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Abstract

Finding a compromise between information and regret in clinical trials

Joint work with Luc Pronzato. We consider the treatment allocation problem in the setting of comparative clinical trials in which patients arrive sequentially. For this type of trials, response adaptive and/or covariate-adjusted designs can be used to construct the sequence of allocation probabilities to satisfy the study objectives. The most common target for allocation designs is a maximum precision of the estimation of treatment's model parameters, e.g. in some generalized linear models. This can be achieved through the maximization of an information criterion, a concave function of the Fisher information matrix. But ethical clinical study should also reduce the number of patients who receive inferior treatments. We propose a compromise criterion defining a trade-off between information and ethics objectives through the convex combination of an information criterion and a regret function. Under mild conditions, we show the existence and give an explicit construction of the locally optimal (maximizing the compromise criterion) allocation measure on the space of covariates. This allocation measure is then used in an oracle covariate-adaptive allocation procedure. However the construction of the optimal allocation measure is complicated and requires an a prioriknowledge of covariates distribution. We show how these difficulties can be avoided by using a covariate-adaptive allocation rule based on empirical allocation measures, which we show to converge to the optimal measure. To deal with the unknown model parameters, we propose a response-adaptive allocation rule that uses current Maximum Likelihood estimates of model parameters. Comparison of our allocation designs with recently proposed adaptive designs from literature will be given.