MATH 267 FINAL PROJECT

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Simulation Study of a Bayesian decision-theoretic design for two-agent phase I trials

The simulation study employs the proposed design for two-agent phase I trials by Lee et al. [1] to find the maximum tolerable dose (MTD). The proposed design is useful in terms of ease of implementation and the savings in sample size. With an understanding of phase I trials and a basic knowledge of statistics, the method can be implemented using the R program attached. This report describes the guidelines for using the R program and presents the results of the simulation study.

Consider a phase I 4x4 combination trial with 4 doses of agent A and 4 doses of agent B, for which maximum sample size is 50 patients and minimum sample size is 10 patients. In each set of simulations, 10,000 trials with cohort sizes of 1 were generated under the six scenarios (A, B, C, D, E, F) for which target toxicity rate is 20%. The operating characteristics of the design are examined under two sets of simulations, denoted LFL^{NS} – does not allow skipping of doses and LFL – allows skipping of doses.

Outline of the Algorithm:

- **Step 1:** The first patient is treated at the lowest dose combination (1,1) and then the dose is randomly escalated by one unit of agent A or agent B to the next patient. If the dose of one agent reaches maximum, care is taken to escalate the dose of the other agent alone. The outcome of each dose modeled as a Bernoulli random variable using DLT probability is checked. This process of escalating the dose is repeated until first toxicity is observed or the highest dose combination (4,4) is reached.
- **Step 2:** Parameters a, b are updated based on the outcome of the toxicity of the dose. If the current dose is toxic matrix a is updated, otherwise matrix b is updated.
- **Step 3:** If minimum sample size is reached, stopping criteria are checked. If any of the stopping criteria is met, the loop breaks and records the current dose combination as MTD for the trial.
- **Step 4:** If the stopping criteria is not met, dose combination for the next patient is suggested based on the (i,j) corresponding to the largest value of the expected utility function. Here, if dose skipping is not allowed ($LFL^{NS)}$, if (i,j) is current dose commination, the next dose is limited to (r,s) such that $r \leq i$, $j \leq s$, (i+1,j), (i,j+1)
- **Step 5:** The outcome of the dose modeled as a Bernoulli random variable using DLT probability is checked for the patient.
- **Step 6**: Step 2 – Step 5 is repeated until the loop breaks through one of the stopping rules.
- **Step 7**: Steps 1 through 6 are repeated 10,000 times. Average number of patients treated in each trial, number of trials in which no MTD is recommended, MTD selection percentages are recorded.

Guidelines on using the R program:

- Define the DLT probabilities under the scenarios (A, B, C, D, E, F).
- Run the function `Run.Clinical.Trials`. It takes as an input the DLT probability and "`NS`" or "`WS`" to denote LFL^{NS} and LFL respectively.
- Run the function `Display.Results` to get the operating characteristics of the design. This function is called within the function `Run.Clinical.Trials`. It does all the calculations to compute operating characteristics of the design based on the scenario.

Sample function call: `Run.Clinical.Trials(true.A, "NS")`

Here, `true.A` is the DLT probability matrix under scenario A. This displays MTD selection % matrix, % of recommendations at target, within 1 -10 points of target, outside 10 points of target, no recommendations, average sample size.

Table 1 lists the six scenarios for which operating characteristics can be computed using the R code provided. The code can be used for any other DLT probability scenario as well.

Table 1. DLT probabilities (x100) for the three scenarios examined.

		Agent B			
Scenario	Agent A	1	2	3	4
A	1	4	10	16	22
	2	8	14	**20**	26
	3	12	18	24	30
	4	16	22	28	34
B	1	2	5	8	11
	2	4	7	10	13
	3	6	9	12	15
	4	8	11	14	17
C	1	10	25	40	55
	2	**20**	35	50	65
	3	30	45	60	75
	4	40	55	70	85
D	1	44	50	40	55
	2	48	54	50	65
	3	52	58	60	75
	4	56	62	70	85
E	1	8	9	10	11
	2	18	19	**20**	21
	3	28	29	30	31
	4	29	30	31	41
F	1	12	16	44	50
	2	13	18	45	52
	3	14	20	46	54
	4	15	22	47	55

The results of the simulation are summarized in Table 2. Below are the key findings:

- Operating characteristics of LFL^{NS} and LFL are nearly identical in terms of selection probabilities of dose combinations and average sample size.
- In scenario A, the percentage of recommendations at target are observed to be slightly

different for LFL^{NS} and LFL (13 and 18 respectively). A plausible explanation is that, since in scenario A there are many dose combinations that are below target DLT, dose skipping (LFL) gives more chance of reaching the target while without dose skipping (LFL^{NS}) allows other adjacent doses whose DLT probabilities are within ± 10 points of target.

- In scenario B, the average sample size is higher compared to all other scenarios because all dose combinations are below target DLT, it takes longer (i.e. more number of patients) to meet the stopping criteria.
- The percentage of recommendations at target is highest (54%) in scenario C compared to the other scenarios. This is because there are very dose combinations whose DLT probabilities are close to target DLT (20%).
- Scenario D has all DLT probabilities above target DLT, it has the highest percentage of no recommendations.
- The percentage of recommendations are higher near the target DLT combination.

Table 2: Operating characteristics of the proposed designs

		Percentage of recommendation				Average sample size
Scenario	Design	At target	1-10 pts of target	< or > 10 pts of target	None recommended	
A	LFL (NS)	13	77	10	0	25
	LFL	18	74	8	0	24
B	LFL (NS)	0	83	17	0	41
	LFL	0	83	17	0	40
C	LFL (NS)	54	25	19	2	21
	LFL	54	28	16	2	21
D	LFL (NS)	0	0	1	99	10
	LFL	0	0	1	99	10
E	LFL (NS)	9	78	13	0	26
	LFL	9	80	11	1	25
F	LFL (NS)	11	86	0	3	24
	LFL	12	86	0	2	23