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Adaptive designs for dose finding clinical trials with time-to-event outcomes.

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Background and Objectives

Many clinical trials use time-to-event (TTE) outcomes as primary measures of efficacy or safety. For instance, in dose finding cancer trials the goals may be to estimate a dose-response relationship and to identify a dose level that yields the longest progression-free survival for testing in subsequent studies. Efficient designs for such trials are needed but finding such designs in practice may be complicated due to uncertainty about the model for event times, delayed responses and censored observations. In this work we develop optimal and adaptive designs for dose finding clinical trials with TTE outcomes .

Methods and Materials

We consider an accelerated failure time (AFT) model [1] assuming a quadratic dose-response model for log-transformed TTE outcomes with a Weibull distribution that are subject to right censoring with a fixed censoring time. The optimal designs for the quadratic model with normally distributed error term are considered in [2] for *D*-optimality and in [3] for *c*-optimality but, to our knowledge, the AFT model with censored data has not been considered previously. The model has the following form:

$$\log T = \beta_0 + \beta_1 x + \beta_2 x^2 + b\varepsilon,$$

$$t = \min(T, \tau) \text{ — observed time,}$$

where τ is censoring time, x is dose, ε has a p.d.f. $f(w) = exp(w\text{-}exp(w))$ with $\mathbf{E}(\varepsilon) = -\gamma = -0.577216$ and $\mathbf{Var}(\varepsilon) = \pi^2/6$.

We obtain the *D*-optimal design for the most precise estimation of the dose-response curve applying the general equivalence theorem [4], while including fixed right censoring [5]. The design depends on the parameters of the model which are unknown at the beginning of the experiment. As a consequence, for implementing optimal designs in practice, we propose a multi-stage adaptive design. To resolve this issue we start from uniform design (three-points design with equal allocations, which is *D*-optimal when there is no censoring). Some initial number of patients are randomised with such a design. When these subjects respond, we do *Maximum Likelihood Estimation* of the model parameters and then define a new design that depends on the parameters' MLE. Then we either can use this design till the last subject (two-stage design) or reestimate it multiple times (multi-stage design). In this work we apply a 3-stage adaptive design to simulate 4 different scenarios of dose-response relationships (4 sets of model parameters) in 1000 simulations of a trial with 45 subjects divided into three cohorts of 15 subjects per cohort, and we do adaptation after every cohort. Relative *D*-efficiencies of the *D*-optimal and adaptive *D*-optimal designs comparing to the uniform design are studied:

$$D_{eff} = |\text{FIM}(\xi^*, \theta)|^{1/k} / |\text{FIM}(\xi_U, \theta)|^{1/k},$$

where $\theta = (\beta_0, \beta_1, \beta_2, b)$ — vector of model parameters, ξ_U — uniform design, ξ^* — optimal design, k — number of model parameters.

Results

Table 1 shows that when data is censored the *D*-optimal design is shifted from the uniform. *D*-optimal designs approach the uniform design when censoring time increases. The proposed adaptive optimal designs generate the allocation of patients to the most informative dose levels and achieve higher efficiency in estimating the parameters of interest compared to the popular equal allocation designs in the presence of censoring. The adaptive designs perform nearly as well as the optimal designs. In Fig. 1 we compare uniform, *D*-optimal and adaptive D-optimal designs simulated 1000 times for the one of the scenarios. The uniform design is clearly inferior, while the adaptive and d-optimal designs are similar. Results of 1000 simulations of adaptive D-optimal designs for the rest of scenarios are depicted in Fig. 2 and show good properties. Fig. 3. shows that accuracy of the estimation depends on how much censored data we have. Numerical simulation shows that the estimation is poor for all designs when <45% of patients respond.

	Scenario #1 θ = (1.5, 4.0, -2.0, 0.5)		Scenario #2 θ = (0.5, 2.0, 2.0, 0.5)		Scenario #3 θ = (0.5, 2.0, -2.0, 0.5)		Scenario #4 θ = (1.5, -2.0, 2.0, 0.5)	
τ	Design	D_{eff}	Design	D_{eff}	Design	D_{eff}	Design	D_{eff}
5	x = (-1, -0.17, 1) w = (0.38, 0.37, 0.25)	1.16/1.15	x = (-1, -0.32, 0.37) w = (0.35, 0.35, 0.30)	2.34/2.32	x = (-0.37, 0.32, 1) w = (0.30, 0.35, 0.35)	2.34/2.32	x = (-1, 0.23, 1) w = (0.30, 0.35, 0.35)	1.10/1.10
10	x = (-1, -0.04, 1) w = (0.38, 0.37, 0.25)	1.02/1.01	x = (-1, -0.25, 0.5) w = (0.35, 0.35, 0.30)	2.04/1.99	x = (-0.5, 0.25, 1) w = (0.30, 0.35, 0.35)	2.04/2.00	x = (-1, 0.4, 1) w = (0.32, 0.34, 0.34)	1.01/1.00
20	x = (-1, 0, 1) w = (0.38, 0.37, 0.25)	1.01/1.01	x = (-1, -0.18, 0.64) w = (0.34, 0.34, 0.32)	1.67/1.65	x = (-0.64, 0.18, 1) w = (0.32, 0.34, 0.32)	1.67/1.66	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1
40	x = (-1, 0, 1) w = (0.37, 0.37, 0.26)	1.01/1.00	x = (-1, -0.12, 0.77) w = (0.34, 0.34, 0.32)	1.35/1.34	x = (-0.77, 0.12, 1) w = (0.32, 0.34, 0.34)	1.35/1.34	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1
80	x = (-1, 0, 1) w = (0.35, 0.34, 0.31)	1.01/1.00	x = (-1, -0.05, 0.89) w = (0.34, 0.34, 0.32)	1.10/1.10	x = (-0.89, 0.05, 1) w = (0.32, 0.34, 0.34)	1.10/1.10	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1
∞	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1	x = (-1, 0, 1) w = (0.33, 0.33, 0.33)	1/1

Table 1. D-optimal designs of four scenarios and relative D-efficiency of D-optmal design/median of relative D-efficiencies of adaptive D-optimal design. x is a vector of optimal design points, and w is a vector of optimal proportions.

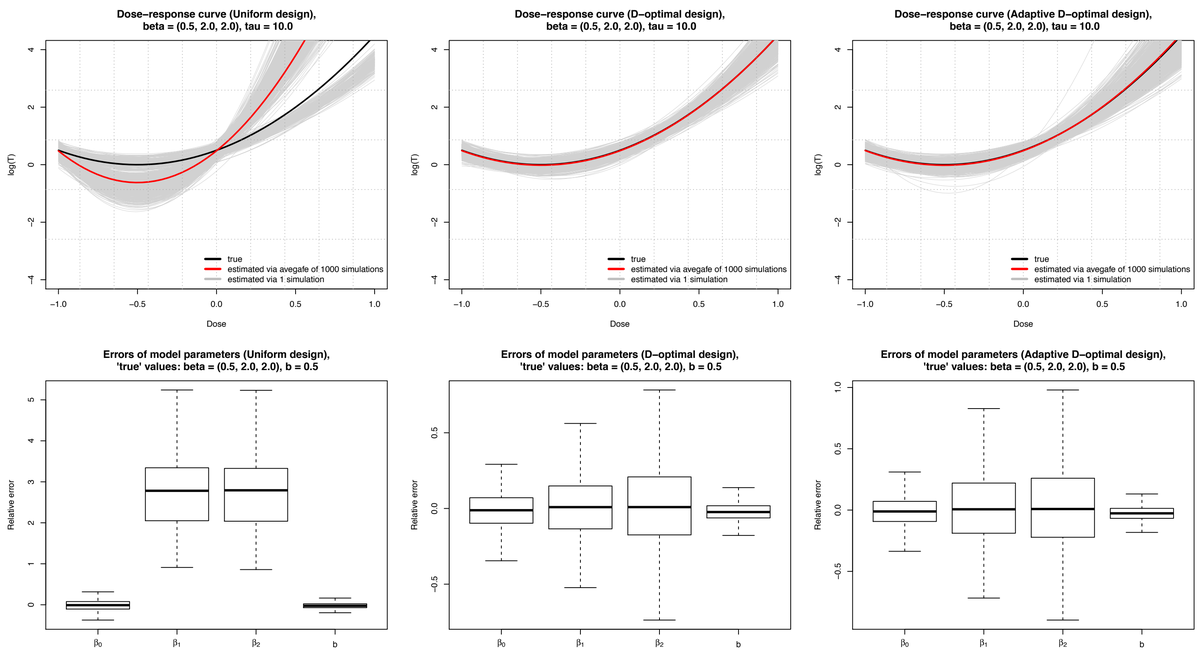

Fig. 1. Dose-response curves and boxplots of relative errors of model parameters for simulated uniform design, d-optimal design and adaptive d-optimal design for beta = (0.5, 2, 2), and tau = 10

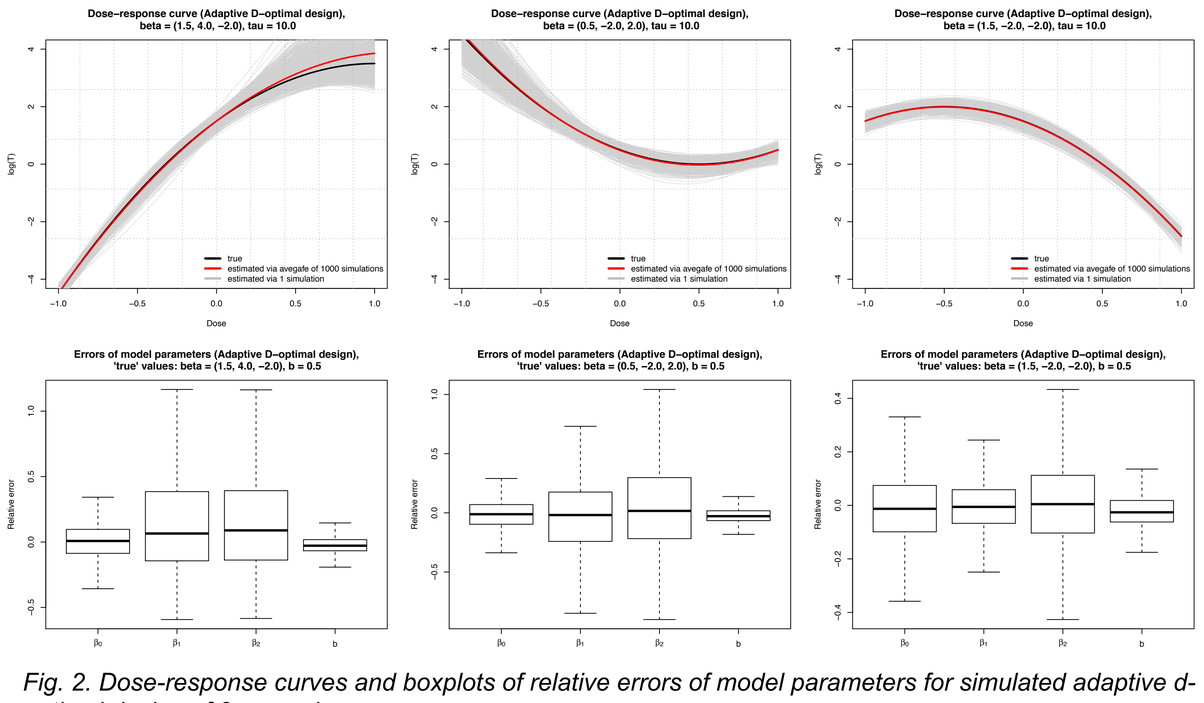

Fig. 2. Dose-response curves and boxplots of relative errors of model parameters for simulated adaptive d-optimal design of 3 scenarios

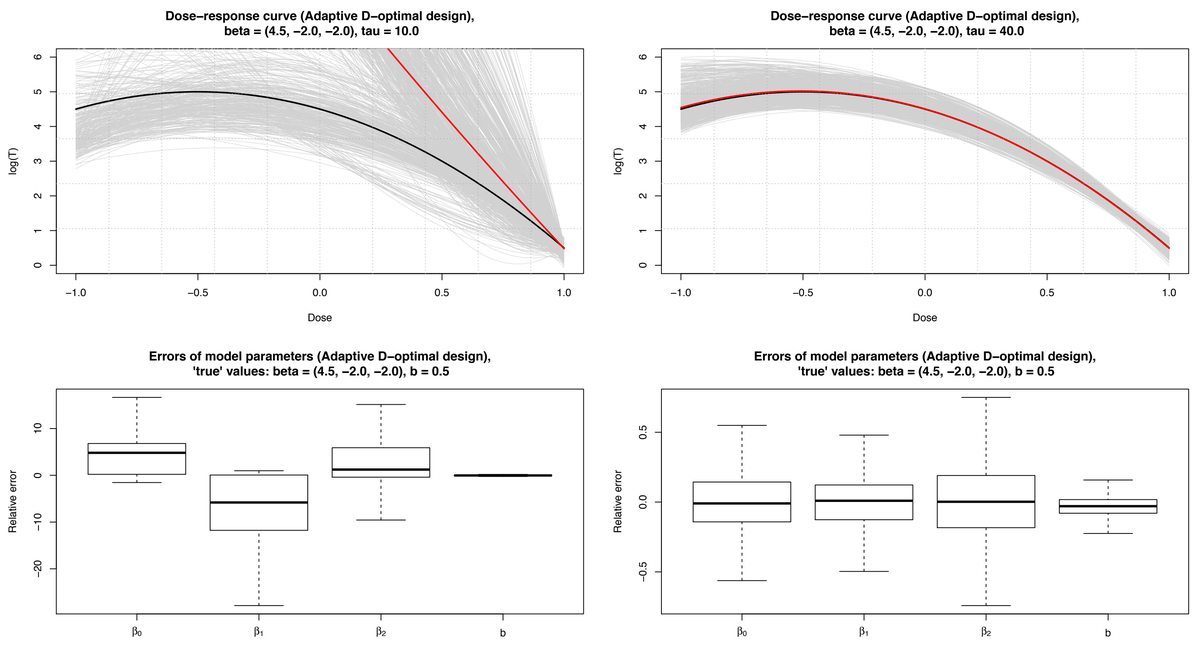

Fig. 3. Estimation when data is too censored (left) and >45% of subjects respond (right).

Conclusions

The proposed designs can improve efficiency of clinical trials with time-to-event outcomes by reasonable allocation of study patients to dose levels that are most informative for the given study objectives. Adaptive designs can be used to approximate the optimal designs; however, if too much data is censored the estimation of the model parameters is inefficient. Further research on the robustness of the proposed designs to model misspecifications and uncertainties around model parameters is ongoing. In addition, dose-concentration-response TTE models will be considered.

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