High Performance Computing and Machine Learning in support of Toxicokinetic-Toxicodynamic Modelling for the understanding of Mixture Effects

Addressing the prediction of mixture effects over time with toxicokinetics-toxicodynamics models of survival (GUTS)

Toxicokinetics-Toxicodynamics (TKTD) models are increasingly used for **inference of toxicity indices** of interest in Environmental Risk Assessment (ERA) thanks to their clear description of numerous **mechanisms**, from the **kinetics of compounds** inside organisms (Toxicokinetics, TK) to their related damages and **effect dynamics at the individual level** (Toxicodynamics, TD) [1]. TKTD models offer the advantage of accounting for temporal aspects of both exposure and toxicity, considering data points all along the time course of experiments. In addition, TKTD models allow predictions under untested situations from time-variable exposure profiles either measured in the field or simulated in risk assessment scenarios. Although **ERA can follow a compound-by-compound approach**, in practice, **ecosystems are exposed to many chemical products**, from agricultural, industrial and domestic sources. Using TKTD models to describe such mixture effects over time requires making assumptions *a priori* on potential interactions of involved products [2]. These assumptions are then tested and evaluated based on fitting TKTD models to observed data under exposure to mixtures. This poster illustrates how **high performance computing** [3] and **machine learning** [4] may be of particular help for the inference of TKTD models without a priori knowledge on **emerging chemical interactions that leads to cocktail effects**.

Deep Neural Network to make emerge chemical interactions in mixtures and their effects on survival damages

Environment

Toxicokinetics

$$\frac{dC_{A_{int}}}{dt} = k_{dA}(C_{A_{ext}}(t) - C_{A_{int}})$$
$$\frac{dC_{B_{int}}}{dt} = k_{dB}(C_{B_{ext}}(t) - C_{B_{int}})$$

Input layer **hidden layer** **output layer**

Deep Neural Network on interactions between intake compounds with metabolism

Toxicodynamics

Instantaneous death $h(t) = b_w \max(D(t) - z, 0)$

Survival probability $\frac{dS(t)}{dt} = -(h(t) + h_b)S(t)$

Parameters	Definitions
$C_{A_{ext}}, C_{B_{ext}}$	External exposure concentration
$C_{A_{int}}, C_{B_{int}}$	Scaled internal concentration
k_{dA}, k_{dB}	Toxicokinetics dominant rates
$h(t), S(t)$	Hazard rate and Survival probability
h_b, b_w, z	Mechanistic parameters of the survival model (background mortality, killing rate and damage threshold)

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Model calibration and analysis of relationships between parameters and variables

Observed and simulated survival probability over time with uncertainties from the last 70% epochs of training

(Left) Median prediction and 95% uncertainty limits of the TKTD GUTS model superimposed to observations [2].

Loss curve of the training

(Right) Fitting loss curve with no over- or under-fitting

Heatmap of the damage derivative as a function of internal concentrations

Machine learning implementation allows to visualize the time derivative of damage according to internal concentrations ($C_{A_{int}}$ and $C_{B_{int}}$). (Left) Heatmap providing an understanding of how contaminants interact with each other within the body: the time derivative of damage becomes positive when $C_{A_{int}}$ increases and negative with increase of $C_{B_{int}}$. Such a heatmap highlights the role of each contaminant in the mixture on the resulting damage over time: **the derivative with time increases with the increase of both compounds, but they have opposite effect** being positive for compound A and negative for compound B.

Correlation matrices between mechanistic parameters of the TKTD GUTS model

(Right) The correlation matrix between pairs of parameters over the last 70% epochs allows to see how parameters interact and the range of their values. It also allows to better understand how the machine learning algorithm has adapted to reach optimal parameter estimates, providing an understanding of the "black box" of the neural network (NN) optimization: **k_{dA} , k_{dB} (before NN) and b_w (after NN) are strongly linearly correlated.**

(Left) Time course of damage as a function of the external concentrations for both compounds. The time dimension highlights how the damage intensity changes over time. The initial condition at time $t = 0$ reflects no initial damage. Concentration dimensions illustrate the variation of resulting damage with compound B having a stronger effect on survival damage than compound A. **Hence, damage increases over time with A and B, and their interaction.**

Proof of concept of Mixed Neural Ordinary Differential Equations to decipher mixture effects on survival

- 1 - Our results show that Machine Learning provides a very good fit of TKTD GUTS model to observed data. The advantage of embedding deep neural network within mechanistic model is that no assumptions are required in advance on the potential interactions between studied chemical compounds.
- 2 - From these estimates, we can predict the time course of both the scale internal concentration and the latent survival damages to predict the survival probability according to co-varying ranges of compounds within the mixture, leading to point out situations of interest that have not been tested experimentally.
- 3 - Our study is a very promising proof of concept coupling Machine Learning technics with mechanistic effect models to decipher mixture effects on survival. In particular, we demonstrated the added value of the approach to make merge the most plausible interactions when between studied chemical compounds. The number of interacting compounds could easily be increased.
- 4 - The next step will be to combine this innovative Mixed Neural Ordinary Differential Equations with Bayesian inference in order to better quantify uncertainties on parameter estimates.

References

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