

Title: A Statistical Software Approach to Bayesian Response-Adaptive Design for Dose Finding

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Objectives

There are clear advantages of response adaptive design in identifying dose(s) from early phase clinical trials to carry forward in to later phases. These include significant productivity / timeline gains and avoidance of later stage failure due to incorrect dose selection in early stage trials.

Methods

We describe a general statistical software framework for Bayesian response-adaptive design dose finding, comprising 3 core objects/methods namely

- inner model(s) objects for toxicity and efficacy dose-response;
- outer adaptation procedures;
- simulation model objects for anticipated responses.

Inner toxicity and efficacy models are typically fairly simple parameterizations given the usual small data set sizes in early phase trials. Examples include Thall and Russell (1998) and O'Quigley (2001) with the logit(response) being linear in dose, and Gaussian priors on the dose-response parameters. Outer adaptation procedures can comprise many different clinical business rules such as those in Thall and Cook (2004) and Thall and Russell (1998) e.g. drop a dose if 90% of the posterior efficacy probability distribution is less than 0.5.

Simulation dose-response models that may be readily envisaged by clinical researchers include various Emax models, quadratic, logistic and linear models e.g. as considered by Bretz et al. (2006).

From an end-user perspective, the workflow sequence is as follows:

1. Define a set of candidate designs
 - set cohort size and #cohorts
 - define toxicity and efficacy probability thresholds
 - set up the outer procedure for adapting the trial to the observed toxicity and efficacy probability posterior distributions
 - set up the inner models for toxicity and efficacy
2. Simulate response data from a variety of potential response models e.g. Emax, quadratic etc.
3. Fit the toxicity and efficacy models in the designs to the simulated data
 - obtain the samples and return an object of class posterior
 - convert posterior parameter estimates to probabilities of toxicity and efficacy
 - use the posterior samples for parameter inference
4. Summarize the model results graphically for each design and simulation combination
5. Compare candidate designs across response simulation models and decide on a design for the trial e.g. in terms of robustness to simulated response models.

Results

An example design by simulation combination is provided in Figure 1 below. This example uses the adaptation method of Thall and Russell (1998) with efficacy rule of dropping a dose if 90% of the posterior efficacy probability distribution is less than 0.5; and toxicity rule of dropping a dose if 90% of the posterior efficacy

probability distribution is greater than 0.1. In Figure 1, the dose that survives the efficacy and toxicity thresholds is 5.0 ug.

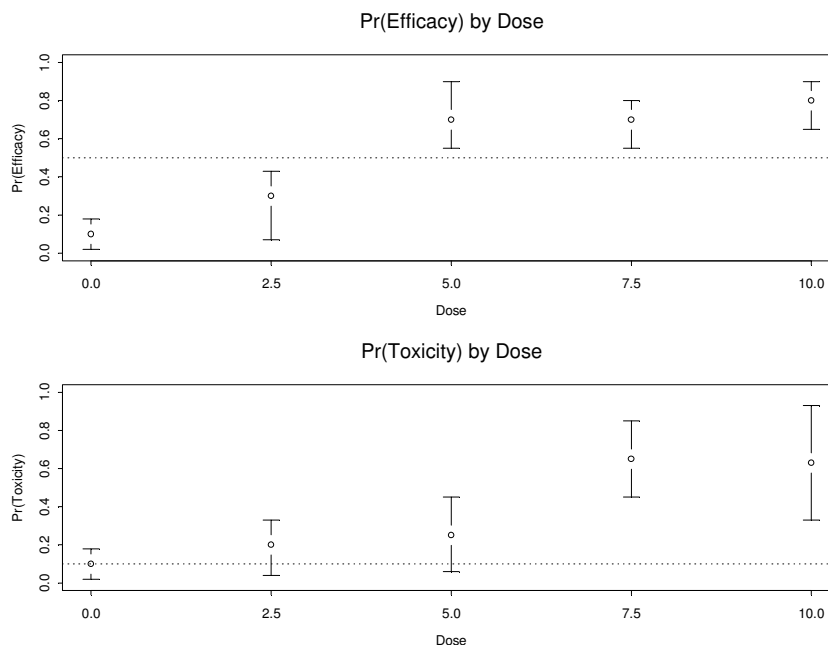


Figure 1. Posterior Efficacy and Toxicity distributions by dose for a trial design using the adaptation method of Thall and Russell (1998).

Conclusion

Our statistical software framework encompasses many Bayesian response-adaptive design flavors and a variety of anticipated outcome responses. This framework and software enables comparisons of candidate designs across outcome response simulation scenarios, and careful choice of designs for rapid and accurate dose finding.

References:

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