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Model-based dose finding under model uncertainty using general parametric models

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Statistical methodology for the design and analysis of clinical Phase II dose response studies, with related software implementation, are well developed for the case of a normally distributed, homoscedastic response considered for a single timepoint in parallel group study designs. In practice, however, binary, count, or time-to-event endpoints are often used, typically measured repeatedly over time and sometimes in more complex settings like crossover study designs. In this paper we develop an overarching methodology to perform efficient multiple comparisons and modeling for dose finding, under uncertainty about the dose-response shape, using general parametric models. The framework described here is quite general and covers dose finding using generalized non-linear models, linear and non-linear mixed effects models, Cox proportional hazards (PH) models, etc. In addition to the core framework, we also develop a general purpose methodology to fit dose response data in a computationally and statistically efficient way. Several examples, using a variety of different statistical models, illustrate the breadth of applicability of the results. For the analyses we developed the R add-on package DoseFinding, which provides a convenient interface to the general approach adopted here.

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