A new on-line tool for the calculation of bioaccumulation factors of active substances within living organisms: $\text{MOSAIC}_{\text{bioacc}}$.

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Abstract

Today, there are no ready-to-use convenient tools in ecotoxicology to diagnose and predict the accumulation and effects of chemical substances on living organisms, accounting for exposure situations that are known to be complex (routes of exposure, metabolization processes, cocktail effects, etc.). Among available methods, toxicokinetic/toxicodynamic (TKTD) models are now strongly recommended to describe the exposure time-dependency on individual life-history traits from experimental data collected through standard toxicity tests. In particular, the TK part is used to relate the exposure medium concentration to the internal concentration within organisms, considering various processes such as accumulation, depuration, metabolization and excretion (ADME). Regarding plant protection products in marketing authorization applications, regulation No 283/2013 (EU) defines the data requirements for active substances with a bioaccumulation test on fish according to OECD guideline 305, which consists in an accumulation phase followed by a depuration phase. The concentration of the substance within fishes is followed over time during both phases thus allowing to model the time course of the exposure within organisms, summarized via bioaccumulation factors. On a regulation point of view, these factors are decision criteria for further estimating the concentration of active substances

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present in food items of vertebrates and more particularly of piscivorous birds and mammals. This paper presents a new ready-to-use web tool providing the estimation of the bioaccumulation factors associated with their uncertainty to facilitate the daily work of regulators, but also of any user, by benefiting of a freely available and user-friendly on-line interface avoiding to invest into underlying technicalities. This tool, $\text{MOSAIC}_{\text{bioacc}}$, is available from the following address: https://mosaic.univ-lyon1.fr/bioacc, and can be used as a turn-key decision making tool in the framework of environmental risk assessment.

Keywords: *Active substances, Bayesian inference, Bioaccumulation factors, Environmental Risk Assessment, R software, Toxicokinetic models, Uncertainty.*

1. Introduction

Nowadays, ecotoxicology has to provide relevant and effective methods and tools in a predictive (prior risk assessment) and diagnostic (posterior identification of effects and their remediation) perspective. The aims of these methods and tools are to quantify the exposure routes of potentially hazardous substances to assess dose-response relationships and to define critical effect concentrations, helping in understanding the underlying biological and ecological mechanisms, and developing indicators for environmental quality. In this context, toxicokinetic/toxicodynamic (TKTD) models are now strongly recommended to describe the exposure time-dependency on individual life-history traits from experimental data collected through standard toxicity tests (Ockleford et al., 2018). In particular, the TK part is used to relate the exposure medium concentration to the internal concentration within organisms, considering various processes such as accumulation, depuration, metabolization and excretion (ADME). Regarding plant protection products in marketing authorization applications, regulation No 283/2013 (EU) (European Commission, 2013) defines the data requirements for active substances with a bioaccumulation test on fish according to OECD guideline 305 (OECD, 2012), which consists in an accumulation phase followed by a depuration phase. During the accumulation phase, individuals are exposed to the substance under interest at a range of concentrations, chosen according to the mode of action of the substance. Then, organisms are transferred to a clear medium for the depuration phase. The concentration of the substance within fishes is followed over time during both phases leading *in fine* to the estimation of the bioconcentration factor (BCF), the biomagnification factor (BMF) or the bioaccumulation factor (BAF) according to the exposure route (via water, food or sediment, respectively). On a regulation point of view, such factors are decision criteria for further estimating the concentration of active substances

present in food items of vertebrates and more particularly of piscivorous birds and mammals. A test with fish according to OECD TG 305 is also preferred where experimental information on bioaccumulation is needed for PBT/vPvB assessment under REACH regulation (European Commission, 2006; ECHA, 2017). In most cases, preference is also given to experimentally derived BCF values to be used for secondary poisoning assessment under Biocidal Products Regulation (European Commission, 2012).

In the past decades, many types of methods have been proposed to estimate parameters of simple TK models, making it possible to deduce bioaccumulation factors values (especially BCF) depending on the kinetics of accumulation and depuration observed in dedicated experiments (OECD, 2012). Nevertheless, still today TK model parameters are rarely estimated as a whole, considering simultaneously both uncertainties of parameter estimates and parameter correlations. However, it is crucial to properly estimate parameters of TK models for a better risk assessment and this remains a challenge. Besides, regulators are sceptical about the diversity and complexity of the possible methods and tools to perform this, while thinking about their standardization at the same time (Tan et al., 2020). Ratier et al. (2019) recently proposed a full revisit of the approach based on a unified inference method to estimate parameters of TK models for both accumulation and depuration phases simultaneously. This innovative process has been thought to make it possible to incorporate the TK part into complete TKTD model.

This paper presents a new ready-to-use web tool, $\text{MOSAIC}_{\text{bioacc}}$, leading to the estimation of bioaccumulation factors associated with their uncertainty according to this new approach. Its purpose is to facilitate the daily work

of regulators, but also of any user, benefiting of a freely available and user-friendly interface avoiding to invest into underlying statistical and technical aspects. This web tool clearly takes advantage of the new conceptual framework developed by Ratier et al. (2019) in order to estimate parameters of a one-compartment TK model as a whole including several exposure routes (water, food, sediment), accounting for metabolization of the chemical substance and possibly for growth dilution. The use of $\text{MOSAIC}_{\text{bioacc}}$ will only require to upload standard experimental data, then some clicks to get all the results. In particular, BCF/BMF/BAF are right away delivered as probability distributions summarized by a median and a 95% credible intervals. In addition, a collection of goodness-of-fit criteria is provided to allow the user to carefully check the robustness of the results. At last, all outputs can be downloaded for further inclusion into any home-made document, while a full report can be directly downloaded in different convenient formats.

2. Description

$\text{MOSAIC}_{\text{bioacc}}$ was developed as a Shiny environment, available at https://mosaic.univ-lyon1.fr/bioacc and hosted at the Rhône-Alpes Bioinformatics Center PRABI (2016). A user guide and an explanatory video are available at the beginning of the application to assist the user. Details on underlying ordinary differential equations and their solving are also provided (see SI, **Annex 1**).

2.1. Data uploading

When using $\text{MOSAIC}_{\text{bioacc}}$, the first step is to upload input data (**Fig. 1-a**). $\text{MOSAIC}_{\text{bioacc}}$ expects to receive toxicity test data as a .txt file or a .csv file (comma, semicolon or tabular separator) with a specific format. Each line of the table corresponds to a time point for a given replicate and a given exposure

concentration of the contaminant. The table must contain four columns, with the exact following header names, the order of column not mattering (**Table 1**): 'time' (the time point of the measurement at the exposure concentration, in hours, minutes, days or weeks), 'exposure' (the concentration of the contaminant in the exposure medium, in $\mu g.mL^{-1}$), 'replicate' (a number or a character that is unique for each replicate, dimensionless), and 'concentration' (the concentration of the contaminant within the organism, in $\mu g.g^{-1}$).

Table 1: Example of a data set ready to be used with a TK model.

time	concentration	exposure	replicate
0	0.000	0.0044	2
3	0.225	0.0044	2
7	0.355	0.0044	2
14	0.553	0.0044	2
21	0.658	0.0044	2
28	0.785	0.0044	2

As shown on **Fig. 1-a**, the user of $\text{MOSAIC}_{\text{bioacc}}$ can either upload its own data set with a click on 'Browse' (by taking care about the format specification of its file) or try the web tool with an example data set. When the upload is complete, the user has to manually select the corresponding separator, the appropriate time unit and the duration of the accumulation phase. The application first provides an overview of the raw data which allows the user to check if the data were correctly entered. The user can also visualize a plot of the data (**Fig. 1-b**). In case the user uploads a file with several exposure concentration, it has to select the one for which it wants to see the fitting results. Indeed, only one file at a time can be analysed. It should be also noted that for each new

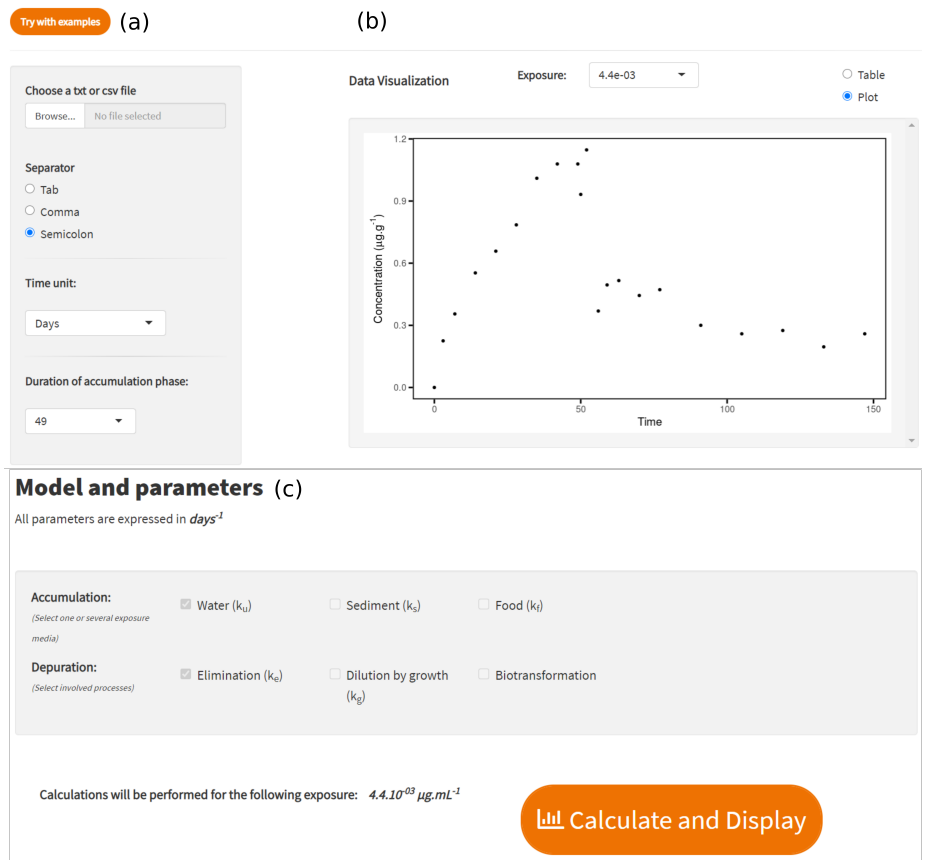

Figure 1: Data uploading and user information to enter from the MOSAIC$_{bioacc}$ homepage.

choice of exposure concentration, the duration of the accumulation phase is reset and framed in orange to invite the user to update it before to proceed to new calculations.

Some example files are provided in MOSAIC$_{\text{bioacc}}$ to illustrate the format and help the users in running the web tool at the beginning. MOSAIC$_{\text{bioacc}}$ is presented in this paper from a typical data set of a toxicokinetic bioassay where concentrations were collected for rainbow trout (*Oncorhynchus mykiss*) exposed via contaminated water to a highly hydrophobic chemical ($\log K_{ow} = 9.06$) at an

exposure concentration of 0.0044 $\mu g.mL^{-1}$ over 49 days, with one replicate at each time point. After 49 days, fishes were transferred in a clean medium for 98 days more (Crookes & Brooke, 2011). The data set can be downloaded directly from the website.

2.2. Model and parameters

In the TK models we are dealing with here, the organisms considered as single compartments for which a first-order kinetic bioaccumulation model accounting for several exposure and elimination routes can be expressed in a generic way as follows (Eqs. (1) to (4)):

$$\begin{cases} \frac{dC_p(t)}{dt} = U - (E+M)C_p(t) \quad (1) \\ \frac{dC_{m_\ell}(t)}{dt} = k_{m_\ell}C_p(t) - k_{e_m\ell}C_{m_\ell}(t) \quad (2) \end{cases} \quad for \quad 0 \leq t \leq t_c$$

$$\begin{cases} \frac{dC_p(t)}{dt} = -(E+M)C_p(t) \quad (3) \\ \frac{dC_{m_\ell}(t)}{dt} = k_{m_\ell}C_p(t) - k_{e_m\ell}C_{m_\ell}(t) \quad (4) \end{cases} \quad for \quad t > t_c$$

where $C_p(t)$ is the internal concentration of the parent compound at time t ($\mu g.g^{-1}$), $C_{m,\ell}(t)$ the internal concentration of metabolite ℓ ($\forall \ell = 1 \ldots L$ with L the total number of metabolites) at time t ($\mu g.g^{-1}$), U the sum of all uptake terms, E the sum of all elimination terms for the parent compound, M the sum of all elimination terms for the metabolites, $k_{m,\ell}$ the metabolization rate of metabolite ℓ ($time^{-1}$) and $k_{e,m\ell}$ the elimination rate of metabolite ℓ ($time^{-1}$). A summary of the meaning of parameters and variables is provided in **Table 2**.

The previous dynamical system can explicitly be solved when exposure concentration is assumed to be constant over time (**Annex 1**).

Table 2: Meaning of parameters and variables of the TK model used in $\text{MOSAIC}_{\text{bioacc}}$.

Symbol	**Meaning**
i	index of exposure routes, $i = 1 \dots I$
j	index of elimination processes, $j = 1 \dots J$
ℓ	index of metabolites, $\ell = 1 \dots L$
I	total number of exposure routes
J	total number of elimination processes
L	total number of metabolites
t	time (in time unit)
c_i	exposure concentration of route i (in $\mu g.mL^{-1}$)
$C_p(t)$	internal concentration of the parent compound at time t (in $\mu g.g^{-1}$)
$C_{m_\ell}(t)$	internal concentration of metabolite ℓ (in $\mu g.g^{-1}$)
k_{u_i}	uptake rate of exposure route i (expressed in $time^{-1}$)
k_{e_j}	elimination rate of elimination process j (expressed in $time^{-1}$)
$k_{e_{m\ell}}$	elimination rate of metabolite ℓ (expressed in $time^{-1}$)
k_{m_ℓ}	metabolization rate of metabolite ℓ (expressed in $time^{-1}$)
t_c	duration of the accumulation phase (in time unit)
$\mathcal{N}$	Gaussian probability distribution
$C_{obs,p}(t)$	internal measured concentration of the parent compound at time t (in $\mu g.g^{-1}$)
$C_{obs,m_\ell}(t)$	internal measured concentration of metabolite ℓ (in $\mu g.g^{-1}$)

Symbol	Meaning
σ	standard deviation for the internal concentration of the parent compound (in $\mu g.g^{-1}$)
σ_{met_ℓ}	standard deviation for the internal concentration of metabolite ℓ (in $\mu g.g^{-1}$)
$U = \sum_{i=1}^{I} k_{u_i} c_i$	sum of all uptake terms
$E = \sum_{j=1}^{J} k_{e_j}$	sum of all elimination terms for the parent compound
$M = \sum_{\ell=1}^{L} k_{m_\ell}$	sum of all elimination terms for metabolite ℓ

For questions of calculation time, within $\text{MOSAIC}_{\text{bioacc}}$, we choose to only propose three routes of exposure ($I = 3$, *i.e.*, water, food and sediment), three processes of elimination ($J = 3$, *i.e.*, excretion, growth dilution and metabolization) and a maximum of three metabolites which directly come from the parent compound ($L = 3$). Hence, the maximum number of parameters is 18 when the model is complete. In total, the user has 56 possible models depending on the combination it chooses (**Annex 2**). According to its experimental design, the user is invited to select the corresponding parameters (**Fig. 1-c**). We assumed a Gaussian probability distribution for measured concentration variables of the parent compound and its metabolites within the organisms (Eqs. (5) and (6)):

$$C_{obs,p}(t) \sim \mathcal{N}(C_p(t), \sigma^2) \quad (5)$$

$$C_{obs,m_\ell}(t) \sim \mathcal{N}(C_{m_\ell}(t), \sigma^2_{met_\ell}) \quad (6)$$

where variables and parameters are those given in **Table 2**.

In this paper, the results will be exemplified with a data set considering only the water exposure route (k_u) with the corresponding elimination rate (k_e), that is one of the simplest models among the 56 possibilities. The corresponding

first-order TK model can simply be expressed as follows (Eqs. (7) and (8)):

$$\begin{cases} \frac{dC(t)}{dt} = k_u \times C_w - k_e \times C(t) & \text{for } 0 \leq t \leq t_c \quad (7) \\ \frac{dC(t)}{dt} = -k_e \times C(t) & \text{for } t > t_c \quad (8) \end{cases}$$

Then there are only two parameters to estimate: k_u, water for the exposure medium and k_e, excretion for the depuration process. If the file has correctly been uploaded and the exposure concentration has been chosen for the analysis, a reminder of the latter is displayed on the screen and the button for launching the calculations is unlocked. When the user clicks on the 'Calculate and Display' button (**Fig. 1-c**), the calculations are launched with a progress bar that informs about their progress. When calculations are finished, results are displayed, as plots and tables by default, and complementary outputs for the goodness-of-fit checking.

2.3. Calculations

2.3.1. Definition of prior distributions

For simplicity reasons, in $\text{MOSAIC}_{\text{bioacc}}$, the choice of priors is hidden to the user with no possibility to change them. To keep priors the most generic as possible, they were assumed following a non-informative (-5, 5) log10-uniform distribution for all uptake and elimination rate constants, and a non-informative (0.001, 0.001) Gamma distribution for all standard deviations, as usually done in the field of bioaccumulation studies (Lambert et al., 2005; Ratier et al., 2019; Richards & Chaloupka 2009).

2.3.2. Bayesian inference

Model computations that underline $\text{MOSAIC}_{\text{bioacc}}$ calculations are performed with JAGS (Plummer, 2019) and R software (version 3.6.3, R Core Team 2020) via the `rjags` package (Plummer, 2019). Models are fitted to bioaccumulation

data using Bayesian inference via Monte Carlo Markov Chain (MCMC) sampling. For each model chosen by the user, running starts with a short sampling on three MCMC chains (5,000 iterations after a burn-in phase of 10,000 iterations) using the Raftery and Lewis method (Raftery & Lewis, 1992) to set the necessary thinning and number of iterations to reach a precise and accurate estimation of each model parameter. Thanks to `rjags`, model parameters are retrieved as a joint posterior distribution from the likelihood of the observed data combined with prior distributions on parameters. All details on this approach can be found in the original research paper (Ratier et al., 2019) but also in many other papers in the field of ecotoxicology (Billoir et al., 2011; Ockleford et al., 2018).

2.3.3. Bioaccumulation factors

In $\text{MOSAIC}_{\text{bioacc}}$, bioaccumulation factors are calculated and provided as the first output This paper illustrates the case of an organism exposed via contaminated water, leading to both the kinetic bioconcentration factor (BCF_k) and the steady state bioconcentration factor (BCF_{ss}), automatically displayed by the web application. These bioaccumulation factors have exact mathematical expressions (Eqs. (9) and (10)):

$$BCF_k = \frac{k_u}{k_e} \quad (9)$$

$$BCF_{ss} = \frac{C_p(t_c)}{C_w} \quad (10)$$

where $C_p(t_c)$ is the internal parent compound concentration (in $\mu g.g^{-1}$) at the end of the accumulation phase (that is at $t = t_c$, in time) and C_w is the exposure contaminant concentration in the medium ($\mu g.mL^{-1}$).

Table 3: Example of BCF (a) and parameters (b) estimates expressed as medians (50% quantile) and 95% credibility intervals (2.5% - 97.5% quantiles). The hyphen stands for dimensionless parameters.

	2.5%	50%	97.5%	Units
(a)				
BCF_k	232	276	338	-
BCF_{ss}	148	233	317	-
(b)				
k_u	7.405	10.63	15.52	d^{-1}
k_e	0.02323	0.03871	0.0613	d^{-1}
σ	0.1244	0.1675	0.2466	$\mu g.g^{-1}$

2.4. Fitting results

2.4.1. Bioconcentration factors

When the user clicks on 'Calculate and Display' button, some results are provided by default. First, the BCF_k is given as a probability distribution (**Fig. 2-a**) and summarized with its median and its 95% uncertainty limits (95% credible interval, **Table 3-a**). If the user asks for the BCF_{ss}, its probability distribution is also given (**Fig. 2-b**) as well as its uncertainty limits (**Table 3-a**).

2.4.2. Predictions

After BCF plots and tables, the fitted curve superimposed to the observations is provided (**Fig. 2-c**). From the joint posterior distribution of parameters, $\text{MOSAIC}_{\text{bioacc}}$ also provides the marginal posterior distributions for each parameter, which are also summarized in a table (**Table 3-b**). All estimated parameters are given as medians (for point estimates) and 2.5 and 97.5% quantiles (for 95% credible intervals) of marginal posterior distributions. Credible intervals are crucial information to quantify the uncertainty on parameter estimates.

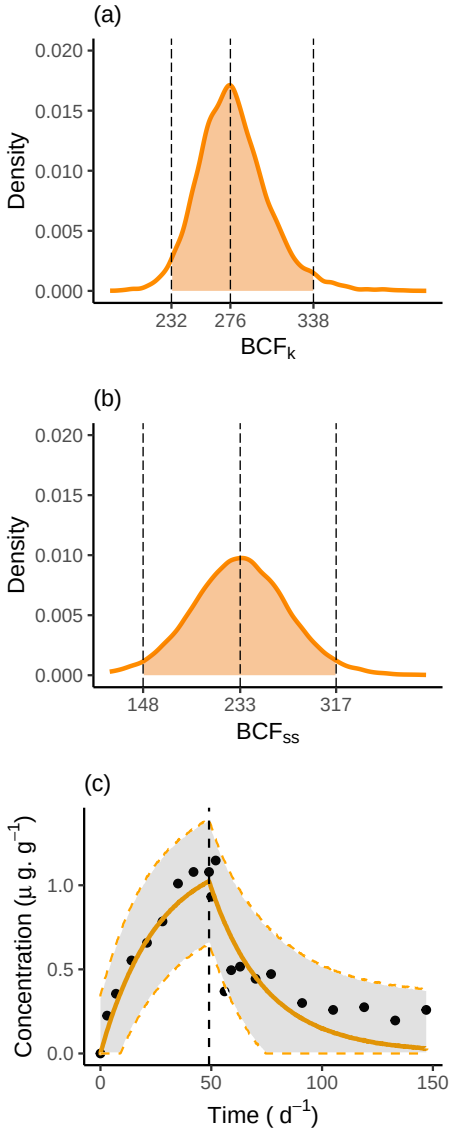

Figure 2: Probability distributions of BCF_k (a) and BCF_{ss} (b). The middle-dotted line represents the median value, while left and right dotted lines are the 2.5 and 97.5% quantiles. (c): Measured (black dots) and predicted contaminant concentrations in the organisms (µg.g^{-1}), where the median is represented by the orange plain line and the uncertainty band by the gray zone, delimited by the 2.5% and 97.5% quantiles in orange dotted lines.

2.4.3. Goodness-of-fit criteria

Several goodness-of-fit criteria follow in a prioritized order we chose based on their relevance and thir ease of interpretation. The fitting quality of the model can be first checked using the posterior predictive check plot: the idea is to compare each observed value to its prediction from the fitted model at the corresponding exposure concentration associated with its 95% credible interval. If the fit is correct, we expect to see 95% of the observed values falling within the 95% credible intervals of their predictions. As shown on **Fig. 3-a**, the observed values are read on the x-axis, while the y-axis reports the median predictions (black dots) and their 95% credible intervals (vertical segments).

The robustness of the inference process can be secondly checked using the comparison of prior and posterior distributions. The overall expectation is to get a narrower posterior distribution compared to the prior one, what reflects that data contributed enough to precisely estimate parameters (**Fig. 3-b**).

$\text{MOSAIC}_{\text{bioacc}}$ then provides the correlation plot (**Fig. S1**), which allows the user to visualize the correlations between parameters. This plot is obtained by projecting the joint posterior distribution in a plot matrix in planes of parameter pairs. This plot also gives marginal posterior distribution of each model parameter and Pearson correlation coefficients. Correlations between parameters are important to consider in particular when they are high (namely, greater than 0.75) what would mean that one parameter estimate could considerably influence the other.

The convergence of the MCMC chains is checked with the Gelman-Rubin diagnostic (Gelman & Rubin, 1992) expressed via the potential scale reduction factor (PSRF) which is expected to be close to 1.00 (**Fig. S1**). It can be also visually verified by the MCMC traceplot, which shows the time series of the sampling process leading to the posterior distribution ; we expect to obtain the

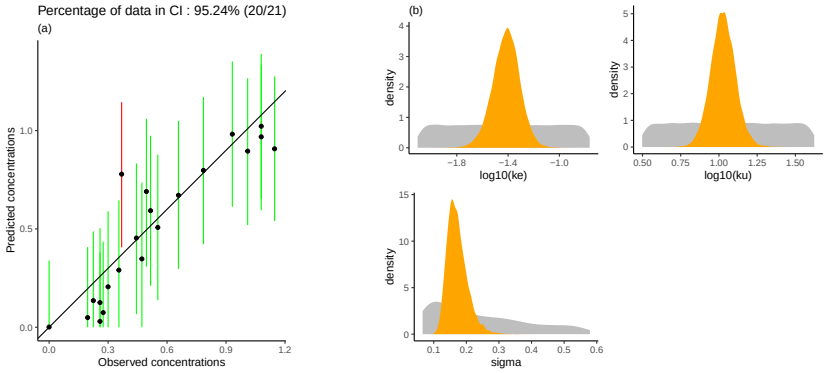

Figure 3: Some goodness-of-fit criteria as given in MOSAIC$_{\text{bioacc}}$: (a) Posterior Predictive Check (PPC) where the observed values are read on the x-axis, while the y-axis reports the median predictions (black dots) and their 95% credible intervals (vertical segments, coloured in green if it contains the observed value, in red otherwise) ; (b) prior (gray) and posterior (orange) distributions of parameters for the simplest TK model.

overlapping of the three chains (**Fig. S1**).

The Deviance Information Criterion (DIC) is also given. It is a penalized deviance statistics accounting for the number of parameters and it is used to compare several models fitted to the same data set. Models with lower DIC values will be preferred. So, the DIC should be used when comparing several models based on different choices of parameters from all the possible combinations that the user can chose at the beginning according to its available data.

2.5. Downloads

All results can be downloaded from the bottom of the web page as well as a report with all the results. The user can also download the R code corresponding to all calculations and graphs from its data set. This guarantees the transparency and the reproducibility of all MOSAIC$_{\text{bioacc}}$ results. This R code can be used as a stepping stone to change default options and to perform further analyses directly in R. For example, the user can modify figures at its convenience, or make several analyses on several data sets at the same time.

3. Conclusions

The development of readily-to-use tool as $\text{MOSAIC}_{\text{bioacc}}$ raises important methodological issues: (1) the automatization of the inference process, in particular for Bayesian inference; (2) the default options to fix and the choices left to the discretion of the users; (3) the outputs to primarily provide, the goodness-of-fit to show, the downloads to propose, the kind of analysis report to render. We are convinced that $\text{MOSAIC}_{\text{bioacc}}$ may be particularly useful to estimate parameters of TK models and to predict chemical concentrations bioaccumulated in organism from standard data. Besides its user-friendliness, this application is free of use and guarantees the privacy of the uploaded data as well as the transparency and the reproducibility of the results, together with a short response time. This tool could thus be used by risk assessors and decision makers in their daily work of assessing dossiers, *e.g.*, for the authorization of substances on the market (Ockleford et al., 2018), since all results provided by $\text{MOSAIC}_{\text{bioacc}}$ account for uncertainty and correlations between parameters. It could also be used by any environmental scientists, ecotoxicologists and managers when OECD n°305 tests are performed and need to be analysed. Further developments are already in progress to make $\text{MOSAIC}_{\text{bioacc}}$ available as a new module dedicated to TK modelling approaches in the MOSAIC platform (Charles, Veber & Delignette-Muller 2018). Above all, this application will be soon extended to provide a prediction section that could allow to better design TK experiments in order to collect more relevant data for the model fitting and the estimation of bioaccumulation factors.

4. Authors' contributions

GM contributed to the Shiny application development, from a basic script provided by CL. The whole TK model has been developed by AR and CL. All

authors equally contributed to make the script the most generic as possible, then allowing to facilitate the Shiny application development. AR and SC led the writing of the manuscript.

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6. Data accessibility

Directly within $\text{MOSAIC}_{\text{bioacc}}$ at https://mosaic.univ-lyon1.fr/bioacc.

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