In kinetic modeling, rate constants and formation fractions are often fitted directly to observed data applying statistical methods that depend on the assumption of normal distribution of the estimators. As rate constants and formation fractions can only take on positive values and formation fractions are restricted to a sum of 1, the assumption of normal distribution is not satisfied which induces bias to statistical tests and assessments of parameter uncertainty. To solve this problem kinetic rate constants can be transformed using log transformation as proposed e.g. by Bates and Watts (1988). The estimators of the transformed parameters are random variables with the standard error obtained by the fitting routine. Confidence intervals for the transformed parameters as random variables with the standard error obtained by the fitting routine. Confidence intervals for the transformed parameters can then be obtained as percentiles of the backtransformed random variables. Calculation of confidence intervals is not yet implemented in mkin.

### Fitting rate constants
Kinetic rate constants can only be positive real values. However, when using least squares optimization, parameters are estimated iteratively together with their standard error and statistical significance tests are commonly applied. However, estimating a standard error supposes normal distribution. To solve this problem, kinetic rate constants \( k_i \) are replaced by terms of the form \( \log k_i \) as proposed e.g. by Bates and Watts (1988). The estimators of the \( k_i \) values are assumed to better fit the assumption of normal distribution.

### Confidence limits for model parameters
Standard optimisation routines generally provide a standard error for the parameter estimate in their output. The reparameterisation of the model aimed to obtain a symmetrical distribution of estimates that more closely follow a normal distribution. Therefore it is proposed to construct confidence intervals for the transformed parameters based on the assumption that they follow a normal distribution.

For a simple one-to-one relationship between transformed parameters and model parameters, the boundaries of these confidence intervals can simply be backtransformed for the construction of confidence intervals of the model parameters.

In the ILR transformation, parameters are not transformed one by one, but in parameter sets. In order to construct confidence intervals for the transformed parameters, it is suggested to use Monte Carlo Analysis, feeding transformed parameters as random variables with the standard error obtained by the fitting routine. Confidence intervals for the backtransformed parameters can then be obtained as percentiles of the backtransformed random variables.

Calculation of confidence intervals is not yet implemented in mkin.

### ILR data representation
Formation fractions always sum up to 1. These two properties lend them to treatment as compositional data. In order to better fulfill the assumptions of least squares fitting, it is proposed here to fit formation fractions using isometric log ratio transformation (ILR) in the form proposed by Filzmoser and Hron (2008):

Let \( x = (x_1,...,x_D) \) be a formation fraction with \( x_i > 0 \) for all \( i=1,...,D \) and \( \sum_{i=1}^{D} x_i = 1 \).

Then the ILR transform of \( x \) is denoted as \( z = (z_1,...,z_{D-1}) \) and given by \( z_i = \frac{1}{(D-1)!} \prod_{j=1}^{D} \log x_j - \frac{1}{D-1} \log x_i \) for \( i=1,...,D-1 \).

### Fitting formation fractions
Formation fractions always have values between 0 and 1. Furthermore, in fitting a single degradation experiment they always have to sum up to exactly 1. These two properties lend them to treatment as compositional data. In order to better fulfill the assumptions of least squares fitting, it is proposed here to fit formation fractions using isometric log ratio transformation (ILR) in the form proposed by Filzmoser and Hron (2008):

Let \( y = (y_1,...,y_D) \) be the model to be fitted to observed data \( y_1,...,y_D \) where \( y_j \) is the vector of initial values of the observed variables. It is the parameter vector and \( x \) is a multivariate random variable. For \( x \in \mathbb{R}^D \) let \( \text{diag}(x) \) be the matrix with entries \( x \) on its diagonal and 0 otherwise. In this work, we assume \( y_i \) to be independent and identically normal distributed with expected value \( E(y_i) = \theta_i \) and covariance matrix \( V(y) = \text{diag}(\sigma^2) \) where \( \sigma \) is the standard deviation of the normal distribution of \( y_i \).

### Development version mkin 0.9.2 from r-forge
Starting values for optimised parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Type</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>parent_0</td>
<td>100.0</td>
<td>state</td>
<td>0</td>
<td>Inf</td>
</tr>
<tr>
<td>k_parent_sink</td>
<td>0.1</td>
<td>deparm</td>
<td>0</td>
<td>Inf</td>
</tr>
<tr>
<td>k_ml_sink</td>
<td>0.1</td>
<td>deparm</td>
<td>0</td>
<td>Inf</td>
</tr>
<tr>
<td>k_parent_m1</td>
<td>0.1</td>
<td>deparm</td>
<td>0</td>
<td>Inf</td>
</tr>
</tbody>
</table>

Fixed parameter values:

- value | type | state
- 0 | 0 | state

Optimised parameters:

- Estimate Std. Error t value Pr(>|t|)
- parent_0 9.96e+01 1.61e+00 6.1720 < 2e-16 ***
- k_parent_sink 4.792e-02 3.75e-03 1.2778 3.09e-01 ***
- k_ml_sink 5.261e-03 7.159e-04 7.3489 5.76e-01 ***
- k_parent_m1 5.078e-02 2.09e-03 24.2480 < 2e-16 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

### Output from mkin 0.8.11 as published on CRAN
Starting values for optimised parameters:

- initial | type | lower | upper
- parent_0 100.0 | state | 0 | Inf
- k_parent_sink 0.1 | deparm | 0 | Inf
- k_ml_sink 0.1 | deparm | 0 | Inf
- k_parent_m1 0.1 | deparm | 0 | Inf

Fixed parameter values:

- value | type | state
- 0 | 0 | state

Optimised parameters:

- Estimate Std. Error t value Pr(>|t|)
- parent_0 9.96e+01 1.61e+00 6.1720 < 2e-16 ***
- k_parent_sink 4.792e-02 3.75e-03 1.2778 3.09e-01 ***
- k_ml_sink 5.261e-03 7.159e-04 7.3489 5.76e-01 ***
- k_parent_m1 5.078e-02 2.09e-03 24.2480 < 2e-16 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

### Future aspects in research
Relaxing the assumption of i.i.d. error variables \( e \), fitting a nonlinear mixed effects model can be used to overcome the problem of inhomogeneous error variances often observed in experiments. Inhomogeneous error variances cause serious bias in statistical tests and computation of confidence intervals if not adjusted. Allowing for different error variances for parent and metabolites has been previously proposed. However, a more general variance model would allow for a more precise description of the uncertainties of the fitting procedure.

### References