EXCELLENCE SINCE 1817

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Project Work
Adaptive Allocation in Randomized Clinical Trials

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Introduction:

Adaptive randomization is a method of changing the allocation probability according to the progress and position of the study. It is widely used to meet the ethical requirement in assigning a number of subjects to one of the several competing treatments. The idea behind adaptive allocation schemes is that it uses all the available information on previous subjects' responses to kew the current allocation toward the improved efficacy of the treatment. (and more...)

Assumptions:

Suppose we have two treatments: A & B, and they are applied to a group of patients/subjects such that,

- The size of the group $= n =$ prefixed.
- Any patient will recieve either A or B.
- Patients enter the clinic and get the treatments one by one sequentially.
- The response obstained from a treatment is continuous and higher the response, better the condition.
- A covariate information is collected from each patient before applying treatment.
- We assume the responses follow Normal Distribution.

Proposed Adaptive Allocation Design:

Suppose,

$$X_A = \text{ Response from treatment A.}$$

$$X_B = \text{ Response from treatment B.}$$

We assume,

$$\begin{cases} X_A \sim & N(\mu_A, \sigma_A^2) \\ X_B \sim & N(\mu_B, \sigma_B^2) \end{cases} \text{, independently}$$

Let, first n_0 patients are treated with treatment-A and next n_0 patients are treated with treatment-B.

So,

$$X_{A1}, X_{A2}, ..., X_{An_0} \overset{i.i.d}{\sim} N(\mu_A, \sigma_A^2)$$

$$X_{B1}, X_{B2}, ..., X_{Bn_0} \overset{i.i.d}{\sim} N(\mu_B, \sigma_B^2)$$

Then,

$$\hat{\mu}_A = \frac{1}{n_0}\sum_{i=1}^{n_0} X_{Ai} \ , \ \hat{\sigma^2}_A = \frac{1}{n_0}\sum_{i=1}^{n_0}(X_{Ai} - \hat{\mu}_A)^2$$

and,

$$\hat{\mu}_B = \frac{1}{n_0}\sum_{i=1}^{n_0} X_{Bi} \ , \ \hat{\sigma^2}_B = \frac{1}{n_0}\sum_{i=1}^{n_0}(X_{Bi} - \hat{\mu}_B)^2$$

We define,
$R_A = P(X_A > X_B)$.
$= P(X_A - X_B > 0)$
$= P(\frac{(X_A - X_B)-(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}}) > -\frac{(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}}$
$= \Phi(\frac{(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}})$

Let δ be an indicator function which takes the value 1 if a patient is treated with treatment A and 0 otherwise. Then

$$\begin{aligned} P[\delta = 1] =& P[\text{a randomly chosen patient will be allocated to treatment } A] \\ =& P[X_A > X_B] \end{aligned}$$

Neyman's optimum allocation

$$\begin{aligned} V(\hat{\mu}_A - \hat{\mu}_B) &= V(\bar{X}_A - \bar{X}_B) \\ &= \frac{\sigma_A^2}{n_A} + \frac{\sigma_B^2}{n_B}, \quad n_A + n_B = n \\ &= \frac{\sigma_A^2}{n_A} + \frac{\sigma_B^2}{n - n_A} \\ &= \frac{\sigma_A^2}{n.(n_A/n)} + \frac{\sigma_B^2}{1 - n.(n_A/n)} \\ &= \psi(\omega_A), \quad \text{where } \omega_A = \frac{n_A}{n} \end{aligned}$$

Now we need to maximise $\psi(\omega_A)$ w.r.t ω_A

$$\begin{aligned} \psi'(\omega_A) &= 0 \\ \implies \frac{1}{n}(-\frac{\sigma_A^2}{\omega_A^2} + \frac{\sigma_B^2}{(1-\omega_A)^2}) &= 0 \\ \implies \frac{\omega_A^2}{(1-\omega_A^2)} &= \frac{\sigma_A^2}{\sigma_B^2} \\ \implies \omega_{A_{opt}} &= \frac{\sigma_A}{\sigma_A + \sigma_B} \\ \implies \frac{n_{A_{opt}}}{n} &= \frac{\sigma_A}{\sigma_A + \sigma_B} \end{aligned}$$

According to Neyman's optimum allocation, the probability that a randomly chosen patient will be allocated to treatment A i.e. $P[\delta = 1] = \frac{n_{A_{opt}}}{n} = \frac{\sigma_A}{\sigma_A+\sigma_B}$

Problem with Neyman's optimum allocation rule.

Suppose $\begin{cases} \mu_A << \mu_B & \text{(A is worse than B)} \\ \sigma_A >> \sigma_B & \text{(A has high variability than B)} \end{cases}$

then this procedure allocates more subjects to treatment A which is inferior than treatment B, which is far from ethical.

Thus keeping all these in mind, one can propose a compromise between these two aspects

Solution

If $\mu_A > \mu_B$

$P[\delta = 1] = \max\{\frac{\sigma_A}{\sigma_A+\sigma_B}, \Phi(\frac{(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}})\}$

If $\mu_A \leqslant \mu_B$

$P[\delta = 1] = \min\{\frac{\sigma_A}{\sigma_A+\sigma_B}, \Phi(\frac{(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}})\}$

Thus $P[\delta = 1] = \max\{\frac{\sigma_A}{\sigma_A+\sigma_B}, \Phi(\frac{(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}})\}.I(\mu_A > \mu_B) + \min\{\frac{\sigma_A}{\sigma_A+\sigma_B}, \Phi(\frac{(\mu_A-\mu_B)}{\sqrt{\sigma_A^2+\sigma_B^2}})\}I(\mu_A \leqslant \mu_B)$.

Now suppose $X_{A1}, X_{A2} \overset{iid}{\sim} N(\mu_A, \sigma_A^2)$, $X_{B1}, X_{B2} \overset{iid}{\sim} N(\mu_B, \sigma_B^2)$

$$\begin{aligned} P[|X_{A1} - X_{A2}| > |X_{B1} - X_{B2}|] =& P[|\frac{X_{B1} - X_{B2}}{X_{A1} - X_{A2}}| < 1] \\ =& P[-1 < \frac{X_{B1} - X_{B2}}{X_{A1} - X_{A2}} < 1] \end{aligned}$$

Let $Z_A = \frac{X_{A1}-X_{A2}}{\sqrt{2}\sigma_A} \sim N(0,1)$, $Z_B = \frac{X_{B1}-X_{B2}}{\sqrt{2}\sigma_B} \sim N(0,1)$ independently

$$\begin{aligned} P[|X_{A1} - X_{A2}| > |X_{B1} - X_{B2}|] =& P[-1 < \frac{Z_B\sqrt{2}\sigma_B}{Z_A\sqrt{2}\sigma_A} < 1] \\ =& P[-\frac{\sigma_A}{\sigma_B} < (\frac{Z_B}{Z_A}) < \frac{\sigma_A}{\sigma_B}] \end{aligned}$$

Now $Z = \frac{Z_B}{Z_A} \sim C(0,1)$.

$$\begin{aligned} P[|X_{A1} - X_{A2}| > |X_{B1} - X_{B2}|] =& 2\int_0^{\frac{\sigma_A}{\sigma_B}} \frac{1}{\pi(1+z^2)} dz \\ =& \frac{2}{\pi}\arctan(\frac{\sigma_A}{\sigma_B}) \\ =& \frac{2}{\pi}\arcsin(\sqrt{\frac{\sigma_A^2}{\sigma_A^2+\sigma_B^2}}) \end{aligned}$$

Now $P[|X_{A1} - X_{A2}| > |X_{B1} - X_{B2}|] > \frac{1}{2}$ implies $\frac{2}{\pi} \arcsin(\sqrt{\frac{\sigma_A^2}{\sigma_A^2+\sigma_B^2}}) > \frac{1}{2}$

$$\begin{aligned} \frac{2}{\pi} \arcsin(\sqrt{\frac{\sigma_A^2}{\sigma_A^2+\sigma_B^2}}) &> \frac{1}{2} \\ \leftrightarrow \arcsin(\sqrt{\frac{\sigma_A^2}{\sigma_A^2+\sigma_B^2}}) &> \frac{\pi}{4} \\ \leftrightarrow \frac{\sigma_A^2}{\sigma_A^2+\sigma_B^2} &> \frac{1}{2} \end{aligned}$$

Thus $P[|X_{A1} - X_{A2}| > |X_{B1} - X_{B2}|] > \frac{1}{2} \Leftrightarrow \frac{\sigma_A^2}{\sigma_A^2+\sigma_B^2} > \frac{1}{2}$

Therefore we can rewrite $P[\delta = 1]$ as

$$P[\delta = 1] = \max\{P[|X_{A1} - X_{A2}| > |X_{B1} - X_{B2}|], P[X_A > X_B]\}.I(U > c) + \min\{P[|X_{A1} - X_{A2}| > |X_{B1} -$$

where U is such that , if $U > c$ then treatment A is preffered otherwise treatment B is preffered and c is a threshold