Population Modeling of Toxicological Combination Effects

Marcus Baaz[1,2], Tim Cardilin[2], Mats Jirstrand[2] and Torbjörn Lundh[1]

[1] **Department of Mathematical Sciences, University of Gothenburg and Chalmers University of Technology, Sweden**
[2] **Fraunhofer-Chalmers Centre, Gothenburg, Sweden**

CONTACT:
Marcus.Baaz@fcc.chalmers.se

Background & Motivation

- Nonlinear Mixed Effects **(**NLME) modeling is a powerful mathematical framework for analyzing time-series data.
- NLME is widely used in medicine to *e.g.,* quantify how a population responds to different combinations of drugs.
- Equivalent Exposure Curves (EEC) describe all exposure pairs that result in some predetermined event, such as tumor stasis or a critical toxicological event.
- EEC is a useful tool for analyzing combination effects since all exposure combinations of a set of drugs or pollutants cannot be tested experimentally,

Objective

- We aim to show how these two tools can be used to,
    1. Analyze how combinations of pollutants affect marine organisms
    2. Aid decision-makers in determining what pollutant is most important to reduce
    3. Reduce the need for animal testing by allowing for simulation-based analysis

NLMEModeling Package

- A user-friendly Wolfram Mathematica application package for nonlinear mixed effects modeling.
- Functionality for parameter estimation, model validation, and generation of synthetic data.
- Applications in pharmacometrics (clinical and pre-clinical data) and microbiology (multiple single cell data).
- Free: nlmemodeling@fcc.chalmers.se

Leander, J. et al (2021) Nonlinear Mixed Effects Modeling of Deterministic and Stochastic Dynamical Systems in Wolfram Mathematica https://doi.org/10.1016/j.ifacol.2021.08.394

Methods

Modeling Approaches

- **Naïve pooled data (NPD) method**
    1. Fit model assuming all data from one hyper-subject
- **Standard Two Stage (STS) method**
    1. Fit model to each individual separately
    2. Compute properties of parameter distribution empirically (mean, variance)
- **Nonlinear Mixed Effects (NLME)**
    1. Assume population distribution for parameters
    2. Formulate and solve maximum likelihood estimate of population parameters

Nonlinear mixed effect modeling

- Models based on systems of ordinary differential equations (ODEs) or stochastic differential equations
- Several layers of variability are quantified simultaneously including *e.g.,* between subject variability (BSV)
- The parameters in the model are assumed to either be the same for all individuals (fixed effects) or specific for each individual (random effects)
- Each observation is described by a measurement expression and a measurement error

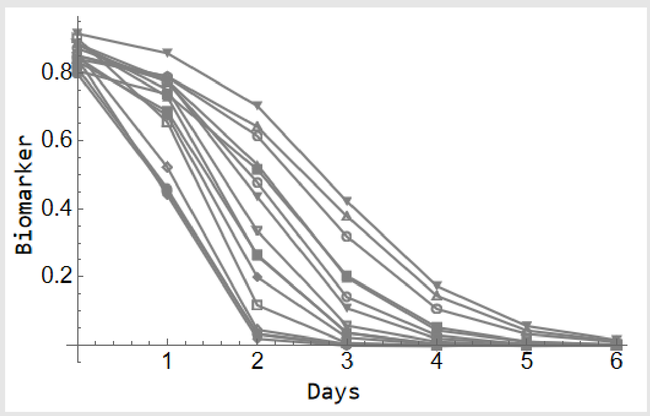

Fig 1. Example of time-series data.

Example model: Growth and Yolk sac depletion of zebra fish embryo*

Control group

$$\frac{dY_i}{dt} = -\beta e^{\eta_i} LY\left(1 - \frac{Y}{K_2}\right), \mathrm{Y}(0) = \mathrm{Y}_{\mathrm{ini}}$$

$$\frac{dL_i}{dt} = \gamma LY\left(1 - \frac{L}{K_1}\right), L(0) = L_{ini}$$

Combination of two pollutants

$$\frac{dY_i}{dt} = -(1 + a\, C_A)\beta e^{\eta_i} LY\left(1 - \frac{Y}{K_2}\right), \mathrm{Y}(0) = \mathrm{Y}_{\mathrm{ini}}$$

$$\frac{dL_i}{dt} = (1 - \frac{C_B}{C_B + IC_{50}})\gamma LY\left(1 - \frac{L}{K_1}\right), L(0) = L_{ini}$$

Fixed effects: $\boldsymbol{\alpha, \beta, \gamma, K_1, K_2, L_{ini}, Y_{ini}, a, IC_{50}}$
Random effect: $\boldsymbol{\eta_i \sim N(0, \omega)}$
Average exposure: $\boldsymbol{C_A, C_B}$

Equivalent Exposure Curves

- All exposure combinations of two pollutants that result in a certain event, *e.g.,* the final length of embryos reduced with 30%
- Can be solved either by finding analytical expressions based on the system equations or through simulation-based methods
- The curve gives an idea of what pollutant is most important to reduce in order for the critical toxicological event not to happen

Results

- The model was fitted to both experimental data from the literature* and simulated data
- Results from the model fitting are presented below

Table 1. Parameter estimates after model fitting

Parameters	Estimate (RSE%)	BSV (RSE%)
β	1.6 (6)	10% (46)
γ	1.4 (6)	
K_1	0.9 (1)	
K_2	0.5 (2)	
L_0	0.5 (1.7)	6% (47)
Y_0	0.86 (2.1)	3% (52)
IC_{50}	3.76 (11)	
a	0.56 (7)	

RSE: Relative standard error

BSV: Between subject variability

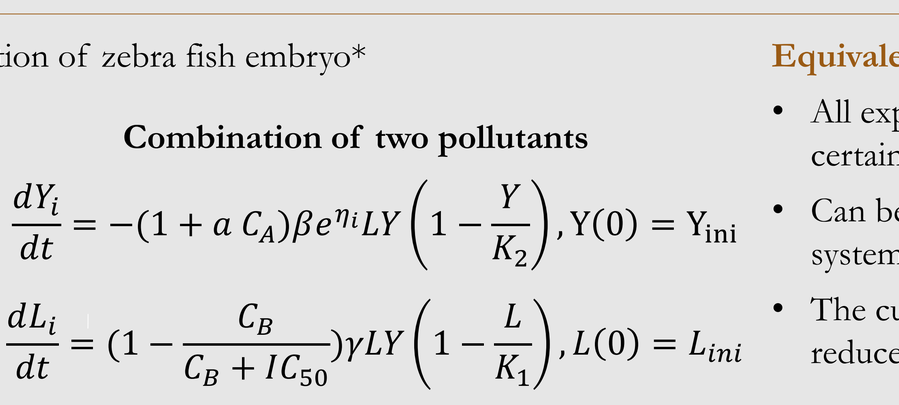

Fig 2. Individual prediction (black) together with experimental data (red)

An example of an EEC curve is shown in figure 3. Exposure pairs above the blue line (red area) result in the final embryo length being reduced by at least 30% compared to the control group for the median individual.

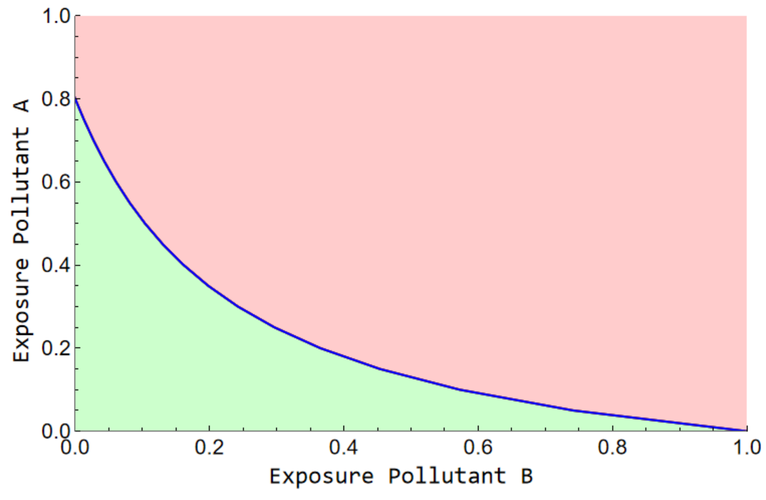

Fig 3. x and y-axis represent average exposure of pollutants A and B, respectively. Manageable exposure (green) too high exposure (red)

Conclusions

- The toxicological combination effect of several pollutants can be analyzed using the EEC curve
- The model can be used to perform further simulation studies, as a complement to animal studies

Future work

- Investigate experimental data with combinations of pollutants

*. Schwartz *et al*. Mathematical modeling of the interaction between yolk utilization and fish growth in zebrafish, Development (2021)