Public Abstract

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Title:TWO STAGE ADAPTIVE OPTIMAL DESIGN WITH APPLICATIONS TO DOSE-FINDING CLINICAL TRIALS

In adaptive optimal designs, each stage uses an estimate of the optimal design derived using cumulative data from all prior stages. This dependency on prior stages affects the properties of maximum likelihood estimates. To illuminate the effects, we assume for simplicity a nonlinear regression model with normal errors and that there are only two stages with a fixed first stage design point. Fisher's information is motivated for adaptive designs by deriving the Cramer-Rao lower bound for such experiments. Then the usefulness of Fisher's information is shown from both a design and analysis perspective. From a design perspective Fisher's information is used in a procedure that is developed to select the proportion of observations assigned to the first stage. From an analysis perspective the information measure most commonly used in the optimal design literature is compared with Fisher's information. Several estimates of information are compared and a procedure for selecting the proportion of subjects allocated to stage 1 is recommended.

Asymptotics for regular models with fixed number of stages are typically motivated by assuming the sample size of each stage goes to infinity as the overall sample size goes to infinity. However, it is not uncommon for a small pilot study of fixed size to be followed by a much larger experiment. We show that the distribution of the maximum likelihood estimates converges to a scale mixture family of normal random variables.