

mk_{in} -
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 **mk_{in}** 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.

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Key words: Kinetics, FOCUS, nonlinear optimisation

1 Introduction

Many approaches are possible regarding the evaluation of chemical degradation data. The **kinfit** package (Ranke, 2013a) in R (R Development Core Team, 2014) 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, 2011) for simple data series for one parent compound in one compartment.

The **mkim** package (Ranke, 2013b) extends this approach to data series with transformation products, commonly termed metabolites, and to more than one compartment. It is also possible to include back reactions, so equilibrium reactions and equilibrium partitioning can be specified, although this oftentimes leads to an overparameterisation of the model.

When **mkim** was first published in May 2010, the most commonly used tools for fitting more complex kinetic degradation models to experimental data were KinGUI (Schäfer et al., 2007), a MATLAB[®] based tool with a graphical user interface that was specifically tailored to the task and included some output as proposed by the FOCUS Kinetics Workgroup, and ModelMaker, a general purpose compartment based tool providing infrastructure for fitting dynamic simulation models based on differential equations to data.

At that time, the R package **FME** (Flexible Modelling Environment) (Soetaert and Petzoldt, 2010) was already available, and provided a good basis for developing a package specifically tailored to the task. The remaining challenge was to make it as easy as possible for the users (including the author of this vignette) to specify the system of differential equations and to include the output requested by the FOCUS guidance, such as the relative standard deviation that has to be assumed for the residuals, such that the χ^2 goodness-of-fit test as defined by the FOCUS kinetics workgroup would pass using a significance level α of 0.05.

Also, **mkim** introduced using analytical solutions for parent only kinetics for improved optimization speed. Later, Eigenvalue based solutions were introduced to **mkim** for the case of linear differential equations (*i.e.* where the FOMC or DFOP models were not used for the parent compound), greatly improving the optimization speed for these cases.

Soon after the publication of **mkim**, two derived tools were published, namely KinGUII (available from Bayer Crop Science) and CAKE (commissioned to Tessella by Syngenta), which added a graphical user interface (GUI), and added fitting by iteratively reweighted

least squares (IRLS) and characterisation of likely parameter distributions by Markov Chain Monte Carlo (MCMC) sampling.

CAKE focuses on a smooth use experience, sacrificing some flexibility in the model definition, allowing only two primary metabolites in parallel. KinGUI offers quite a flexible widget for specifying complex kinetic models. Back-reactions (non-instantaneous equilibria) were not present in the first version of KinGUI, and only simple first-order models could be specified for transformation products. As of May 2014 (KinGUI version 2.1), back-reactions and biphasic modelling of metabolites are also available in KinGUI.

Currently (May 2014), the main feature available in **mkim** which is not present in KinGUI or CAKE, is the estimation of parameter confidence intervals based on transformed parameters. For rate constants, the log transformation is used, as proposed by Bates and Watts ([Bates and Watts, 1988](#), p. 77, p. 149). Approximate intervals are constructed for the transformed rate constants (compare [Bates and Watts, 1988](#), p. 153), *i.e.* for their logarithms. Confidence intervals for the rate constants are then obtained using the appropriate backtransformation using the exponential function.

In the first version of **mkim** allowing for specifying models using formation fractions, a home-made reparameterisation was used in order to ensure that the sum of formation fractions would not exceed unity.

This method is still used in the current version of KinGUI (v2.1), with a modification that allows for fixing the pathway to sink to zero. CAKE uses penalties in the objective function in order to enforce this constraint.

In 2012, an alternative reparameterisation of the formation fractions was proposed together with René Lehmann ([Ranke and Lehmann, 2012](#)), based on isometric logratio transformation (ILR). The aim was to improve the validity of the linear approximation of the objective function during the parameter estimation procedure as well as in the subsequent calculation of parameter confidence intervals.

In the first attempt at providing improved parameter confidence intervals introduced to **mkim** in 2013, confidence intervals obtained from FME on the transformed parameters were simply all backtransformed one by one to yield asymmetric confidence intervals for the backtransformed parameters.

However, while there is a 1:1 relation between the rate constants in the model and the transformed parameters fitted in the model, the parameters obtained by the isometric logratio transformation are calculated from the set of formation fractions that quantify the paths to each of the compounds formed from a specific parent compound, and no such 1:1 relation exists.

Therefore, parameter confidence intervals for formation fractions obtained with this method only appear valid for the case of a single transformation product, where only one formation fraction is to be estimated, directly corresponding to one component of the ilr transformed parameter.

The confidence intervals obtained by backtransformation for the cases where a 1:1 relation between transformed and original parameter exist are considered by the author of this vignette to be more accurate than those obtained using a re-estimation of the Hessian matrix after backtransformation, as implemented in the FME package.

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