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High performance computing and neural network in support of toxicokinetic-toxicodynamic modelling for the understanding of mixture effects

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Modeling Mixture Interactions with Neural Networks

Plant protection products are formulated to control target pest species, including mixtures of active ingredients. Being able to predict joint effects of formulation agents and active ingredients is of great importance for both risk assessment and pest control.

Time variable effects can be assessed with toxicokinetic (TK) and toxicodynamic (TD) models. The mixture toxicity have recently been implemented (Bart et al., 2021) with linear interactions (Concentration Addition and Independent Action) and so missing potential synergism and antagonism effects (Cedergreen, 2014).

In this regard, we provide a standalone pipeline coupling TKTD mechanistic models based on Ordinary Differential Equation with Neural Network (NN), called Neural ODEs (Chen et al., 2018), benefiting from both worlds: (1) the TKTD approach to fit experimental data (under a Bayesian framework) on active substances alone and in combination with other active substances or additives; (2) using the NN to map potential interactions between active substances in combinations or in formulations.

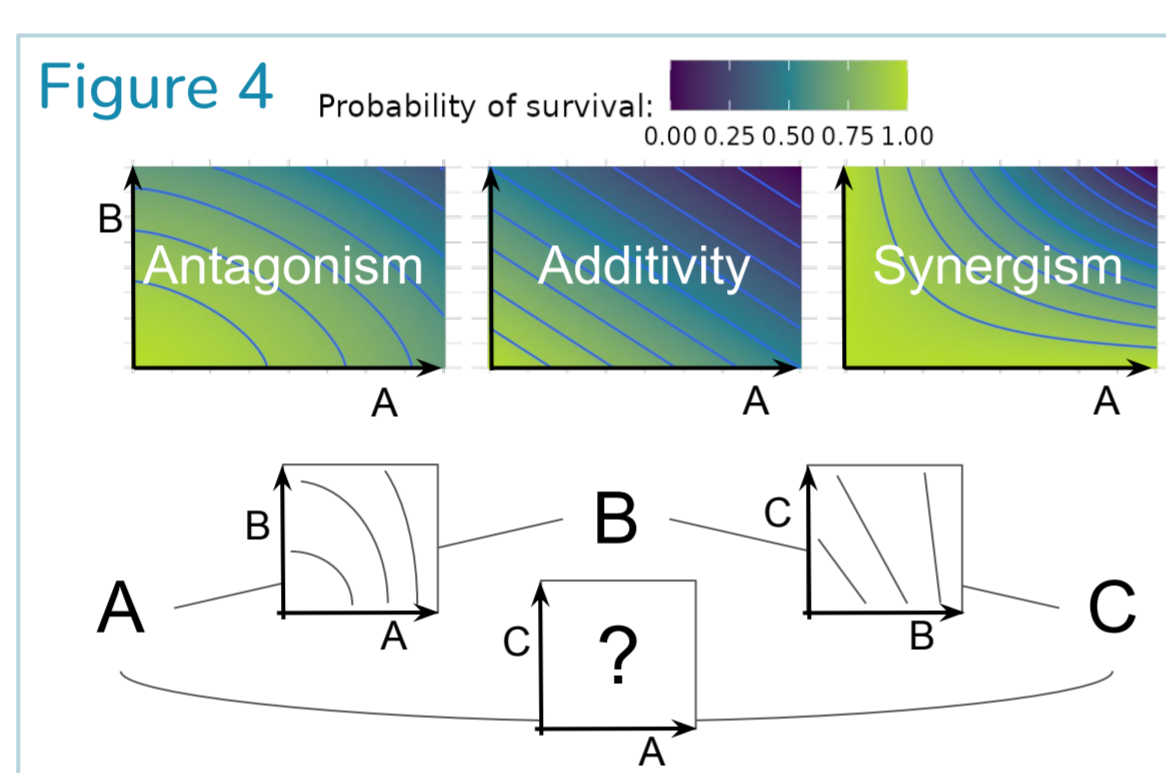
Here, we introduce a first analysis demonstrating the robustness of the Neural ODEs, together with preliminary results on the type of interactions.

Using interactions within AB and BC to predict AC interaction

Theory of interaction

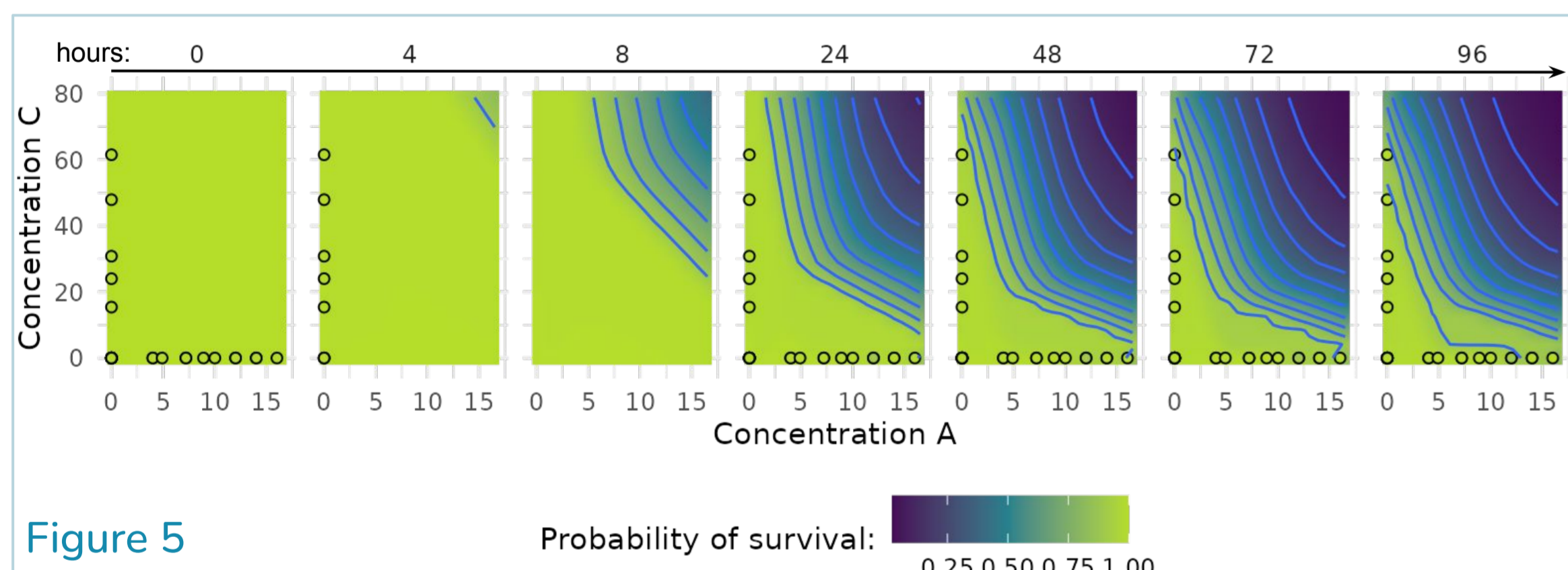
A physiological response, r , may exhibit several patterns when exposed to mixtures of A and B. A simple and classical classification is:

- Additive: $r(A+B) = r(A) + r(B)$
- Antagonism: $r(A+B) < r(A) + r(B)$
- Synergism: $r(A+B) > r(A) + r(B)$



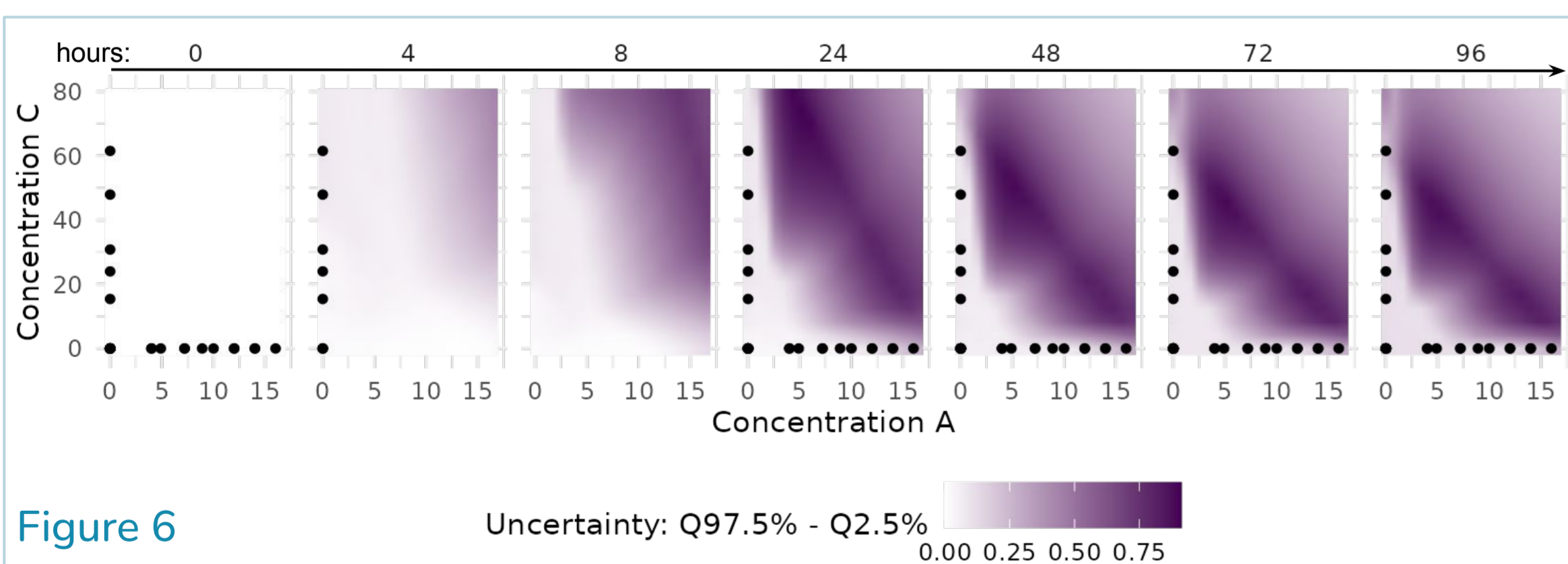
Also, an additivity for A-B and B-C might not result in additivity for A-C.

Prediction



Based on survival data on A, B, AB and BC, the heatmap represent estimation of survival probability at different time points (hours) and with different proportions of A and C. The dots represent data, so only single compounds data are available. Blue curves are isolines linking pixels with the same level of survival probability.

The NN models predicts a synergistic effect of A and C since the effect is more than the sum of the marginal effects of each compounds. The Linear models were not able to account for this pattern.



Level of uncertainty of the prediction is computed as the difference between the upper minus the lower bounds of the 95% credible interval. This score stands between 0 and 1, where 0 (white) represents a high degree of certainty while 1 (purple) is highly uncertain. Compared with the graphic above, we see that the transition from high to low survival probability (the inflexion region) is the most uncertain to predict, which was expected as it's the region with the most of variation.

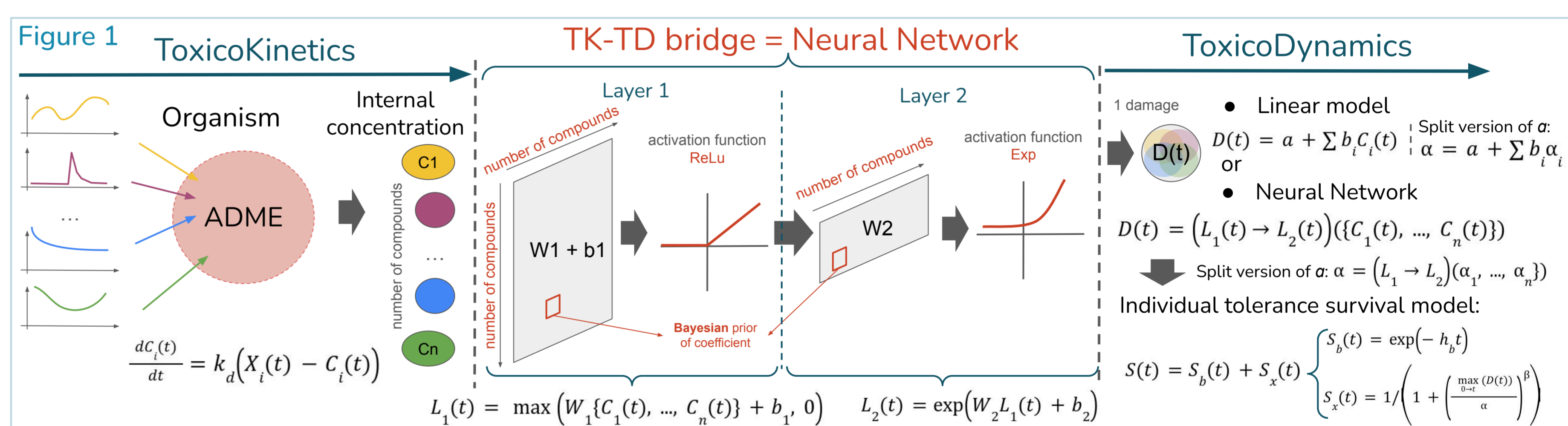
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Modelling Hypothesis & Methods

The model is made up of three parts:

1. the **toxicokinetics** (TK) defined by Ordinary Differential Equation (ODEs) to account for time-variable exposure profile. The reduced version of the General unified threshold model of survival (GUTS) (Jager et al., 2011). For each compound with exposure profile $X_i(t)$, the scaled internal concentration is $C_i(t)$ including k_d named the *dominant toxicokinetic rate constant*.
2. the **toxicodynamics** (TD) takes the damage as a single input variable resulting from the combination of TK output variables according to the chosen weights, either by linear function or through neural network. Then the Individual Tolerance model of survival is applied, including the background mortality and the additional mortality due to toxicant respectively named $S_b(t)$ and $S_x(t)$ hereafter.
3. the **bridge between TK and TD**, with 2 variants: (1) a **linear matrix** consisting only in matrix W_2 of layer 2 (by-passing layer 1) without activation function, or (2) a simple **neural network (NN)** consisting of 2 layers, a first layer defined by matrix $W_1 + b_1$ of size $n \times n$ (with n the number of compound) and an ReLU activation function, and a second layer defined by a matrix W_2 reducing the number of variables from n to 1 (the damage) with an exponential activation function (which ensures positivity of the damage variable). We considered two options: either one parameter, α , a common individual median threshold for all compounds, or one parameter **split** into singular $\{\alpha_1, \dots, \alpha_n\}$ associated to each compound and computed using the TK-TD bridge. These models are named Linear split and NN split respectively.



Data

The inference process has been tested on 99 acute toxicity (survival) studies with fish (OECD 203 standard), grouped into 4 datasets (resp. 38, 19, 21, 21 studies). Each of the 4 datasets allowed studying the interactions between 5 to 6 different active substances. Three artificial data sets were also created to test the possibility for the algorithm to capture interaction pattern of additivity, synergism and antagonism. Mortalities and visible abnormalities related to appearance and behaviour are recorded in order to determine, where possible, the concentrations to kill 50% of the fish (LC50).

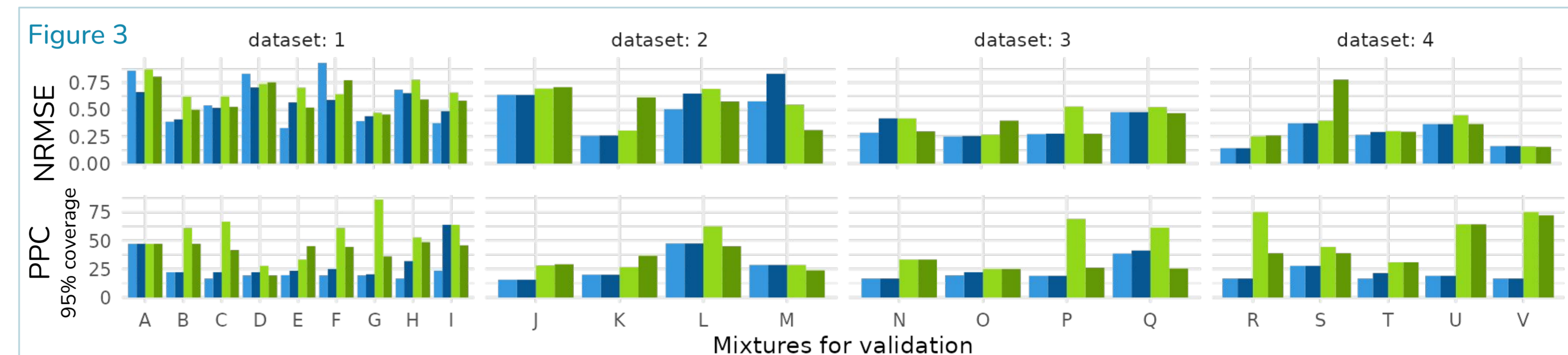
Results of Bayesian Inference - calibration & validation

Calibration

Calibration was made with Bayesian inference for all datasets, the NRMSE (Normalized Root Mean Square Error) suggests that the Neural Network (NN, NN split) are always better than Linear models. Using the WAIC, (adding a cost on the parameter number), Linear models appears slightly better for 2 datasets and similar for the others.

The cost of Neural Networks models (number of parameters, time of inference) is all the more compensated as non-linearities are present in the interactions.

Validation through extrapolation



For each dataset, validation was done by calibrating the models on a subset of data (training data) and then tested on another subset (test data) symbolized by letters. NRMSE and Posterior Predictive Check (PPC) were computed based on the prediction on the test data only. The validation of exogenous mixture is complex and pretty low for all models. From PPC, the uncertainty of Neural Network is greater leading to a larger coverage of data, while from NRMSE, the linear model suggest a better fit of 3 datasets and equivalent for the fourth one.

Conclusion

1. This study introduces the combination of Neural Network (NN) with ODEs (named Neural ODEs) in order to explore the interaction between active ingredient of mixtures.
2. This hypothesis is to benefit from the both worlds: the mechanistic description to control well-known mechanism (TK and TD) and free-constraint model for the 'damage part' where assumptions of interaction are not availables.
3. Within this modelling framework, the use of the Bayesian approach for calibration, validation and prediction provides a measure of uncertainty. The uncertainty can be propagated in predictions to give a measure of their reliabilities.
4. On itself, this approach of Bayesian Neural ODEs is new, and it also reveals to be very efficient and promising in the exploration of non-linear interactions between active ingredients.
5. We found a generic NN tuning (layers structures and activations functions) for every data set (and its subsets) based on the number of active ingredient in the mixture, so which can be automatically set.
6. While NN is very efficient for the calibration task, the validation process is better with linear models. Understanding how to deal with the strengths and weaknesses of Neural ODEs deserves further exploration.
7. This scope, which focuses only on concentration, is very narrow for the potential of this framework. Coupling NNs to classical TKTD models offers the possibility to include, without any mechanistic a priori, any other variables that may influence the effects of mixtures (such as temperature, organism age, chemical properties of active ingredients, etc.).