Proceedings of the 2025 Winter Simulation Conference
E. Azar, A. Djanatliev, A. Harper, C. Kogler, V. Ramamohan, A. Anagnostou, and S. J. E. Taylor, eds.

STOPPING RULES FOR SAMPLING IN PRECISION MEDICINE

Mingrui Ding[1]

[1]Deptartment of Systems Engineering, City University of Hong Kong, Kowloon, Hong Kong, CHINA

ABSTRACT

Precision medicine (PM) aims to tailor treatments to patient profiles. In PM practice, treatment performance is typically evaluated through simulation models or clinical trials. Despite differences in sampling subjects and requirements, both rely on a sequential sampling process and require a stopping time to ensure, with prespecified confidence, the best treatment is correctly identified for each patient profile. We propose unified stopping rules for both settings by adapting the generalized likelihood ratio (GLR) test then calibrating it using mixture martingales with a peeling method. The rules are theoretically grounded and can be integrated with different types of sampling strategies. Their effectiveness are demonstrated in a case study.

1 INTRODUCTION

Suppose there are k treatment alternatives $\mathscr{K} = \{1,2,...,k\}$ for the disease and m patient profiles $\mathscr{X} = \{\boldsymbol{x}_1, \boldsymbol{x}_2, ..., \boldsymbol{x}_m\}$ in total. At each sampling time t, the decision maker chooses to sample treatment i_t under profile $\boldsymbol{x}_{j_t}$ according to some sampling strategy. The observed outcome is $Y_t \sim N\left(y_{i_t}(\boldsymbol{x}_{j_t}), \sigma^2_{i_t}(\boldsymbol{x}_{j_t})\right)$. The sampling process continues until a stopping time τ, when the estimated best treatment is selected for each profile. Figure 1 illustrates this process. The goal is to determine τ as early as possible.

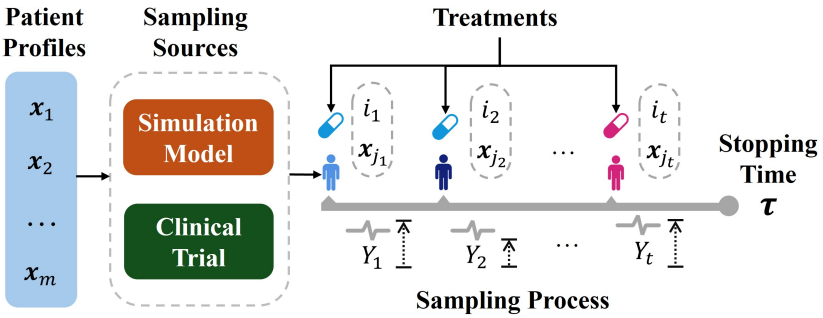

Figure 1: Illustration of PM sampling process.

In the simulation environment, existing methods are based on the indifference-zone (IZ) formulation, whose stopping rules must be integrated with certain types of sampling strategies with low efficiency, resulting in conservative stopping conditions. In the clinical trial environment, existing stopping rules are typically developed under the assumption of known variances. We propose stopping rules applicable to both settings that do not require this assumption and have the potential to terminate earlier when combined with efficient sampling strategies.

2 STOPPING RULES

We develop stopping rules for two extensions of the probability of correct selection (PCS) over the profile space $\mathscr{X}$: $\text{PCS}_\text{E} = \mathbb{E}\left[\mathbb{P}\left(\hat{i}_\tau(\boldsymbol{X}) = i^*(\boldsymbol{X})\right)\right]$ and $\text{PCS}_\text{A} = \mathbb{P}\left(\forall \boldsymbol{x} \in \mathscr{X}, \hat{i}_\tau(\boldsymbol{x}) = i^*(\boldsymbol{x})\right)$, where $i^*(\boldsymbol{x})$ is the true best treatment under profile $\boldsymbol{x}$ and $\hat{i}_\tau(\boldsymbol{x}) = \arg\max_{i \in \mathscr{K}} \bar{y}_{\tau,i}(\boldsymbol{x})$ the estimated best.

Let $N_{t,i}(\boldsymbol{x})$ and $S^2_{t,i}(\boldsymbol{x})$ be the sample size and variance up to time t. We use the statistic

$$Z_i^s(\boldsymbol{x},t) = \inf_{u\in[\bar{y}_{t,i}(\boldsymbol{x}),\bar{y}_{t,\hat{i}_t(\boldsymbol{x})}(\boldsymbol{x})]} \sum_{c\in\{i,\hat{i}_t(\boldsymbol{x})\}} N_{t,c}(\boldsymbol{x})\frac{(\bar{y}_{t,c}(\boldsymbol{x})-u)^2}{2S^2_{t,c}(\boldsymbol{x})} = \frac{1}{2}\frac{(\bar{y}_{t,i}(\boldsymbol{x})-\bar{y}_{t,\hat{i}_t(\boldsymbol{x})}(\boldsymbol{x}))^2}{S^2_{t,i}(\boldsymbol{x})/N_{t,i}(\boldsymbol{x})+S^2_{t,\hat{i}_t(\boldsymbol{x})}(\boldsymbol{x})/N_{t,\hat{i}_t(\boldsymbol{x})}(\boldsymbol{x})}$$

to quantify the evidence against i being the best treatment under profile $\boldsymbol{x}$ at time t. A larger statistic $Z_i^s(\boldsymbol{x},t)$ indicates that treatment i is less likely to be the best. Define the threshold for treatment i as $\phi_i(\boldsymbol{N}_t,\alpha,\boldsymbol{x})$, a function of confidence level α, profile $\boldsymbol{x}$ and the sample size vector $\boldsymbol{N}_t$. When all statistics $Z_i^s(\boldsymbol{x},t)$ exceed their corresponding thresholds, the stopping rule is triggered:

$$\tau_\alpha = \inf\{t\in\mathbb{N}|\forall \boldsymbol{x}\in\mathscr{X},\forall i\neq\hat{i}_t(\boldsymbol{x}),Z_i^s(\boldsymbol{x},t)>\phi_i(\boldsymbol{N}_t,\alpha,\boldsymbol{x})\}.$$

We calibrate the threshold ϕ_i separately for $\mathrm{PCS_E}$ and $\mathrm{PCS_A}$ using mixture martingales with a peeling method. The obtained stopping rules are denoted as τ_α^{E} and τ_α^{A}.

3 CASE STUDY

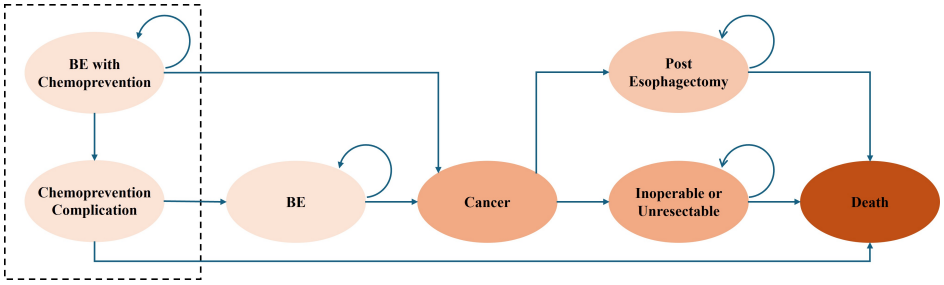

Figure 2: Transition diagram of the Markov simulation model.

We consider an esophageal cancer prevention case shown in Figure 2, where BE denotes Barrett's esophagus. PM-guided early intervention strategies can improve patient QALYs by tailoring treatment plans based on individual profiles. We consider four treatments and eight patient profiles with confidence level 0.95. Our stopping rules are combined with the C-OCBA sampling strategy of Gao et al. (2019). For $\mathrm{PCS_E}$, we compare against the KN-IZ method of Keslin et al. (2022) and the TS-IZ method of Shen et al. (2021); for $\mathrm{PCS_A}$, we compare against KN-IZ. Results in Table 1 show that our method achieves the prespecified confidence level while using fewer samples.

Table 1: Performance comparison of stopping rules and IZ methods.

τ_α^{E}			τ_α^{A}		
Method	**$\mathrm{PCS_E}$**	**Avg. SSize ± 95% CI**	**Method**	**$\mathrm{PCS_A}$**	**Avg. SSize ± 95% CI**
C-OCBA	0.99	271,163 ± 9,988	C-OCBA	0.99	340,644 ± 11,257
KN-IZ	0.98	581,597 ± 18,174	KN-IZ	0.96	1,054,615 ± 32,976
TS-IZ	0.98	632,948 ± 18,874			

REFERENCES

Gao, S., J. Du, and C.-H. Chen. 2019. "Selecting the Optimal System Design under Covariates". In *2019 IEEE 15th International Conference on Automation Science and Engineering (CASE)*, 547–552. USA: Institute of Electrical and Electronics Engineers.

Keslin, G., B. L. Nelson, M. Plumlee, B. K. Pagnoncelli, and H. Rahimian. 2022. "A Classification Method for Ranking and Selection with Covariates". In *2022 Winter Simulation Conference (WSC)*, 1–12.

Shen, H., L. J. Hong, and X. Zhang. 2021. "Ranking and Selection with Covariates for Personalized Decision Making". *INFORMS Journal on Computing*:ijoc.2020.1009.