Estimation of Hurst exponent for sequential monitoring of clinical trials with covariate adaptive randomization

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Abstract

Background: Classical Brownian motion (BM) has been commonly used in monitoring clinical trials including those with covariate adaptive randomization (CAR). Independent increment property is commonly assumed in the sequential monitoring process of the clinical trials with CAR designs. However, in reality, correlation may exist in the error terms of the underlying model, resulting **in** dependent increment in the sequential monitoring process.

Methods: We conducted simulations for estimating the Hurst exponent to evaluate the stochastic property in the covariate adaptive randomized clinical trials under two scenarios: 1. CAR designs with independent and identically distributed error terms. 2. CAR designs with correlated error terms. The theoretical properties of covariate adaptive randomized clinical trials with correlated error structure were investigated. A test statistic including the covariance pattern of the error terms was proposed.

Conclusion: In our study, the sequential test statistics under CAR procedure is shown to be asymptotically Brownian motion when the error structure is correctly specified. Further, Brownian motion is a special case of fractional Brownian motion when Hurst exponent equals to 0.5. Our simulations are consistent with the theoretical asymptotic results.

Keywords: Hurst exponent, Covariate adaptive randomized clinical trial, Sequential monitoring, Brownian motion, Fractional Brownian motion

1. Introduction

After been discussed and promoted by the U.S. Food and Drug Administration (FDA), the usage of adaptive designs in clinical trials attracts more and more attention from medical professionals and pharmaceutical companies (Center for Drug Evaluation and Research, 2020). Adaptive design approaches reduce the costs, optimize the balance between bias and covariates assignments, and make the trials more efficient (Pallmann et al., 2018). It would be more appropriate to consider the covariate when designing the clinical trials since most trial studies include comprehensive demographic characteristics, medical history, physical assessment, and lab reports. Various biomarkers are being investigated as they may relate to underline diseases (Hu & Hu, 2012; Khan et al., 2010). This highlights the fact that, when treatment effects are evaluated in clinical trials, it is possible that the significance of these covariates may differ from one another. Attention should be paid to balance those dominant covariates in clinical trials. Covariate adaptive randomization (CAR) procedures can minimize the imbalance across the subgroups in clinical trials by assigning participants to different groups based on previous treatment assignments, covariates, and current patient's covariates (Hu & Rosenberger, 2006). Stratified permuted block randomization (SPB), Pocock and Simon minimization designs (PS) are the commonly used CAR designs (Zelen, 1974; Pocock & Simon,1975; Zhu & Hu, 2019; Yu & Lai, 2019).

In 2010, a ground-breaking study investigated theoretical results for testing hypotheses after covariate-adaptive randomization (Shao et al., 2010). Then, the theory of hypothesis testing and the corresponding asymptotic distributions of the testing statistics for the covariate-adaptive randomized clinical trials were extensively studied in

2015 (Ma et al., 2015). The asymptotical properties of the sequential monitoring **of** CAR procedures were also derived (Zhu & Hu, 2019). There are some recent studies regarding the statistical inference under CAR designs (Bugni et al., 2018; Ma et al., 2019). For the impact of misclassification under CAR, see Fan et al., 2018 and Wang & Ma, 2020. These studies established the theoretical foundations of CAR applications in clinical trials.

The sequential test statistics in CAR procedures can be adjusted to be an asymptotically Brownian motion (BM) under some regulatory conditions if the error terms are assumed to be independent and identically distributed (i.i.d.) (Zhu & Hu, 2019). However, the independent increment assumptions may not be completely met in some other occasions. For example, patients in clinical trials may come from the same clinical center or may accept the treatments from the same physician group. Hence, the error terms in the underlying model with CAR designs may be correlated. It is necessary to investigate the properties of sequential monitoring of CAR with correlated error structures. In this study, a new sequential test statistics was derived corresponding to the covariance pattern of the error terms and the sequential test statistics under CAR procedure was shown to be asymptotically Brownian motion when the error structure was correctly specified.

In this article, Section 2.1 is the general structure for the linear model with covariate-adaptive randomization designs when error terms are independent and identically distributed. In Section 2.2, we describe design properties of CAR when error terms are correlated. In the Section 3, Hurst exponent estimations are studied for the sequential monitoring of the covariate-adaptive randomized clinical trials with correlated error structure. Numerical simulation studies were performed to verify the reliable method of estimating Hurst exponent and evaluate the theoretical results. All simulations

in this study were conducted by R software (Foundation for Statistical Computing, Vienna, Austria). Some concluding remarks and discussions are provided in Section 4.

2. Methods

British hydrologist Harold Edwin Hurst studied the hydrological and geophysical time series. His studies exposed that the statistical behaviour was different from the classical Brownian motion process, based on his scientific insight and data analysis for the characterization of the long-term variability in Nile River flow records (Hurst, 1951). The results of Hurst motivated the formulation of fractional Brownian motion (FBM) by Mandelbrot and van Ness (1968). Fractional Brownian motion is a Gaussian process with the covariance function of $Cov(B_H(s)B_H(t)) = \frac{1}{2}(t^{2H} + s^{2H} - |t-s|^{2H})$ (Taqqu, 2003; Zili, 2017). $B_H(t)$ is denoted as fractional Brownian motion with the Hurst parameter H, where $0 < \mathrm{H} < 1$. When $\mathrm{H} = 0.5$, fractional Brownian motion $B_H(t)$ is reduced to the classical Brownian motion (Mandelbrot & van Ness, 1968).

The application of MLE method for estimating the Hurst exponent of the FBM was proposed in Lai (2004). The log likelihood function of $B_H = (B_H(t_1), \dots B_H(t_n))^t$ is given as $L_n(x, H) = -\mathrm{nlog}\frac{2\pi}{2} - \log|\sum(H)|/2 - x^{\mathrm{t}}\Sigma^{-1}(H)x/2$, where $x = (x_{t_1,\dots,}x_{t_n})^t$ is the observed value of B_H. $\sum(H)$ is the variance covariance matrix of B_H (Lai, 2004).

In this paper, we estimated Hurst exponent by the maximum likelihood estimation (MLE) method in simulation studies to assess whether the sequential process of CAR procedure still follow Brownian motion with the hypothesis test concerning the covariance structure.

2.1 CAR designs with independent and identically distributed error terms

Consider a two-arm trial with the treatment assignment indicator I_i, where I_i=1 is for the treatment group 1 and I_i=0 is for the treatment group 2, i=1, 2, … N. Here, N is the total sample size. Let μ_1 and μ_2 be the parameters to measure the treatment

effects in each group respectively. Let $X_{i,1}\ldots X_{i,p}$ be the covariates that are independent from each other. Assume the response Y_i follows the following model:

$$Y_i = \mu_1 I_i + \mu_2(1 - I_i) + \beta_1 X_{i,1} + \cdots + \beta_p X_{i,p} + \varepsilon_i \qquad (i = 1, \ldots, N) \tag{1}$$

Let $Y = (Y_1, Y_2, \ldots, Y_N)^T$, $\beta = (\mu_1, \mu_2, \beta_1, \ldots, \beta_p)^T$, $\varepsilon = (\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_N)^T$

$$X = \begin{bmatrix} I_1 & 1 - I_1 & X_{1,1} & \cdots & X_{1,p} \\ I_2 & 1 - I_2 & X_{2,1} & \cdots & X_{2,p} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ I_N & 1 - I_N & X_{N,1} & \cdots & X_{N,p} \end{bmatrix}$$

where $\beta_1 \ldots \beta_p$ are unknown parameters for the covariate effects and ε_i are the error terms. The matrix form of the expression (1) is: $Y = X\beta + \varepsilon$

Assume the ε_is in the model with CAR design are independent and identically distributed random errors. $\varepsilon_i \sim N(0, \sigma^2)$.

The hypothesis for testing the equality of treatment effect is:

$H_0: \mu_1 - \mu_2 = 0$ vs $H_A: \mu_1 - \mu_2 \neq 0$

The test statistics of a general linear hypothesis at time point t in the sequential monitoring process can be denoted as Z_t:

$$Z_t = \frac{L\hat{\beta}(t)}{\sqrt{\hat{\sigma}(t)^2 L(X(\lfloor Nt \rfloor)^T X(\lfloor Nt \rfloor))^{-1} L^T}} \tag{2}$$

$t = \frac{n}{N}$, $t \in [0,1]$

For the hypothesis of equal treatment effect, we have:

$L = (1, -1, 0, \ldots, 0)$

At time t, $\hat{\beta}$ is the ordinary least square estimator for unknown parameters β. $\hat{\sigma}$ is used to estimate the true error variance σ^2.

$\hat{\beta}(t) = X(\lfloor Nt \rfloor)^T X(\lfloor Nt \rfloor))^{-1} X(\lfloor Nt \rfloor)^T Y(\lfloor Nt \rfloor))$

$\hat{\sigma}^2(t) = (Y(\lfloor Nt \rfloor) - X(\lfloor Nt \rfloor)\hat{\beta}(t))^{\mathrm{T}} (Y(\lfloor Nt \rfloor) - X(\lfloor Nt \rfloor)\hat{\beta}(t))/(\lfloor Nt \rfloor - p - 2)$

$\lfloor \cdot \rfloor$ is denoted as the floor function.

It was proved that under H_0, the sequential test statistics, $B(t) = Z_t t^{1/2}$ of the covariate adaptive randomized clinical trials converge to an asymptotic Brownian motion (Zhu & Hu, 2019).

Using Maximum likelihood method, in our study, we numerically estimated the Hurst exponent via simulations of the B-value. Our simulation results are consistent with the theoretical results in Zhu and Hu (2019).

2.2 CAR designs with correlated error terms

The original assumption of the $\varepsilon_i s$ in the expression (1) was independent and identically normally distributed. However, the independent assumption may not be met in some situations. If ε_is in the model (1) are correlated and follow some special covariance patterns, we extended the test statistic (2) to a weighted version. We showed that the B-value still forms a Brownian motion if the variance-covariance matrix is correctly specified.

Furthermore, we performed the simulation studies to demonstrate the proposed derivation. MLE techniques were used to estimate the Hurst exponent of test statistics in the interim analysis. We outlined our deviation of Brownian motion of test statistic when the variance-covariance matrix V is given. The theoretical properties of the null hypothesis test and sequential monitoring processes were derived as follows. Assume the error terms in a two-arm linear model with CAR design (expression (1)) are correlated with some certain covariance pattern.

For the hypothesis:

$$H_0: \mu_1 - \mu_2 = 0 \quad vs \quad \mu_1 - \mu_2 \neq 0$$

At time point t, the sequential test statistics of the CAR models with correlated error terms was defined as following:

$$Z_t = \frac{L\widehat{\beta}(t)}{\sqrt{\widehat{\sigma}(t)^2 L(X(\lfloor Nt \rfloor)^T (V(t))^{-1} X(\lfloor Nt \rfloor))^{-1} L^T}} \tag{3}$$

At each time t, $\sigma^2(t)V(t) = Cov(\varepsilon|X)$. This covers both traditional analysis of covariance model and many repeated model models such as AR(1) error correlation structure. V represents the correlated structure in the error terms.

$$B_H(t) = \frac{\sqrt{t}L\hat{\beta}(t)}{\sqrt{\hat{\sigma}(t)^2 L(X(\lfloor Nt \rfloor)^T (V(t))^{-1} X(\lfloor Nt \rfloor))^{-1} L^T}} \quad (4)$$

At time point t, the new estimator $\hat{\beta}$ and $\hat{\sigma}$ are shown below:

$$\hat{\beta}(t) = (X(\lfloor Nt \rfloor)^T (V(t))^{-1} X(\lfloor Nt \rfloor))^{-1} X(\lfloor Nt \rfloor)^T (V(t))^{-1} Y(\lfloor Nt \rfloor)) \quad (5)$$

$$\hat{\sigma}(t)^2 = [Y(\lfloor Nt \rfloor) - X(\lfloor Nt \rfloor)\hat{\beta}(t)]^T (V(t))^{-1} (Y(\lfloor Nt \rfloor) - X(\lfloor Nt \rfloor)\hat{\beta}(t))/ (\lfloor Nt \rfloor - p - 2) \quad (6)$$

Assume V is a known square matrix with non-zero off-diagonal elements. At each time point t, $Var[\varepsilon] = \sigma^2 V$. Let K be the squared root of V, $V = K^T K = KK$. Let $g = K^{-1}\varepsilon$. Then the expectation of g is equal to 0 and variance of g is equal to $\sigma^2 I$.

Two conditions were assumed: (1) $D_{\lfloor Nt \rfloor} = O_P(1)$; (2) $D_{\lfloor Nt \rfloor}(\mathrm{k}) = O_P(1)$, $\mathrm{k} = 1, 2$ (Ma et al., 2015). The numerator and the denominator of the equation (3) were evaluated separately. The numerator of the equation (3) was $L\hat{\beta}(t)$. $L\hat{\beta}(t)$=$\hat{\mu}_1(t)$-$\hat{\mu}_2(t)$ = $\mu_1(t)$ - $\mu_2(t)$ + L($\frac{X(\lfloor Nt \rfloor)^T (V(t))^{-1} X(\lfloor Nt \rfloor)}{\lfloor Nt \rfloor}$)$^{-1}$ $\frac{X(\lfloor Nt \rfloor)^T (V(t))^{-1} X(\lfloor Nt \rfloor)}{\lfloor Nt \rfloor}$. $\sqrt{\lfloor Nt \rfloor}$($\hat{\mu}_1(t)$ - $\hat{\mu}_2(t)$) = $\sqrt{\lfloor Nt \rfloor} L\hat{\beta}(t) \xrightarrow{D} N(0,\ 4\sigma_\varepsilon^2)$. The denominator part of the equation (3) is $\hat{\sigma}(\mathrm{t})^2 L(X(\lfloor Nt \rfloor)^T (V(t))^{-1} X(\lfloor Nt \rfloor))^{-1} L^T = \frac{4}{\lfloor Nt \rfloor}\sigma^2 + O_p(\frac{1}{\lfloor Nt \rfloor})$. Under null hypothesis $H_0: \mu_1 - \mu_2 = 0, Z_t \xrightarrow{D} N(0, 1)$.

Based on the theoretical deviation, the new test statistics formula converges to Gaussian process. In the sequential process, $\{ Z_{t_1}, Z_{t_2}, \ldots Z_{t_i} \}$ is multivariate normal, $E(Z_{t_i})$=0, and $Cov(B_H(s), B_H(t)) \xrightarrow{p} s$, $0 \le s \le t \le 1$. Under null hypothesis H_0, the new sequential statistics $B_H(t)$ for the covariate adaptive randomization procedures with

correlated error terms are asymptotically a standard Brownian motion. The detailed theoretical derivations were shown in the Yang (2020). The derivation was challenging since the treatment assignments and covariates are correlated to each other.

3. Simulation results

The motivations of simulations are 1. to evaluate the MLE method for estimating the Hurst exponents; 2. to validate that the sequential test statistic of the covariate adaptive randomized clinical trial converges to an asymptotic Brownian motion, which means H value should be equal to 0.5; 3. to illustrate the increment properties for the sequential monitoring processes of CAR procedures with newly derived hypothesis testing formula (3) when error terms are correlated. Formula (3) in the above section is the newly derived hypothesis testing based on a linear model framework for CAR design under the assumption of correlated error terms.

Simulation 1: Hurst estimation for fractional Brownian motion

There are many different approaches for generating fractional Brownian motion (FBM) series. One way to create realization of one-dimension fractional Brownian motion is to use the fbm() function in the R software (Huang, 2013). Another way is the exact direct simulation method proposed in 2004 (Lai, 2004). An independent and identically distributed Gaussian process was multiplied by $\sum^{1/2}$ in the direct simulation method, where $\sum$ is the variance-covariance matrix of the FBM. Fractional Brownian motion series with Hurst exponent H =0.5, 0.6, 0.7, 0.8, 0.9 were generated with sample sizes of N =10, 20, 50, 80. 1000 replications were applied to the simulations. To estimate the Hurst exponents, maximum likelihood estimation method was performed under different scenarios.

The accuracy of both fbm() function and exact direct simulation were evaluated in the simulations. Table 1 showed the estimated mean and standard deviation of the H

values from 1000 replicated simulations. Based on the results from Table 1, both fbm() function and direct simulation methods reached close results compared to the original Hurst exponent of the FBM series, especially when the sample size is greater than 20. For example, we used fbm() to generated a fractional Brownian motion time series with H=0.6. The Hurst exponent estimating result are close to 0.6 by MLE method. As the sample size increased, the mean estimate of Hurst exponents became closer to the true generated H value. The estimated standard deviations of Hurst exponents decreased when the sample size increased. MLE method was validated to be a reliable technique to estimate the Hurst exponent.

Table 1 Hurst exponent estimation by maximum likelihood method

Sample size	Method		H=0.5	H=0.6	H=0.7	H=0.8	H=0.9
N=10	Direct Simulation	Mean	0.5197	0.6160	0.7122	0.8080	0.9031
		SD	0.0939	0.0846	0.0726	0.0567	0.0348
N=20	fbm() function	Mean	0.4999	0.5971	0.6964	0.7953	0.8953
		SD	0.0489	0.0484	0.0401	0.0331	0.0220
N=20	Direct Simulation	Mean	0.5064	0.6054	0.7044	0.8031	0.9014
		SD	0.0503	0.0463	0.0409	0.0333	0.0216
N=50	Direct Simulation	Mean	0.5028	0.6026	0.7022	0.8018	0.9010
		SD	0.0247	0.0231	0.0209	0.0176	0.0121
N=80	Direct Simulation	Mean	0.5016	0.6015	0.7013	0.8011	0.9007
		SD	0.0174	0.0163	0.0150	0.0128	0.0091

Simulation 2: Hurst estimation for sequential monitoring covariate adaptive randomized clinical trials with error terms i.i.d.

The increment properties for the sequential monitoring processes of models with CAR designs under different assumptions were evaluated. When the Hurst exponent is 0.5, the sequential monitoring processes follows a Brownian motion.

Normalized B value in the sequential monitoring procedures were calculated when error terms in the model are independent and identically distributed. Different sample sizes, including the total sample size N =1000 with 50 sliced observations of the time series generated after each of 20 patients , N =2000 with 100 sliced observations of the time series, N =3000 with 200 sliced observations of the time series, N =5000 with 250 sliced observations of the time series, and N =7500 with 500 sliced observations of the time series, were performed to the CAR procedures by the expression (1).

The first scenario, for example, totally 1000 patients were enrolled in the study with a uniformly distributed enter time. For each interim analysis, we may slice the information after every 20 new patients finished the study. 50 statistical test results were obtained from this simulation. The adaptive design parts were applied by I_i, that is the indicator variable for ith patient assigned to the different treatment groups. Patients were assumed sequentially randomized to two treatment groups by the complete randomization (CR), stratified permuted block randomization (SPB), and Pocock and Simon minimization (PS) method (Zelen, 1974; Pocock & Simon,1975). Despite multiple covariates can be analyzed in the covariate adaptive randomized clinical trials, we only considered no covariate, one single discrete covariate, one single continuous covariate, two continuous covariates, two discrete covariates and mix type (one continuous and one discrete) covariates in our simulation studies. We simulated discrete covariate as the Bernoulli distribution with the probability of "success" 0.5 and the continuous covariate as the normal distribution as $N(0,1)$.

In the equation (1), $\mu_1,\ \mu_2,\ \beta_1,\ \beta_2$ are unknown parameters. p_1, p_2 are the probability of "success" respectively in Bernoulli distribution when the covariates are binary variables. $\mu_1,\ \mu_2,\ \beta_1,\ \beta_2, p_1, p_2$ were set up as 0.5, 0.5, 1, 1, 0.5, 0.5 respectively. ε_i's were assumed to be independent and identity distribution following the normal distribution as $N(0,1)$. The sequential monitoring test statistic formula with multiple interim analyses were shown as the formula (2). Maximum likelihood method was used to estimate the Hurst exponent for B value transformed by the interim normalized Z value.

Table 2 indicated that the Hurst exponents estimated by maximum likelihood method are approximate to 0.5 for covariate adaptive randomized clinical trial when ε terms are independent and identically distributed (asymptotically, H=0.5). As the sample size increased, the standard deviation of the estimated H value decreased. From the histograms, the distributions of the mean estimated H value are close to normal distribution. The models with no covariate, one single covariate and two covariates reached similar Hurst exponent results. The theory that the sequential monitoring test statistics of standard CAR procedures asymptotically converge to Brownian motion was verified (Zhu & Hu, 2019). The conclusions were not affected by the types of the covariates.

Table 2 Hurst exponent estimation for CAR with ε i.i.d.

	Designs		N=1000, n=50	N=2000, n=100	N=3000, n=200	N=5000, n=250	N=7500, n=500
μ_1, μ_2	No covariate						
(0.5, 0.5)	CR	Mean	0.4997	0.4999	0.4998	0.4999	0.5000

		SD	0.0259	0.0153	0.0091	0.0079	0.0051
	PS	Mean	0.5001	0.5008	0.5000	0.5000	0.4999
		SD	0.0249	0.0150	0.0096	0.0083	0.0048
	SPB	Mean	0.5004	0.5003	0.4995	0.5005	0.5000
		SD	0.0245	0.0145	0.0089	0.0080	0.0051
$\mu_1, \mu_2, \beta_1, p_1$	One discrete covariate						
(0.5, 0.5, 1, 0.5)	CR	Mean	0.4995	0.4996	0.4992	0.4996	0.4999
		SD	0.0254	0.0153	0.0092	0.0077	0.0060
	PS	Mean	0.5010	0.5003	0.5002	0.4997	0.5001
		SD	0.0250	0.0152	0.0092	0.0080	0.0059
	SPB	Mean	0.5003	0.5002	0.4994	0.5004	0.4999
		SD	0.0245	0.0145	0.0089	0.0080	0.0051
μ_1, μ_2, β_1	One continuous covariate						
(0.5, 0.5, 1)	CR	Mean	0.5004	0.4990	0.4998	0.4994	0.4999
		SD	0.0255	0.1480	0.0089	0.0080	0.0051
	PS	Mean	0.5010	0.5011	0.4997	0.4997	0.4999
		SD	0.0261	0.0155	0.0097	0.0079	0.0051
	SPB	Mean	0.5002	0.5000	0.5002	0.4996	0.4998
		SD	0.0252	0.0147	0.0094	0.0080	0.0051
$\mu_1, \mu_2, \beta_1, \beta_2, p_1, p_2$	Two discrete covariates						
(0.5, 0.5, 1, 1, 0.5, 0.5)	CR	Mean	0.4997	0.4988	0.4996	0.4993	0.4998
		SD	0.0255	0.0147	0.0089	0.0080	0.0051
	PS	Mean	0.4999	0.5007	0.4999	0.5000	0.5001
		SD	0.0249	0.0150	0.0096	0.0083	0.0059

	SPB	Mean	0.5001	0.5002	0.4994	0.5004	0.5002
		SD	0.0245	0.0145	0.0089	0.0080	0.0058
$\mu_1, \mu_2, \beta_1, \beta_2$	Two continuous covariates						
	CR	Mean	0.4972	0.4993	0.4992	0.4997	0.4997
		SD	0.0256	0.0152	0.0094	0.0077	0.0062
(0.5, 0.5, 1, 1)	PS	Mean	0.5004	0.5009	0.4995	0.4995	0.4998
		SD	0.0262	0.0155	0.0096	0.0080	0.0052
	SPB	Mean	0.5000	0.4998	0.5001	0.4995	0.4998
		SD	0.0252	0.0148	0.0094	0.0008	0.0051
$\mu_1, \mu_2, \beta_1, \beta_2, p_1$	One continuous and one discrete						
	CR	Mean	0.5004	0.4990	0.4998	0.4994	0.4999
		SD	0.0255	0.1480	0.0089	0.008	0.0051
(0.5, 0.5, 1, 1, 0.5)	PS	Mean	0.5013	0.5002	0.4999	0.5002	0.5000
		SD	0.0244	0.0153	0.0092	0.0080	0.0051
	SPB	Mean	0.5025	0.5009	0.5001	0.5001	0.5000
		SD	0.0241	0.0157	0.0091	0.0080	0.0051

Simulation 3: Hurst estimation for sequential monitoring CAR procedures with correlated error terms

Furthermore, numerical simulations were created to illustrate the newly derived hypothesis testing formula (3) for the CAR procedures with correlated error terms. Different population numbers, covariate types and adaptive design methods were illustrated. The first simulation, for example, included totally 50 patients who were enrolled in the study with an equally distributed enter time. Suppose an interim analysis

should be performed when we have 50 patients, we can form first observation of the monitoring time series when first 21 patients finished the follow up; the second observation with the first 22 patients; the third observation with the first 23 patients; in the same analogy, the thirty observation was done with the first 50 patients; totally 30 normalized B values were calculated under this scenario. Then we can estimate the H and make statistical inference on the H value for conducting the interim analysis.

The error ε_i's in the formula (1) were assumed to follow fractional Gaussian process with $H = 0.8$ for the covariance structure. Fractional Gaussian process is the increments of fractional Brownian motion defined as $W_i = B_H(t_i) - B_H(t_{i-1})$ (Qian, 2003). The sequential monitoring test statistic formula (3) and (4) with multiple interim analyses were performed with new derived parameters $\hat{\beta}$ and $\hat{\sigma}^2$ as showed in formula (5) and (6). "V" matrix represented the covariance matrix of the fractional Gaussian process, which is the $R(u,\ v) = E(W_u W_v) = \frac{1}{2}\{|u-(v+1)|^{2H} + |v-(u+1)|^{2H} - 2|u-v|^{2H}\}$ (Delignières, 2015). Table 3 demonstrated the mean and standard deviation estimations for the Hurst exponents in the sequential monitoring process with no covariate, with two discrete covariates, and with two continuous covariates simulation results. The discrete covariates were simulated as the Bernoulli distribution with the probability of "success" 0.5. and the continuous covariates as the normal distribution $N(0,1)$. Figure 1-3 displayed the histograms for CAR designs when ε's following increments of fractional Brownian motion structures considering the correlated pattern of error terms in the test statistics formula with complete randomization designs, SPB adaptive designs, and PS adaptive designs respectively. From Table 3 and Figure 1-3, all Hurst exponent mean estimated results are close to 0.5. The standard deviation decreased along with the trail sample size increased. When the sample size was only 50 and no covariates assumed in the model, H values deviated more from 0.5. Based on the

simulation results, it can be verified that the sequential monitoring processes of covariate adaptive randomized clinical trials followed Brownian motion properties if the covariate form was considered in the test statistics formula.

Table 3 Hurst exponent estimation for CAR with ε's correlated

	Designs		N=50 n=30	N=100 n=80	N=200 n=180	N=250 n=230	N=500 n=480
μ_1, μ_2	No covariates						
(0.5, 0.5)	CR	Mean	0.5031	0.4982	0.4978	0.4978	0.4981
		SD	0.0863	0.0368	0.0197	0.0163	0.0088
	PS	Mean	0.5050	0.4993	0.4975	0.4984	0.4986
		SD	0.0832	0.0400	0.0199	0.0164	0.0086
	SPB	Mean	0.5092	0.4997	0.4984	0.4973	0.4986
		SD	0.0789	0.036	0.0194	0.0172	0.0082
$\mu_1, \mu_2, \beta_1, \beta_2, p_1, p_2$	Two discrete covariates						
(0.5, 0.5, 1, 1, 0.5, 0.5)	CR	Mean	0.5016	0.4928	0.4944	0.4949	0.4969
		SD	0.0803	0.0378	0.0193	0.0163	0.0089
	PS	Mean	0.5057	0.4980	0.4962	0.4972	0.4979
		SD	0.0872	0.0415	0.0198	0.0166	0.0089
	SPB	Mean	0.5053	0.4977	0.4976	0.4965	0.4980
		SD	0.0790	0.0366	0.0195	0.0172	0.0084
$\mu_1, \mu_2, \beta_1, \beta_2$	Two continuous covariates						
	CR	Mean	0.4998	0.4959	0.4952	0.4954	0.4975
		SD	0.0826	0.0359	0.0189	0.016	0.0087

(0.5, 0.5, 1, 1)	PS	Mean	0.5061	0.4971	0.4955	0.4969	0.4983
		SD	0.0881	0.0409	0.0218	0.0179	0.0102
	SPB	Mean	0.5069	0.4930	0.4961	0.4966	0.4977
		SD	0.0779	0.0369	0.0201	0.0163	0.0085

Figure 1 Histogram for complete randomization CAR designs ε correlated with no covariate: (a) Sample size 50, (b) Sample size 100, (c) Sample size 200, (d) Sample size 250, (e) Sample size 500.

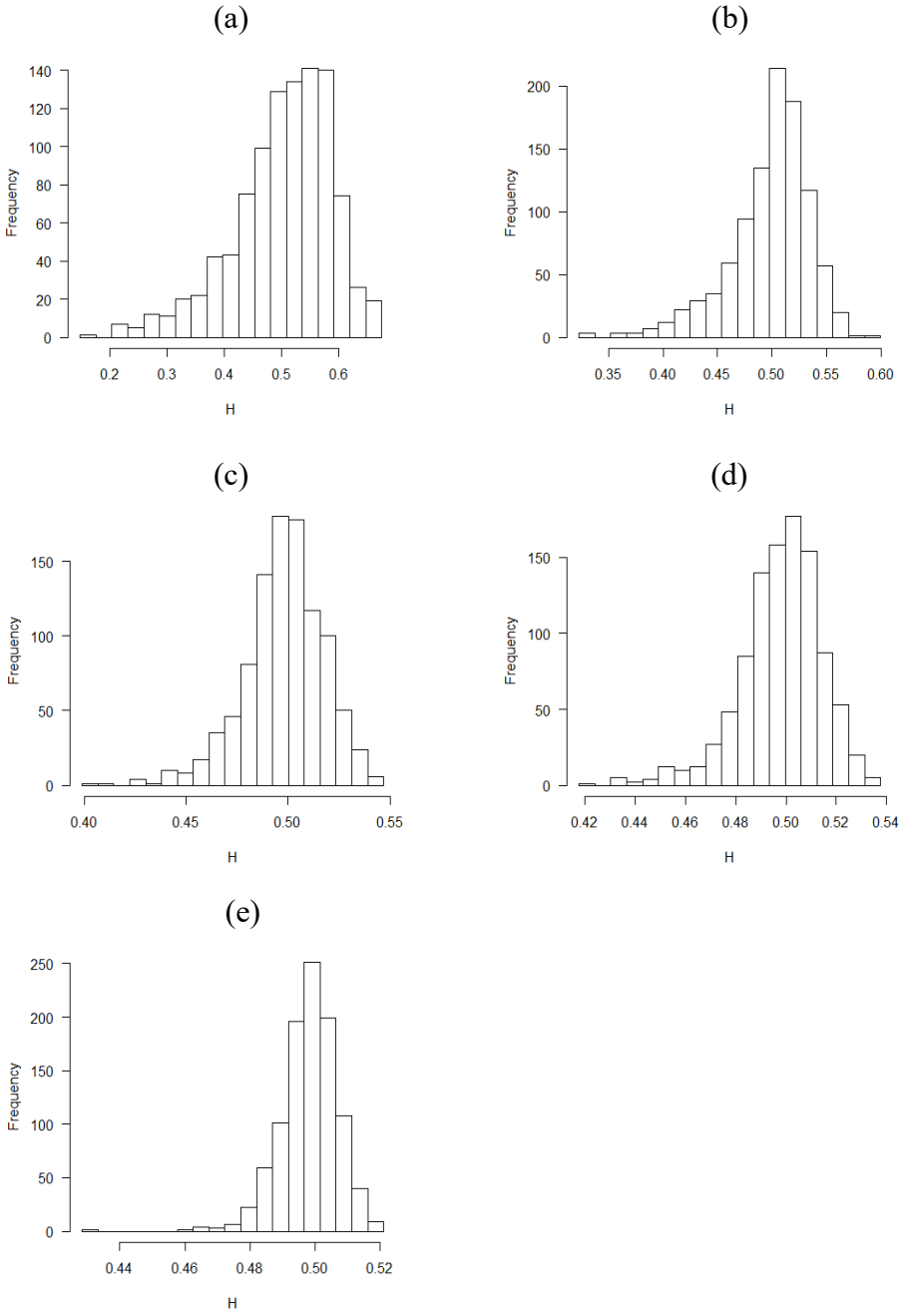
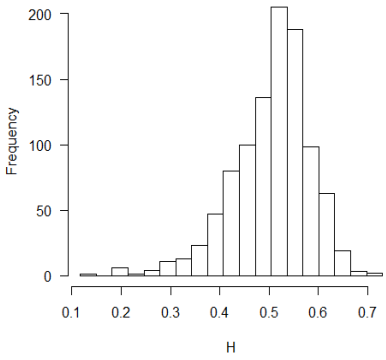
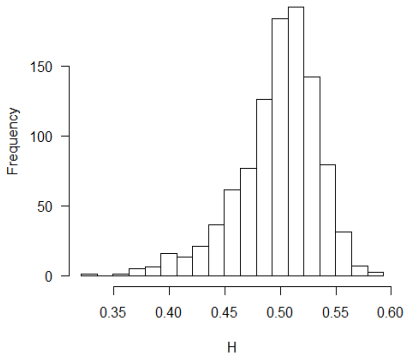


Figure 2 Histogram for SPB adaptive CAR designs ε correlated with **two** discrete covariates: (a) Sample size 50, (b) Sample size 100, (c) Sample size 200, (d) Sample size 250, (e) Sample size 500.

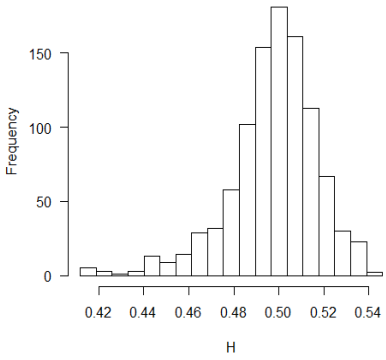
(a)



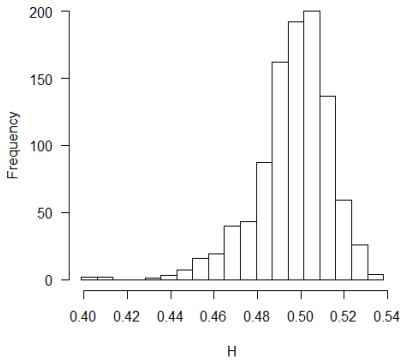
(b)



(c)



(d)



(e)

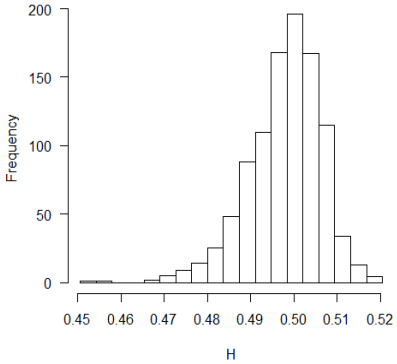
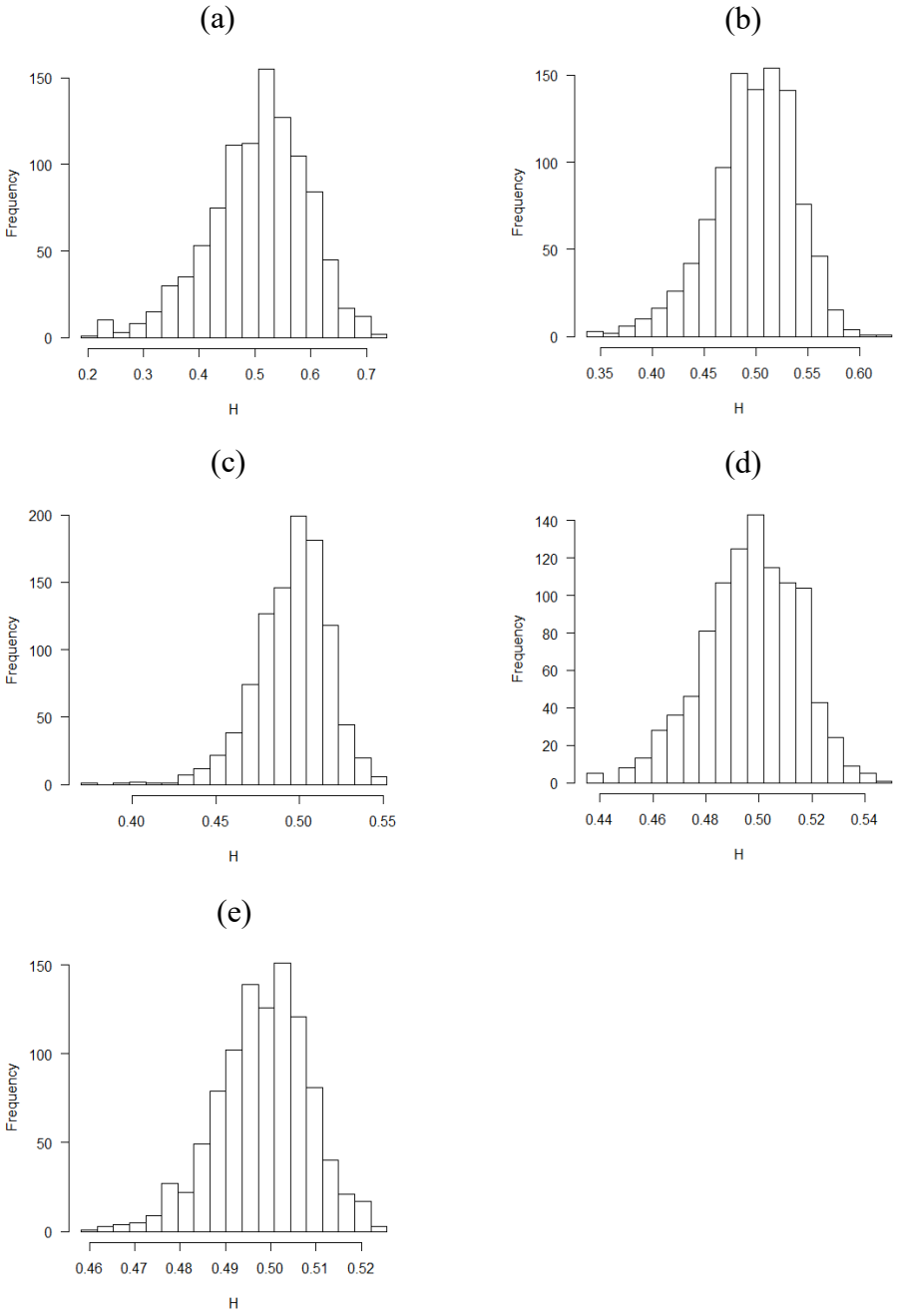


Figure 3 Histogram for PS adaptive CAR designs ε correlated with **two** continuous covariates: (a) Sample size 50, (b) Sample size 100, (c) Sample size 200, (d) Sample size 250, (e) Sample size 500.



4. Discussion

Classical Brownian motion has been recognized as the fundamental test for monitoring outcome effects in the clinical trials (Lan & Wittes, 1988). Covariate adaptive randomized designs are of great use for balancing the covariates in the clinical trial. One

of the challenges for studying the properties of covariate adaptive randomized clinical trial is that the treatment assignments and covariates are not independent.

The Brownian motion properties are theoretically investigated for the sequential monitoring processes with CAR designs under i.i.d. error structure (Zhu & Hu, 2019). However, in some situations, the error terms of the model may not be independent and identically distributed. In our study, a new test statistic formula was proposed including the "V" matrix being the covariance pattern of the error terms in the model. The theoretical derivation showed that the corresponding asymptotic distributions of the new test statistics were normal distribution under the null hypothesis. The asymptotic results of the theoretical derivation were demonstrated for the proposed new derived model. The distribution of sequential process based on the new test statistics form was derived to follow asymptotically Brownian motion. If ignoring the covariance in the error terms, the inferenced parameters in the model with CAR procedures will be misleading. The power calculation in both interim analyses and final analysis for the whole population would not be accurate.

Comprehensive simulation studies were used to illustrate the theorical results with 1000 replications for all the simulations. In the first simulation, the mean estimate of Hurst exponents can more closely represent the true generated H value, along with the increasing of the sample size. The mean estimated Hurst exponent values for normalized B values were all close to 0.5 by using maximum likelihood estimation method. Brownian motion theory is still suitable for the sequential monitoring processes with the test statistics when the error terms are not independent and identically distributed as long as the covariance matrix is correctly specified.

However, the true variance-covariance matrix is generally unknown and likely to be misspecified. Then the resulting stochastic process of the test statistic would not follow

Brownian motion. We have investigated these scenarios further separately (Yang et al., 2021).

Authors' contributions

Study designs: Dejian Lai and Hongjian Zhu.

Simulation studies: Yiping Yang.

Theory derivation, manuscript writing, and review: All authors

Final approval of manuscripts: All authors.

Potential conflicts of interest

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This publication was neither originated nor managed by AbbVie, and it does not communicate results of AbbVie-sponsored Scientific Research. Thus, it is not in scope of the AbbVie Publication Procedure (PUB-100).

Funding

This work was partially supported by Cancer Prevention Research Institute of Texas (RP170668). This work was partly supported by grant DMS-2014951 from the National Science Foundation (USA) (Dr. Hongjian Zhu).

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