TWO TREATMENT TWO PERIOD CROSSOVER DESIGN FOR RECURRING DISEASE

Semester IV Project

M.Sc. Statistics

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ABSTRACT

Crossover design is an important field in clinical trials. Majority of the works have been performed in cases of dichotomous or binary responses as well as continuous responses. This project emphasizes upon a crossover design of recurrence of any disease over two periods, considering two treatments, having carryover effects and involving count data responses. This project brings into limelight the creation of a statistical model for the crossover design and performing the necessary estimation and hypothesis testing to make some inferences about the effectiveness of our model upon implementation for the crossover design and draw some conclusions.

Keywords: Crossover design, Carryover effect, Statistical model, estimation, hypothesis testing, count data responses.

INTRODUCTION

A crossover design is a repeated measurements design such that each experimental unit (patient) receives different treatments during the different time periods, that is, the patients cross over from one treatment to another during the course of the trial. This is in contrast to a parallel design in which patients are randomized to a treatment and remain on that treatment throughout the duration of the trial. To clearly understand what a crossover design is, we have to know what actually happens in a crossover design. In a crossover design, each participant is randomized to a sequence of two or more treatments therefore the participant is used as his or her own control. Moreover, these subjects or participants receive these treatments over several study periods.

The reason to consider a crossover design when planning a clinical trial is that it could yield a more efficient comparison of treatments than a parallel design, that is, fewer patients might be required in the crossover design in order to attain the same level of statistical power or precision as a parallel design. Intuitively, this seems reasonable because each patient serves as their own matched control. Every patient receives both treatment A and B. Crossover designs are popular in medicine, agriculture, manufacturing, education, and many other disciplines.

There have been several works previously done in the area of crossover design, majority of which have been for dichotomous or binary responses. To name a few, works are done: - by U.Bandyopadhyay, A.Biswas, and S.Mukherjee (2007, 2009); by UttamBandyopadhyay, Atanu Biswas, Shirsendu Mukherjee (2011); among many others. Many of the works have also been for continuous responses. To name a few, they are: - by Uttam Bandyopadhyay &Shirsendu Mukherjee (2015); among many others. Moreover, there have been a few works in the area of crossover design for count data responses, namely, by M. W. J.

Layard and J. N. Arvesen (1978); among few others. But statistical modeling of crossover design in count data response is very rare in past works. In this project, we are working upon building a statistical model for crossover design in count data responses since it is not unnatural or inapplicable even if it is rare and no past literature is present on modeling in crossover design for count data responses.

Thus, as suggested earlier, in our project, we develop a statistical model for crossover design of recurrence of any disease based on count data responses. The layout of our project is as follows: Section 2 deals with detail of the problem handled and the statistical modeling used. The inferential aspects, mainly estimation and hypothesis testing, are discussed elaborately in Section 3. Section 4 deals with detailed simulation study and display of related power curves. Finally, Section 5 concludes our project.

SECTION:-2

STATEMENT OF THE PROBLEM AND UNDERLYING MODEL

In this problem we are dealing with a two treatment two period pure crossover design for recurring disease with count response.

Here we consider two treatments A and B.

Then the possible combinations are AA,BB,AB,BA but since it is pure AA and BB is not considered.

Here KK' states the combination in which the treatment K is in the first period and K' is in the second period.

We are dealing with the number of recurrences of the disease in a population of N individuals both in the first and second periods and modelling them as follows:-

Let, K = A, B; KK' = AB, BA

Let, X_k = number of recurrence of a chronic disease with treatment K in the first period.

$X_{kk'}$ = number of recurrence of a chronic disease with treatment K' in the second period, provided treatment K($\neq$K') was applied in first period.

Let, U : prognostic variant or covariate, assumed to remain same for a patient in both periods, like age, sex, some genotype etc.

Also suppose U assumes G+1 ordinal categories with scores 0, 1,….., G; i.e. U is assumed to be ordinal categorical variable with, $P[U = u] = \pi_u$ say, such that,

$$\sum_{u=0}^{G} \pi_u = 1\,, \qquad 0 < \pi_u < 1 \;\forall\; u$$

Assuming that higher value (level) of U restricts a treatment to perform satisfactorily, i.e. higher value (level) of U reduces effect of a treatment we propose probability models as,

1) $X_k|U = u$ ~ Poisson with, $E(X_k|U = u) = \lambda_k a^{G-u}$, where *a* is a known prognostic index, $0<a<1$.
2) $X_{kk'}|X_k = x_k, U = u$ ~ Poisson with,

$$E(X_{kk'}|X_k = x_k, U = u) = \frac{\{\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k)\}a^{G-u} + \beta x_k}{1+\beta}$$

Some realizations about these probability models:

I. $E(X_k) = E\,E(X_k|U) = \lambda_k \pi$ where, $\pi = E[a^{G-u}] = \sum_{u=0}^{G} a^{G-u}\pi_u$

II. $$E(X_{kk'}|U = u) = E_{X_k|U}E(X_{kk'}|X_k, U = u)$$
$$= \frac{(\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k))a^{G-u} + \beta\,\lambda_k a^{G-u}}{1+\beta}$$
$$= \lambda_{kk'}a^{G-u}$$

$\Rightarrow E(X_{kk'}) = \lambda_{kk'}\pi$

III. If N_k patients are assigned to treatment k in first period, k=A,B
Then, $N_A + N_B = N$, N : prefixed number

Define, δ_{ki} = | 1 if i^{th} patient is assigned to treatment k
0 if else

Then the joint distribution will be,

$$f_\theta(X, U) = \prod_{i=1}^{N}\{f(x_{Ai}, x_{ABi}, u_i)\}^{\delta_{Ai}} f(x_{Bi}, x_{BAi}, u_i)^{\delta_{Bi}}, \quad \theta=\lambda_A, \lambda_B, \lambda_{AB}, \lambda_{BA}$$

$$= \prod_{i=1}^{N} \left\{ x_{ui} . \frac{e^{-\lambda_A a^{G-ui}} \left(\lambda_A a^{G-ui}\right)^{x_{Ai}}}{x_{Ai}!} . \frac{e^{-\left\{\frac{\{\lambda_{AB}+\beta(\lambda_{AB}-\lambda_A)\}a^{G-ui}+\beta x_{Ai}}{1+\beta}\right\}} \left(\frac{\{\lambda_{AB}+\beta(\lambda_{AB}-\lambda_A)\}a^{G-ui}+\beta x_{Ai}}{1+\beta}\right)^{x_{ABi}}}{x_{ABi}!} \right\}^{\delta_{Ai}}$$

$$\times \left\{ x_{ui} . \frac{e^{-\lambda_B a^{G-ui}} \left(\lambda_B a^{G-ui}\right)^{x_{Bi}}}{x_{Bi}!} . \frac{e^{-\left\{\frac{\{\lambda_{BA}+\beta(\lambda_{BA}-\lambda_B)\}a^{G-ui}+\beta x_{Bi}}{1+\beta}\right\}} \left(\frac{\{\lambda_{BA}+\beta(\lambda_{BA}-\lambda_B)\}a^{G-ui}+\beta x_{Bi}}{1+\beta}\right)^{x_{BAi}}}{x_{BAi}!} \right\}^{\delta_{Bi}}$$

$$= \left(\prod_{i=1}^{N} \pi_{ui} \right) e^{-\lambda_A \sum_{i=1}^{N} \delta_{Ai} a^{G-ui}} \lambda_A^{\sum \delta_{Ai} x_{Ai}} e^{-\frac{(\lambda_{AB}+\beta(\lambda_{AB}-\lambda_A))}{1+\beta} \sum \delta_{Ai} a^{G-ui}}$$

$$\times \left(\prod_{i=1}^{N} \pi_{ui} \right) e^{-\lambda_B \sum_{i=1}^{N} \delta_{Bi} a^{G-ui}} \lambda_B^{\sum \delta_{Bi} x_{Bi}} e^{-\frac{(\lambda_{BA}+\beta(\lambda_{BA}-\lambda_B))}{1+\beta} \sum \delta_{Bi} a^{G-ui}}$$

SECTION 3:-INFERENTIAL PROCEDURES

ESTIMATION OF PARAMETERS

Define, $S_k = \sum_{i=1}^{N} \delta_{ki} X_{ki}$ and $S_{kk'} = \sum_{i=1}^{N} \delta_{ki} X_{kk'i}$

Also, note that, $N_k = \sum_{i=1}^{N} \delta_{ki}$

Now, $E(S_k | \underset{\sim}{d}_k) = \sum_{i=1}^{N} \delta_{ki} E(X_{ki}) = \lambda_k \pi \sum_{i=1}^{N} \delta_{ki} = \lambda_k \pi N_k$

$$\Longrightarrow E\left(\frac{S_k}{\pi N_k}\right) = \lambda_k, \qquad k = A, B$$

$Var(S_k | \underset{\sim}{d}_k) = \sum_{i=1}^{N} \delta_{ki} Var(X_{ki})$

$$= \sum_{i=1}^{N} \delta_{ki} \left[E_U Var(X_{ki}|U) + Var_U E(X_{ki}|U)\right]$$

$$= \sum_{i=1}^{N} \delta_{ki} \left[E_U(\lambda_k a^{G-u}) + Var_U(\lambda_k a^{G-u})\right]$$

$$= \sum_{i=1}^{N} \delta_{ki} \left[\lambda_k \pi + {\lambda_k}^2 \pi^*\right] = (\lambda_k \pi + {\lambda_k}^2 \pi^*) N_k$$

$$\Longrightarrow Var\left(\frac{S_k}{\pi N_k}\right) = \frac{\lambda_k(\pi + \lambda_k \pi^*)}{\pi^2 N_k} \longrightarrow 0, \text{as } N \longrightarrow \infty \text{ with, } \min(N_A, N_B) \longrightarrow c$$

$E(S_{kk'}) = \sum_{i=1}^{N} \delta_{ki} E(X_{kk'i}) = \lambda_{kk'} \pi \sum_{i=1}^{N} \delta_{ki} = \lambda_{kk'} \pi N_k$

$$\Longrightarrow E\left(\frac{S_{kk'}}{\pi N_k}\right) = \lambda_{kk'}, kk' = AB, BA$$

$Var(S_{kk'}) = \sum_{i=1}^{N} \delta_{ki} Var(X_{kk'i})$

Now, $Var(X_{kk'}) = E\ Var(X_{kk'}|X_k, U) + Var\ E(X_{kk'}|X_k, U)$

$$= \mathrm{E}\left[\frac{\{\lambda_{kk'}+\beta(\lambda_{kk'}-\lambda_k)\}a^{G-u}+\beta x_k}{1+\beta}\right] + \mathrm{Var}\left[\frac{\{\lambda_{kk'}+\beta(\lambda_{kk'}-\lambda_k)\}a^{G-u}+\beta x_k}{1+\beta}\right]$$

Again, $\mathrm{Var}[\{\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k)\}a^{G-u} + \beta x_k]$

$$= \mathrm{E_U Var}[\{\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k)\}a^{G-u} + \beta x_k \big| U] + \mathrm{Var_U E}[\{\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k)\}a^{G-u} + \beta x_k | U]$$

$$= \mathrm{E_U Var}(\beta X_k | U) + \mathrm{Var_U}\left(\overline{1+\beta}\ \lambda_{kk'} a^{G-u}\right)$$

$$= \beta^2 \mathrm{E_U}\left(\lambda_k a^{G-u}\right) + (1+\beta)^2 {\lambda_{kk'}}^2 \pi^*$$

$$= \lambda_k \beta^2 \pi + (1+\beta)^2 {\lambda_{kk'}}^2 \pi^*$$

$$\Rightarrow \mathrm{Var}(X_{kk'}) = \lambda_{kk'}\pi + \frac{\lambda_k \beta^2 \pi + (1+\beta)^2 {\lambda_{kk'}}^2 \pi^*}{(1+\beta)^2}$$

$$\Rightarrow \mathrm{Var}(S_{kk'}) = \left[\lambda_{kk'}\pi + \frac{\lambda_k \beta^2 \pi + (1+\beta)^2 {\lambda_{kk'}}^2 \pi^*}{(1+\beta)^2}\right] N_k$$

$$\Rightarrow \mathrm{Var}\left(\frac{S_{kk'}}{\pi N_k}\right) = \frac{1}{\pi^2}\left[\lambda_{kk'}\pi + \frac{\lambda_k \beta^2 \pi + (1+\beta)^2 {\lambda_{kk'}}^2 \pi^*}{(1+\beta)^2}\right]\frac{1}{N_k} \longrightarrow 0 \text{ as}$$

$$N \longrightarrow \infty \text{ with } \min(N_A, N_B) \longrightarrow \infty$$

$\Rightarrow \frac{S_k}{\pi N_k}$ and $\frac{S_{kk'}}{\pi N_k}$ are the consistent estimators of λ_k and $\lambda_{kk'}$respectively.

To avoid their estimates to be 0, we adjust the estimates as follows:

$$\widehat{\lambda_k} = \frac{S_k + {}^1/_2}{\pi(N_k+1)} \text{ and } \widehat{\lambda_{kk'}} = \frac{S_{kk'} + {}^1/_2}{\pi(N_k+1)},$$

$$\Rightarrow \mathrm{Var}(\widehat{\lambda_k}) = \mathrm{Var}\left(\frac{S_k}{\pi N_k}\right) = \frac{\lambda_k(\pi + \lambda_k \pi^*)}{\pi^2 N_k} \longrightarrow \frac{2}{N}{\sigma_k}^2,$$

where, ${\sigma_k}^2 = \frac{\lambda_k(\pi+\lambda_k\pi^*)}{\pi^2}$ and $N_k \longrightarrow EN_k = {}^N/_2$

$$\Rightarrow \mathrm{Var}\left(\widehat{\lambda_{kk'}}\right) = \mathrm{Var}\left(\frac{S_{kk'}}{\pi N_k}\right) \longrightarrow \frac{2}{N}{\sigma_{kk'}}^2,$$

where, ${\sigma_{kk'}}^2 = \frac{1}{\pi^2}\left[\lambda_{kk'}\pi + \frac{\lambda_k\beta^2\pi + (1+\beta)^2{\lambda_{kk'}}^2\pi^*}{(1+\beta)^2}\right]$ and $N_k \longrightarrow EN_k = {}^{N}/_{2}$

Now,

$$\mathrm{Cov}\left(\widehat{\lambda_k}, \widehat{\lambda_{kk'}}\right) = \frac{1}{\pi^2{N_k}^2}\mathrm{Cov}\left(\sum_{i=1}^{N}\delta_{ki}X_{ki}\,, \sum_{i=1}^{N}\delta_{ki}X_{kk'i}\right)$$

$$= \frac{1}{\pi^2{N_k}^2}\sum_{i=1}^{N}\delta_{ki}\mathrm{Cov}(X_{ki}, X_{kk'i})$$

Again,

$$\mathrm{Cov}(X_{ki}, X_{kk'i}) = E(X_{ki}X_{kk'i}) - E(X_{ki})E(X_{kk'i})$$

$$= E_U E_{X_k|U}[X_k E(X_{kk'}|X_k, U)] - \pi^2\lambda_k\lambda_{kk'}$$

$$= E_U E_{X_k|U}\left[\frac{\{\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k)\}X_k a^{G-u} + \beta{X_k}^2}{1+\beta}\right] - \pi^2\lambda_k\lambda_{kk'}$$

$$= E_U\left[\frac{\{\lambda_{kk'} + \beta(\lambda_{kk'} - \lambda_k)\}\lambda_k(a^{G-u})^2 + \beta\{\lambda_k a^{G-u} + {\lambda_k}^2(a^{G-u})^2\}}{1+\beta}\right] - \pi^2\lambda_k\lambda_{kk'}$$

$$= E_U\left[\lambda_k\lambda_{kk'}\left(a^{G-u}\right)^2 + \frac{\beta}{1+\beta}\lambda_k a^{G-u}\right] - \pi^2\lambda_k\lambda_{kk'}$$

$$= \lambda_k\lambda_{kk'}(\pi^* + \pi^2) + \frac{\beta}{1+\beta}\lambda_k\pi - \pi^2\lambda_k\lambda_{kk'}\,, \text{where}, \pi^* = \mathrm{Var}(a^{G-u})$$

$$= \left(\frac{\beta}{1+\beta}\pi + \lambda_{kk'}\pi^*\right)\lambda_k$$

$\Rightarrow \mathrm{Cov}\left(\widehat{\lambda_k}, \widehat{\lambda_{kk'}}\right) \longrightarrow \frac{2}{N}\sigma_{k,kk'}$ where, $\sigma_{k,kk'} = \left(\frac{\beta}{1+\beta}\pi + \lambda_{kk'}\pi^*\right)\lambda_k$ and $N_k \longrightarrow EN_k = {}^{N}/_{2}$

So, $\sqrt{\mathrm{N}}\left(\widehat{\lambda_{\mathrm{A}}}-\lambda_{\mathrm{A}},\widehat{\lambda_{\mathrm{B}}}-\lambda_{\mathrm{B}},\widehat{\lambda_{\mathrm{AB}}}-\lambda_{\mathrm{AB}},\widehat{\lambda_{\mathrm{BA}}}-\lambda_{\mathrm{BA}}\right)\xrightarrow{\mathcal{D}}\mathrm{N}_4(0,\Sigma)$ where,

$$\Sigma=\begin{pmatrix}\sigma^2{}_A & 0 & \sigma_{A,AB} & 0\\ 0 & \sigma_B{}^2 & 0 & \sigma_{B,BA}\\ \sigma_{A,AB} & 0 & \sigma_{AB}{}^2 & 0\\ 0 & \sigma_{B,BA} & 0 & \sigma_{BA}{}^2\end{pmatrix}$$

Since, this asymptotic distribution does not depend on allocation (n), we describe the procedures under $N_A = N_B = n$ i.e. N/2 = n.

Define,

$\log \lambda_k = \alpha_k$ and $\log \lambda_{kk'} = \alpha_{k'} + \phi$, k=A,B and kk'=AB,BA where α_k is the main effect due to treatment k and ϕ is the period effect. No carryover effect is present in the model by assuming sufficiently large washout.

Testing of Hypotheses

To access which of the two treatments is better we suggest the following tests.

TEST 1:-

Suppose we want to test the following hypotheses:-

H_0: effects of two treatments are same

versus H_1: treatment A is superior to treatment B

i.e H_0: α_A=α_B versus H_1:α_A>α_B.

Now,

$\log \lambda_A$-$\log \lambda_B$=α_A-α_B

Again $\log \lambda_{BA}$-$\log \lambda_{AB}$=α_A-α_B

$\therefore \alpha_A - \alpha_B = \frac{[\log \lambda_A - \log \lambda_B + \log \lambda_{BA} - \log \lambda_{AB}]}{2}$

$\widehat{\alpha_A - \alpha_B} = \frac{[\log \widehat{\lambda_A} - \log \widehat{\lambda_B} + \log \widehat{\lambda_{BA}} - \log \widehat{\lambda_{AB}}]}{2}$

$= \psi(\widehat{\lambda_A}, \sigma\widehat{\lambda_B}, \widehat{\lambda_{AB}}, \widehat{\lambda_{BA}})$

Using Delta Method (first order) we get

$E[\psi(\widehat{\lambda_A}, \widehat{\lambda_B}, \widehat{\lambda_{BA}}, \widehat{\lambda_{AB}})] \approx \psi(\lambda_A, \lambda_B, \lambda_{BA}, \lambda_{AB}) = \alpha_A - \alpha_B$

$V[\psi(\widehat{\lambda_A}, \widehat{\lambda_B}, \widehat{\lambda_{BA}}, \widehat{\lambda_{AB}})]$

$\approx$

$(\frac{\partial\psi}{\partial\lambda_A})^2 V(\widehat{\lambda_A}) + (\frac{\partial\psi}{\partial\lambda_B})^2 V(\widehat{\lambda_B}) + (\frac{\partial\psi}{\partial\lambda_{BA}})^2 V(\widehat{\lambda_{BA}}) + (\frac{\partial\psi}{\partial\lambda_{AB}})^2 V(\widehat{\lambda_{AB}}) + 2Cov(\widehat{\lambda_A}, \widehat{\lambda_{AB}})(\frac{\partial\psi}{\partial\lambda_A})(\frac{\partial\psi}{\partial\lambda_{AB}}) + 2Cov(\widehat{\lambda_B}, \widehat{\lambda_{BA}})(\frac{\partial\psi}{\partial\lambda_B})(\frac{\partial\psi}{\partial\lambda_{BA}})$

$$\approx \frac{1}{4\lambda_A^2}\frac{2}{N}\sigma_A^2 + \frac{1}{4\lambda_B^2}\frac{2}{N}\sigma_B^2 + \frac{1}{4\lambda_{BA}^2}\frac{2}{N}\sigma_{BA}^2 + \frac{1}{4\lambda_{AB}^2}\frac{2}{N}\sigma_{AB}^2 + 2.\frac{2}{N}.\sigma_{A,AB}.\frac{1}{2\lambda_A}.\frac{1}{2\lambda_{AB}} + 2.\frac{2}{N}.\sigma_{B,BA}.\frac{1}{2\lambda_B}.\frac{1}{2\lambda_{BA}}$$

$= \frac{2}{N}[\frac{\sigma_A^2}{4\lambda_A^2} + \frac{\sigma_B^2}{4\lambda_B^2} + \frac{\sigma_{BA}^2}{4\lambda_{BA}^2} + \frac{\sigma_{AB}^2}{4\lambda_{AB}^2} + \frac{\sigma_{A,AB}}{2\lambda_A\lambda_{AB}} + \frac{\sigma_{B,BA}}{2\lambda_B\lambda_{BA}}]$

$= \sigma^2.\frac{2}{N}$,say

$\therefore \sqrt{N}(\widehat{\alpha_A - \alpha_B} - \overline{\alpha_A - \alpha_B}) \xrightarrow{D} N(0, 2\sigma^2)$

Under H_0: $\alpha_A = \alpha_B$,

$\lambda_A = \lambda_B = \lambda_1$ and $\lambda_{BA} = \lambda_{AB} = \lambda_2$.

$\therefore \sigma_B^2 = \sigma_A^2 = \sigma_{11}$, $\sigma_{AB}^2 = \sigma_{BA}^2 = \sigma_{22}$ and $\sigma_{A,AB} = \sigma_{B,BA} = \sigma_{12}$.

So under H_0,

$\sigma^2 = \frac{\sigma_{11}}{2\lambda_1^2} + \frac{\sigma_{22}}{2\lambda_2^2} + \frac{\sigma_{12}}{\lambda_1\lambda_2} = \sigma_0^2$(say)

With equal allocation weight that is with $N_A = N_B = \frac{N}{2}$,

$\lambda_1 = \frac{\lambda_A + \lambda_B}{2}$ and $\lambda_2 = \frac{\lambda_{AB} + \lambda_{BA}}{2}$

So under H_0,

$T_1 = \frac{\sqrt{N}(\widehat{\alpha_A} - \alpha_B)}{\sqrt{2\widehat{\sigma_0}}} \xrightarrow{D} N(0,1)$ as N$\to \infty$

where

$\widehat{\sigma_0^2} = \frac{\widehat{\sigma_{11}}}{2\widehat{\lambda_1^2}} + \frac{\widehat{\sigma_{22}}}{2\widehat{\lambda_2^2}} + \frac{\widehat{\sigma_{12}}}{\widehat{\lambda_1}\widehat{\lambda_2}}$,

Here $\widehat{\lambda_1} = \frac{\widehat{\lambda_A} + \widehat{\lambda_B}}{2}$ and $\widehat{\lambda_2} = \frac{\widehat{\lambda_{AB}} + \widehat{\lambda_{BA}}}{2}$

We reject the null hypotheses H_0 at 5% level of significance if $T_1 > \tau_{0.05} = 1.645$.

TEST-2:-

Suppose the test is presented as

$H_0: \lambda_A = \lambda_B$, $\lambda_{AB} = \lambda_{BA}$ vs $H_0: \lambda_A \geq \lambda_B$, $\lambda_{BA} \geq \lambda_{AB}$ with strict inequality in atleast one case.

Now,

$\sqrt{N}(\widehat{\lambda_A} - \widehat{\lambda_B} - \overline{\lambda_A - \lambda_B}, \widehat{\lambda_{BA}} - \widehat{\lambda_{AB}} - \overline{\lambda_{BA} - \lambda_{AB}}) \xrightarrow{\mathcal{D}} N(\underset{\sim}{0}, \begin{bmatrix} 2(\sigma_A^2 + \sigma_B^2) & -2(\sigma_{A,AB} + \sigma_{B,BA}) \\ -2(\sigma_{A,AB} + \sigma_{B,BA}) & 2(\sigma_{BA}^2 + \sigma_{AB}^2) \end{bmatrix})$

Under H_0 ,

$\sqrt{N}(\widehat{\lambda_A} - \widehat{\lambda_B} - \overline{\lambda_A - \lambda_B}, \widehat{\lambda_{BA}} - \widehat{\lambda_{AB}} - \overline{\lambda_{BA} - \lambda_{AB}}) \xrightarrow{\mathcal{D}} N(\begin{pmatrix}0\\0\end{pmatrix}, 2\begin{bmatrix}2\sigma_{11} & -2\sigma_{12}\\ -2\sigma_{12} & 2\sigma_{11}\end{bmatrix})$

Define:-

$D_1 = \frac{\sqrt{N}(\widehat{\lambda_A} - \widehat{\lambda_B})}{2\sqrt{\widehat{\sigma_{11}}}}$ and $D_2 = \frac{\sqrt{N}(\widehat{\lambda_{BA}} - \widehat{\lambda_{AB}})}{2\sqrt{\widehat{\sigma_{22}}}}$

Then

$(D_1, D_2) \underset{H_0}{\overset{\mathcal{D}}{\sim}} \mathrm{N}\left(\begin{pmatrix}0\\0\end{pmatrix}, \begin{bmatrix}1 & \rho_0\\ \rho_0 & 1\end{bmatrix}\right)$ where $\rho_0 = \frac{\sigma_{12}}{\sqrt{\sigma_{11}\sigma_{22}}}$

Using the approach as in Chatterjee and De(1972) we define the following test through the test statistic T_2:-

$$T_2 = \frac{\sqrt{D_1^2 + D_2^2 - 2\widehat{\rho_0} D_1 D_2}}{\sqrt{1 - \widehat{\rho_0}^2}}, \; D_1 > 0, D_2 > 0$$

$$= \frac{D_2 - \widehat{\rho_0} D_1}{\sqrt{1 - \widehat{\rho_0}^2}}, D_2 \geq D_1, D_1 \leq 0$$

$$= \frac{D_1 - \widehat{\rho_0} D_2}{\sqrt{1 - \widehat{\rho_0}^2}}, \; D_1 \geq D_2, D_2 \leq 0$$

We reject H_0 in favour of H_1 at level of significance γ if

$$P_{H_0}(T_2 > c) = \gamma$$

Where $c=c(\rho_0)$ is either obtained by simulation or by using Table 2.1 of Chatterjee and De(1972).

TEST-3:-

Using Multiple Testing Procedure(MTP) we define a third test statistic as follows:-

T_3=max$\{D_1 , D_2\}$

Now the critical region for testing $H_0: \lambda_A = \lambda_B , \lambda_{AB} = \lambda_{BA}$ vs $H_0: \lambda_A \geq \lambda_B , \lambda_{BA} \geq \lambda_{AB}$ with SIFAO case will be:-

$$T_3 > c^*$$

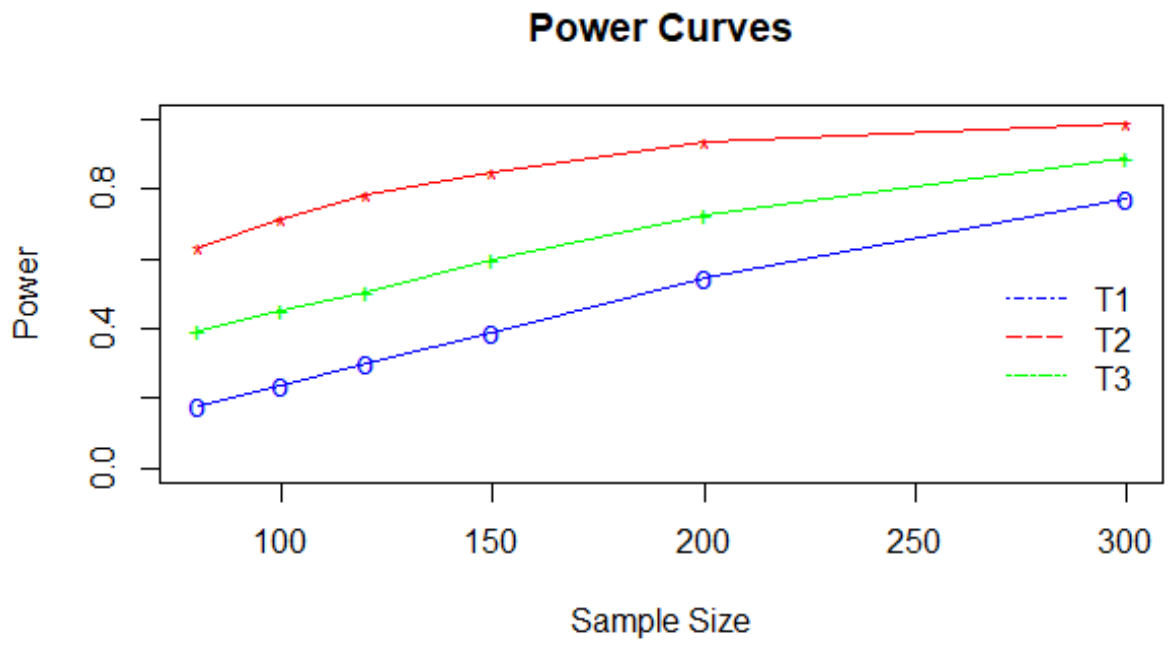
where c^* is obtained from size condition using Monte Carlo simulation.

Section 4:- Simulation Study

We work with a simulated data and based on that we get the power and standard error for the test statistics under different parameter choices.Then we plot the power curves of the three aforementioned tests for different sample sizes and parametric choices and study the properties.

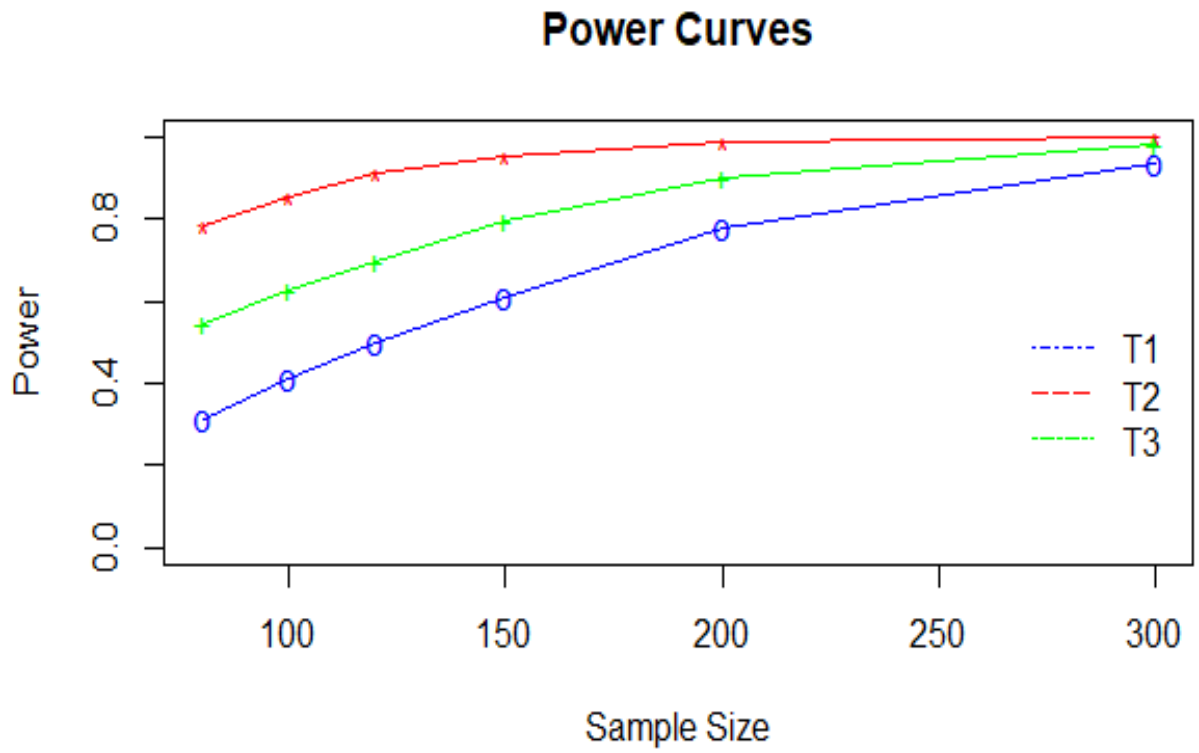
For the parametric choice $(\lambda_A,\lambda_B,\lambda_{AB},\lambda_{BA}) = (2,2.5,1.5,1.3)$ and sample sizes (80,100,120,150,200,300) :

```
> power
        [,1]   [,2]   [,3]
[1,] 0.1808 0.6358 0.3926
[2,] 0.2397 0.7139 0.4518
[3,] 0.3011 0.7836 0.5024
[4,] 0.3859 0.8491 0.6008
[5,] 0.5464 0.9376 0.7275
[6,] 0.7736 0.9883 0.8876
```



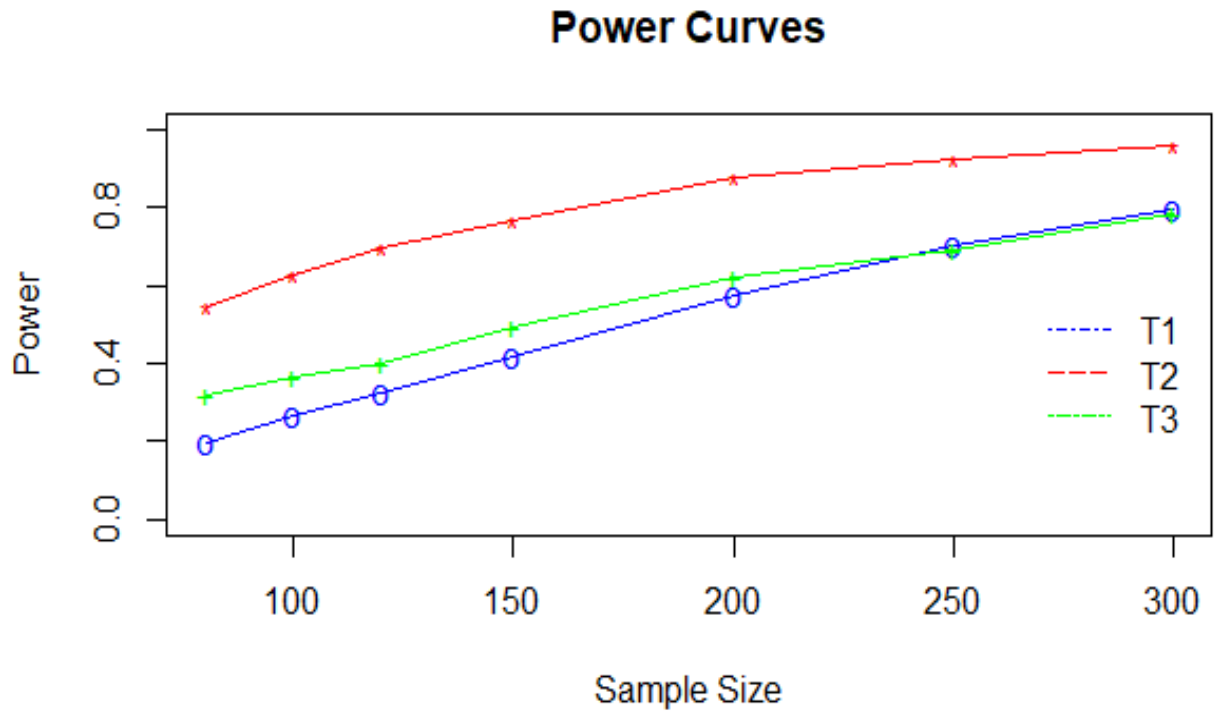
For the parametric choice $(\lambda_A,\lambda_B,\lambda_{AB},\lambda_{BA})$ = (1.6,2.2,1.4,1.2) and sample sizes (80,100,120,150,200,300) :

```
>power
       [,1]   [,2]   [,3]
[1,] 0.3137 0.7837 0.5489
[2,] 0.4106 0.8572 0.6294
[3,] 0.4986 0.9102 0.6979
[4,] 0.6100 0.9512 0.7991
[5,] 0.7771 0.9868 0.9025
[6,] 0.9380 0.9992 0.9816
```



For the parametric choice $(\lambda_A,\lambda_B,\lambda_{AB},\lambda_{BA})$ = (2.9,3.3,2.7,2.3) and sample sizes (80,100,120,150,200,250,300) :

```
>power
        [,1]   [,2]   [,3]
[1,] 0.1953 0.5484 0.3194
[2,] 0.2648 0.6277 0.3641
[3,] 0.3253 0.6960 0.3994
[4,] 0.4180 0.7662 0.4926
[5,] 0.5754 0.8784 0.6198
[6,] 0.7042 0.9266 0.6902
[7,] 0.7959 0.9625 0.7831
```



REMARKS:-

In the above power matrices the rows indicates the respective sample sizes and the columns indicate the tests.

1)With the increase in sample sizes the power of all the three tests are tending to 1 which indicates that all the three tests are consistent.

2)The tests involving the statistics T2 and T3 performs comparatively better than T1 with T2 being the best.

CONCLUSION

In our project, if we observe our simulation study, we have performed simulation work for known β. We tried the same for unknown β but could not complete it. So, we would eagerly want to venture the aspect of unknown β in our future work.

Moreover, in our project, we have assumed equal number of allocation of patients for application of both the treatments. So we would eagerly want to venture the aspect of random allocation of patients for application of both the treatments for our crossover design in the near future.

Similarly, we have considered the treatment combinations AB, BA after carryover to the second period. In the near future, we would want to take up the other possible combinations namely AA and BB and perform the similar tasks in the hope of getting better results.

Our proposed model can easily be generalized for more than two periods but its practical usefulness would much less than two period crossover design. So, at present, we do not discuss it in detail but we would definitely venture it in near future.

Moreover, we would also want to venture the possibility of more than two treatments in two or more periods in the near future.

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