mkin - Routines for fitting kinetic models with one or more state variables to chemical degradation data

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Abstract

In the regulatory evaluation of chemical substances like plant protection products (pesticides), biocides and other chemicals, degradation data play an important role. For the evaluation of pesticide degradation experiments, detailed guidance has been developed, based on nonlinear optimisation. The R add-on package **mkin** implements fitting some of the models recommended in this guidance from within R and calculates some statistical measures for data series within one or more compartments, for parent and metabolites.

Contents

Key words: Kinetics, FOCUS, nonlinear optimisation

1 Introduction

Many approaches are possible regarding the evaluation of chemical degradation data. The **kinfit** package (Ranke, 2010a) in R (R Development Core Team, 2010) implements the approach recommended in the kinetics report provided by the FOrum for Co-ordination of pesticide fate models and their USe (FOCUS Work Group on Degradation Kinetics, 2006) for simple data series for one parent compound in one compartment.

The **mkin** package (Ranke, 2010b) extends this approach to data series with metabolites and more than one compartment and includes the possibility for back reactions.

2 Example

In the following, requirements for data formatting are explained. Then the procedure for fitting the four kinetic models recommended by the FOCUS group to an example dataset for parent only given in the FOCUS kinetics report is illustrated. The explanations are kept rather verbose in order to lower the barrier for R newcomers.

2.1 Data format

The following listing shows example dataset C from the FOCUS kinetics report as distributed with the **kinfit** package

```
R> library("mkin")
```

```
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Operator of Argonne National Laboratory.

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http://www.netlib.org/minpack/disclaimer for the full license.
```

```
R> FOCUS_2006_C
```

```
    name time value
1 parent    0  85.1
2 parent    1  57.9
3 parent    3  29.9
4 parent    7  14.6
5 parent   14   9.7
6 parent   28   6.6
7 parent   63   4.0
8 parent   91   3.9
9 parent  119   0.6
```

Note that the data needs to be in the format of a data frame containing a variable `name` specifying the observed variable, indicating the compound name and, if applicable, the compartment, a variable `time` containing sampling times, and a numeric variable `value` specifying the observed value of the variable. If a further variable `error` is present, this will be used to give different weights to the data points (the higher the error, the lower the weight, see the help page of the `modCost` function of the **FME** package (Soetaert and Petzoldt, 2010)). Replicate measurements are not recorded in extra columns but simply appended, leading to multiple occurrences of the sampling times `time`.

Small to medium size dataset can be conveniently entered directly as R code as shown in the following listing

```
R> example_data <- data.frame(
+   time = c(0, 1, 3, 7, 14, 28, 63, 91, 119),
+   parent = c(85.1, 57.9, 29.9, 14.6, 9.7, 6.6, 4, 3.9, 0.6)
+ )
```

2.2 Model definition

The next task is to define the model to be fitted to the data. In order to facilitate this task, a convenience function `mkinmod` is available.

```
R> SFO <- mkinmod(spec = list(parent = list(type = "SFO", to = NA, sink = TRUE)))
R> SFORB <- mkinmod(spec = list(parent = list(type = "SFORB", to = NA, sink = TRUE)))
R> SFO_SFO <- mkinmod(spec = list(
+   parent = list(type = "SFO", to = "m1", sink = TRUE),
+   m1 = list(type = "SFO", to = NA, sink = TRUE)))
R> SFORB_SFO <- mkinmod(spec = list(
+   parent = list(type = "SFORB", to = "m1", sink = TRUE),
+   m1 = list(type = "SFO", to = NA, sink = TRUE)))
```

2.3 Fitting the model

Then the model parameters should be fitted to the data. The function `mkinfit` internally creates a cost function using `modCost` from the **FME** package and the produces a fit using `modFit` from the same package.

```
R> # Do not show significance stars as they interfere with vignette generation
R> options(show.signif.stars = FALSE)
R> SFO.fit <- mkinfit(SFO, FOCUS_2006_C)
```

```
Model cost at call  1 :  4718.97
Model cost at call  4 :  4718.97
Model cost at call  5 :  637.0033
Model cost at call  7 :  637.0033
Model cost at call  8 :  287.321
Model cost at call  10 :  287.321
Model cost at call  11 :  207.3576
Model cost at call  13 :  207.3576
Model cost at call  14 :  197.3848
Model cost at call  16 :  197.3848
Model cost at call  17 :  196.5886
Model cost at call  19 :  196.5886
Model cost at call  20 :  196.5369
Model cost at call  22 :  196.5369
Model cost at call  23 :  196.5338
Model cost at call  25 :  196.5338
Model cost at call  26 :  196.5336
Model cost at call  27 :  196.5336
Model cost at call  28 :  196.5336
Model cost at call  29 :  196.5336
Model cost at call  30 :  196.5336
Model cost at call  31 :  196.5336
Model cost at call  32 :  196.5336
```

```
R> summary(SFO.fit)
```

```
Parameters:
             Estimate Std. Error t value Pr(>|t|)
parent_0      82.4920     4.7402  17.403 5.09e-07
k_parent_sink  0.3061     0.0459   6.668 0.000286

Residual standard error: 5.299 on 7 degrees of freedom

Parameter correlation:
             parent_0 k_parent_sink
parent_0       1.0000        0.5212
k_parent_sink  0.5212        1.0000
```

```
R> SFORB.fit <- mkinfit(SFORB, FOCUS_2006_C)
```

```
Model cost at call  1 :  7044.136
Model cost at call  4 :  7044.136
Model cost at call  7 :  2652.855
Model cost at call  9 :  2652.855
Model cost at call  13 :  865.7892
Model cost at call  15 :  865.7892
Model cost at call  18 :  47.70489
Model cost at call  19 :  47.70488
Model cost at call  23 :  43.2794
Model cost at call  25 :  43.2794
Model cost at call  28 :  7.013637
Model cost at call  30 :  7.013636
Model cost at call  32 :  7.013636
Model cost at call  33 :  4.424051
Model cost at call  35 :  4.424051
Model cost at call  37 :  4.424051
Model cost at call  38 :  4.363099
Model cost at call  40 :  4.363099
Model cost at call  42 :  4.363099
Model cost at call  51 :  4.363098
Model cost at call  53 :  4.363098
Model cost at call  55 :  4.363098
Model cost at call  56 :  4.363095
Model cost at call  57 :  4.363095
Model cost at call  61 :  4.363091
Model cost at call  63 :  4.363090
Model cost at call  65 :  4.363090
Model cost at call  66 :  4.363087
Model cost at call  67 :  4.363087
Model cost at call  68 :  4.363087
Model cost at call  70 :  4.363087
Model cost at call  71 :  4.363084
Model cost at call  72 :  4.363084
Model cost at call  73 :  4.363083
Model cost at call  75 :  4.363083
Model cost at call  76 :  4.363082
Model cost at call  77 :  4.363082
Model cost at call  81 :  4.363080
Model cost at call  83 :  4.363080
Model cost at call  84 :  4.363080
```

```
R> summary(SFORB.fit)
```

```
Parameters:
                   Estimate Std. Error t value Pr(>|t|)
parent_free_0       84.999203   0.890977  95.400  2.4e-09
k_parent_free_sink   0.394914   0.014386  27.452  1.2e-06
k_parent_free_bound  0.061482   0.007503   8.195  0.00044
k_parent_bound_free  0.020687   0.004158   4.975  0.00419
```

```
Residual standard error: 0.9341 on 5 degrees of freedom

Parameter correlation:
                   parent_free_0 k_parent_free_sink k_parent_free_bound
parent_free_0            1.00000             0.5217              0.1834
k_parent_free_sink       0.52169             1.0000              0.6718
k_parent_free_bound      0.18342             0.6718              1.0000
k_parent_bound_free      0.08489             0.3249              0.6995
                   k_parent_bound_free
parent_free_0                  0.08489
k_parent_free_sink             0.32485
k_parent_free_bound            0.69952
k_parent_bound_free            1.00000
```

```
R> SFO_SFO.fit <- mkinfit(SFO_SFO, FOCUS_2006_D)
```

```
Model cost at call  1 :  18994.29
Model cost at call  3 :  18994.29
Model cost at call  8 :  15888.53
Model cost at call  9 :  15888.53
Model cost at call  13 :  9262.857
Model cost at call  14 :  9262.857
Model cost at call  18 :  1784.538
Model cost at call  20 :  1784.538
Model cost at call  23 :  387.3642
Model cost at call  25 :  387.3642
Model cost at call  28 :  371.2285
Model cost at call  30 :  371.2285
Model cost at call  31 :  371.2285
Model cost at call  33 :  371.2127
Model cost at call  34 :  371.2127
Model cost at call  35 :  371.2127
Model cost at call  36 :  371.2127
Model cost at call  38 :  371.2127
```

```
R> summary(SFO_SFO.fit)
```

```
Parameters:
              Estimate Std. Error t value Pr(>|t|)
parent_0      9.960e+01  1.614e+00  61.720  < 2e-16
k_parent_sink 4.792e-02  3.750e-03  12.777 6.10e-15
k_m1_sink     5.261e-03  7.159e-04   7.349 1.15e-08
k_parent_m1   5.078e-02  2.094e-03  24.248  < 2e-16

Residual standard error: 3.211 on 36 degrees of freedom

Parameter correlation:
             parent_0 k_parent_sink k_m1_sink k_parent_m1
parent_0      1.00000       0.60752   -0.1701    -0.06623
```

```
k_parent_sink  0.60752       1.00000   -0.6252    -0.08738
k_m1_sink     -0.17005      -0.62525    1.0000     0.47166
k_parent_m1   -0.06623      -0.08738    0.4717     1.00000
```

```
R> SFORB_SFO.fit <- mkinfit(SFORB_SFO, FOCUS_2006_D)
```

```
Model cost at call  1 :  16413.78
Model cost at call  3 :  16413.78
Model cost at call  10 :  11483.34
Model cost at call  11 :  11483.34
Model cost at call  17 :  1264.848
Model cost at call  18 :  1264.848
Model cost at call  24 :  558.853
Model cost at call  25 :  558.8529
Model cost at call  30 :  558.8529
Model cost at call  31 :  370.7626
Model cost at call  32 :  370.7625
Model cost at call  39 :  353.7513
Model cost at call  41 :  353.7513
Model cost at call  47 :  352.3025
Model cost at call  50 :  352.3025
Model cost at call  55 :  352.2217
Model cost at call  56 :  352.2217
Model cost at call  63 :  352.2049
Model cost at call  64 :  352.2049
Model cost at call  72 :  352.2047
Model cost at call  73 :  352.2047
Model cost at call  74 :  352.2047
Model cost at call  76 :  352.2047
Model cost at call  80 :  352.2047
```

```
R> summary(SFORB_SFO.fit)
```

```
Parameters:
                     Estimate Std. Error t value Pr(>|t|)
parent_free_0       1.011e+02  2.020e+00  50.034  < 2e-16
k_parent_free_sink  6.408e-02  2.691e-02   2.381   0.0230
k_parent_free_bound 1.680e-01  5.142e-01   0.327   0.7458
k_parent_bound_free 5.239e-01  8.544e-01   0.613   0.5438
k_m1_sink           5.213e-03  7.210e-04   7.230 2.29e-08
k_parent_free_m1    6.563e-02  2.542e-02   2.582   0.0143

Residual standard error: 3.219 on 34 degrees of freedom

Parameter correlation:
                    parent_free_0 k_parent_free_sink k_parent_free_bound
parent_free_0              1.0000             0.5432             0.34390
k_parent_free_sink         0.5432             1.0000             0.94317
k_parent_free_bound        0.3439             0.9432             1.00000
k_parent_bound_free        0.1950             0.8179             0.95432
```

```
k_m1_sink                -0.1801            -0.2031            -0.09286
k_parent_free_m1          0.4402             0.9752             0.96052
                  k_parent_bound_free k_m1_sink k_parent_free_m1
parent_free_0                 0.19504  -0.18007          0.44016
k_parent_free_sink            0.81787  -0.20307          0.97518
k_parent_free_bound           0.95432  -0.09286          0.96052
k_parent_bound_free           1.00000  -0.08809          0.83987
k_m1_sink                    -0.08809   1.00000         -0.03944
k_parent_free_m1              0.83987  -0.03944          1.00000
```

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