Ring-test of different implementations of the General Unified Threshold model of Survival (GUTS)

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The GUTS ring-test

Making sense of toxic effects over time requires mechanistic models, and thus explicit consideration of toxicokinetics and toxicodynamics (TKTD). For the endpoint survival, all existing TKTD models can now be viewed as special cases of an overarching framework: GUTS, the General Unified Threshold model for Survival (Jager et al, 2011).

Since its inception in 2010, interest in GUTS has been rapidly increasing, leading to the creation of several software implementations. In a CEFIC-LRI funded project, we carried out a ring-test of eleven different implementations of GUTS. The ring test uses the two simplest cases of GUTS with toxicokinetics and damage dynamics combined, GUTS-RED-SD and GUTS-RED-IT.

A combination of real experimental data and synthetic data were used. Users were asked to carry-out a range of exercises, including calibration and forecasting. We then compared the resulting parameter estimates and predictions.

Results of the GUTS ring-test

Example calibration results are shown in Fig. 1 and 2. The first example resulted from a well-behaved data set; all implementations agreed well on the best-fit model parameters, although the width of confidence intervals differed. The second example resulted from data that was challenging due to:

- sharp exposure concentration pulses requiring attention to ensure correct numerical handling, and
- survival data at low, constant exposure concentrations showed some increase in mortality towards the end of the experiment.

A very good fit, explaining all the patterns in the data, is thus impossible to achieve with the standard GUTS models. This is why we see differences between the different GUTS implementations in Fig. 2.

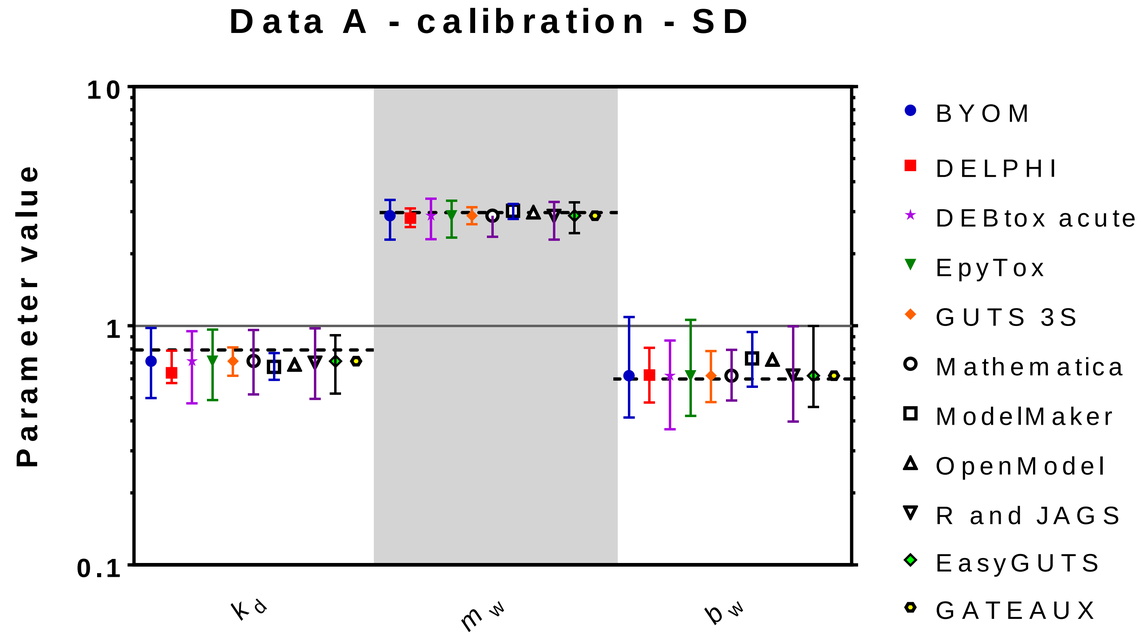


Fig. 1. Example of calibration results in good agreement.

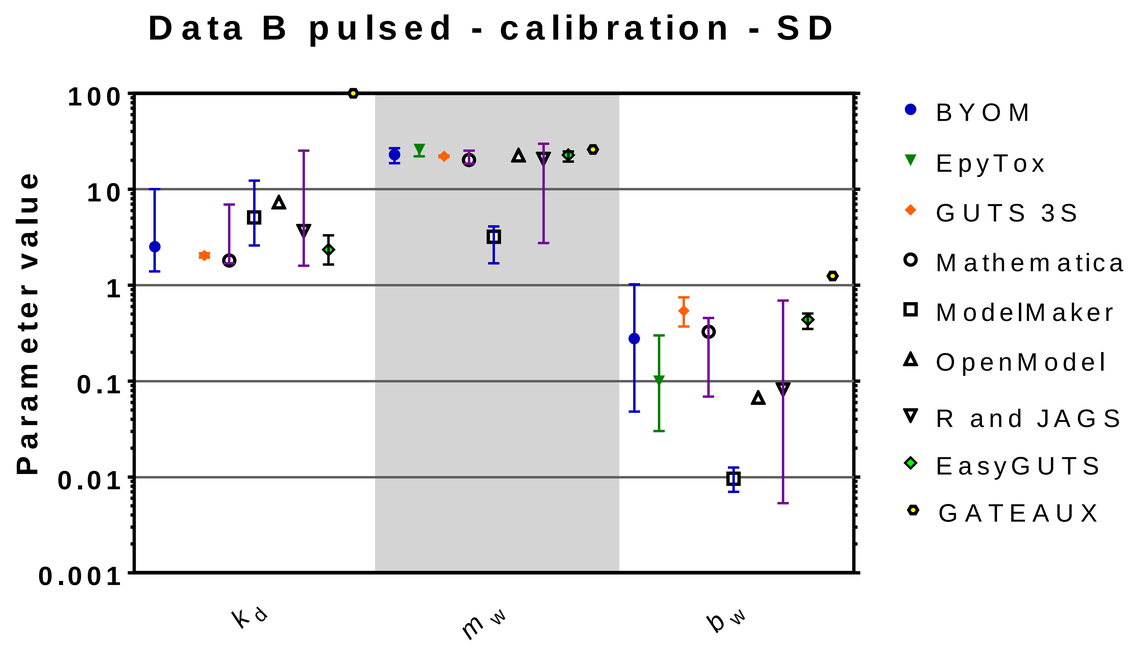


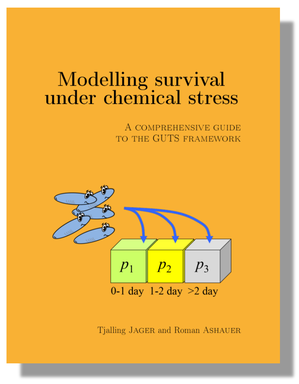
Fig. 2. Example of calibration results in poor agreement.

See GUTS e-book for more details

The ring-test, its results, and a detailed discussion are included in the GUTS e-book. It can be downloaded for free from:

https://leanpub.com/guts_book

(or use the QR code)



Conclusions

Reducing user-induced error and variability:

- New users/implementations should be trained/tested using this ring-test, and refer to these results as benchmark.
- Standardisation of use cases can help.

Standardising computational approaches for regulatory use:

- Optimisation algorithm, Bayesian vs. frequentist statistics, method for calculating confidence intervals.
- Analytical solution versus ODE solver, numerical methods, convergence and parameter estimation settings.

Way forward

For regulatory risk assessment use we need:

- User-friendly, freely-available, open-source, robust and well-tested GUTS software (→ follow-up project 2018/19).
- GUTS training courses.

Scientific questions:

- When do the GUTS assumptions hold? When not?
- Do GUTS parameters vary systematically across chemicals and species?

Web support:
http://www.debtox.info/book_guts.html
https://www.ecotoxmodels.org/guts/
http://cefic-lri.org/projects/eco39-review-ring-test-and-guidance-for-tktd-modelling/

References

Jager T, Albert C, Preuss TG, Ashauer R (2011). General Unified Threshold model of Survival - a toxicokinetic-toxicodynamic framework for ecotoxicology. Environ Sci Technol 45:2529-2540.

Acknowledgements

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