User-friendly software for survival modelling with GUTS

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About GUTS

The General Unified Threshold model for Survival (GUTS) is a toxicokinetic-toxicodynamic (TKTD) model for the endpoint survival, described in detail in a recent e-book (Jager & Ashauer, 2018). Since its inception in 2010, interest in GUTS has been rapidly increasing. In 2018, this culminated into an EFSA opinion stating that GUTS is “ready to be used” in risk assessment of pesticides (EFSA, 2018).

The software project

Routine application in risk assessment requires efficient, robust and user-friendly software. In this project, funded by Cefic-LRI, we set out to develop such a software in the form of a standalone Windows executable. The software is planned to be available by the end of 2019.

Models included

The software will contain the reduced GUTS models for stochastic death (SD) and individual tolerance (IT), and is thus able to work with routine toxicity data (lacking information on body residues). The model is shown in Fig. 1.

Workflow

The software is designed to follow the workflow as laid down in the EFSA opinion, shown in Fig. 2. In the prediction step, a safety margin or LP*x* can be calculated: the factor by which the exposure profile needs to be multiplied to yield *x*% effect at the end of the profile.

Features

Open: the software will be open source and freely downloadable. The fully-functional Matlab prototype will also be made available.
User-friendly: fit models and derive confidence intervals without requiring user interaction (e.g., no need for starting values).
Robust: find optima and intervals even for awkward data sets.
Flexible: allow time-varying exposure, missing data, simultaneous fitting on multiple data sets, etc.
Efficient: rapid screening of exposure profiles (e.g., FOCUS output) by batch processing.

Statistical framework

The software applies frequentist inference, which we think can be automated in a more robust manner, and avoids discussion on prior distributions. Optimisation and construction of confidence intervals relies on a genetic algorithm coupled with likelihood profiling, providing an ultra-robust sample from parameter space (Fig. 3), without worrying about starting values or local optima. This sample forms the basis for intervals on model predictions.

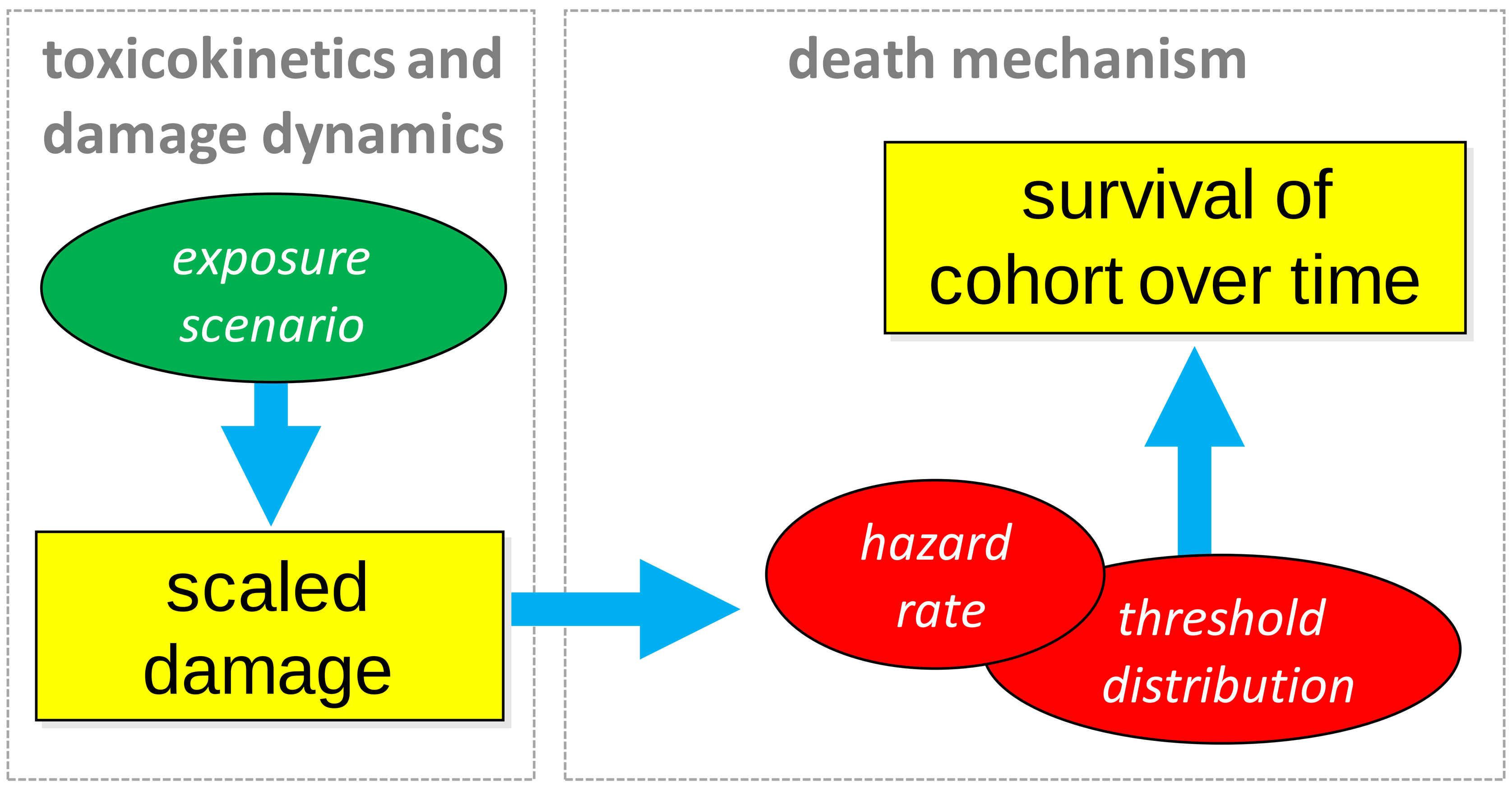


Fig. 1. Schematic representation of the reduced GUTS models. Toxicokinetics and damage kinetics are combined. The death mechanism either relies on a hazard rate (stochastic death) or on a distribution of thresholds (individual tolerance)

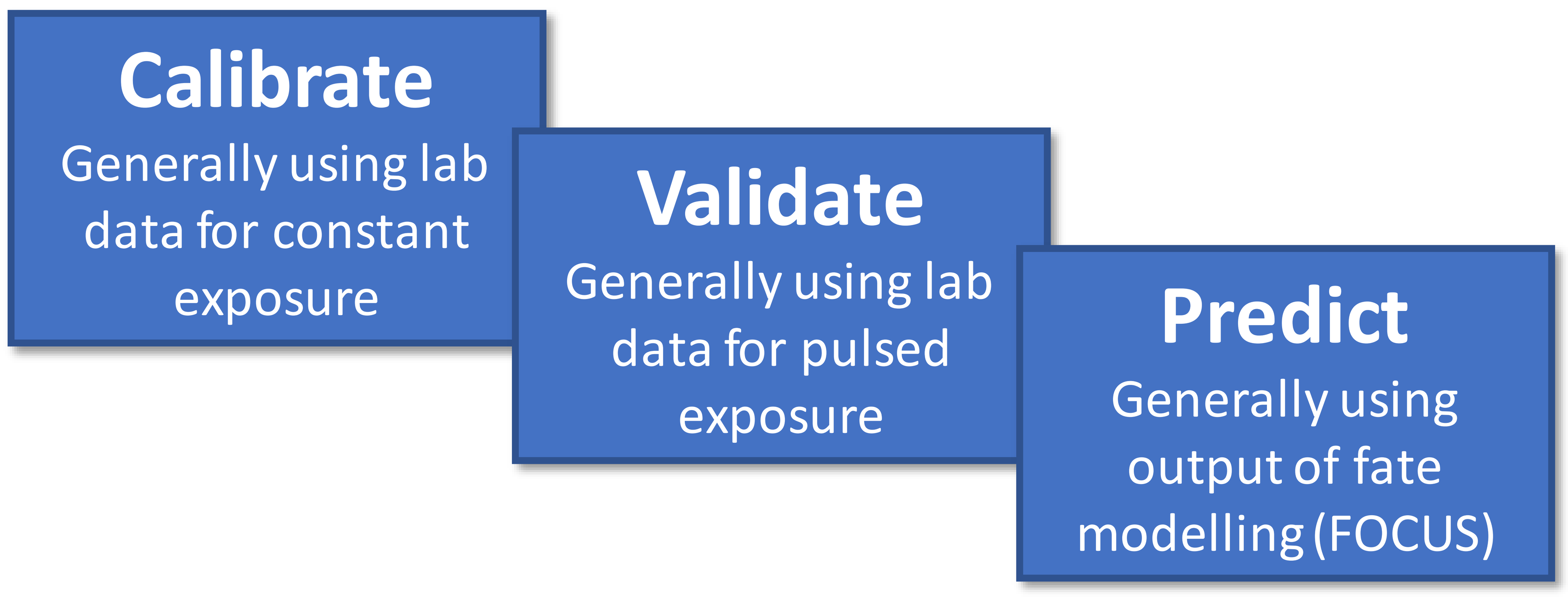
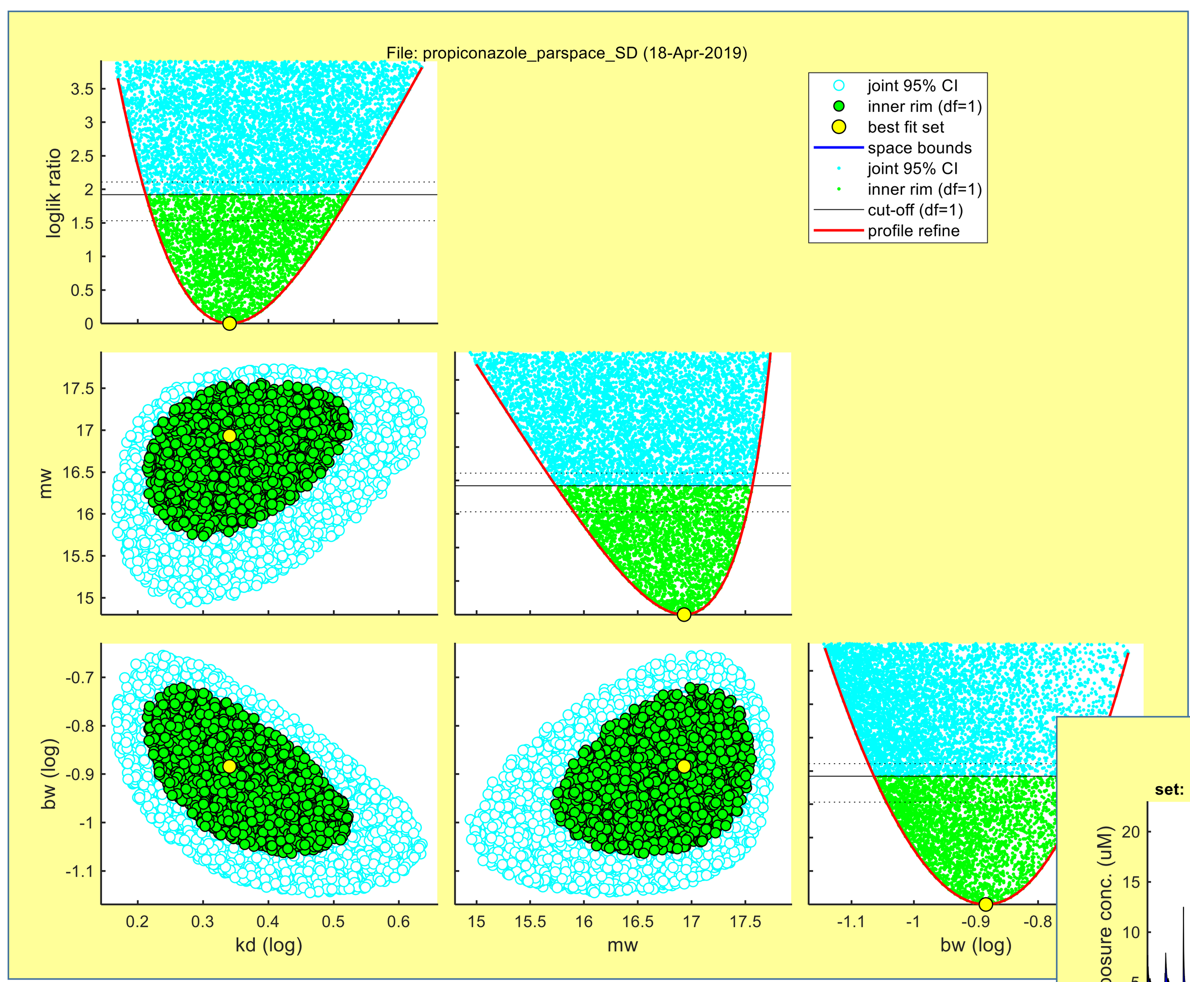


Fig. 2. Workflow for GUTS analyses, as laid down in the EFSA opinion on TKTD models (EFSA, 2018).



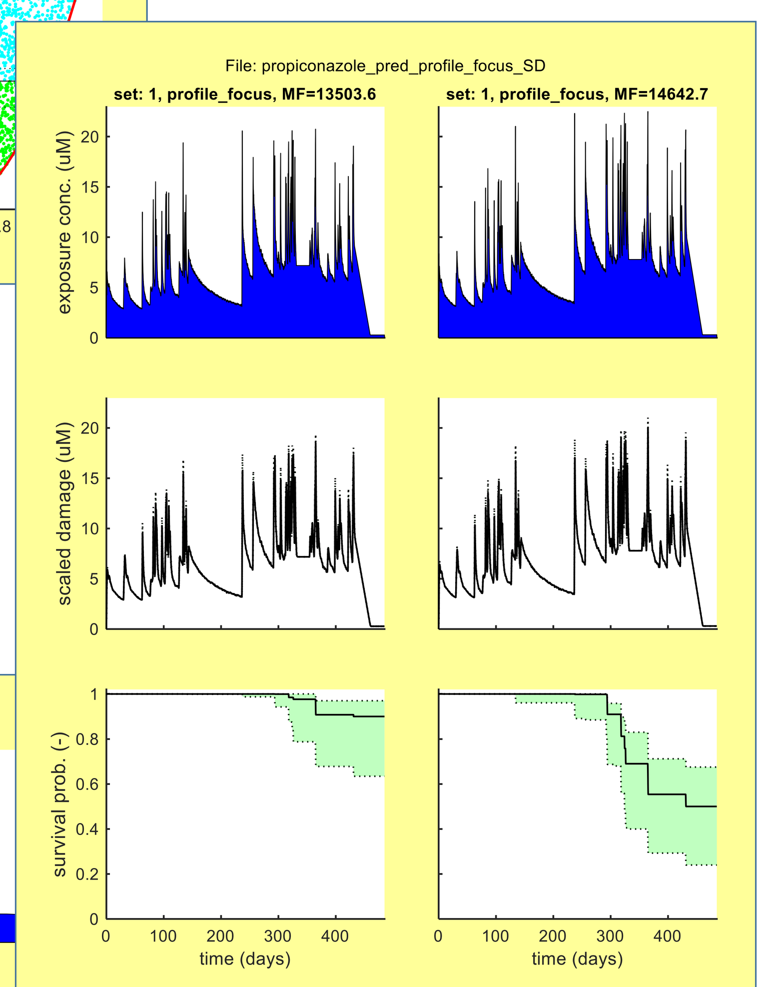
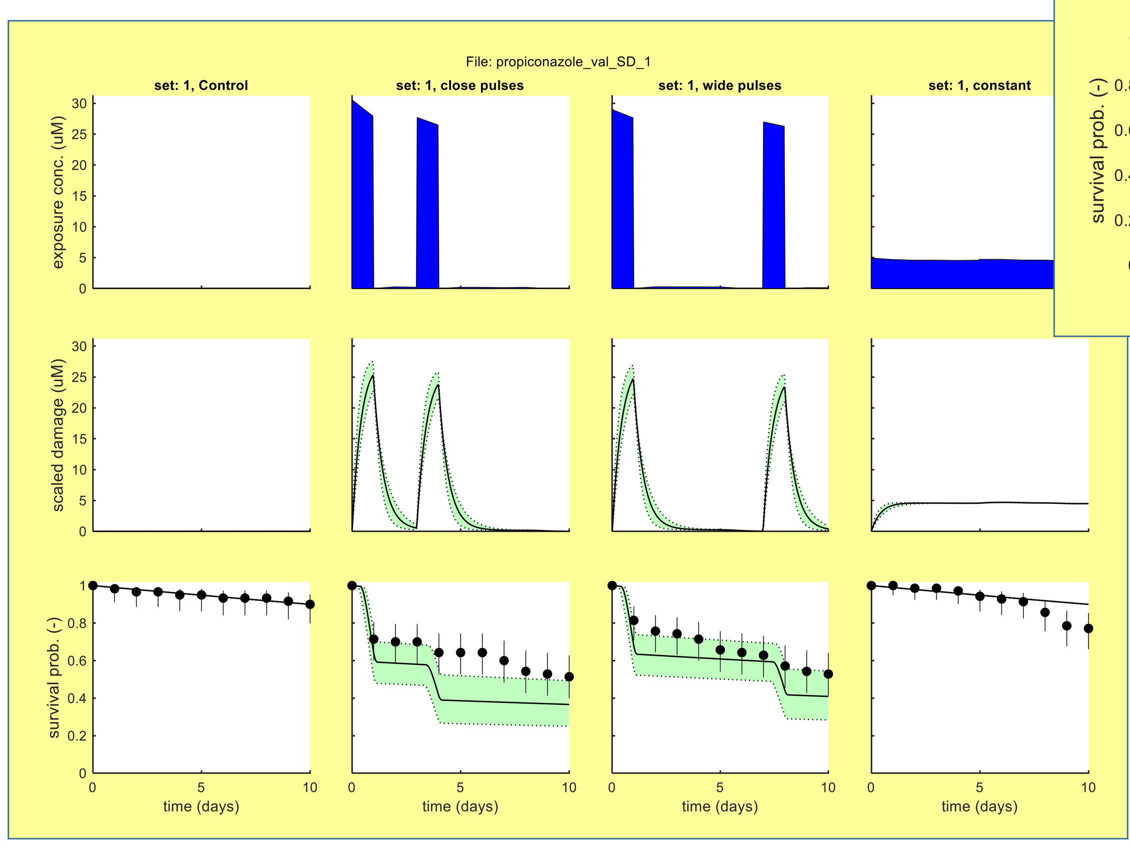


Fig. 3. Examples of calibration (top), validation (bottom), and prediction plots (right) from the prototype of the software. Data for propiconazole in Gammarus pulex.



References

EFSA (2018). Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms. EFSA journal 16(8): 5377.

Jager T and R Ashauer (2018). Modelling survival under chemical stress. A comprehensive guide to the GUTS framework. Version 2.0. Available from Leanpub: https://leanpub.com/guts_book.

More info

project page at
www.debtox.nl/projects/project_guts2.html
(includes link to GUTS courses)

Acknowledgements

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