rDEBtktd, an R-package for analysis and forward-prediction of sublethal effects

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Introduction

- The development of a consistent and relevant modelling approach of sub-lethal effects of chemical compounds is a major challenge for the regulatory environmental risk assessment.
- According to a recent EFSA Scientific Opinion, toxicokinetic-toxicodynamic (TKTD) models based on the Dynamic Energy Budget (DEB) theory⁽¹⁾ adapted for ecotoxicology (DEB-TKTD models) are considered as valuable tools for environmental risk assessment ⁽²⁾.

Model description

Dynamic Energy Budget (DEB) model

- Describes how the fluxes of energy are allocated in the organism from food assimilation to growth and reproduction processes ⁽¹⁾(Fig. 1)
- Is expressed in terms of primary DEB parameters (Table 1)
- 2 types of DEB models are available: standard DEB and abj DEB (includes a metabolic acceleration between birth and metamorphosis)

Toxicokinetic-toxicodynamic (TKTD) model

- Describes how the exposure of an organism to a chemical leads to a disturbance of the normal energy allocation.^{(3) (4)}
- TK is modelled as a scaled internal concentration C_i , which has the same units than the measured external concentrations C_w (Eq. 1)
- In the TD part, the internal concentration affects the value of one or more DEB parameters involved in the corresponding physiological mode of action (pMoA) (Fig.1)
- The degree of stress s applied on a DEB parameter depends on the internal concentration and is calculated in Eq.2.

Table 1. Standard DEB parameters

Parameter	Description	Units
$\{p_{Am}\}$	surface-area-specific max. assimilation rate	$J.m^{-2}.d^{-1}$
$\dot{v}$	Energy conductance	$m.d^{-1}$
κ	Somatic fraction	-
$[E_G]$	Vol. spec. costs for growth	$J.m^{-3}$
$[p_M]$	Vol. spec. costs for maintenance	$J.m^{-3}.d^{-1}$
$\dot{k}_J$	Maturity maintenance rate	d^{-1}
κ_R	Egg production efficiency	-
E_H^b	Maturity threshold for birth	J
E_H^p	Maturity threshold for puberty	J
f	Scaled functional response	-

$$\frac{dC_i}{dt} = k_d \times (C_w - C_i) - C_i \times \frac{3}{L} \times \frac{dL}{dt} \quad (\text{Eq. 1})$$

With L the structural length of the organism, k_e as the dominant rate constant at maximum size L_m reached under control conditions

$$s = \frac{1}{C_T} * \max(0, C_i - c_0) \quad (\text{Eq. 2})$$

Table 2. TKTD parameters

Parameter	Description	Units
k_d	Dominant rate constant	d^{-1}
c_0	No-effect concentration	conc. units
C_T	Tolerance concentration	conc. units

Physiological modes of action (pMoAs)

- 1 Decrease in assimilation
- 2 Increase in maintenance costs
- 3 Increase in costs for structure and maturation
- 4 Increase in the costs for egg production
- 5 Hazard during oogenesis

Objectives

Develop a user-friendly and transparent tool in agreement with EFSA's scientific opinion on good modelling practices, which allows:

- The estimation of DEB-TKTD parameters from toxicity test results (length and reproduction data)
- The calculation of body length and reproduction predictions over time for given exposure scenarios, including uncertainty propagation

Data Input

1. Enter your length and reproduction datasets as text file following a specific format (Table 3) – Data sets from different experiments can be entered at the same time

- Length (in cm) measured over time is preferable, but one data point at the end of the experiment is also accepted
- Reproduction data (number of offspring over time) can be entered as a daily amount or as a cumulated amount, per individual or per group of individuals.
- The model still requires both reproduction and growth data - Analysis of reproduction or length only datasets has to be further explored.

Table 3. Example of a length dataset for *Daphnia magna* as entered by the user

replicate	conc	time	L
1	1	0	0.060
2	2	0	0.100
3	3	0	0.100
4	4	0	0.130
5	5	0	0.110
6	6	0	0.120
7	7	0	0.110
8	8	0	0.120

2. Plot your data sets for visual checking

Model & parameters

3. Choose pMoA to be tested (Assim, Maint, Growth, Repro or Haz)
4. Specify the scientific name of the species corresponding to the entered data (e.g. *Daphnia magna*)
5. Define which parameters to estimate depending on data quantity and design (Table 3)

Table 3. Estimated parameters depend on data set characteristics

Characteristics of the data sets	Estimated parameters
<ul style="list-style-type: none">• Repro. over time• Length over time• 1 study only	$\dot{v}, \kappa, [p_M], f, E_H^b, k_d, c_0, C_T$
<ul style="list-style-type: none">• Repro. over time• Length over time• several studies	$\dot{v}, \kappa, [p_M], E_H^b, k_d, c_0, C_T$ One f per study k_J (differences in feeding between studies have to be large enough)
<ul style="list-style-type: none">• Length at the end of the experiment only• Repro. over time	$\dot{v}, \kappa, f, k_d, c_0, C_T$

Bayesian inference & prior distributions

- The model parameters are estimated within a Bayesian framework with the software R and Stan ⁽⁵⁾.
- Prior distribution for physiological DEB parameters : Normal distribution centred on their Add-my-Pet value of the species of interest ⁽⁶⁾
- Prior distribution for TKTD parameters : defined from the experimental design ⁽⁷⁾

Save the Date : rDEBtktd package will be available on CRAN from June 2021 !

Fits to data

Figure 2. Model fits to body length data for *D. magna* exposed to different concentrations of chemical (simulated data) – pMoa: Assimilation

Figure 3. Model fits to reproduction data for *D. magna* exposed to different concentrations of chemical (simulated data) – pMoa: Assimilation

Figure 4. PPC plot

Goodness-of-Fit criteria

- The Posterior Predictive Check (PPC) lets you quickly see if 95% of the observed data are in the predicted 95% credibility intervals, as expected (Fig. 4).
- The posterior distributions (Fig.5, in orange) indicate if your data bring enough information compared to the prior distributions (Fig. 5, in grey).
- You can also check for correlations between parameters (Fig. 6).
- pMoAs are fitted separately and can be compared using leave-one-out cross-validation (LOO-CV) and the Widely Applicable Information Criterion WAIC. ⁽⁸⁾

Figure 5. prior-posterior plot

Figure 6. correlation plot

- Body length and reproduction predictions can be computed for any untested time-variable exposure scenario (Fig. 7, 8 & 9)
- The grey bands on Figures 8 & 9 correspond to the propagation of uncertainties on estimated model parameters (95% credibility band)
- Prediction functions can also be used to validate the model against additional data sets

Figure 7. Exposure profile for predictions

Figure 8. Forward-predictions for body length (pMoa: Assimilation)

Figure 9. Forward-predictions for reproduction (pMoa: Assimilation)

Figure 1. Conceptual diagram of the DEB-TKTD model

CALIBRATION

PREDICTIONS

[1] Kooijman, S.A.L.M., 2010. Dynamic Energy Budget Theory for Metabolic Organisation. Cambridge University Press. [2] EFSA Panel on Plant Protection Products and their Residues (PPR), et al. "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 (2018): e05377. [3] Kooijman, S.A.L.M., Bedaux, J.J.M., 1995. The Analysis of Aquatic Toxicity Data. VU University Press. [4] Jager, T., Zimmer, E.J., 2012. Simplified dynamic energy budget model for analysing ecotoxicity data. Ecol. Model. 225, 74–81. [5] Stan Development Team (2020). RStan: the R interface to Stan. R package version 2.21.2. <http://mc-stan.org/>. [6] Add-My-Pet. https://www.vu.nl/nhb/deb/deblab/add_my_pet/ [7] Delignette-Muller, M. L., Ruiz, P., & Veber, P. (2017). Robust fit of toxicokinetic-toxicodynamic models using prior knowledge contained in the design of survival toxicity tests. Environmental science & technology, 51(7), 4038-4045. [8] Vehtari, A., Gelman, A., and Gabry, J. (2017a). Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. Statistics and Computing, 27(5), 1413–1432. doi:10.1007/s11222-016-9696-4