

**Title.** Treatment versus experimentation dilemma in dose-finding studies - consistency considerations.

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**Abstract.** One central aim of phase I studies is to determine the maximum tolerated dose (MTD) of a given drug. This is particularly important in severe diseases, typically cancer, where strong and even lethal side effects are present. This is usually done by a sequential experiment for reasons of efficiency and for ethical reasons. We use the following notation: let  $x$  be a dose of a certain drug and  $y|x$  be the (binary) response at dose  $x$ ;  $y = 1, y = 0$  represents a toxic or non-toxic response accordingly. The dose space is denoted by  $D := \{d_1 < d_2 < \dots < d_K\}$ . Let  $m(d_j)$  be the probability of toxic response at dose  $d_j$ , i.e.,  $y|(x = d_j) \sim \text{Bernoulli}(m(d_j))$ .  $m$  is some unknown increasing function. This is a non-parametric model since no assumptions are made on  $m$  beside that it is an increasing function. We are interested in finding the dose  $d_{j^*}$  which is the closest dose in  $D$  that corresponds to a certain known response level  $m^*$ ; that is  $j^* = \arg \min |m(d_j) - m^*|$ ;  $d_{j^*}$  is the MTD.

In phase I studies there are two different purposes: **A.** To treat each subject with the (estimated) MTD. **B.** To have a good estimate for the MTD (at least for large enough  $n$ ). The choice between the two is known as the treatment versus experimentation dilemma (see, e.g, Bartroff and Lai, 2009). In the case of continuous response modeled by a simple linear regression model (and assuming also that the dose space is continuous), Lai and Robbins (1982) showed that this dilemma can be resolved asymptotically by assigning to each subject the estimated MTD based on truncated version of the least square estimates. However, in our context we show that this cannot be done. Specifically, we show that a design that assigns for each subject the estimated MTD (no matter what the estimation method is) cannot be consistent for all  $m$ . By consistency we mean that the estimate of the MTD is the true MTD for large enough experiment.

We describe consistent designs with the following properties: **A.** If  $y^* \in (m(d_{j'}), m(d_{j'+1}))$  then  $x_n \in \{d_{j'}, d_{j'+1}\}$  for large enough  $n$ . **B.** The estimates for the MTD are strongly consistent. Property 1 is a relaxation of the ethical requirement to treat the  $n$ 'th subject with the estimated MTD for large enough  $n$ ; instead it is required that the  $n$ 'th subject will be assigned with one of the two closest doses to  $m^{-1}(y^*)$ .

We also describe a specific design with the following properties: **A.**  $P(x_n = d_{j^*}) \rightarrow 1$ . **B.** The estimates for the MTD are strongly consistent. For this kind of design the ethical requirement is that the probability of treating the  $n$ 'th subject the true MTD tends to 1 as  $n$  grows.

## References

- Bartroff J., Lai T.L. (2009). Approximate dynamic programming and its applications to the design of phase I cancer trials, to appear in *Statistical Science*.
- Lai T.L., Robbins H. (1982), Iterated least squares in multiperiod control, *Advances in Applied Mathematics*, **3** , 50 – 73.