0.2547	1.00000	0.56390		
k_Z3_sink	-0.6832	0.56390	1.00000		



The error level of the fit, but especially of metabolite Z3, can be improved if the SFORB model is chosen for this metabolite, as this model is capable of representing the tailing of the metabolite decline phase.

Using the SFORB additionally for Z1 or Z2 did not further improve the result.

```
R> Z.mkin.5 <- mkinmod(Z0 = list(type = "SFORB", to = "Z1", sink = FALSE),
+                      Z1 = list(type = "SFO", to = "Z2", sink = FALSE),
+                      Z2 = list(type = "SFO", to = "Z3"),
+                      Z3 = list(type = "SFORB"))
R> m.Z.mkin.5 <- mkinfit(Z.mkin.5, FOCUS_2006_Z_mkin,
+   parms.ini = c(k_Z1_Z2 = 0.2), quiet = TRUE)
R> plot(m.Z.mkin.5)
R> summary(m.Z.mkin.5, data = FALSE)
```

```
mkin version:    0.9.16
R version:      2.15.2
Date of fit:    Tue Mar  5 01:41:04 2013
Date of summary: Tue Mar  5 01:41:04 2013
```

Equations:

```
[1] d_Z0_free = - 0 - k_Z0_free_bound * Z0_free + k_Z0_bound_free * Z0_bound - k_Z0_free
[2] d_Z0_bound = + k_Z0_free_bound * Z0_free - k_Z0_bound_free * Z0_bound
[3] d_Z1 = + k_Z0_free_Z1 * Z0_free - 0 - k_Z1_Z2 * Z1
```

```

[4] d_Z2 = + k_Z1_Z2 * Z1 - k_Z2_sink * Z2 - k_Z2_Z3_free * Z2
[5] d_Z3_free = + k_Z2_Z3_free * Z2 - k_Z3_free_sink * Z3_free - k_Z3_free_bound * Z3_free
[6] d_Z3_bound = + k_Z3_free_bound * Z3_free - k_Z3_bound_free * Z3_bound

```

Starting values for optimised parameters:

	initial	type	transformed
Z0_free_0	1e+02	state	100.000000
k_Z1_Z2	2e-01	deparm	-1.609438
k_Z0_free_bound	1e-01	deparm	-2.302585
k_Z0_bound_free	2e-02	deparm	-3.912023
k_Z0_free_Z1	1e-01	deparm	-2.302585
k_Z2_sink	1e-01	deparm	-2.302585
k_Z2_Z3_free	1e-01	deparm	-2.302585
k_Z3_free_sink	1e-01	deparm	-2.302585
k_Z3_free_bound	1e-01	deparm	-2.302585
k_Z3_bound_free	2e-02	deparm	-3.912023

Fixed parameter values:

	value	type
Z0_bound	0	state
Z1	0	state
Z2	0	state
Z3_free	0	state
Z3_bound	0	state

Optimised, transformed parameters:

	Estimate	Std. Error	Lower	Upper
Z0_free_0	97.4300	1.88700	93.6400	101.2000
k_Z1_Z2	-0.7813	0.05861	-0.8992	-0.6634
k_Z0_free_bound	-2.1470	0.36930	-2.8900	-1.4040
k_Z0_bound_free	-4.8230	1.46300	-7.7650	-1.8800
k_Z0_free_Z1	0.8459	0.05334	0.7386	0.9532
k_Z2_sink	-1.6300	0.22080	-2.0740	-1.1850
k_Z2_Z3_free	-1.4850	0.19600	-1.8800	-1.0910
k_Z3_free_sink	-2.5950	0.38470	-3.3690	-1.8220
k_Z3_free_bound	-5.2570	1.37200	-8.0160	-2.4970
k_Z3_bound_free	-13.4400	282.00000	-580.8000	553.9000

Backtransformed parameters:

	Estimate	Lower	Upper
Z0_free_0	9.743e+01	9.364e+01	1.012e+02
k_Z1_Z2	4.578e-01	4.069e-01	5.151e-01
k_Z0_free_bound	1.169e-01	5.559e-02	2.457e-01
k_Z0_bound_free	8.044e-03	4.242e-04	1.525e-01
k_Z0_free_Z1	2.330e+00	2.093e+00	2.594e+00
k_Z2_sink	1.960e-01	1.257e-01	3.056e-01
k_Z2_Z3_free	2.264e-01	1.526e-01	3.358e-01
k_Z3_free_sink	7.462e-02	3.442e-02	1.618e-01
k_Z3_free_bound	5.214e-03	3.301e-04	8.234e-02

k_Z3_bound_free 1.458e-06 5.692e-253 3.734e+240

Residual standard error: 3.73 on 47 degrees of freedom

Chi2 error levels in percent:

	err.min	n.optim	df
All data	17.890	10	47
Z0	14.666	4	13
Z1	15.049	1	13
Z2	21.991	2	11
Z3	8.433	3	10

Estimated disappearance times:

	DT50	DT90
Z0	0.3043	1.185
Z1	1.5141	5.030
Z2	1.6409	5.451
Z3	9.5901	41.258

Estimated formation fractions:

	ff
Z0_free_Z1	1.000
Z1_Z2	1.000
Z2_sink	0.464
Z2_Z3_free	0.536
Z3_free_sink	1.000

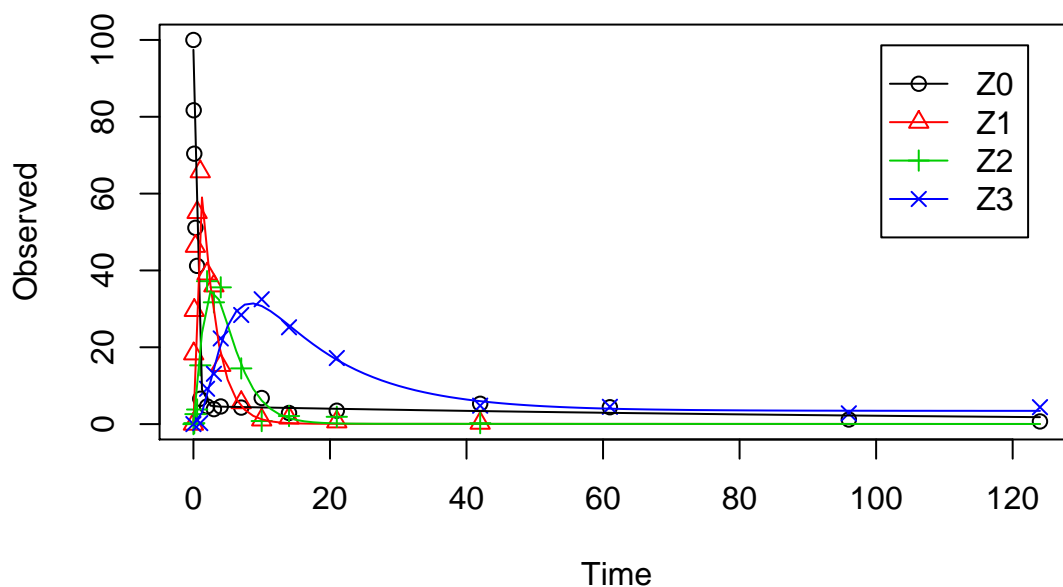
Estimated Eigenvalues of SFORB model(s):

	Z0_b1	Z0_b2	Z3_b1	Z3_b2
	2.447e+00	7.658e-03	7.983e-02	1.363e-06

Parameter correlation:

	Z0_free_0	k_Z1_Z2	k_Z0_free_bound	k_Z0_bound_free	k_Z0_free_Z1
Z0_free_0	1.00000	0.24874	0.079292	0.073662	0.09072
k_Z1_Z2	0.24874	1.00000	-0.223885	-0.082769	-0.10368
k_Z0_free_bound	0.07929	-0.22389	1.000000	0.542876	0.42696
k_Z0_bound_free	0.07366	-0.08277	0.542876	1.000000	0.16540
k_Z0_free_Z1	0.09072	-0.10368	0.426958	0.165399	1.00000
k_Z2_sink	0.31619	0.36741	-0.287122	-0.168222	-0.08266
k_Z2_Z3_free	-0.03185	-0.05441	0.008287	0.013478	-0.01908
k_Z3_free_sink	-0.12037	-0.22367	0.070584	0.024242	-0.01842
k_Z3_free_bound	0.01629	0.01906	0.009670	0.031837	0.03607
k_Z3_bound_free	0.03781	0.08868	-0.055136	-0.008975	-0.06574
	k_Z2_sink	k_Z2_Z3_free	k_Z3_free_sink	k_Z3_free_bound	
Z0_free_0	0.31619	-0.031847	-0.12037	0.01629	
k_Z1_Z2	0.36741	-0.054405	-0.22367	0.01906	
k_Z0_free_bound	-0.28712	0.008287	0.07058	0.00967	
k_Z0_bound_free	-0.16822	0.013478	0.02424	0.03184	
k_Z0_free_Z1	-0.08266	-0.019083	-0.01842	0.03607	

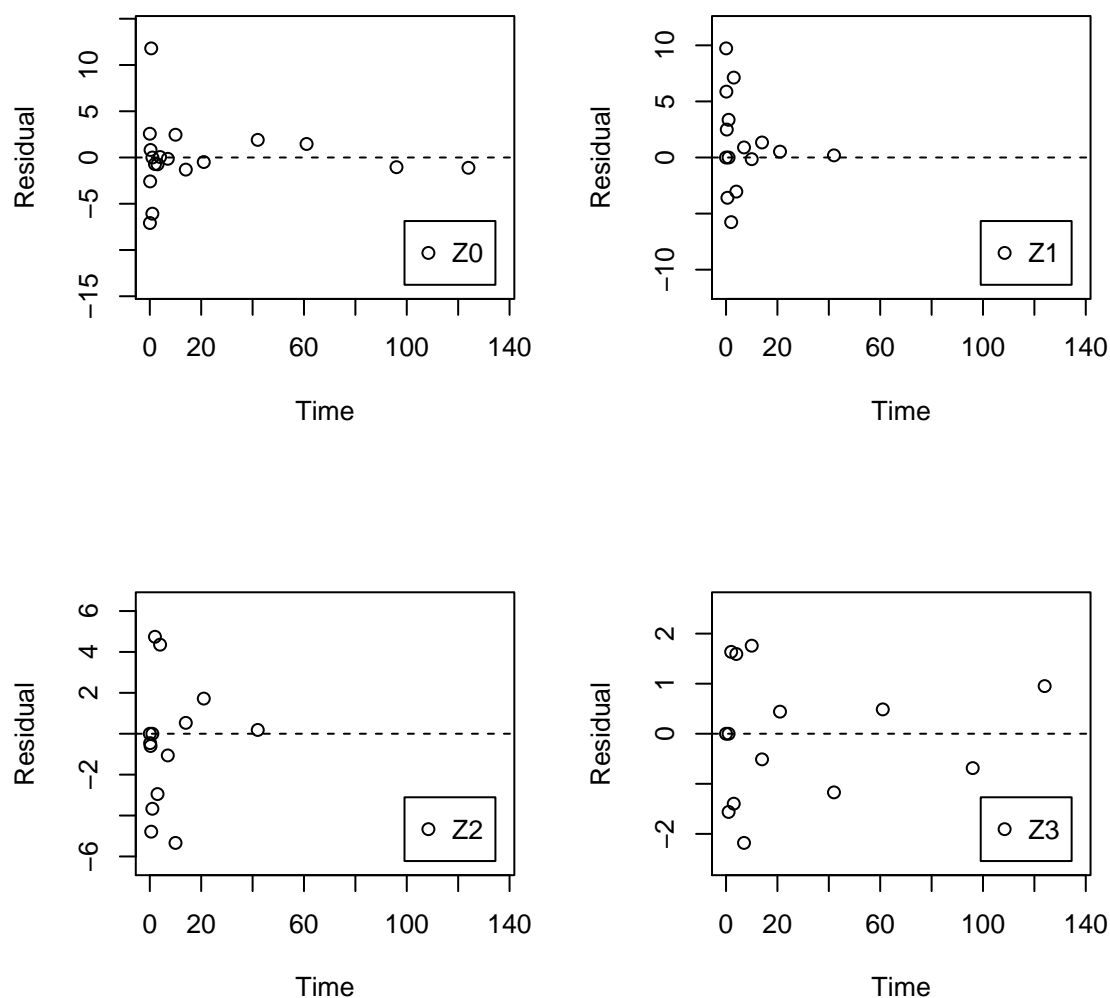
k_{Z2_sink}	1.00000	-0.069361	-0.66596	0.02603
$k_{Z2_Z3_free}$	-0.06936	1.000000	-0.26493	0.73477
$k_{Z3_free_sink}$	-0.66596	-0.264933	1.00000	-0.36064
$k_{Z3_free_bound}$	0.02603	0.734774	-0.36064	1.00000
$k_{Z3_bound_free}$	0.23931	0.774434	-0.71123	0.81143
	$k_{Z3_bound_free}$			
$Z0_free_0$	0.037814			
k_{Z1_Z2}	0.088677			
$k_{Z0_free_bound}$	-0.055136			
$k_{Z0_bound_free}$	-0.008975			
$k_{Z0_free_Z1}$	-0.065741			
k_{Z2_sink}	0.239308			
$k_{Z2_Z3_free}$	0.774434			
$k_{Z3_free_sink}$	-0.711226			
$k_{Z3_free_bound}$	0.811433			
$k_{Z3_bound_free}$	1.000000			



Looking at the confidence intervals of the SFORB model parameters of Z3, it is clear that nothing can be said about a degradation rate of Z3. However, this appears to be a feature of the data.

```
R> par(mfrow = c(2, 2))
R> mkinresplot(m.Z.mkin.5, "Z0", lpos = "bottomright")
R> mkinresplot(m.Z.mkin.5, "Z1", lpos = "bottomright")
R> mkinresplot(m.Z.mkin.5, "Z2", lpos = "bottomright")
```

```
R> mkinresplot(m.Z.mkin.5, "Z3", lpos = "bottomright")
```



As expected, the residual plots are much more random than in the case of the all SFO model for which they were shown above. In conclusion, the model `Z.mkin.5` is proposed as the best-fit model for the dataset from Appendix 7 of the FOCUS report.

References

FOCUS Work Group on Degradation Kinetics. *Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration. Report of the FOCUS Work Group on Degradation Kinetics*, 2006. URL

<http://focus.jrc.ec.europa.eu/dk>. EC Document Reference Sanco/10058/2005 version 2.0.

FOCUS Work Group on Degradation Kinetics. *Generic guidance for estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration*, 1.0 edition, November 2011. URL <http://focus.jrc.ec.europa.eu/dk>.

Johannes Ranke. *kinfit: Routines for fitting simple kinetic models to chemical degradation data*, 2012. URL <http://CRAN.R-project.org>.