

The Effect of Dosage Errors and Step Selection Method on the Performance of the Up-and-Down Method

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Background

- Up-and-Down (UaD) Method is a common approach for estimating median effective stress
 - Originally developed by the Explosives Research Laboratory, Bruceton, PA in early 1940's, and the Bruceton Method was basis for work of Dixon and Mood (1948)
 - Extensive documentation shows that the method provides an accurate estimate while keeping number of trials to a minimum
 - Numerous testing applications
 - Explosives
 - Metal fatigue
 - Development of Medical Procedures
 - Toxicology and Pharmacology
 - Median effective stress ==> median effective dose/dosage (ED_{50})

Background--Conducting an UaD Bioassay Experiment

- Technique is simple to execute but has inspired extensive discussions on how to analyze the data
 - Trials are conducted one at a time until stopping criteria is met
 - For trial i , a subject is given some administered log dose (d_i) and the binary response is recorded (R_i)
 - The log dose for the next trial (d_{i+1}) is dependent on value for R_i
 - If a response occurs ($R_i = X$ or 1): $d_{i+1} = d_i - \Delta d$
 - If a response does not occur ($R_i = O$ or 0): $d_{i+1} = d_i + \Delta d$
 - Δd is the step size
 - In original method, Δd kept fixed in value throughout experiment
- Several modifications of the basic method have been developed
 - Example: various schemes for changing Δd during course of experiment

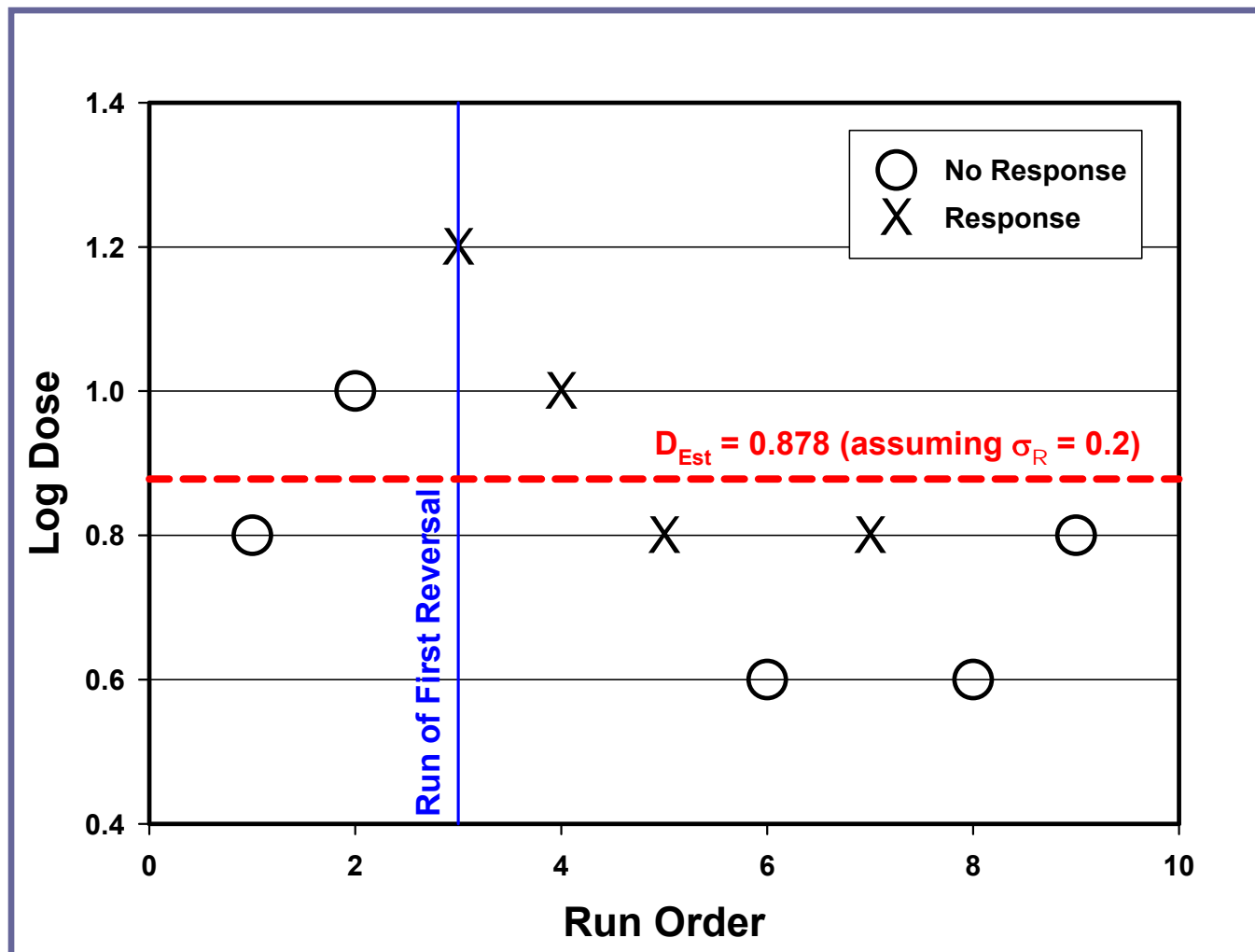
Obtaining an Estimate of the ED_{50}

- Maximum Likelihood Estimation (MLE) used to find estimate, D_{Est} , of the true $\log(ED_{50})$, D_{Tr}
 - Normal distribution is favorite though others used (ex. Little (1974))
 - For bioassays, normal distribution obtained by working with the logarithms of the doses
 - With small sample sizes, D_{Est} is solved for while σ_R is set equal to Δd (Dixon (1965))
- Precision of D_{Est} increases as Δd decreases
- Speed of convergence towards region of D_{Tr} decreases as Δd decreases

Characteristics of UaD Bioassay Experiment

- Optimum Δd range:
 - $(\sigma_R / 2) < \Delta d < (2\sigma_R)$
 - σ_R -- standard deviation of distribution of effective dosages, which needs to be estimated prior to start of experiment
 - Above range represents a trade-off between precision and efficiency
- Standard error (σ_{ED}) of D_{Est} from UaD experiment
 - σ_{ED} approximately equals $\{(\sigma_R)(2 / N)^{(1/2)}\}$ (from Dixon (1965))
 - It is assumed that σ_R equals Δd
 - N is the nominal sample size (versus N_T the total number of trials conducted)
 - Common practice is to base N on N_{FR} (run of first reversal {O to X, or X to O})
 - $N = N_T - N_{FR} + 2$

Example of an Up and Down Experiment



$$\Delta d = 0.2$$

$$N_T = 9$$

$$N_{FR} = 3$$

$$N = 8$$

UaD Method and Errors in Dosage Administration and Measurement

- What happens when irregular spacing of dosages occurs--found with UaD in inhalation toxicology?
 - Dosage errors (assumed to be normally distributed)
 - Administration error: σ_A
 - Difficulty in precisely generating the target dosage
 - Measurement error: σ_M
 - Error involved in measuring the actual dosage produced by generation device
 - Total error: $\sigma_{\text{Total}} = (\sigma_A^2 + \sigma_M^2)^{1/2}$
- Vast majority of work/theory on UaD method assumes that both types of errors essentially equal zero.
- How are the accuracy and efficiency of UaD method affected by nonzero σ_A and/or σ_M ?



Experimental Method

- Monte Carlo simulations were performed using MINITAB® v. 13
- Three different dosage parameters were tracked
 - d_T -- The target value for the log dosage to be administered
 - d_A -- The actual log dosage administered
 - d_M -- The measured/observed value of the administered log dosage
- Binary responses generated from the following underlying normal distribution of effective dosages
 - D_{Tr} set equal to $\log_{10}(80)$
 - σ_R set equal to $(1/15)$ (or 0.0667)
- Each UaD experiment consisted of 10 trials
 - Wish to examine situations where number of available runs at premium

Binary Response Simulation Procedure

- $d_{T,i}$ is calculated from result of previous trial or chosen as initial guess
 - Dosage step can be taken from either d_T or d_M of previous step
 - Method T (previous target): $d_{T,i+1} = d_{T,i} \pm \Delta d$
 - Method M (previous measured): $d_{T,i+1} = d_{M,i} \pm \Delta d$
- $d_{A,i+1}$ is randomly generated from $d_{T,i+1}$
 - Distribution: $N(d_{T,i+1}, \sigma_A^2)$
- $d_{M,i+1}$ is randomly generated from $d_{A,i+1}$
 - Distribution: $N(d_{A,i+1}, \sigma_M^2)$
- R_{i+1} generated from binomial distribution
 - Probability of response ($R_{i+1} = X$) equals the area under $N(D_{Tr}, \sigma_R^2)$ between the limits of $-\infty$ to $d_{A,i+1}$

Calculation of ED_{50} for Individual Experiment

- A MLE solution for D_{Est} was obtained numerically using the Newton-Raphson method and a probit link function
 - A MINITAB® macro was written to perform the calculations
 - d_M values were used in the calculations for D_{Est}
 - As default for MLE calculations, σ_R was set equal to the Δd value used for the experiment
 - However, sometimes large values of σ_A and/or σ_M will produce situations where no solution was possible (using MINITAB®) unless σ_R was increased
 - Calculation artifacts would occur due to arbitrary cutoff of normit values by MINITAB®
 - Values below -7 were rounded up to -7, and values above 7 were rounded down to 7.
- Several other MLE related parameters were calculated
 - Wald Test statistic
 - Score Test statistic
 - Likelihood-Ratio Test statistic
 - Log Likelihood of final MLE fit



Factors Investigated

Factor	Description	Definition
A	Step Size	$(\Delta d / \sigma_R)$
B_A	Administration Error	(σ_A / σ_R)
B_M	Measurement Error	(σ_M / σ_R)
C	Location Initial Log Dosage	$([d_{T,1} \pm D_{Tr}] / \sigma_R)$
D	Basis for Calculation of Next Dosage	Method T: $d_{T,i+1} = d_{T,i} \pm \Delta d$ Method M: $d_{T,i+1} = d_{M,i} \pm \Delta d$



Factor Level Values

Factor	Level Values								
	1	2	3	4	5	6	7	8	9
A	0.500	0.707	1.000	1.414	2.000	2.828	4.000	5.657	
B _A	0.000	0.125	0.250	0.500	1.000	2.000			
B _M	0.000	0.125	0.250	0.500	1.000	2.000			
C	-3.000	-2.250	-1.500	-0.750	0.000	0.750	1.500	2.250	3.000
D	T	M							

Values in shaded boxes were not used with Method M

50 experiments per coordinate point

Method	T	M	Total
# Coordinates	2592	1440	4032
# Experiments	129600	72000	201600




Results

● Efficiency

- Number of experiments that “failed”
 - Experiments that consists of either all responses or all non-responses
- Run of first reversal (RFR)
 - Indication of how quickly region of the median has been reached
- Number of responses in an experiment
 - Indication of how well region of the median has been covered

● Precision

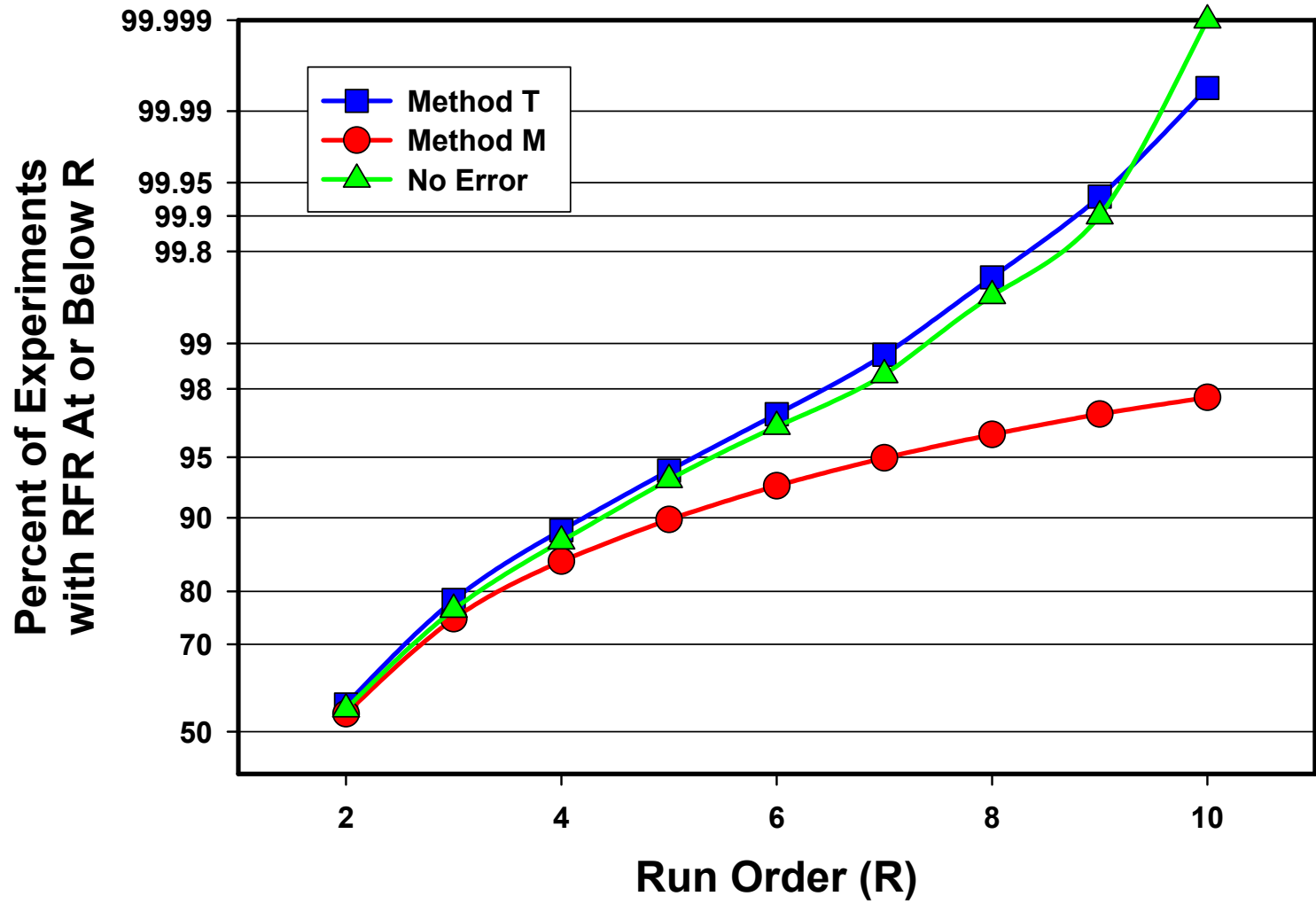
- Standard error (SE) of D_{est}
 - Expressed as multiples of σ_R
- Mean square error (MSE) of D_{est}
 - Expressed as multiples of σ_R^2



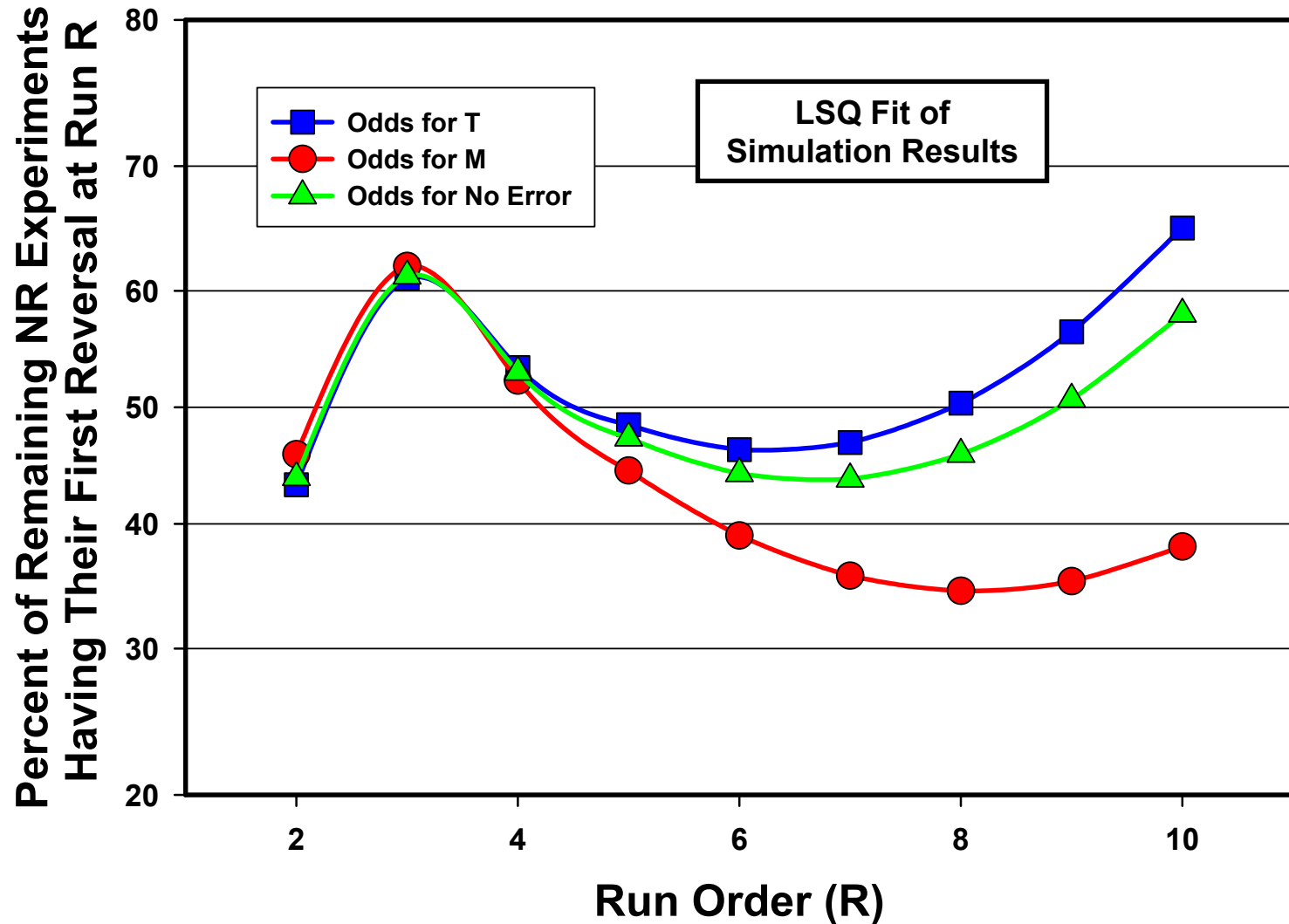
Efficiency Results

- Obtaining Early Run of First Reversal (RFR)
 - Factors in order of decreasing importance: A, D, CC, B_A , B_M and AA
 - Many statistically significant interactions also exist
 - Target dosage basis (D) more important than dosage errors (B_A and B_M)
- Success rate (T vs. M): Method T slightly better
 - Success rate of Method T closely parallels that of experiments executed with $B_A = B_M = 0$ as a function of Run of First Reversal (RFR)

Run of First Reversal Breakdown by Method and Run Order



Chance of Non-Reversed (NR) Experiment having a Reversal

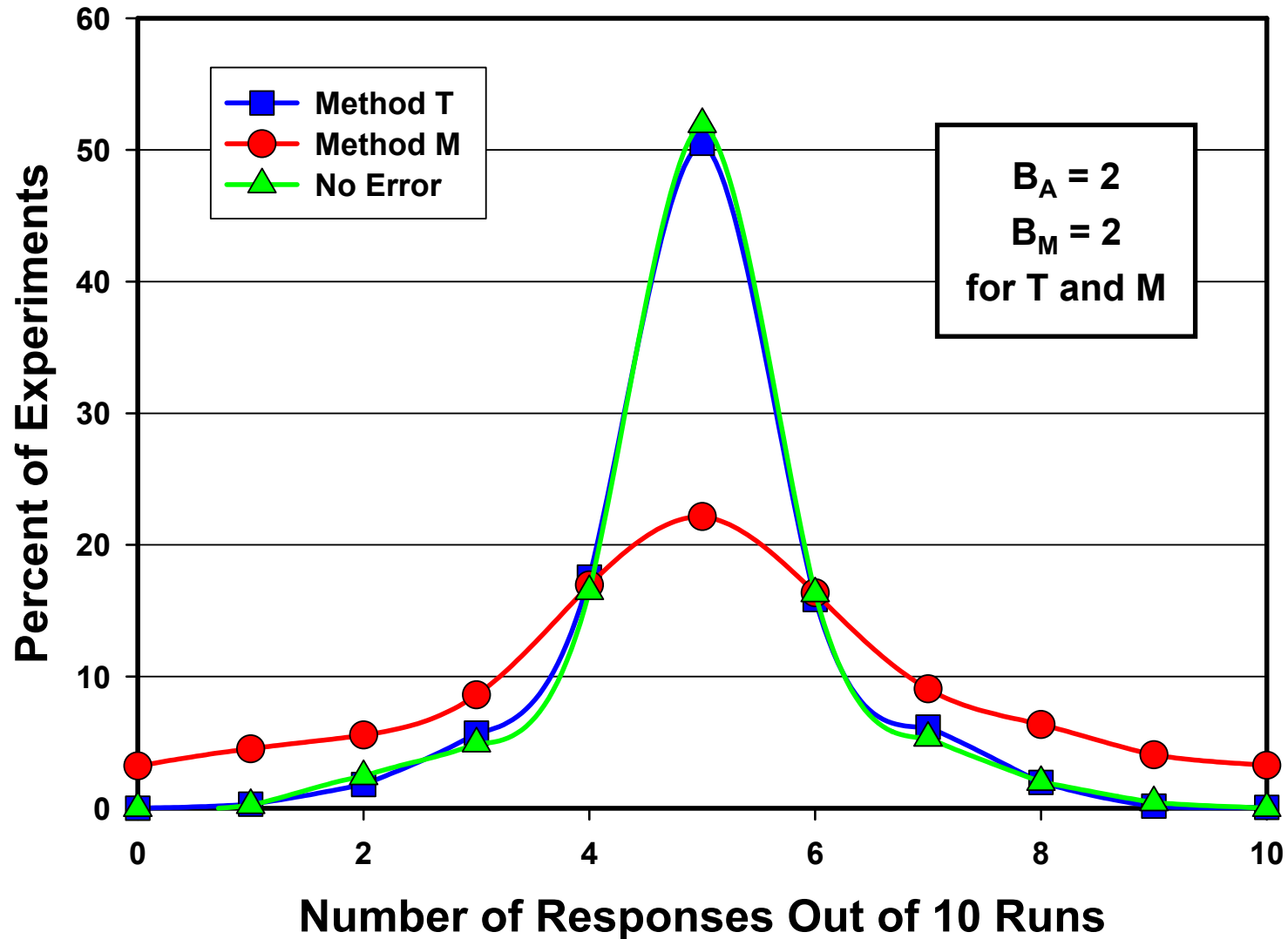




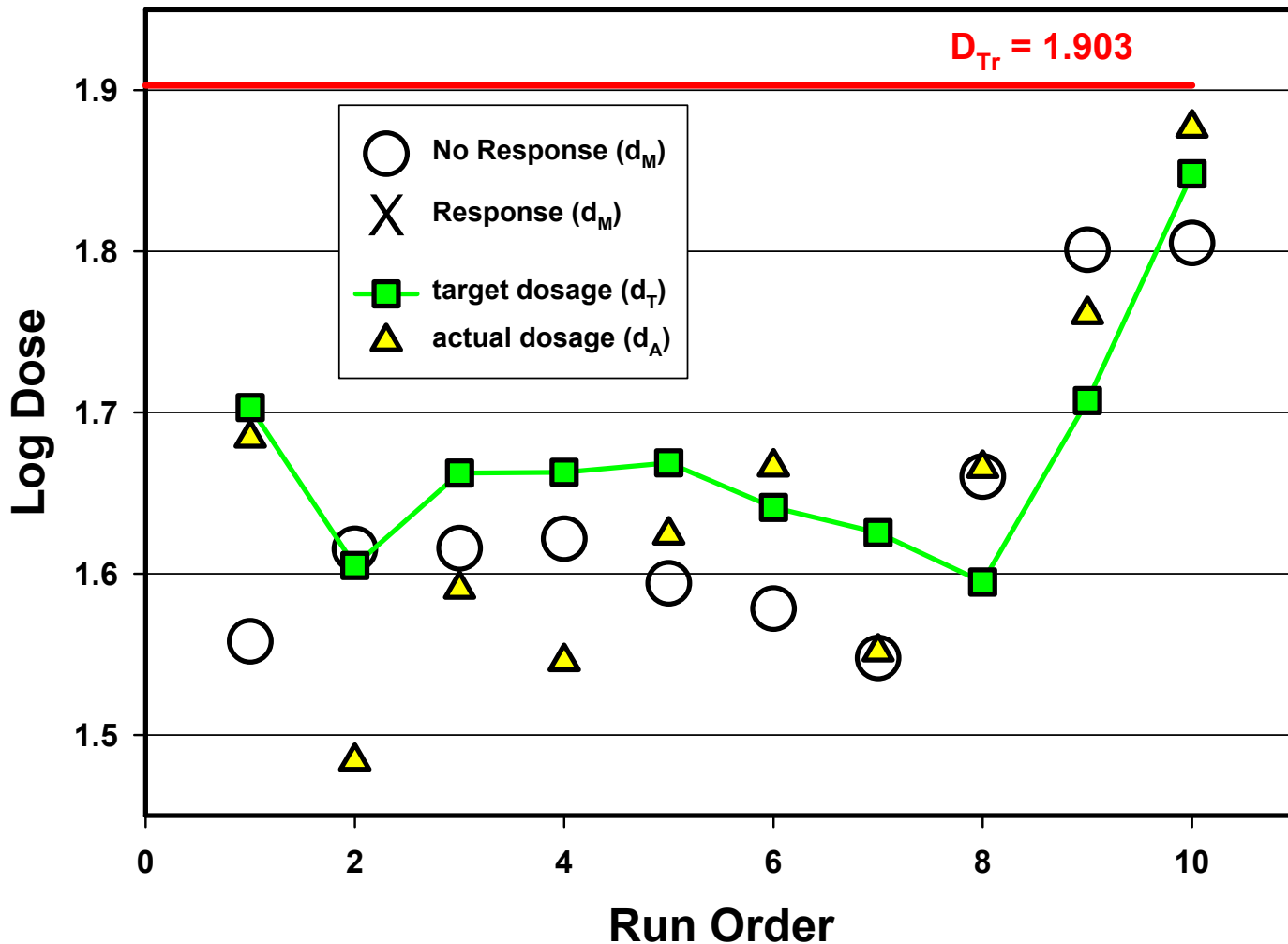
Efficiency Results (Cont.)

- Distribution of Number of Responses
 - Results for Method T (with any dosage errors present) mirrors that of UaD operated with no dosage errors
 - Distribution for Method M becomes shorter and broader as the dosage error increases
- Method T is more robust in recovering from “dead ends” than Method M
 - Target dosages in Method M are more readily influenced by fluctuations resulting from administration (σ_A) and measurement (σ_M) errors
 - Smaller step sizes can be easily overwhelmed
 - Advice on recommended step size ($\Delta d = \sigma_R$ or $A = 1$) may need to be revised

Distribution of Number of Response



Example of a Wandering Experiment with Method M



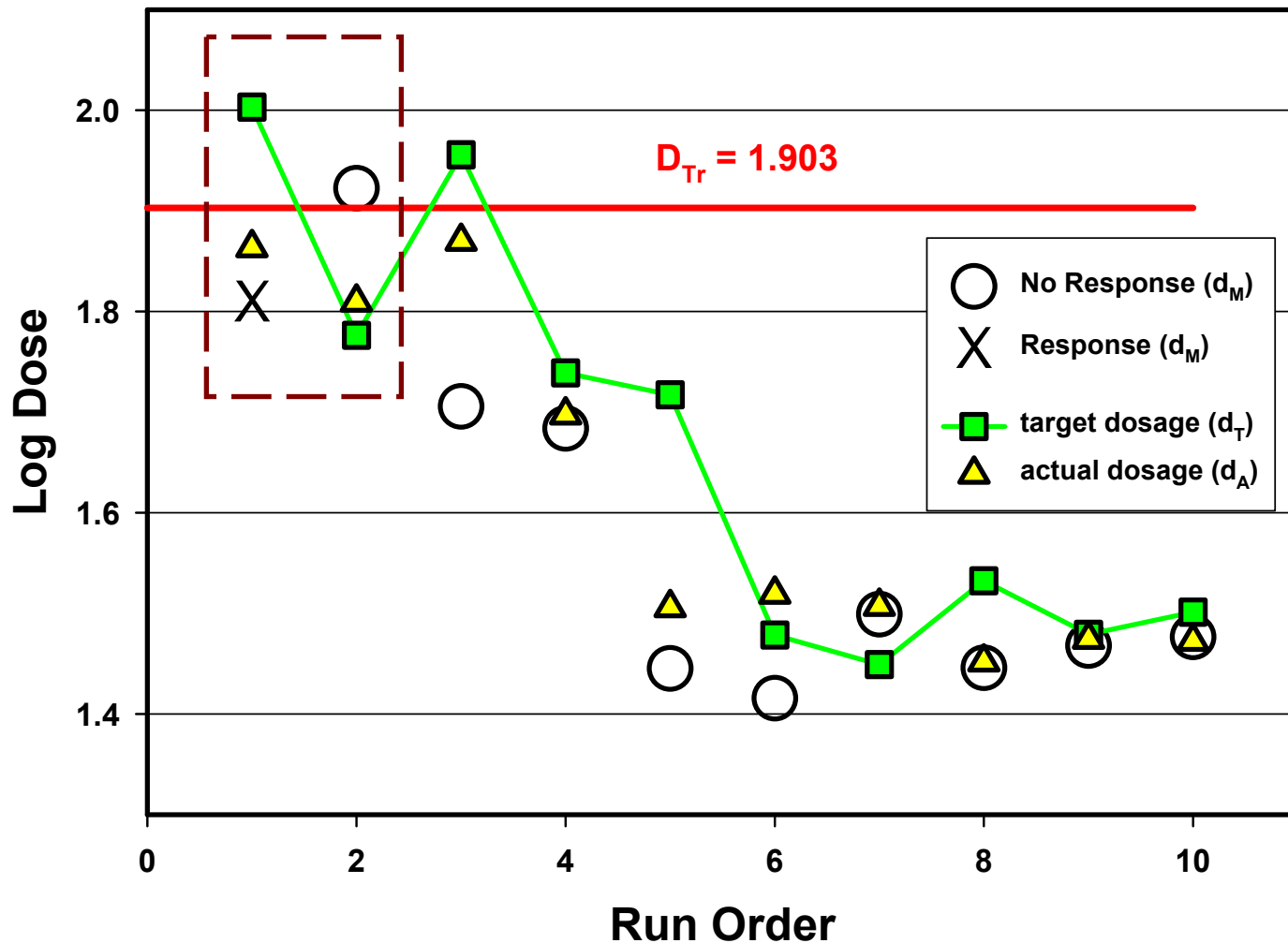
Expt 64040M

Method M

 $\Delta d = (0.047)$ $\sigma_R = (1/15)$ $A = 0.707$ $B_A = 1$ $B_M = 1$ $C = -3$

**No Estimate of
 D_{Tr} Possible**

Example of a Negative Step Direction with Method M

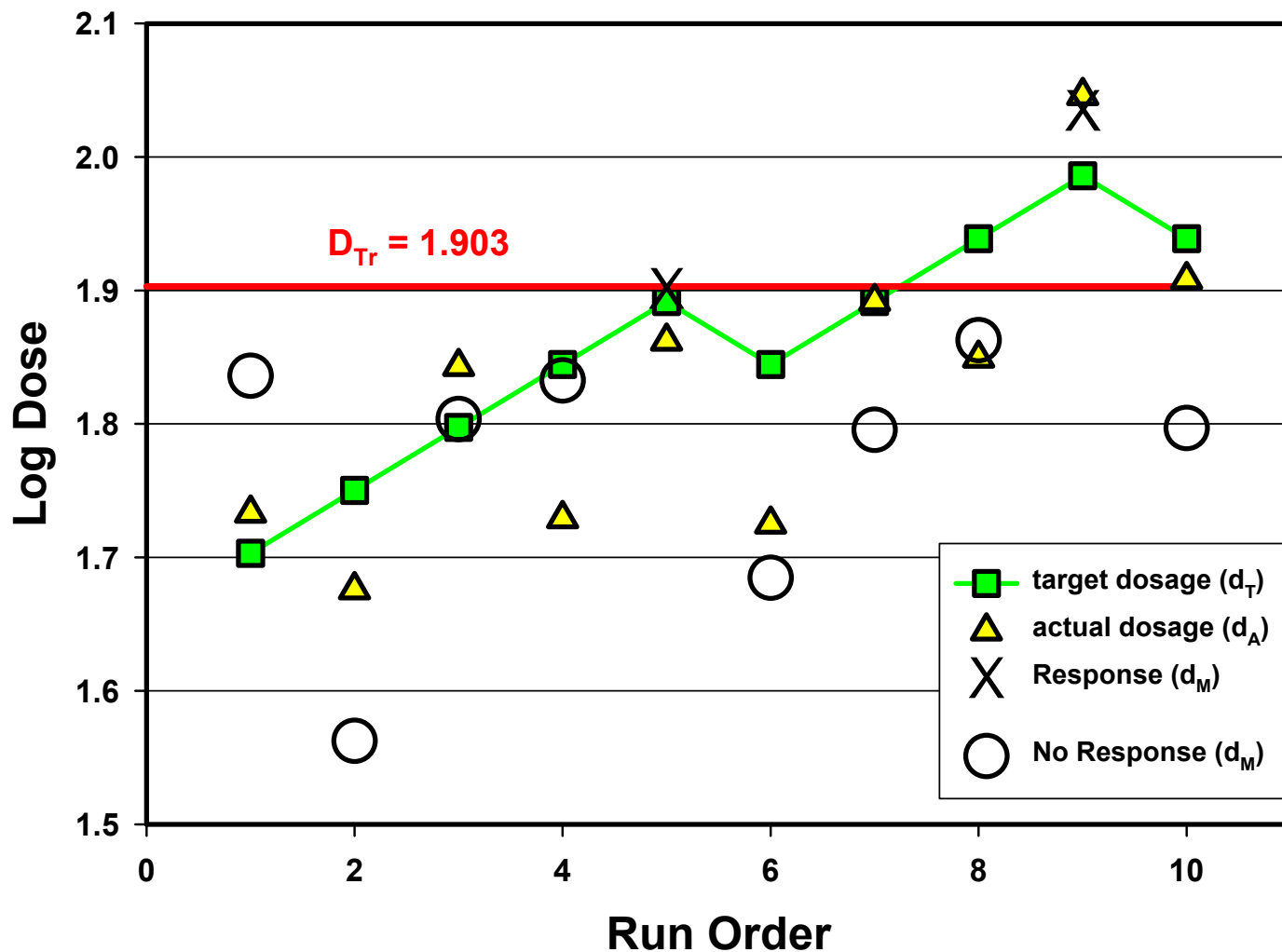


Expt 28159M

Method M

 $\Delta d = (1/30)$ $\sigma_R = (1/15)$ $A = 0.5$ $B_A = 1$ $B_M = 1$ $C = 1$ $D_{Est} = 1.866$

Example of an Experiment with Method T



Expt 64013T

Method T

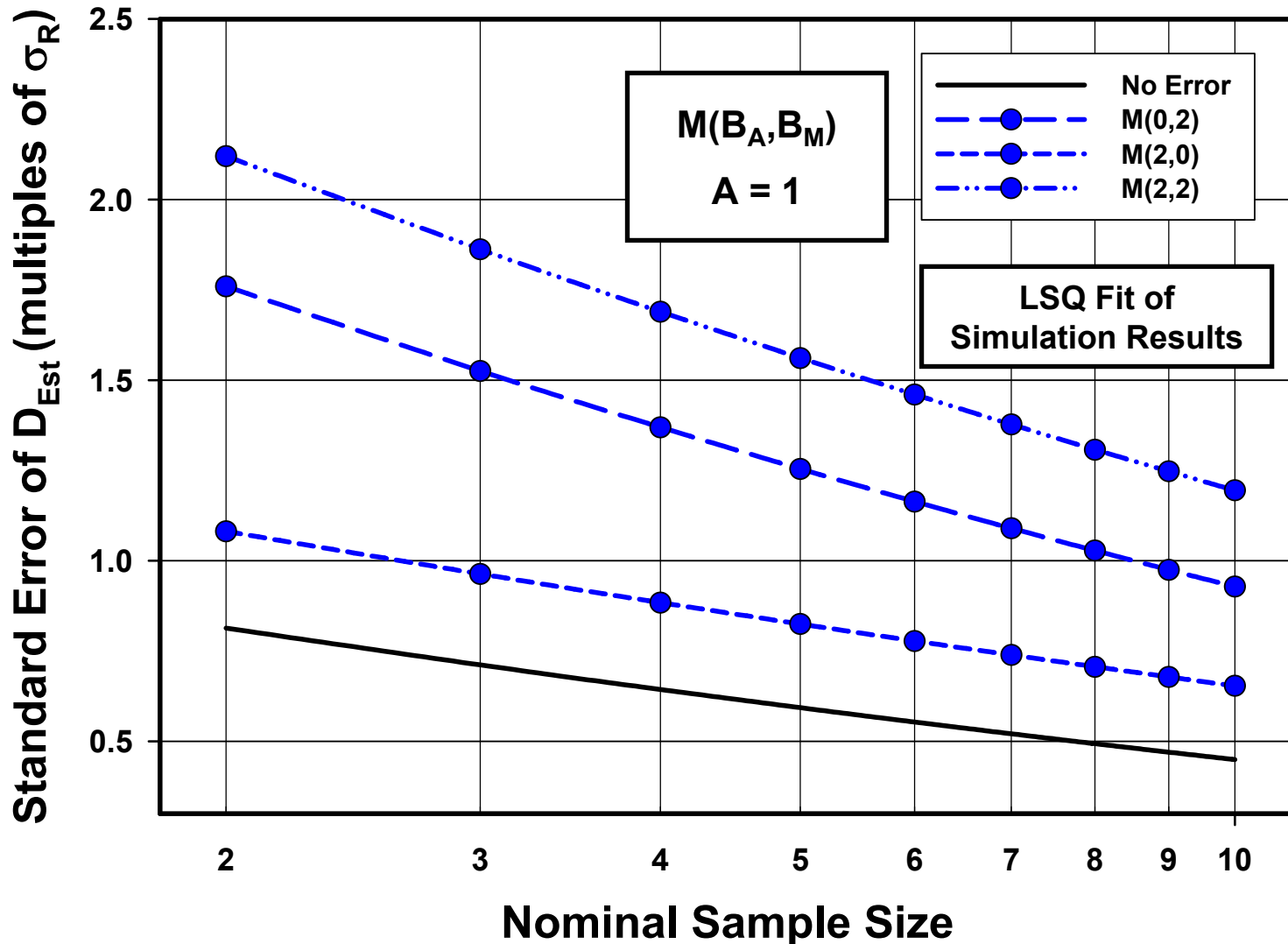
 $\Delta d = (0.047)$ $\sigma_R = (1/15)$ $A = 0.707$ $B_A = 1$ $B_M = 1$ $C = -3$ $D_{Est} = 1.901$



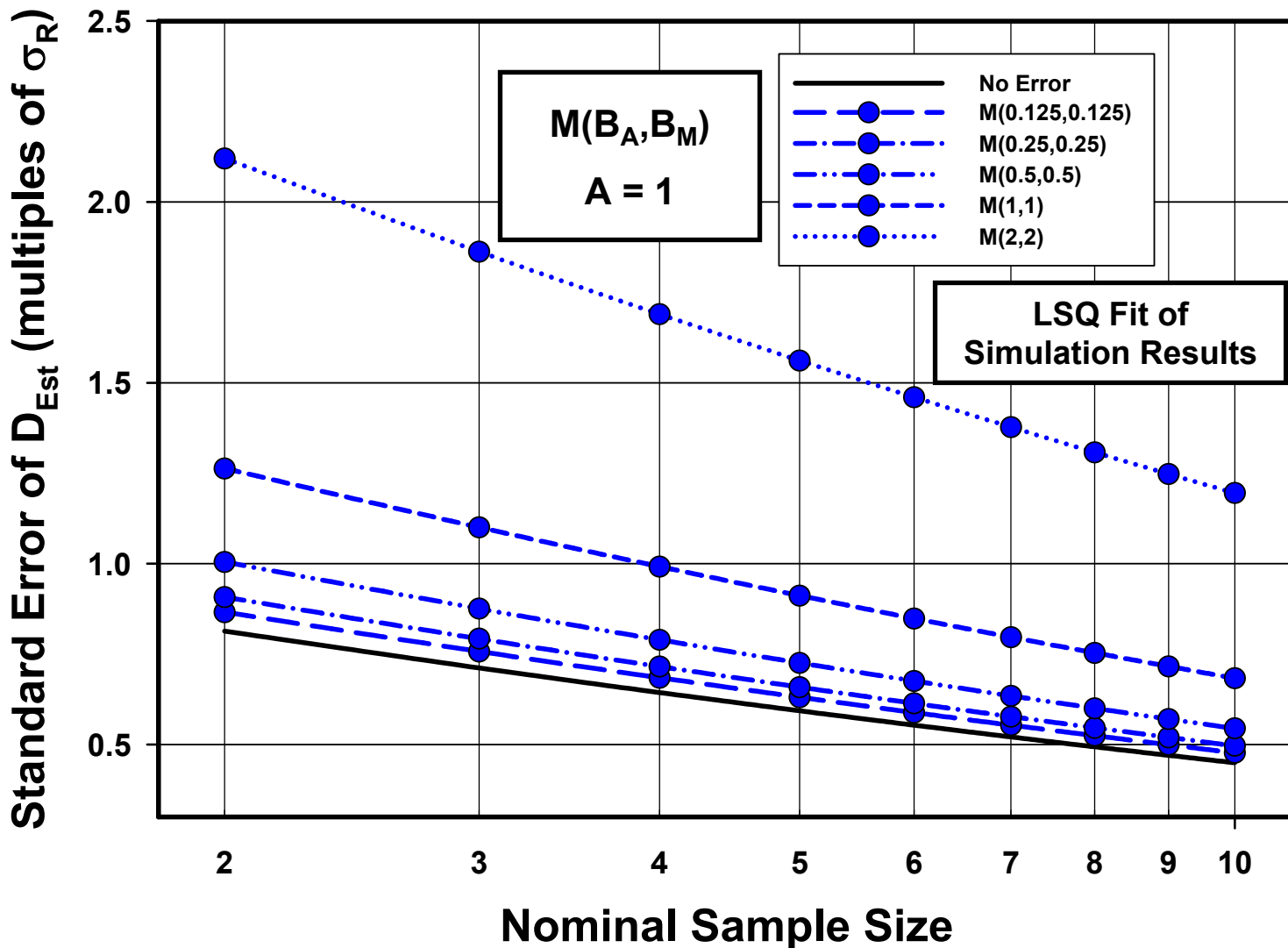
Precision Results

- Additional factor introduced--N (nominal sample size)
 - Accomplished by dividing up the 50 runs per coordinate point into five equal size groups having N_T values of 6, 7, 8, 9 and 10, respectively
 - Knowing RFR for each experiment, N was calculated from N_T and N_{FR}
 - Values of N from 2 to 10 obtained
- Factors in order of decreasing importance: $\log N$, B_M , A , B_A , $B_M B_M$ and $B_A B_A$
 - Many statistically significant interactions also exist
 - D is only significant when involved in an interaction (ex. AD and $B_M D$)
 - Dosage errors (B_A and B_M) more important than agent dosage basis (D)
 - This is in contrast to the reverse being true for experiment success rate
- Standard error for D_{Est} is smaller using Method T than with Method M

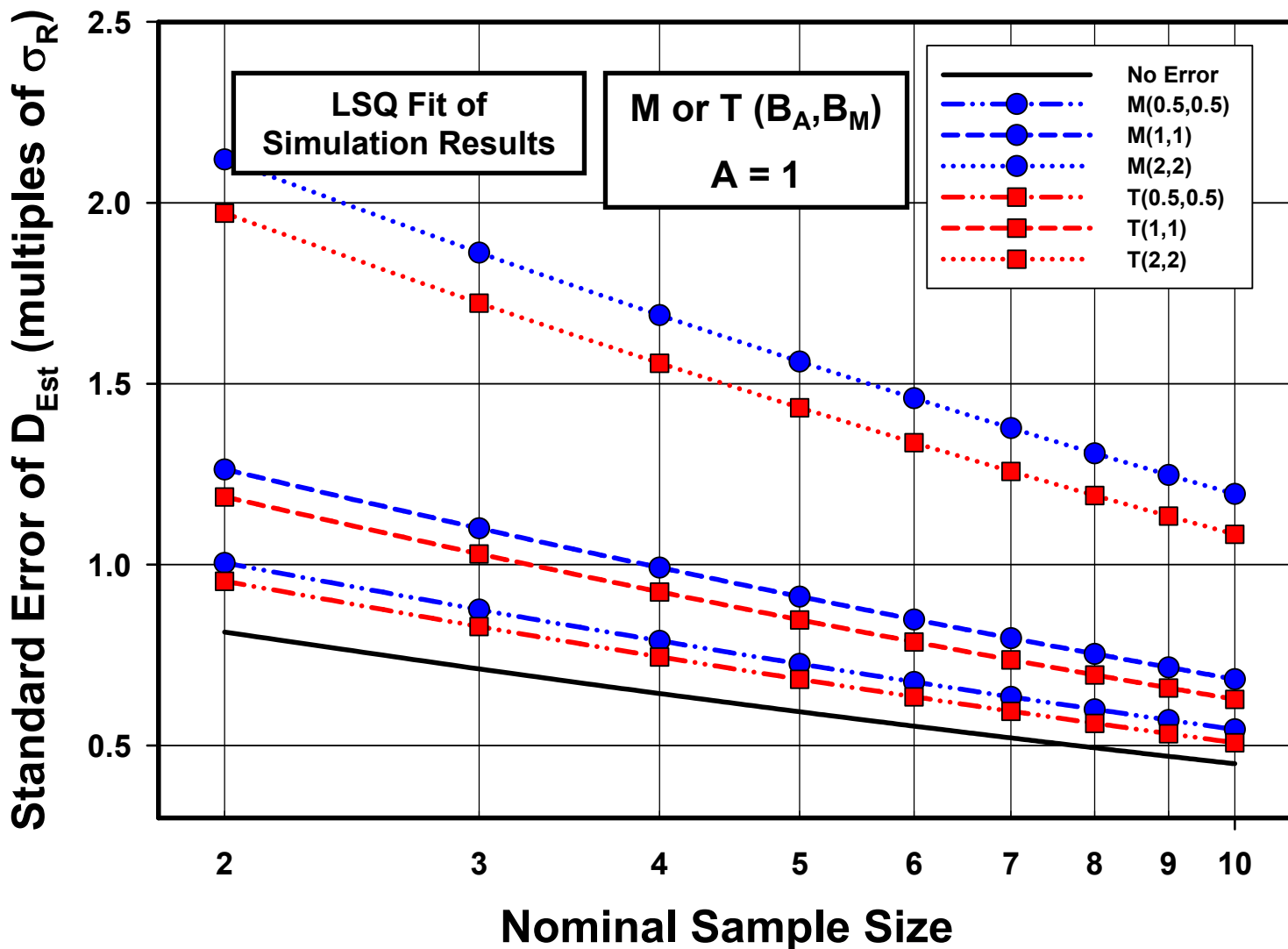
Standard Error of D_{Est} for Method M as a Function of N , B_A and B_M



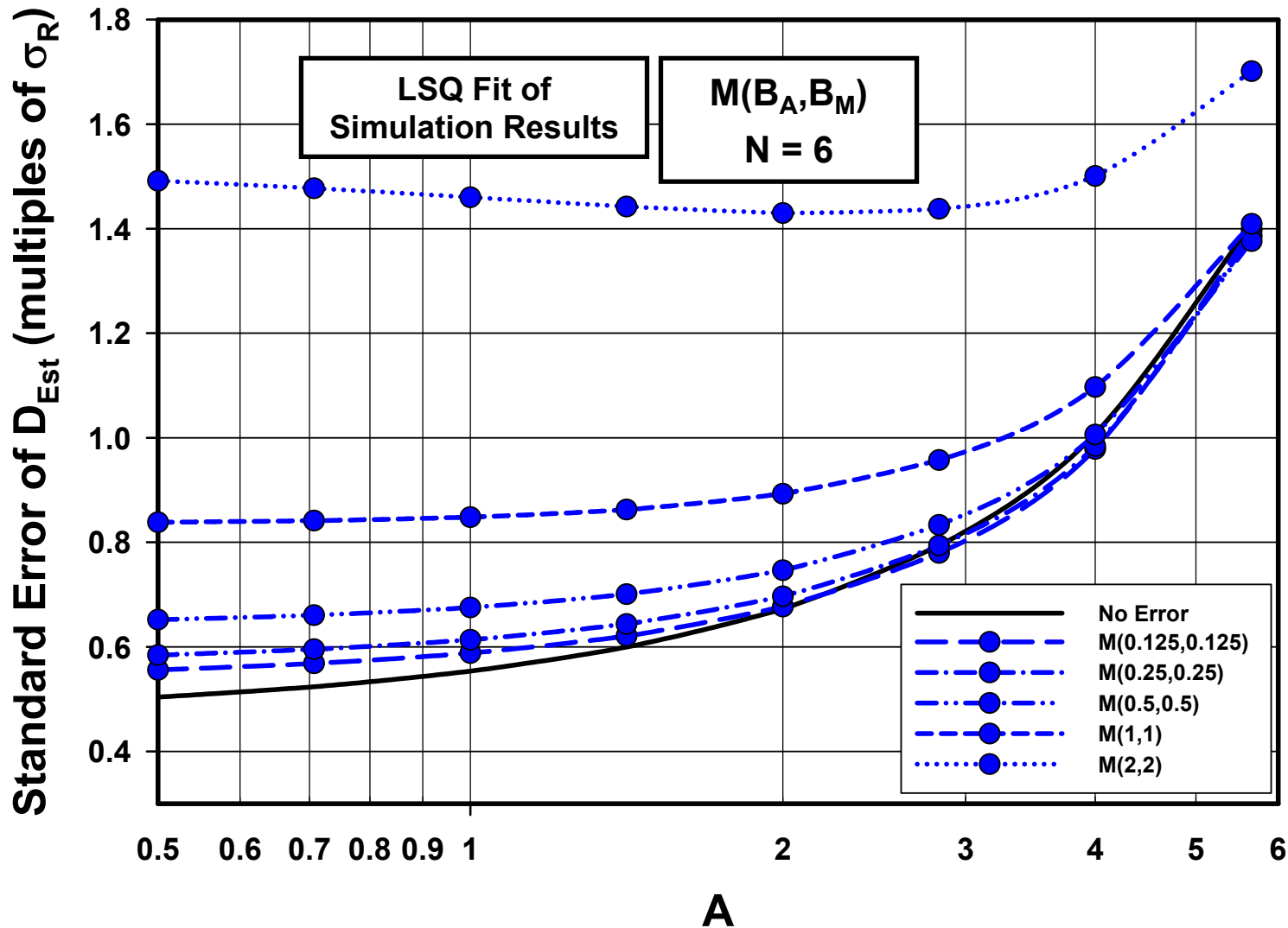
Standard Error of D_{Est} for Method M as a Function of N and $(B_A + B_M)$



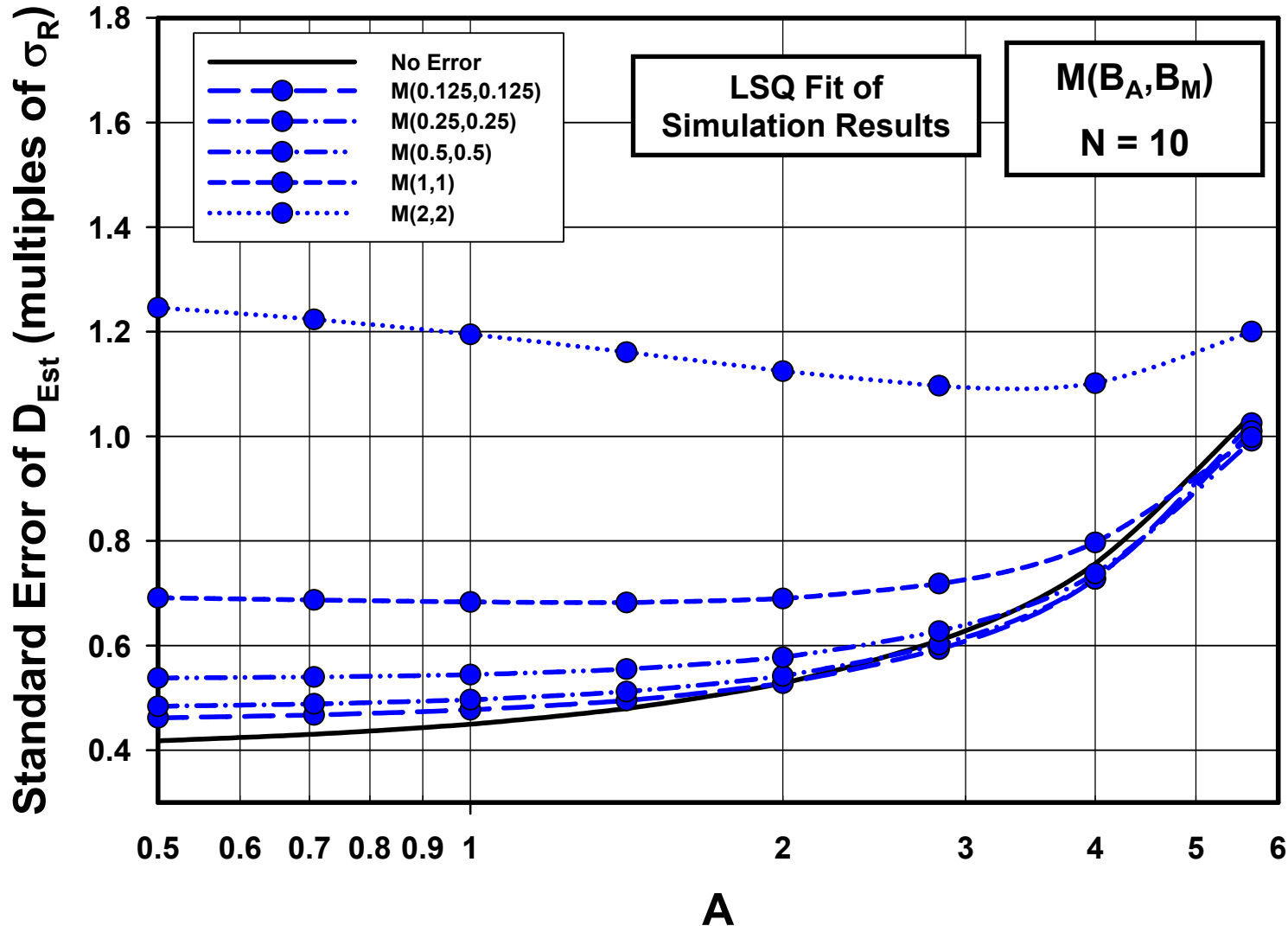
Standard Error of D_{Est} for Methods M and T as a Function of N and $(B_A + B_M)$



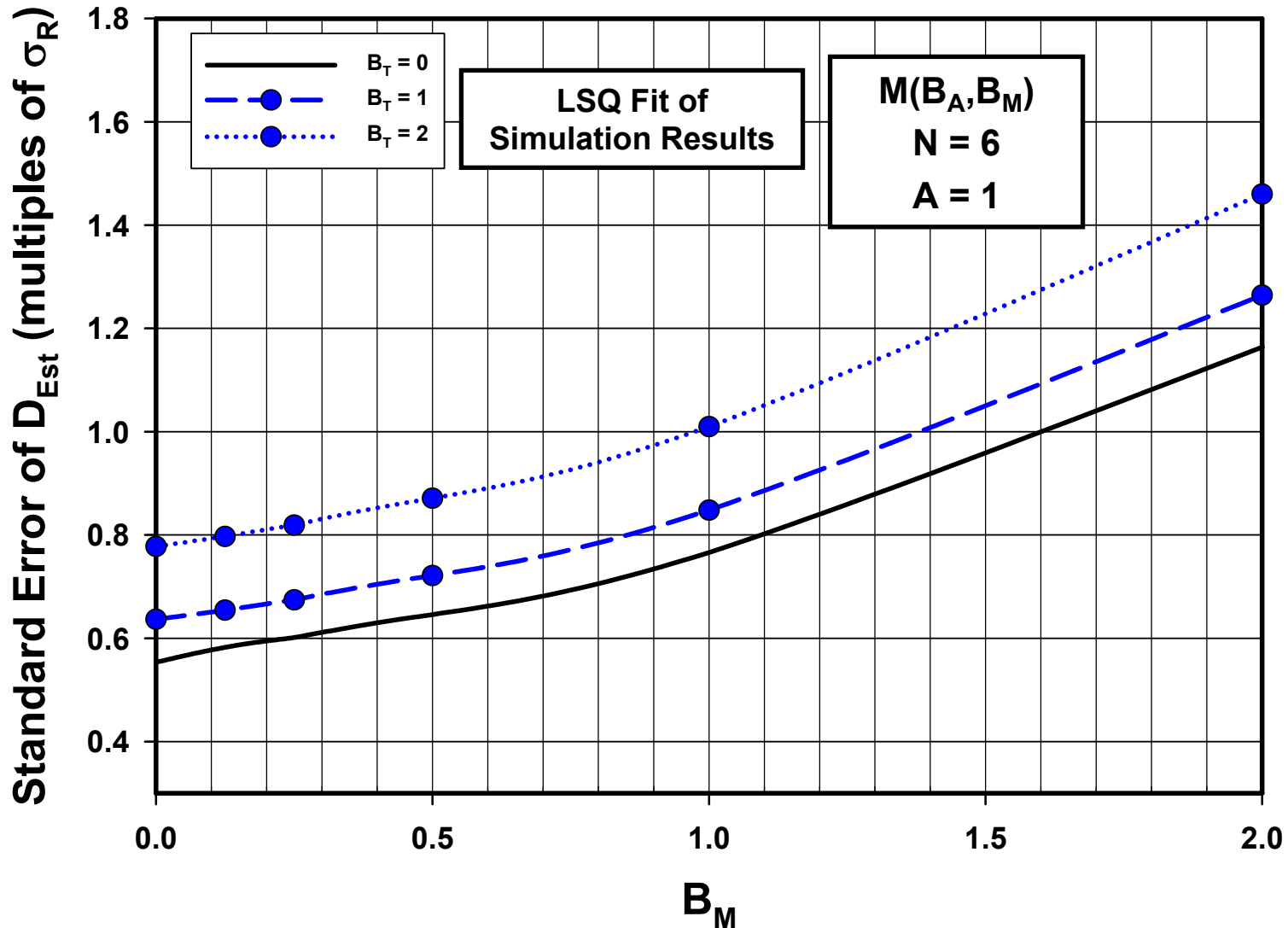
Standard Error of D_{Est} for Method M as a Function of A and $(B_A + B_M)$



Standard Error of D_{Est} for Method M as a Function of A and $(B_A + B_M)$



Standard Error of D_{Est} for Method M as a Function of B_A and B_M





Summary

- With non-zero dosage errors (B_A & B_M), UaD Method is robust with respect to efficiency & precision in the following parameter space
 - $-3 \leq C$ (initial dosage) ≤ 3
 - Neither B_A and/or B_M exceeds roughly 0.25 to 0.5
- When selecting next target dosage (Factor D), Method T is better than Method M overall
 - Difference between methods becomes more pronounced as:
 - A decreases
 - B_A and/or B_M increases
 - $|C|$ increases
 - Method T is more able to resist effects of large values of B_A & B_M



Summary (Cont.)

- Method T produces a distribution of number of responses and Run of First Reversal that is essentially identical to what is produced by traditional UaD (no dosage errors)
- Method T produces more precise D_{Est} values than Method M
 - However, dosage errors (B_A & B_M) have larger impact on precision than Factor D (Methods T and M) (the reverse is true for efficiency)



Conclusions

- Dosage administration and measurements errors do have an effect on the efficiency and precision of the Up-and-Down Method
- The effect of dosage errors on efficiency is significant overall
 - Can be practically eliminated by using Method T (basing next step on the previous target dosage) instead of Method M (basing next step on the previous measured dosage)
- The greater precision afforded by smaller step sizes is increasingly eroded by increasing dosage errors
 - Dosage measurement error has greater impact than both step size and dosage administration error on precision