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Sample size determination for group sequential test under fractional Brownian motion

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Abstract: Many clinical trials are monitored through interim analysis. Group sequential tests are popular statistical tools for interim analysis. Sample size determination for interim analysis under group sequential setting is studied in comparing to the design without interim analysis. The effects on sample size determination were examined for both classic and fractional Brownian motion of the monitoring statistic. Selective results were obtained for two commonly used error spending functions with various conditions. The results showed that the drift parameter was generally smaller when $H > 0.5$ under fractional Brownian motion and would lead to smaller sample sizes. The R code for carrying out the computation is also provided.

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1. Introduction

Interim analysis plays a critical role in designing and monitoring clinical trials. A vast amount of literature based on Brownian motion is available for various aspects of interim statistical analysis of clinical trials (Pocock 1977 [26], O'Brien and Fleming 1979 [25], Lan and DeMets 1983 [20], Lachin 2005 [16]). Sample size determination is pivotal in planning a successful clinical trial. For ethical and economic considerations, interim analysis has been utilized for monitoring almost all large scale clinical trials (Friede and Kieser 2006 [7], Temple 2006 [27], DeMets and Lan 1994 [6]). One of the widely used techniques in monitoring clinical trials is based on group sequential setting that interim analysis would be conducted at a number of discrete calendar or information time points during the trial course (Jennison and Turnbull 1997 [12], Jennison and Turnbull

2000 [13]). Several popular boundaries derived through classic Brownian motion were proposed and used (Lan and DeMets 1983 [20]). Under Brownian motion, the classic O'Brien and Fleming as well as Pocock group sequential boundaries under the fixed information assumption were extended to more flexible monitoring schemes by Lan and DeMets (1983 [20]) using α-spending (error spending) functions:

$$\alpha_1(t) = 2(1 - \Phi(z_{1-\alpha/2}/\sqrt{t})) \tag{1}$$

and

$$\alpha_2(t) = \alpha \log(1 + (e-1)t) \tag{2}$$

respectively, where Φ is the cumulative distribution function of the standard normal random variable, α is the type I error rate and $Z_{1-\alpha/2}$ is the $100(1-\alpha/2)$th percentile of the standard normal random variable, $\alpha_1(t)$ and $\alpha_2(t)$ are the α-spending functions at interim time t for one-sided test. Mathematically, the (symmetric) two-sided boundaries can be similarly studied. Hence, in this article, we focused our illustration for one-sided test in determining the drift parameter defined in Section 3 for sample size calculation. The approaches of using α-spending functions in monitoring clinical trials have been very popular since its inception by Lan and DeMets (1983 [20]). The merits of α-spending functions were reviewed in DeMets and Lan (1994 [21]).

In determining the sample size for group sequential analysis and comparing to the design without interim analysis of level α and power 1-β for one sided test, Kim and DeMets (1992 [15]) demonstrated that the sample size determination having K interim analyses should be modified according to a drift parameter ξ. After reviewing Brownian motion and fractional Brownian motion in Section 2, we define the drift parameter ξ for measuring the treatment effect and report the results of the drift parameter ξ under classic Brownian motion and fractional Brownian motion in Section 3. Our results are linked to a proposed large scale clinical trial submitted to the National Institutes of Health. Existing results in the literature on sample size determination for group sequential interim analysis were all based on Brownian motion assumption of the monitoring statistic. In this article, we extend the sample size determination results to fractional Brownian motion that contains the classic Brownian motion as a special case. Some concluding remarks are given in Section 4.

2. Brownian motion and fractional Brownian motion

Brownian motion and fractional Brownian motion have been used in many fields such as in economics and dynamic systems (Hu, Okendal and Sulem 2003 [11], Jumarie 2006 [14]). Theoretical and empirical results based on Brownian motion have provided many useful tools in monitoring clinical trials (Lan and Wittes 1988 [21], Davis and Hardy 1990 [4], 1994 [5]). One of the fundamental assumptions in applying the Brownian motion to the test statistic is that the increment of the monitoring statistic would be independent. However, this assumption may not be true in some cases since the test statistic is usually an aggregate indicator

of many underlying processes. In this article, we investigate the effects of fractional Brownian motion on the sample size determination for group sequential tests on designing clinical trials.

Under the null hypothesis of no treatment effect, we assume the test statistic form a fractional Brownian motion $B_H(t)$ over calendar or information time in [0,1], where 0 denotes the time at the beginning of the trial and 1 denotes the time at the end. More specifically, $B_H(t)$ is a Gaussian process with stationary increments and has the following properties (Beran 1994 [2]):

$$E(B_H(t)) = 0 \tag{3}$$

and

$$Cov(B_H(t), B_H(s)) = \frac{1}{2}\sigma^2 \left(|t|^{2H} + |s|^{2H} - |t-s|^{2H}\right). \tag{4}$$

We let $B_H(0) = 0$ and $\sigma^2 = 1$ in our study since we usually perform interim statistical analysis on standardized test statistic. When the variance σ^2 is unknown, one may use an estimate from the literature or from the partial realizations of the test statistic to estimate σ^2. Once the σ^2 is given, the effect of H is the same as in the case when σ^2 is assumed to be 1. The parameter H in the fractional Brownian motion is defined in (0,1) and it is called the Hurst coefficient (Davies and Harte 1987 [3]). For $H > 0.5$, the fractional Brownian motion poses long memory. The distribution of the future path of a long memory process would depend on the current and the past status. However, for a process of short memory, the distribution of the future path would be independent of the its past if the current status is given. That is, process of short memory has Markov property whereas the long memory process does not have Markov property. For $H < 0.5$, fractional Brownian motion has short memory (Mandelbrot and Van Ness 1968 [23]). Recent developments for $H < 0.5$ can be found in Bardina and Jolis (2006 [1]), Leon and Nualart (2006 [22]). Both the classic and the fractional Brownian motion were Gaussian. When $H = 1/2$, $B_H(t)$ becomes the classic Brownian motion, which has the property of independent increments and it is of short memory. The assumption of classic Brownian motion in clinical trial monitoring is strong. It is very likely that the monitoring statistic is an aggregated process of many different processes. Therefore, its future path would depend on its past and current values. It was shown that, even if the underlying processes were of short memory, the aggregated process could be of long memory (Beran 1994 [2], Granger 1980 [9]). Hence fractional Brownian motion is a natural model for the test statistic.

Applications of fractional Brownian motion in clinical trials in terms of conditional power were studies in Lai, Davis and Hardy (2000 [17]) and Lai (2004 [18]). The group sequential boundaries of Lan and DeMets (1983 [20]) as well as O'Brien and Fleming (1979 [25]), Pocock (1977 [26]) were examined under fractional Brownian motion (Lai 2010 [19]). Many other characteristics such as asymmetric group sequential design, repeated confidence intervals and recruitment monitoring of clinical trials have been studied under fractional Brownian motion (Zhang 2012 [28], Zhang 2011 [29], Zhang and Lai 2010 [30], Zhang and

Lai 2011 [31]). In next section, we computed the factor for sample size determination for group sequential setting under fractional Brownian motion

3. Sample size determination

Interim analysis of clinical trials would require multiple evaluations during the course of the trials. As it is illustrated in the Introduction section, when the monitoring statistic $B(t_k)$ follows Brownian motion, we have

$$B(t) \sim N(t\xi, t) \tag{5}$$

and

$$Cov(B(t), B(s)) = \frac{1}{2}(t + s - |t - s|), \tag{6}$$

where ξ is the drift parameter. Under classic Brownian motion, the drift parameter $\xi = z_{1-\alpha} + z_{1-\beta}$ without interim analyses. The sample size determination factor due to group sequential monitoring is (Kim and DeMets 1992 [15]):

$$(\xi/(z_{1-\alpha} + z_{1-\beta}))^2 \tag{7}$$

for a one sided level α test with a power of 1-β. For classic Brownian motion, the drift parameter ξ can be estimated through following numerical computation:

$$P(B(t_1) \le b_1, B(t_2) \le b_2, \ldots, B(t_{i-1}) \le b_{i-1}, B(t_i) > b_i | H_0) = \alpha(t_i) - \alpha(t_{i-1}) \tag{8}$$

and

$$P(B(t_1) \le b_1, B(t_2) \le b_2, \ldots, B(t_K) \le b_K | H_a) = \beta, \tag{9}$$

where $i = 1, 2, \ldots, K$ and b_i's are the upper boundaries at interim time t_i, H_0 denotes the null hypothesis without treatment effect and H_a denotes the alternative hypothesis that the treatment group is better than the control group. The above computation for Brownian motion can be extended to the fractional Brownian motion $B_H(t)$ with variance-covariance of elements of expression (4) instead of expression (6).

In solving for the drift parameter ξ, we need to simultaneously to find ξ that satisfies both expressions (8) and (9) for the given number of interim analyses K, the type I error rate α, the type II error rate β and the Hurst coefficient H. One important step in searching for the parameter is to evaluate the probability of multivariate normal distribution. We used the R function *mvtnorm*. The R function was based on the algorithm developed by Genz (1992 [8]). The algorithm performed a sequence of three transformations that converted the original integral of multivariate normal cumulative distribution into an integral over a unit hypercube. It started with a Cholesky decomposition, followed by inverse Gaussian transform that produced a simpler integrand with more complicated integration region. Then a change variable transformation led it to an integrand with constant limit that can be numerically calculated with standard algorithm. The results derived from our computation were compared to those in

TABLE 1
Drift Parameter of $B_H(t)/\sqrt{t}$ under Fractional Brownian Motion and One-sided Test with α_1, $H = 0.1, 0.3, 0.5, 0.7, 0.9$, $K = 1, 2, 3, 4, 5$ and Power = 0.80 and Power = 0.9

		Power = 0.8				Power = 0.9			
H	K	$\alpha = 0.005$	$\alpha = 0.01$	$\alpha = 0.025$	$\alpha = 0.05$	$\alpha = 0.005$	$\alpha = 0.01$	$\alpha = 0.025$	$\alpha = 0.05$
0.1									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.3872	3.1268	2.7416	2.4094	3.8289	3.5693	3.1856	2.8554
	3	3.4176	3.1659	2.7916	2.4622	3.8579	3.6068	3.2344	2.9079
	4	3.4251	3.1774	2.8107	2.4885	3.8637	3.6164	3.2515	2.9320
	5	3.4259	3.1810	2.8192	2.5022	3.8626	3.6183	3.2584	2.9442
0.3									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.4077	3.1537	2.7789	2.4562	3.8481	3.5944	3.2204	2.8988
	3	3.4286	3.1823	2.8193	2.5036	3.8692	3.6231	3.2614	2.9472
	4	3.4394	3.1958	2.8388	2.5299	3.8801	3.6371	3.2813	2.9743
	5	3.4468	3.2044	2.8499	2.5449	3.8877	3.6460	3.2929	2.9898
0.5									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.4186	3.1792	2.8068	2.4962	3.8586	3.6103	3.2471	2.9369
	3	3.4256	3.1793	2.8195	2.5115	3.8658	3.6200	3.2606	2.9537
	4	3.4327	3.1875	2.8289	2.5221	3.8735	3.6287	3.2710	2.9653
	5	3.4387	3.1940	2.8360	2.5295	3.8798	3.6356	3.2787	2.9736
0.7									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.4220	3.1769	2.8226	2.5250	3.8619	3.6168	3.2625	2.9650
	3	3.4204	3.1723	2.8101	2.5024	3.8604	3.6126	3.2506	2.9433
	4	3.4231	3.1755	2.8128	2.5022	3.8634	3.6160	3.2537	2.9437
	5	3.4254	3.1782	2.8157	2.5050	3.8659	3.6189	3.2570	2.9469
0.9									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.4224	3.1781	2.8276	2.5388	3.8623	3.6180	3.2675	2.9788
	3	3.4176	3.1684	2.8036	2.4937	3.8575	3.6083	3.2436	2.9337
	4	3.4176	3.1683	2.8025	2.4885	3.8576	3.6083	3.2422	2.9284
	5	3.4178	3.1685	2.8025	2.4883	3.8577	3.6085	3.2425	2.9281

Kim and DeMets (1992 [15]) under classic Brownian motion. For computing the results under fractional Brownian motion, we only need to provide the general variance-covariance structure of expression (4) instead of expression (6) to the R function. The main R code of deriving the results is presented in the appendix.

For error spending function α_1, we tabulated the values of the drift parameter ξ with a power of 0.8 and 0.9 in Table 1.

From Table 1, in comparing to the design with one fixed test at the end of one-sided level 0.025 and power 0.80, the sample size determination factor for a trial with 4 interim analyses (5 total tests) would be $(2.8360/2.8016)^2 = 1.0247$, indicating about 2.5% increase of the sample size if the test statistic follows classic Brownian motion. However, if it follows fractional Brownian motion with $H = 0.7$, the sample size determination factor becomes $(2.8157/2.8016)^2 = 1.0050$, indicating about 0.5% increasing of the sample size. In general, under the classic Brownian motion, the sample size determination factor increases as the number of interim analyses, but this monotone relation does not hold

TABLE 2
Drift Parameter of $B_H(t)/\sqrt{t}$ under Fractional Brownian Motion and One-sided Test with α_2, H = 0.1, 0.3, 0.5, 0.7, 0.9, $K = 1$, 2, 3, 4, 5 and Power = 0.80 and Power = 0.9

		Power = 0.8				Power = 0.9			
H	K	$\alpha = 0.005$	$\alpha = 0.01$	$\alpha = 0.025$	$\alpha = 0.05$	$\alpha = 0.005$	$\alpha = 0.01$	$\alpha = 0.025$	$\alpha = 0.05$
0.1									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.4944	3.2365	2.8563	2.5280	3.9522	3.6961	3.3187	2.9929
	3	3.5603	3.2959	2.9031	2.5610	4.0204	3.7589	3.3709	3.0328
	4	3.5773	3.3114	2.9145	2.5666	4.0365	3.7740	3.3828	3.0401
	5	3.5776	3.3112	2.9128	2.5617	4.0356	3.7730	3.3808	3.0360
0.3									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.5468	3.2896	2.9095	2.5804	3.9980	3.7424	3.3647	3.0376
	3	3.6317	3.3690	2.9785	2.6377	4.0858	3.8255	3.4387	3.1013
	4	3.6778	3.4130	3.0175	2.6705	4.1330	3.8710	3.4801	3.1375
	5	3.7064	3.4404	3.0421	2.6916	4.1622	3.8992	3.5060	3.1605
0.5									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.6022	3.3469	2.9683	2.6390	4.0476	3.7936	3.4167	3.0891
	3	3.6699	3.4130	3.0310	2.6972	4.1177	3.8623	3.4825	3.1511
	4	3.7057	3.4480	3.0642	2.7286	4.1547	3.8988	3.5176	3.1843
	5	3.7282	3.4700	3.0851	2.7481	4.1780	3.9216	3.5395	3.2053
0.7									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.6595	3.4085	3.0344	2.7066	4.1011	3.8506	3.4774	3.1506
	3	3.6718	3.4251	3.0596	2.7409	4.1156	3.8693	3.5046	3.1866
	4	3.6710	3.4230	3.0578	2.7416	4.1166	3.8691	3.5046	3.1891
	5	3.6705	3.4203	3.0529	2.7360	4.1171	3.8679	3.5009	3.1847
0.9									
	1	3.4174	3.1680	2.8016	2.4865	3.8574	3.6079	3.2415	2.9264
	2	3.7121	3.4711	3.1096	2.7890	4.1520	3.9111	3.5497	3.2292
	3	3.6345	3.3981	3.0532	2.7569	4.0756	3.8392	3.4942	3.1978
	4	3.5942	3.3533	3.0031	2.7055	4.0364	3.7955	3.4451	3.1474
	5	3.5721	3.3281	2.9727	2.6707	4.0148	3.7708	3.4153	3.1131

for fractional Brownian motion. Similar observations are true for the sample determination factor with power of 0.9.

For error spending function α_2, under classic Brownian motion, the sample size determination factor would be $(3.0851/2.8016)^2 = 1.2126$, indicating a more than 21% increasing of sample size for 4 interim analyses with a level of 0.025 and power of 0.80. If it follows fractional Brownian motion with $H = 0.7$, the determination factor is $(3.0529/2.8016)^2 = 1.1874$ for the same design with an almost 19% increase of the sample size comparing to the design without interim analysis. The impact of group sequential test on sample size under fractional Brownian motion by α_2 is larger than that by α_1. The selected results of the drift parameter ξ for α_2 are shown in Table 2.

The reasoning discussed above under classic Brownian motion ($H = 0.5$) was applied in designing a large clinical trial and the proposal was submitted to the National Institutes of Health. The author of the current article is the statistician for the submitted proposal. In that study, there were two possible treatments. It was expected that treatment A would have a response rate at

3.6% and treatment B would have the response rate of 6.3%. Based on normal approximation (Brownian motion) and a two sided level $\alpha = 0.05$ (one sided $\alpha = 0.025$) and power $= 0.9$, it was estimated that 2709 patients are needed for detecting the difference of $\delta = 2.7\%$. For 4 interim analyses with error spending function α_1, we had the sample size determination factor of 2.3% $(3.2787/3.2415)^2$. We used 5% as the inflation factor to account for possible loss due to follow up (2.5%) and the sample size determination factor due to group sequential test (2.3%) for the sample size and obtained 2844 as the total sample size. However, for a sensitivity analysis, if spending function α_2 was used, we would have the sample size determination factor being 19.2% $(3.5395/3.2415)^2$ for $H = 0.5$ and 16.6% $(3.5009/3.2415)^2$ for $H = 0.7$. In the final proposal, we used 3000 as the proposed sample size for the study, which would be enough for both loss to follow up and group sequential tests under most settings.

4. Concluding remarks

In this article, we studied the effect of classic Brownian motion and fractional Brownian motion on the sample size determination for clinical trials with interim analysis under group sequential monitoring. The classic Brownian motion is a well accepted stochastic process for clinical trial monitoring. The classic Brownian motion has the property that the probability distribution of the future values depends only through the current value. However, fractional Brownian motion as an extension of the classic Brownian motion possesses a long memory that all values in the past would influence the probability of its future values. Although many test statistics have been shown to be approximately Brownian motion (Gu and Lai 1991 [10]) under various conditions, in many practical settings, these conditions may be violated or hard to be justified. Hence the fractional Brownian motion may provide more useful tools for interim data analysis.

Fractional Brownian motion was used to reanalyze the data from the Beta-Blocker Heart Attack Trial (BHAT) (Lai, Davis and Hardy 2000 [17]). The BHAT trial was terminated prior to the planed stopping date based on the conditional power under Brownian motion and other considerations. If fractional Brownian motion were used, the BHAT trial could be terminated a couple of months earlier.

In clinical trials, the monitoring statistic can be viewed as an aggregated stochastic process generated from many other processes through space and time. In fact, it was shown that aggregating processes could have long memory even the sub-processes have only short memory (Granger 1980 [9]).

For fractional Brownian motion, there is an extra parameter H as compared to the classic Brownian motion. In this article, we reported the effect of the Hurst coefficient H on the sample size determination under group sequential setting. The value of H can be estimated via maximal likelihood method (Lai 2004 [18]) or other techniques (Mielniczuk and Wojdyllo 2007 [24]) using historic

data as well as the partial observations prior to the interim analysis. In applying the classic Brownian motion to clinical trial monitoring, we implicitly assumed that $H = 1/2$ in fractional Brownian motion. The estimate of H based on maximal likelihood method was shown to be approximately normally distributed (Lai 2004 [18]). In actual data analysis, one may perform hypothesis testing on $H = 1/2$. Fractional motion Brownian has been applied in many diversified fields, however, many theoretical and empirical properties of fractional Brownian motion in designing and monitoring clinical trials are still unknown and worth pursuing.

Appendix: The main R Code for computation

```
# Estimating the drift parameter in sample size determination for
# group sequential test under fractional Brownian motion, one sided.
ki <- c(1,2,3,4,5)
betai <- c(0.2,0.1)
hi <- c(0.1,0.3,0.5,0.7,0.9)
alphai <- c(0.005,0.01,0.025,0.05,0.10)
for (jk in c(1:5)) {
 k <- ki[jk]
 print("number of tests")
 print(k)
 alpha1 <- rep(0,k+1)
 alpha2 <- alpha1
  for (jb in c(2:2)) {
   print("type II error")
   print(betai[jb])
    for (jh in c(1:5)) {
    h <- hi[jh]
    print("Hurst coefficient")
    print(h)
    for (ja in c(1:5)) {
     alpha <- alphai[ja]
     print("alpha")
     print(alpha)
   covmatrix <- matrix(rep(0,(k+1)*(k+1)),ncol=k+1,byrow=T)
   tij <- (seq(0:k)-1)/k
   print(tij)
   # the covariance matric of B(t)/sqrt(t)
   for (i in c(1:(k+1))) {
          for (j in c(1:(k+1))) {
                  covmatrix[i,j] <- (1/2)*(tij[i]^(2*h)+tij[j]^(2*h)
                  -(abs(tij[i]-tij[j]))^(2*h))/sqrt(tij[i]*tij[j])
          }
   }
   # print(covmatrix)
   covbm <- covmatrix
   # one sided
```

```
for (i in c(1:k)) {
 alpha1[i+1] <- 2-2*pnorm(qnorm(1-alpha/2)/sqrt(i/k))
 alpha2[i+1] <- alpha*log(1+(exp(1)-1)*(i/k))
}
# print(alpha1)
# print(alpha2)
# compute the boundaries given the alpha value
a1b <- rep(0,k)
a2b <- a1b
# one sided
a1b[1] <- qnorm(1-alpha1[2])
a2b[1] <- qnorm(1-alpha2[2])
# fx1, one sided
fx1 <- function(x,ub,covm,tprob) {
 # kn number of (upper) boundary already known
 kn <- length(ub)
 lb <- rep(-Inf,kn)
 pmv <- pmvnorm(lower=c(lb,x),upper=c(ub,Inf),sigma=covm)[1]
 tprob-pmv
}
# compute the boundary, one sided
a1ub <- NULL
a2ub <- a1ub
if (k > 1 ) {
 for (i in c(2:k)) {
  a1ub <- c(a1ub,a1b[i-1])
  a2ub <- c(a2ub,a2b[i-1])
  # print(a1ub)
  a1b[i] <- uniroot(fx1,interval=c(1,5),lower=1,upper=10,ub=a1ub,
     covm=covmatrix[2:(i+1),2:(i+1)],tprob=alpha1[i+1]-alpha1[i])$root
  a2b[i] <- uniroot(fx1,interval=c(1,5),lower=1,upper=10,ub=a2ub,
     covm=covmatrix[2:(i+1),2:(i+1)],tprob=alpha2[i+1]-alpha2[i])$root
 }
}
#print(a1b)
#print(a2b)
# search for the mean, hence the drift parameter theta=mean/sqrt(t)
fxlai <- function(x,ub,covm,tprob) {
 # x is the drift parameter
 # kn number of (upper) boundary already known
 kn <- length(ub)
 lb <- rep(-Inf,kn)
 lmean <- x*sqrt(seq(1:kn)/kn)
 pmv <- pmvnorm(lower=lb,upper=ub,mean=lmean,sigma=covm)[1]
 tprob-pmv
}
# compute theta
theta1 <- uniroot(fxlai,interval=c(1,5),lower=1,upper=10,ub=a1b,
          covm=covmatrix[2:(k+1),2:(k+1)],tprob=betai[jb])$root
print("theta1")
```

```
   print(theta1)
   theta2 <- uniroot(fxlai,interval=c(1,5),lower=1,upper=10,ub=a2b,
             covm=covmatrix[2:(k+1),2:(k+1)],tprob=betai[jb])$root
   print("theta2")
   print(theta2)
   } # jalpha
  } # jhurst
 } # jbeta
} # jk
```

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