Monitoring Ongoing Clinical Trials under Fractional Brownian Motion with Drift#

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INTRODUCTION

- Brownian motion with a linear drift is the fundamental structure used for monitoring ongoing clinical trials in practice, where the most current one-point statistic is sufficient.
- However. the sponsor/IDMC would like to make a decision/recommendation based on "trend", not a one-point statistic.
- Introduce and advance the fBm with drift model to formally accommodate this need.

MATERIALS AND METHODS

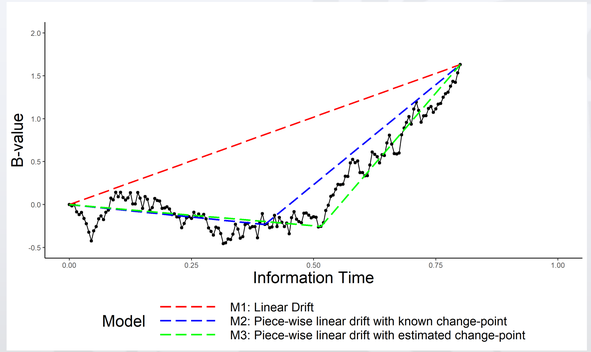
- A standardized fBm (Mandelbrot & Ness, 1968) is defined as a Gaussian process $\{B_H(t); t \geq 0\}$ satisfying
  1) $B_H(0) = 0$
  2) For any $t \geq 0, E\big(B_H(t)\big) = 0$
  3) For any $t, s \geq 0, Cov\big(B_H(t), B_H(s)\big) = \frac{1}{2}(t^{2H} + s^{2H} - |t-s|^{2H})$

  When H = 0.5, it reduces to the standard Bm.
- fBm with drift: $B'_H(t) = \theta t + B_H(t)$
- fBm with non-linear drift: $B^*_H(t) = g(\boldsymbol{\theta}, t) + B_H(t)$. Specifically, piece-wise linear drift with on change-point M:

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

EXAMPLES

Example 1: Predictions from different models



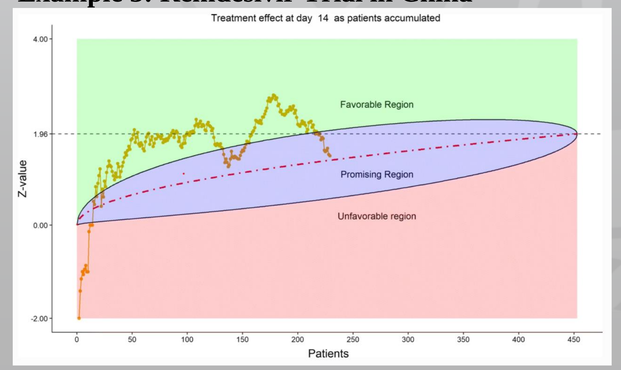
	Model 1	Model 2	Model 3
Change-point M	1	0.4	0.515
LRT statistic T_{LR}	NA	5.49	9.29
P-value	NA	0.02	0.06 $(c^* = 3.11, \sqrt{T_{LR}} = 3.05)$
Drift parameter $\hat{\theta}_1$	2.04	-0.58	-0.5
Drift parameter $\hat{\theta}_2$	2.04	4.66	6.62
Conditional Power	0.57	0.91	0.99

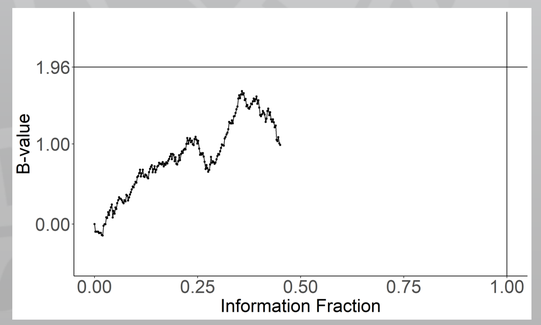
Example 2: BHAT Study

			Bm linear drift		fBm		fBm linear drift		
Death	t=n/N	Z-value	$\hat{\theta}_{Bmld}$	CP_{Bmld}	$\hat{H}_{fBm}$	CP_{fBm}	$\hat{\theta}_{fbmld}$	$\hat{H}_{fBmld}$	CP_{fBmld}
125	0.314	2.345	4.185	0.996	0.539	0.243	4.244	0.470	0.997
165	0.415	2.214	3.437	0.973	0.533	0.266	3.449	0.461	0.973
215	0.540	1.924	2.618	0.834	0.543	0.224	2.628	0.470	0.838
263	0.661	2.280	2.804	0.927	0.552	0.500	2.785	0.480	0.920
267	0.671	2.258	2.757	0.918	0.555	0.489	2.745	0.483	0.913
300	0.754	2.665	3.069	0.987	0.557	0.844	3.058	0.486	0.986
326	0.819	2.898	3.202	0.998	0.559	0.974	3.196	0.488	0.998

- Comparison between Bm with linear drift and fBm with linear drift: similar estimates for drift parameters and conditional power.
- Comparison between fBm and fBm with linear drift: different estimates for Hurst exponent and conditional power at an earlier stage when compared with fBm. This indicates that conditional power under fBm appears more conservative when linear drift is not considered into the model.

Example 3: Remdesivir Trial in China





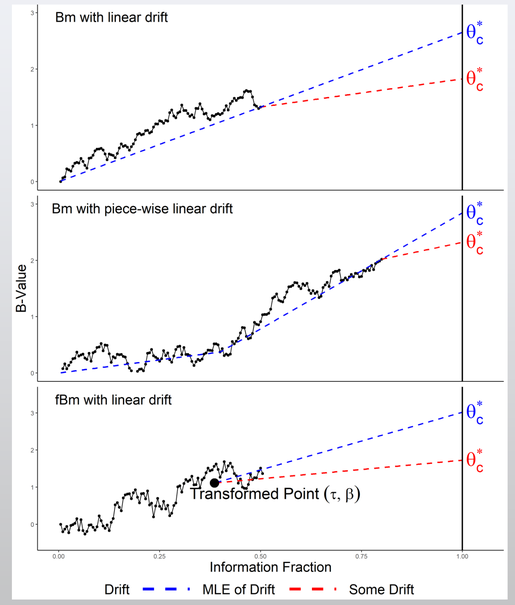
$\hat{H} = 0.488$, 95% CI $(0.469, 0.505)$, p-value $= 0.11$ $(T_{LR} = 2.57)$

MONITORING

- Conditional Power: Based on current information, the probability of trial success at the end.

$$CP(\theta_1, \theta_2, M, H) = P(Z_N = B^*_H(1) > z_\alpha | \theta_1, \theta_2, H, M, B^*_H(\boldsymbol{t})) = \Phi\left(\frac{\theta^*_c - z_\alpha}{\sigma^*_c}\right)$$

- Function of conditional mean



- Sample Size Re-estimation:

$$1 - \beta' = P\big(Z_{N_S} = B^*_H(t^*_S)/\sqrt{t^*_S} > c^*_1 \big| \theta, H, M, B'_H(\boldsymbol{t})\big)$$

SUMMARY

- Provide procedures for testing assumptions of independence and linear drift.
- Visualize the sequence of statistics and recognize the trend of ongoing clinical trial.
- Calculate conditional power and SSR under different models.

#: The paper has been submitted to publication