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Treatment Effects Estimation for Incomplete Crossover Trial with Binary Data

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Abstract

Incomplete crossover design, which only considers a subset of treatments under comparison, is frequently employed to evaluate the effects of various drug treatments. This design frequently involves binary data, presenting unique challenges such as restricted information, small sample sizes, and a lack of flexible analytical approaches. In this manuscript, we review several approaches for the incomplete crossover design and focus more on the recent approaches proposed, which overcome the above mentioned challenges.

Keywords: Binary Data; Crossover Trial; Incomplete Block Crossover Trial

Abbreviations: IBCD: Incomplete block crossover designs; CMLE: Conditional Maximum Likelihood Estimator; MSE: Mean Square Error

Introduction

Crossover trials, a popular variant of the randomized block design, involves administering multiple treatments to subjects across several periods, allowing each individual to serve as their own control and reducing variability in treatment comparisons. They are widely used in pharmaceutical and medical studies to compare treatments for diseases. For example, in the most commonly used crossover design [1,2] with only 2 treatments A and B, some subjects receive treatment A first and B second, while the others receive treatment B first and A second. Many current statistical literature focuses on crossover trials with continuous outcomes. However, there are more and more studies with a binary response, e.g., reflief/no relief or improvement/no improvement to evaluate drugs effects. However, limited approaches are proposed to address such studies.

Incomplete block crossover designs (IBCD) Senn [3] are often employed due to practical considerations such as resource constraints and potential subject dropout. In IBCD, each subject receives only a subset of treatments, presenting unique challenges like small sample sizes and limited data. There are some limited studies evaluating the IBCD. For example, Senn [3] proposed an approach for continuous data. Lui and Chang [4] proposed the weighted least squares approach for binary data. Lui (2017) further developed a conditional likelihood approach for binary data. However, the previous approaches have some limitations: either for only continuous data or difficulties to accommodate zero counts with binary data and subject to asymptotic theorem. Yang [5] proposed a Bayesian approach for the IBCD. In this article, we review and compare several popular approaches for the IBCD and their performance.

The article is organized as follows: Section 2 describes the Frequentist approaches. Section 3 describes the Bayesian approach of Yang [5]. Section 4 provides a simulation study. And section 5 concludes with a discussion.

Frequentist Approaches

General Description

Jones and Kenward [6] considered a study in a three-period crossover trial which compared two treatments and placebo for the relief of primary dysmenorrhea. They proposed a log-linear linear model which mirrored the analysis of continuous data. However, such studies have common challenges such as logistic supports, longer duration of studies and potential risk of being lost

or follow-up in crossover trials. In addition, Jones and Kenward [6] proposed a fairly complicated model. Its main drawback with higher-order designs is that many extra parameters are needed.

To overcome the challenges of the IBCD, Lui [7] fitted a random effects logistic regression model and derived teh conditional maximum likelihood estimator (CMLE) for the relative effect between treatments with binary responses. For a study comparing two experimental treatment A and B with a placebo (P) under a 2-period crossover trial, denote X-Y the group with the treatment sequence in which a patient receives treatment X and then crossover to receive treatment Y and the second period. Lui [7] derived the logistic regression model:

$$P(Y_{iz}^{g}=1\mid X_{iz1}^{g},X_{iz2}^{g},1_{iz1}^{g})=\frac{\exp(\mu_i^g+\eta_{AP}^g X_{iz1}^g+\eta_{BP}^g X_{iz2}^g+\gamma 1_i^g(z=2))}{1+\exp(\mu_i^g+\eta_{AP}^g X_{iz1}^g+\eta_{BP}^g X_{iz2}^g+\gamma 1_i^g(z=2))} \quad (1)$$

where μ_i^g denotes the random effects with the i[th] patient assigned to group g; η_{AP} and η_{BP} denote the relative treatments effect of A and B to the placebo, respectively. The relative treatment effect is estimated as

$$\log(L(\psi_{AP}))=K+2a_1\log(\psi_{AP})-\log(\sum_x\binom{t_1}{x}(a_+^{(1,2)^{t_2}}-x)\psi_{AP}^{2x}$$
$$+a_3\log(\psi_{AP})-\log(\sum_\mu\binom{t_3}{\mu}(a_+^{(3,5)^{t_5}}-\mu)\psi_{AP}^{\mu})$$
$$+a_6\log(\psi_{AP})-\log(\sum_\upsilon(a_+^{(4,6)^{t_4}}-\upsilon)\binom{t_6}{\upsilon}\psi_{AP}^{\upsilon})$$

and an estimated asymptotic variance for $\log(\psi_{AP})$ is obtained as

$$\widehat{Var}(\log(\psi_{AP}))=1/Var(S\mid a_+^{1,2},a_+^{1,2},a_+^{1,2},t,\psi_{AP}) \quad (2)$$

where $\psi_{AP}=\exp(\eta_{AP})$. Based on the above equations, Lui [7] derived an approximate 100(1- α%) confidence interval for ψ_{AP} as

$$[\psi_{AP}=\exp(-Z_{\alpha/2}\sqrt{Var(\log(\psi_{AP}))}),\psi_{AP}\exp(Z_{\alpha/2}\sqrt{Var(\log(\psi_{AP}))})]$$

All the other relative treatment effects are derived similarly. Obviously, we can see the above results are fairly complicated. In particular, the IBCD studies generally have small sample sizes and thus the results might not be accurate. More detailed info can be referred to Lui [7].

Later on, Lui and Chang (2017) developed much simpler results using a logistic random effect model. For example, the estimated relative treatment effects η_{AP}

$$\eta_{AP}=1/2\log\left(\frac{\eta_{01}^1\eta_{10}^2}{\eta_{10}^1\eta_{01}^2}\right) \quad (3)$$

and the estimated variance of η_{AP}

$$Var\left(\eta_{AP}\right)=1/4(1/\eta_{01}^1+1/\eta_{10}^2+1/\eta_{10}^1+1/\eta_{01}^2) \quad (4)$$

where n_{rc}^g denotes the number of patients in group g withe the vector of response $Y_{i1}^g=r,Y_{i2}^g=c,$, where r=1,0, c=1,0 among n_g patients.

Although the results seem very straight forward, however, there are many times those values n_{rc}^1 or n_{rc}^1 are 0. Thus, it would be very difficult to obtain the estimated treatment effects and the corresponding variances [8].

Bayesian Approach Yang [5]

To overcome the above challenges of the Frequentist approaches, Yang [5]proposed a Bayesian approach for the IBCD studies. For a general crossover design consisting of J periods and M treatments, denoted as $T_1, T_2, \cdots, T_M$. A subset of M treatments is applied during the J periods with the crossover design. For instance, a sequence (g(1), g(2), · · · , g(J)) is formed when the treatments $T_{g(1)}, \cdots, T_{g(J)}$ are applied for the J periods. (Let y_{gij} denote the continuous outcome from subject i at period j under treatment sequence g, the model can be specified as

$$y_{gij}=u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}+\varepsilon_{gij},\ \varepsilon_{gi}j\sim N(0,\sigma^2) \quad (5)$$

where ψ_j is the fixed effect of the j[th] period; u0 is the overall mean; η_g is the fixed effect of the g[th] sequence, g = 1, · · · ,G; $t_{l(g,j)}$ is the fixed treatment effect, and l(g, j) is the treatment index; and ϵ_{gij} is a random error assumed to follow a normal distribution, μ_{gi} is the random effect of i[th] subject from the g[th] sequence, i = 1, · · · , n_g with $\mu_{gi}\sim N(0,\rho^2)$ In the above model, the carryover effect is omitted assuming sufficient washout between dosing periods.

Yang [5] further used several cutting-edge algorithms such as data augmentation, scaled mixture of normals representation, parameter expansion to improve efficiency. Specifically, the logistic model [9] is defined as follows:

$$y_{gij}\sim \text{Bernoulli}\left(H^{-1}(X_{gij})\right),\ X_{ij}=u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi} \quad (6)$$

where H(.) is the logistic link function with H(κ) = log(κ/(1 − κ)).

Obviously, the conditional conjugacy cannot be achieved with the posteriors since the logistic model is nonlinear. To overcome the cumbersome nonlinear issue, Yang [5] take several approaches of approximation to convert the nonlinear model to the standard linear models. First, we take the approach that the logistic distribution can be closely approximated by the t distribution (Albert and Chib [10]; Holmes and Knorr-Held [11]; O'Brien and Dunson [12]). With auxiliary variables, Model (6) is equivalent to the following representation:

$$y_{gij}=1:y_{gij}^*>0$$
$$y_{gij}=0:y_{gij}^*\le 0$$

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where y^*_{gij} is an underlying value with the logistic distribution with location parameter $u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}$ and density function as follows:

$$f\left(y^*_{gij}|\bullet\right)=\frac{\exp\{y^*_{gij}-(u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}))\}}{\left\{1+\exp[-y^*_{gij}-((u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}))]\right\}^2} \quad (7)$$

Second, as noted by West [13], the t distribution can be expressed as a scale mixture of normals. Thus y^*_{gij} is approximated as a non-central t distribution with location parameter $u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}$, degree of freedom υ and scale parameter σ^2. Then we can express it as a scale mixture of normals and get the following model:

$$y^*_{gij}=u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}+\varepsilon_{gij},\ \varepsilon_{gi}j\sim N(0,\sigma^2/\phi_{gij}) \quad (8)$$

where ϕ_{gij} has a Gamma prior G(υ/2, υ/2). As suggested by O'Brien and Dunson [12], we take υ = 7.3 and $\sigma^2=\pi^2(v-2)/3\upsilon$ to make the approximation almost exact.

Priors and Posteriors

Yang [5] used the same priors for the continuous outcomes as in model (5). Yang [5] specified a normal distribution $N(\mu_1,\sigma_1^2)$ for the overall mean $u_0=N(\mu_1,\sigma_1^2)$. Similar priors are selected for the sequence effect, period effect, and the treatment effect: $\eta_g\sim N(\mu_2,\sigma_2^2)$, $\psi_j\sim N(\mu_3,\sigma_3^2)$ and $t_m\sim N(\mu_4,\sigma_4^2)$. The random effect μgi is specified as $\mu_{gi}\sim N(0,\rho^2)$, the hyperparameter ρ^2 is placed an Inverse Gamma distribution $\rho^2\sim IG(a_0, b_0)$, and ϕ_{gij} is placed a prior of Gamma distribution G(υ/2, υ/2). Based on the model and prior specifications, we can easily derive the joint posterior distribution for $\tilde{\theta}=(u_0,\eta,\psi,t,\phi)$ as follows:

$$p(\tilde{\theta}|y)\alpha p(\bullet)[\prod_g\prod_i N(\mu_{gi};\rho^2)\prod_j N(y_{gij};u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi};\sigma^2/\phi_{gij})\omega_{gij}|] \quad (9)$$

where wgij = {1(y_{gij*} > 0) y_{gij} + 1(y^*_{gij} < 0)(1 − y_{gij})} p(ϕ_{gij}), and p(.) = p(ρ^2)p(u_0)p(t)p(η)p(ψ). Obviously, this is a very complicated posterior formula that we cannot sample directly. By introducing the latent variable y^*_{gij} we have applied a data augmentation[14] algorithm and can easily sample the parameters and hyperparameters of interest using Gibbs sampler. From the above model, the auxiliary variable can be easily updated using the Gibbs sampler from a posterior normal distribution truncated below or above 0 according to the value of y_{gij}.

The conditional posterior of the auxiliary variable is:

$$p(y^*_{gij}|\theta,y_{gij})=\frac{N(y_{gij};q_{gij},\sigma^2/\phi_{gij})\{1(y_{gij*}>0)y_{gij}+1(y^*_{gij}<0)(1-y_{gij})\}}{\phi(0;q_{gij},\sigma^2/\phi_{gij})^{(1-y_{gij})}\{1-\phi(0;q_{gij},\sigma^2/\phi_{gij})\}^{y_{gij}}} \quad (10)$$

where $q_{gij}=u_0+\eta_g+\psi_j+t_{l(g,j)}+\mu_{gi}$. The full conditional posterior distributions is specified in (9). The procedures and most of the conditional posterior distributions [14] are very similar to those of the continuous outcomes. The detailed sampling steps are listed in the Appendix. We run the Gibbs sampler by iteratively sampling all the parameters, and hyperparameters of interest.

Simulation

To evaluate the performance of the above mentioned approaches, we conduct a simulation example for a logistic mixed effects models. We consider comparing two experimental treatments A, B, and placebo P under a two-period crossover design. We use C-D to denote the group with the treatment sequence in which a subject receives treatment C at the first period and treatment D at the second period. Thus, there are totally 6 groups (A-P, B-P, P-A,P-B, A-B, B-A). We assume that there are no carry-over effects with an adequate washout period for the simulation. We arbitrarily set the overall mean u0 equal to 0.10. We generate the random effects μgi independently and identically from a normal distribution with mean 0 and standard deviation 0.5, 1.0, and 2.0, respectively; We set the following four cases for treatment effects (placebo, A, and B): -0.15, 0.30, -0.15 (case 1); -0.25, 0.00, 0.25 (case 2);-0.15, -0.15, 0.30 (case 3); 0.15, 0.15, -0.30 (case 4); and the number of patients per group n=15, 20, 25. In clinical trials [15], researchers are generally interested in the relative effects among treatments. Thus, we focus on the results of the relative effects in the simulation. We use $t_{cd}=t_c-t_d$ to denote the relative treatment effect between treatment c and d. For the above 4 cases, the relative treatment effects (t_{21}, t_{31}, t_{32}) are: 0.45, 0.00, -0.45 (case1); 0.25, 0.50, 0.25 (case 2); 0.00, 0.45, 0.45 (case 3); 0.00, -0.45, -0.45 (case 4); and the period effect and group effect are all set 0 since they are much less of interest compared to the relative treatment effects. For the priors, we specify $\mu_1=\mu_2=\mu_3=\mu_4=0.5$, $\sigma_1=\sigma_2=\sigma_3=\sigma_4=5.0$, and $a_0=b_0=0.2$.

We generate 500 simulated samples of n subjects per group with the bivariate outcome (y_{gi1}, y_{gi2}). About 5% (n=25, σ = 0.5) to 70% (n=15, σ = 2.0) data sets have zero frequency cells. We run the Gibbs sampling algorithm as described in the previous section and the Appendix. Three independent chains with widely dispersed starting values were run to assess convergence. After an initial 5,000 iterations, the scale reduction factors of the Gelman- Rubin [16] approach (Gelman and Rubin [17]) indicate good convergence. We use the next 20,000 iterations to calculate the parameter estimate for the parameters of interest. We also run simulations by varying the means and variances of the priors for the hyperparameters to evaluate the effects. We do not observe any noticeable differences in the parameter estimation.

(Table 1) provides the bias and mean square error (MSE) of the relative treatment effect difference of varying scenarios. (Table 2) provides the 95% coverage of the relative treatment effect difference. From the tables, we can see that the performance of our approach is pretty good. In particular, the approach of

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Yang [5], unlike those of Lui and Change [4] and Lui [7], does not suffer from zero frequencies for some cells. We also note that the percentage of generated data sets with zero frequency cells can be up to almost 80% for some cases. Although Lui [5] and Lui and Chang [4] suggested to add 0.5 for cells with zero counts, this would significantly impacted the estimated results.

Table 1: The estimated bias and MSE (in parenthesis) of the relative treatment effect difference.

σ	t21	t31	t32	n	$\hat{t}_{21}$	$\hat{t}_{31}$	$\hat{t}_{32}$
0.5	0.45	0	-0.45	15	0.0540(0.223)	0.003(0.215)	-0.051(0.216)
				20	0.018(0.163)	0.013(0.152)	-0.017(0.153)
				25	-0.023(0.123)	-0.014(0.126)	0.009(0.123)
	0.25	0.5	0.25	15	0.017(0.230)	0.007(0.228)	-0.011(0.220)
				20	0.008(0.148)	0.035(0.143)	0.027(0.146)
				25	-0.001 (0.113)	0.010(0.123)	0.012(0.111)
	0	0.45	0.45	15	0.001(0.230)	0.050(0.216)	0.048(0.237)
				20	-0.008(0.146)	0.017(0.149)	0.026(0.144)
				25	0.009(0.110)	0.008(0.110)	-0.001(0.117)
	0	-0.45	-0.45	15	0.002(0.207)	-0.022(0.199)	-0.025(0.202)
				20	0.003(0.137)	-0.012(0.136)	-0.015(0.146)
				25	0.006(0.112)	-0.024(0.111)	-0.029(0.117)
1	0.45	0	-0.45	15	-0.033(0.212)	-0.011(0.192)	0.022(0.206)
				20	-0.058(0.141)	-0.030(0.145)	0.028(0.136)
				25	-0.023(0.123)	-0.014(0.126)	-.009(0.123)
	0.25	0.5	0.25	15	-0.009(0.176)	-0.046(0.175)	-0.037(0.180)
				20	-0.019(0.136)	-0.050(0.140)	-0.031(0.128)
				25	-0.036(0.105)	-.0.06(0.107)	-0.028(0.104)
	0	0.45	0.45	15	-0.007(0.194)	-0.029(0.207)	-0.021(0.191)
				20	0.021(0.137)	-0.042(0.147)	-0.063(0.138)
				25	-0.002(0.105)	-0.044(0.105)	-0.042(0.108)
	0	-0.45	-0.45	15	-0.003(0.200)	0.029(0.203)	0.032(0.206)
				20	0.008(0.150)	0.029(0.147)	0.021(0.164)
				25	-0.007(0.099)	0.058(0.107)	0.065(0.105)
2	0.45	0	-0.45	15	-0.006(0.428)	0.001(0.364)	0.007(0.427
				20	0.101(0.396)	0.0085(0.369)	-0.103(0.399)
				25	0.095(0.298)	-0.002(0.265)	-0.097(0.286)
	0.25	0.5	0.25	15	-0.040(0.292)	-0.072(0.325)	-0.032(0.312)
				20	0.008(0.289)	-0.032(0.267)	0.005(0.269)
				25	0.040(0.275)	0.098(0.279)	0.058(0.272)
	0	0.45	0.45	15	-0.009(0.467)	0.013(0.466)	0.023(0.450)
				20	0.019(0.397)	0.035(0.314)	0.016 (0.337)
				25	-0.008(0.255)	0.094(0.292)	0.087(0.304)
	0	-0.45	-0.45	15	0.007(0.596)	-0.079(0.576)	-0.086(0.610)
				20	0.007(0.415)	-0.087(0.413)	-0.093(0.394)
				25	0.002(0.211)	-0.009(0.220)	-0.011(0.231)

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Table 2: The estimated coverage of the relative treatment effect difference.

σ	t_{21}	t_{31}	t_{32}	n	$\hat{t}_{21}$	$\hat{t}_{31}$	$\hat{t}_{32}$
0.5	0.45	0	-0.45	15	0.946	0.948	0.944
				20	0.933	0.94	0.946
				25	0.952	0.936	0.943
	0.25	0.5	0.25	15	0.939	0.94	0.945
				20	0.958	0.952	0.951
				25	0.951	0.943	0.947
	0	0.45	0.45	15	0.94	0.943	0.939
				20	0.944	0.954	0.953
				25	0.949	0.954	0.951
	0	-0.45	0.45	15	0.942	0.952	0.951
				20	0.961	0.955	0.954
				25	0.954	0.956	0.948
1	0.45	0	-0.45	15	0.95	0.953	0.951
				20	0.962	0.953	0.958
				25	0.952	0.936	0.943
	0.25	0.5	0.25	15	0.957	0.965	0.962
				20	0.956	0.961	0.971
				25	0.96	0.956	0.96
	0	0.45	0.45	15	0.954	0.951	0.957
				20	0.965	0.958	0.959
				25	0.962	0.96	0.959
	0	-0.45	-0.45	15	0.959	0.963	0.961
				20	0.944	0.955	0.941
				25	0.965	0.96	0.959
2	0.45	0	-0.45	15	0.919	0.928	0.927
				20	0.922	0.924	0.92
				25	0.923	0.935	0.925
	0.25	0.5	0.25	15	0.955	0.951	0.968
				20	0.939	0.947	0.952
				25	0.935	0.928	0.934
	0	0.45	0.45	15	0.945	0.934	0.938
				20	0.937	0.936	0.931
				25	0.929	0.921	0.916
	0	-0.45	-0.45	15	0.93	0.925	0.921
				20	0.934	0.928	0.937
				25	0.944	0.938	0.932

Discussion

For crossover trials [18-20], there are many challenging issues such as logistic support, long duration of experiment, small sample size etc. Even for modelings of IBCD, there are many challenging issues of identifiability, reliability, intense computation etc. In this manuscript, we review several popular approaches to compare their results and performance: the frequentist approaches of Kenward and Jones [6], Lui and Chang [7]; Lui (2017); and the Bayesian approach of Yang [5]. Obviously, we can see that the

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frequentist approaches for IBCD easily suffer from barriers of cell counts of 0 while the Bayesian approach of Yang [5] does not. In particular, the approach of Yang [5] used several cutting-edge algorithms such as data augmentation, scaled mixture of normal representation, parameter expansion etc. and get the closed form for posterior distributions and improve efficiency. By extensive simulation, we can see that the Bayesian approach [21,22] provides very reliable and good results and performance.

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