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td2pLL: An intuitive time-dose-response model for cytotoxicity data with varying exposure times

Modeling approaches for dose-response or concentration-response analyses are slowly becoming more popular in toxicological applications. For cytotoxicity assays, not only the concentration but also the exposure or incubation time of the compound administered to cells can be varied and might have influence on the response. A popular concentration-response model is the four-parameter log-logistic (4pLL) or, more specific and tailored to cytotoxicity data, the two-parameter log-logistic (2pLL) model. Both models, however, model the response based on the concentration only.

We propose a two-step procedure and a new time-concentration-response model for cytotoxicity data in which both concentration and exposure time are varied. The parameter of interest for the estimation is the EC50 value, i.e. the concentration at which half of the maximal effect is reached. The procedure consists of a testing step and a modeling step. In the testing step, a nested ANOVA test is performed to decide if the exposure time has an effect on the shape of the concentration-response curve. If no effect is identified then a classical 2pLL model is fitted. Otherwise, a new time-concentration-response model called td2pLL is fitted. In this model, we incorporate exposure time information into the 2pLL model by making the EC50 parameter dependent on the exposure time.

In simulation studies inspired by and based on a real data set, we compare the proposed procedure against various alternatives with respect to the precision of the estimation of the EC50 value. In all simulations, the new procedure provides estimates with higher or comparable precision, which demonstrates its universal applicability in corresponding toxicological experiments. In addition, we show that the use of optimal designs for cytotoxicity experiments further improves the EC50 estimates even if the design is little informative. In order to facilitate the application in toxicological practice, the developed methods are made available through the R package td2pLL.