# ANCOVA: A HETEROSCEDASTIC GLOBAL TEST WHEN THERE IS CURVATURE AND TWO COVARIATES

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#### ABSTRACT

For two independent groups, let  $M_j(\mathbf{X})$  be some conditional measure of location for the *j*th group associated with some random variable *Y* given  $\mathbf{X} = (X_1, X_2)$ . Let  $\Omega = {\mathbf{X}_1, \ldots, \mathbf{X}_K}$  be a set of *K* points to be determined. An extant technique can be used to test  $H_0: M_1(\mathbf{X}) = M_2(\mathbf{X})$  for each  $\mathbf{X} \in \Omega$  without making any parametric assumption about  $M_j(\mathbf{X})$ . But there are two general reasons to suspect that the method can have relatively low power. The paper reports simulation results on an alternative approach that is designed to test the global hypothesis  $H_0: M_1(\mathbf{X}) = M_2(\mathbf{X})$  for all  $\mathbf{X} \in \Omega$ . The main result is that the new method offers a distinct power advantage. Using data from the Well Elderly 2 study, it is illustrated that the alternative method can make a practical difference in terms of detecting a difference between two groups.

Keywords: ANCOVA, trimmed mean, smoothers, Well Elderly 2 study

## **1** Introduction

For two independent groups, consider the situation where for the *j*th group  $(j = 1, 2) Y_j$ is some outcome variable of interest and  $\mathbf{X} = (X_1, X_2)$  is a vector of two covariates. Let  $M_j(\mathbf{X})$  be some conditional robust measure of location associated with Y given  $\mathbf{X}$ . A basic and well known goal is determining whether the groups differ in terms of  $M_1(\mathbf{X})$  and  $M_2(\mathbf{X})$ . The classic ANCOVA (analysis of covariance) method assumes that

$$Y_j = \beta_{0j} + \beta_1 X_{1j} + \beta_2 X_{2j} + \epsilon, \tag{1}$$

where  $\beta_{0j}$ ,  $\beta_1$  and  $\beta_2$  are unknown parameters estimated via least squares regression and  $\epsilon$ is a random variable having a normal distribution with mean zero and unknown variance  $\sigma^2$ . So the regression planes are assumed to be parallel and the goal is to compare the intercepts. It is well known, however, that there are serious concerns with this approach. First, there is a vast literature establishing that methods based on means, and more broadly least squares regression, are not robust (e.g., Staudte and Sheather, 1990; Marrona et al., 2006; Heritier et al., 2007; Hampel et al., 1986; Huber and Ronchetti, 2009; Wilcox, 2012). A practical consequence is that power can be relatively low even under a small departure from normality. Moreover, even a single outlier can yield a poor fit to the bulk of the points when using least squares regression. Another concern is that two types of homoscedasticity are assumed. The first is that for each group, the variance of the error term does not depend on the value of the covariate. If this assumption is violated the wrong standard error is being used. The second is that the variance of the error term is the same for both groups. Violating these assumptions can result in poor control over the Type I error probability. Yet another fundamental concern with (1) is that the true regression surfaces are assumed to be planes. Certainly, in some situations, this is a reasonable approximation. When there is curvature, using some obvious parametric regression model might suffice. (For example, include a quadratic term.) But it is known that this approach can be inadequate, which has led to a substantial collection of nonparametric regression methods, often called smoothers, for dealing with curvature in a more flexible manner (e.g., Härdle, 1990; Efromovich, 1999; Eubank, 1999; Fox, 2001; Györfi, et al., 2002). Yet another concern is the assumption that the regression surfaces are parallel. One could test the assumption that the slope parameters are equal, but it is unclear when such a test has enough power to detection situations where this assumption is violated to the point that it makes a practical difference.

Here, the model given by (1) is replaced with the less restrictive model

$$Y_j = M_j(\mathbf{X}) + \epsilon_j,\tag{2}$$

where  $M_j(\mathbf{X})$  is some unknown function that reflects some conditional robust measure of location associated with Y given  $\mathbf{X}$ . The random variable  $\epsilon_j$  has some unknown distribution with variance  $\sigma_j^2$ . So unlike the classic approach where it is assumed that

$$M_j(\mathbf{X}) = \beta_{0j} + \beta_{1j}X_1 + \beta_{2j}X_2,$$

no parametric model for  $M_j(\mathbf{X})$  is specified and  $\sigma_1^2 = \sigma_2^2$  is not assumed. In particular it is not assumed that the regression surfaces are parallel. The goal here is to test the global hypothesis

$$H_0: M_1(\mathbf{X}) = M_2(\mathbf{X}), \,\forall \, \mathbf{X} \in \{\mathbf{X}_1, \dots, \mathbf{X}_K\},\tag{3}$$

where  $\mathbf{X}_1, \ldots, \mathbf{X}_K$  are K vectors chosen empirically in a manner to be determined.

For the case of a single covariate, Wilcox (2012, section 11.11.1) describes a method that tests  $H_0$ :  $M_1(X_k) = M_2(X_k)$  for each k, k = 1, ..., K. Roughly, for each  $X_k$ , identify values

of the covariate that are close to  $X_k$  and then compare the groups based on the corresponding Y values using a method based on a robust measure of location. For this special case, it is a relatively simple matter to choose values for the covariate in a manner that is likely to find any differences that might exist.

When dealing with two covariates, Wilcox (2012) suggests a simple extension where the values of the covariate are chosen based on how deeply they are nested within the cloud of covariate values. (This is method M1 in section 2.1 of this paper.) The K points are chosen to include the point in the first group having the deepest half space depth plus the points on the .5 depth contour. (More precise details are given in section 2.) This typically results in a relatively small number of covariate values where the corresponding Y values are compared based on a robust measure of location. Again K tests are performed and the probability of one or more Type I errors can be controlled using some improvement on the Bonferroni method (e.g., Rom, 1990; Hochberg, 1988). But it is not all clear when this relatively simple approach will choose covariate values that are likely to detect true differences between the groups. A way of dealing with this issue is to select a larger collection of covariate values, but if the familywise error rate (the probability of one or more Type I errors) is controlled, power can be relatively poor due to the large number of hypotheses that are tested. Switching to a method that controls the false discovery rate when dealing with dependent test statistics (e.g., Benjamini & Yekutieli, 2001) would suffer from the same concern. So the focus here is on testing (3) using a specified proportion of the deepest covariate values within the cloud of covariate values that are available.

The paper is organized as follows. Section 2 reviews the method in Wilcox (2012) followed by a description of an alternative method aimed at testing (3). Two variations of the alternative method are compared via simulations in Section 3 in terms of both power and their ability to control the Type I error probability. The power of both variations is compared to the power of the method in Wilcox (2012). Section 4 uses data from the Well Elderly 2 study to illustrate that the new method can make a practical difference.

## 2 Description of the Methods

The methods compared here are based in part on a method derived by Yuen (1974) for comparing the population trimmed means of two independent groups. To describe it, momentarily ignore the covariates and consider the goal of testing

$$H_0: \mu_{t1} = \mu_{t2}, \tag{4}$$

the hypothesis that two independent groups have equal population trimmed means. For the *j*th group (j = 1, 2), let  $n_j$  denote the sample size and let  $Y_{(1)j} \leq \ldots \leq Y_{(n_j)j}$  denote the  $Y_{ij}$  values written in ascending order. For some  $0 \leq \gamma < .5$ , the  $\gamma$ -trimmed mean for the *j*th group is

$$\bar{Y}_j = \frac{1}{n - 2g_j} \sum_{i=g_j+1}^{n-g_j} Y_{(i)j},$$

where  $g_j = [\gamma n_j]$  is the greatest integer less than or equal to  $\gamma n_j$ . Here the focus is on  $\gamma = .2$ , a 20% trimmed mean. Under normality, this choice has good efficiency relative to the sample mean (Rosenberger & Gakso, 1983). Moreover, the sample 20% trimmed mean enjoys certain theoretical advantages. First, it has a reasonably high breakdown point, which refers to the proportion of values that must be altered to destroy it. Asymptotic results and simulations indicate that it reduces substantially concerns about the impact of skewed distributions on the probability of a Type I error. This is not to suggest that 20% trimming is always the optimal choice: clearly this is not the case. The only suggestion is that it is a reasonable choice among the many robust estimators that might be used.

Winsorizing the  $Y_{ij}$  values refers to setting

$$W_{ij} = \begin{cases} Y_{(g+1)j}, & \text{if } Y_{ij} \le Y_{(g_j+1)j} \\ Y_{ij}, & \text{if } Y_{(g_j+1),j} < Y_{ij} < Y_{(n-g_j)j} \\ Y_{(n_j-g_j)j}, & \text{if } Y_{ij} \ge Y_{(n-g)j}. \end{cases}$$
(5)

The Winsorized sample mean corresponding to group j is

$$\bar{W}_j = \frac{1}{n_j} \sum W_{ij},$$

and the Winsorized variance is

$$s_{wj}^2 = \frac{1}{n_j - 1} \sum (W_{ij} - \bar{W}_j)^2.$$

Let  $h_j = n_j - 2g_j$ . That is,  $h_j$  is the number of observations left in the *j*th group after trimming. Let

$$d_j = \frac{(n_j - 1)s_{wj}^2}{h_j(h_j - 1)}.$$
(6)

Yuen's test statistic is

$$T_y = \frac{\bar{X}_{t1} - \bar{X}_{t2}}{\sqrt{d_1 + d_2}}.$$
(7)

The null distribution is taken to be a Student's t distribution with degrees of freedom

$$\hat{\nu}_y = \frac{(d_1 + d_2)^2}{\frac{d_1^2}{h_1 - 1} + \frac{d_2^2}{h_2 - 1}}$$

### 2.1 Method M1

Method M1 is described in Wilcox (2012, section 11.11.3). A complete description of the many computational details is not provided here, but an outline of the method is provided with the goal of explaining how it differs from method M2 in the next section.

Let  $\mathbf{X}_{ij}$   $(i = 1, \dots, n_j; j = 1, 2)$  denote the  $n_j$  covariate points corresponding to the *j*th group. Momentarily consider a single covariate point,  $\mathbf{X}$ . Method M1 estimates  $M_j(\mathbf{X})$  using the  $Y_{ij}$  such that the corresponding  $\mathbf{X}_{ij}$  values are close to  $\mathbf{X}$ . More precisely,  $\mathbf{X}_{ij}$   $(i = 1, \dots, n_j; j = 1, 2)$  for the *j*th group, compute a robust covariance matrix based on  $\mathbf{X}_{ij}$   $(i = 1, \dots, n_j)$ . There are many ways of computing a robust covariance matrix with no single estimator dominating. Here a skipped covariance matrix is used, which is computed as follows. For fixed *j*, outliers among the  $\mathbf{X}_{ij}$  values are identified using a projection-type multivariate outlier detection technique (e.g., Wilcox, 2012, section 6.4.9). These outliers are removed and the usual covariance matrix is computed using the remaining data.

Next, compute robust Mahalanobis distances for each covariate point based on the robust covariance matrix just described, with **X** taken to be the center of the data. The point  $\mathbf{X}_{ij}$ is said to be close to **X** if its robust Mahalanobis distance is small, say less than or equal to f, which is called the span. Generally f = .8 performs reasonably well when the goal is to approximate the regression surface. Of course exceptions are encountered, but henceforth f = .8 is assumed. Let  $P_j(\mathbf{x})$  be the subset of  $\{1, 2, \ldots, n_j\}$  that indexes the  $\mathbf{X}_{ij}$  values such that the Mahalanobis distance associated with  $\mathbf{X}_{ij}$  is less than or equal to f. Let  $N_j(\mathbf{X})$  be the cardinality of the set  $P_j(\mathbf{X})$  and let  $M_j(\mathbf{X})$  denote the 20% trimmed mean based on the  $Y_{ij}$  values for which  $i \in P_j(\mathbf{X})$ . Then for the single point  $\mathbf{X}$ , (3) can be tested by applying Yuen's method with the  $Y_{ij}$  values for which  $i \in P_j(X)$  provided both  $N_1(X)$  and  $N_2(X)$  are not too small. Following Wilcox (2012), this is taken to mean that Yuen's method can be applied if simultaneously  $N_1(X) \ge 12$  and  $N_2(X) \ge 12$ , in which case the two groups are said to be comparable at  $\mathbf{X}$ .

Now consider the issue of choosing covariate values where the regression surfaces will be compared. For fixed j, compute how deeply each  $\mathbf{X}_{ij}$  is nested within the cloud of points  $\mathbf{X}_{ij}$  $(i = 1, ..., n_j)$ . This is done with a projection type method that is similar to an approach discussed by Donoho and Gasko (1992). Computational details are described in section 2.2. Consider the deepest point as well as those on the polygon containing the central half of the data. (Liu et al., 1999, call this polygon the .5 depth contour.) Method M1 applies Yuen's method at each of these points provided the regression surfaces are comparable at these points as previously defined. The probability of one or more Type I errors is controlled using the method in Hochberg (1988).

### 2.2 Method M2

There are several positive features of method M1 but some negative features as well. First, Yuen's method for comparing trimmed means has been studied extensively and appears to perform relatively well in terms of both Type I errors and power. The method for choosing the covariate values seems reasonable in the sense that it uses points that are nested deeply within the cloud of covariate points, which reflect situations where the regression surfaces are comparable. Roughly, deeply nested points correspond to situations where the regression surfaces can be estimated in a relatively accurate manner. If a point  $\mathbf{X}$  is not deeply nested in the cloud of covariate values, finding a sufficiently large number of other points that are close to  $\mathbf{X}$  might be impossible.

But a concern about M1 is that perhaps true differences might be missed because of the relatively small number of covariate values that are used. A way of dealing with this possibility is to use all of the covariate points that are deeply nested in the cloud of all covariate points and then test the global hypothesis given by (3). This is the strategy behind method M2.

Method M2 begins by computing the projection depth (e.g., Wilcox, 2012, section 6.2.5) for each  $\mathbf{X}_{i1}$  (the *i*th covariate vector in group 1) in the same manner as method M1. To describe the computational details, momentarily focus on a single  $n \times p$  matrix of data,  $\mathbf{Z}$ . Let  $\hat{\tau}$  be some robust measure of location based on  $\mathbf{Z}$ . For simplicity, the marginal medians (based on the usual sample median) are used. Let

$$\mathbf{U}_i = \mathbf{Z}_i - \hat{\tau}$$

 $(i=1,\ldots,n),$ 

$$C_i = \mathbf{U}_i \mathbf{U}_i$$

For any j  $(j = 1, \ldots, n)$ , let

$$V_{ij} = \sum_{k=1}^{J} U_{ik} U_{jk},$$
  
$$T_{ij} = \frac{V_{ij}}{C_i} (U_{i1}, \dots, U_{ip})$$
(8)

and

$$D_{i\ell} = \|T_{ij}\|,$$

where  $||T_{ij}||$  is the Euclidean norm associated with the vector  $T_{ij}$  (i = 1, ..., n; j = 1, ..., n). Let

$$d_{ij} = \frac{D_{i\ell}}{q_{i2} - q_{i1}},$$

where  $q_{i2}$  and  $q_{i1}$  are estimates of the upper and lower quartiles, respectively, based on  $D_{i1}, \ldots, D_{in}$ . (Here,  $q_{i2}$  and  $q_{i1}$  are based on the so-called ideal fourths; see Friqqe et al., 1989.) The projection distance of  $\mathbf{Z}_j$ , the *j*th row of  $\mathbf{Z}$ , relative to the cloud of points represented by  $\mathbf{Z}$ , is the maximum value of  $d_{ij}$ , say  $p_d(\mathbf{Z}_j)$ , the maximum being taken over  $i = 1, \ldots, n$  (cf. Donoho & Gasko, 1992). Following Liu et al. (1999), the depth of  $\mathbf{Z}_j$  is taken to be

$$P_D(\mathbf{Z}_j) = \frac{1}{1 + p_d(\mathbf{Z}_j)}.$$

Let the set  $\{\mathbf{X}_1, \ldots, \mathbf{X}_K\}$  indicate the deepest half of the points in the first group. Points where the regression surfaces are not comparable (i.e.,  $N_1(\mathbf{X}) < 12$  or  $N_2(\mathbf{X}) < 12$ ) are discarded. Because K can be relatively large, controlling FWE via Hochberg's method seems likely to have relatively low power, which is verified in the simulations in section 4. The reason for choosing the deepest half, rather than some larger proportion, is based on preliminary simulations. Using the deepest half, typically the regression surfaces are comparable at all K points when the sample sizes for both groups are greater than or equal to 50. For a larger proportion of points, this is often not the case. There are, of course, many other variations. Some other measure of the depth might be used or one could use all of the covariate points where the regression surfaces are comparable. The goal here is to find at least one variation that controls the Type I error probability reasonably well and simultaneously offers a power advantage over method M1.

Method M2 begins in the same manner as method M1: test  $H_0: M_1(\mathbf{X}) = M_2(\mathbf{X})$  for each  $\mathbf{X} \in {\mathbf{X}_1, \ldots, \mathbf{X}_K}$ . Label the resulting p-values  $p_1, \ldots, p_K$ . The idea is to test (3) using some function of these K p-values. Perhaps the best-known method for testing some global hypothesis based on p-values is a technique derived by Fisher (1932). But Zaykin et al. (2002) note that the ordinary Fisher product test loses power in cases where there are a few large p-values. They suggest using instead a truncated product method (TPM), which is based on the test statistic

$$W = \prod_{k=1}^{K} p_k^{I(p_i \le \tau)}$$

where I is the indicator function. Setting  $\tau = 1$  yields Fisher's method, but Zaykin et al. suggest using  $\tau = .05$ . Zaykin et al. derive the null distribution of W when all Ktests are independent. But the K tests performed here are not independent simply because  $P_j(\mathbf{X}_k) \cap P_j(\mathbf{X}_\ell), k \neq \ell$ , is not empty. If this dependence among the tests is ignored when computing a critical value for W, control over the Type I error probability is poor. For the dependent case, Zaykin et al. suggest using a bootstrap method, but this results in relatively high execution time for the situation at hand making this approach difficult to study via simulations. Consequently, an alternative approach was used: Proceed as done by Gosset in his derivation of Student's t and assume normality with the goal of determining the  $\alpha$ quantile of W, say w, in which case (3) is rejected at the  $\alpha$  level if  $W \leq w$ . Here, the critical value w was determined via simulations using (2) with  $M_j(\mathbf{X}) \equiv 0$  and  $\epsilon_j$  having a standard normal distribution. More precisely, for each j,  $(Y_{ij}, \mathbf{X}_{ij})$  ( $i = 1, \ldots n_j; j = 1, 2$ ) were generated from a trivariate normal distribution where all correlations are zero. Then W was computed and this process is repeated say B times yielding  $W_1, \ldots, W_B$ . Put these B values in ascending order yielding  $W_{(1)} \leq \ldots \leq W_{(B)}$ . Then w was estimated to be  $W_{(k)}$ , where k is  $\alpha B$  rounded to the nearest integer. Here, B = 4000 was used.

One of many alternative methods is to use instead the test statistic

$$\bar{Q} = \frac{1}{K} \sum_{k=1}^{K} p_k.$$

Unexpectedly, this alternative test statistic performed relatively well, in terms of power, under a shift in location model, as illustrated in section 4. Now reject (3) if  $\bar{Q} \leq q_{\alpha}$ , the  $\alpha$ quantile of  $\bar{Q}$ , which again is determined via simulations in the same manner as the critical value w.

## **3** Simulation Results

As is evident, a basic issue is the impact on the Type I error probability when dealing with non-normal distributions as well as situations where there is an association with the covariate variables. Simulations were used to address this issue with  $n_1 = n_2 = 50$ . Smaller sample sizes, such as  $n_1 = n_2 = 30$ , routinely result in situations where no covariate values can be found where comparisons can be made. That is,  $N_1(\mathbf{X}) < 12$  or  $N_2(\mathbf{X}) < 12$  for all  $\mathbf{X} \in {\mathbf{X}_1, \ldots, \mathbf{X}_K}$ .

Estimated Type I error probabilities,  $\hat{\alpha}$ , were based on 4000 replications. Four types of distributions were used: normal, symmetric and heavy-tailed, asymmetric and light-tailed, and asymmetric and heavy-tailed. More precisely, values for the error term,  $\epsilon_j$  in (2) were generated from one of four g-and-h distributions (Hoaglin, 1985) that contain the standard normal distribution as a special case. If Z has a standard normal distribution, then by definition

$$V = \begin{cases} \frac{\exp(gZ) - 1}{g} \exp(hZ^2/2), & \text{if } g > 0\\ Z \exp(hZ^2/2), & \text{if } g = 0 \end{cases}$$

has a g-and-h distribution where g and h are parameters that determine the first four moments. The four distributions used here were the standard normal (g = h = 0), a symmetric heavy-tailed distribution (h = 0.2, g = 0.0), an asymmetric distribution with relatively light tails (h = 0.0, g = 0.2), and an asymmetric distribution with heavy tails (g = h = 0.2). Table 1 shows the skewness  $(\kappa_1)$  and kurtosis  $(\kappa_2)$  for each distribution. Additional prop-

g	h	$\kappa_1$	$\kappa_2$
0.0	0.0	0.00	3.0
0.0	0.2	0.00	21.46
0.2	0.0	0.61	3.68
0.2	0.2	2.81	155.98

Table 1: Some properties of the g-and-h distribution.

erties of the g-and-h distribution are summarized by Hoaglin (1985). The  $\mathbf{X}_{ij}$  values were generated from a bivariate normal distribution with correlation equal to zero.

Three types of associations were considered. The first two deal with situations where  $Y_{ij} = \beta X_{ij} + \epsilon$ . The two choices for the slope were  $\beta = 0$  and 1. The third type was  $Y_{ij} = X_{ij}^2 + \epsilon$ . These three situations are labeled S1, S2 and S3, respectively. Additional simulations were run where the correlation between the two covariates is .5. But this had almost no impact on the results, so for brevity they are not reported.

Estimated Type I error probabilities are reported in Table 2. Although the seriousness of a Type I error depends on the situation, Bradley (1978) suggests that as a general guide, when testing at the .05 level, the actual level should be between .025 and .075. Based on this criterion, both TPM and the method based on  $\bar{Q}$  provide adequate control over the Type I error probability. A possible appeal of TPM is that when testing at the .05 level, the actual level was estimated to be less than or equal to .050 among all of the situations considered. As for the method based on  $\bar{Q}$ , the estimate exceeds .05 in some situations, particularly when dealing with heavy-tailed distributions (h = .2), the largest estimate being .069.

Table 3 shows the estimated power when for the first group, (2) is replaced by  $Y_1 = M_1(\mathbf{X}) + \epsilon_1 + .5$ . As is evident, method M2 based on  $\bar{Q}$  has the highest power among all of the situations considered and method M1 has the lowest power. For some situations, the higher power using  $\bar{Q}$ , rather than TPM, is presumably due in part to a lower Type I error probability associated with TPM. Note, however, that even in situations where both methods have similar Type I error probabilities,  $\bar{Q}$  has a higher estimated power.

Some additional simulations were run where for the first group,  $Y_j = M_j(\mathbf{X}) + \epsilon_j + .5I_{X_1>0}$ . The idea was that the two versions of method M2 are a function of the pattern of the

g	h	$\mathbf{S}$	Q	TPM
0.0	0.0	1	.050	.050
0.0	0.0	2	.036	.042
0.0	0.0	3	.048	.049
0.0	0.2	1	.061	.046
0.0	0.2	2	.050	.043
0.0	0.2	3	.064	.048
0.2	0.0	1	.055	.046
0.2	0.0	2	.042	.038
0.2	0.0	3	.052	.046
0.2	0.2	1	.064	.047
0.2	0.2	2	.053	.042
0.2	0.2	3	.069	.048

Table 2: Estimated Type I error probabilities when testing at the  $\alpha = .05$  level,  $n_1 = n_2 = 50$ 

Ta	ble 3:	3: Estimated power, $n_1 = n_2 = 50$					
	g	h	$\mathbf{S}$	$\bar{Q}$	$\mathrm{TPM}$	M1	
	0.0	0.0	1	.409	.345	.318	
	0.0	0.0	2	.332	.301	.262	
	0.0	0.0	3	.341	.307	.270	
	0.0	0.2	1	.387	.290	.283	
	0.0	0.2	2	.299	.245	.229	
	0.0	0.2	3	.315	.255	.239	
	0.2	0.0	1	.410	.327	.324	
	0.2	0.0	2	.327	.303	.276	
	0.2	0.0	3	.342	.287	.270	
	0.2	0.2	1	.388	.286	.284	
	0.2	0.2	2	.299	.243	.231	
	0.2	0.2	3	.318	.247	.232	

individual p-values and that perhaps a situation where a difference between the two regression surfaces exists only for a subset of the covariate values might result in TPM having higher power than  $\bar{Q}$ . But again,  $\bar{Q}$  had higher power than TPM. However, results in section 4 indicate that in practice,  $\bar{Q}$  does not dominate TPM in terms of power.

## 4 Illustrations

Data from the Well Elderly 2 study (Clark et al., 2011; Jackson et al., 2009) are used to illustrate that the choice of method can make a practical difference. A general goal in the Well Elderly 2 study was to assess the efficacy of an intervention strategy aimed at improving the physical and emotional health of older adults. A portion of the study was aimed at understanding the impact of intervention on a measure of meaningful activities which was measured with the Meaningful Activity Participation Assessment (MAPA) instrument (Eakman et al., 2010). Two covariates are used here. The first is a measure of depressive symptoms based on the Center for Epidemiologic Studies Depressive Scale (CESD). The CESD (Radloff, 1977) is sensitive to change in depressive status over time and has been successfully used to assess ethnically diverse older people (Lewinsohn et al., 1988; Foley et al., 2002). Higher scores indicate a higher level of depressive symptoms.

The other covariate was the cortisol awakening response (CAR). Saliva samples were taken at four times over the course of a single day: on rising, 30-60 minutes after rising, but before taking anything by mouth, before lunch, and before dinner. Then samples were assayed for cortisol. Extant studies (e.g., Clow et al., 2004; Chida & Steptoe, 2009) indicate that measures of stress are associated with the cortisol awakening response (CAR), which is defined as the change in cortisol concentration that occurs during the first hour after waking from sleep. (CAR is taken to be the cortisol level upon awakening minus the level of cortisol after the participants were awake for about an hour.) The sample size for the control group was 187 and the sample size for the group that received intervention was 228. Based on method M1, no significant differences were found with the familywise error rate set at .05. In contrast, method M2 based on  $\bar{Q}$  rejects (the p-value is .008) and the TPM version of method M2 rejects as well (the p-value is .021). Method M2 indicates that there is a difference between the two groups, but there is the issue of where and by how much. A seemingly natural conclusion is that the groups differ at the point corresponding to the smallest p-value. Here, the minimum p-value occurs for CAR equal to -.218 and CESD equal to 4.00, which correspond to a relatively high increase in cortisol after awakening coupled with a low CESD measure of depressive symptoms. Among the 74 covariate points that were used, 39% of the p-values are less than or equal to .05. More information can be gleaned from a plot of the p-values as well as the estimated difference between the regression surfaces where comparisons were made. Figure 1 shows a plot of the p-values for the situation at hand, which suggests that the strongest evidence for a significant difference occurs when CESD is low regardless of what CAR might be.

Figure 2 shows the estimated difference between the predicted MAPA scores. With one exception, all estimated differences are positive indicating that predicted MAPA scores are higher among the group receiving intervention. The highest estimated differences occur for two subgroups of participants. The first consists of those with a relatively high increase in cortisol after awakening coupled with a low CESD measure of depressive symptoms; the corresponding p-values are relatively low. The second subgroup consists of those participants who have both a relatively high CAR and a relatively high CESD; these points have relatively low p-values as well. Among participants who have relatively high depressive symptoms and relatively low (negative) CAR values, the difference between predicted MAPA scores is small. And as indicated in Figure 1, among these particular participants, highly non-significant results were obtained.

Another dependent variable in the Well Elderly study was the RAND 36-item Health Survey (SF-36), a measure of self-perceived physical health and mental well-being (Hays, 1993; McHorney et al., 1993). Higher scores reflect greater perceived health and well-being. Here, the control group and the experimental group are compared based on subset of the SF-36 items that reflect perceived physical health, again using CESD and the CAR as covariates. The deepest half of the data consisted of 74 covariate points. Despite performing 74 tests, method M1 resulted in a significant result for 6 of the 74 tests that were performed, again with FWE set equal to .05. The TPM version of Method M2 also rejects, but  $\bar{Q}$  does not reject; its p-value is .126.



Figure 1: The p-values associated with the covariate points where the regression surfaces were compared. The plot indicates that the strongest evidence for a significant difference occurs when CESD is low.



Figure 2: The z-axis indicates the estimated difference between the predicted MAPA scores. (Positive values indicate higher predicted MAPA scores for participants in the intervention group.) Estimated differences are relatively high for two subgroups: when the CAR is negative (cortisol increases shortly after awakening) and CESD is relatively low, and when both CESD and the CAR are relatively high.

## 5 Concluding Remarks

In summary, all indications are that both versions of method M2 control the Type I error probability reasonably well. An apparent advantage of the TPM version of method M2 is that it avoids Type I error probabilities greater than the nominal level. But simulations indicate that choice of method can make a practical difference in terms of power, with  $\bar{Q}$ seeming to have an advantage. However, the illustrations based on the Well Elderly 2 study suggest that  $\bar{Q}$  does not dominate in terms of power.

In principle, method M2 is readily extended to more than two covariates. But in practice this might require a relatively large sample size due to the curse of dimensionality: neighborhoods with a fixed number of points become less local as the dimensions increase (Bellman, 1961).

There are many reasonable variations of method M2 and perhaps variations other than those studied here often provide a practical advantage. For example, when using TPM, some other choice for  $\tau$  might be more optimal in practice. In addition, there are many alternative test statistics that might be used that are function of the individual p-values (e.g., Cousins, 2008). As is evident, resolving this issue is non-trivial.

Finally, the R function ancov2COV, which is stored on the author's web page, performs both versions of method M2.

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