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Correspondence/Rebuttal

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Response to Comment on "Robust Fit of Toxicokinetic–Toxicodynamic Models Using Prior Knowledge Contained in the Design of Survival Toxicity Tests"

CENSORED DATA

Multinomial and conditional binomial formulations are indeed equivalent (as we wrote in the paper). We merely meant that censored data can be expressed very conveniently in the conditional binomial model. Moreover, the way to do so is formally described,[1] while to our knowledge this is not the case for the multinomial model.

ANALYTICAL SOLUTION FOR IT MODELS

In the last part of our discussion, we suggested the extension of our approach to the GUTS-IT model. Though, in fact, we had in mind the extension to the full model including the individual tolerance together with stochastic death or no death (in that part of our paper, we refer to the model discussed in Albert et al. 2016[2]). So, our formulation was an unsatisfactory shortcut and we thank Dr Jager for his clarification on the fact that the GUTS-IT model is analytically integrated as soon as the cumulative distribution of the threshold can be written in a closed form.

PRIOR INFORMATION FROM TEST DESIGN

An experimental design can be viewed as the material embodiment of a hypothesis about parameter true values. We believe our definition of prior ranges is a way to quantitatively express the logical consequences of this hypothesis on parameter values. In that respect, it was certainly misleading on our part to say our prior implied a "realistic" range. What the prior really defines is the range of values that can be reasonably estimated given the experimental design. In his comment, Dr Jager stresses that the choice of experimental settings may be partially arbitrary or unrelated to actual knowledge on the model parameters (for instance, dictated by technical constraints). Basing priors on these choices may then lead to arbitrarily biased estimation.

Our general answer to this is that, either the assumptions entailed by the experimental design are correct and the prior has a negligible effect on the estimated values, or they are wrong and in this case, our estimates are potentially biased but advertised as such. Our prior is constructed by calculating a normal distribution whose 95% interval matches a certain range. With that definition, values at the mode of the prior are only 6.8 times more probable that values at one end of the range. That means the prior will have very little effect on the estimation when the true value lies in the defined range. As a matter of fact, our simulations in the paper show that there is very little bias in this case. Our prior also allows estimation outside the defined range, but in that case, its weight on the estimation becomes non negligible. We feel it is more appropriate to warn the user when the results significantly depend on the choice of the experimental design.

More precisely, let us examine what happens in the three cases mentioned by Dr Jager: the case where the no effect concentration NEC is very low (below the smallest non null concentration), and the cases where the dominant rate k_d is very low or very high. This discussion is based on many trials we did on simulated data sets, trials that can be easily performed thanks to the R scripts provided with our paper or the Morse package.

If the NEC is just below the smallest non null tested concentration, it will be estimated with a little bias using the Bayesian approach but outside the prior range with both approaches. If the NEC is too far below the smallest non null tested concentration, it will be very difficult to estimate, with any chosen approach. It could even render the background instantaneous mortality rate m_0 very difficult to estimate especially for data sets with no mortality in the control: it is then difficult to know if the mortality at low concentrations is due to natural mortality or to an effect of the contaminant. In this situation, maximum likelihood inference frequently produces very unrealistically low estimations of m_0 corresponding to average lifetime $(1/m_0)$ beyond millions of years. So, our choice in such cases is to alert the user to the difficulty in estimating parameters, as soon as the estimate is outside the prior range (as done in the Morse package).

Now let us consider the case where k_d is below the prior range defined from the design chosen, such that internal concentration only reaches 0.1% of external concentration at the end of the experiment. Similar survival curves will be obtained at every tested concentration, only governed by m_0. Presumably, none of the three other parameters can be estimated in such a case, whatever the approach. The case where k_d is high is more familiar to investigators and was already discussed for similar models in 2008 by Billoir et al.[3] Nevertheless, as soon as large values of k_d are interpreted cautiously, this problem is not really blocking: whatever the chosen approach it should not significantly affect the estimation of other parameters as the k_d value has no impact on the model above a certain value.

The core of our contribution is to show how the experimental design of a bioassay can be leveraged to provide a fully automated parameter inference in GUTS-SD models. Be it for maximum likelihood or Bayesian inference, distribution on parameter space must be defined (respectively to draw optimization starting points or to define a prior). To our knowledge, this technical difficulty is usually handled very empirically, which is not only a concern for the wide adoption of TKTD models, but also for the reproducibility of published results. In any case, while we can argue about the potential biases of each approach, controlled evaluations on simulated and real data remain the best way to settle the question, which is one more reason to promote the development of fully automated inference procedures for GUTS-like models. Ref 3.

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