

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:      0.9.12
R version:         2.15.2
Date of fit:       Mon Feb 18 09:34:23 2013
Date of summary:   Mon Feb 18 09:34:23 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
parent_0      92.471      1.368
k_parent_sink -2.347      0.041
```

```
Backtransformed parameters:
              Estimate
parent_0      92.471
k_parent_sink  0.096
```

```
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:

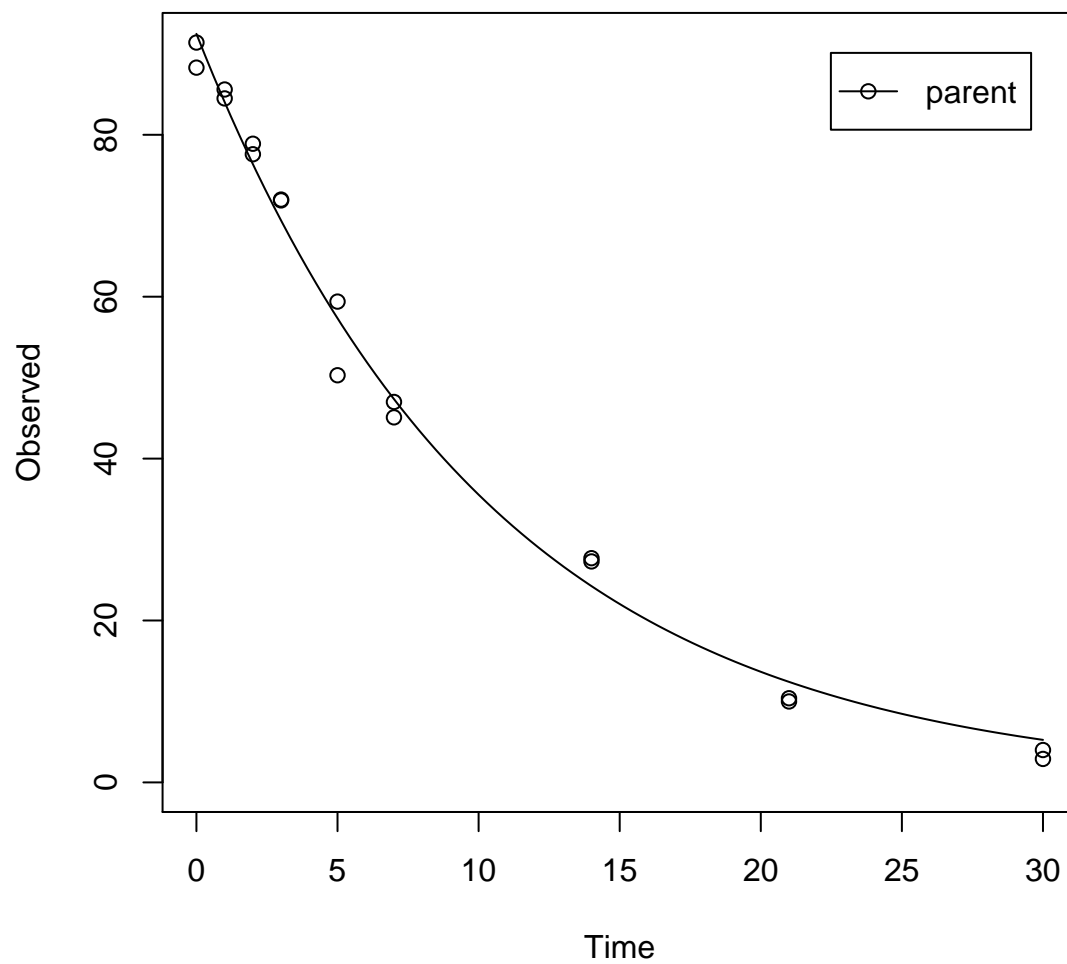
	parent_0	k_parent_sink
parent_0	1.0000	0.6248
k_parent_sink	0.6248	1.0000

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

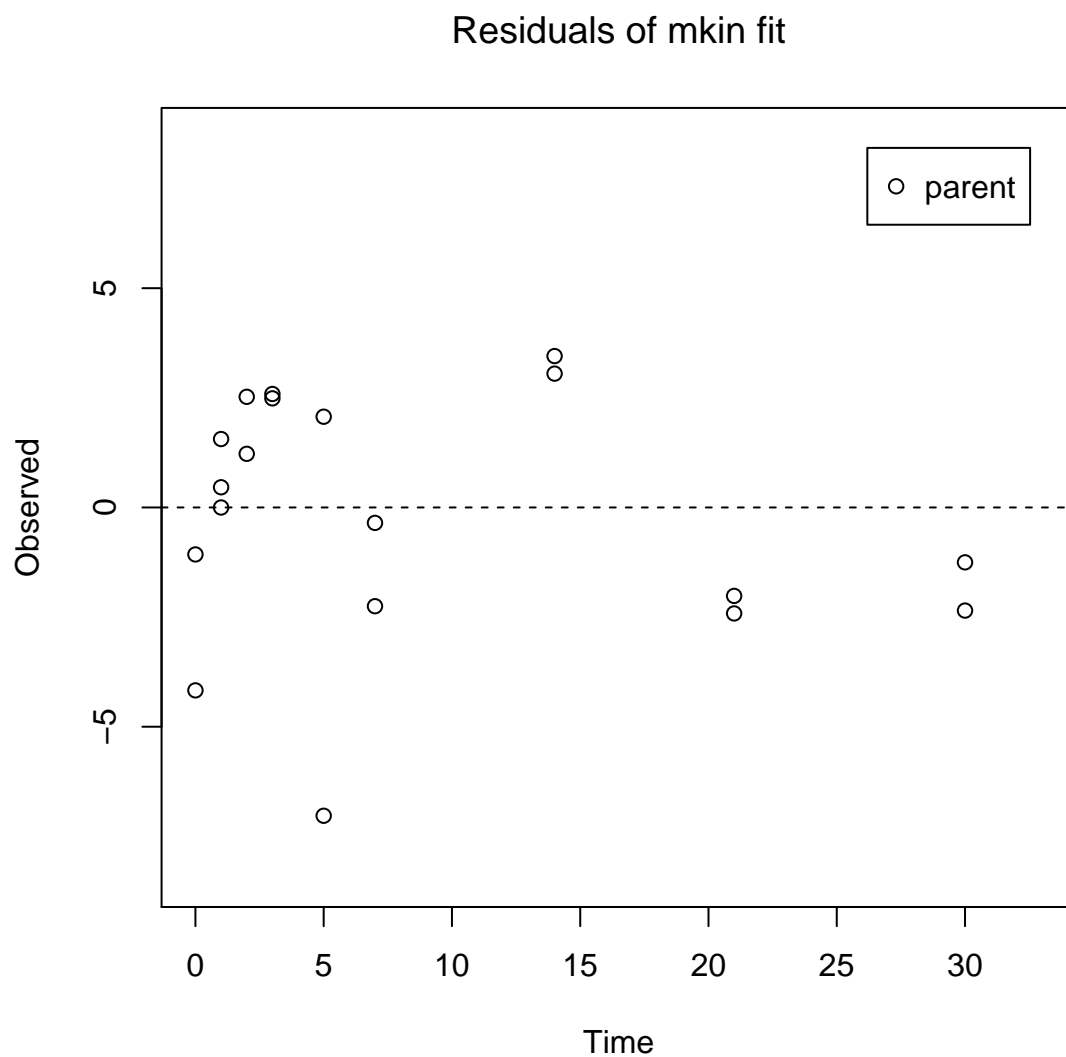
A plot of the fit is obtained with the plot function for mkinfit objects.

```
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> s.m.L1.FOMC <- summary(m.L1.FOMC)
R> s.m.L1.FOMC$errmin
```

	<i>err.min</i>	<i>n.optim</i>	<i>df</i>
<i>All data</i>	0.03618911	3	6
<i>parent</i>	0.03618911	3	6

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%).

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)
```

```
mkin version:      0.9.12
R version:       2.15.2
Date of fit:    Mon Feb 18 09:34:24 2013
Date of summary: Mon Feb 18 09:34:24 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
parent_0      91.4656      3.807
k_parent_sink -0.4112      0.107
```

```
Backtransformed parameters:
              Estimate
parent_0      91.466
k_parent_sink  0.663
```

```
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:

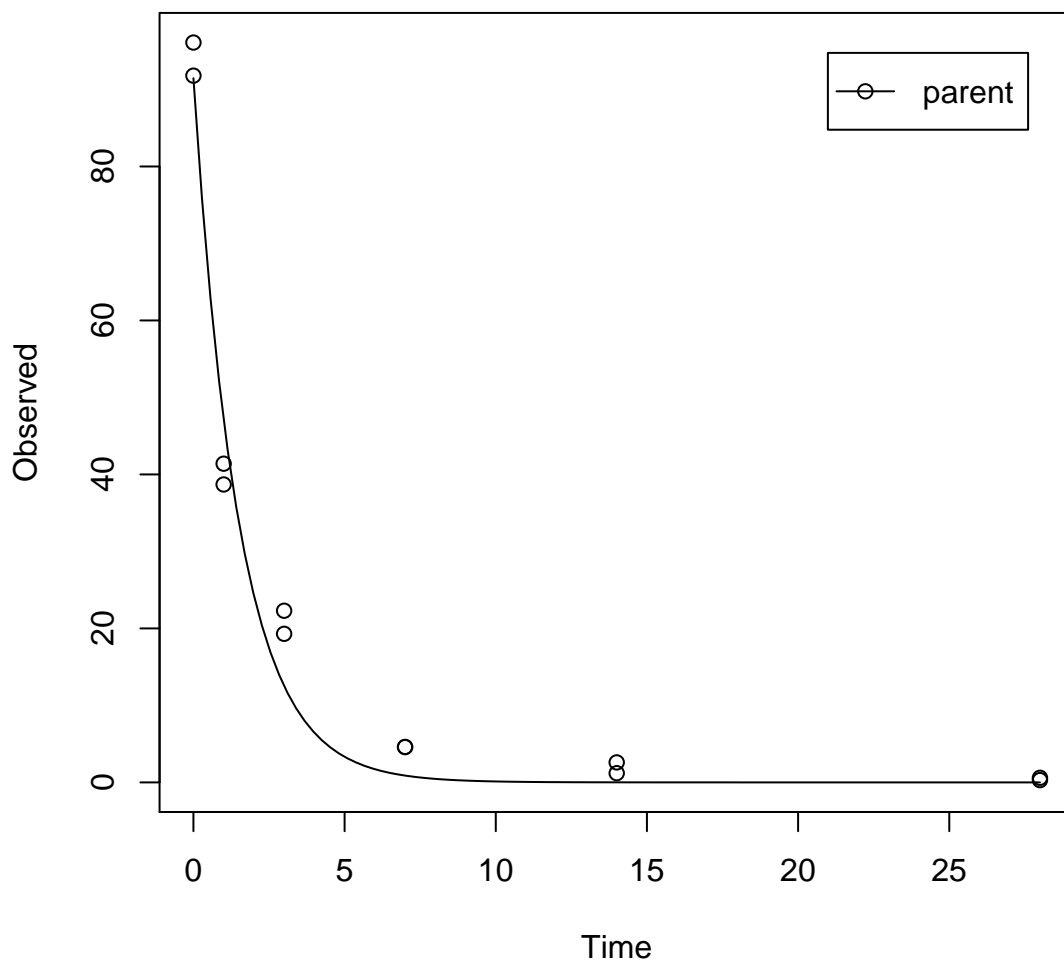
```
      parent_0 k_parent_sink
parent_0      1.0000      0.4295
k_parent_sink 0.4295      1.0000
```

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

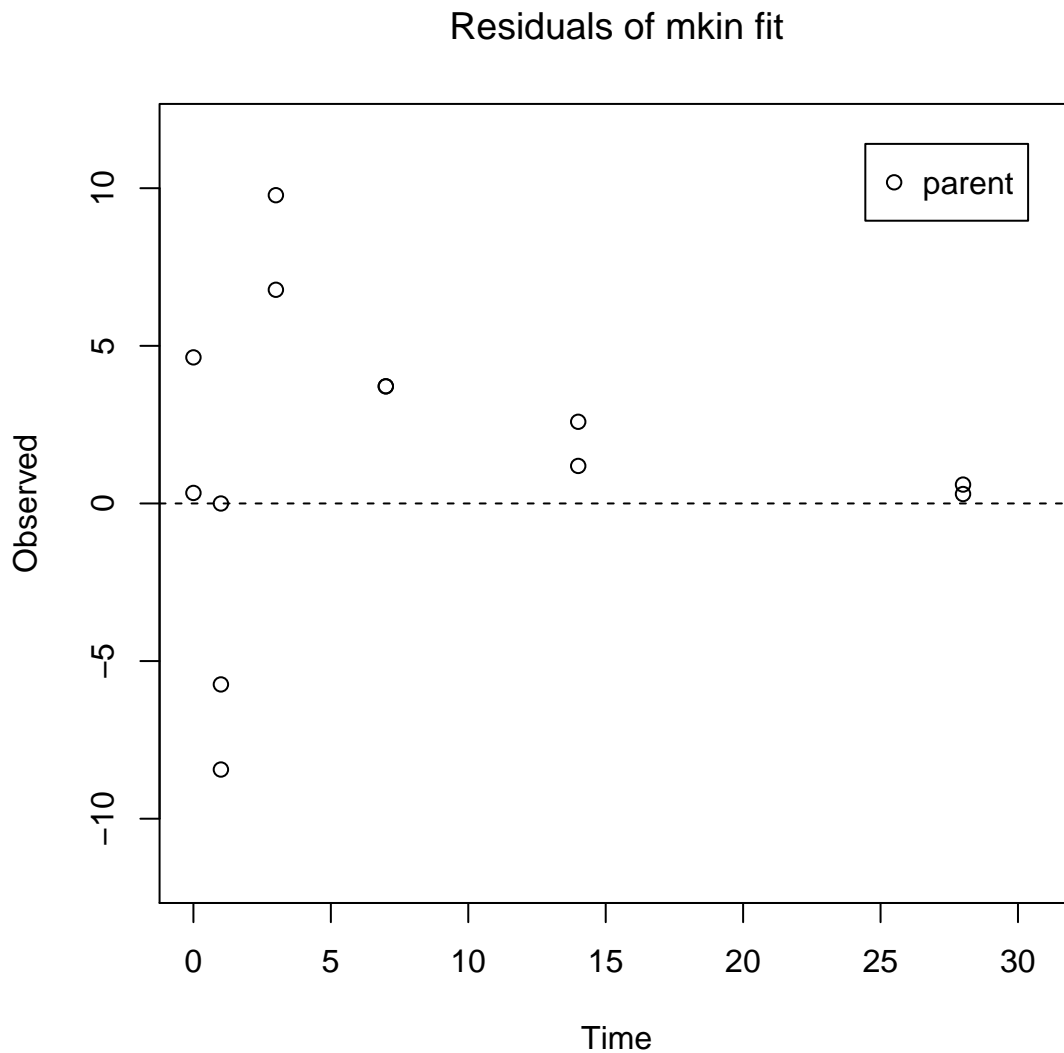
The χ^2 error level of 14% suggests that the model does not fit very well. This is also obvious from the plots of the fit and the residuals.

```
R> plot(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.

```
R> mkinresplot(m.L2.SF0, ylab = "Observed", xlab = "Time")
```

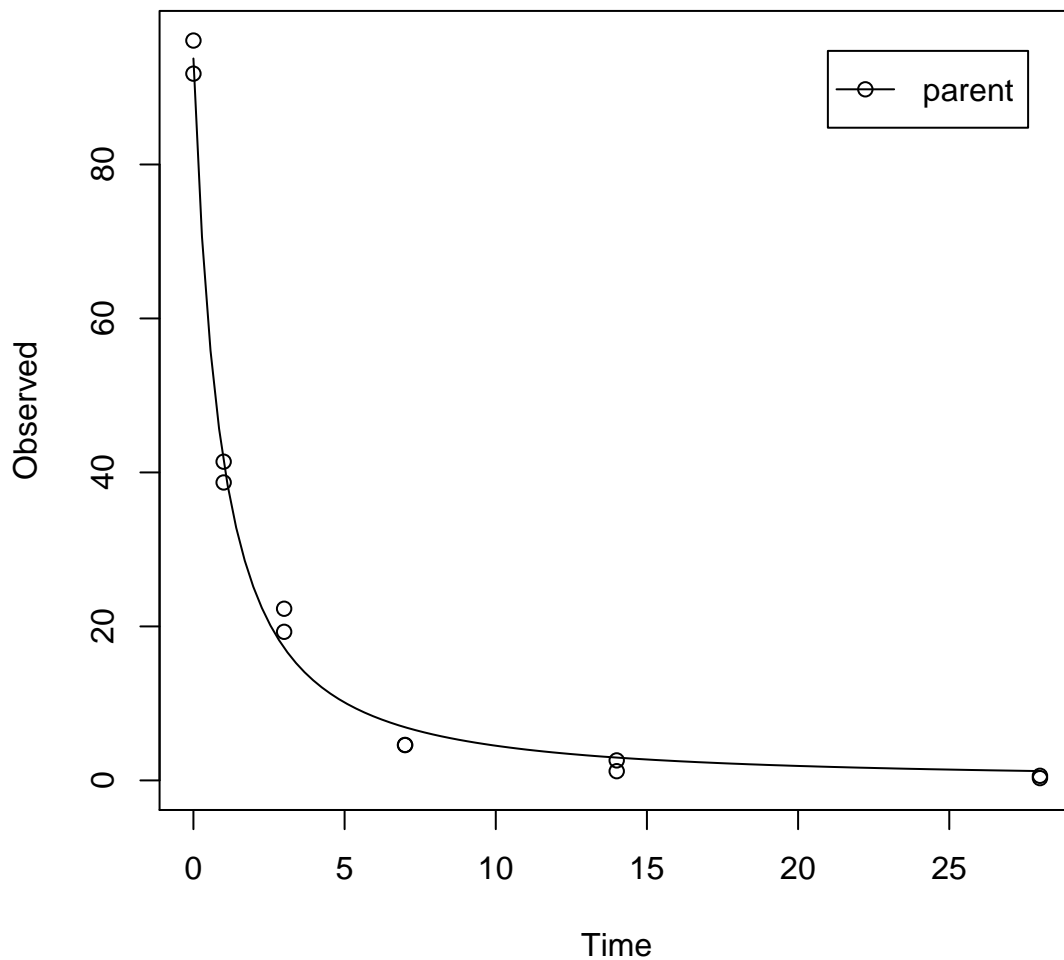


We may add that it is difficult to judge the random nature of the residuals just from the three samplings at days 0, 1 and 3. Also, it is not clear why a consistent underestimation after the approximate DT90 should be irrelevant.

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> plot(m.L2.FOMC)
R> s.m.L2.FOMC <- summary(m.L2.FOMC)
R> s.m.L2.FOMC$errmin
```

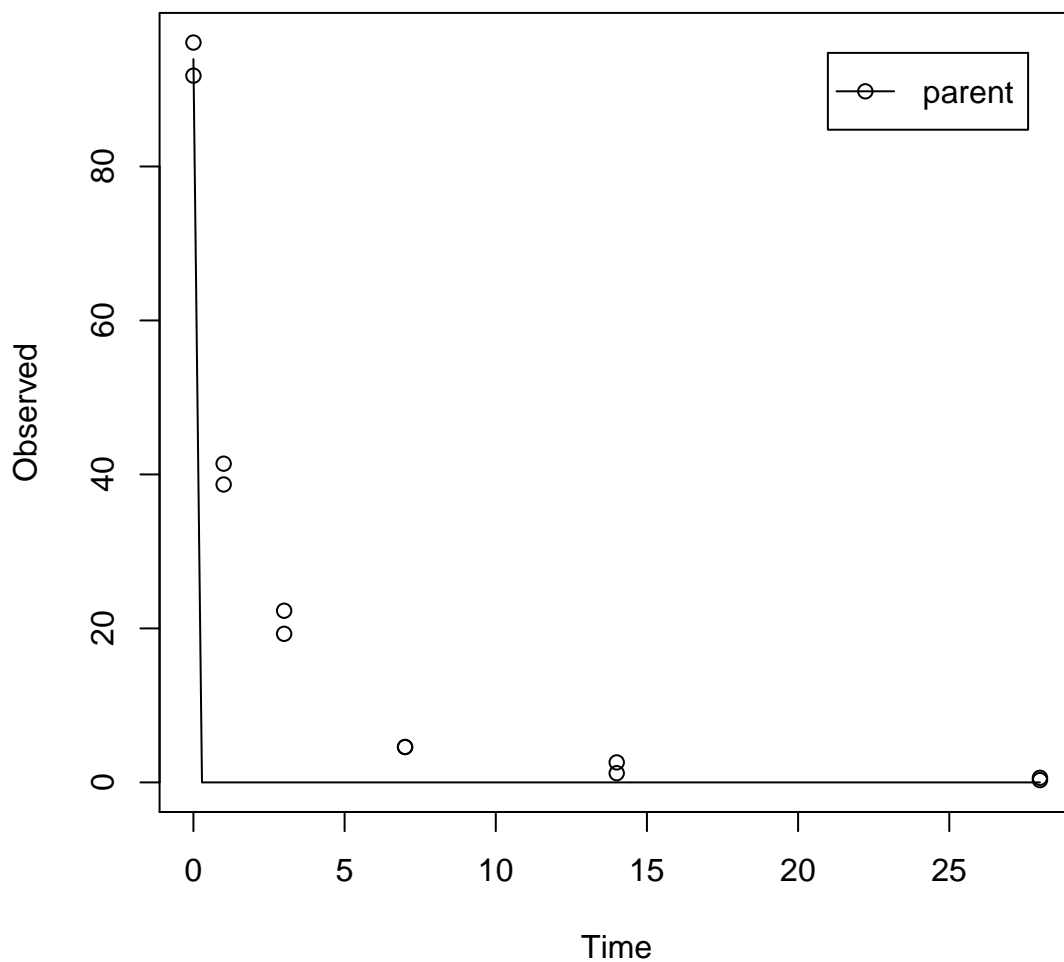
	<i>err.min</i>	<i>n.optim</i>	<i>df</i>
<i>All data</i>	0.06204245	3	3
<i>parent</i>	0.06204245	3	3



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 does not further reduce 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)
```

```
mkim version:    0.9.12
R version:       2.15.2
Date of fit:     Mon Feb 18 09:34:25 2013
Date of summary: Mon Feb 18 09:34:25 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
parent_0	93.9500	NA
k1	4.9589	NA
k2	-1.0880	NA
g	-0.2821	NA

Backtransformed parameters:

	Estimate
parent_0	93.950
k1	142.434
k2	0.337
g	0.402

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

Estimated formation fractions:

```
[1] ff  
<0 rows> (or 0-length row.names)
```

Data:

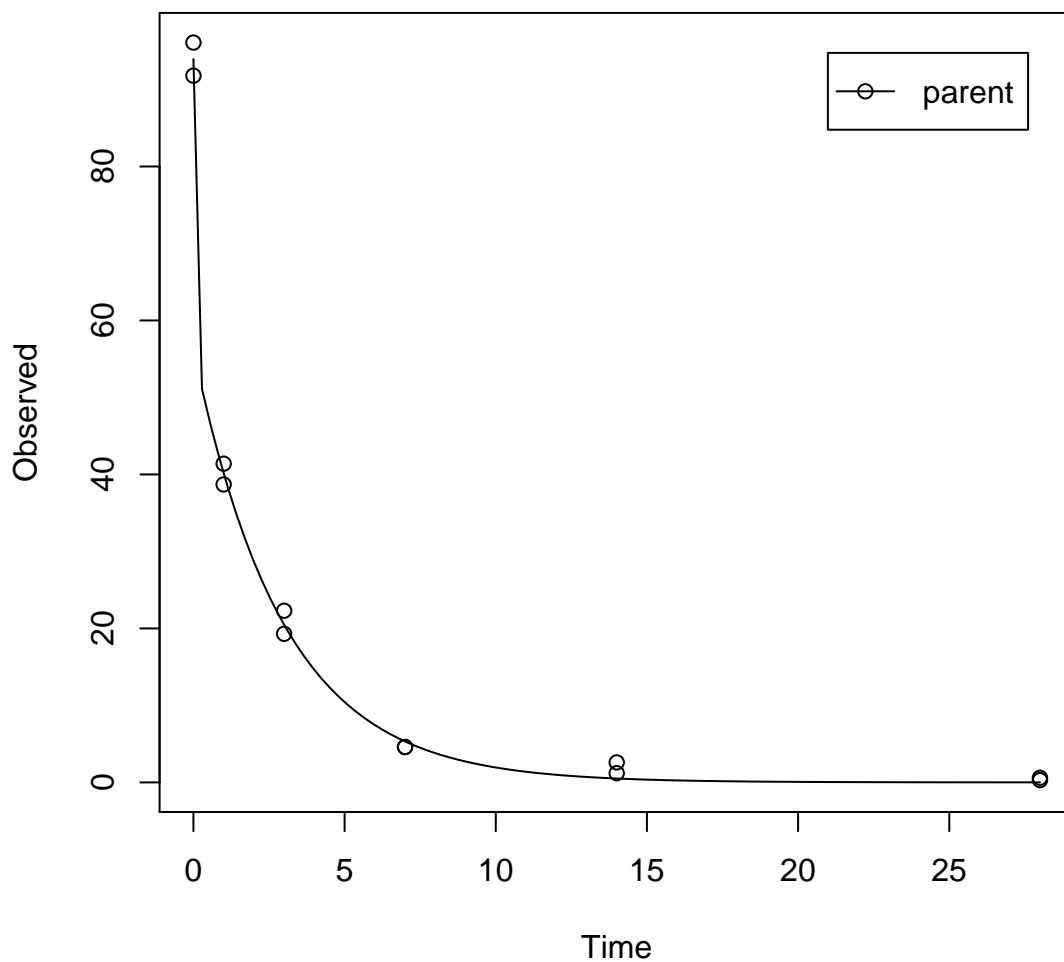
time	variable	observed	predicted	residual
0	parent	96.1	93.950000	2.1500
0	parent	91.8	93.950000	-2.1500
1	parent	41.4	40.143423	1.2566
1	parent	38.7	40.143423	-1.4434

3	parent	19.3	20.464500	-1.1645
3	parent	22.3	20.464500	1.8355
7	parent	4.6	5.318322	-0.7183
7	parent	4.6	5.318322	-0.7183
14	parent	2.6	0.503070	2.0969
14	parent	1.2	0.503070	0.6969
28	parent	0.3	0.004501	0.2955
28	parent	0.6	0.004501	0.5955

```
R> s.m.L2.DFOP <- summary(m.L2.DFOP)
```

```
R> s.m.L2.DFOP$errmin
```

	<i>err.min</i>	<i>n.optim</i>	<i>df</i>
<i>All data</i>	0.02528763	4	2
<i>parent</i>	0.02528763	4	2



Therefore, the FOMC model is clearly the best-fit model based on the χ^2 error level criterion.

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.SF0 <- mkinfit(SF0, FOCUS_2006_L3_mkin, quiet=TRUE)
```

```
R> summary(m.L3.SF0)
```

```
mkim version:      0.9.12
R version:         2.15.2
Date of fit:       Mon Feb 18 09:34:25 2013
Date of summary:   Mon Feb 18 09:34:25 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
parent_0	74.873	8.458
k_parent_sink	-3.678	0.326

Backtransformed parameters:

	Estimate
parent_0	74.873
k_parent_sink	0.025

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:

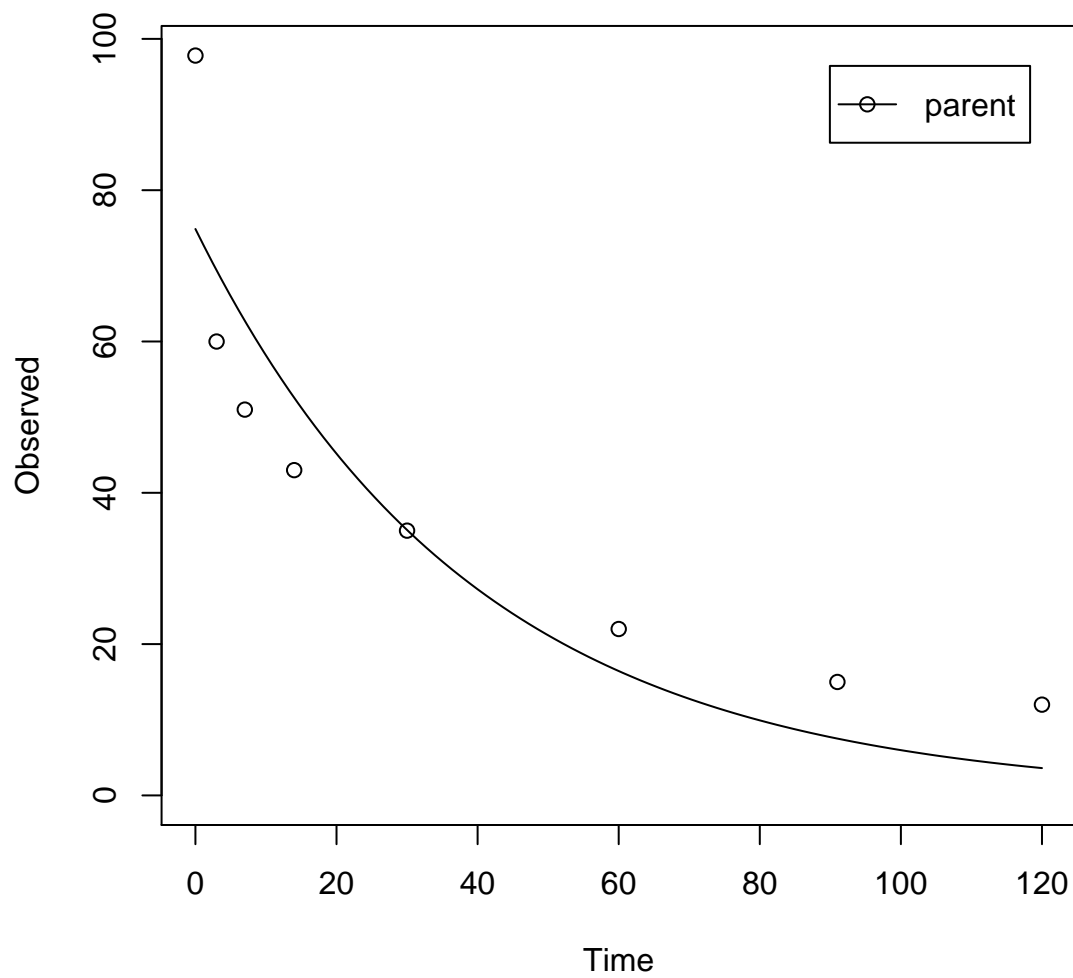
	parent_0	k_parent_sink
parent_0	1.0000	0.5484

k_parent_sink 0.5484 1.0000

Data:

<i>time</i>	<i>variable</i>	<i>observed</i>	<i>predicted</i>	<i>residual</i>
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

R> plot(m.L3.SF0)



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> s.m.L3.FOMC <- summary(m.L3.FOMC)
R> s.m.L3.FOMC$errmin
```

```
              err.min n.optim df
All data 0.07321867      3  5
parent   0.07321867      3  5
```

```
R> endpoints(m.L3.FOMC)
```

```
$distimes
```

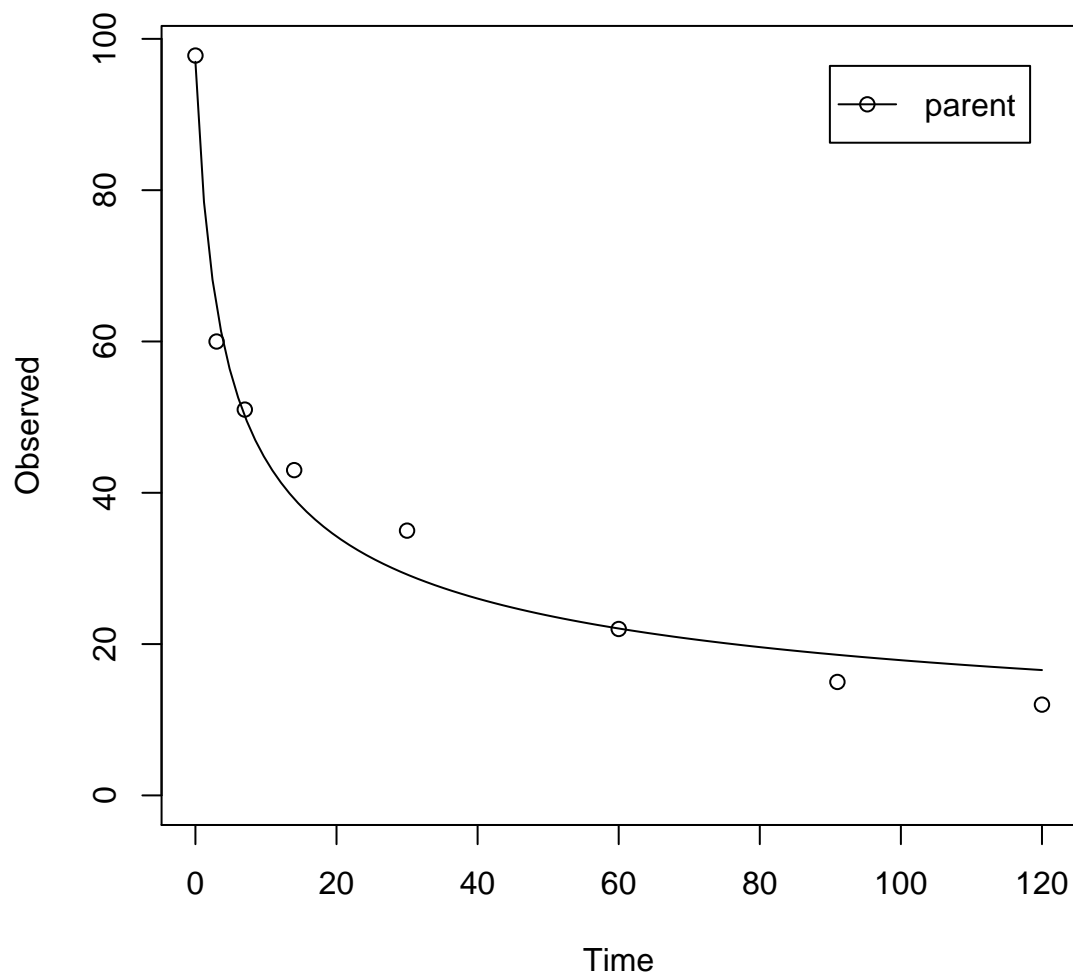
```
          DT50      DT90
parent 7.729478 431.2428
```

```
$ff
```

```
logical(0)
```

```
$SFORB
```

```
logical(0)
```

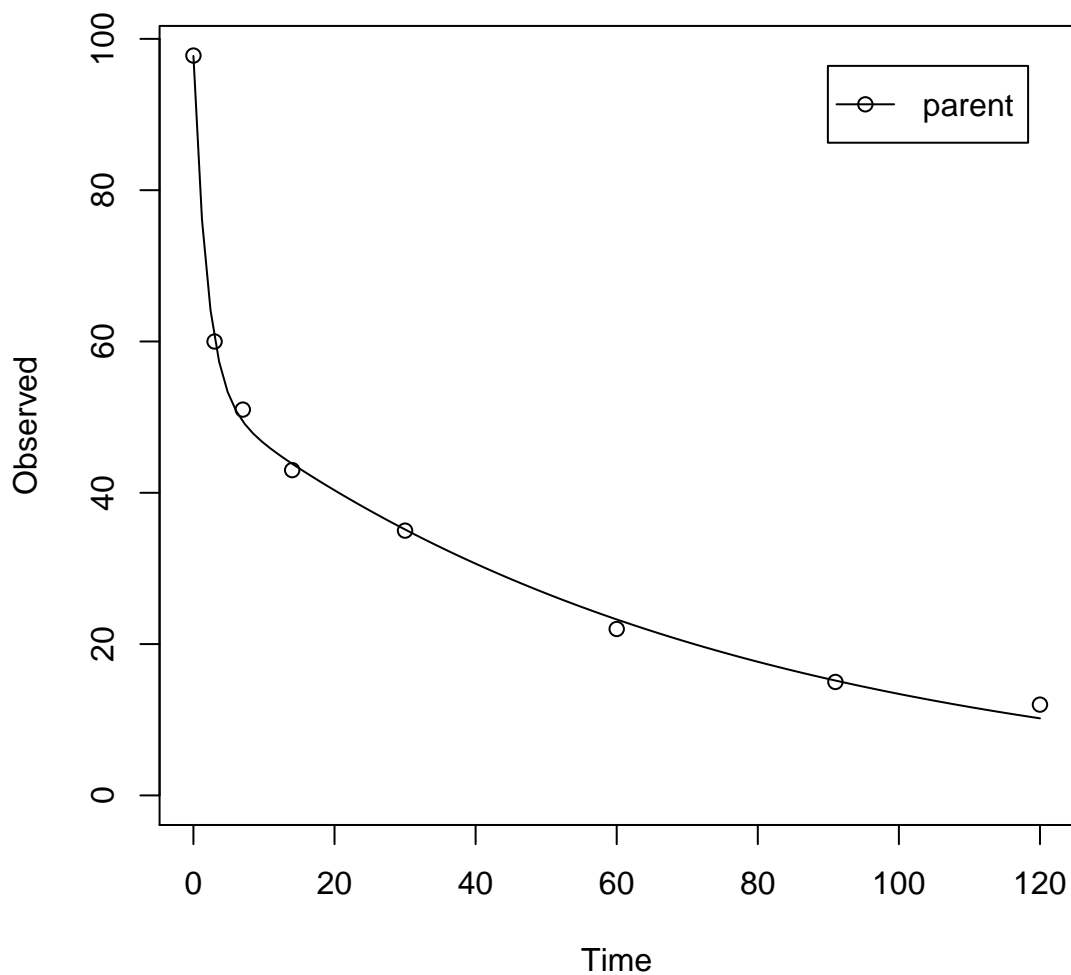


The error level at which the χ^2 test passes is 7% in this case.

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> s.m.L3.DFOP <- summary(m.L3.DFOP)
R> s.m.L3.DFOP$errmin
```

```
      err.min n.optim df
All data 0.02223992    4  4
parent   0.02223992    4  4
```



Therefore, the DFOP model is 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.SF0 <- mkinfit(SF0, FOCUS_2006_L4_mkin, quiet=TRUE)
```

```
R> summary(m.L4.SF0)
```

```
mkim version:      0.9.12
R version:         2.15.2
Date of fit:       Mon Feb 18 09:34:26 2013
Date of summary:   Mon Feb 18 09:34:26 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
parent_0	96.44	1.949
k_parent_sink	-5.03	0.080

Backtransformed parameters:

	Estimate
parent_0	96.442
k_parent_sink	0.007

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:

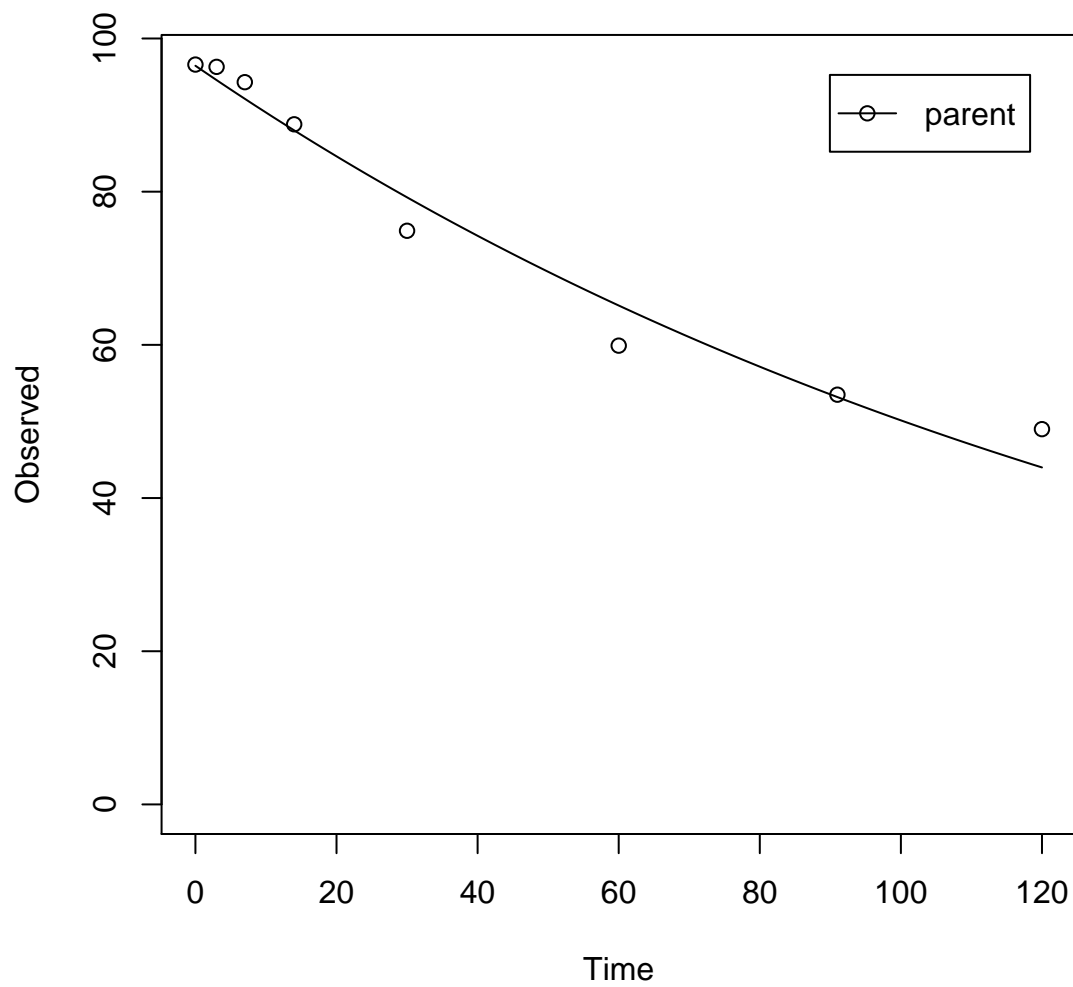
	parent_0	k_parent_sink
parent_0	1.0000	0.5865

k_parent_sink 0.5865 1.0000

Data:

<i>time</i>	<i>variable</i>	<i>observed</i>	<i>predicted</i>	<i>residual</i>
0	parent	96.6	96.44	0.1585
3	parent	96.3	94.57	1.7324
7	parent	94.3	92.13	2.1744
14	parent	88.8	88.00	0.7972
30	parent	74.9	79.26	-4.3589
60	parent	59.9	65.14	-5.2376
91	parent	53.5	53.18	0.3167
120	parent	49.0	43.99	5.0054

R> plot(m.L4.SF0)

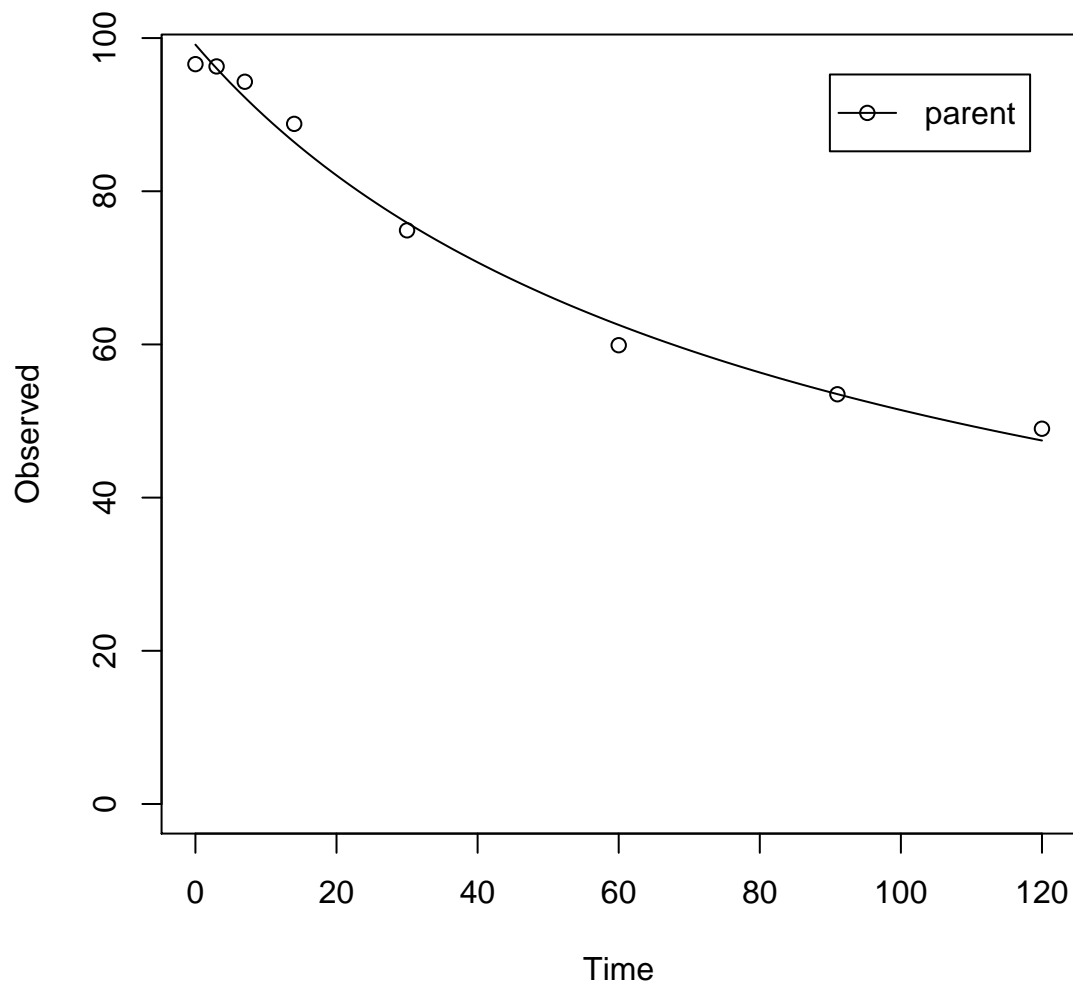


The χ^2 error level of 3.3% as well as the plot suggest that the model fits very well.

The FOMC model for comparison

```
R> m.L4.FOMC <- mkinfit(FOMC, FOCUS_2006_L4_mkin, quiet=TRUE)
R> plot(m.L4.FOMC)
R> s.m.L4.FOMC <- summary(m.L4.FOMC)
R> s.m.L4.FOMC$errmin
```

	<i>err.min</i>	<i>n.optim</i>	<i>df</i>
<i>All data</i>	0.02027643	3	5
<i>parent</i>	0.02027643	3	5



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

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>.

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),
+   Z = 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, 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(Z = list(type = "SF0", to = "Z1"),
+                 Z1 = list(type = "SF0"))
R> Z.2a.ff <- mkinmod(Z = list(type = "SF0", to = "Z1"),
+                   Z1 = list(type = "SF0"), use_of_ff = "max")
R> m.Z.2a <- mkinfit(Z.2a, FOCUS_2006_Z_mkin)
```

```
Model cost at call 1 : 30553.16
Model cost at call 4 : 30553.16
Model cost at call 5 : 30553.16
Model cost at call 7 : 9763.132
Model cost at call 8 : 9763.132
Model cost at call 12 : 7280.781
Model cost at call 13 : 7280.781
Model cost at call 17 : 1167.09
Model cost at call 18 : 1167.09
Model cost at call 22 : 772.958
Model cost at call 23 : 772.958
Model cost at call 27 : 700.265
Model cost at call 28 : 700.265
Model cost at call 32 : 692.3945
Model cost at call 33 : 692.3945
Model cost at call 37 : 692.3839
Model cost at call 38 : 692.3839
Model cost at call 42 : 692.3838
Model cost at call 47 : 692.3838
```

```
R> summary(m.Z.2a, data = FALSE)
```

```
mkin version: 0.9.12
R version: 2.15.2
Date of fit: Mon Feb 18 09:34:27 2013
Date of summary: Mon Feb 18 09:34:27 2013
```

Equations:

```
[1] d_Z = - k_Z_sink * Z - k_Z_Z1 * Z      d_Z1 = + k_Z_Z1 * Z - k_Z1_sink * Z1
```

Starting values for optimised parameters:

	initial	type	transformed
Z_0	100.0	state	100.000000
k_Z_sink	0.1	deparm	-2.302585
k_Z_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
Z_0	97.0149	NA
k_Z_sink	-36.2915	NA
k_Z_Z1	0.8047	NA
k_Z1_sink	-0.7296	NA

Backtransformed parameters:

	Estimate
Z_0	97.015
k_Z_sink	0.000
k_Z_Z1	2.236
k_Z1_sink	0.482

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
Z	18.56	4	13
Z1	15.75	1	13

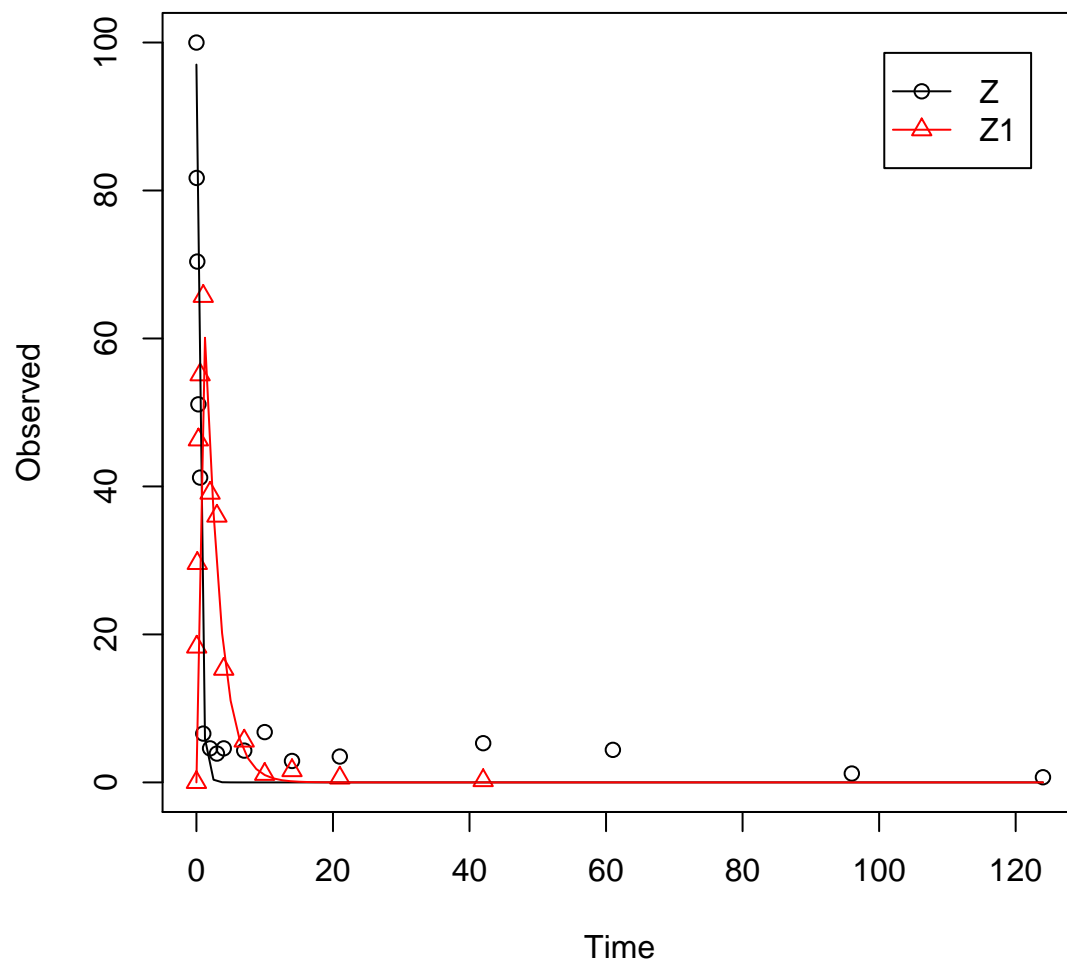
Estimated disappearance times:

	DT50	DT90
Z	0.255	0.8471
Z1	1.438	4.7759

Estimated formation fractions:

	ff
Z_sink	6.375e-17
Z_Z1	8.226e-01
Z1_sink	1.000e+00

R> plot(m.Z.2a)



```
R> Z.2b <- mkinmod(Z = list(type = "SF0", to = "Z1", sink = FALSE),
+                 Z1 = list(type = "SF0"))
R> Z.2b.ff <- mkinmod(Z = list(type = "SF0", to = "Z1", sink = FALSE), # needs warning
+                   Z1 = list(type = "SF0"), use_of_ff = "max")
R>
```