TOPICS IN THE DESIGN OF EXPERIMENTS
PART 2: SEQUENTIAL DESIGN
Exercise Sheet 2

Please try to attempt all of the questions. You are welcome to discuss your solutions with me during my office hours.

1. A clinician has to decide whether or not to recommend a new drug in the treatment of a rare disease. There is a standard drug which is successful in about 40% of the cases treated, but it is hoped that the new drug will do better, although it is more expensive and can have occasional side-effects. The clinician agrees to treat a sequence of patients with the new drug and to apply a sequential probability ratio test to the results. If the new drug has a success rate of 70%, then the test should accept it with probability 0.98, but if the success rate is only 35%, then the test should accept it with probability only 0.01. Thus, the respective values of α and β are 0.01 and 0.02.
   (a) Construct a sequential probability ratio test with approximately the above error probabilities.
   (b) Find the approximate expected sample size when the true success rate for the new drug is 70%.
   (c) Suppose that S denotes a 'success' and F a 'failure'. Use a graph to carry out the test in part (a) when the responses for the first 16 patients are as follows: F, S, S, F, F, S, F, S, S, S, S, S, S, S, S, F.

2. Suppose that $X_1, X_2, \ldots$ is a sequence of independent and identically distributed random variables with finite mean μ and finite variance σ^2. Let $S_n = \sum_{k=1}^{n} X_k$ and let N be a stopping time such that $P(N < \infty) = 1$.
   (a) Prove that Wald's fundamental identity is a special case of Theorem 3.
   (b) Assuming that differentiation under the expectation can be justified, differentiate Wald's fundamental identity with respect to t at $t = 0$ to reproduce Theorem 1.
   (c) By differentiating Wald's fundamental identity twice with respect to t at $t = 0$, show that $E\{(S_N - N\mu)^2\} = \sigma^2 E(N)$.

3. Consider a group sequential test that stops at stage

$$T = \min\{\text{first } k \geq 1 \text{ such that } Z_k \notin (a_k, b_k), K\},$$

   where Z_k denotes the standardised test statistic calculated from the first k groups of observations, and a_k and b_k are the critical values for the kth analysis for $k = 1, 2, \ldots, K$. Assume that the sequence of test statistics $\{Z_1, \ldots, Z_K\}$ have the canonical joint distribution with information levels $\{\mathcal{I}_1, \ldots, \mathcal{I}_K\}$ for the parameter θ.
   (a) By writing down the joint density of $(Z_1, \ldots, Z_k)$, show that the maximum likelihood estimator of θ is $\hat{\theta} = Z_T/\sqrt{\mathcal{I}_T}$.
   (b) Derive an expression for the variance of $\hat{\theta}$.
   (c) Now consider a two-stage test in which the critical values for the first analysis are a and b. Obtain the form of the bias of $\hat{\theta}$ in this case.

4. Let $X_{A1}, X_{A2}, \ldots$ be independent exponential random variables with parameter λ_A and let $X_{B1}, X_{B2}, \ldots$ be independent exponential random variables with parameter λ_B. The parameter of interest is $\theta = \log(\lambda_A/\lambda_B)$, and interest lies in testing $H_0 : \theta = 0$ against $H_1 : \theta \neq 0$.
   (a) Derive the approximate information level at analysis k and give the standardised statistics for testing H_0 for $k = 1, 2, \ldots, K$.
   (b) Find the maximum information level for an O'Brien and Fleming test with type I error probability $\alpha = 0.05$, power $1 - \beta = 0.9$ when $\theta = \pm 0.75$ and a maximum of $K = 6$ analyses.
   (c) Obtain the group size and critical values for the test.

5. Consider a two-treatment clinical trial in which the responses are independent with variance σ^2. Then the covariance matrix of the estimated means after n assignments is $\sigma^2 \text{diag}(1/n_{1n}, 1/n_{2n})$, where n_{jn} denotes the number of patients on treatment j for $j = 1, 2$.
   (a) State which criterion the D-optimum design minimises, and hence show that this design assigns the next patient to treatment 1 if $n_{2n} > n_{1n}$ and to treatment 2 if $n_{1n} > n_{2n}$.
   (b) Construct a biased coin design from this deterministic design and state the asymptotic properties of N_{1n}/n. How does the asymptotic variance of N_{1n}/n for this design compare with that of complete randomisation?
   (c) Derive the D-optimum design if the variance of the responses on treatment j is σ_j^2 for $j = 1, 2$.

6. Suppose that the responses in a two-treatment clinical trial are binary and that the probability of success for treatment j is p_j for $j = 1, 2$. Assume that the usual large-sample Z test is used.
   (a) Show that the allocation that minimises the total sample size subject to a fixed power is
   $$\rho = \frac{\sqrt{p_1 q_1}}{\sqrt{p_1 q_1} + \sqrt{p_2 q_2}},$$
   where $q_j = 1 - p_j$ for $j = 1, 2$.
   (b) Explain how a sequential maximum likelihood estimation rule may be constructed for this target allocation and state the asymptotic properties of N_{1n}/n.
   (c) Verify that the lower bound on the asymptotic variance of the allocation proportions for this target allocation is $B(p_1, p_2)/n$, where
   $$B(p_1, p_2) = \frac{1}{4(\sqrt{p_1 q_1} + \sqrt{p_2 q_2})^3} \left\{ \frac{p_2 q_2 (q_1 - p_1)^2}{\sqrt{p_1 q_1}} + \frac{p_1 q_1 (q_2 - p_2)^2}{\sqrt{p_2 q_2}} \right\}.$$