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

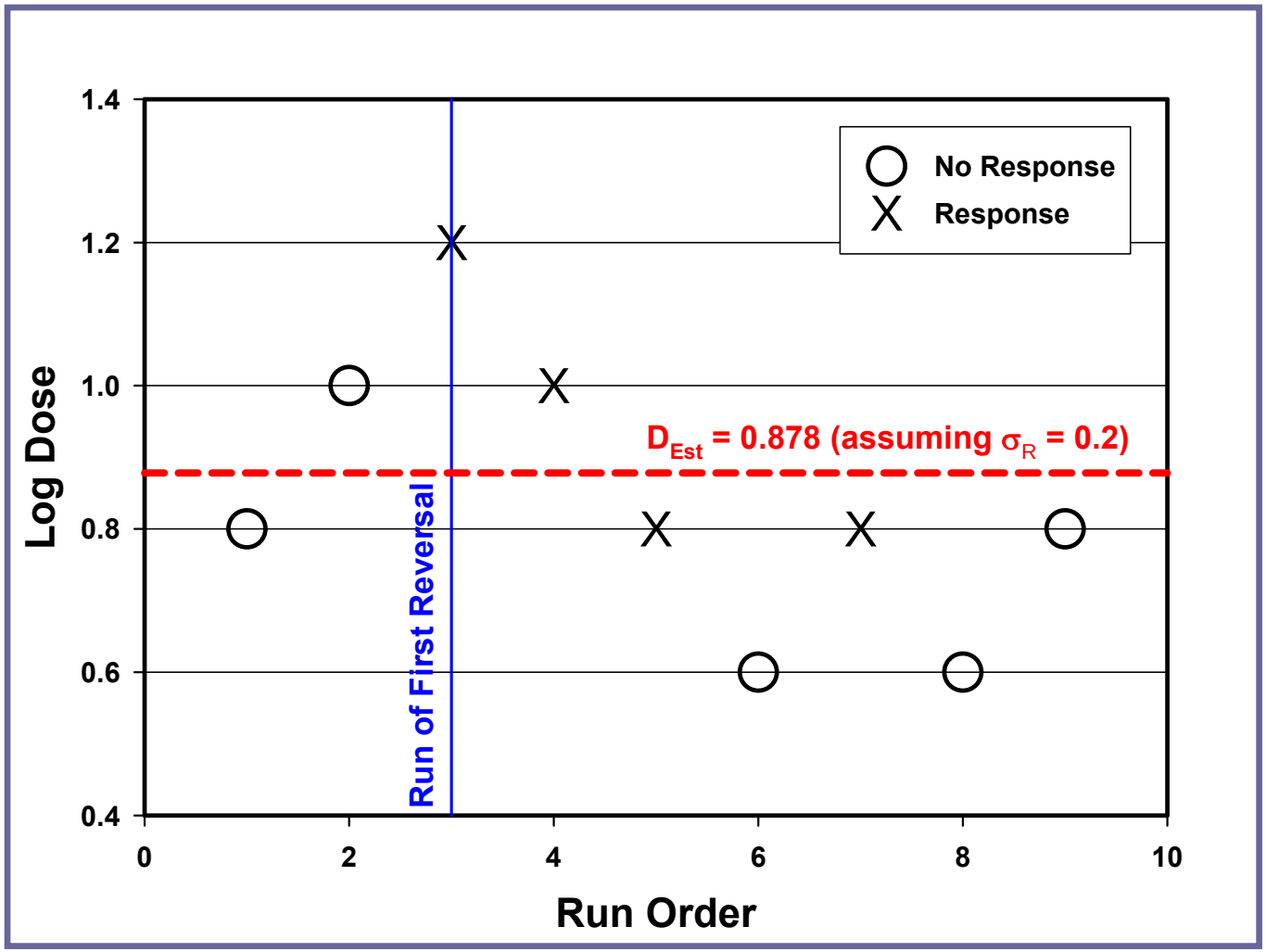
Obtaining an Estimate of the ED_{50}

- 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: $\sigma_{Total} = (\sigma_A^2 + \sigma_M^2)^{(1/2)}$
- 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

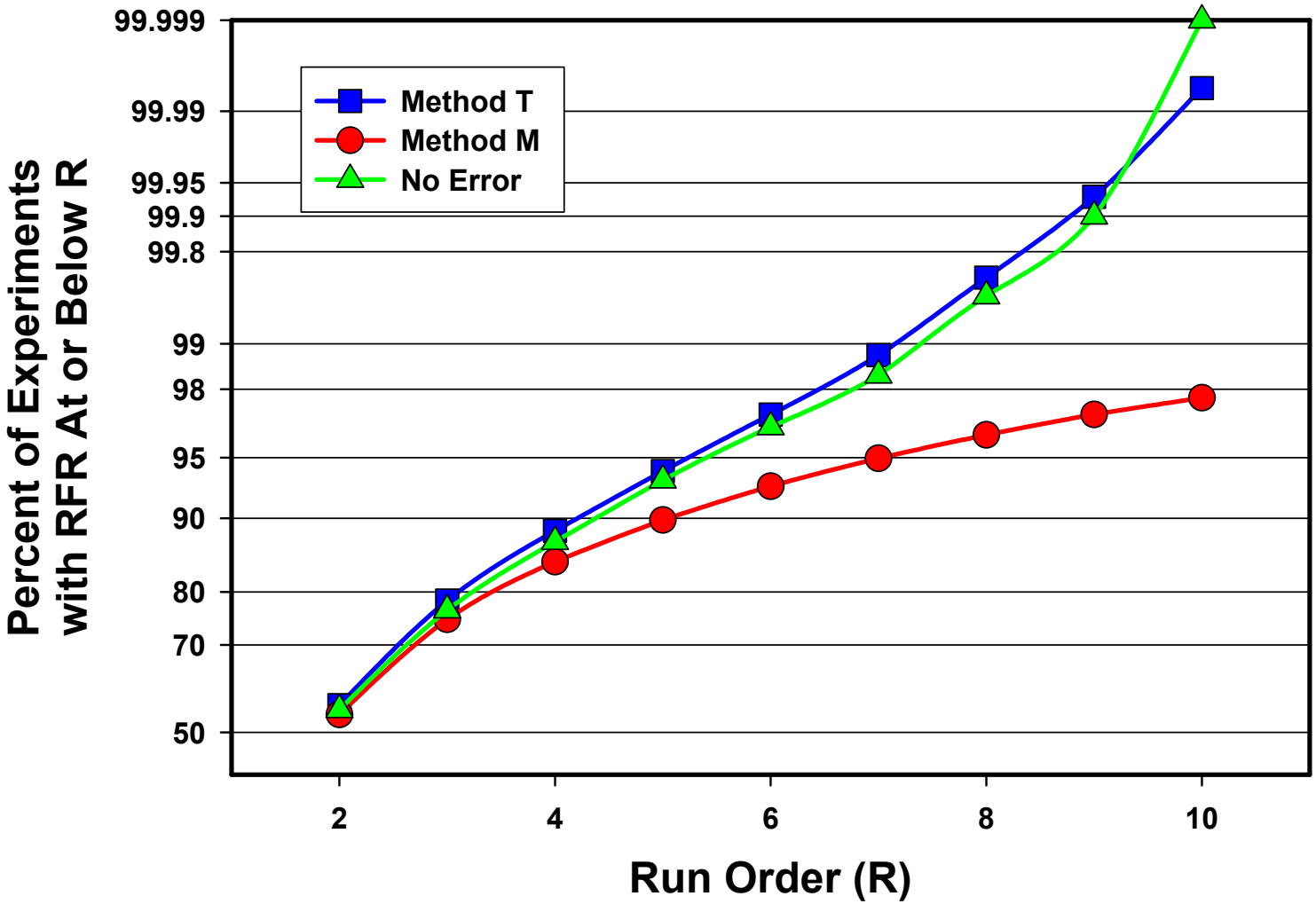
Results

- 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

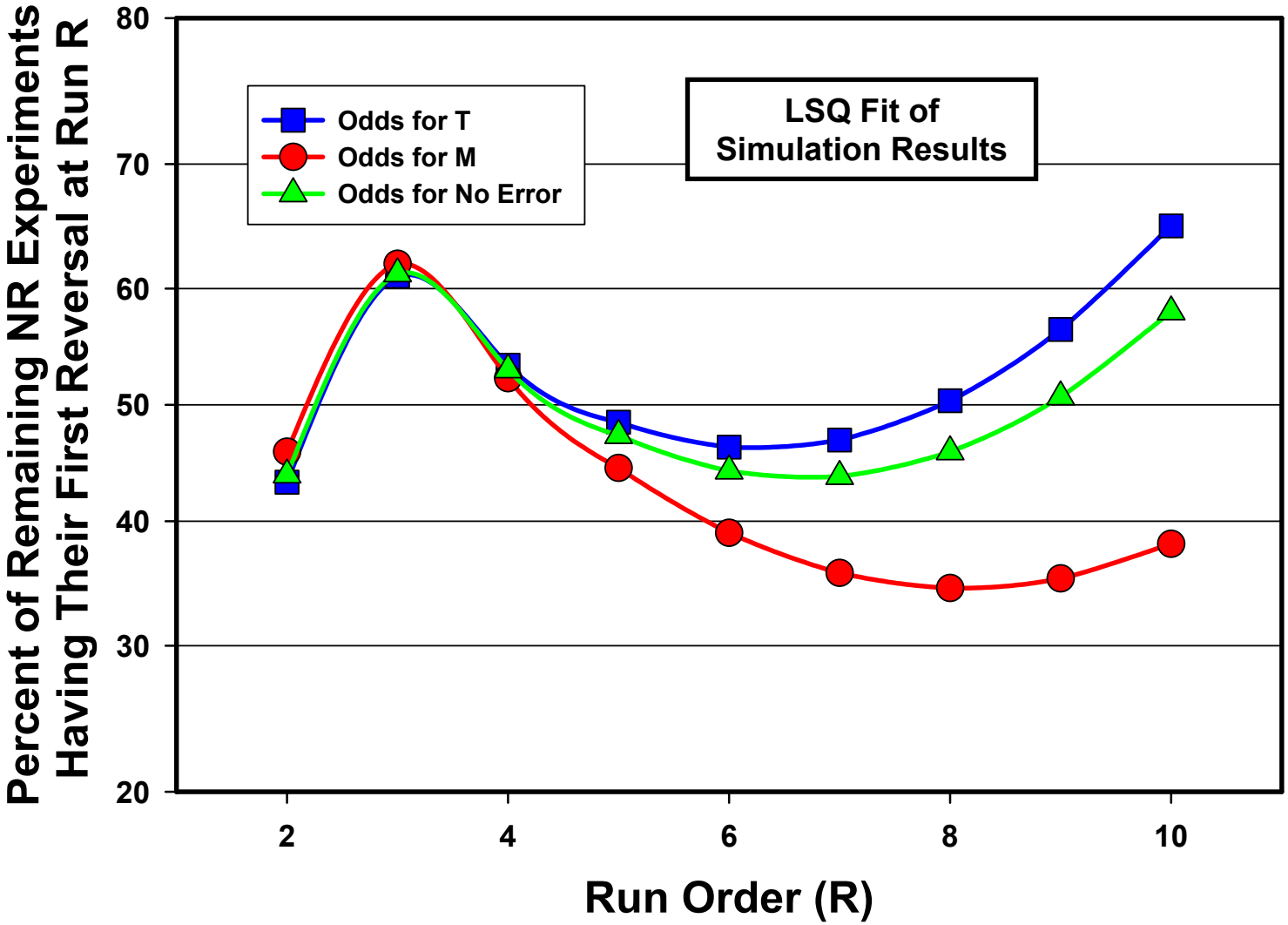
Efficiency Results

- 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



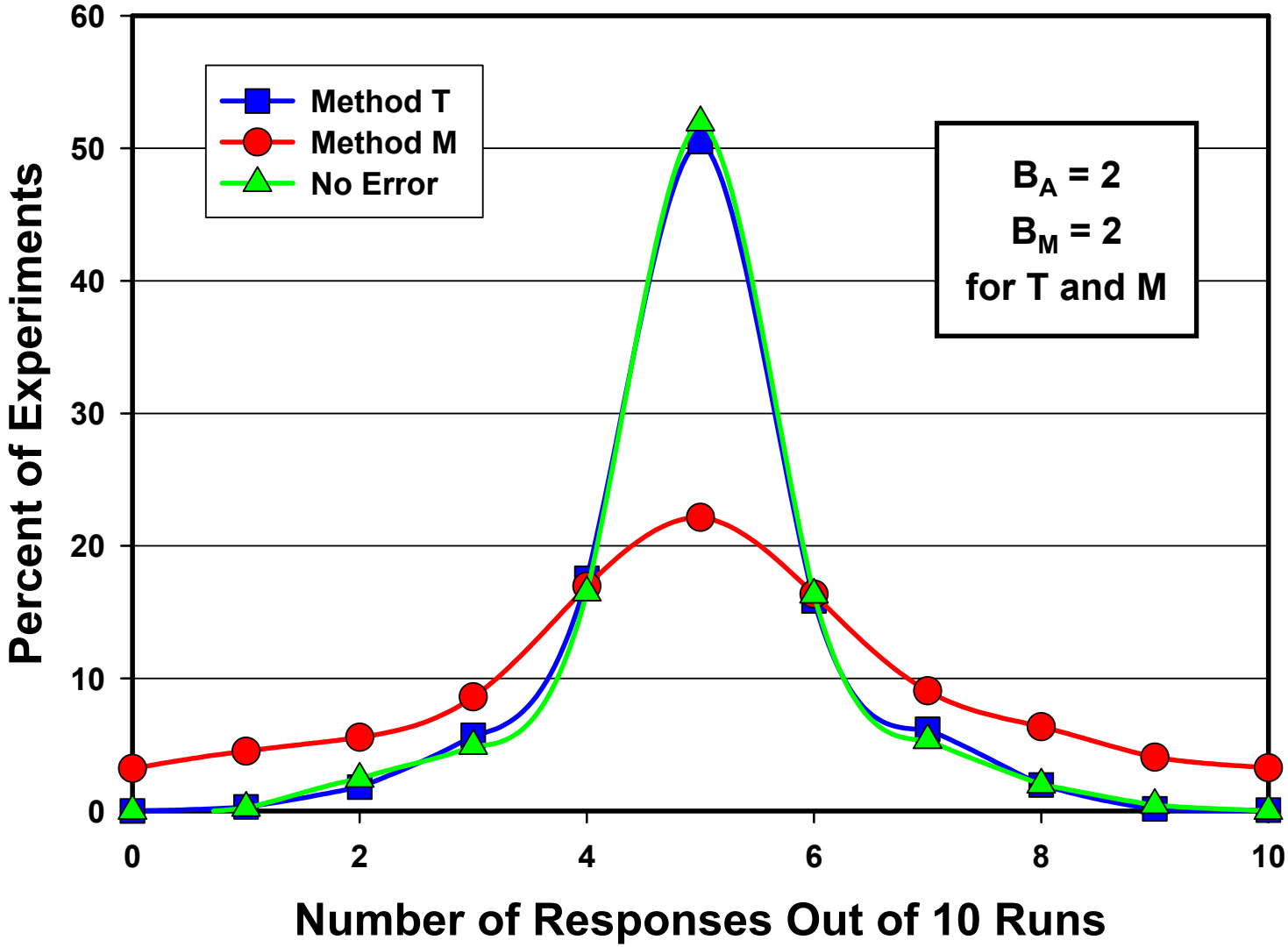
Chance of Non-Reversed (NR) Experiment having a Reversal



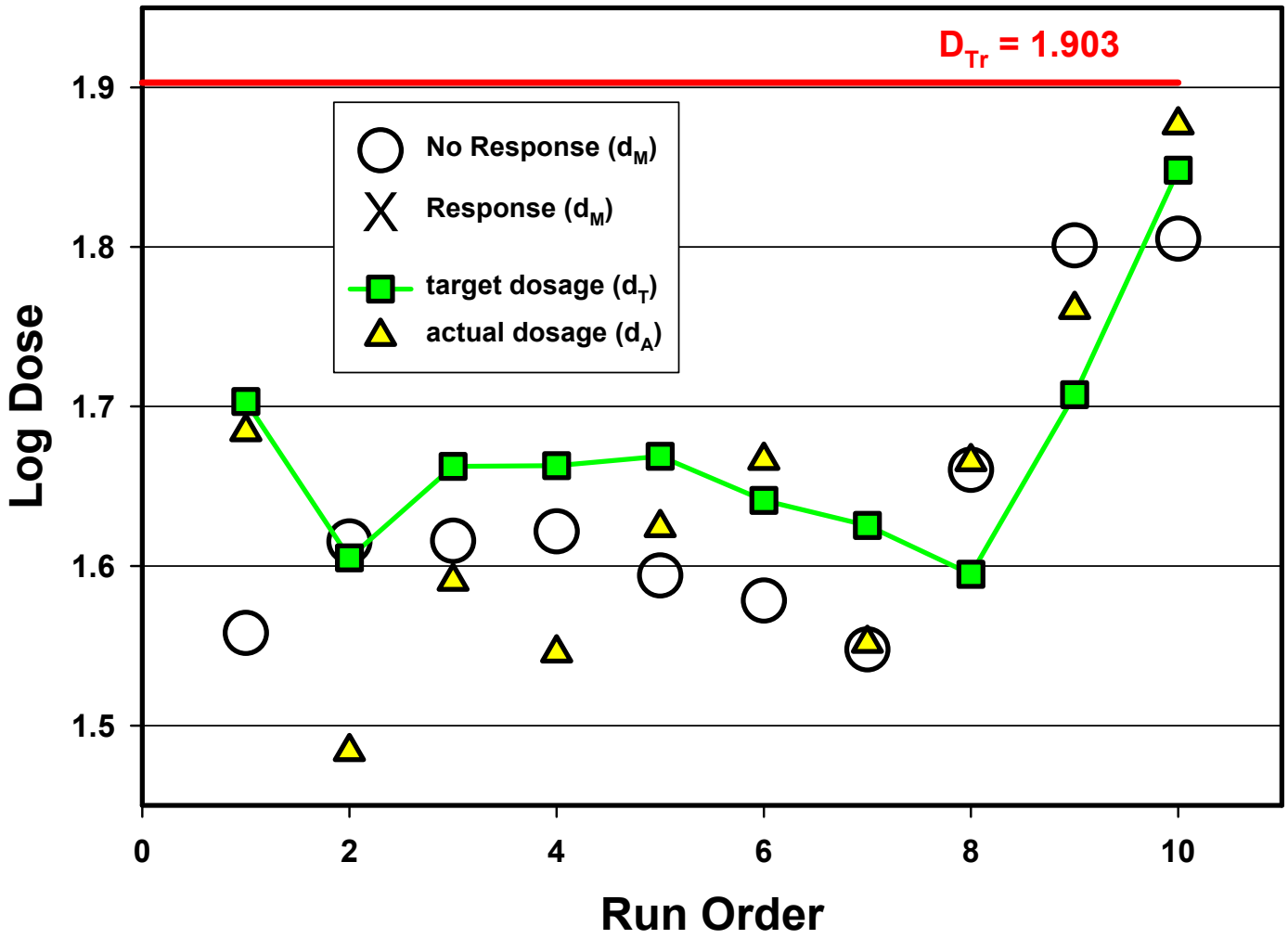
Efficiency Results (Cont.)

- Distribution of Number of Responses
  - Results for Method T (with any dosage errors present) mirrors than 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

$\Delta d = (0.047)$

$\sigma_R = (1/15)$

$A = 0.707$

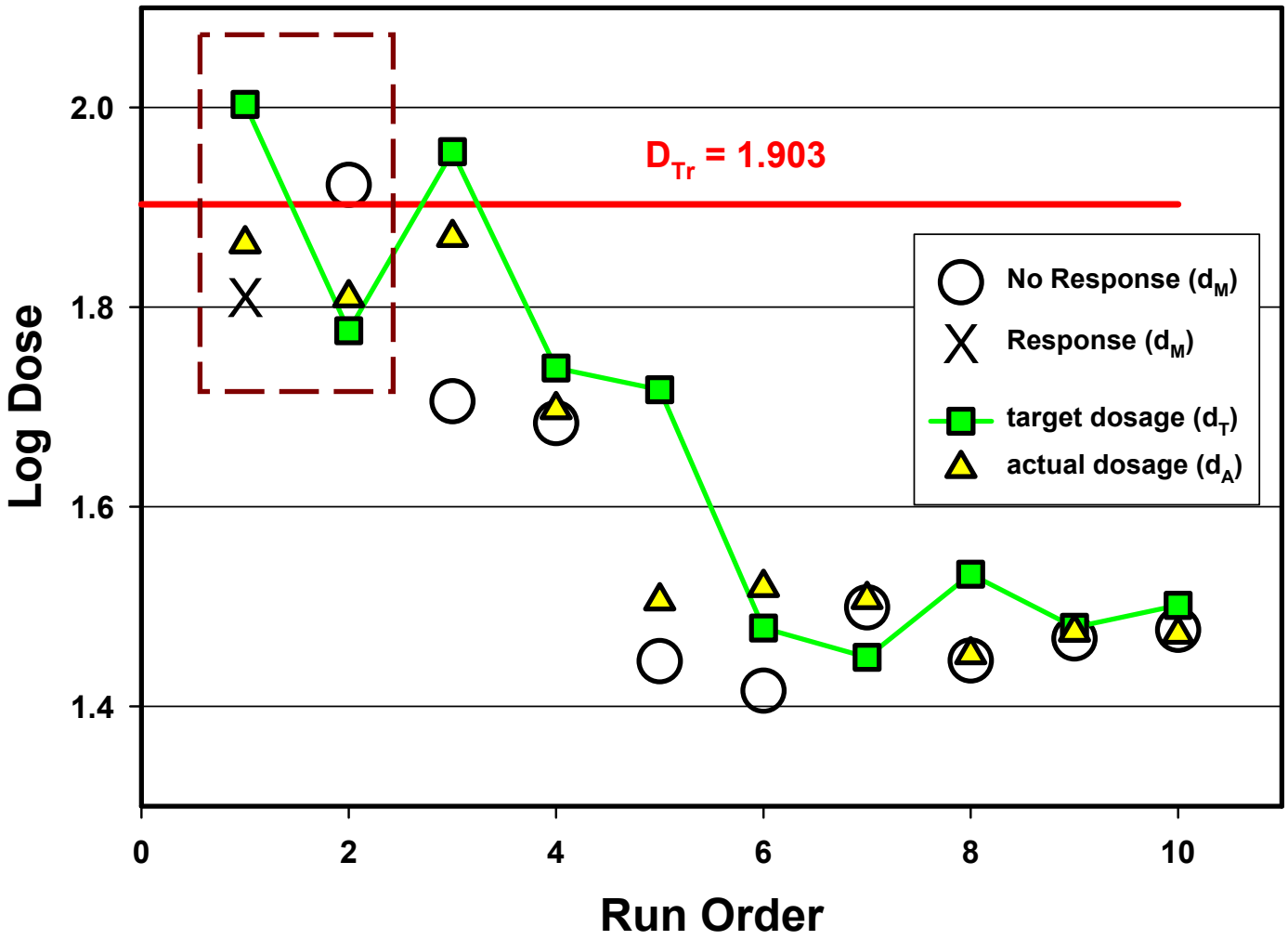
$B_A = 1$

$B_M = 1$

$C = -3$

No Estimate of D_{Tr} Possible

Example of a Negative Step Direction with Method M



Expt 28159M

Method M

$\Delta d = (1/30)$

$\sigma_R = (1/15)$

$A = 0.5$

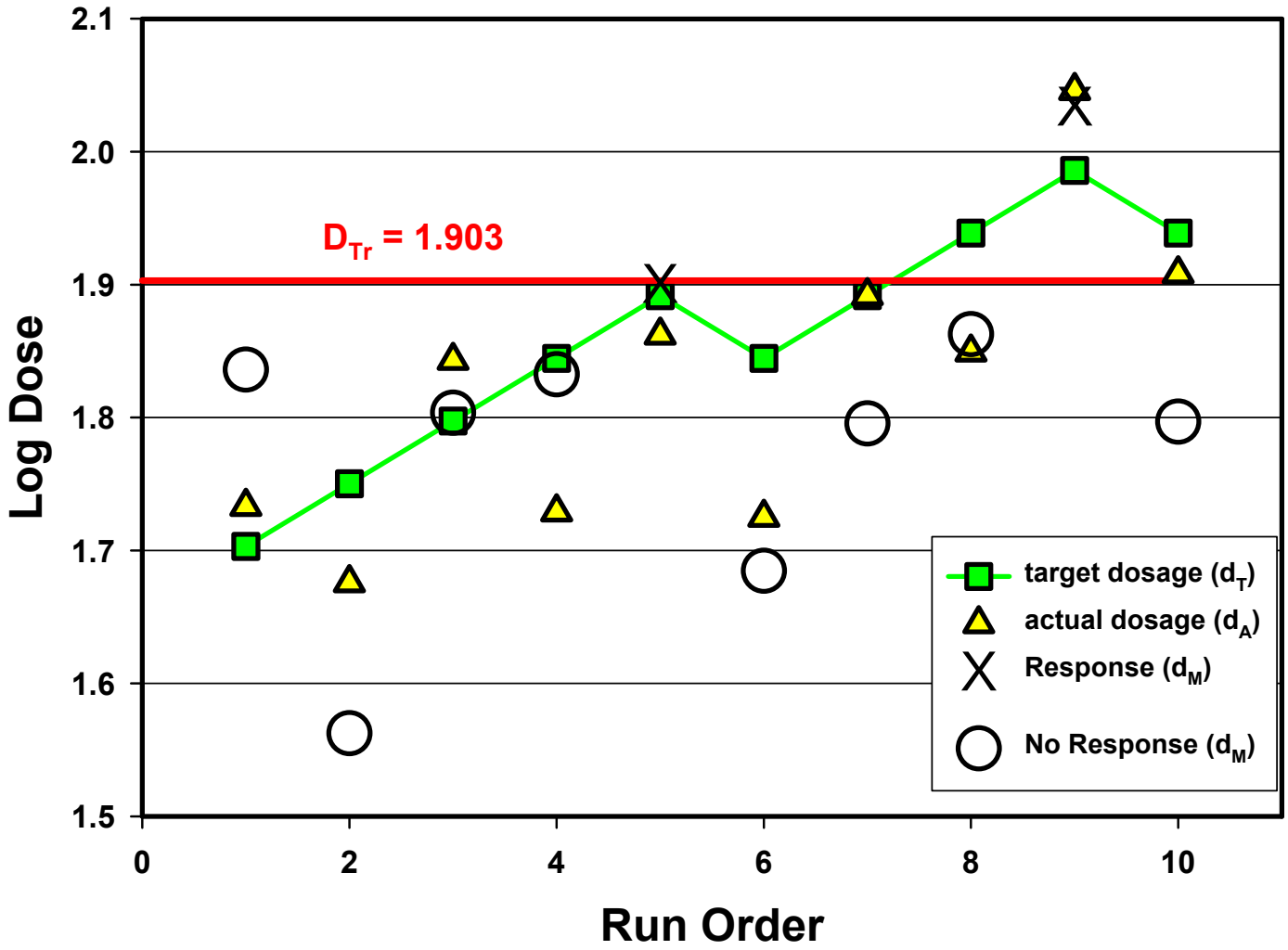
$B_A = 1$

$B_M = 1$

$C = 1$

D_{Est} = 1.866

Example of an Experiment with Method T



Expt 64013T

Method T

$\Delta d = (0.047)$

$\sigma_R = (1/15)$

$A = 0.707$

$B_A = 1$

$B_M = 1$

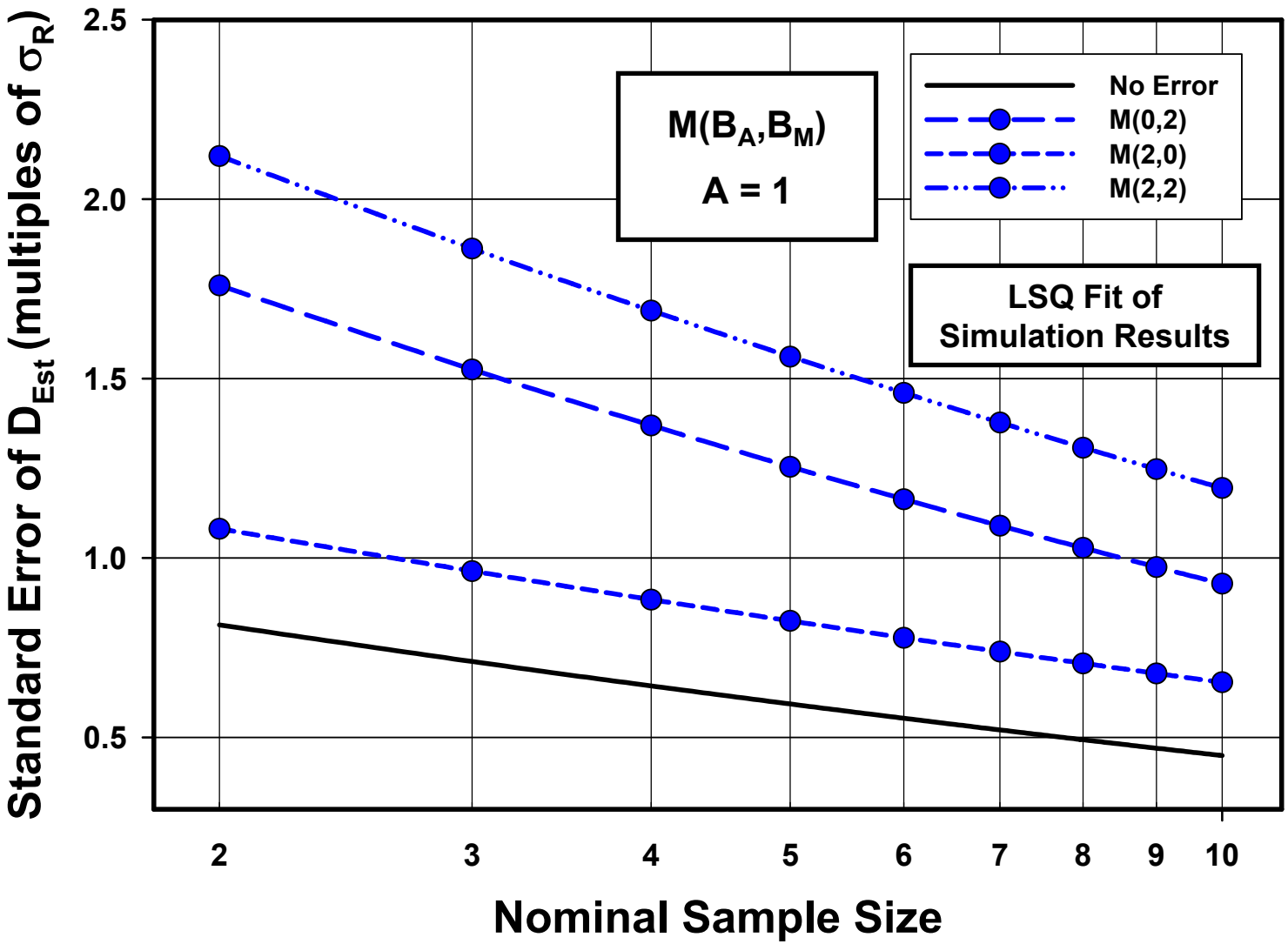
$C = -3$

$D_{Est} = 1.901$

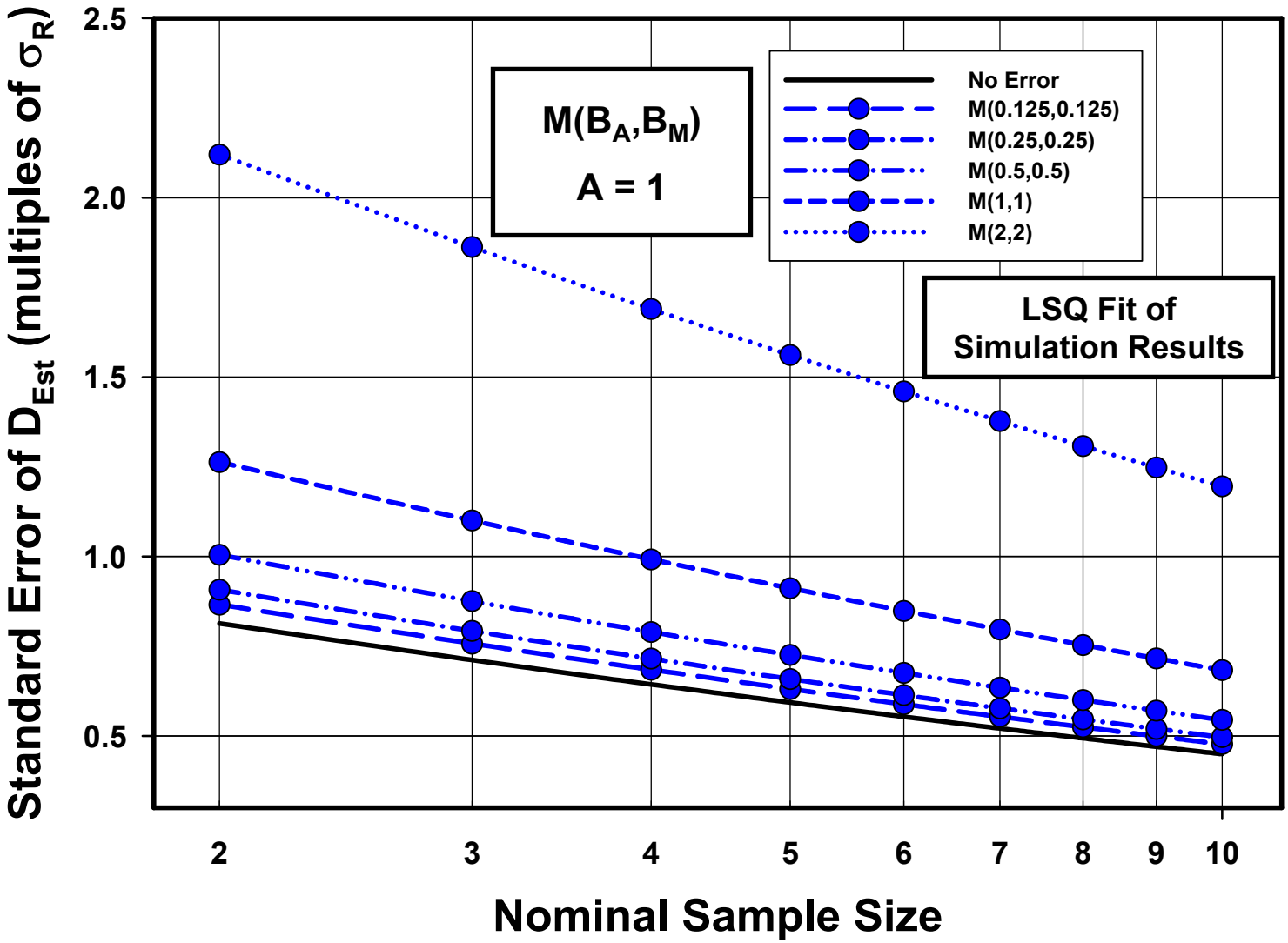
Precision Results

- 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: logN, B_M, A, B_A, B_MB_M and B_AB_A
  - Many statistically significant interactions also exist
  - D is only significant when involved in an interaction (ex. AD and B_MD)
  - 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

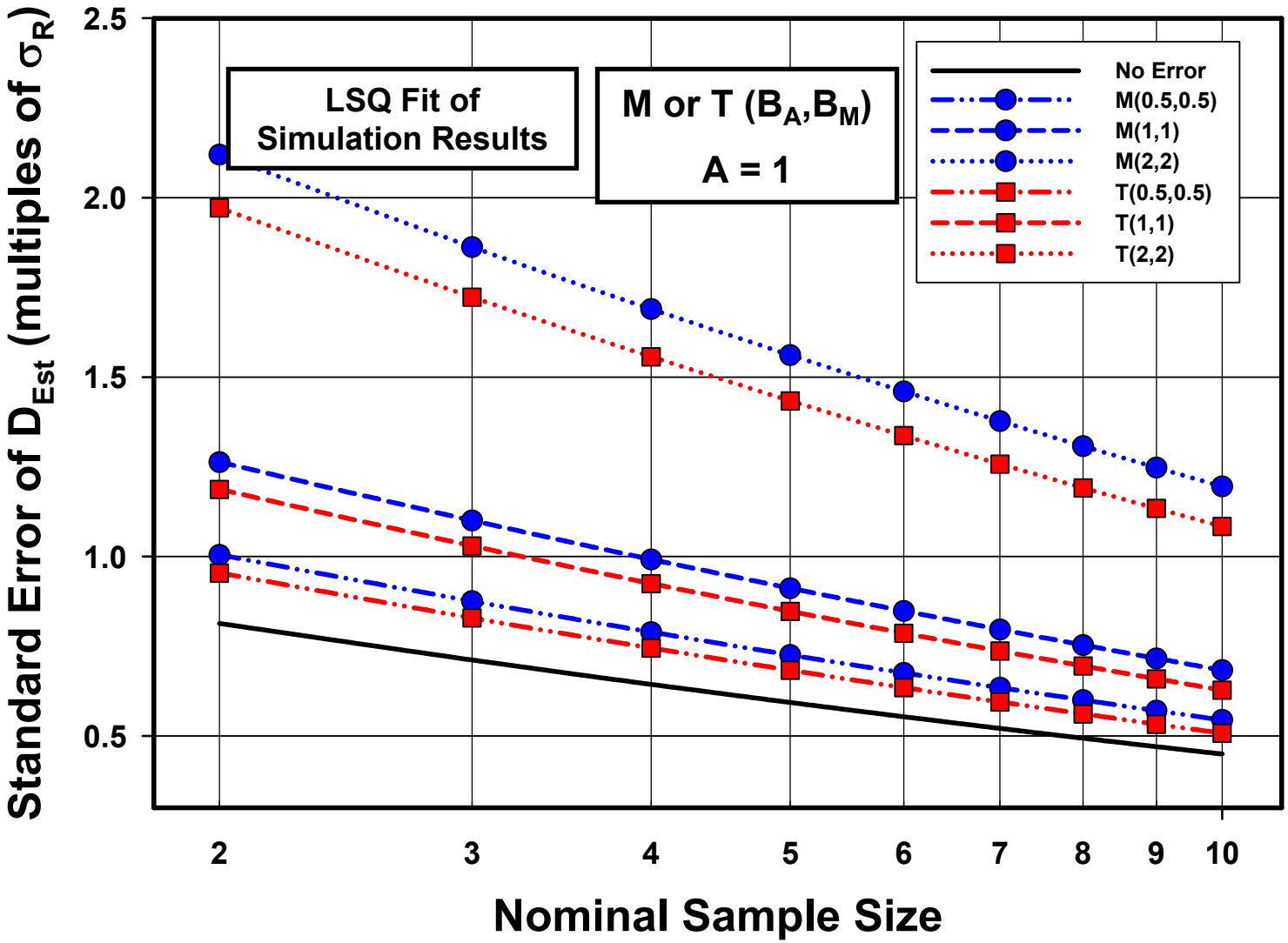
Standard Error of D_{Est} for Method M as a Function of N, B_A and B_M



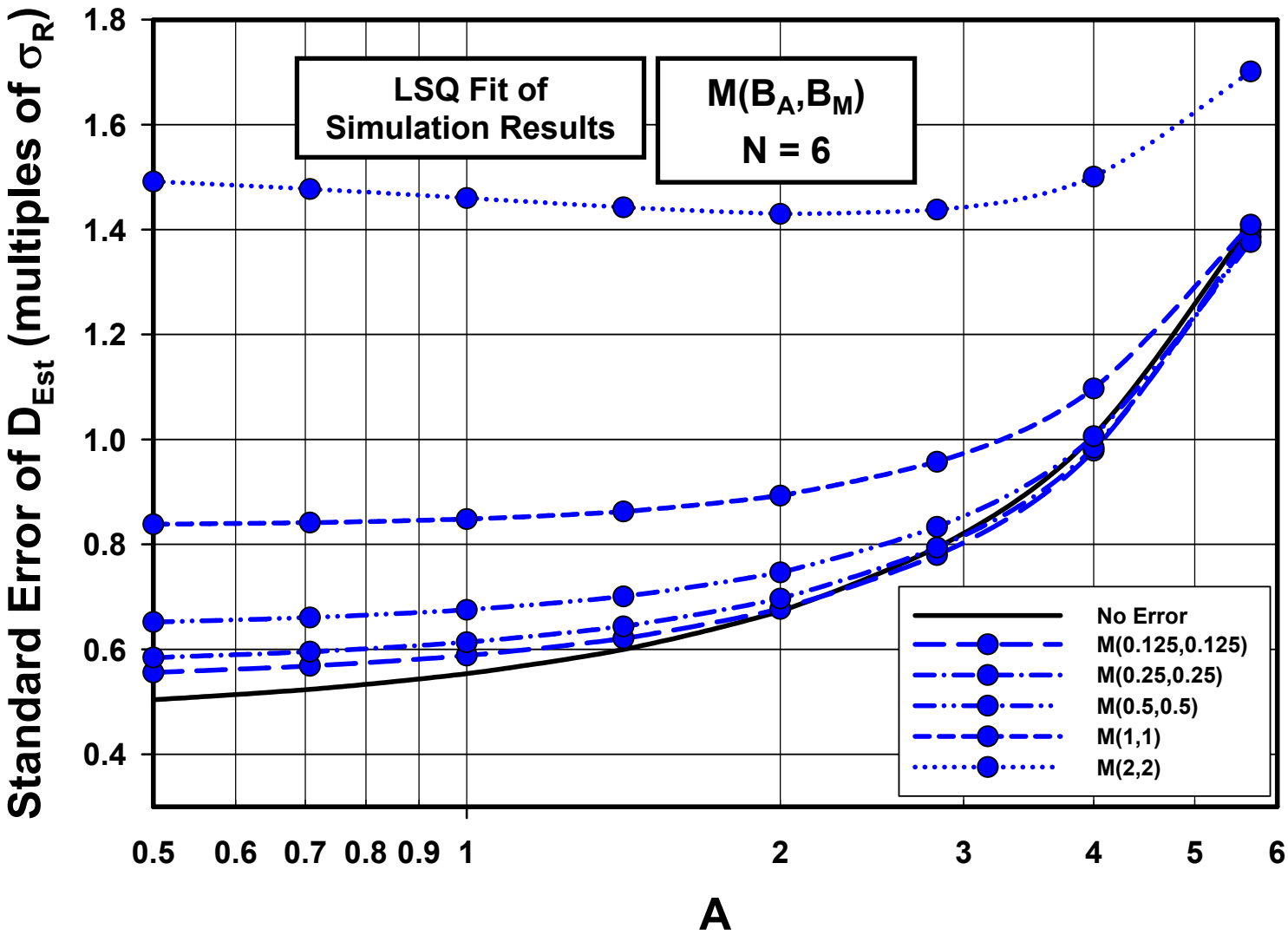
Standard Error of D_{Est} for Method M as a Function of N and (B_A + B_M)



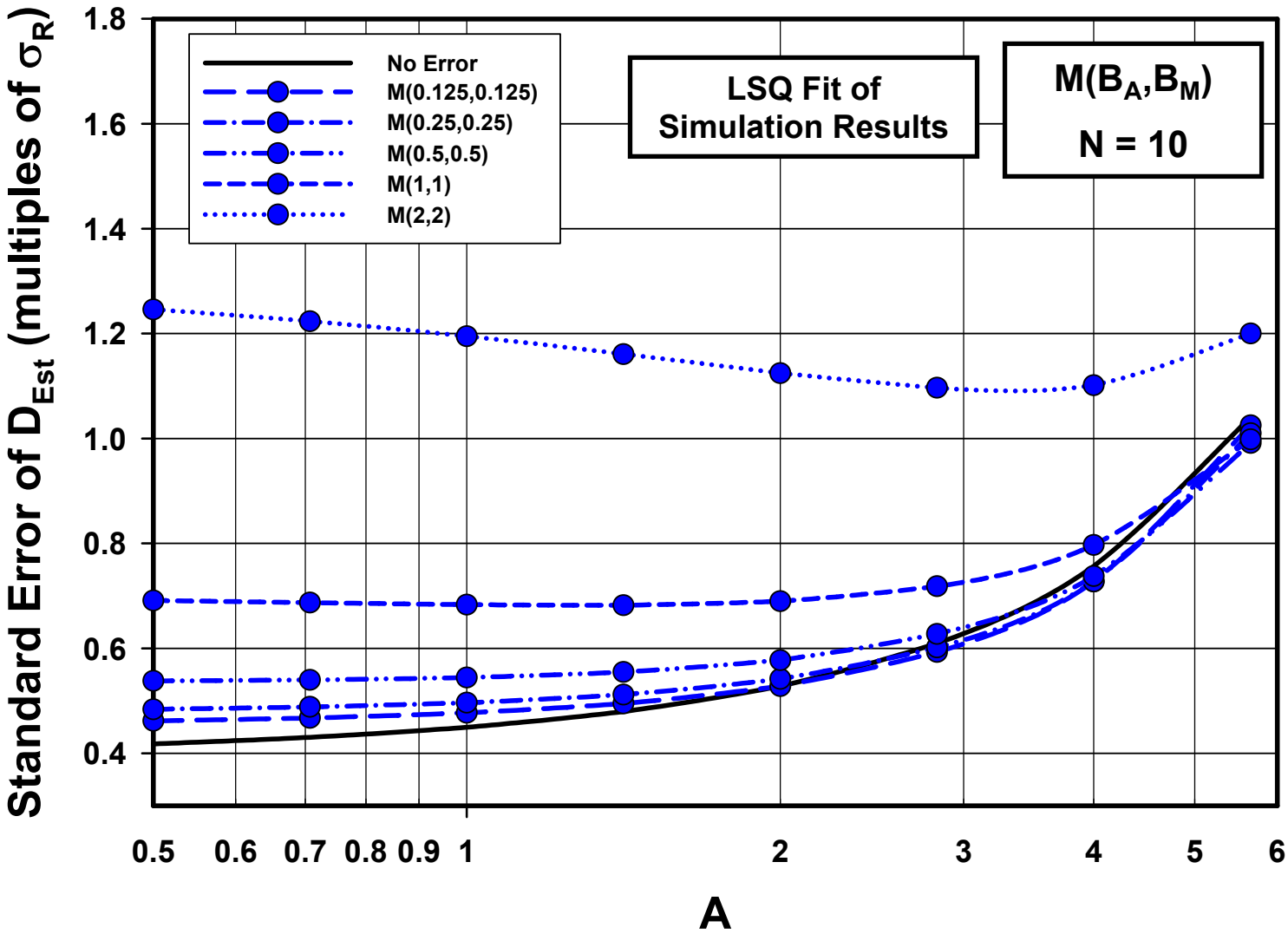
Standard Error of D_{Est} for Methods M and T as a Function of N and (B_A + B_M)



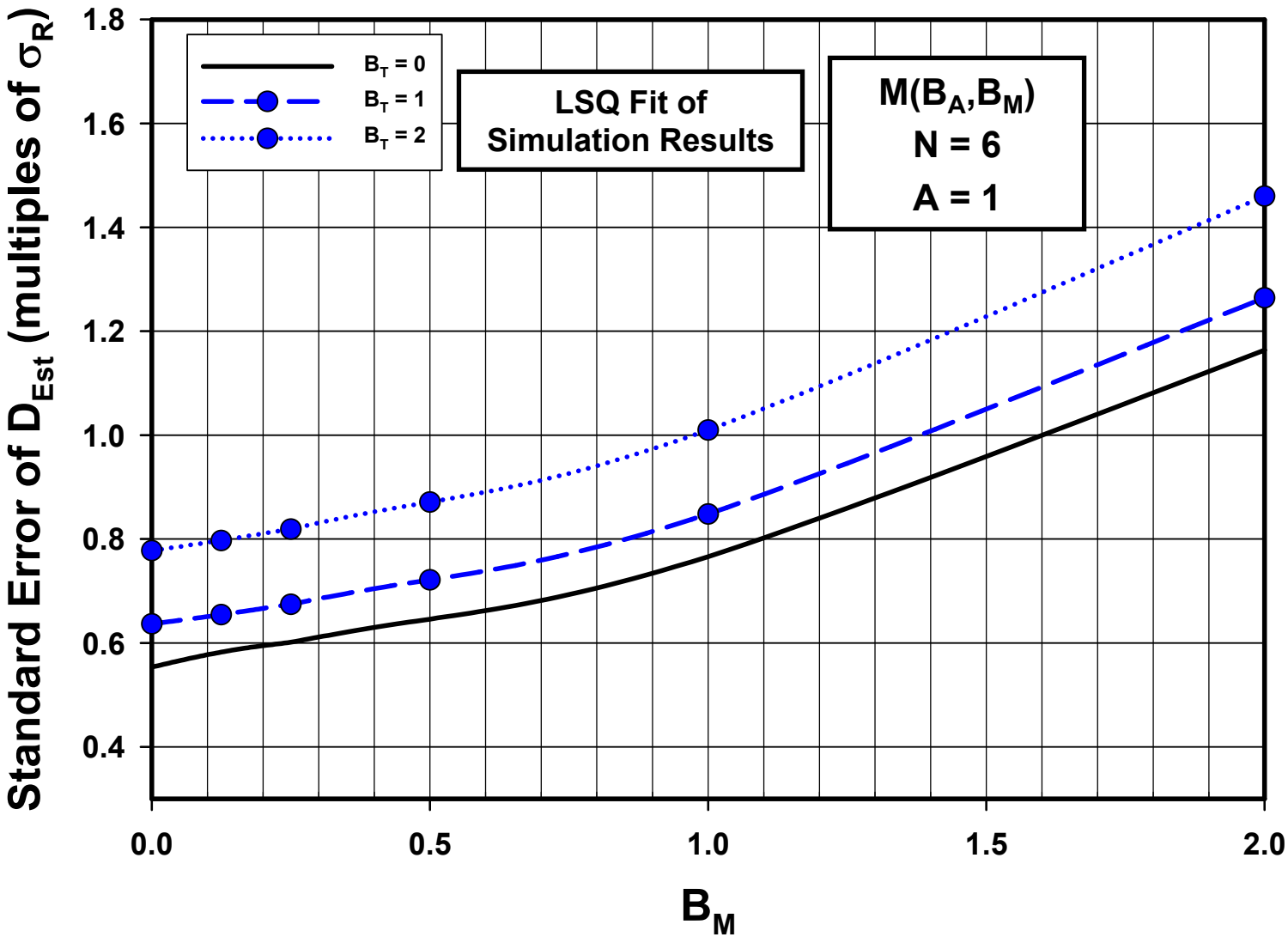
Standard Error of D_{Est} for Method M as a Function of A and (B_A+ B_M)



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

- Witn 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