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# **Adaptive Designs for Sequential Treatment Allocation**

**Alessandro Baldi Antognini  
Alessandra Giovagnoli**



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# **Adaptive Designs for Sequential Treatment Allocation**

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*This book is dedicated to all those teachers and colleagues  
who have made us love and respect mathematics.*





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## Preface

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This book addresses the issue of designing experiments for comparing two or more treatments, when the experiment is sequential and the experimenter wishes to make use of the information accrued along the way. This type of experimental design is called *adaptive*. The aim of the book is reviewing and reorganizing the existing results of adaptive design theory, with particular attention to its mathematical foundation. It is intended primarily as a research book. Our approach is essentially theoretical, highlighting the mathematical difficulties and the statistical properties of adaptive designs as regards statistical inference following the experiment. We feel that this approach is needed, since the choice of an experimental design cannot be made without a full understanding of its properties, and we hope that this book will complement part of the present day literature in which a large number of authors base their conclusions on simulations. Simulations are generally very useful, but not always sufficiently convincing, and in some cases they may be plainly misleading. Ours is a book mainly devoted to general results, so it does not address problems related only to particular applications. Specifically, it is *not* a book on clinical trials, although a large number of the designs we present are clearly inspired by clinical and pharmaceutical research, and the vast bibliography dedicated to this field. These designs are discussed, in particular, in Atkinson and Biswas' survey *Randomized Response-Adaptive Designs in Clinical Trials*, 2014; our motivations are different and we have chosen to dwell on general aspects more than on individual trials, so there is little overlap, and we think of our book as a complement to theirs. This book follows the lead of two fundamental works by W. F. Rosenberger and his coauthors (Hu and Rosenberger, *The Theory of Response-Adaptive Randomization in Clinical Trials*, 2006, and Rosenberger and Lachin, *Randomization in Clinical Trials: Theory and Practice*, 2002), to whom we are deeply indebted. We have updated several results and included new topics.

The first chapter introduces the terminology and the statistical models most commonly used in comparative experiments. We present target allocations of the treatments motivated by inferential considerations, and give new conditions for the convergence of a sequential experiment to a given target. A discussion of asymptotic inference plays a central role in the chapter. We also introduce a unifying definition (*Markovian Designs*) to describe a large class of adaptive designs that share interesting properties. We emphasize the role of randomization throughout, as an important tool to avoid several types of bias. The randomized adaptive designs that we present in the remaining chapters are grouped mainly according to methods of construction. In Chapter 2 we illustrate designs whose assignment rule takes into account past treatment allocations only, namely the renowned biased coins and some urn ones. Then

in Chapter 3 there come designs that make use of past data, too: sequential maximum likelihood designs and doubly-adaptive designs, with a further section on the topic of up-and-down experiments. In Chapters 4 and 5 we present multipurpose adaptive experiments, involving also utilitarian choices and/or ethical issues: these are classified according to whether the decision on how to proceed is based on a step-by-step compromise among the different objectives (Chapter 4), or an overall strategy that seeks a compound optimal allocation target (Chapter 5); the latter is a fairly novel approach, so the relative designs too are almost all new. The acquisition of covariate information (like prognostic factors, biomarkers) about the statistical units involved in the experiment is also of fundamental importance and should not be ignored in the design. In Chapter 6 adaptive experiments are revisited to include covariates and new adaptive methods for this context are presented. Throughout this book we make extensive reference to design optimality in the context of adaptive experiments, and the basic tools of optimal design theory used in this book are included as a separate appendix. There is also another appendix on Bayesian adaptive designs: this is a widely used methodology, and although our approach is frequentist, we regard this type of design conceptually very important, so much so as to deserve a full book devoted to them.

We are aware that several issues of great relevance for applied adaptive designs are not included or not fully discussed in this monograph, such as dose-ranging estimation, sample size re-estimation, adaptive hypotheses designs and seamless trial designs, to mention just a few. We do not feel that the theoretic study of some of these methodologies has reached sufficient maturity to be included in this monograph. Some other central topics are just hinted at, the most prominent of which is stopping rules (at the end of Chapter 1). This is due to the fact that there already exist outstanding books on this subject. Lastly, note that ours is a model-based approach, thus we do not include designing experiments for randomization-based inference.

We hope that researchers working in the area of adaptive designs will find this book a useful reference. Teachers of graduate-level courses on designs may find this useful since it includes a fair number of examples. The degree of mathematical sophistication required from the readers is a knowledge of elementary algebra, calculus and probability, and rudimentary notions of stochastic processes—in particular the theory of Markov chains. We have tried to avoid making explicit use of more advanced mathematical tools, such as Martingale theory, although some of the results we present (without proofs) are indeed based on such theories.

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