Item ID Number	03035	☐ **Not Scanned**
Author	Angleton, George M.	
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Report/Article Title	Typescript: Relative Variation vs. Absolute Variation in the Study of Treatment Effects	
Journal/Book Title		
Year	1974	
Month/Day	November	
Color	☐	
Number of Images	6	
Descripton Notes	Contract F056117490182, Colorado State University	

RELATIVE VARIATION VS ABSOLUTE VARIATION IN THE STUDY OF TREATMENT EFFECTS

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November 1974

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FOREWORD

This report was prepared by Colorado State University, Fort Collins, Colorado, under Contract No. F0561174-90182.

Dr. George M. Angleton, Associate Professor of Radiation Biology and Biostatistics, Colorado State University (CSU) was program manager at CSU for this research program.

Dr. Alvin L. Young was senior scientist and final program manager for the United States Air Force (USAF) for this contract. Dr. John W. Watters was the original program manager for the USAF. Dr. Louis F. Wailly was responsible for initiating the collaborative effort between CSU and the USAF.

ABSTRACT

A fallacy of using the ratio of two response variables to study the effect of some treatment when measurements for both responses are taken on the same subject for the same time is disclosed. An alternative to the use of the ratio is proposed, namely to use one of the terms as an independent variable and take into account covariation through a regression relationship,

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The effects of a treatment are frequently studied in terms of a dependent variable which is the ratio of two responses. In the event that the two responses represent two different measurements made on one subject at a given time, their ratio may be an insensitive statistic relative to the detecting of treatment effects. The principal reason for this is that if both responses were affected proportionally then their ratio would not change. In many studies it would be more appropriate to treat one of the variables in the ratio as a dependent variable and the second variable as an independent variable.

Such situations frequently occur when the weight data obtained during a necropsy are analyzed. For example, in the case of a subject previously receiving some treatment (T) such as an exposure to ionizing radiation or an exposure to some chemical substance, the endpoints of interest might be the lung weight (L) and the total body weight (B) with the dependent variable being defined as the ratio (R) of the lung weight to the body weight. Thus,

$$R = L/B.$$

The first order dependence of R on T is given by the linear relationship

$$R = \alpha_1 + \alpha_2 T$$

where α_1 is the expected value of R for T equal to zero and α_2 is the expected change in R per unit change in T. Alternately,

$$L/B = \alpha_1 + \alpha_2 T.$$

Least squares estimation techniques can be used to obtain estimates of the parameters α_1 and α_2 and hence of the regression line for R.

$$\hat{R} = (\widehat{L/B}) = \hat{\alpha}_1 + \hat{\alpha}_2 T$$

If the R_i, that is the ratio L_i/B_i for the i-th observation set L_i and B_i corresponding to T_i, can be assumed to be somewhat normally distributed with constant variance about the expected values of R_i as estimated by the values of $\hat{R}_i$, then the hypothesis that α_2 is equal to zero can be tested using analysis of variance techniques.

However, it is both interesting and important to note that this is not a complete test of the simple hypothesis of no effect due to treatment. The hypothesis being tested is that the response variables L and B on a proportional scale are not affected differently by the treatment. In essence, then it can be shown that the test of the hypothesis that α_2 is equal to zero is a test of no body-weight and treatment, BT, interaction given that the response variable of principal interest is the lung weight L.

If the equation for R is rewritten in terms of L and B and then solved for L, then the fact that testing the hypothesis that α_2 is equal to zero is the same as testing the hypothesis that there is no BT interaction becomes immediately clear.

$$L/B = R$$
$$= \alpha_1 + \alpha_2 T;$$

so that

$$L = \alpha_1[B] + \alpha_2[BT].$$

The equation in this latter form states that lung weight is directly proportional to body weight when the treatment level is zero, the proportionality constant being α_1. However, for non-zero values of T, the lung weight is also linear dependent on BT, the interactive term whose coefficient is α_2. Hence, as the level of treatment increases the lung weight changes proportionately providing there is no effect of treatment on body weight. However, if the treatment were to lead to a change in the body weight, as might be expected in many cases, then the effect due to treatment alone could not be estimated since the only term involving T is the interactive term BT.

A more meaningful approach to the analysis would be to postulate a model whereby the terms of its equation would not impose the restrictions of the previous model. One such equation is as follows:

$$L = \alpha_1 + \alpha_2(B) + \alpha_3(T) + \alpha_4(BT)$$

In this equation both body weight and level of treatment are considered to be independent variables. The hypothesis of no significant effect due to a body-weight with level of treatment interaction could be performed by testing the hypothesis that α_4 is equal to zero. The hypothesis of no effect due to treatment could also be tested by testing the joint hypothesis that α_3 and α_4 are both equal to zero.

Summary

The use of the ratio of two different response measurements in testing the null hypothesis of no effects due to treatment can be an insensitive and a meaningless test when the treatment affects both responses in a proportionate manner. When this is the case a more meaningful approach may be to treat one of the responses, say R_2, as an independent variable and to formulate a four term linear model, expressing the dependence of the other response, say R_1, on R_2 and the level of treatment T. Thus,

$$R_1 = \alpha_1 + \alpha_2(R_2) + \alpha_3(T) + \alpha_4(TR_2).$$

Null hypotheses concerning any of the parameters could be tested. A particular hypothesis of interest would be to test that α_1 is equal to zero for the data whereby T is equal to zero. Such a test as can be seen would test the basic plausibility of using ratio statistics as considered initially.