MONITORING ONGOING CLINICAL TRIALS UNDER FRACTIONAL BROWNIAN MOTION WITH DRIFT

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And approved by

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by Peng Zhang

Dissertation Directors: Yong Lin and Weichung Joe Shih

Over the past decades, there have been lots of methods developed for monitoring clinical trials and adaptive design under Brownian motion structure. Early efficacy, futility stopping could be conducted by looking at the treatment effect or Z-value at the interim. Conditional power could predict the trial success in the end and sample size re-estimation could be conducted to achieve desired power while a low conditional power is observed. Those approached were built under Brownian motion (Bm) structure, which assumes the independent and identical distribution. However, in real clinical trials, sponsor or Data monitoring committee usually could not make the decision based on the one-point statistics but would like to see if any trend exists, in terms of dependence or mean change. While fractional Brownian motion (fBm) model take dependence into consideration, we could both assume non-linear drift into the model to handle mean change. In this dissertation, we proposed the procedure for inference of Hurst exponent for dependence under fBm with linear drift. Numerical results have been given to detect the property under finite sample size. Moreover, the formulas of conditional power and SSR under fBm with linear drift are given. We provide examples to illustrate how to apply the methods on the real study and compare the results between different model structures. Further, adjusted critical boundary calculation is given if an extreme Hurst exponent is observed to protect type I error rate. Finally, a
model of fractional Brownian motion with piece-wise linear drift is developed. Estimation, test of change-point is discussed as well as conditional power calculation under fBm with non-linear drift.
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Dedication

To my family and friends always supporting and embracing me.
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1.1 Monitoring Clinical Trials

In a randomized clinical trial, we need to calculate sample size with an assumed treatment effect based on previous studies. When all patients’ measurements have been collected, we can determine efficacy at the end of the study. This type of experiment is called fixed-sample design. However, if the sample size is calculated based on pessimistic treatment effect, the efficacy could not be claimed early, resulting in a long waiting period and wasted resources. To claim efficacy at an early stage, we could calculate early critical boundary by various methods [Pocock 1977; O’Brien and Fleming 1979; Lan and DeMets 1983]. In this case, early efficacy could be claimed if the observed Z-value crosses the critical boundary at interim analysis, and the trial would be stopped for efficacy with smaller sample size. Also, when the observed treatment effect at interim analysis is much lower than expected, we might terminate the trial for futility and stop wasting resources and time to prevent patients from receiving ineffective treatments [Gould and Pecore 1982]. Further, we could monitor the trial and calculate out the probability of trial success in terms of conditional power [Lan and Wittes 1988] based on observed treatment effect. There is one more scenario that power is not enough if we overly optimistic assumed treatment effect. In this case, sample size re-estimation or re-calculation (SSR) would be implemented to recruit more patients than the original sample size. SSR was first introduced by [Gould and Shih 1992] for blinded data and later was used for unblinded data to achieve desired power [Li et al. 2002; Chen et al. 2004; Gao et al. 2008]. Note that some actions should be included to control type I error rate after SSR: We shall change test statistics [Cui et al. 1999] or critical boundary [Li et al. 2002; Gao et al. 2008]. Another method called Promising Zone approach has been developed [Chen et al. 2004; Mehta and Pocock 2011], which
stated that SSR could be implemented without any adjustment if observed treatment effect is promising, corresponding to an acceptable conditional power. Therefore, adaptive design becomes flexible and practical for the kinds of scenarios listed above.

1.2 Brownian Motion and Fractional Brownian Motion

Brownian motion has been widely used for sequentially monitoring clinical trials (Lan and Wittes, 1988). The method is intuitive and easy to illustrate and interpret. As computation develops, it is easier to monitor the data flexibly in terms of timing and frequency of the interim analyses. Based on a recent study of Remdesivir in China (Shih et al., 2020), it is feasible to monitor and visualize the data instantaneously for specific statistics, e.g., B-value or Z-value, as shown in Figure 1.1. For some trials, we might find an observed sequence of B-value violating the assumption of Brownian motion (e.g., independent increment). In this case, we might need a more inclusive class of stochastic process that generalizes Brownian motion, which is called fractional Brownian motion (fBm) (Mandelbrot and Ness, 1968).

Figure 1.1: Treatment effect in terms of Z-value as patient accumulated at day 14
fBm could capture the correlation of process, utilizing more information from past observations. Lai et al. (2000) first introduced the concept of fractional Brownian motion into clinical trials. It claimed that in long-term clinical trials, patients are usually followed in the same center, and observed and treated by the same physician over a long period of time. Also, certain variable of the increments of statistics over time might exhibit long-term dependence, violating the assumption of Brownian motion. This long-memory features of data (or slowly decaying correlation) (Beran 1994) could be characterized by $H$, Hurst exponent. The term long-memory is used when correlations between observations far apart (in time or space) decay to zero at a slower rate than we would expect. In this case, even observations are far away (in terms of time) with each other, correlation might still exist. Further, Lai (2004) studied a maximum likelihood procedure for estimating the Hurst exponent $H$, and related conditional power by providing examples. More topics regarding fBm such as sample size calculation and critical boundary calculation under group sequential tests have been discussed (Lai 2010, 2013). In a recent paper, Huang and Lai (2019) gave the form of conditional power under fBm and studied the property by simulation. However, this method only showed the formula for conditional probability under the null but not the current trend or alternative. To calculate the latter types of conditional probability, we would need to estimate mean together with Hurst exponent. Under this circumstance, we need another model, fractional Brownian motion with linear drift (fBmld), to include all those information collectively. Hu et al. (2011) provided a method of estimation of mean and/or variance parameters under fBmld and Xiao et al. (2015) extended this method to estimate Hurst exponent sequentially through profile likelihood.

1.3 Change-Point Analysis

There have been lots of scenarios that treatment effects are not the same all along with the trials, especially for the trial with survival endpoints Luo et al. (1997). The delay in observable treatment effect may happen due to this lag effect. Also, as mentioned in the Proschan et al. (2006), suppose that midway through the trial, in response to lagging recruitment, the entry criteria is changed to make more patients eligible. If the newly recruited patients are different from those previously recruited, the mean difference may
vary. This might lead to the process with mixture of trends. Note that this topic is similar to that from some certain time point, the treatment effect becomes different from the one in previous stage, which is called change-point analysis.

Change-point analysis arises originally in the context of quality control, where one observes the output of a production process sequentially and wants to signal any departure of the average output, from some known target value Siegmund (1986). The likelihood ratio test James et al. (1987) could be applied on the data to test if the known change-point is significant or not. There is another scenario that we do not have information about change-point, which could be derived by maximum likelihood estimate Hinkley (1971). The estimate of change-point could be tested with similar statistics. However, as this statistic is maximally selected around statistics calculated at each point, it would follow a different distribution. Gombay and Horvath (1996) gives asymptotic distribution of the statistics in terms of square root.

As we might be not that confident on a single point during the trial or at interim analysis, more tools regarding the sequence of statistics should be applied on the clinical trials. FBm model and change-point analysis provide different angles to the ongoing clinical trials with more information. In the next chapter, we will review the literature for these different approaches.
Chapter 2

Literature Review

2.1 Brownian Motion (Bm) and Brownian Motion with Linear Drift (Bmld)

2.1.1 Brownian Motion (Bm)

Brownian motion with variance parameter $\sigma^2$ is a stochastic process \{B(t); t \geq 0\} \cite{Lawler} satisfying:

- $B(0) = 0$ and $B(t)$ is a continuous function of $t$.
- For any $s_1 \leq t_1 \leq s_2 \leq ... \leq s_n \leq t_n$, the random variables $B(t_1) - B(s_1), ..., B(t_n) - B(s_n)$ are independent. (Independent increment)
- For any $s < t$, the random variable $B(t) - B(s)$ has a normal distribution with mean 0 and variance $(t - s)\sigma^2$.

2.1.2 Brownian Motion with Linear Drift (Bmld)

Brownian motion with linear drift \{B'(t); t \geq 0\} could be constructed by adding a drift parameter $\theta$ to Brownian motion that

\[ B'(t) = B(t) + \theta t, t \geq 0 \] (2.1)

Also \{B'(t); t \geq 0\} satisfies:

- $B'(0) = 0$ and $B'(t)$ is a continuous function of $t$.
- For any $s_1 \leq t_1 \leq s_2 \leq ... \leq s_n \leq t_n$, the random variables $B'(t_1) - B'(s_1), ..., B'(t_n) - B'(s_n)$ are independent.
For any \( s < t \), the random variable \( B'(t) - B'(s) \) has a normal distribution with mean \( \theta(t - s) \) and variance \( (t - s)\sigma^2 \).

A standard Brownian motion is a Brownian motion with \( \sigma = 1 \).

An intuitive illustration between Bm and Bmld would be shown in Figure 2.1.

![Figure 2.1: Comparison between Brownian motion (Bm) and Brownian motion with linear drift (Bmld)](image)

2.2 Application in Clinical Trials under Structure of Bm and Bmld

2.2.1 Early Efficacy

In recent ages, there have been lots of literature discussing about how to stop the trial for early efficacy. Lots of popular methods such as Pocock boundary \cite{Pocock1977}, O’Brien-Fleming Boundary \cite{OBrienFleming1979}, alpha-spending function \cite{LanDeMets1983}, HSD boundary \cite{Hwangetal1990} have been introduced. The critical boundaries from all those results are derived from numerical integration by searching root for the solutions. By adding different restrictions on the relationship among the boundaries or significance level at each look, different kinds of boundaries would be derived.
To find the critical boundaries, we express the significance level $\alpha$ as

$$\alpha = P_{H_0}(Z_1 > c_1, \ldots, Z_k > c_k) \quad (2.2)$$

where $k$ is the total looks of the analysis. To solve for the unique solution of $c_1, \ldots, c_k$, additional restrictions should be given. Pocock (1977) and O’Brien and Fleming (1979) both mentioned that to stop the trial for early efficacy, equal spaced interim should be assumed. Also Pocock boundaries specified that

$$c_1 = \ldots = c_k \quad (2.3)$$

and O’Brien-Fleming boundaries specified that

$$c_1 \sqrt{t_1} = c_2 \sqrt{t_2} = \ldots = c_k \sqrt{t_k} \quad (2.4)$$

where time fraction $t_i = n_i/N, i = 1, \ldots, k$ with $n_i$ is the sample size at the $i$th look and $N$ is the total sample size.

While Pocock (1977) and O’Brien and Fleming (1979) gave restrictions on the boundaries, Lan and DeMets (1983) specified the restrictions on the alpha spent at each look by giving alpha spending function $\alpha(t)$. To calculate the boundaries, the cumulative alpha spent at the $i$th look would be calculated from $\alpha_i = \alpha(t_i)$, or equivalently, the alpha spent at the $i$th interim calculated from $\alpha_i^* = \alpha(t_i) - \alpha(t_{i-1})$. Then we have

$$\alpha_1 = P_{H_0}(Z_1 > c_1)$$

$$\alpha_2^* = P_{H_0}(Z_1 < c_1 \text{ and } Z_2 > c_2)$$

$$\vdots$$

$$\alpha_k^* = P_{H_0}(Z_1 < c_1, \ldots, Z_{K-1} < c_{K-1}, Z_K > c_k)$$

As alpha spent at each interim would be calculated from alpha-spending function, the critical boundaries would be derived sequentially by those equations. Moreover, this method allow unequal space of the interim analysis. Lan and DeMets (1983) provided two useful
types of critical boundaries based on different alpha spending functions: O’Brien-Fleming type boundary derived from $\alpha_1(t) = 2(1 - \Phi(z_{\alpha/2}/\sqrt{t}))$, Pocock type boundary derived from $\alpha_2(t) = \alpha(\ln(1 + (e - 1)t))$, which showed similar results to O’Brien-Fleming boundary and Pocock boundary.

Later, Hwang et al. (1990) provided a more inclusive alpha-spending function by adding another parameter $\gamma$ into the calculation. Alpha spent at each interim could be specified by given different values of $\gamma$ that

$$\alpha(\gamma, t) = \begin{cases} 
\alpha & \text{if } \gamma = 0 \\
\frac{1 - \exp(-\gamma t)}{1 - \exp(-\gamma)} & \text{if } 0 \leq t \leq 1 \\
\alpha t & \text{if } \gamma \neq 0 
\end{cases} \quad (2.6)$$

Then the boundaries could become more flexible by setting different values of $\gamma$.

### 2.2.2 Conditional Power

The concept of conditional power was first proposed by Lan and Wittes (1988). Conditional power is illustrated as probability of rejecting the null hypothesis conditional on current information. Under different assumptions, e.g., under the null, under the alternative, or under the current trend, we might have different formulas for the calculation and different results and interpretations.

Consider a two-arm trial with continuous endpoint with hypothesis test $H_0 : \mu = 0$ vs $H_a : \mu = \mu_a$. Suppose $N$ is the total sample size per arm. Denote $Z_n$ as the Z-value from first $n$ observations per arm and B-value is calculated as $B_n = Z_n \sqrt{t}$ with $t = n/N$, then CP could be calculated as

$$CP(\theta) = Pr(B_N = Z_N \geq z_{\alpha} | B_n, \theta)$$

$$= 1 - \Phi\left(\frac{z_{\alpha} - B_n - \theta(1 - t)}{\sqrt{1 - t}}\right) \quad (2.7)$$

where $\Phi(.)$ is cumulative density function of normal distribution. We could insert $\theta$ by using different values: $\theta = 0$ under $H_0$, $\theta = \sqrt{N/2}\mu_a$ under $H_a$. Moreover, researchers might be interested in the probability based on the current trend, e.g., current estimate of treatment
effect. Rather than using assumed treatment effect in the alternative, an estimate of drift parameter \( \theta = \hat{\theta} = B_n/t \) is used for calculation.

### 2.2.3 Sample Size Re-estimation (SSR)

Sample size plays a crucial role in clinical trials and a lot of flexible sample-size design has been recognized (Shih et al., 2016). One of those flexible sample-size designs includes sample size re-estimation, which calculates a new sample size based on current estimate of treatment effect to achieve desired power. Under this circumstance, original sample size would be replaced by the new sample size, and thus, the sponsor would need to recruit additional patients. Usually, there would be a capped sample size for SSR. If the new sample size calculated exceeds the cap, we would not implement the sample size re-estimation to waste resources for desired power or use the capped sample size as the new sample size with limited resources. Also, even SSR is implemented, we need additional actions to prevent the inflation of type I error rate. We would review SSR from type I error rate control and sample size re-estimation.

#### Type I Error Rate Control

At the design stage of a clinical trial, we need to specify type I error rate for sample size calculation. If SSR is implemented using current information at one interim analysis, type I error rate might be inflated or deflated. Theoretically, there are two ways to prevent inflation of type I error rate.

The first way is to change test statistic (Cui et al., 1999). In this method, we could keep the original critical value \( c_0 \) but change the calculation of Z-value that

\[
Z_{N_s}^* = \sqrt{t}Z_n + \sqrt{1-t}Z_{N_s-n}
\]

Where \( Z_{N_s-n} = \sum_{i=n+1}^{N_s} (x_i - y_i) / \sqrt{2(N_s - n)} \), \( N_s \) is new sample size per arm, \( t \) is the time of interim analysis with \( n \) patients per arm and \( Z_n \) is observed Z-value at the interim. In this method, after increasing sample size, we compare \( Z_{N_s}^* \) with \( c_0 \).

The second way is to change critical boundary (Li et al., 2002; Gao et al., 2008). Li
et al. (2002) changed the critical boundary by controlling 'Overall' type I error rate. This method views new critical boundary $c_1$ as a function of $Z_n$, the observed Z-value at the interim. Then $c_1$ could be solved by numeric integration from

$$1 - \alpha = \int_{-\infty}^{k} \Phi\left( \frac{c_1(z_n) \sqrt{n + n_2 - z_n \sqrt{n}}}{\sqrt{n_2}} \right) \phi(z_n) dz_n$$

(2.9)

where $\Phi(.)$ is c.d.f of normal distribution and $\phi(.)$ is p.d.f of normal distribution, $n$ is sample size per arm at the interim, $n_2$ is additional sample size per arm to recruit and $k$: Early efficacy boundary at the interim. Under this circumstance, $c_1$ could be specified in the protocol without the information of $z_n$.

Another approach proposed by Gao et al. (2008) controls the type I error rate by controlling 'conditional' type I error rate, which is conditional on observed treatment effect. This method keeps the original calculation of statistic and calculate a new critical boundary $c_1$ at new sample size per arm $N_s$ satisfying

$$c_1 \sqrt{N_s/N - Z_n \sqrt{t}} = c_0 - Z_n \sqrt{t}$$

(2.10)

Where $N_s$ is new sample size per arm, $N$ is original sample size per arm, $t$ is time of interim analysis with n patients per arm, $Z_n$ is observed Z-value at the interim, $c_0$ is original critical value at the end of planned study. Note that this method requires the value of $Z_n$ and new critical value could not be specified previously in the protocol.

Moreover, ‘promising zone’ approach has been developed in recent age (Chen et al., 2004; Mehta and Pocock, 2011). They claimed that there is no need to change the critical boundary or statistic to protect the type I error rate if their observed treatment effect is promising in a certain range called promising zone. Intuitively, if we observe a ‘promising’ treatment effect, we do not need additional change.

**Calculation of New Sample Size**

The purpose of SSR is to achieve desired power by increasing sample size. Suppose we control type I error rate by adjusting critical boundary. To achieve a conditional power at
1 − β' level, we have

\[
1 - \beta' = P\left( Z_{N_s} > c_1 | \theta = \hat{\theta} \right) = P\left( \frac{Z_{N_s} \sqrt{N_s/N} - Z_n \sqrt{t} - \hat{\theta}(N_s/N - t)}{\sqrt{N_s/N - t}} > \frac{c_1 \sqrt{N_s/N} - Z_n \sqrt{t} - \hat{\theta}(N_s/N - t)}{\sqrt{N_s/N - t}} \right)
\]

(2.11)

\[
= \Phi\left( \frac{\hat{\theta}(N_s/N - t) + Z_n \sqrt{t} - c_1 \sqrt{N_s/N}}{\sqrt{N_s/N - t}} \right)
\]

\[
= \Phi\left( \frac{\hat{\theta} \sqrt{N_s/N - t} - c_1 \sqrt{N_s/N} - Z_n \sqrt{t}}{\sqrt{N_s/N - t}} \right)
\]

then by substitution of c₁ by c₀, we have

\[
1 - \beta' = \Phi\left( \frac{\hat{\theta} \sqrt{N_s/N - t} - c_0 - Z_n \sqrt{t}}{\sqrt{N_s/N - t}} \right)
\]

(2.12)

and

\[
N_s = N \left( \left( \frac{\Phi^{-1}(1 - \beta') \sqrt{1 - t} + c_0 - Z_n \sqrt{t}}{\hat{\theta} \sqrt{1 - t}} \right)^2 + t \right)
\]

(2.13)

Note that here the new sample size calculation is based on only current information (i.e. \((\hat{\theta}, Z_n, t)\)) without adjusted critical value \(\text{[Gao et al., 2008]}\).

2.3 Fractional Brownian Motion (fBm) and Fractional Brownian Motion with Linear Drift (fBmld)

Traditionally, snap-shot Z-value is sufficient for estimating treatment effect. However, inference might not be correct if observations of truly correlated. Under this circumstance, the whole historical path are needed for estimation and we need consider a more inclusive model with consideration of correlation: fractional Brownian motion (fBm).
2.3.1 Fractional Brownian Motion (fBm)

It is well known and established to monitor the trial under Brownian motion \cite{Lan1988} with independent increment. However, the assumption might be violated when recruiting patients in a long period or even a short period because of correlation between observations. \cite{Lai2000} Then fractional Brownian motion (fBm) would be helpful to solve this problem of dependent increment.

(Standardized) Fractional Brownian motion (fBm) \cite{Mandelbrot1968, Beran1994, Mishura2008} is defined as a Gaussian process \{B_H(t); t \geq 0\} satisfying

- \( B_H(0) = 0 \)
- For any \( t \geq 0 \), \( E(B_H(t)) = 0 \)
- For any \( t, s \geq 0 \), \( \text{Cov}(B_H(t), B_H(s)) = \frac{1}{2} (t^{2H} + s^{2H} - |t - s|^{2H}) \)

Under the assumption of fBm, B-value will be characterized as \( B_H(t) \) with the Hurst exponent \( H \) with range \( 0 < H < 1 \). Specifically, \( B_H(t) \) is a Brownian motion with \( \sigma = 1 \) when \( H = 0.5 \).

For \( 0 \leq s \leq t \), we have

\[
\text{Cov}(B_H(s), B_H(t) - B_H(s)) = \frac{1}{2} (t^{2H} - s^{2H} - (t - s)^{2H}) \begin{cases} > 0 & H > 1/2 \\ = 0 & H = 1/2 \\ < 0 & H < 1/2 \end{cases} \quad (2.14)
\]

Then positive correlation of increments would be resulted from \( H > 1/2 \) and negative correlation of increments would be resulted from \( H < 1/2 \).

Under different values of Hurst exponent, the process might present different volatility. Figure 2.2 uses simulations to illustrate this property under different Hurst exponent. As displayed in the plots, the smaller the Hurst exponent, the larger the volatility of plot would be. Equivalently, when Hurst exponent becomes bigger, the plot would be more smooth.
2.3.2 Fractional Brownian Motion with Linear Drift (fBmld)

Fractional Brownian motion with linear drift (fBmld) \( \{ B'_H(t); t \geq 0 \} \) (Hu et al. 2011; Xiao et al. 2015) is introduced by adding drift parameters \( \theta \) and volatility parameter \( \sigma \) to fBm that

\[
B'_H(t) = \theta t + \sigma B_H(t)
\]

Also, \( \{ B'_H(t); t \geq 0 \} \) satisfies that:

- \( B'_H(0) = 0 \)
- For any \( t \geq 0 \), \( E(B'_H(t)) = \theta t \)
- For any \( t, s \geq 0 \), \( \text{Cov}(B'_H(t), B'_H(s)) = \frac{\sigma^2}{2} (t^{2H} + s^{2H} - |t - s|^{2H}) \)

An intuitive illustration of fBmld would be shown in Figure 2.3.
2.4 Development under Structure of fBm and fBmld

2.4.1 Estimation of Hurst exponent under fBm

Hurst exponent could be estimated through the maximum likelihood estimation method (Lai, 2004). Specify $B_H(t) = (B_H(t_1), ..., B_H(t_n))^T$ as the observed value of a fractional Brownian motion $\{B_H(t); t \geq 0\}$ defined in subsection 2.3.1 with sample size $n$ and $t = (t_1, ..., t_n)^T$, then the log-likelihood function would be written as

$$l_n(B_H(t), H) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} B_H(t)^T \Sigma_H^{-1} B_H(t) \quad (2.16)$$

as $B_H(t) \sim MVN(0, \Sigma_H)$ and $\Sigma_H$ defined in subsection 2.3.1. Then maximum likelihood estimation of Hurst exponent could be derived by maximizing the log-likelihood function $l_n(x, H)$. As there is no closed-form of estimation, we could search the MLE by optimization of log-likelihood.
2.4.2 Estimation of Hurst exponent and drift parameter under fBmld

Consider a fractional Brownian motion with linear drift \( B'_H(t) = \theta t + B_H(t) \) defined in 2.3.2 by assuming \( \sigma = 1 \). The MLE of drift parameter \( \theta \) could be expressed as a function of Hurst exponent (Hu et al., 2011). Denote \( B'_H(t) = (B'_H(t_1), ..., B'_H(t_n))^T \) as the observed value of \( \{B'_H(t); t \geq 0\} \) with sample size \( n \) and \( t = (t_1, ..., t_n)^T \), then the log-likelihood function would be written as

\[
l_n(B'_H(t), H, \theta) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} (B'_H(t) - \theta t)^T \Sigma_H^{-1} (B'_H(t) - \theta t) \tag{2.17}\]

as \( Y \sim MVN(\theta t, \Sigma_H) \) and \( \Sigma_H \) defined in subsection 2.3.2. Setting derivative of \( l_n(b'_H(t), H, \theta) \) w.r.t to \( \theta \) to be zero that

\[
\frac{\partial l_n(y; H, \theta)}{\partial \theta} = t^T \Sigma_H^{-1} b'_H(t) - t^T \Sigma_H^{-1} t \theta = 0 \tag{2.18}
\]

where \( b'_H(t) \) is observed value of \( B'_H(t) \). This leads to the closed-form maximum likelihood estimate

\[
\hat{\theta}_{MLE}(H) = \frac{t^T \Sigma_H^{-1} b'_H(t)}{t^T \Sigma_H^{-1} t} \tag{2.19}
\]

Note that \( \hat{\theta}_{MLE} \) depends on the value of \( H \), which means MLE of Hurst exponent \( H \) could be estimated by profile likelihood (Xiao et al., 2015), inserting \( \hat{\theta}_{MLE} \) into the likelihood function. Then log-likelihood would be written as a function of only one parameter \( H \) that

\[
l_n(B'_H(t), H) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} (B'_H(t) - \hat{\theta}(H)t)^T \Sigma_H^{-1} (B'_H(t) - \hat{\theta}(H)t) \tag{2.20}\]

Similarly, MLE of Hurst exponent \( H \) could be derived by optimization method and then \( \hat{H}_{MLE}(H) \) could be estimated by inserting \( \hat{H}_{MLE} \).
2.4.3 Conditional Power under fBm

Because of Markov property under Brownian motion structure, the conditional probability of rejecting the null could be calculated just based on the current state $B(t)$ rather than all past states. But under the assumption of fractional Brownian motion, all the states in the past should be taken into consideration for calculation. Lai et al. (2000) and Lai (2004) introduced the calculation of conditional probability with fractional Brownian motion structure by R/S estimate and MLE of Hurst exponent.

Assume $X = (B_H(t_1), ..., B_H(t_{K-1}), B_H(t_K))^T$ follows a multivariate normal distribution $MVN(0, \Sigma)$. The parameters are characterized as

$$
\Sigma = \begin{bmatrix}
\sigma_1^2 & \sigma_{12} & \cdots & \sigma_{1K} \\
\sigma_{21} & \sigma_2^2 & \cdots & \sigma_{2K} \\
\vdots & \vdots & \ddots & \vdots \\
\sigma_{K1} & \sigma_{K2} & \cdots & \sigma_K^2
\end{bmatrix} = \begin{bmatrix}
\Sigma^{(11)} & \Sigma^{(12)} \\
\Sigma^{(21)} & \Sigma^{(22)}
\end{bmatrix}
$$

(2.21)

Denote $B_H(t) = (B_H(t_1), ..., B_H(t_{K-1}))^T$ with at $t = (t_1, ..., t_{K-1})$ $b_H(t)$ as the observations. Then conditional distribution of $B_H(t_k)$ given $B_H(t) = b_H(t)$ would be

$$B_H(t_k) | B_H(t) = b_H(t) \sim N(\mu_c, \sigma_c^2)$$

(2.22)

with conditional mean

$$\mu_c = \Sigma^{(21)}(\Sigma^{(11)})^{-1}x^{(1)}$$

(2.23)

and conditional variance

$$\sigma_c^2 = \sigma_{KK}^2 - \Sigma^{(21)}(\Sigma^{(11)})^{-1}\Sigma^{(12)}$$

(2.24)
Then conditional probability under fBm $CP_H$ could be calculated by

$$CP_H = P(Z_N = B_H(1) > z_\alpha | H, B_H(t)) = 1 - \Phi \left( \frac{z_\alpha - \mu_c}{\sigma_c} \right)$$

(2.25)

We could use assumed value of $H$ or estimate $\hat{H}$ for the calculation.

### 2.4.4 Early Efficacy under fBm

When there is true correlation between observations, i.e. $H \neq 0.5$, calculation of critical boundaries of group sequential design are not the same as the ones under Brownian motion structure, as $Z$-values at each of the interim analysis are correlated with each other.

Without loss of generality, we assume five looks in a two-arm clinical trials with equally space $t = (0.2, 0.4, 0.6, 0.8, 1)$. Following fractional Brownian motion structure, we have

$$\begin{align*}
Var(B(t)) &= Cov(B(t), B(t)) = \frac{1}{2}(t^{2H} + t^{2H}) = t^{2H} \\
Cov(B(t), B(s)) &= \frac{1}{2}(t^{2H} + s^{2H} - |t - s|^{2H})
\end{align*}$$

(2.26)

Consider calculation of O’Brien-Fleming type boundary and Pocock type boundary. Lan and DeMets (1983) has given out OB-F type boundaries based on Alpha spending function $\alpha(t) = 2 - 2\Phi(z_\alpha/\sqrt{t})$. Lai (2010) applied this function on boundaries calculation of $H \neq 0.5$,

<table>
<thead>
<tr>
<th>$H$</th>
<th>Boundary Type</th>
<th>$c_1$</th>
<th>$c_2$</th>
<th>$c_3$</th>
<th>$c_4$</th>
<th>$c_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>O’Brien-Fleming type</td>
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<td>3.68</td>
<td>2.82</td>
<td>2.36</td>
<td>2.06</td>
</tr>
<tr>
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<td>3.36</td>
<td>2.68</td>
<td>2.29</td>
<td>2.03</td>
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<tr>
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<td>2.52</td>
<td>2.46</td>
<td>2.41</td>
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<tr>
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<td>2.43</td>
<td>2.41</td>
<td>2.40</td>
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<tr>
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<td>2.09</td>
<td>2.16</td>
<td>2.24</td>
<td>2.30</td>
</tr>
</tbody>
</table>

Table 2.1: Efficacy boundary under different Hurst exponent from the same alpha spending function
Figure 2.4: Visualization of efficacy boundary under different Hurst exponent from the same alpha spending function
2.5 Change-point analysis

2.5.1 Test for known change-point

Consider only fixed sample problems involving a finite sequence $X_1, \ldots, X_n$, where $X_i$ are independent and normally distributed with mean $\mu_{(i)}$ and variance of 1. We would like to test the null hypothesis of no change against the alternatives of exactly one change

$$H_0 : \mu_{(1)} = \ldots = \mu_{(n)}$$

vs

$$H_a : \exists 1 \leq m < n \text{ such that } \mu_{(1)} = \ldots = \mu_{(m)} = \mu_1 \neq \mu_2 = \mu_{(m+1)} = \ldots = \mu_{(n)}$$

A likelihood ratio test (LRT) could be applied (James et al., 1987) for this hypothesis testing:

$$T_{LR} = -2 \log \left( \frac{\sup_{\mu \in M_0} L(\mu|X)}{\sup_{\mu_1, \mu_2 \in M_a} L(\mu_1, \mu_2|X)} \right)$$

(2.27)

where $M_0$ is the sets of parameter $\mu$ under the $H_0$ and $M_a$ is the sets of parameter $(\mu_1, \mu_2)$ under the $H_a$. The MLE of $\mu$ could be derived as $\hat{\mu} = \frac{1}{n} \sum_{i=1}^{n} X_i = \bar{X}$ and given the change-point $m$, MLE of $\mu_1, \mu_2$ $\hat{\mu}_1 = \frac{1}{m} \sum_{j=1}^{m} X_j = \bar{X}_1$, $\hat{\mu}_2 = \frac{1}{n-m} \sum_{k=m+1}^{n} X_k = \bar{X}_2$

Then this LRT statistics could be calculated as

$$T_{LR} = -2 \log \left( \frac{\left( \frac{1}{\sqrt{2\pi}} \right)^n \exp \left( -\frac{\sum_{i=1}^{n} (X_i - \bar{X})^2}{2} \right)}{\left( \frac{1}{\sqrt{2\pi}} \right)^n \exp \left( -\frac{\sum_{j=1}^{m} (X_j - \bar{X}_1)^2}{2} - \frac{\sum_{k=m+1}^{n} (X_k - \bar{X}_2)^2}{2} \right)} \right)$$

(2.28)

$$= \frac{n}{m(n-m)} \left( S_m - \frac{m}{n} S_n \right)^2$$

where $S_i = \sum_{j=1}^{i} X_j$. This test statistic is the normalized difference between the mean of the first $m$ observations, $S_m/m$ and the overall mean, $S_n/n$. Then under regularity conditions, $T_{LR} \xrightarrow{d} \chi^2_1$ as $n \to \infty$ under the null.
2.5.2 Estimate and test of unknown change-point

Usually, we would not have the information of the change-point, i.e., when we have different mean. In this case we need to estimate the change-point to make more inference. The change-point $m$ here would be therefore a random variable. If the information of $m$ is unknown, the maximum likelihood estimate of change point $\hat{m}$ could be derived [Hinkley (1971)] from

$$\hat{m} = \arg\max_{1 \leq m < n} \left( \frac{1}{\sqrt{2\pi}} \right)^n \exp\left( -\frac{1}{2} \sum_{j=1}^{m} (X_j - \bar{X}_1)^2 - \frac{1}{2} \sum_{k=m+1}^{n} (X_k - \bar{X}_2)^2 \right) \tag{2.29}$$

After $\hat{m}$ is derived, the likelihood ratio statistic would be calculated as

$$T_{LR}^* = \frac{n}{\hat{m}(n - \hat{m})} \left( S_m - \frac{\hat{m}}{n} S_n \right)^2 \tag{2.30}$$

It would be in a similar form but follows a different distribution. [Gombay and Horvath (1996)] gave asymptotic distribution of this statistics in terms of square root.

Denote $Z_n = (T_{LR}^*)^{1/2}$, $a(t) = (2 \log(t))^{1/2}$, $b(t) = 2 \log(t) + 1/2 \log(\log(t)) - \log(\Gamma(1/2))$ where $\Gamma(.)$ is Gamma function. Then we have

$$\lim_{n \to \infty} P(a(\log(n))Z_n \leq t + b(\log(n))) = \exp(-2e^{-t}) \tag{2.31}$$

However, the rate of convergence to extreme value distributions is usually slow and therefore a large sample size is needed to apply this formula. Then they found another way to calculate the critical value $r(h(n), l(n))$ where

$$\lim_{n \to \infty} P\{Z_n > r(h(n), l(n))\} = \alpha \tag{2.32}$$

and

$$r(h, l) = \frac{x}{\sqrt{2\Gamma(1/2)}} \left\{ T - \frac{1}{x^2} T + \frac{1}{x^2} \right\} \tag{2.33}$$

$$T = \log((1 - h)(1 - l)/(hl))$$
They claimed that $h(n) = l(n) = (\log(n))^{3/2}/n$ could give very good critical values and are the same or better than critical values obtained by 2.31.
Chapter 3

Research Questions and Objectives

There have been lots of methods for monitoring clinical trials under Bm and Bmld. But in some cases, especially in the early stage, there might be dependence between each observation and Brownian motion structure might be no longer used for monitoring clinical trials. Under this circumstance, fBm model could introduce Hurst exponent to explain dependence information, and there has been development of conditional power under fBm. However, to better interpret conditional power as 'the probability of trial success in the end conditional on current information, we need both the estimations of dependence and treatment effect in our calculation. Without including estimation of treatment effect, the inference of Hurst exponent might be invalid and misleading. Therefore, we should introduce fBmld into monitoring clinical trials. So far, there are no approaches regarding Hurst exponent inference based on MLE, conditional power, or SSR under fBmld. In the further, if an extreme Hurst exponent is observed, we shall consider some adaptations while monitoring ongoing studies. On the other hand, current development focus on linear drift rather than any other non-linear drift which might happen when a change-point exists. A model under fBm with piece-wise drift should be developed to deal with mean change.

The dissertation includes four objectives:

- Propose a test and inference procedure of Hurst exponent under fractional Brownian motion with linear drift (fBmld).
- Derive formula of conditional power calculation and sample size re-estimation under fBmld.
- Find adjusted critical boundaries for an extreme observed Hurst exponent to protect type I error rate.
• Calculate conditional power based on piece-linear drift under fBm.

We will organize the dissertation into two part:

In part I, we will introduce inference of Hurst exponent. Likelihood Ratio Test procedure for testing $H_0 : H = 0.5$ vs $H_A : H \neq 0.5$ and confidence interval of Hurst exponent would be given. Formulas of conditional power calculation and sample size re-estimation would be derived. We will apply the methods on numeric examples and real study and compare them with the method under Bmld and fBm. More properties are detected with simulation results among sample size, Hurst exponent and likelihood ratio test and confidence interval.

In part II, We will further discuss the topics related to extreme observed Hurst exponent. First, it would be critical to protect type I error rate when we observe a Hurst exponent less than 0.5, where adjusted boundaries should be derived. Second, if different trends are observed in the same trial, we shall take piece-wise linear drift model into consideration.
Part I

Monitoring Clinical Trials under Fractional Brownian Motion with Linear Drift (fBmld)
Chapter 4

Inference on Hurst Exponent

Without loss of generality, consider a randomized clinical trial with $N$ patients per arm in both control group and treatment group (total $2N$ patients). Suppose we observe a sample $X_1, X_2, ..., X_N$ from a normal population with mean $\mu$ and variance 1 in treatment group and $Y_1, Y_2, ..., Y_N$ from a normal population with mean 0 and variance 1 in control group. At the end of trial, we have the test statistic $Z_N = \frac{\sum_{i=1}^{N}(X_i - Y_i)}{\sqrt{2/N}}$. Following the definition from section 2.3.2, we could form a fractional Brownian motion with linear drift (fBmld) \{B^H_H(t), t \geq 0\} with Hurst exponent $H$, drift parameter $\theta = E(Z_N) = \sqrt{N/2}\mu$ and volatility parameter $\sigma = 1$. Observed B-values could be calculated from $B_n = Z_n\sqrt{t}, n = 1, ..., N$ and $t = n/N$ represents the time fraction.

4.1 Introduction

As discussed in section 2.4.1, Hurst exponent $H$ and drift parameter $\theta$ could be estimated sequentially by profile likelihood under fBmld. Before directly using those estimates for further calculation of conditional power, we should first derive inference of the Hurst exponent to see if a fBmld structure is needed, compared to the model Brownian motion with linear drift (Bmld). We would discuss the property in terms of hypothesis testing and confidence interval of Hurst exponent.
4.2 Likelihood Ratio Test (LRT)

As described in subsection 2.4.2 under the structure of fBmld, we have log-likelihood of observed B-value

\[
l_n(Y, H, \theta) = \log(L_n(Y, H, \theta))
\]

\[
= -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} (Y - \theta t)^T \Sigma_H^{-1} (Y - \theta t) \tag{4.1}
\]

The estimate of Hurst exponent could be derived by maximizing profile likelihood as described in subsection 2.4.2.

4.2.1 Test Statistic

To test the null hypothesis \( H_0 : H = 0.5 \) vs \( H_a : H \neq 0.5 \), then we have likelihood ratio statistic

\[
T_{LR} = -2 \log \left( \frac{L_n(Y, H = 0.5, \hat{\theta}_{MLE}(H = 0.5))}{\sup_{H \in (0,1)} L_n(Y, H, \hat{\theta}_{MLE}(H))} \right)
\]

\[
= -2 \left( l_n(Y, H = 0.5, \hat{\theta}_{MLE}(H = 0.5)) - l_n(Y, \hat{H}_{MLE}, \hat{\theta}_{MLE}(\hat{H}_{MLE})) \right) \tag{4.2}
\]

Then under regularity conditions, \( T_{LR} \xrightarrow{d} \chi^2_1 \) as \( n \to \infty \) under the null. This property has been well explained and proved by Wilks’ theorem from Wilks (1938). Thus, P-value could be derived through calculate \( P(\chi^2 > \chi^2_1(\alpha)) \).

4.2.2 Finite Sample Property of LRT with Simulation Results

We want to check the performance of likelihood ratio test for \( H_0 : H = 0.5 \) on finite sample. Given sets of parameters \((N, \mu, H)\), for each simulation, we will conduct the procedure as below:

1. Draw a vector sample of B-value \( B_H'(t_1), ..., B_H'(t_N) \) from \( \text{MVN}(\theta t, \Sigma_H) \), where

\[
t = (t_1, ..., t_N)^T = (1/N, ..., N/N)^T
\]

\[
\theta = \sqrt{N/2\mu}
\]
\[ \Sigma_H = [\sigma_{ij}]_{i,j=1,\ldots,N}, \sigma_{ij} = \frac{1}{2} \left( t_i^{2H} + t_j^{2H} - |t_i - t_j|^{2H} \right) \]

2. Calculate \( T_{LR} \)

3. Record the simulation as a rejection if \( T_{LR} > \chi^2_{1,\alpha=0.05} \); Otherwise record the simulation as an acceptance.

The simulation is conducted 1000 times for each set of \((\mu, H, N)\). For each set, calculate the percentage of rejection \( p_r \) that

\[ p_r = \frac{\# \text{ of rejections}}{1000} \quad (4.3) \]

Then type I error rate or power would be approximated by \( p_r \). General relationship among the parameters would be explored by 10 sets of parameter that \( N = 100, \mu = (0, 0.4), H = (0.4, 0.45, 0.5, 0.55, 0.6) \). The results are shown in Table 4.1. With a sample size of \( N = 100 \)

<table>
<thead>
<tr>
<th>Treatment effect ( \mu )</th>
<th>Hurst Exponent ( H )</th>
<th>Proportion of rejection of LRT for ( H_0 : H = 0.5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.40</td>
<td>1.000</td>
</tr>
<tr>
<td>0.0</td>
<td>0.45</td>
<td>0.914</td>
</tr>
<tr>
<td>0.0</td>
<td>0.50</td>
<td>0.038</td>
</tr>
<tr>
<td>0.0</td>
<td>0.55</td>
<td>0.934</td>
</tr>
<tr>
<td>0.0</td>
<td>0.60</td>
<td>1.000</td>
</tr>
<tr>
<td>0.4</td>
<td>0.40</td>
<td>1.000</td>
</tr>
<tr>
<td>0.4</td>
<td>0.45</td>
<td>0.894</td>
</tr>
<tr>
<td>0.4</td>
<td>0.50</td>
<td>0.048</td>
</tr>
<tr>
<td>0.4</td>
<td>0.55</td>
<td>0.923</td>
</tr>
<tr>
<td>0.4</td>
<td>0.60</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table 4.1: Simulation results of LRT performance for \( H_0 : H = 0.5 \) vs \( H_\alpha : H \neq 0.5 \) with treatment effect \( \mu \) in \((0,0.4)\), sample size \( N = 100 \), Hurst exponent \( H \) from 0.4 to 0.6 by 0.05.

per arm, type I error rate is controlled well under \( H = 0.5 \). If true Hurst exponent \( H \) is in \((0.4, 0.45, 0.55, 0.6)\), a big power would be detected and we are likely to claim that the Bmld structure would not hold for the data. Moreover, LRT performs similarly under different treatment effect.

To detect how LRT performs under other scenarios, simulations are conducted for different sets of parameters: Treatment effect \( \mu \) from 0 to 0.4 by 0.05, sample size \( N \) from 50
to 200 by 50. Hurst exponent from 0.4 to 0.5 by 0.01. To have a intuitive understanding of the results, we illustrate them in Figure 4.1 and Figure 4.2.

From Figure 4.1, we might see that the relationship between proportion of rejection of LRT and Hurst exponent $H$ and sample size $N$ is consistent across treatment effect $N$. For each treatment effect $\mu$, when sample size becomes larger, we might have a higher probability to reject the null if true Hurst exponent $H$ is not 0.5, which indicates that power becomes larger if sample size becomes larger; On the other hand, the probability to reject the null keeps the same across all the sets of sample size $N$, which indicates that type I error rate keeps the same at assumed significance level 0.05 and is not related to sample size.
Figure 4.1: Visualization of LRT performance by treatment effect $\mu$ of simulation results for Treatment effect $\mu$ from 0 to 0.4 by 0.05, sample size $N$ in 50 to 200 by 25, Hurst exponent $H$ from 0.4 to 0.5 by 0.01.
Figure 4.2: Visualization of LRT performance by sample size $N$ of simulation results for Treatment effect $\mu$ from 0 to 0.4 by 0.05, sample size $N$ in 50 to 200 by 25, Hurst exponent $H$ from 0.4 to 0.5 by 0.01.
From Figure 4.2, we could see a more clear pattern that given the same sample size, the relationship between Hurst exponent and proportion of rejection of LRT keeps the same across treatment effect $\mu$. This indicates that treatment effect $\mu$ has little effect on the inference of Hurst exponent $H$.

4.3 Confidence Interval

4.3.1 Calculation

As estimate of Hurst exponent is derived, an $100(1 - \alpha)$% confidence interval based on LRT would be calculated by solving $H$ from

$$l_n(y, \hat{H}) - l_n(y, H) < \frac{1}{2} \chi^2_1(\alpha)$$

(4.4)

The confidence interval would be derived by searching method.

4.3.2 Finite Sample Property of 95% Confidence Interval Coverage with Simulation Results

We want to check the performance of confidence interval coverage on finite sample. Similarly, for confidence interval coverage, we would like to first have a general look of the effect by 10 sets of parameter that $N = 100, \mu = (0, 0.4), H = (0.4, 0.45, 0.5, 0.55, 0.6)$. Given sets of parameters $(N, \mu, H)$, for each simulation, we will conduct the procedure as below:

1. Draw a vector sample of B-value $B_H(t_1), ..., B_H(t_N)$ from $MVN(\theta t, \Sigma_H)$, where

$$t = (t_1, ..., t_N)^T = (1/N, ..., N/N)^T$$

$$\theta = \sqrt{N/2\mu}$$

$$\Sigma_H = [\sigma_{ij}]_{i,j=1,...,N}, \sigma_{ij} = \frac{1}{2}(t_i^{2H} + t_j^{2H} - |t_i - t_j|^{2H})$$

2. Calculate 95% Confidence Interval of $H$.

3. Record if lower bound is larger than $H$

4. Record if upper bound is smaller than $H$
The simulation is conducted 1000 times for each set of \((\mu, H, N)\). For each set, calculate \(p_l\), the proportions of lower bound larger than \(H\) that

\[
p_l = \frac{\# \text{ of lower bound larger than } H}{1000}
\] (4.5)

and calculate \(p_u\), the proportions of upper bound smaller than \(H\) that

\[
p_u = \frac{\# \text{ of upper bound smaller than } H}{1000}
\] (4.6)

Then 95% confidence interval coverage would be approximated by \(1 - p_u - p_l\). General performance would be explored by 10 sets of parameter that \(N = 100, \mu = (0, 0.4), H = (0.4, 0.45, 0.5, 0.55, 0.6)\). Then results are shown in Table 4.2. We could clearly see consistency of the 95% confidence interval coverage across Hurst exponent \(H\), treatment effect \(\mu\). We then further conduct simulations for more sets of parameters to see how good LRT confidence interval works with treatment effect \(\mu\) from 0 to 0.4 by 0.05, sample size \(N\) from 50 to 150 by 25, Hurst exponent \(H\) from 0.4 to 0.6 by 0.01. The results shows approximately 95% confidence interval coverage across all the sets of \((N, \mu, H)\), which indicates an correct confidence interval calculation of Hurst exponent \(H\). Illustrative figures summarizing the results are shown in Figure 4.3 and Figure 4.4.

<table>
<thead>
<tr>
<th>Treatment Effect (\mu)</th>
<th>Hurst Exponent (H)</th>
<th>Proportion of Lower bound (&gt; H)</th>
<th>Proportion of Upper bound (&lt; H)</th>
<th>95% CI Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.40</td>
<td>0.024</td>
<td>0.013</td>
<td>0.963</td>
</tr>
<tr>
<td>0.0</td>
<td>0.45</td>
<td>0.024</td>
<td>0.031</td>
<td>0.945</td>
</tr>
<tr>
<td>0.0</td>
<td>0.50</td>
<td>0.028</td>
<td>0.009</td>
<td>0.963</td>
</tr>
<tr>
<td>0.0</td>
<td>0.55</td>
<td>0.027</td>
<td>0.013</td>
<td>0.960</td>
</tr>
<tr>
<td>0.0</td>
<td>0.60</td>
<td>0.022</td>
<td>0.021</td>
<td>0.957</td>
</tr>
<tr>
<td>0.4</td>
<td>0.40</td>
<td>0.022</td>
<td>0.017</td>
<td>0.961</td>
</tr>
<tr>
<td>0.4</td>
<td>0.45</td>
<td>0.033</td>
<td>0.022</td>
<td>0.945</td>
</tr>
<tr>
<td>0.4</td>
<td>0.50</td>
<td>0.034</td>
<td>0.010</td>
<td>0.956</td>
</tr>
<tr>
<td>0.4</td>
<td>0.55</td>
<td>0.032</td>
<td>0.019</td>
<td>0.949</td>
</tr>
<tr>
<td>0.4</td>
<td>0.60</td>
<td>0.025</td>
<td>0.018</td>
<td>0.957</td>
</tr>
</tbody>
</table>

Table 4.2: Simulation results of confidence interval coverage for treatment effect \(\mu\) in \((0,0.4)\), sample size \(N = 100\), Hurst exponent \(H\) from 0.4 to 0.6 by 0.05 with 1000 draws for each set of parameter \((\mu, H)\).
Figure 4.3: Visualization by treatment effect $\mu$ of simulation results of confidence interval coverage for Treatment effect $\mu$ from 0 to 0.4 by 0.05, sample size $N$ from 50 to 150 by 25, Hurst exponent $H$ from 0.4 to 0.6 by 0.01 with 1000 draws for each set of parameter ($N, \mu, H$)
Figure 4.4: Visualization by sample size $N$ of simulation results of confidence interval coverage for Treatment effect $\mu$ from 0 to 0.4 by 0.05, sample size $N$ from 50 to 150 by 25, Hurst exponent $H$ from 0.4 to 0.6 by 0.01 with 1000 draws for each set of parameter $(N, \mu, H)$
Based on the illustrations from Figure 4.3 and 4.4, we could clearly see consistency of the 95\% confidence interval coverage across both sample size \( N \) and treatment effect \( \mu \) without a certain pattern.

### 4.4 Discussion

Based on the analysis and results from this chapter, there are some recommendations to be used in the real study.

- Based on the results from BHAT study or Remdesivir trial (Discussed later in Chapter 6), we would like to define an extreme Hurst exponent 0.05 away from 0.5, as usually, we would not see Hurst exponent beyond this range. If we observe an extreme Hurst exponent with a sample size much larger than that, we should take a close look at the data or any action we have during the protocol to check if anything during the trial would cause such correlation, either positive or negative.

- Usually in a trial, the most curious question is, when should we trust the results, or, which interim analysis should we make a decision. This usually depends on the sample size that we have and the number of results we have already collected. More sample size or measurement we have, the more confidence that we can make decisions. Based on the results in Figure 4.2, we could believe in the test result for the Hurst exponent under \( fBmld \) when we have a sample size more than 125 per arm. This sample size gives us around 90\% power to detect a Hurst exponent with difference of 0.05 from 0.5, where \( H = 0.5 \) means the assumption of Brownian motion.

- In this Chapter, we provide a confidence interval of Hurst exponent estimate. As it would be hard for sponsor or Data Monitoring Committee members to make a decision or provide recommendations based on Hurst exponent, the lower or upper bound of confidence interval would help. If we do observe a lower bound of 95\% CI larger than 0.55 or upper bound less than 0.45, even we could not figure out the correlation problem instantly, there should be issues regarding the trial, e.g. data issue.
Chapter 5

Conditional Power and Sample Size Re-estimation (SSR) with Fractional Brownian Motion with Linear Drift (fBmld)

5.1 Introduction

After we complete the inference of Hurst exponent, we could use the estimate of Hurst exponent to provide information of current trial in terms of conditional power, and do sample size re-estimation under fBmld. In this chapter, we would derive the formula of calculation for conditional power and SSR.

5.2 Conditional power under fBmld

Denote sequence of B-value as $B_H'(t) = (B_H'(t_1), ..., B_H'(t_{K-1}))^T$ with observations of $b_H'(t)$. Then conditional distribution of $B_H'(1)$, B-value at the end of trial, given $B_H'(t) = b_H'(t)$ would be

$$B_H'(1)|B_H'(t) = b_H'(t) \sim N(\theta_c, \sigma_c^2) \quad (5.1)$$

Where conditional mean

$$\theta_c = \theta + \Sigma^{(21)}(\Sigma^{(11)})^{-1}(b_H'(t) - \theta t) \quad (5.2)$$

Conditional variance

$$\sigma_c^2 = \sigma_K^2 - \Sigma^{(21)}(\Sigma^{(11)})^{-1}\Sigma^{(12)} \quad (5.3)$$
and covariance matrix $\Sigma$ is defined as in $2.21$, $t = (t_1, ..., t_{K-1})$. Under assumption of fBmld, the conditional power $CP(\theta, H)$ would be calculated based on all the states in the past. As we derived the conditional distribution of $B'_H(1)$, conditional power $CP(\theta, H)$ could be calculated as

$$CP(\theta, H) = P (Z_N = B'_H(1) > z_\alpha | H_a, B'_H(t))$$

$$= P \left( \frac{B'_H(1) - \theta_c}{\sigma_c} > \frac{z_\alpha - \theta_c}{\sigma_c} \right)$$

$$= 1 - \Phi \left( \frac{z_\alpha - \theta_c}{\sigma_c} \right)$$

(5.4)

As the conditional power under fBmld is a function of Hurst exponent $H$ and drift parameter $\theta$, we have the following ways for the calculation:

- Insert value of $\theta = \theta_a = \mu_a \sqrt{N/2}$ and assumed Hurst exponent $H$.
- Insert value of $\theta = \theta_a$ and MLE of $H$ without information of $H$.
- Insert $\hat{H}$ and $\hat{\theta}$ through profile likelihood without both assumption of $\theta$ and $H$

Note that in the third option, as all the parameters could be estimated through data rather than assuming a certain value (e.g., under the null/alternative), those data-driven estimates could result in a better interpretation for 'conditional power based on current trend'. This would describe the data comprehensively by including more information.

We provide two examples below to illustrate the conditional power between two models of Bmld and fBmld. As shown in Figure 5.1, a sequence of B-value is simulated with 200 points, treatment effect $\mu = 0.2, H = 0.2$ and the time of interim analysis is $t = 0.67$. We could observe the blue line is conditional distribution of B-value at $t = 1$ under Bmld while the red line is conditional distribution of B-value at $t = 1$ under fBmld. As the conditional mean calculated under fBmld is larger than the one under Bmld and they have comparable conditional variance, the conditional power calculated under fBmld is 0.873, 0.168 large than the one under Bmld of 0.705.
Figure 5.1: Comparison of conditional power under Brownian motion with linear drift (Bmld) and fractional Brownian motion with linear drift (fBmld); The example is simulated by $H=0.2$

Similarly, sequence of B-value is simulated with 200 points, treatment effect $\mu = 0.2$, $H = 0.8$ and the time of interim analysis is $t = 0.67$ as shown in Figure 5.2 a. We could observe the blue line is conditional distribution of B-value at $t = 1$ under Bmld while the red line is conditional distribution of B-value at $t = 1$ under fBmld. The conditional mean calculated under fBmld is similar to the one under Bmld. However, the conditional variance calculated under fBmld are smaller than the one under Bmld. Therefore, the conditional power calculated under fBmld is 0.808, large than the one under Bmld of 0.746.
Figure 5.2: Comparison of conditional power under Brownian motion with linear drift (Bmld) and fractional Brownian motion with linear drift (fBmld); The example is simulated by $H > 0.5$

Illustrated from the examples above, we might find that the conditional power under fBmld is determined by two factors of conditional mean and also conditional variance.

5.3 SSR under Current Trend with fBmld

Similarly to the method under Bmld, if we observe a relatively low conditional power, we might need to increase sample size to achieve desired power. As mentioned before, whatever new sample size we set to achieve desired power, we can always make adaptations (change test statistics or critical boundary) to protect type I error rate. Therefore, under fBmld, only pay attention on calculating the new sample size for a desired $1 - \beta'$ power level.

Denote sequence of B-value as $B_H'(t) = (B_H'(t_1), ..., B_H'(t_{K-1}))^T$ with observations of $b_H'(t)$. if we have target sample size $N_S$ per arm to provide $1 - \beta'$ power with planned
sample size $N$ per arm and $t_S = N_S/N$, covariance matrix for time points ($t_1, ..., t_{K-1}, t_S$):

$$
\tilde{\Sigma} = \begin{bmatrix}
\sigma_1^2 & \sigma_{12} & \cdots & \sigma_{1S} \\
\sigma_{21} & \sigma_2^2 & \cdots & \sigma_{2S} \\
\vdots & \vdots & \ddots & \vdots \\
\sigma_{S1} & \sigma_{S2} & \cdots & \sigma_S^2
\end{bmatrix} = \begin{bmatrix}
\tilde{\Sigma}^{(11)} & \tilde{\Sigma}^{(12)} \\
\tilde{\Sigma}^{(21)} & \tilde{\Sigma}^{(22)}
\end{bmatrix}
$$

we have

$$
B_H'(t_S)\big| B_H'(t) = b_H'(t) \sim N(\tilde{\theta}_c, \tilde{\sigma}_c^2)
$$

Where conditional mean

$$
\tilde{\theta}_c = \theta t_s + \tilde{\Sigma}^{(21)}(\tilde{\Sigma}^{(11)})^{-1}(b_H'(t) - \theta t)
$$

c_conditional variance

$$
\tilde{\sigma}_c^2 = \sigma_S^2 - \tilde{\Sigma}^{(21)}(\tilde{\Sigma}^{(11)})^{-1}\tilde{\Sigma}^{(12)}
$$

To achieve desired power $1 - \beta'$, we have

$$
1 - \beta' = P(Z_{N_S} = B_H'(t_S)/\sqrt{t_S} > c_1|\theta, H, B_H'(t)) = \Phi\left(\tilde{\theta}_c - c_1 \sqrt{\frac{N_S/N}{\tilde{\sigma}_c}}\right)
$$

where $c_1$ is new critical boundary adjusted for new sample size per arm that

$$
\frac{c_1\sqrt{N_S/N} - Z_n\sqrt{t}}{\sqrt{N_S/N} - t} = \frac{c_0 - Z_n\sqrt{t}}{\sqrt{1 - t}}
$$

Then the new sample size $N_S$ would be a function of $\tilde{\theta}_c$ and $\tilde{\sigma}_c$. We could derive the sample size by searching root of the equation.
5.4 Discussion

- Here we provide a solution of how to calculate conditional power under fBmld. Note that even we do not have a significant Hurst exponent estimate, we could always calculate this conditional power by inserting the Hurst exponent estimate. However, this would lead to little difference from the one calculated under Bmld.

- Also, even when we observe an extreme Hurst exponent with significance, it would be possible that there is only a little difference, as the conditional power under fBmld depends on both conditional mean and conditional variance.

- There has been already an approach of conditional power taking correlation into consideration under fBm model ([Lai et al., 2000]). However, they did not estimate the treatment effect but simply assume it as 0 under the null. It would be fine to calculate the conditional power under the null, but the problem might happen when we estimate Hurst exponent under fBm. This would lead to a bias in Hurst exponent. This would be discussed in Chapter 6 by BHAT study.

- As mentioned in formula 5.10, the new critical boundary would be calculated based on new sample size. Note that this method is according to the calculation in [Gao et al., 2008]. In a real clinical trial, we might have different decision on the boundary to be used in the final after SSR. However, $c_1$ could be always calculated based on a different method. We here provide a solution that even we are calculating new sample size bases on fBmld model, in a real trial, we should protect the type I error rate under Brownian motion, which is assumed in the protocol. The new sample size here is a more accurate calculation based on the information of both observations and correlation. Therefore, the new sample size would be a better one to achieve power at the desired level. We should use simulations to confirm how better would SSR under fBmld be. This would be completed in further research.
Chapter 6
Application of Monitoring under fBmld

So far, we have discussed how to conduct inference of Hurst exponent under fBmld, how to calculate conditional power and new sample size under fBmld. In this chapter, we would like to use simulated example and real study to illustrate idea and make comparison.

6.1 Remdesivir Trial for COVID-19 in China

Two phase-III, double-blind, randomized clinical trials of remdesivir plus SOC (standard of care) versus placebo plus SOC have been conducted in Wuhan hospitals by Chinese investigators during the urgent COVID-19 epidemic (Shih et al., 2020). During DMC meeting, a Dynamic Data Monitoring (DDM) technique is requested and applied to the data. DDM feature records the statistics such as Z-value or B-value as each patient enrolled and displays them on top of a radar system, which is a figure showing Z-value and B-value on different regions divided by different conditional power. An example plot is shown as below.
Figure 6.1: treatment effect in terms of Z-value as patient accumulated at day 14

The X-axis is the number of patients enrolled while Y-axis is Z-value. The figure is divided into three regions. Favorable region is defined as conditional power under a current estimate larger than 90%. Promising region is defined as conditional power under current estimate is between 90% and 5% while Unfavorable region is defined as conditional power under current estimate is less than 5%. The red dashed line in promising region stands for conditional power under current estimate equal to 50%. The figure shows that at most of the time, the trial is in the promising region and conditional power is around 50%. We do not have the exact Z-value from the trial and thus use a software ‘xyscan’, which is available on https://rhig.physics.yale.edu/~ullrich/software/xyscan/ and helps to retrieve the numeric values from the plot, to extract the Z-value points from the pictures. Those extracted points would be transformed into B-values and re-analysis using our approach based on current trend with fBm.
First, we could derive the estimate of Hurst exponent that $\hat{H} = 0.488$ with 95% confidence interval $(0.469, 0.505)$. Then we apply hypothesis testing on Hurst exponent with $H_0 : H = 0.5$ and $H_a : H \neq 0.5$. A likelihood ratio statistic $T_{LR} = 2.57$ with p-value $= 0.11$. Therefore, we shall accept $H = 0.5$ and conclude that Bmld would be a good fit for the model.

### 6.2 BHAT Study

We’ll continue to discuss more details under fBmld by comparing results with BHAT study using conditional power under fBm in Lai (2004) as well as methods of Bmld in Lan and Wittes (1988). As described, the BHAT study was sponsored by the National Heart, Lung and Blood Institute and designed to test the effectiveness of reducing mortality by taking propanolol for patients who have recently suffered heart attacks (DeMets et al., 1984). we use the Z-value directly from the paper and transform them into B-value and then calculate the conditional power under current trend.
Then under fBmld, we could derive conditional power and estimate of Hurst exponent $H$ and drift parameter $\theta$. A comparison between the methods of Bmld and fBmld, fBm and fBmld are shown as below in 6.1 6.2
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Table 6.1: BHAT study results comparison between Bmld and fBmld
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Table 6.2: BHAT study results comparison between fBm and fBmld
Based on the results from Table 6.1, we got similar estimates for drift parameter $\theta$ and similar conditional power. From Table 6.2, we get different estimate for Hurst exponent and conditional power at earlier stage. This indicates that conditional power under fBm appears more conservative.

6.3 Simulated Examples

In this section, we simulate three examples to explain the difference of results between Bmld and fbmld.

6.3.1 Example 1

Assume that we have planned sample size $N = 100$ per arm. $N_1 = 75$ observed B-values are simulated from $H = 0.8$. The information fraction of the analysis is at $t_1 = N_1/N = 0.75$. The B-value is plotted at Figure 6.3.

Figure 6.3: Simulated B-values of example 1
Based on the results in Table 6.3 for this simulated example, p-value < 0.05 for Likelihood ratio test on Hurst exponent $H = 0.5$. Therefore, fBmld would be a good fit for the model. Moreover, there is a relatively large difference between estimate of drift parameter. Conditional power under fBmld is 0.144 larger than that under Bmld. And 47 less sample size (27% decrease) would be resulted for SSR under fBmld compared to Bmld.

6.3.2 Example 2

Assume that we have planned sample size $N = 100$ per arm. $N_1 = 75$ observed B-values are simulated from $H = 0.3$. The information fraction of the analysis is at $t_1 = N_1/N = 0.75$. The B-value is plotted at Figure 6.4.
Based on the results in Table 6.4 for this simulated example, p-value < 0.05 for Likelihood ratio test on Hurst exponent $H = 0.5$. Therefore, fBmld would be a good fit for the model. And there is a relatively large difference between estimate of drift parameter. Conditional power under fBmld is 0.146 smaller than that under Bmld 34 more sample size (28 % increase) would be resulted for SSR under fBmld compared to Bmld. From this example, we might find that the value of new sample size might not always decrease but
might depend on the value of Hurst exponent.

### 6.3.3 Example 3

Assume that we have planned sample size $N = 100$ per arm. $N_1 = 75$ observed B-values are simulated from $H = 0.3$. The information fraction of the analysis is at $t_1 = N_1/N = 0.75$. The B-value is plotted at Figure 6.5.

![Figure 6.5: Simulated B-values of example 3](image)

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Table 6.5: Results of simulated example 3
Based on the results in Table 6.5 for this simulated example, p-value < 0.05 for Likelihood ratio test on Hurst exponent $H = 0.5$. Therefore, fBmld would be a good fit for the model. There is a relatively large difference between estimate of drift parameter. Conditional power under fBmld is similar to that under Bmld. 90 more sample size (16% increase) would be resulted for SSR under fBmld compared to Bmld. Moreover, for SSR under low conditional power, we need a higher adjusted critical boundary to protect type I error rate.

6.4 Discussion

- For the Remdesivir trial described in section 6.1, we could see that there is zigzag curve of the sequence of Z-values as well as B-values. We would like to doubt if the Brownian motion assumption still holds. By fitting fBmld model, we fail to find a significant Hurst exponent with p-value = 0.11. However, this shows a trend that a negative correlation might exist between the observations. Intuitively, the observations seem more volatile than expected.

- For the BHAT study in section 6.2, we compared the result with two other methods. Note that in this analysis we do not use the observations as each patient enrolled in but the observations available at a certain time. So the sample size here would be smaller than we expected, as fewer observations of B-value are used into Hurst exponent estimation.

- By comparison between the model of Bmld and fBmld, we do not see much difference here between the two analyses in terms of conditional power. One main reason is that our Hurst exponent is not that extreme enough. Also, the estimates of drift parameters are really similar to each other at the time of events. Another possible reason, as we mentioned in chapter 5, the conditional power is related to conditional mean and conditional variance. So in some studies, it would be possible that conditional power does not vary a lot when observing a Hurst exponent not equal to 0.5.

- Moreover, by comparison between the model of fBm and fBmld, we observe different results. The Hurst exponent first shows two directions. fBm gave the estimates of
Hurst exponent larger than 0.5 at each time of event while ours gave the estimates less than 0.5. Under this circumstance, fBm model illustrates a positive correlation between or among observations while fBmld model gives a negative correlation. This would lead to the study with different investigation. Also, as fBm model does not estimate drift parameter but assumes it as 0. This would lead to a small conditional power at the middle of the trial, e.g. time of events when $D = 125$ to 245, resulting in a conditional power less than 30%. The results here appear much more conservative. However, too conservative conditional power might lead sponsor or Data Monitoring Committee members to stop the trial for futility. Under this circumstance, conditional power under fBm might not describe the trial correctly and be misleading.

- For simulated examples in section 6.3 we would like to visualize the shape of observations under different assumptions. In the first example, we could see that if an extreme Hurst exponent larger than 0.5 is observed, the curve would present quite smooth. In the second example, there is a considerable difference between conditional power and new sample size based on SSR. This would be resulted from including estimation of Hurst exponent as correlation might play a great role among the data. In the third example, we want to point out that even the Hurst exponent and drift parameters vary between each other, there is still the possibility that two conditional powers are similar. However, the new sample size might be different from each other, as we see a sample size of 90 per arm difference.
Part II

Practical Problem of ongoing trial under fBm structure
Chapter 7

Adjusted Critical Boundaries under fBm

7.1 Introduction

As we mentioned in the previous chapter, we focus on the inference on Hurst exponent with the application on conditional power and sample size re-estimation. We provide the method for more accurate information on the current trial. However, we get the estimates of Hurst exponent $\hat{H} < 0.5$ based on the real clinical trial. This is in contrast to the result of $\hat{H}$ mentioned in Lai et al. (2000). If $\hat{H} < 0.5$ is observed, a type I error inflation might happen and we might need to adjust critical boundaries to protect type I error rate. In this chapter, we would discuss how type I error rate inflates or deflates in different scenarios in section 7.2. Adjusted boundaries calculation are discussed when $K = 2$ in section 7.3 and a general scenario of $K \geq 2$ in section 7.3, where O'Brien-Fleming type boundary and Pocock boundary is used for illustration. Finally, a discussion is given about application in the real clinical trial.

7.2 Type I error inflation and deflation

As mentioned in (Lai 2010), we could calculate out critical boundaries under different assumptions of Hurst exponent $H$. However, in real studies, we might not have information of Hurst exponent and usually calculate boundaries under Brownian motion assumption. If there is true positive or negative correlation, type I error rate might inflate or deflate.

Consider a trial with five looks and one-sided alpha level $\alpha = 0.025$. Based on the results from (Lan and DeMets 1983), we have O'Brien-Fleming type boundary $(4.88, 3.36, 2.68, 2.29, 2.03)$ and Pocock type boundary $(2.44, 2.43, 2.41, 2.40, 2.39)$ at $t = (0.2, 0.4, 0.6, 0.8, 1)$. If true Hurst exponent $H = 0.5$, then type I error rate would be controlled well. However, if
true Hurst exponent $H \neq 0.5$, the type I error rate would be shown as below in Table 7.1.

Here $\alpha_i = \alpha(t_i)$ for cumulative alpha spent at each look.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Boundary Type</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\alpha_3$</th>
<th>$\alpha_4$</th>
<th>$\alpha_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>O’Brien-Fleming Type</td>
<td>0.0000</td>
<td>0.0011</td>
<td>0.0060</td>
<td>0.0153</td>
<td>0.0281</td>
</tr>
<tr>
<td>0.5</td>
<td>O’Brien-Fleming Type</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.0038</td>
<td>0.0122</td>
<td>0.0250</td>
</tr>
<tr>
<td>0.7</td>
<td>O’Brien-Fleming Type</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0015</td>
<td>0.0084</td>
<td>0.0218</td>
</tr>
<tr>
<td>0.4</td>
<td>Pocock Type</td>
<td>0.0190</td>
<td>0.0282</td>
<td>0.0341</td>
<td>0.0384</td>
<td>0.0417</td>
</tr>
<tr>
<td>0.5</td>
<td>Pocock Type</td>
<td>0.0074</td>
<td>0.0131</td>
<td>0.0177</td>
<td>0.0216</td>
<td>0.0250</td>
</tr>
<tr>
<td>0.7</td>
<td>Pocock Type</td>
<td>0.0004</td>
<td>0.0020</td>
<td>0.0045</td>
<td>0.0078</td>
<td>0.0114</td>
</tr>
</tbody>
</table>

Table 7.1: Cumulative Alpha spending at each look using O’Brien-Fleming type boundaries of (4.88, 3.36, 2.68, 2.29, 2.03) and Pocock type boundaries of (2.44, 2.43, 2.41, 2.40, 2.39) at $t = (0.2, 0.4, 0.6, 0.8, 1)$

Note that in both cases, when true Hurst exponent $H = 0.7 > 0.5$, we would have the test more conservative. While true Hurst exponent $H = 0.4 < 0.5$, type I error rate inflation would be resulted.

In a real clinical trial, we might observe a significant Hurst exponent estimate $\hat{H} < 0.5$. Under this circumstance, we should make adaptations to original boundaries and calculate new critical boundaries based on the estimate of Hurst exponent.

### 7.3 Adjusted Boundary for Type I error rate control when $K = 2$

Without loss of generality, we would consider the case of only one interim analysis first for illustration. Consider a clinical trial with only one interim and one-sided significance level $\alpha = 0.025$ for hypothesis testing $H_0 : \mu = 0$ vs $H_a : \mu > 0$ is applied on the study with value of $(c_1, c_2)$ at $t = (t_1, t_2)$. As illustrated above, when true Hurst exponent is less than 0.5, type I error rate inflation might happen.

For this certain case, when boundaries under Brownian motion structure is applied, type I error rate would be calculated as

$$\alpha = P_{H_0}(\text{Reject the null } | H = 0.5)$$

$$= P_{H_0}(Z(t_1) > c_1 \text{ or } (Z(t_1) < c_1 \text{ and } Z(t_2) > c_2)|H = 0.5)$$

(7.1)

When observing a sequence of Z-value, equivalently a sequence of B-value, we could derive
inference of Hurst exponent. If a significant Hurst exponent is observed, we want to adjust the critical boundaries for this Hurst exponent to protect the Type I error rate. As illustrated in section 7.2, type I error rate would be only inflated when Hurst exponent $H < 0.5$. In this case, we only need to adjust the critical boundaries when observing a significant Hurst exponent $\hat{H} < 0.5$.

### 7.3.1 Adaptations based on the results at the interim

As we would not consider adjusted critical boundaries for Hurst exponent before the trial starts in most cases, it is reasonable that we make this adaptation during the interim analysis, when observing a relatively extreme correlated observations, i.e., significant Hurst exponent. To maintain a desired alpha level calculated at the design stage, based on $\hat{H}$, adjusted critical boundaries would be calculated for this interim and final analysis.

At the interim, the alpha should be spent at a designed level $\alpha_1$. However, the critical boundary $c_1$ is calculated for $\alpha_1$ under Brownian motion model, i.e. $H = 0.5$. If we observe a significant $\hat{H}$, we need adjust the critical boundaries at both interim and final and derive $c'_1$ and $c'_2$. Note that for any look $1 \leq j \leq K$ and any boundary $C$, the event $\{Z(t_j) < C\}$ is equivalent to $\{B(t_j) < C\sqrt{t_j}\}$. As B-value at the interim $t = t_1$ follows a distribution that $B(t_1) \sim N(0, t_1^{2\hat{H}})$, $c'_1$ could be derived from

$$
\alpha_1 = P_{H_0} \left(Z(t_1) > c'_1 | \hat{H}\right) = P_{H_0} \left(B(t_1) > c'_1 \sqrt{t_1} | \hat{H}\right) = P_{H_0} \left(\frac{B(t_1)}{t_1^{\hat{H}}} > \frac{c'_1 \sqrt{t_1}}{t_1^{\hat{H}}}\right) = 1 - \Phi \left(\frac{c'_1 \sqrt{t_1}}{t_1^{\hat{H}}}\right) \quad (7.2)
$$

Then we have

$$
1 - \alpha_1 = \Phi \left(\frac{c'_1 \sqrt{t_1}}{t_1^{\hat{H}}}\right) \quad (7.3)
$$

$$
c'_1 = \Phi^{-1} \left(1 - \alpha_1\right) \times t_1^{\hat{H} - 1/2}
$$
As an adjusted boundary $c'_1$ is calculated at this interim $t_1$, we could first compare the calculated Z-value at the interim $Z_1$ with $c'_1$. If $Z_1 > c'_1$, then we could stop the trial for early efficacy at a designed level $\alpha_1$. Otherwise, we need to continue the trial and see if we could claim efficacy at the end of the trial.

Similarly, we need to control the type I error rate at the end. Therefore, an adjusted critical boundary at the end $c'_2$ should be calculated. Under this circumstance, the remaining alpha level spent at the final would be still $\alpha - \alpha_1$. Then we have

$$\alpha - \alpha_1 = P_{H_0}(Z(t_1) < c'_1 \text{ and } Z(t_2) > c'_2|\hat{H})$$

$$= P_{H_0}(B(t_1) < c'_1 \sqrt{t_1} \text{ and } B(t_2) > c'_2|\hat{H})$$

$$= \int_{c'_2}^{\infty} \int_{-\infty}^{c'_1 \sqrt{t_1}} \int_{B(t_1),B(t_2)}(b_1,b_2)db_1db_2$$

(7.4)

where

$$\begin{pmatrix}
B(t_1)|\hat{H} \\
B(t_2)|\hat{H}
\end{pmatrix} \sim BVN
\begin{pmatrix}
0 \\
0
\end{pmatrix},
\begin{pmatrix}
\hat{\sigma}_{11} & \hat{\sigma}_{12} \\
\hat{\sigma}_{21} & \hat{\sigma}_{22}
\end{pmatrix}$$

(7.5)

and $\hat{\sigma}_{ij} = \frac{1}{2}(t_i^{2\hat{H}} + t_j^{2\hat{H}} - |t_i - t_j|^{2\hat{H}}), i, j = 1, 2$.

Consider an O’Brien-Fleming type boundary is used at $t = (0.75, 1)$ under $\alpha = 0.025$ for a one-sided test with $(c_1, c_2) = (2.340, 2.012)$. If no adaption is taken, the type I error rate would be inflated under Hurst exponent $H < 0.5$, as shown in Table 7.2. Here $\alpha_i^* = \alpha_i - \alpha_{i-1}$ for alpha spent at each interim.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Boundary Type</th>
<th>Overall Type I error rate</th>
<th>$\alpha_1^*$</th>
<th>$\alpha_2^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>O’Brien-Fleming Type</td>
<td>0.0294</td>
<td>0.0136</td>
<td>0.0158</td>
</tr>
<tr>
<td>0.35</td>
<td>O’Brien-Fleming Type</td>
<td>0.0281</td>
<td>0.0125</td>
<td>0.0156</td>
</tr>
<tr>
<td>0.40</td>
<td>O’Brien-Fleming Type</td>
<td>0.0269</td>
<td>0.0115</td>
<td>0.0154</td>
</tr>
<tr>
<td>0.45</td>
<td>O’Brien-Fleming Type</td>
<td>0.0259</td>
<td>0.0105</td>
<td>0.0154</td>
</tr>
<tr>
<td>0.50</td>
<td>O’Brien-Fleming Type</td>
<td>0.0250</td>
<td>0.0096</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

Table 7.2: Overall Alpha and Alpha spending at each look using O’Brien-Fleming type boundaries of (2.340, 2.012) at $t = (0.75, 1)$
However, as discussed above, if new critical boundaries is calculated adjusted for $\hat{H}$, the
type I error rate would be protected at $\alpha$ level, as well as $\alpha_1$ level calculated at the design
stage for the alpha spent at the first interim. Simulation is conducted 100,000 times for
each Hurst exponent for the confirmation.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Overall Type I error</th>
<th>$\alpha_1^*$</th>
<th>$\alpha_2^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.02475</td>
<td>0.00952</td>
<td>0.01523</td>
</tr>
<tr>
<td>0.35</td>
<td>0.02525</td>
<td>0.00929</td>
<td>0.01596</td>
</tr>
<tr>
<td>0.40</td>
<td>0.02454</td>
<td>0.00898</td>
<td>0.01556</td>
</tr>
<tr>
<td>0.45</td>
<td>0.02491</td>
<td>0.00959</td>
<td>0.01532</td>
</tr>
<tr>
<td>0.50</td>
<td>0.02529</td>
<td>0.00949</td>
<td>0.01580</td>
</tr>
</tbody>
</table>

Table 7.3: Overall Alpha and Alpha spending at each look using O’Brien-Fleming
type boundaries of (2.340,2.012) at $t = (0.75, 1)$ with adjusted critical boundary
for $\hat{H}$ observed at the interim by 100,000 simulations

Based on the results in Table 7.3 we could recognize that the type I error rate would
be protected at a designed level $\alpha = 0.025$ by adjusting boundary for $\hat{H}$, and also designed
level $\alpha_1^*$.

### 7.3.2 Adaptation based on the result at the final

As we illustrate above, we need to check the independence assumption first and then see if
original boundary could still be used. Similarly, if we do not allow a test for Hurst exponent
at the interim but rather than at the final, similar procedure would be applied. Under this
circumstance, only an adjusted boundary $c_2'$ would be calculated from

$$\alpha - \alpha_1 = P_{H_0}(Z(t_1) < c_1 \text{ and } Z(t_2) > c_2'|\hat{H})$$

$$= P_{H_0}(B(t_1) < c_1\sqrt{t_1} \text{ and } B(t_2) > c_2'|\hat{H})$$

$$= \int_{c_2'}^{\infty} \int_{-\infty}^{c_1\sqrt{t_1}} f_{B(t_1),B(t_2)}(b_1,b_2)db_1db_2 \quad (7.6)$$

where
\[
\begin{pmatrix}
B(t_1) | \hat{H} \\
B(t_2) | \hat{H}
\end{pmatrix} \sim BVN \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \hat{\sigma}_{11} & \hat{\sigma}_{12} \\
\hat{\sigma}_{21} & \hat{\sigma}_{22} \end{pmatrix}
\]
(7.7)

and \( \hat{\sigma}_{ij} = \frac{1}{2} (t_i^2 \hat{H} + t_j^2 \hat{H} - |t_i - t_j|^2 \hat{H}) \), \( i, j = 1, 2 \). Simulation conducted to show this type I error rate protection.

\[
\begin{array}{c|c|c|c|c}
H & \text{Overall Type I error} & \alpha_1^* & \alpha_2^* \\
\hline
0.30 & 0.02469 & 0.0096 & 0.01509 \\
0.35 & 0.02543 & 0.0096 & 0.01583 \\
0.40 & 0.02533 & 0.0096 & 0.01573 \\
0.45 & 0.02491 & 0.0096 & 0.01531 \\
0.50 & 0.02538 & 0.0096 & 0.01578 \\
\end{array}
\]

Table 7.4: Overall Alpha and Alpha spending at each look using O'Brien-Fleming type boundaries of \((2.340, 2.012)\) at \( t = (0.75, 1) \) with adjusted critical boundary for \( \hat{H} \) observed at the final by 100,000 simulations.

Based on the results in Table 7.4, \( \alpha_1 \) is set at a designed level with \( c_1 \). \( c_2' \) is calculated to protect type I error rate at a desired level \( \alpha = 0.025 \) for \( \hat{H} \).

Also, this method would be applied on the other type of boundaries. Take Pocock type boundary as an example, if no adaptation is observed, type I error rate would inflate as shown in Table 7.5. If we would like to adjust the boundaries based on \( \hat{H} \) observed at the interim, the type I error rate would be protected as the designed level, as shown in Table 7.6. If we would like to adjust the boundaries based on \( \hat{H} \) observed at the final, the type I error rate would be also protected as the designed level, as shown in Table 7.7.
### Table 7.6: Overall Alpha and Alpha spending at each look using Pocock type boundaries of (2.040, 2.258) at \( t = (0.75, 1) \) with adjusted critical boundary for \( H \) observed at the interim by 100,000 simulations

<table>
<thead>
<tr>
<th>( H )</th>
<th>Overall Type I error</th>
<th>( \alpha_1^* )</th>
<th>( \alpha_2^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.02448</td>
<td>0.02054</td>
<td>0.00394</td>
</tr>
<tr>
<td>0.35</td>
<td>0.02501</td>
<td>0.02072</td>
<td>0.00429</td>
</tr>
<tr>
<td>0.40</td>
<td>0.02443</td>
<td>0.01997</td>
<td>0.00446</td>
</tr>
<tr>
<td>0.45</td>
<td>0.02473</td>
<td>0.02045</td>
<td>0.00428</td>
</tr>
<tr>
<td>0.50</td>
<td>0.02553</td>
<td>0.02096</td>
<td>0.00457</td>
</tr>
</tbody>
</table>

### Table 7.7: Overall Alpha and Alpha spending at each look using Pocock type boundaries of (2.040, 2.258) at \( t = (0.75, 1) \) with adjusted critical boundary for \( H \) observed at the final by 100,000 simulations

<table>
<thead>
<tr>
<th>( H )</th>
<th>Overall Type I error</th>
<th>( \alpha_1^* )</th>
<th>( \alpha_2^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.02461</td>
<td>0.0207</td>
<td>0.00391</td>
</tr>
<tr>
<td>0.35</td>
<td>0.02476</td>
<td>0.0207</td>
<td>0.00406</td>
</tr>
<tr>
<td>0.40</td>
<td>0.02515</td>
<td>0.0207</td>
<td>0.00445</td>
</tr>
<tr>
<td>0.45</td>
<td>0.02505</td>
<td>0.0207</td>
<td>0.00435</td>
</tr>
<tr>
<td>0.50</td>
<td>0.02524</td>
<td>0.0207</td>
<td>0.00454</td>
</tr>
</tbody>
</table>

### 7.4 Adjusted Boundary for Type I error rate control when \( K \geq 2 \)

It is usual that we have group sequential design with look \( K > 2 \). Under this circumstance, multiple boundaries would be adapted for type I error rate. In this section, we would like to give formulas for the general case.

For any number \( K \), the type I error rate at the design stage would be calculated as

\[
\alpha = P_{H_0}(Z(t_1) > c_1 \text{ or } (Z(t_1) < c_1, Z(t_2) > c_2) \text{ or } ... \text{ or } (Z(t_1) < c_1, ..., Z(t_K) > c_K))
\]

(7.8)

If we observe a significant \( \hat{H} \) at \( j \)th look, where \( 1 \leq j \leq k \), then we have two scenarios to discuss.

For \( j = 1 \), the alpha spent is equal to 0, then we could just adjust all the boundaries based on this \( \hat{H} \) to protect type I error rate at each look as the same as the one calculated
at the designed stage based on Brownian motion. Then we have
\[
\begin{align*}
\alpha_1^* &= P_{H_0}(Z(t_1) > c_1^*) | \hat{H} \\
\alpha_2^* &= P_{H_0}(Z(t_1) < c_1^*, Z(t_2) > c_2^*) | \hat{H} \\
&\vdots \\
\alpha_K^* &= P_{H_0}(Z(t_1) < c_1^*, \ldots, Z(t_K) > c_K^*) | \hat{H}
\end{align*}
\] (7.9)

Then adjusted boundaries at each interim would be calculated sequentially. And for any looks \(1 \leq j_1 \leq \ldots \leq j_k \leq K\), we could always have multivariate normal distribution that
\[
\begin{pmatrix}
B(t_{j_1}) | \hat{H} \\
\vdots \\
B(t_{j_K}) | \hat{H}
\end{pmatrix} \sim \text{MVN}
\begin{pmatrix}
0 \\
\vdots \\
0
\end{pmatrix},
\begin{pmatrix}
\hat{\sigma}_{j_1,j_1} & \cdots & \hat{\sigma}_{j_1,j_k} \\
\vdots & \ddots & \vdots \\
\hat{\sigma}_{j_k,j_1} & \cdots & \hat{\sigma}_{j_k,j_k}
\end{pmatrix}
\] (7.10)

where \(\hat{\sigma}_{ab} = \frac{1}{2} \left( t_a^{2\hat{H}} + t_b^{2\hat{H}} - |t_a - t_b|^{2\hat{H}} \right)\), \(a, b = \{j_1, \ldots, j_k\}\). Then the probability could be always calculated based on numerical integral at a similar way.

For \(1 < j \leq k\), as we would not consider the dependence between observations before \(j\)th interim and all procedure would be conducted under Brownian motion model, then the cumulative alpha spent in the all past \(j - 1\) interim analysis would be \(\alpha_{j-1} = \alpha(t_{j-1})\), as the same as calculated at the design stage. Under this circumstance, the efficacy could be claimed using original boundaries. When it comes to the \(j\)th interim, which means that we observe non-significant treatment effect before \(j\)th interim. Then for \(j\)th interim until final look, we could similarly derive adjusted boundaries from
\[
\begin{align*}
\alpha_j - \alpha_{j-1} &= \alpha_j^* = P_{H_0} \left( \cap_{m=1}^{j-1} (Z(t_m) < c_m) \text{ and } Z(t_j) > c_j^* | \hat{H} \right) \\
\alpha_{j+1}^* &= P_{H_0} \left( \cap_{m=1}^{j-1} (Z(t_m) < c_m), Z(t_j) = c_j^* \text{ and } Z(t_{j+1}) > c_{j+1}^* | \hat{H} \right) \\
&\vdots \\
\alpha_K^* &= P_{H_0} \left( \cap_{m=1}^{j-1} (Z(t_m) < c_m), \cap_{n=j}^{K-1} (Z(t_n) < c_n') \text{ and } Z(t_K) > c_K' | \hat{H} \right)
\end{align*}
\] (7.11)
Then the type I error rate could be maintain at the same level as the design stage from $j$th interim until the final.

Consider O’Brien-Fleming type boundary is used at $t = (0.2, 0.4, 0.6, 0.8, 1)$ under $\alpha = 0.025$ for a one-sided test with $(4.88, 3.36, 2.68, 2.29, 2.03)$. If no adaption is taken, the type I error rate would be inflated under Hurst exponent $H < 0.5$, as shown in Table 7.8.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Overall type I error rate</th>
<th>$\alpha_1^*$</th>
<th>$\alpha_2^*$</th>
<th>$\alpha_3^*$</th>
<th>$\alpha_4^*$</th>
<th>$\alpha_5^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.0329</td>
<td>0.0002</td>
<td>0.0025</td>
<td>0.0068</td>
<td>0.0104</td>
<td>0.0130</td>
</tr>
<tr>
<td>0.35</td>
<td>0.0303</td>
<td>0.0001</td>
<td>0.0017</td>
<td>0.0057</td>
<td>0.0099</td>
<td>0.0129</td>
</tr>
<tr>
<td>0.4</td>
<td>0.0281</td>
<td>0.0000</td>
<td>0.0011</td>
<td>0.0049</td>
<td>0.0093</td>
<td>0.0128</td>
</tr>
<tr>
<td>0.45</td>
<td>0.0264</td>
<td>0.0000</td>
<td>0.0007</td>
<td>0.0041</td>
<td>0.0089</td>
<td>0.0127</td>
</tr>
<tr>
<td>0.5</td>
<td>0.0250</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.0034</td>
<td>0.0084</td>
<td>0.0128</td>
</tr>
</tbody>
</table>

Table 7.8: Overall Alpha and Alpha spending at each look using O’Brien-Fleming type boundaries of $(4.88, 3.36, 2.68, 2.29, 2.03)$ at $t = (0.2, 0.4, 0.6, 0.8, 1)$

As discussed above, we could adjust critical boundaries to protect type I error rate. Suppose we would like to estimate Hurst exponent at the third interim $t_1 = 0.6$ and adjust boundaries at $(0.6, 0.8, 1)$ for this $\hat{H}$. Then the alpha level $\alpha_1$ and $\alpha_2$ would be spent at the designed level. From $j$th interim, based on the formula we discussed above, we could have new critical boundaries ($c'_3, c'_4, c'_5$) adjusted for $\hat{H}$ observed at $t = (0.6, 0.8, 1)$. Then overall type I error rate would be protected at $\alpha$ level. Simulation is conducted for this scenario for the confirmation as in Table 7.9.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Overall type I error rate</th>
<th>$\alpha_1^*$</th>
<th>$\alpha_2^*$</th>
<th>$\alpha_3^*$</th>
<th>$\alpha_4^*$</th>
<th>$\alpha_5^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.02499</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.00326</td>
<td>0.00875</td>
<td>0.01258</td>
</tr>
<tr>
<td>0.35</td>
<td>0.02472</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.00368</td>
<td>0.00819</td>
<td>0.01245</td>
</tr>
<tr>
<td>0.4</td>
<td>0.02435</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.00318</td>
<td>0.00825</td>
<td>0.01252</td>
</tr>
<tr>
<td>0.45</td>
<td>0.02542</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.00343</td>
<td>0.00852</td>
<td>0.01307</td>
</tr>
<tr>
<td>0.5</td>
<td>0.02503</td>
<td>0.0000</td>
<td>0.0004</td>
<td>0.00361</td>
<td>0.00884</td>
<td>0.01218</td>
</tr>
</tbody>
</table>

Table 7.9: Overall Alpha and Alpha spending at each look with adjusted boundaries for $\hat{H}$ at $t=0.6$ using O’Brien-Fleming type boundaries of $(4.88, 3.36, 2.68, 2.29, 2.03)$ at $t = (0.2, 0.4, 0.6, 0.8, 1)$ with $100,000$ simulations for each Hurst exponent

Similarly, we could apply the method on other boundaries, e.g., Pocock boundary. Consider Pocock type boundary is used at $t = (0.2, 0.4, 0.6, 0.8, 1)$ under $\alpha = 0.025$ for a
one-sided test with (2.44, 2.43, 2.41, 2.40, 2.39). If no adaption is taken, the type I error rate would be inflated under Hurst exponent $H < 0.5$, as shown in Table 7.10.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Overall type I error rate</th>
<th>$\alpha_1^*$</th>
<th>$\alpha_2^*$</th>
<th>$\alpha_3^*$</th>
<th>$\alpha_4^*$</th>
<th>$\alpha_5^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.0676</td>
<td>0.0386</td>
<td>0.0139</td>
<td>0.0074</td>
<td>0.0046</td>
<td>0.0031</td>
</tr>
<tr>
<td>0.35</td>
<td>0.0534</td>
<td>0.0277</td>
<td>0.0115</td>
<td>0.0066</td>
<td>0.0045</td>
<td>0.0031</td>
</tr>
<tr>
<td>0.40</td>
<td>0.0417</td>
<td>0.0190</td>
<td>0.0092</td>
<td>0.0059</td>
<td>0.0043</td>
<td>0.0033</td>
</tr>
<tr>
<td>0.45</td>
<td>0.0322</td>
<td>0.0122</td>
<td>0.0074</td>
<td>0.0052</td>
<td>0.0041</td>
<td>0.0033</td>
</tr>
<tr>
<td>0.50</td>
<td>0.0250</td>
<td>0.0074</td>
<td>0.0057</td>
<td>0.0046</td>
<td>0.0039</td>
<td>0.0034</td>
</tr>
</tbody>
</table>

Table 7.10: Overall Alpha and Alpha spending at each look using Pocock type boundaries of (2.44, 2.43, 2.41, 2.40, 2.39) at $t = (0.2, 0.4, 0.6, 0.8, 1)$

If a similar procedure is conducted as we described previously, the type I error rate would be protected as well. Suppose we would like to estimate Hurst exponent at the third interim $t_1 = 0.6$ and adjust boundaries at $(0.6, 0.8, 1)$ for this $\hat{H}$. Then the alpha level $\alpha_1$ and $\alpha_2$ would be spent at the designed level. From $j$th interim, based on the formula we discussed above, we could have new critical boundaries ($c'_3, c'_4, c'_5$) adjusted for $\hat{H}$ observed at $t = (0.6, 0.8, 1)$. Then overall type I error rate would be protected at $\alpha$ level. Simulation is conducted for this scenario for the confirmation as in Table 7.11.

<table>
<thead>
<tr>
<th>$H$</th>
<th>Overall type I error rate</th>
<th>$\alpha_1^*$</th>
<th>$\alpha_2^*$</th>
<th>$\alpha_3^*$</th>
<th>$\alpha_4^*$</th>
<th>$\alpha_5^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.02454</td>
<td>0.0074</td>
<td>0.0057</td>
<td>0.00447</td>
<td>0.00398</td>
<td>0.00299</td>
</tr>
<tr>
<td>0.35</td>
<td>0.02504</td>
<td>0.0074</td>
<td>0.0057</td>
<td>0.00479</td>
<td>0.00380</td>
<td>0.00335</td>
</tr>
<tr>
<td>0.4</td>
<td>0.02545</td>
<td>0.0074</td>
<td>0.0057</td>
<td>0.00447</td>
<td>0.00409</td>
<td>0.00379</td>
</tr>
<tr>
<td>0.45</td>
<td>0.02498</td>
<td>0.0074</td>
<td>0.0057</td>
<td>0.00472</td>
<td>0.00370</td>
<td>0.00346</td>
</tr>
<tr>
<td>0.5</td>
<td>0.02498</td>
<td>0.0074</td>
<td>0.0057</td>
<td>0.00469</td>
<td>0.00357</td>
<td>0.00362</td>
</tr>
</tbody>
</table>

Table 7.11: Overall Alpha and Alpha spending at each look with adjusted boundaries for $\hat{H}$ at $t=0.6$ using Pocock type boundaries of (2.44, 2.43, 2.41, 2.40, 2.39) at $t = (0.2, 0.4, 0.6, 0.8, 1)$ with 100,000 simulations for each Hurst exponent

### 7.5 Discussion

- As we discussed in this chapter, type I error rate inflation or deflation would only happen when a group sequential design is used. This is because when $t = 1$, the variance of Z-value at the end of study would always equal to 1 regardless of the value of Hurst exponent, as $Var(Z) = Var(B) = 1^{2H} = 1$. Also, if we observe a
Hurst exponent larger than 0.5, we do not have the problem of type I error inflate but deflation. Type I error deflation would cause the trial to be more conservative but might cause power loss.

- We discussed the case when type I error rate is inflated at the first interim and we adjust the boundaries based on observed $\hat{H}$. Actually in a clinical trial, it would be rare that we adjust boundaries for correlation in the early stage, especially when the sample size is not large. We might consider it when the sample size is large enough and Hurst exponent is considered reliable. Based on the inference that we have in Chapter 4, if we could achieve a sample size more than 125 per arm at the interim analysis, we might consider this adaptation.

- In this Chapter, we discuss different scenarios of critical boundaries in terms of O’Brien-Fleming (OBF) type boundary and Pocock type Boundary. Actually they are quite different boundaries that OBF boundary spends really small alpha at the beginning while Pocock boundary spends relatively large alpha. Therefore, if an extreme Hurst exponent less than 0.5 truly exists, it would become easier to cross the boundary at the beginning for both types of boundary but with different probability increases. As we could see in table 7.8 with OBF boundary, if Hurst exponent $H = 0.3$, which is extreme, we would observe $(0.0002, 0.0025 − 0.0004) = (0.0002, 0.0021)$ inflated at first two interim analyses but this increment is relatively small. If we take a look at table 7.10 if Hurst exponent $H = 0.3$, we would observe $(0.0386 − 0.0074, 0.0139 − 0.0057) = (0.0312, 0.0082)$ at first two looks. This would be a huge difference that even the first look would inflate type I error more than twice. Based on this information, if we do know that there is negative correlation among the observations $H < 0.5$, OBF type boundary would be preferred to allow a small type I error rate inflation.

- As we discussed here in the previous bullet point, we have huge inflation at the early stage when Pocock boundary is selected at $H < 0.5$. However, what we adjust here is to adjust the boundaries after the current interim. This means that we have already continued the trial to current interim, after we do not observe significance before current results. So we do not need to worry about this inflation if we have already
come to the later stage of the trial. The alpha was spent at a designed level. What we do here is to protect the type I error rate in current interim and further interim analysis. In the same tables 7.8 and 7.10, there would not be a huge difference of type I error rate in the later stage, especially in the final look OBF boundary gives only 0.0002 inflation while Pocock boundary becomes deflated. Therefore, it would not be a big concern. However, if we take a look at the previous case when $K = 2$ and we have looks at $t = (0.75, 1)$. Even both of the time is considered as later stage, the type I error rate would not be neglected, as shown in table 7.2 ($0.0294 - 0.025 = 0.0044$) and table 7.5 ($0.0326 - 0.025 = 0.0076$).
Chapter 8

Conditional Power under Fractional Brownian Motion with Piece-wise Linear Drift

8.1 Introduction

As mentioned in subsection 2.4.2, a fractional Brownian motion with linear drift could be defined as \( B'_H(t) = \theta t + B_H(t) \) in 2.3.2 by assuming \( \sigma = 1 \). Note that this formula is given under assumption of identical distribution of each observation, which would result a linear drift for the process. However, in some cases, there would be some observed or unobserved changes to the trial that we might have a non-linear drift for the process, which leads to the violation of identical distribution. As described in Xie et al. (2021), we might observe a piece-wise linear drift rather than linear drift for observed B-value as shown in 8.1

Under this circumstance, we could construct another model with non-linear drift \( g(\theta, t) \) that

\[
B^*_H(t) = g(\theta, t) + B_H(t) \tag{8.1}
\]

Denote \( B^*_H(t) = (B^*_H(t_1), ..., B^*_H(t_n)) \) as the observed values of \( \{B^*_H(t); t \geq 0\} \) with sample size \( n \) and \( t = (t_1, ..., t_n) \). If this non-linear drift is considered, we would have \( B^*_H(t) \sim \text{MVN} \left( g(\theta, t), \Sigma_H \right) \) where nonlinear function

\[
g(\theta, t) = (g(\theta, t_1), g(\theta, t_2), ..., g(\theta, t_n))^T \tag{8.2}
\]
Figure 8.1: Observed three pieces of linear trend
is given. In this case, we could specify the the log-likelihood for the observed B-values that:

\[
\begin{align*}
    l_n(B^n_H(t), H, \theta) &= -\frac{n}{2} \log (2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} (B^n_H(t) - g(\theta, t))^T \Sigma_H^{-1} (B^n_H(t) - g(\theta, t)) \\
   &= -\frac{n}{2} \log (2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} (B^n_H(t) - g(\theta, t))^T \Sigma_H^{-1} (B^n_H(t) - g(\theta, t)) \\
   \end{align*}
\]  

(8.3)

For a general form of non-linear drift \( g(\theta, t) \), we could use optimization method to find maximum likelihood estimation of \((H, \theta)\). Compared to the model with linear drift, this would lead to different formula of drift estimation and conditional power. Specifically, if a piece-wise drift with one change-point is assumed, then \( g(\theta, t) \) would be expressed as \( g(\theta_1, \theta_2, M, t) \) that

\[
g(\theta_1, \theta_2, M, t) = \begin{cases} 
    \theta_1 t & \text{if } t \leq M \\
    \theta_2 (t - M) + \theta_1 M & \text{if } t > M 
\end{cases} 
\]  

(8.4)

where \( M \) is the change point and could be either given or unknown with \( 0 < M \leq 1 \).

We have reviewed the change-point analysis in section 2.5 which is a similar scenario to the piece-wise linear drift problem. In this chapter, we would illustrate the relationship between B-value and partial sum in section 8.2. We would then discuss about the estimation of piece-wise linear drift with a change-point in section 8.3 for two scenarios of known and unknown change-point. After estimation of piece-wise linear drift is derived, we would discuss the test for the change-point in section 8.4. In section 8.5, we would discuss how to calculate the conditional power under a piece-wise linear drift. In section 8.7, we provide examples to illustrate how to apply the method on the sequence of B-values. In section 8.6, we would discuss the illustration of different model by visualization. And in section 8.8, we provide discussion section of this chapter.

8.2 B-value and partial sum

As we talked about B-value in the previous chapter, if we observe a non-linear trend of B-value shown in Figure 8.2, which is a piece-wise trend with different drifts in two period, the estimation and the test for change-point of B-value would be identical to the one of
partial sum.

Figure 8.2: B-value and Partial sum of simulated Example (N=80) with $\mu_1 = 0.2$ in first 40 observations and $\mu_2 = 0.4$ for later 40 observations. Dashed lines describe a general trend of the two pieces.

For a finite sequence $X_1, ..., X_n$, where $X_i$ are independent and normally distributed with mean $\mu$ and variance of 1, for any $1 \leq m < n$ we have partial sum $S_m = \sum_{i=1}^{m} X_i$ and B-value $B_m = \sum_{i=1}^{m} \sqrt{m} \bar{X}_m \sqrt{m/n} = \sum_{i=1}^{m} X_i / \sqrt{n}$. Then $S_m = B_m \sqrt{n}$, which is a linear transformation of B-value with a fixed $n$. For a two-sample problem, we have $S_m = B_m \sqrt{2n}$. This indicates that, if we have a sequence of B-value, we could apply the change-point method similarly on the B-value to do the inference of change-point.

### 8.3 Model of Piece-wise Linear Drift with one change-point

As we mentioned in the section 8.1, we have the log-likelihood for the observed B-values $B^*_H(t) = (B^*_H(t_1), ..., B^*_H(t_n))$ under piece-wise linear drift with sample size $n$ and $t = (t_1, ..., t_n)$, that:

$$
\begin{align*}
&l(B^*_H(t), H, \theta_1, \theta_2, M) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log|\Sigma_H| \\
&\quad - \frac{1}{2} (B^*_H(t) - g(\theta_1, \theta_2, M, t))^T \Sigma_H^{-1} (B^*_H(t) - g(\theta_1, \theta_2, M, t))
\end{align*}
$$

(8.5)
where

\[ \mathbf{g}(\theta_1, \theta_2, M, \mathbf{t}) = (g(\theta_1, \theta_2, M, t_1), ..., g(\theta_1, \theta_2, M, t_n))^T \]  \hspace{1cm} (8.6)

and

\[
g(\theta_1, \theta_2, M, t) = \begin{cases} 
\theta_1 t & \text{if } t \leq M \\
\theta_2(t - M) + \theta_1 M & \text{if } t > M 
\end{cases} \]  \hspace{1cm} (8.7)

and there is only one \( k \) that \( t_{k-1} = M \), as we would expect the change-point to be discrete and could be only one of those \( n \) points of \((t_1, ..., t_n)\).

### 8.3.1 Estimation of Piece-wise Linear Drift with known change-point

If change-point is known, this would give us a fixed change-point \( M \). We could re-write formula (8.5) as

\[
l(B^*_H(t), H, \theta_1, \theta_2, M) = -\frac{n}{2} \log (2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} B^*_H(t)^T \Sigma_H^{-1} B^*_H(t) \\
+ \frac{1}{2} \mathbf{g}^T(\theta_1, \theta_2, M, \mathbf{t}) \Sigma_H^{-1} B^*_H(t) + \frac{1}{2} B^*_H(t)^T \Sigma_H^{-1} \mathbf{g}(\theta_1, \theta_2, M, \mathbf{t}) \\
- \frac{1}{2} \mathbf{g}^T(\theta_1, \theta_2, M, \mathbf{t}) \Sigma_H^{-1} \mathbf{g}(\theta_1, \theta_2, M, \mathbf{t}) \]  \hspace{1cm} (8.8)

Denote \( \mathbf{M}_1 = (t_1, ..., t_{k-1}, M, ..., M)^T \) and \( \mathbf{M}_2 = (0, ..., 0, t_k - M, ..., t_n - M)^T \), we make derivative w.r.t. \( \theta_1 \) and \( \theta_2 \) and setting them to 0 that

\[
\frac{\partial l(B^*_H(t), H, \theta_1, \theta_2, M)}{\partial \theta_1} = \mathbf{M}_1^T \Sigma_H^{-1} B^*_H(t) - \mathbf{M}_1^T \Sigma_H^{-1} \mathbf{g}(\theta_1, \theta_2, \mathbf{t}) = 0 \\
\frac{\partial l(B^*_H(t), H, \theta_1, \theta_2, M)}{\partial \theta_2} = \mathbf{M}_2^T \Sigma_H^{-1} B^*_H(t) - \mathbf{M}_2^T \Sigma_H^{-1} \mathbf{g}(\theta_1, \theta_2, \mathbf{t}) = 0 \]  \hspace{1cm} (8.9)
Note that we could write

\[
g(\theta_1, \theta_2, t) = \begin{pmatrix}
\theta_1 t_1 \\
\vdots \\
\theta_1 t_{k-1} \\
\theta_2(t_k - M) + \theta_1 M \\
\vdots \\
\theta_2(t_n - M) + \theta_1 M
\end{pmatrix} = \left( \theta_1 M_1 + \theta_2 M_2 \right)
\]  

(8.10)

Then we have

\[
M_1^T \Sigma_H^{-1} B_H^*(t) - M_1^T \Sigma_H^{-1} M_1 \theta_1 - M_1^T \Sigma_H^{-1} M_2 \theta_2 = 0
\]

\[
M_2^T \Sigma_H^{-1} B_H^*(t) - M_2^T \Sigma_H^{-1} M_1 \theta_1 - M_2^T \Sigma_H^{-1} M_2 \theta_2 = 0
\]

(8.11)

Denote

\[
A = \begin{pmatrix}
M_1^T \Sigma_H^{-1} M_1 & M_1^T \Sigma_H^{-1} M_2 \\
M_2^T \Sigma_H^{-1} M_1 & M_2^T \Sigma_H^{-1} M_2
\end{pmatrix},
C = \begin{pmatrix}
M_1^T \Sigma_H^{-1} B_H^*(t) \\
M_2^T \Sigma_H^{-1} B_H^*(t)
\end{pmatrix}
\]  

(8.12)

This would lead to

\[
A \begin{pmatrix}
\theta_1 \\
\theta_2
\end{pmatrix} = C
\]  

(8.13)

Then we have maximum likelihood estimate of \(\theta_1, \theta_2\) that

\[
\hat{\theta}(H, M) = \begin{pmatrix}
\hat{\theta}_1(H, M) \\
\hat{\theta}_2(H, M)
\end{pmatrix} = A^{-1} C
\]  

(8.14)

After \(H\) is calculated through maximum likelihood or given, \(\hat{\theta}_{1,MLE}(H, M), \hat{\theta}_{2,MLE}(H, M)\) could be calculated.
8.3.2 Estimation of Piece-wise Linear Drift with unknown change-point

We might need to estimate the change-point $M$ if it’s not given. As we mentioned in subsection 8.3.1, the log-likelihood function would be re-written as a function of $(H, M)$ by inserting $\hat{\theta}_{1, MLE}(H, M), \hat{\theta}_{2, MLE}(H, M)$ into the log-likelihood.

If $H$ is given, then $\hat{M}_{MLE}$ would be equal to the time-point with the largest log-likelihood that

$$
\hat{M}_{MLE} = \arg\max_{t_1 \leq M < t_n} l \left( B_H^n(t), H, \hat{\theta}_{1, MLE}(H, M), \hat{\theta}_{2, MLE}(H, M), M \right)
$$

Then the estimate of drift parameters could be calculated by $\hat{\theta}_1(H, \hat{M}_{MLE}), \hat{\theta}_2(H, \hat{M}_{MLE})$

If $H$ is not given,

1. For each time-point in $(t_1, ..., t_n)$, find $\hat{H}_{MLE}$ and corresponding maximum log-likelihood.

2. $\hat{M}_{MLE}$: estimated by searching the time-point with the largest log-likelihood:

$$
\hat{M}_{MLE} = \arg\max_{t_1 \leq \hat{M} < t_n} l \left( B_H^n(t), \hat{H}_{MLE}(M), \hat{\theta}_1(\hat{H}_{MLE}(M), M), \hat{\theta}_2(\hat{H}_{MLE}(M), M), M \right)
$$

3. Calculate $\hat{\theta}_1(\hat{H}_{MLE}(\hat{M}_{MLE}), \hat{M}_{MLE}), \hat{\theta}_2(\hat{H}_{MLE}(\hat{M}_{MLE}), \hat{M}_{MLE})$

8.4 Test of Change-point

Based on a given or estimated change-point, we would like to test if change-point is significant or not. Recall that in 2.20, we have log-likelihood function for linear drift that

$$
l_n(Y, H, \theta) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\Sigma_H| - \frac{1}{2} (B_H^n(t) - \theta t)^T \Sigma_H^{-1} (B_H^n(t) - \theta t)
$$

To differentiate the Hurst exponent in two types of model, we refer $H_l$ as the Hurst exponent in the model with linear drift and $H_p$ as the Hurst exponent in the model with piece-wise
linear drift. The estimate of \((\theta, H_t)\) could be derived from profile likelihood that

\[
\hat{\theta}_{MLE}(H_t) = t^T \Sigma^{-1}_H b_H^*(t) t^T \Sigma^{-1}_H t
\]  

(8.18)

and \(H_t\) could be given or estimated by maximizing log-likelihood function through optimization method.

### 8.4.1 Known change-point given Hurst exponent

For a given time-point \(t_0\), we could test that

\[
H_0 : \theta_1 = \theta_2 = \theta \text{ vs } H_a : \theta_1 \neq \theta_2
\]  

(8.19)

with likelihood ratio test

\[
T^{*}_{LR}(H) = -2 \log \left( \frac{\sup_{\theta \in \Theta} L(\theta | B^*_H(t), H)}{\sup_{\theta_1, \theta_2 \in \Theta} L(\hat{\theta}_1, \hat{\theta}_2 | B^*_H(t), H, M)} \right)
\]

\[
= -2 \left( l(\hat{\theta} | B^*_H(t), H) - l(\hat{\theta}_1, \hat{\theta}_2 | B^*_H(t), H, M) \right)
\]

\[
= -2 \left( \frac{1}{2} (B^*_H(t) - \hat{\theta} t)^T \Sigma^{-1}_H (B^*_H(t) - \hat{\theta} t) - \left( \frac{1}{2} \left( B^*_H(t) - g(\hat{\theta}_1, \hat{\theta}_2, t) \right)^T \Sigma^{-1}_H \left( B^*_H(t) - g(\hat{\theta}_1, \hat{\theta}_2, t) \right) \right) \right)
\]

\[
= (B^*_H(t) - \hat{\theta} t)^T \Sigma^{-1}_H (B^*_H(t) - \hat{\theta} t) - (B^*_H(t) - g(\hat{\theta}_1, \hat{\theta}_2, t))^T \Sigma^{-1}_H (B^*_H(t) - g(\hat{\theta}_1, \hat{\theta}_2, t))
\]  

(8.20)

where \(\hat{\theta}\) stands for MLE of \(\theta\). This test statistic is the same as formula \(2.30\) when \(H = 0.5\) and has been discussed by different approach. Under regularity conditions, \(T^{*}_{LR}(H) \overset{d}{\to} \chi^2_1\) as \(n \to \infty\) under the null. This property has been well explained and proved by Wilks’ theorem from \[Wilks, 1938\]. Thus, P-value could be derived through calculate \(P(T^{*}_{LR}(H) > \chi^2_1(\alpha))\).

We conduct simulations to have a general look of the type I error rate performance under finite sample in Table \[8.1\]. For each simulation, we compare the likelihood ratio test statistic with \(\chi^2_{1,0.05}\).

We could see that the Type I error rate works around the alpha level \(\alpha = 0.05\) across all the numbers of B-values and Hurst exponent. This confirm that the likelihood ratio
<table>
<thead>
<tr>
<th>$H$</th>
<th>Number of B-values</th>
<th>Type I error of LRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>40</td>
<td>0.0529</td>
</tr>
<tr>
<td>0.40</td>
<td>80</td>
<td>0.0514</td>
</tr>
<tr>
<td>0.40</td>
<td>160</td>
<td>0.0524</td>
</tr>
<tr>
<td>0.45</td>
<td>40</td>
<td>0.0510</td>
</tr>
<tr>
<td>0.45</td>
<td>80</td>
<td>0.0519</td>
</tr>
<tr>
<td>0.45</td>
<td>160</td>
<td>0.0508</td>
</tr>
<tr>
<td>0.50</td>
<td>40</td>
<td>0.0485</td>
</tr>
<tr>
<td>0.50</td>
<td>80</td>
<td>0.0497</td>
</tr>
<tr>
<td>0.50</td>
<td>160</td>
<td>0.0497</td>
</tr>
<tr>
<td>0.55</td>
<td>40</td>
<td>0.0466</td>
</tr>
<tr>
<td>0.55</td>
<td>80</td>
<td>0.0526</td>
</tr>
<tr>
<td>0.55</td>
<td>160</td>
<td>0.0505</td>
</tr>
<tr>
<td>0.60</td>
<td>40</td>
<td>0.0488</td>
</tr>
<tr>
<td>0.60</td>
<td>80</td>
<td>0.0497</td>
</tr>
<tr>
<td>0.60</td>
<td>160</td>
<td>0.0534</td>
</tr>
</tbody>
</table>

Table 8.1: Given information of Hurst exponent and change-point, Type I error of likelihood ratio test statistic for different sample size under different Hurst exponent by 10,000 simulations under $\alpha = 0.05$. The change-point is set at the half of the number of B-values.

statistics test follows a Chi-square distribution with degree of freedom of 1.

**8.4.2 Known change-point with estimation of Hurst exponent**

If information of Hurst exponent $H$ is unknown, then we need to estimate Hurst exponent $H$ by MLE $\hat{H}_l$ for model of linear drift under fBm and MLE $\hat{H}_p$ for model of piece-wise linear drift under fBm. To compare the model with linear drift and piece-wise linear drift, for a time-point $M$, we could test that

$$H_0 : \theta_1 = \theta_2 = \theta \text{ vs } H_a : \theta_1 \neq \theta_2$$

(8.21)
with likelihood ratio test

\[
T_{LR}^* = -2log\left( \frac{\sup_{\theta \in \Theta} \sup_{H \in c(0,1)} L(\theta, H|Y)}{\sup_{\theta_1, \theta_2 \in \Theta} \sup_{H \in c(0,1)} L(\theta_1, \theta_2, H|Y, M)} \right)
\]

\[
= -2\left( l(\hat{\theta}(H_l)|Y) - l(\hat{\theta}_1(H_{p}), \hat{\theta}_2(H_{p})|Y, M) \right)
\]

\[
= -2\left( -\frac{1}{2} \log |\Sigma_{H_l}| - \frac{1}{2} \left( B_{H_l}^*(t) - \hat{\theta}(H_l)t \right)^T \Sigma_{H_l}^{-1} \left( B_{H_l}^*(t) - \hat{\theta}(H_l)t \right) - \left( -\frac{1}{2} \log |\Sigma_{H_p}| \right) \right)
\]

\[
= \log |\Sigma_{H_l}| + \left( B_{H_l}^*(t) - \hat{\theta}(H_l)t \right)^T \Sigma_{H_l}^{-1} \left( B_{H_l}^*(t) - \hat{\theta}(H_l)t \right) - \log |\Sigma_{H_p}|
\]

\[
= \left( B_{H_l}^*(t) - g(\hat{\theta}_1(H_{p}), \hat{\theta}_2(H_{p}), M, t)) \right)^T \Sigma_{H_l}^{-1} \left( B_{H_l}^*(t) - g(\hat{\theta}_1(H_{p}), \hat{\theta}_2(H_{p}), M, t) \right)
\]

(8.22)

Under regularity conditions, \( T_{LR}^* \stackrel{d}{\to} \chi^2_1 \) as \( n \to \infty \) under the null. This property has been well explained and proved by Wilks' theorem from Wilks (1938). Thus, P-value could be derived through calculate \( P(T_{LR}^* > \chi^2_1(\alpha)) \). We conduct simulations to have a general look of the type I error rate performance under finite sample in table 8.2. For each simulation, we compare the likelihood ratio test statistic with \( \chi^2_{1,0.05} \).

Based on the table, we could see that, even Hurst exponent information is unknown, we could use estimate of Hurst exponent to detect the change-point and conduct likelihood ratio test. The Type I error rate similarly works around the alpha level \( \alpha = 0.05 \) across all the numbers of B-values and Hurst exponent. This confirm that the likelihood ratio statistics test follows a Chi-square distribution with degree of freedom of 1.

### 8.4.3 Unknown change-point given Hurst exponent

For unknown change-point, i.e, we do not have information of \( M \). In this case we need to get MLE of \( M \) and test if this \( \hat{M} \) is significant. The statistic for this test is different from the one we discussed above for known change-point, mainly because we need to search for this \( \hat{M} \) among all the time points, resulting a maximally selected chi-square statistics. Denote
<table>
<thead>
<tr>
<th>$H$</th>
<th>Number of B-values</th>
<th>Type I error of LRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>40</td>
<td>0.0488</td>
</tr>
<tr>
<td>0.40</td>
<td>80</td>
<td>0.0509</td>
</tr>
<tr>
<td>0.40</td>
<td>160</td>
<td>0.0502</td>
</tr>
<tr>
<td>0.45</td>
<td>40</td>
<td>0.0515</td>
</tr>
<tr>
<td>0.45</td>
<td>80</td>
<td>0.0491</td>
</tr>
<tr>
<td>0.45</td>
<td>160</td>
<td>0.0475</td>
</tr>
<tr>
<td>0.50</td>
<td>40</td>
<td>0.0551</td>
</tr>
<tr>
<td>0.50</td>
<td>80</td>
<td>0.0489</td>
</tr>
<tr>
<td>0.50</td>
<td>160</td>
<td>0.0543</td>
</tr>
<tr>
<td>0.55</td>
<td>40</td>
<td>0.0553</td>
</tr>
<tr>
<td>0.55</td>
<td>80</td>
<td>0.0538</td>
</tr>
<tr>
<td>0.55</td>
<td>160</td>
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</tr>
<tr>
<td>0.60</td>
<td>40</td>
<td>0.0547</td>
</tr>
<tr>
<td>0.60</td>
<td>80</td>
<td>0.0569</td>
</tr>
<tr>
<td>0.60</td>
<td>160</td>
<td>0.0500</td>
</tr>
</tbody>
</table>

Table 8.2: Given information of change-point without information of Hurst exponent, Type I error of likelihood ratio test statistic for different sample size under different Hurst exponent by 10,000 simulations under $\alpha = 0.05$. The change-point is set at the half of the number of B-values.

the statistic for unknown change-point as $T_{LR}^{u,*}(H)$, we have

$$T_{LR}^{u,*}(H) = \max_{t_1 \leq M < t_n} (T_{LR}^*(H))$$ (8.23)

The asymptotic distribution of $T_{LR}^{u,*}(H)$ would be detected by a transformation. When $H = 0.5$, the asymptotic distribution has been derived with formula 2.33. We try to apply this critical value under different Hurst exponent with simulation in table 8.3. From the table, we could see that the type I error rate works well at $H = 0.5$ across all the sample size, especially at larger sample size. When $H < 0.5$, we could see that the test statistics become more conservative while $H > 0.5$, there would be a little type I error rate inflation. However, the inflation would not be that much.
<table>
<thead>
<tr>
<th>$H$</th>
<th>Number of B-values</th>
<th>Type I error of LRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>40</td>
<td>0.0466</td>
</tr>
<tr>
<td>0.40</td>
<td>80</td>
<td>0.0434</td>
</tr>
<tr>
<td>0.40</td>
<td>160</td>
<td>0.0417</td>
</tr>
<tr>
<td>0.45</td>
<td>40</td>
<td>0.0489</td>
</tr>
<tr>
<td>0.45</td>
<td>80</td>
<td>0.0496</td>
</tr>
<tr>
<td>0.45</td>
<td>160</td>
<td>0.0450</td>
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<td>0.50</td>
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<td>0.0518</td>
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<tr>
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<tr>
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</tr>
<tr>
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<td>0.0591</td>
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<td>0.60</td>
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<td>0.0612</td>
</tr>
<tr>
<td>0.60</td>
<td>160</td>
<td>0.0676</td>
</tr>
</tbody>
</table>

Table 8.3: Given information of Hurst exponent without information of change-point, Type I error of likelihood ratio test statistic for different sample size under different Hurst exponent by 10,000 simulations under $\alpha = 0.05$.

### 8.4.4 Unknown change-point with estimation of Hurst exponent

If both the information of Hurst exponent and change-point are unknown, the test statistics would utilize both the estimate of $H$ and $M$ and

$$T_{LR}^{u,*} = \max_{t_1 \leq M < t_n} (T_{LR}^*) \quad (8.24)$$

We try to apply this critical value as in 8.4.2 under different Hurst exponent with simulation in table 8.4. But the performance here is not consistent across all the Hurst exponent and computation speed is not efficient when sample size is large.

### 8.5 Conditional Power calculation

As we could conduct a test for the change-point, if we could have a significant change-point, we would like to calculate the conditional power based on this piece-wise linear drift model. As described in 8.1 for observed B-value $B_{H}^{*}(t) = (B_{H}^{*}(t_1), ..., B_{H}^{*}(t_n))$ with
<table>
<thead>
<tr>
<th>$H$</th>
<th>Number of B-values</th>
<th>Type I error of LRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.40</td>
<td>40</td>
<td>0.0453</td>
</tr>
<tr>
<td>0.40</td>
<td>80</td>
<td>0.0475</td>
</tr>
<tr>
<td>0.45</td>
<td>40</td>
<td>0.0540</td>
</tr>
<tr>
<td>0.45</td>
<td>80</td>
<td>0.0476</td>
</tr>
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<td>0.50</td>
<td>40</td>
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<td>0.50</td>
<td>80</td>
<td>0.0563</td>
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<tr>
<td>0.55</td>
<td>40</td>
<td>0.0674</td>
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<tr>
<td>0.55</td>
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<td>0.0576</td>
</tr>
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<td>0.60</td>
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<td>0.0713</td>
</tr>
<tr>
<td>0.60</td>
<td>80</td>
<td>0.0736</td>
</tr>
</tbody>
</table>

Table 8.4: Without information of change-point and Hurst exponent, Type I error of likelihood ratio test statistic for different sample size under different Hurst exponent by 10,000 simulations under $\alpha = 0.05$.

sample size $n$ and $t = (t_1, ..., t_n)$. If this non-linear drift is considered, we would have $B_H^*(t) \sim MVN\left(g(\theta_1, \theta_2, M, t), \Sigma_H\right)$. For the further observation $B_H^*(1)$, we would first have the joint distribution that

$$
\begin{align*}
\begin{pmatrix}
B_H^*(t) \\
B_H^*(1)
\end{pmatrix}
\sim
\begin{pmatrix}
g(\theta_1, \theta_2, M, t) \\
g(\theta_1, \theta_2, M, 1)
\end{pmatrix}
\begin{pmatrix}
\Sigma^*_{(11)} & \Sigma^*_{(12)} \\
\Sigma^*_{(21)} & \Sigma^*_{(22)}
\end{pmatrix}
\end{align*}
$$

(8.25)

where $\Sigma^*$ could be calculated based on definition of fBm and $H$. Then we have the conditional distribution of $B_H^*(1)$ that

$$
B_H^*(1)|B_H^*(t) = b_H^*(t) \sim N(\theta_c^*, (\sigma_c^*)^2)
$$

(8.26)

Where conditional mean

$$
\theta_c^* = g(\theta_1, \theta_2, M, 1) + \Sigma^*_{(21)}(\Sigma^*_{(11)})^{-1}(b_H^*(t) - g(\theta_1, \theta_2, M, t))
$$

(8.27)

conditional variance

$$
(\sigma_c^*)^2 = (\sigma_K^*)^2 - \Sigma^*_{(21)}(\Sigma^*_{(11)})^{-1}\Sigma^*_{(12)}
$$

(8.28)
and \((\sigma^*_K)^2 = \Sigma^*_{(22)}\). Then conditional power based on piece-wise drift with one known change-point would be expressed as

\[
CP_H(\theta_1, \theta_2, M) = P \left( Z_N = B_H^*(1) > z_\alpha | \theta_1, \theta_2, H, M, B_H^*(t) \right)
\]

\[
= P \left( \frac{B_H^*(1) - \theta^*_c}{\sigma^*_c} > \frac{z_\alpha - \theta^*_c}{\sigma^*_c} \right)
\]

\[
= 1 - \Phi \left( \frac{z_\alpha - \theta^*_c}{\sigma^*_c} \right)
\]

(8.29)

We could insert \(\hat{\theta}_{1,MLE}(M, H), \hat{\theta}_{2,MLE}(M, H)\) and information of \((H, M)\) into the calculation.

### 8.6 Illustration of Conditional Mean

As presented in Xie et al. (2021), we could visualize the B-value on radar screen. This would give us a comprehensive information of the trial. Therefore, it would be helpful to see how conditional power could be visualized on a plot. Note that in formula 8.5, if we know the information of Hurst exponent or by assumption, conditional variance \((\sigma^*_c)^2\) would be fixed and thus, conditional power is a function of conditional mean \(\theta^*_c\). We would pay more attention on how \(\theta^*_c\) performs by different weight on piece-wise drift and observations.

#### 8.6.1 Under Brownian motion assumption and linear drift

We would like to discuss the scenario of a classic model, which we usually assume linear drift under Brownian motion. In this case, we have \(\theta_1 = \theta_2 = \theta, M = 1\) and

\[
g(\theta_1, \theta_2, M, t) = \theta t \quad \text{for } 0 \leq t \leq 1
\]

(8.30)
and when \( H = 0.5 \), we have

\[
\Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1} = \begin{pmatrix}
0 \\
0 \\
\vdots \\
0 \\
1
\end{pmatrix} \quad (8.31)
\]

and

\[
\theta^{*}_c = \theta + \Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1}(b^{*}_H(t) - \theta t) \\
= \theta + b^{*}_H(t_n) - \theta t_n \\
= b^{*}_H(t_n) + \theta(1 - t_n) \quad (8.32)
\]

where \( b^{*}_H(t_n) \) is the observation of \( B^*_H(t_n) \). This conditional mean is a projection of point \( b^{*}_H(t_n) \) from \( t = t_n \) to \( t = 1 \) with a slope \( \theta \). If \( \hat{\theta} = b^{*}_H(t_n)/t_n \) we have

\[
\theta^{*}_c = b^{*}_H(t_n)/t_n \quad (8.33)
\]

With MLE of drift parameter \( \hat{\theta} \), we would have conditional mean as a projection of original point from \( t = 0 \) to \( t = 1 \) with a slope \( b^{*}_H(t_n)/t_n \). The illustration would be shown at figure...
8.6.2 Under Brownian motion assumption and piece-wise linear drift

As mentioned in formulas 8.27 and 8.31, we have conditional mean under piece-wise linear drift that

\[ \theta_c^* = g(\theta_1, \theta_2, M, 1) + \Sigma_{(21)}^* \Sigma_{(11)}^* (b_H(t) - \theta_2(t - M) - \theta_1 M) \]
\[ = \theta_2(1 - M) + \theta_1 * M + (b_H(t_n) - \theta_2(t_n - M) - \theta_1 M) \quad (8.34) \]
\[ = b_H^*(t_n) + \theta_2(1 - t_n) \]

Then conditional mean could be expressed as the projection of point \( b_H^*(t_n) \) from \( t = t_n \) to \( t = 1 \) with a slope \( \theta_2 \).

As the observation \( b_H^*(t_n) \) is fixed, the conditional mean is only related to the time \( t_n \) and second piece of drift \( \theta_2 \). If the estimate of \( \theta_2 \) is inserted, we would have
\[ \theta_c^* = b_H^*(t_n) + \frac{b_H^*(t_n) - b_H^*(M)}{t_n - M} (1 - t_n) \]
\[ = b_H^*(t_n) + \frac{b_H^*(t_n) - b_H^*(M)}{t_n - M} (1 - M - (t_n - M)) \]
\[ = b_H^*(M) + \frac{b_H^*(t_n) - b_H^*(M)}{t_n - M} (1 - M) \]  \hspace{1cm} (8.35)

Note that conditional mean is also a function of \( M \). Then the conditional mean could be expressed as the projection of point \( b_H^*(M) \) from \( t = M \) to \( t = 1 \) with a slope \( \frac{b_H^*(t_n) - b_H^*(M)}{t_n - M} \).

The illustration would be shown at figure 8.4.

Figure 8.4: Illustration for conditional Mean under different scenarios for piecewise linear drift model with Brownian motion assumption

8.6.3 Under fractional Brownian motion assumption and linear drift

for the linear drift model, we still have \( \theta_1 = \theta_2 = \theta, M = 1 \) with the same \( g(.) \) function as in formula 8.30. When \( H \neq 0.5 \), we do not have the nice property as in 8.31. Then we would re-arrange the formula of conditional mean that
\[
\theta^*_c = \theta + \Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1}(b_H^*(t) - \theta t)
= \theta(1 - \Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1}t) + \Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1}b_H^*(t)
\] (8.36)

Denote a transformed time \( \tau = \Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1}t \) and transformed observation \( \beta = \Sigma^{*,(21)}(\Sigma^{*,(11)})^{-1}b_H^*(t), \) we would have

\[
\theta^*_c = \theta(1 - \tau) + \beta
\] (8.37)

This could be interpreted as the projection of point \( \beta \) from time \( t = \tau \) to time \( t = 1 \) with slope \( \theta \). If \( \hat{\theta}_{MLE}(H) = \frac{t^T(\Sigma^{*,(11)})^{-1}b_H^*(t)}{t^T(\Sigma^{*,(11)})^{-1}t} \) could be inserted to the formula but we would not get a simplified expression. The concept could be illustrated in the plot 8.5.

Figure 8.5: Illustration for conditional Mean under different scenarios for linear drift model with fractional Brownian motion assumption, simulated from \( H = 0.3 \)
8.6.4 Under fractional Brownian motion assumption and piece-wise linear drift

As mentioned in formula \([8.27]\), we have conditional mean under piece-wise linear drift that

\[
\theta^*_c = g(\theta_1, \theta_2, M, 1) + \Sigma^*(21)(\Sigma^*(11))^{-1}(b_H^*(t) - \theta_2(t - M) - \theta_1 M)
\]

\[= \theta_2(1 - M) + \theta_1 M + \Sigma^*(21)(\Sigma^*(11))^{-1}(b_H^*(t) - \theta_2(t - M) - \theta_1 M)
\]  

(8.38)

If we use the same notation in the previous subsection that transformed time \(\tau = \Sigma^*(21)(\Sigma^*(11))^{-1} t\), transformed observation \(\beta = \Sigma^*(21)(\Sigma^*(11))^{-1} b_H^*(t)\) and another transformation \(\tau_M = \Sigma^*(21)(\Sigma^*(11))^{-1} M1_n\), we would have

\[
\theta^*_c = \theta_2(1 - M) + \theta_1 M + \beta - \theta_2 \tau + \theta_2 \tau_M - \theta_1 \tau_M
\]

\[= \beta + \theta_1 (M - \tau_M) + \theta_2 (1 - (\tau - \tau_M + M))
\]  

(8.39)

This could be interpreted as the projection of point \(\beta + \theta_1 (M - \tau_M)\) from time \(t = \tau - \tau_M + M\) to time \(t = 1\) with slope \(\theta_2\). However, this is not similar to formula \([8.34]\) which does not include calculation of \(\theta_1\). So there we do not go further into the illustration of this model as well as the one with MLE, as we have not found the intuitive calculation so far. The matrix algebra could be completed in further research.

8.7 Application of sequence of B-value

8.7.1 Piece-wise linear drift under Bm \((H = 0.5)\)

Suppose we have total sample size as \(N = 200\) per group. We observe a sequence of 160 observations of B-value. Then we separately fit model with linear drift, piece-wise linear drift with known change-point at \(M = 0.4\) and piece-wise linear drift with unknown change-point. Then we could derive the results that

- Based on linear drift model, we have the estimate of drift is \(\hat{\theta} = 2.04\) and related conditional power is 0.57.

- If we assume a change-point \(M = 0.4\) as a given information, we would have \(\hat{\theta}_1 = \)
−0.58 and \( \hat{\theta}_2 = 4.66 \) and corresponding conditional power is 0.91. P-value for comparing linear drift model and piece-wise linear drift model is 0.02 (\( T_{LR}^* = 5.49 \)).

- If we assume unknown change-point, then change-point would be estimated as \( \hat{M} = 0.515 \) and \( \hat{\theta}_1 = -0.50 \) and \( \hat{\theta}_2 = 6.62 \) and corresponding conditional power is 0.99. P-value for comparing linear drift model and piece-wise linear drift model is 0.06 (\( T_{LR}^* = 9.29 \)) and critical boundary \( c_2 = 3.105 \).

Note that under Brownian motion model, the estimate of drift and P-value calculation would be equivalent to what we reviewed in the change-point analysis in section 2.5.
Figure 8.6: B-values ($n = 160$) simulated with $\theta_1 = 1$ in first 80 observations and $\theta_2 = 3$ for later 80 observations. Designed sample size is ($N = 200$). Dashed lines describe estimated drift.
Table 8.5: Summary statistics for model comparison between linear drift, piece-wise linear drift with known change-point and piece-wise linear drift with unknown change-point

<table>
<thead>
<tr>
<th>Change-point $M$</th>
<th>Linear Drift</th>
<th>Piece-wise Linear Drift with known change-point</th>
<th>Piece-wise Linear Drift with unknown change-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRT statistic $T_{LR}$</td>
<td>NA</td>
<td>5.49</td>
<td>9.29</td>
</tr>
<tr>
<td>P-value</td>
<td>NA</td>
<td>0.02</td>
<td>0.06 ($c^* = 3.11, Z_n = 3.05$)</td>
</tr>
<tr>
<td>Drift parameter $\hat{\theta}_1$</td>
<td>2.04</td>
<td>$-0.58$</td>
<td>$-0.5$</td>
</tr>
<tr>
<td>Drift parameter $\hat{\theta}_2$</td>
<td>2.04</td>
<td>4.66</td>
<td>6.62</td>
</tr>
<tr>
<td>Conditional Power under current trend</td>
<td>0.57</td>
<td>0.91</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### 8.7.2 Piece-wise linear drift under fBm ($H < 0.5$)

Suppose we have total sample size as $N = 200$ per group and data is simulated from $H = 0.4$. We observe a sequence of 160 observations of B-value and would like to estimate Hurst exponent rather than given $H$. Then we separately fit model with linear drift, piece-wise linear drift with known change-point at $M = 0.4$ and piece-wise linear drift with unknown change-point. Then we could derive the results that

- Based on the linear drift model under Bm, we have the estimate of drift is $\hat{\theta} = 2.03$ and related conditional power of 0.46
- Based on linear drift model, we have the estimate of drift is $\hat{\theta} = 2.00$, Hurst exponent estimate $\hat{H}_l = 0.401$ and related conditional power is 0.52.
- If we assume a change-point $M = 0.4$ as a given information, we would have $\hat{\theta}_1 = 0.80$ and $\hat{\theta}_2 = 3.19$, Hurst exponent estimate $\hat{H}_l = 0.402$ and corresponding conditional power is 0.75. P-value for comparing linear drift model and piece-wise linear drift model is 0.35 ($T_{LR}^* = 0.87$).
- If we assume unknown change-point, then change-point would be estimated as $\hat{M} = 0.335$ and $\hat{\theta}_1 = 0.28$ and $\hat{\theta}_2 = 3.55$, Hurst exponent estimate $\hat{H}_l = 0.402$ and corresponding conditional power is 0.8. P-value for comparing linear drift model and
piece-wise linear drift model is 0.92 ($T_{LR}^* = 2.14$) and critical boundary $c_2 = 3.105$. Here the critical boundary is calculated under $H = 0.5$.
Figure 8.7: B-values ($n = 160$) simulated with $H = 0.4$, $\theta_1 = 0.5$ in first 80 observations and $\theta_2 = 2.5$ for later 80 observations. Designed sample size is ($N = 200$). Dashed lines describe estimated drift.
8.7.3 Piece-wise linear drift under fBm ($H > 0.5$)

Suppose we have total sample size as $N = 200$ per group and data is simulated from $H = 0.6$. We observe a sequence of 160 observations of B-value and would like to estimate Hurst exponent rather than given $H$. Then we separately fit model with linear drift, piece-wise linear drift with known change-point at $M = 0.4$ and piece-wise linear drift with unknown change-point. Then we could derive the results that

- Based on the linear drift model under Bm, we have the estimate of drift is $\hat{\theta} = 2.02$ and related conditional power of 0.56.

- Based on linear drift model under fBm, we have the estimate of drift is $\hat{\theta} = 1.91$, Hurst exponent estimate $\hat{H}_l = 0.604$ and related conditional power is 0.58.

- If we assume a change-point $M = 0.4$ as a given information, we would have $\hat{\theta}_1 = 0.52$ and $\hat{\theta}_2 = 3.30$, Hurst exponent estimate $\hat{H}_l = 0.604$ and corresponding conditional power is 0.76. P-value for comparing linear drift model and piece-wise linear drift model is 0.13 ($T^*_LR = 2.27$).
If we assume unknown change-point, then change-point would be estimated as $\hat{M} = 0.607$ and $\hat{\theta}_1 = -5.81$ and $\hat{\theta}_2 = 0.61$, Hurt exponent estimate $\hat{H}_l = 0.065$ and corresponding conditional power is 0.7. P-value for comparing linear drift model and piece-wise linear drift model is 0.2 ($T_{LR}^* = 6.48$) and critical boundary $c_2 = 3.105$. Here the critical boundary is calculated under $H = 0.5$. 


Figure 8.8: B-values \((n = 160)\) simulated with \(H = 0.4, \theta_1 = 0.5\) in first 80 observations and \(\theta_2 = 2.5\) for later 80 observations. Designed sample size is \((N = 200)\). Dashed lines describe estimated drift.
### Table 8.7: Summary statistics for model comparison between linear drift under Brownian motion, linear drift under fractional Brownian motion, piece-wise linear drift with known change-point under fractional Brownian motion and piece-wise linear drift with unknown change-point under fractional Brownian motion for simulated example from $H = 0.6$

<table>
<thead>
<tr>
<th></th>
<th>Linear Drift under Bm</th>
<th>Linear Drift under fBm</th>
<th>Piece-wise Linear Drift with known $M$ under fBm</th>
<th>Piece-wise Linear Drift with unknown $M$ under fBm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurst exponent $H$</td>
<td>0.5</td>
<td>0.604</td>
<td>0.605</td>
<td>0.607</td>
</tr>
<tr>
<td>Change-point $M$</td>
<td>1</td>
<td>1</td>
<td>0.4</td>
<td>0.065</td>
</tr>
<tr>
<td>LRT statistic $T_{LR}$</td>
<td>NA</td>
<td>NA</td>
<td>2.27</td>
<td>6.48</td>
</tr>
<tr>
<td>P-value</td>
<td>NA</td>
<td>NA</td>
<td>0.13</td>
<td>0.2 $(c^* = 3.11, Z_n = 2.55)$</td>
</tr>
<tr>
<td>Drift parameter $\hat{\theta}_1$</td>
<td>2.02</td>
<td>1.91</td>
<td>0.52</td>
<td>-5.81</td>
</tr>
<tr>
<td>Drift parameter $\hat{\theta}_2$</td>
<td>2.02</td>
<td>1.91</td>
<td>3.30</td>
<td>2.88</td>
</tr>
<tr>
<td>Conditional Power</td>
<td>0.56</td>
<td>0.58</td>
<td>0.76</td>
<td>0.7</td>
</tr>
</tbody>
</table>

#### 8.8 Discussion

- In this Chapter, we provide a general procedure for how to calculate conditional power based on piece-wise linear model with information of Hurst exponent. We could estimate the piece-wise linear drifts, test for change-point to see if this is a better model and finally conditional power could be calculated.

- In the real clinical trial, when we conduct futility analysis, we could use conditional power or observe treatment effect to make a decision, e.g. conditional power less 5% or treatment effect $\hat{\mu} < 0$. This calculation only needs one value at the time of futility analysis rather than the sequence of values. It would be difficult for the sponsor or Data Monitoring Committee to make a decision based on this single point observation as they might suspect one point might not be stable, sample size too small, time-point too early or any other reason. Under this circumstance, if we could take the sequence of values into consideration and try to figure out if a piece-wise linear drift exists, a different result might happen as we have more information about the data along with the trial. This piece-wise linear drift model might be more related to the mean...
change rather than correlation which we discussed in the previous Chapter. Sponsor and stakeholder care about more mean change and thus, we could apply the test on it to see which model would be better to fit the data and gives us more confidence of current trial information.

- In this Chapter, piece-wise linear drift model is a different model from our previous approach by assuming identical distribution. This concern could arise under many circumstances. First, in a real clinical trial, there would be protocol amendment at many stages. People might be concerned about if certain changes to the protocol might cause the mean changes to the observations. In this case, we could assume the time-point as the time of protocol change and test if there is a drift change before and after this time point. Second, there might be lots of protocol deviations from patients. If we do have similar protocol deviations, we would suspect a mean or drift change and would like to see if this protocol deviation would cause any effect. In this case, we could test if there is any significant time-point to cause the change. Third, as a sequence of B-value or Z-value would be visualized, even onto a Radar system proposed by Xie et al. (2021), we might be able to observe the trend of statistic and doubt the assumptions still hold, in terms of independence or identical distribution. We could select the test based on the information we observe from the plot and we could derive more information from current clinical trial.

- Piece-wise linear drift is one of the models with non-linear drift. Generally, we could assume any drift model based on known information. Intuitively, if we do have a sequence of B-value presenting square root trend of square trend, i.e. $B(t) = \theta \sqrt{t}$ of $B(t) = \theta t^2$, we could fit those models for the data and to see if they are significant or not. However, this kind of model might not have a better relationship with the clinical trial from our perspective. Piece-wise linear drift could be associated with some clinical change to the studies and it is reasonable that we assume two different means of observations in two periods. If squared trend or square root trend is observed, it might not be easy to interpret the drift parameter (Note that $\theta = \sqrt{N/2\mu}$ for a two-arm clinical trial with sample size $N$ per arm target on a treatment effect $\mu$). So
those models would be used under other unknown scenarios so far and might not be the focus in this dissertation.

- In this chapter, we mainly discuss piece-wise linear drift with one change-point. It would be possible that we observe a piece-wise linear drift with more than one change-point, as shown in Figure 8.1. This topic has been discussed in other literature by Sequential testing, which means that we would detect more change-points after we conclude a significant model in the previous stage. For example, we would test for a model with two change-points after we have proved the model with one change-point is significant. But intuitively, more change-point in your model, more sample size you would need to claim the significance of the model. Therefore, this topic could be discussed in further research if there is a concern about more than one change-points.

- Note that for test of change-point, we generally have two approaches. If change-point is given, no matter if we have the information of Hurst exponent of not, we would always have test statistics converging by distribution to Chi-square distribution with degree of freedom equals 1. If change-point is not given, we would have another distribution of the test statistics. If $H = 0.5$, we would have Brownian motion assumption, which is the same as the assumption of i.i.d. distribution among the observations, and critical boundary under different sample sizes could be calculated using formula 2.33 from Gombay and Horvath (1996), and this might be the usual case that we have in the real clinical trials. If we do have information of Hurst exponent $H \neq 0.5$ or no information, the distribution is unknown and we might not find exact asymptotic distribution of the statistics. However, as the test of change-point is not the critical interest of the clinical trial and we are using this model to calculate conditional power, we might use the critical boundary under $H = 0.5$ to calculated the extremeness relatively. As shown in Table 8.3 and Table 8.4, we could see that the Type I error are between 0.04 and 0.08, where we expect them to be 0.05, under different Hurst exponent between 0.4 and 0.6 and different sample sizes. In this case, we could set a liberal or conservative level to decide if a piece-wise linear model would be used, say 0.03 or 0.1. As the final goal is to calculate a conditional power, which we expect to
give us more accurate information of the trial success under current trend, it would
be defined by DMC members or sponsor to see this measurement. If we would like to
know more about the statistic distribution, simulations could be conducted to display
more information.
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