

# Bayesian Adaptive Trials

## *Disegni Bayesiani Adattivi*

Lorenzo Trippa

**Abstract** Adaptive randomization schemes are designed for obtaining a more desirable assignment of competing treatments to the overall group of patients enrolled in the study compared to balanced designs. I discuss major tools in this area of research, including (i) the development of testing procedures and decision rules for adaptive phase II trials, (ii) the comparison of designs with different levels of complexity to provide recommendations about their relative advantages and disadvantages and (iii) subgroup-based adaptive designs that simultaneously search for patients subgroups and adaptively allocate patients to the best subgroup-specific treatments during the course of the trial.

*Gli schemi di randomizzazione adattivi sono sviluppati per ottenere, in confronto ai disegni bilanciati, migliori assegnazioni di trattamento nel gruppo di pazienti partecipanti alla prova clinica. Discuto i principali strumenti in questa area di ricerca, includendo (i) regole di decisione che producono raccomandazioni al termine dello studio, (ii) confronti con disegni alternativi per prove cliniche e (iii) disegni adattivi per lo studio di trattamenti in un contesto di medicina personalizzata.*

**Key words:** Adaptive Clinical Trial

## 1 Introduction

Adaptive clinical trials have been proved attractive for testing novel anticancer targeted therapies. These treatments, due to their mechanisms of action, can have highly variable effects across tumor profiles. Biomarkers become essential for testing novel treatments, and delineating groups of patients sensitive to the targeted therapy. Bayesian adaptive trials, in this context, can classify the enrolled patients

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with biomarkers-defined groups, and predict during the course of the trial, which tumor profiles are likely to be responsive to a targeted therapy [4, 2, 6, 1, 13]. Multi arm adaptive trials use Bayesian predictions at the patient level, for calibrating the randomization probabilities [5, 10, 11, 12]. These designs increase during the trial the probability that patients benefit of a positive treatment effect.

I briefly summarizes major goals in this area. First, the development of testing procedures and -go / no go- decision rules for adaptive phase II trials. These are decision rules that indicate if a new treatment should be further studied in a confirmatory phase III trial or not. The phase III trial can be limited to a subset of biomarkers-defined groups. The approach can combine Bayesian modeling with final decision rules having frequentist interpretations, with the control of type I errors at a desired level. Second, it is necessary to compare designs with different levels of complexity to provide recommendations about their relative advantages and disadvantages. Third, subgroup-based adaptive designs simultaneously search for prognostic subgroups and allocate patients adaptively to the best subgroup-specific treatments throughout the course of the trial. The main features of these designs are the inclusion of continuous reclassification of patient subgroups based on a bayesian models and the adaptive allocation of patients to the best treatment arm based on posterior predictive probabilities.

The majority of new anticancer drugs that need to be tested target specific genetic events. New agents and combinations with systemic therapies are currently investigated, and heterogeneous treatment effects across biomarkers-defined patients subgroups are hypothesized based on molecular targets and preclinical studies in tumor models. The standard approaches for testing systemic treatments present several limitations in the setting of personalized medicine. Multi-arm adaptive clinical trial designs have been proposed for new targeted agents [3]. Pairing genetic traits with targeted treatment options is a main focus. Patients subpopulations are typically defined by classifying patients tumors based on genomic characteristics. Subpopulations are defined because of the likely event of treatments effects variations across tumor profiles. The rationale for testing several agents in a single trial is the opportunity of higher efficiency levels compared to two arms comparative trials. Bayesian randomization has been used for testing several treatments in complex trials on heterogeneous populations [8]. Major goals of outcome adaptive randomization are (i) to randomize patients with increasing probabilities to effective arms, by leveraging on the available data, and (ii) efficiency, i.e. the balance between uncertainty on primary findings and the amount of resources to perform the study. Biomarkers, such as cancer driver mutations, can guide patients' randomization. Response adaptive trials are designed to sequentially learn treatments performances within biomarkers-defined subgroups. Recent applications suggest that outcome adaptive approaches can accelerate drug development processes.

## 2 Bayesian Adaptive Trials

Adaptive randomization schemes are designed for obtaining a more desirable assignment of competing treatments to the overall group of patients enrolled in the study compared to balanced designs. Several contributions consider two arm comparative trials and provide motivations for adaptively tuning the randomization probabilities during the study on the basis of the available data. Both frequentist and Bayes methods for sequentially varying the probability that the enrolled patient receives a specific treatment have been studied. In the two arm setting a relevant motivation for the adaptive approach is ethical; these methodologies, when treatment effects differ substantially, assign (at least on average) a higher proportion of individuals to the superior treatment than balanced randomized trials. Ethical motivations, at least in some cases, make adaptive randomization preferable than balanced allocation.

Response adaptive randomization can be defined as the application of a map, used each time a patient is enrolled in the trial, transforming available data into suitable randomization probabilities. The frequentist approach is direct, in that, intuitive and heuristic maps of the data have been proposed and assessed using both simulation studies and asymptotic theoretical results describing the performances of the adaptive design under the assumption of a large sample size [7]. In contrast Bayesian randomization strategies are indirect and model based. Bayesian modeling allows meaningful prediction during the trial. It is typically used to answer fundamental questions such as: (i) *"What is the probability that treatment A, conditionally on the data, has a higher efficacy than the control therapy?"*, (ii) *"What is the probability, conditionally on design, protocol and available data that, at completion of the trial, there will be statistically significant evidence that treatment A outperform the control therapy?"* (iii) *"What is the predicted proportion, conditionally on protocol and available data, of enrolled patient receiving a non inferior treatment?"* These questions can be answered by updating a probability model describing the uncertainty, when the trial start enrolling the 1st patient, over relevant unknown quantities such as median survival times for each arm. The model is formalized as a probability distribution  $p$  and it is updated using Bayes formula. Here, for example, we mention the application of the formula for obtaining probabilistic statements, given the data, over two treatment effects  $(\theta_A, \theta_B)$  assuming a binary outcome, say long vs short survival. In this case we only need a prior for the unknown quantities  $\theta_A = (\text{efficacy of treatment A})$  and  $\theta_B$ , one possible choice is to have  $\theta_A$  and  $\theta_B$  a priori independent and uniformly distributed.

Mainstream Bayesian adaptive strategies are indirect, meaning that they sequentially map probabilistic statements obtained using the Bayesian model into randomization probabilities. In the above example the updated model  $p(\theta_A, \theta_B | \text{available DATA})$  can be used for specifying the probability  $\pi_A$  that a new patient is randomized to treatment A. Note that  $\pi_A$  varies during the trial. Such maps can easily take into account also other elements such as the number of individuals already enrolled and planned overall sample size. The choice of the Bayesian model is fundamental; key guidelines for model choice are (i) simplicity and interpretability of the model, (ii)

low sensitivity of posterior distributions to prior parametrization and (iii) robustness of posterior inference under reasonable deviations from model assumptions, such as proportional hazards. It is also of primary importance the choice of the map transforming probabilistic statements into randomization probabilities; we adopted a mainstream approach in the literature to our setting and performed extensive simulation studies for tuning the adaptive assignment.

## 2.1 Example

We consider a  $k$  arm trial with  $k = 0$  corresponding to the control arm. We use  $F_k$  for denoting the unknown survival probabilities and assume a proportional hazards structure, meaning that, given unknown positive parameters  $\theta = (\theta_1, \theta_2, \theta_3)$ , the equalities  $F_k(t) = [F_0(t)]^{\theta_k}$  hold, for every  $t \geq 0$  and  $k = 1, 2, 3$ . We use identical symmetric distributions with null mean for the unknown quantities  $\log(\theta_1)$ ,  $\log(\theta_2)$  and  $\log(\theta_3)$ ; this choice has a clear interpretation: we assign identical prior probabilities to the scenarios that treatment  $k$  has a positive or negative effect compared to the control regimen.

As detailed in [9] one can perform semi-parametric Bayesian analyses and obtain proper posterior distributions for the relative hazards  $(\theta_1, \theta_2, \theta_3)$  without specifying a prior model for the baseline function  $F_0$ . Accordingly, we construct the adaptive assignment algorithm starting from the updating equation

$$p(\theta \text{ conditionally on DATA}) \propto p(\theta \text{ a priori}) \times \text{Partial-Likelihood}(\theta, \text{DATA}).$$

In the above expression we have the partial-likelihood routinely used for performing inference under proportional hazards model. We consider time varying randomization probabilities

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$$\pi_i^k \propto \frac{p(\theta_k > 1 \text{ conditionally on available DATA})^{\eta(i)}}{\sum_{k=1}^3 p(\theta_k > 1 \text{ conditionally on available DATA})^{\eta(i)}} \quad \text{if } k = 1, 2, 3, \text{ and}$$

$$\pi_i^0 \propto 1/3 \times \exp\left(\max_{k=1,2,3} [\# \text{ of patients randomized to arm } k]\right)^{\eta(i)} \times$$

$$\exp(-[\text{\# of patients randomized to arm 0}])^{\eta(i)}.$$

The above two expressions have clear interpretation. The first one shows that for any choice of the tuning parameters  $\gamma(i) > 0$  the algorithm assigns with higher probabilities patients to those experimental arms  $k = 1, 2, 3$  for which there is evidence of a positive treatment effect  $\theta_k < 1$ . Natural candidates for the tuning parameters  $\gamma(i)$  are non decreasing functions with nearly null values during the initial stage of the trial (i.e.  $\gamma(1) \approx 0$ ). The second expression aims at approximately matching the number of patients assigned to the control treatment and the number of individuals on the experimental arm that has been assigned more frequently. In our study the choice of the parameters  $\eta(i) > 0$  appears of little importance. Values approximately equal to 0.25 of the  $\eta$  function during the final stage of the trial suffices to obtain the desired balance without making treatment assignment highly predictable.

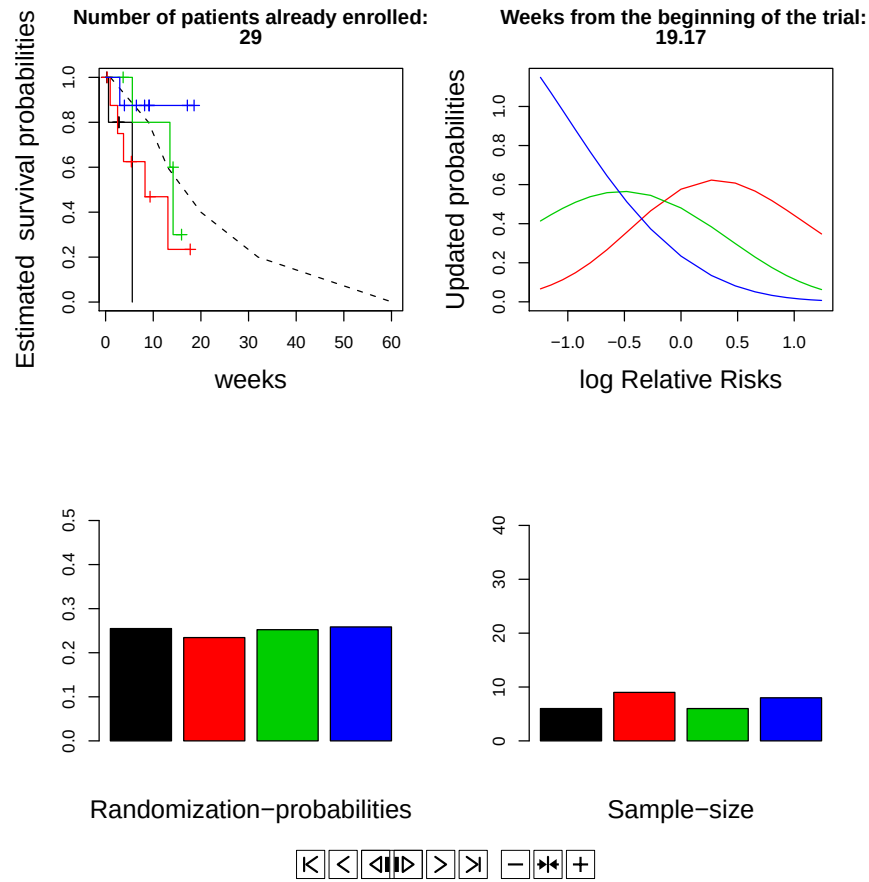
Figure 1 consists in 4 dynamic representations; by starting the animation we can observe a sequence of photograms representative of the trial at different stages. Each photogram corresponds to the instant an enrolled patient get randomized. The first panel represents of the available data by mean of four Kaplan-Meier curves. The second shows the updated distributions of the log-relative-hazards ( $\log(\theta_k)$ ,  $k = 1, 2, 3$ ). The third provides the randomization probabilities. Finally, the fourth shows the number of patients already assigned to each arm.

The need for an accurate choice of the tuning parameters  $\gamma(i)$  becomes evident by considering two extreme cases. If  $\gamma(i) \approx 0$  for  $i = 1, \dots, N$ , trivially the design becomes similar to a balanced randomized trial, loosing the ability of increasing the randomization probabilities for regimens that appears, with substantial evidence, to have a positive effect. On the opposite extreme, with excessive values for  $\gamma(i)$ , a handful of poor responses on an experimental arm with positive effect can be translated into nearly null randomization probabilities during the rest of the trial. That is, the trial operating characteristics depends on  $\gamma(i)$ .

The investigator can choose the tuning parameters by exploring the operating characteristics corresponding to alternative  $\gamma$  functions. The approach can be summarized as follows: (i) we select realistic scenarios including accrual rate and  $(F_k; k = 1, 2, 3)$ , (ii) considere plausible classes such as  $\gamma(i) = a \times (i/N)^b$  or  $\gamma(i) = a \times \mathcal{I}(i > b)$ , where  $a$  and  $b$  are positive constants and  $\mathcal{I}(i > b)$  is equal to one if  $i > b$  and zero otherwise, (iii) specified a grid of possible values for  $(a, b)$  and (iv) computed, by iteratively simulating trials, operating characteristics of interest corresponding to combinations of scenarios and  $\gamma$  functions.

### 3 A Retrospective Simulation Study

In [11] we considered historical data from glioblastoma trials assessing four alternative regimes. We then used as simulation sampling model a partial representation of the data by means of Kaplan Meir estimators, one for each treatment, truncated at 70 weeks. The approach allowed for (i) obtaining hypothetical identical survival



**Fig. 1** Adaptive randomization.

functions for the control therapy and non superior treatments by pooling together the survival data into a single Kaplan Meier curve or (ii) tuning positive treatment effects. This produces plausible scenarios for a specific clinical context. After setting these scenario we compare the Bayesian adaptive approach with the multi-arm balanced randomization scheme, with four arms: the control regimen and three experimental therapies. Our comparison considers also the hypothesis of three separate two-arms balanced comparative trials for assessing three novel therapies.

The main conclusions of this retrospective study contrasts the efficiency of multi armed adaptive trials. Moreover Bayesian adaptive trial design for patients with glioblastoma would result in trials with fewer overall patients with no loss in statistical power and in more patients being randomly assigned to effective treatment arms.

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