Supplement: Umbrella model

The focus of this supplementary material is to explore, through two additional scenarios, MS and MA predictive performances when the true structural model is an unexpected dose-response shape (Umbrella) which cannot be approximated by the set of candidate models.

It is structure with the following subheadings: Materials and methods/ Results / Conclusion /; in which only the sections that differ from the manuscript were integrated.

Materials and methods

Model

The simulation model is identical to the one in the article, except for the dose-response relationship, which was assumed to be a quadratic function (also known as inverted u-shaped) in which higher doses are less effective than lower doses.

$$f\left(d_i, t_j, \Phi_i\right) = VA_{0,i} + \left(1 - e^{-k_{pr,i} \cdot t_j}\right) \cdot \left(\alpha_i \cdot d_i - \kappa \cdot d_i^2 - \beta_i \cdot VA_{0,i}\right)$$

Interindividual variability was assumed for the parameters VA_0, k_{pr}, β and α. Parameters follow a lognormal distribution except for α which follows a normal distribution.

The candidate models are not changed, hence do not include that model.

Simulation scenarios

Clinical trial simulations were used to compare MA and MS predictive performances in two different scenarios with less (supplementary Scenario A) or more (supplementary Scenario B) pronounced quadratic effect (see Figure 1S). The parameter values (Ψ^*) used to simulate the datasets are reported in Table IS. For each scenario, the simulated doses are 0, 150, 300 and 500 µg.

Figure 1S: Representation of the simulated drug effect as a function of the dose assuming either an Emax (green) or Umbrella (pink) dose response relationship. The curves represent the median and the colored area indicates the predictive interval between 20th and 80th percentiles.

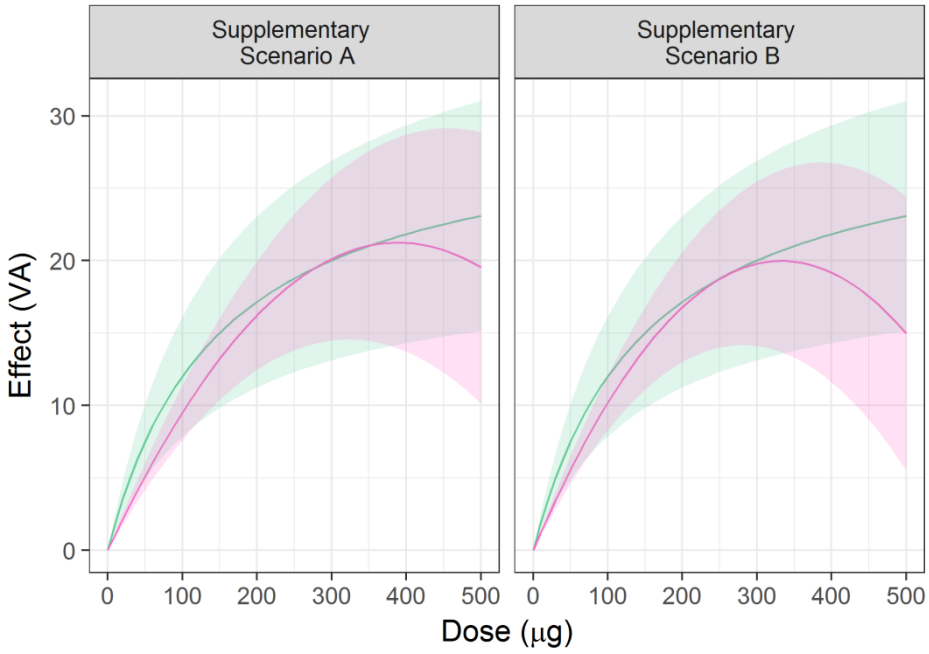


Table IS: Parameter values Ψ^* used to simulate the data assuming an Umbrella dose response model.

Parameter	$\boldsymbol{\mu}$	$\boldsymbol{\omega^2}$	$\boldsymbol{\sigma^2}$
$\boldsymbol{VA_0{}^*(let)}$	55	0.07	-
$\boldsymbol{k_{pr}{}^*\ (Day^{-1})}$	0.005	0.5	-
$\boldsymbol{\beta^*}$	0.2	1.0	-
$\boldsymbol{\alpha^*\ (let/Day)}$			
$Scenario\ A$	0.109	0.0005	-
$Scenario\ B$	0.120	0.0005	-
$\boldsymbol{\kappa^*\ (let/Day^2)}$			
$Scenario\ A$	0.00014	-	-
$Scenario\ B$	0.00018	-	-
$\boldsymbol{\sigma^{2^*}(let)}$	-	-	28

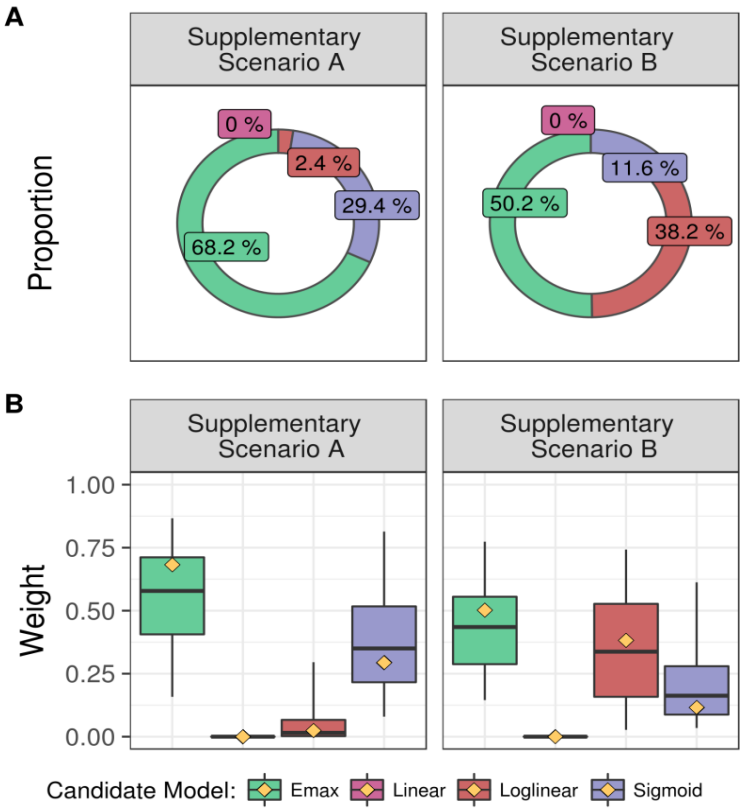
μ: Fixed effect
ω^2: Variance of the random effect
σ^2: Variance of the residual error
let: Letter

Results

Model selection and model averaging

Figure 2S represents the selected proportion and the distribution of estimated weights per candidate model as a function of the simulation scenario using AIC as the information criterion. In supplementary Scenario A, the true dose response relationship is relatively close to an Emax function. Therefore, the proportion and weights are notably higher for this candidate model. From supplementary Scenario B, patients with doses of 150 and 500 µg are subject to a similar drug effects suggesting a maximum of the effect already at the dose of 150 µg and increasing therefore the likelihood of the Loglinear candidate model.

Figure 2S: Representation of the selected proportions, MS (panel A), and distribution of the weights, MA (panel B), per candidate model and for each simulation scenarios using AIC as the information criterion. Yellow diamonds represent the selected proportions using MS.



Evaluation

Clinically relevant drug effect:

Table IIS reports the percentage of trials indicating to a clinically relevant effect (CRE) as a function of the scenario and the modeling approaches. In supplementary Scenario A, in most of the trials replicates, the modeling approaches correctly indicate a CRE. However, in supplementary Scenario B, where the true candidate model cannot be approximated by the set of candidate models, these percentages dropp from 95 to 60% for most of the modelling approaches except for the linear and Umbrella models (reference). Finally, in both simulation scenarios, the predictive performances of MA and MS are equivalent.

Table IIS: Percentage of trials indicating a clinically relevant effect at the 500 μg dose for each modeling approach and each simulation scenario using AIC as the information criterion.

	(%) **of trials indicating a clinically relevant effect**	
	Supplementary Scenario A	**Supplementary Scenario B**
Simulation values	100	100
Emax	94.4	60.8
Linear	99.2	90.6
Log-linear	68.8	46.8
Sigmoid	93.6	61.4
Model selection	94.4	58.0
Model averaging	93.0	59.0
Umbrella	*94.0*	*85.0*

Minimum effective dose:

The ability of the 6 modeling approaches to predict the true target dose, minimum effective dose (MED), is assessed via the RRMSE, the relative bias (Table IIIS) and a boxplot representation of the estimated MED (Figure 3S). Derived from the true model and the population parameters Ψ^*, MED^* is equal to 250 μg for both simulation scenarios.

When focusing on supplementary Scenario A, apart from Linear and Log-linear candidate models and despite a biased estimate of the target dose, all modeling approaches provide relatively good prediction performances. In supplementary Scenario B, for all modelling approaches except the reference (Umbrella), the RRMSE and relative bias are increased by

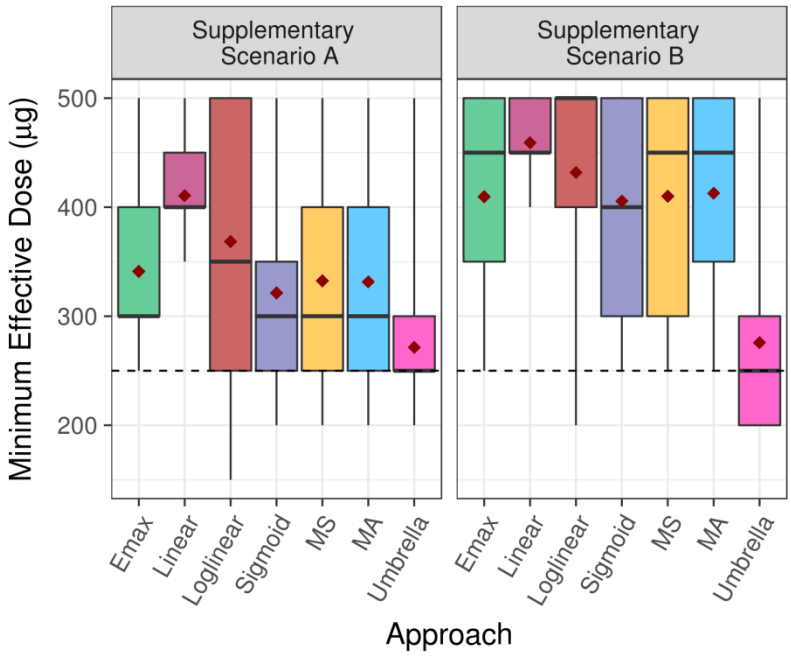
20% and 30%, respectively. Thus, regardless of the modeling approaches, the more pronounced is the inverted U-shape, the worse the predictive performances are. Finally, in accordance with the previous section, regardless of the simulation scenario, MS is equivalent to MA.

Table IIIS: Relative bias and Relative root mean squared error (RRMSE) in the predicted minimal effective dose for each modeling approach and each simulation scenario using AIC as the information criterion.

Approach	**Relative bias (%)**		**RRMSE** (%)	
	Supplementary Scenario A	**Supplementary Scenario B**	**Supplementary Scenario A**	**Supplementary Scenario B**
Emax	36.4	63.8	48.2	74.8
Linear	64.2	83.6	66.1	84.9
Log-linear	47.4	72.7	67.6	82.7
Sigmoid	38.6	62.2	43.6	73.9
Model selection	33.0	64.0	46.7	75.4
Model averaging	32.6	65.1	46.8	76.0
Umbrella	*8.6*	*10.3*	*29.5*	*41.1*

Figure 3S: Representation of the distribution of the predicted minimum effective dose for each modeling approach and each simulation scenario using AIC as the information criterion.

The dashed line represents the predicted MED using the true model and the true population parameters.

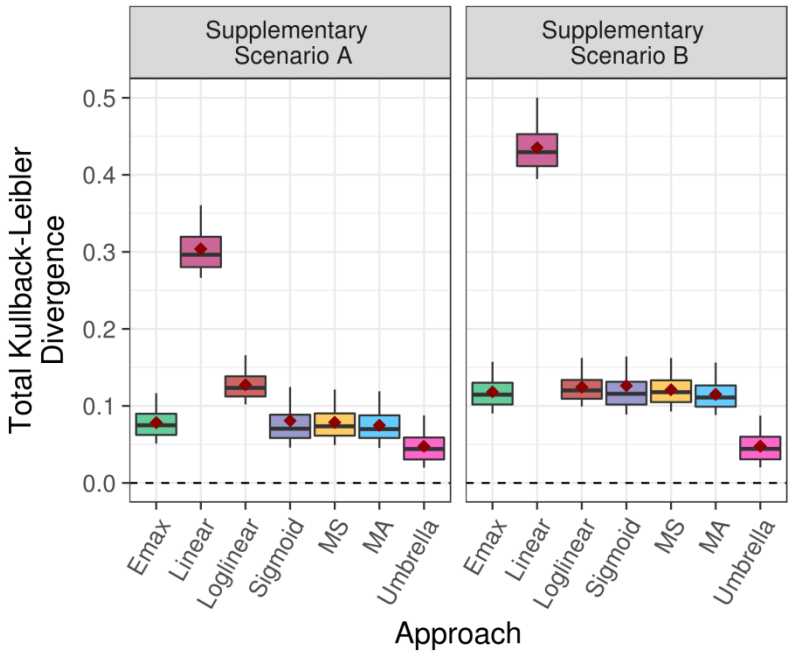


Kullback–Leibler divergence:

As can be seen in Figure 4S, the highest Kullblack-Leibler divergence (D_{KL}) values are associated to the Linear candidate model and the lowest to the Umbrella model. Moreover, KLd values are equivalent for the Emax, Sigmoid, MS and MA modeling approaches. Compared to supplementary Scenario A, apart from the Umbrella and Loglinear models, D_{KL} values are increased for all modeling approaches in supplementary Scenario B and become equivalent to those of the Log-linear model.

Figure 4S: Representation of the distribution of the total Kullback-Leibler divergence for each modeling approach and each simulation scenario using AIC as the information criterion. The

dashed line represents total Kullback-Leibler divergence calculated using the true model and the true population parameters.



Conclusion

These additional results highlights that, MS and MA have similar predictive performances when the true structural model is an unexpected dose-response shape that cannot be approximated by the set of candidate models.