國立交通大學

統計學研究所

碩士論文

由變異數分析來評估化學汙染所產生之交互作用

Assessment of Interactions in Chemical Mixtures by ANOVA Method

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中華民國九十九年六月

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摘　要

將化學物品含量分割成區間水準是探討交互作用常用的做法，但不幸的是透過變異數分析方法並不能告訴我們交互作用在某個特定水準是正(synergistic)還是負(antagonistic)。針對分割成區間水準的問題，我們提出一個分解方法去定義主效應與交互作用。我們導出這些效應的(主效應與交互作用)母體型式。至於交互作用的估計和假設檢定也在此篇有所討論。

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SUMMARY

The investigation of interactions is popularly done by classifying the chemicals into interval levels and verifying it through the analysis of variance technique which unfortunately can not tell us if an interaction in a specific level is positive (synergistic) or negative (antagonistic). We propose a decomposition method to define main effects and interactions for these interval levels. Population type formulations of these effects are developed. Estimation and hypothesis testing are also discussed.

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SUMMARY

The investigation of interactions is popularly done by classifying the chemicals into interval levels and verifying it through the analysis of variance technique which unfortunately can not tell us if an interaction in a specific level is positive (synergistic) or negative (antagonistic). We propose a decomposition method to define main effects and interactions for these interval levels. Population type formulations of these effects are developed. Estimation and hypothesis testing are also discussed.

1. Introduction

The toxicological research has long been devoted to assess the risk with exposure to single chemicals in the environment. However, organisms are rarely environmentally exposed to single chemicals in isolation. More typically, exposures occur to multiple chemicals simultaneously. It has long understood that the behavior of one chemical in the body is affected by other chemicals. Recently much of the literature has been investigated on the important area of toxicology of mixed chemicals. One very important study in chemical mixtures is the detection for existence of interactions and characterization of an interaction being synergistic or antagonistic effect. It is important for this study since one may overestimate the true risk associated with the mixtures of chemicals with assumption of additive effects when an antagonistic effects occur and one may underestimate the true risk with the same assumption when a synergistic effect occur.

There are several approaches for studying the chemical interactions. The most common technique in analysis of toxicologic interactions is by classifying the chemicals into interval levels and verifying it through the analysis of variance (ANOVA). This technique can detect the existence of interactions, however, there is no description of the interaction to be given. The isobolographic method has a long history but is recently popular as an alternative method for the study of chemical interactions. Berenbaum (1981) defined

the interaction index through fixed ratio ray designs to detect if the chemical mixture is additive, synergistic or antagonistic. However, this techniques of isobole require experimental iterations to obtain the doses of the studying chemicals that will cause the same magnitude of effect which is not only labor extensive and require a large number of animal experiments but is not applicable in real data analysis. For references of various interaction detecting techniques and discussions, see Rider and LeBlane (2005), Ei-Masri, Reardon and Yang (1997), Charles et. al. (2002) and Mumtaz et al. (1998).

A systematic investigation of mixed chemicals in the environment or workplace is highly desired while the isobolographic method is not applicable for this practical investigation of interaction characterization. It is interesting to see if we can develop an ANOVA like model deserving the benefit of providing valuable insights into the detection of interactions being synergistic or antagonistic that is done by the isobolographic method.

In Section 2, we state the fundamental framework of a grouping ANOVA model for one response variable and several chemical variables and, in Section 3, we introduce the parameter type main effects and a theory for formulation of these effects. In Section 4, we introduce the main concept of interactions and their relationships and, in Section 5, we provide estimation and hypothesis testing for the unknown interactions.

2. Development of Grouping Two Way ANOVA Model

Let Y be the response variable representing the combined effects and X_1 and X_2 be two variables representing, respectively, the exposures or doses of two chemicals. Let $A_1 = (-\infty, a_1], A_2 = (a_1, a_2], ..., A_m = (a_{m-1}, \infty)$ and $B_1 = (-\infty, b_1], B_2 = (b_1, b_2], ..., B_\ell = (b_{\ell-1}, \infty)$ be respectively, the interval types partitions of the spaces of X_1 and X_2 where a_i's and b_j's are two known increasing sequences. We assume that we have observations $\begin{pmatrix} y_1 \\ x_{11} \\ x_{21} \end{pmatrix}, ..., \begin{pmatrix} y_n \\ x_{1n} \\ x_{2n} \end{pmatrix}$. We can distribute the observations $y_1, ..., y_n$ into rectangle sets $A_j \times B_g = \{\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} : x_1 \in A_j, x_2 \in B_g\}$. Let's re-denote the

distributed observations as follows:

	B_1	B_2	$\dots$	B_ℓ
A_1	$y_{11i}, i = 1, ..., n_{11}$	$y_{12i}, i = 1, ..., n_{12}$	$\dots$	$y_{1\ell i}, i = 1, ..., n_{1\ell}$
A_2	$y_{21i}, i = 1, ..., n_{21}$	$y_{22i}, i = 1, ..., n_2$	$\dots$	$y_{2\ell i}, i = 1, ..., n_{2\ell}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
A_m	$y_{m1i}, i = 1, ..., n_{m1}$	$y_{m2i}, i = 1, ..., n_{m2}$	$\dots$	$y_{m\ell i}, i = 1, ..., n_{m\ell}$

What is appropriate definition of the conditional mean of y on rectangle level $A_j \times B_g$? We denote the joint probability density function (pdf) of Y, X_1 and X_2 by f_{y,x_1,x_2} and joint pdf of X_1 and X_2 by f_{x_1,x_2}. Further letting $f_{y|x_1,x_2}(y)$ be the conditional pdf of y given $X_1 = x_1$ and $X_2 = x_2$, the conditional pdf of y given $A_j \times B_g$, denoting by $f_{y|A_j\times B_g}(y)$, can be defined as the average of $f_{y|x_1,x_2}(y)$ with respect to variable X_1 and X_2 on $A_j \times B_g$, i.e.,

$$f_{y|A_j\times B_g}(y) = \int_{A_j\times B_g} f_{y|x_1,x_2}(y) \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} f_{x_1x_2}(x_1, x_2)dx_1dx_2$$

since $\frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} f_{x_1,x_2}(x_1, x_2)$ is the truncated pdf of X_1 and X_2 on $A_j \times B_g$. However, it may be reformulated as

$$\begin{aligned} f_{y|A_j\times B_g}(y) &= E[f_{y|X_1,X_2} I((X_1, X_2) \in A_j \times B_g)] \\ &= \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} \int_{A_j\times B_g} f_{y,x_1,x_2}(y, x_1, x_2)dx_1dx_2. \end{aligned}$$

The group mean (conditional means) of the response variable y given an interval level $A_j \times B_g$ is $\mu_{jg} = \int_{-\infty}^{\infty} y f_{y|A_j\times B_g}(y)dy$ for $j = 1, ..., m, g = 1, ..., \ell$. Furthermore, by defining the error variables as $\epsilon_{jgi} = y_{jgi} - \mu_{jg}$, we may transform the bivariate sample into location models that we call it an interval grouping ANOVA model as

	B_1	B_2	$\dots$	B_ℓ
A_1	$y_{11i} = \mu_{11} + \epsilon_{11i}$ $i = 1, ..., n_{11}$	$y_{12i} = \mu_{12} + \epsilon_{12i}$ $i = 1, ..., n_{12}$	$\dots$	$y_{1\ell i} = \mu_{1\ell} + \epsilon_{1\ell i}$ $i = 1, ..., n_{1\ell}$
A_2	$y_{21i} = \mu_{21} + \epsilon_{21i}$ $i = 1, ..., n_{21}$	$y_{22i} = \mu_{22} + \epsilon_{22i}$ $i = 1, ..., n_2$	$\dots$	$y_{2\ell i} = \mu_{2\ell} + \epsilon_{2\ell}$ $i = 1, ..., n_{2\ell}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
A_m	$y_{m1i} = \mu_{m1} + \epsilon_{m1i}$ $i = 1, ..., n_{m1}$	$y_{m2i} = \mu_{m2} + \epsilon_{m2i}$ $i = 1, ..., n_{m2}$	$\dots$	$y_{m\ell i} = \mu_{m\ell} + \epsilon_{m\ell i}$ $i = 1, ..., n_{m\ell}$

where $\epsilon_{jg1}, ..., \epsilon_{jgn_{jg}}$ are iid random variables with zero means.

Let's define grand mean $\mu = \mu_{..} = \frac{1}{m\ell}\sum_{g=1}^{\ell}\sum_{j=1}^{m}\mu_{jg}$, group means $\mu_{j.} = \frac{1}{\ell}\sum_{g=1}^{\ell}\mu_{jg}, j = 1, ..., m$ and $\mu_{.g} = \frac{1}{m}\sum_{j=1}^{m}\mu_{jg}, g = 1, ..., \ell$. The parameters for classical ANOVA model are $\alpha_j = \mu_{j.} - \bar{\mu}, j = 1, ..., m$, $\beta_g = \mu_{.g} - \bar{\mu}, g = 1, ..., \ell$ and $\gamma_{jg} = \mu_{jg} - (\mu + \alpha_j + \beta_g), j = 1, ..., m, g = 1, ..., \ell$ while we call α_j's the row effects, β_g's the column effects and γ_{jg}'s the interaction effects. The two way classical ANOVA technique applying on this interval grouping problem is assuming the follwoing ANOVA model

$$y_{jgi} = \mu + \alpha_j + \beta_g + \gamma_{jg} + \epsilon_{jgi}, i = 1, ..., n_{jg} \tag{2.1}$$

where $\sum_{j=1}^{m}\alpha_j = \sum_{g=1}^{\ell}\beta_g = \sum_{j=1}^{m}\gamma_{jg} = \sum_{g=1}^{\ell}\gamma_{jg} = 0$.
There are several comments drawn from this ANOVA model for analyzing the health effects caused by chemical mixtures:
(a) Model (2.1) is classically analyzed through the assumption, for error variables ϵ_{jgi}'s, of normality and constant variance. However, this assumption has never been validated by theory.
(b) The fact $\sum_{j=1}^{m}\gamma_{jg} = \sum_{g=1}^{\ell}\gamma_{jg} = 0$ indicates that the term γ_{jg} doesn't characterize the interaction effects at level $A_j \times B_g$ since its sign to be positive or negative is parametrized. With this, α_j and β_g do not, respectively, represent the main effects for chemical variables X_1 and X_2.
(c) Once we have observation of the exposure or dose for the chemicals from the environment, we are expected to estimate or test hypothesis for the interacation to be synergistic or antagonistic at this level. However, this model do not allow us to achieve this aim.

3. Formulation of Grouping Individual Effects

Consider an experiment in an enviroment that there is only one chemical to affect the response variable and we may define the main effect. Assume that we have response variable Y and chemical variable X_1 with a joint distribution as

$$\begin{pmatrix} Y \\ X_1 \end{pmatrix} \sim N_2(\begin{pmatrix} \mu_y \\ \mu_1 \end{pmatrix}, \begin{pmatrix} \sigma_y^2 & \sigma_{1y} \\ \sigma_{y1} & \sigma_1^2 \end{pmatrix}).$$

The population mean of response variable Y on interval level A_j is $\mu_j^a = E[Y|X_1 \in A_j]$. We consider if there are constants μ_{y1} and b such that this population mean μ_j^a can be decomposed uniformly in j as $\mu_j^a = \mu_{y1} + bE[X_1 I(A_j)]$. We then call $\eta_j^a = bE[X_1 I(A_j)]$ the main effect of chemical X_1 at interval level A_j and the population mean decomposition is

$$\mu_j^a = \mu_{y1} + \eta_j^a.$$

The response variable Y and chemical variable X_2 have a joint distribution as

$$\begin{pmatrix} Y \\ X_2 \end{pmatrix} \sim N_2(\begin{pmatrix} \mu_y \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma_y^2 & \sigma_{2y} \\ \sigma_{y2} & \sigma_2^2 \end{pmatrix})$$

Similarly, if there is a decomposition on the interval level conditional mean $\mu_g^b = E[Y|X_2 \in B_g]$ as

$$\mu_g^b = \mu_{y2} + \eta_g^b$$

with $\eta_g^b = dE[X_2 I(B_g)]$ for some constant b, we call η_g^b the main effect of chemical X_2 at interval level B_g.

Following the results derived in Chan et al. (2008), we have the following theorem.

Theorem 3.1. With normality assumption, we have the decomposition

$$\mu_j^a = \mu_{y1} + \eta_j^a$$

with $\mu_{y1} = \mu_y - \rho_{y1}\frac{\sigma_y}{\sigma_1}\mu_1$ and main effects for chemical variable X_1 as

$$\eta_1^a = \rho_{y1}\frac{\sigma_y}{\sigma_1}\mu_1 - \frac{\rho_{y1}\sigma_y}{\sqrt{2\pi}\Phi(\frac{a_1-\mu_1}{\sigma_1})}e^{-\frac{1}{2}(\frac{a_1-\mu_1}{\sigma_1})^2}$$

$$\vdots$$

$$\eta_j^a = \rho_{y1}\frac{\sigma_y}{\sigma_1}\mu_1 + \frac{\rho_{y1}\sigma_y}{\sqrt{2\pi}(\Phi(\frac{a_j-\mu_1}{\sigma_1})-\Phi(\frac{a_{j-1}-\mu_1}{\sigma_1}))}\{e^{-\frac{1}{2}(\frac{a_{j-1}-\mu_1}{\sigma_1})^2} - e^{-\frac{1}{2}(\frac{a_j-\mu_1}{\sigma_1})^2}\}$$
$$, j = 2, ..., m-1 \quad (3.1)$$

$$\vdots$$

$$\eta_m^a = \rho_{y1}\frac{\sigma_y}{\sigma_1}\mu_1 + \frac{\rho_{y1}\sigma_y}{\sqrt{2\pi}(1-\Phi(\frac{a_{m-1}-\mu_1}{\sigma_1}))}e^{-\frac{1}{2}(\frac{a_{m-1}-\mu_1}{\sigma_1})^2}$$

where $\rho_{y1} = \frac{\sigma_{y1}}{\sigma_y \sigma_1}$ is the correlation coefficient between Y and X_1 and Φ is the distribution function of the standard normal distribution.

On the other hand, we have the decomposition

$$\mu_g^b = \mu_{y2} + \eta_g^b$$

with $\mu_{y2} = \mu_y - \rho_{y2}\frac{\sigma_y}{\sigma_2}\mu_2$ and the main effects for chemical variable X_2 as

$$\eta_1^b = \rho_{y2}\frac{\sigma_y}{\sigma_2}\mu_2 - \frac{\rho_{y2}\sigma_y}{\sqrt{2\pi}\Phi(\frac{b_1-\mu_2}{\sigma_2})}e^{-\frac{1}{2}(\frac{b_1-\mu_2}{\sigma_2})^2}$$

$$\vdots$$

$$\eta_g^b = \rho_{y2}\frac{\sigma_y}{\sigma_2}\mu_2 + \frac{\rho_{y2}\sigma_y}{\sqrt{2\pi}(\Phi(\frac{b_g-\mu_2}{\sigma_2})-\Phi(\frac{b_{g-1}-\mu_2}{\sigma_2}))}\{e^{-\frac{1}{2}(\frac{b_{g-1}-\mu_2}{\sigma_2})^2} - e^{-\frac{1}{2}(\frac{b_g-\mu_2}{\sigma_2})^2}\}$$
$$, g = 2, ..., \ell - 1 \qquad (3.2)$$

$$\vdots$$

$$\eta_\ell^b = \rho_{y2}\frac{\sigma_y}{\sigma_2}\mu_2 + \frac{\rho_{y2}\sigma_y}{\sqrt{2\pi}(1-\Phi(\frac{b_{\ell-1}-\mu_2}{\sigma_2}))}e^{-\frac{1}{2}(\frac{b_{\ell-1}-\mu_2}{\sigma_2})^2}$$

where $\rho_{y2} = \frac{\sigma_{y2}}{\sigma_y \sigma_2}$ is the correlation coefficient between Y and X_2.

Let us consider an example to illustrate the main effects where we have Y and X_1 with bivariate normal distribution with mean and covariance matrix, respectively as

$$\mu = \begin{pmatrix} 0 \\ 5 \end{pmatrix}, \Sigma = \begin{pmatrix} 1 & \sigma_{y1} \\ \sigma_{y1} & 1 \end{pmatrix}.$$

We also consider only three levels ANOVA with cuoff points $a_1 = F_{x_1}^{-1}(1/3)$ and $a_2 = F_{x_1}^{-1}(2/3)$. The corresponding main effects associated with σ_{1y} are displayed in the following table.

Table 1. Main effects

	η_1^a	η_2^a	η_3^a
$\sigma_{1y} = 0.2$	0.781	1	1.218
$\sigma_{1y} = -0.2$	−0.781	−1	−1.218
$\sigma_{1y} = 0.4$	1.563	2	2.436
$\sigma_{1y} = 0.6$	2.345	3	3.654

This example shows that the main effects may be all positive or all negative. We then have a theorem for one property of the main effects.

Theorem 3.2. The group main effects η_j^a's satisfy one of the following three orderings:

(a) $\eta_1^a = \eta_2^a = ... = \eta_m^a$ if $\rho_{y1} = 0$,

(b) $\eta_1^a < \eta_2^a < ... < \eta_m^a$ if $\rho_{y1} > 0$,

(c) $\eta_1^a > \eta_2^a > ... > \eta_m^a$ if $\rho_{y1} < 0$.

The conclusions for main effects η_j^b's are similar.

The above theorem indicates one important property that showing monotone main effects is equivalent to showing nonzer ρ_{y1}. This topic belongs to the restricted statistical inferences discussed in Robertson et al. [11] where likelihood ratio tests are the main techniques applied. However, the tests developed in literature are not appropriate to apply on the interval grouping ANOVA model since the assumptions for likelihood ratio tests require known or partial known variances that are not true in this framework.

With the established main effect formulations, we may define a new one way ANOVA model as

A_1	A_2	...	A_m
$y_{1i} = \mu_{y1} + \eta_1^a + \epsilon_{1i}$ $i = 1, ..., n_1$	$y_{2i} = \mu_{y1} + \eta_2^a + \epsilon_{2i}$ $i = 1, ..., n_2$	...	$y_{mi} = \mu_{y1} + \eta_m^a + \epsilon_{mi}$ $i = 1, ..., n_m$

For chemical variable X_2, the one way ANOVA model is

B_1	B_2	...	B_ℓ
$y_{1i} = \mu_{y2} + \eta_1^b + \epsilon_{1i}$ $i = 1, ..., n_1$	$y_{2i} = \mu_{y2} + \eta_2^b + \epsilon_{2i}$ $i = 1, ..., n_2$	...	$y_{\ell i} = \mu_{y2} + \eta_\ell^b + \epsilon_{\ell i}$ $i = 1, ..., n_\ell$

These one way ANOVA models are not identical to the classical one way ANOVA models since their main effects are not restricted to have zero sums.

4. Additive Effects Model and Additive with Interactions Effects Model

The aim in this section is to formulate the interaction effects in an ANOVA model. We assume that the response variable Y and two chemical variables (X_1, X_2) are jointly normal as

$$\begin{pmatrix} Y \\ X_1 \\ X_2 \end{pmatrix} \sim N_3(\begin{pmatrix} \mu_y \\ \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma_y^2 & \sigma_{1y} & \sigma_{2y} \\ \sigma_{y1} & \sigma_1^2 & \sigma_{12} \\ \sigma_{y2} & \sigma_{21} & \sigma_2^2 \end{pmatrix}) \tag{4.1}$$

where $\begin{pmatrix} \mu_y \\ \mu_1 \\ \mu_2 \end{pmatrix}$ is the mean vector and $\begin{pmatrix} \sigma_y^2 & \sigma_{y1} & \sigma_{y2} \\ \sigma_{1y} & \sigma_1^2 & \sigma_{12} \\ \sigma_{2y} & \sigma_{21} & \sigma_2^2 \end{pmatrix}$) is the covariance matrix.

Again, when the level $A_j \times B_g$ conditional mean $\mu_{jg} = E[Y|X_1 \in A_j, X_2 \in B_g]$ may be written as $a + g'E[\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} I(X_1 \in A_j, X_2 \in B_g)]$, we call $\eta_{jg}^{comb} = g'E \begin{pmatrix} X_1 I(A_j) \\ X_2 I(B_g) \end{pmatrix}$ the level $A_j \times B_g$ combined effect for chemicals X_1 and X_2. We define the difference between the combined effect and the sum of two main effects as the interaction as $\eta_{jg} = \eta_{jg}^{comb} - (\eta_j^a + \eta_g^b)$.

Theorem 4.1. With the normality assumption, we have

$$\mu_{jg} = \mu_{y12} + \eta_{jg}^{comb}$$

with $\mu_{y12} = \mu_y - (\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}^{-1} \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}$ and

$$\eta_{jg}^{comb} = \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} (\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}^{-1} \begin{pmatrix} \int_{B_g} \int_{A_j} x_1 f_{x_1,x_2}(x_1, x_2) dx_1 dx_2 \\ \int_{B_g} \int_{A_j} x_2 f_{x_1,x_2}(x_1, x_2) dx_1 dx_2 \end{pmatrix} \tag{4.2}$$

With the above theorem, the response variables y_{jgi} in interval $A_j \times B_g$ may be formulated into an additive effects model.

Definition 4.2. We call the response variable follows the two way ANOVA model if it may be written as

$$y_{jgi} = \mu_{y12} + \eta_j^a + \eta_g^b + \eta_{jg} + \epsilon_{jgi}, i = 1, ..., n_{jg}$$

with $\eta_{jg} = \eta_{jg}^{comb} - (\eta_j^a + \eta_g^b)$ and where η_j^a and η_g^b main effects defined in (3.1) and (3.2) and η_{jg} is called the interaction effect at interval level $A_j \times B_g$.

The combination of chemical variables X_1 and X_2 contributes to toxicity Y through the a common mechanism of the sum of individual effects and

the interaction effect. When interaction $\eta_{jg} > 0$ the interaction is characterized as synergistic and when $\eta_{jg} < 0$ the interaction is characterized as antagonistic.

The combined effects are available estimated from sample drawn from the natural environment. An interesting question is when will the combining effects be the sum of two main effects such that the ANOVA model is additive? Generally, the combination of chemicals variables X_1 and X_2 contributes to toxicity Y through the a common mechanism of the sum of individual effects and the interaction effect.

Let us give an example for explanation of interactions where we consider the three dimensional normal distribution for Y, X_1, X_2 having mean and covariance matrix as

$$\mu = \begin{pmatrix} 10 \\ 5 \\ 5 \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} 1 & 0.5 & 0.5 \\ 0.5 & 1 & \rho \\ 0.5 & \rho & 1 \end{pmatrix}.$$

Here we choose $\rho_{y1} = \rho_{y2} = 0.5 > 0$ because chemicals in our research are health harmful quantified by variable Y. The interval levels are determined with $a_1 = F_{x_1}^{-1}(1/3), a_2 = F_{x_1}^{-1}(2/3)$ and $b_1 = F_{x_2}^{-1}(1/3), b_2 = F_{x_2}^{-1}(2/3)$. In the following table, we display the true interactions for these inetrval levels.

Table 2. Interaction effects

	$\rho = 0.5$	$\rho = -0.4$	$\rho = 0$
η_{11}	-1.383	2.777	0
η_{12}	-1.453	3.072	0
η_{13}	-1.670	3.344	0
η_{21}	-1.449	3.069	0
η_{22}	-1.664	3.301	0
η_{23}	-1.871	3.627	0
η_{31}	-1.663	3.329	0
η_{32}	-1.871	3.640	0
η_{33}	-1.961	3.798	0

There are comments for the results displayed in Table 2:

(a) The interactions are antagonistic when ρ is positive values, are synergistic when ρ is negative values and it is an additive model when ρ is zero.

(b) There is monotone property for the interactions with

$$\eta_{ij} < \eta_{i+1j} \text{ and } \eta_{ij} < \eta_{ij+1}.$$

This is interesting but not available to be theoretically verified.

(c) Being synergistic or antagonistic is determined from the sign of correlation coefficient ρ for variables X_1 and X_2. We have interactions negative if $\rho > 0$ and positive if $\rho < 0$.

For further investigation of interactions, we consider the following design:

$$\Sigma = \begin{pmatrix} 1 & 0.2 & 0.2 \\ 0.2 & 1 & \rho \\ 0.2 & \rho & 1 \end{pmatrix}, \mu = \begin{pmatrix} 10 \\ 5 \\ 5 \end{pmatrix}, p_{jg} = \frac{\eta_{jg}}{\eta_j^a + \eta_g^b}$$

where p_{jg} measures the ratio between interaction and the sum of main effects. The true interactions and interaction to main effects ratio are displayed in Table 3.

Table 3. Interaction effects and their relative proportions

	$\rho = -0.2$	$\rho = -0.4$	$\rho = -0.6$	$\rho = -0.8$
η_{11}	0.416 (0.266)	1.144 (0.732)	2.584 (1.653)	7.120 (4.553)
η_{12}	0.443 (0.249)	1.218 (0.684)	2.756 (1.547)	7.515 (4.217)
η_{13}	0.493 (0.246)	1.335 (0.667)	3.008 (1.504)	7.992 (3.996)
η_{21}	0.460 (0.258)	1.223 (0.686)	2.766 (1.552)	7.579 (4.253)
η_{22}	0.497 (0.248)	1.325 (0.662)	3.016 (1.508)	7.960 (3.980)
η_{23}	0.553 (0.249)	1.455 (0.656)	3.234 (1.458)	8.448 (3.808)
η_{31}	0.507 (0.253)	1.334 (0.667)	3.006 (1.503)	8.030 (4.015)
η_{32}	0.556 (0.250)	1.442 (0.650)	3.202 (1.443)	8.443 (3.806)
η_{33}	0.570 (0.234)	1.513 (0.621)	3.379 (1.386)	8.979 (3.685)

We have two comments drawn from the results showing in Table 3:

(a) The magnitude of the interaction increases when the magnitude of the correlation coefficient increases.

(b) The magnitude of the interaction to main effect ratio also increases when the magnitude of the correlation coefficient increases.

The additive model in this new ANOVA model is defined in the following definition.

Defintion 4.3. A two way ANOVA model is addditive if it may be wriiten as

$$y_{jgi} = \mu_{y12} + \eta_j^a + \eta_g^b + \epsilon_{jgi}, j = 1, ..., m, g = 1, ..., \ell \qquad (3.3)$$

where $i = 1, ..., n_{jg}$.

We note that these individual effects may be obtained from experiments

in laboratories but they are not shown in natural environment unless that there is no combinational effects for chemicals.

Theorem 4.4. Let us assume that X_1 and X_2 are uncorrelated, i.e., $\sigma_{12} = 0$. We have

$$\mu_{jg}^{comb} = \eta_j^a + \eta_g^b \tag{4.3}$$

indicating that $\eta_{jg} = 0$ for al (jg)'s and the two way ANOVA model is additive with

$$\mu_{y12} = \mu_y - \frac{\sigma_{y1}}{\sigma_1^2}\mu_1 - \frac{\sigma_{y2}}{\sigma_2^2}\mu_2.$$

We conduct a simulation with replication number $100,000$ from a normal distribution with mean and covariance matrix, respectively, as

$$\mu = \begin{pmatrix} 0 \\ 5 \\ 5 \end{pmatrix}, \Sigma = \begin{pmatrix} 1 & 0.2 & 0.2 \\ 0.2 & 1 & -0.2 \\ 0.2 & -0.2 & 1 \end{pmatrix}$$

and the levels are setting as $a_1 = \hat{F}_{x_1}^{-1}(0.3)$ and $b_1 = \hat{F}_{x_2}^{-1}(0.3)$. Let the sample means and sample variances for Y, X_1, X_2 be respectively denoted as $\bar{y}, \bar{x}_1, \bar{x}_2$ and S_y^2, S_1^2, S_2^2. Also, we denote the sample correlation coefficients for $\{Y, X_1\}$ and $\{Y, X_2\}$ be respectively denoted as r_{y1} and r_{y2}. The estimates are defined below:

$$\hat{\mu}_{y1} = \bar{y} - r_{y1}\frac{S_y}{S_1}\bar{x}_1, \hat{\mu}_{y2} = \bar{y} - r_{y2}\frac{S_y}{S_2}\bar{x}_2$$

$$\hat{\mu}_1^a = \frac{\sum_{i=1}^n y_i I(-\infty \le x_{1i} \le \hat{F}_{x_1}^{-1}(0.3))}{\sum_{i=1}^n I(-\infty \le x_{1i} \le \hat{F}_{x_1}^{-1}(0.3))}, \hat{\mu}_2^a = \frac{\sum_{i=1}^n y_i I(\hat{F}_{x_1}^{-1}(0.3) \le x_{1i} < \infty)}{\sum_{i=1}^n I(\hat{F}_{x_1}^{-1}(0.3) \le x_{1i} < \infty)}$$

$$\hat{\eta}_j^a = \hat{\mu}_j^a - \hat{\mu}_{y1}, j = 1, 2 \text{ and } \hat{\eta}_g^b = \hat{\mu}_g^b - \hat{\mu}_{y2}, g = 1, 2$$

$$\hat{\mu}_{1jg} = \frac{1}{n}\sum_{i=1}^n x_{1i} I(x_{1i} \in A_j, x_{2i} \in B_g), \hat{\mu}_{2jg} = \frac{1}{n}\sum_{i=1}^n x_{2i} I(x_{1i} \in A_j, x_{2i} \in B_g),$$

$$\hat{\pi}_{jg} = \frac{1}{n}\sum_{i=1}^n I(x_{1i} \in A_j, x_{2i} \in B_g)$$

$$\hat{\mu}_{jg}^{comb} = \frac{1}{\hat{\pi}_{jg}}(\hat{\sigma}_{y1}, \hat{\sigma}_{y2}) \begin{pmatrix} S_1^2 & \hat{\sigma}_{12} \\ \hat{\sigma}_{21} & S_2^2 \end{pmatrix}^{-1} \begin{pmatrix} \hat{\mu}_{1jg} \\ \hat{\mu}_{2jg} \end{pmatrix}, \hat{\eta}_{jg} = \hat{\mu}_{jg}^{comb} - (\hat{\eta}_j^a + \hat{\eta}_g^b)$$

$$MSE_{jg} = \frac{1}{100,000}\sum_{i=1}^{100,000} (\hat{\eta}_{jgi} - \eta_{jg})^2.$$

The simulated interaction estimates and the corresponding MSE's $\begin{pmatrix} \bar{\eta}_{jg} \\ MSE_{jg} \end{pmatrix}$ are displayed in Table 4.

Table 4. Performance of Interaction effect Estimation

sample size	$\eta_{11} = 0.4318$	$\eta_{12} = 0.4937$	$\eta_{21} = 0.4884$	$\eta_{22} = 0.5179$
$n = 30$	$\begin{pmatrix} 0.4003 \\ 0.3526 \end{pmatrix}$	$\begin{pmatrix} 0.4908 \\ 0.4191 \end{pmatrix}$	$\begin{pmatrix} 0.4898 \\ 0.4187 \end{pmatrix}$	$\begin{pmatrix} 0.5198 \\ 0.4352 \end{pmatrix}$
$n = 50$	$\begin{pmatrix} 0.4157 \\ 0.1922 \end{pmatrix}$	$\begin{pmatrix} 0.4889 \\ 0.2117 \end{pmatrix}$	$\begin{pmatrix} 0.4879 \\ 0.2169 \end{pmatrix}$	$\begin{pmatrix} 0.5197 \\ 0.2250 \end{pmatrix}$
$n = 100$	$\begin{pmatrix} 0.4188 \\ 0.0878 \end{pmatrix}$	$\begin{pmatrix} 0.4905 \\ 0.0985 \end{pmatrix}$	$\begin{pmatrix} 0.4891 \\ 0.0985 \end{pmatrix}$	$\begin{pmatrix} 0.5219 \\ 0.1016 \end{pmatrix}$

5. Detection of Interactions

The practical problem in interaction detection is that we have a data set of variabes Y, X_1 and X_2 and we want to detect if the interaction on some interval level of X_1 and X_2 is positive or greater than some specified critical point. This can be answered by statistical inferences for the unknown population interaction on that level while it is very popular to discuss this through the hypothesis testing. However, the point estimation can also achieve this purpose.

The first we want to investigate is the efficiencies of point estimation in detection of existence of positive interactions. That is, we evaluate the probability of positive interaction when there exists positive interactions. We now evaluate, in a number of $100,000$ replications, the power in observing positive interaction by estimation when the true interaction η_{jgk} is some value greater than zero as

$$\frac{1}{100,000} \sum_{k=1}^{100,000} I(\hat{\eta}_{jgk} > 0 | \eta_{jg} > 0)$$

for various situations of positive inetractions where $\hat{\eta}_{jgk}$ is estimate at kth replication. The simulation will have data drawn from the following distribution

$$\begin{pmatrix} y \\ x_1 \\ x_2 \end{pmatrix} \sim N(\begin{pmatrix} 0 \\ 5 \\ 5 \end{pmatrix}, \begin{pmatrix} 1 & 0.2 & 0.2 \\ 0.2 & 1 & r \\ 0.2 & r & 1 \end{pmatrix}).$$

We consider ANOVA model of two levels with cutoff points $a_1 = \hat{F}_{X_1}^{-1}(0.3)$ and $b_1 = \hat{F}_{X_2}^{-1}(0.3)$.

The simulated levels are displayed in Table 5 where n represents the sample size.

Table 5. Confidence level performance

sample size	η_{11}	η_{12}	η_{21}	η_{22}
$r = -0.2$	(0.4318)	(0.4937)	(0.4884)	(0.5179)
$n = 30$	0.7587	0.7964	0.7966	0.8147
$n = 50$	0.8435	0.8784	0.8788	0.8968
$n = 100$	0.9391	0.9623	0.9621	0.9726
$r = -0.4$	(1.1366)	(1.3042)	(1.3179)	(1.3786)
$n = 30$	0.9374	0.9557	0.9560	0.9625
$n = 50$	0.9850	0.9911	0.9905	0.9931
$n = 100$	0.9994	0.9998	0.9998	0.9998
$r = -0.6$	(2.5216)	(2.9593)	(2.9624)	(3.0788)
$n = 30$	0.9938	0.9938	0.9939	0.9941
$n = 50$	0.9993	0.9994	0.9994	0.9994
$n = 100$	1	1	1	1

We have two comments drawn from the results in Table 5:

(a) For interpretation, the powers are $0.7587, 0.8435, 0.9391$ respectively for sample sizes being $30, 50, 100$ when $\eta_{11} = 0.4318$ with $r = -0.2$. The power values are all more than 0.75 with true interaction value being 0.43 or more.

(b) The power increases when the sample size is larger. This satisfies our expectation.

One question is more interesting in showing the interaction estimate to be higher than a critical point, saying 0.5 when the true interaction is some value c more than 0.5. This can be evaluated in the following index,

$$\frac{1}{100,000} \sum_{k=1}^{100,000} I(\hat{\eta}_{jgk} > 0.5 | \eta_{jg} = c).$$

We display the simulated results in the following table.

Table 6. Confidence level performance

sample size	η_{11}	η_{12}	η_{21}	η_{22}
$r=-0.27(c)$	(0.6240)	(0.7180)	(0.7355)	(0.7688)
$n=30$	0.5097	0.5743	0.5752	0.5925
$n=50$	0.5550	0.6289	0.6296	0.6567
$n=100$	0.6212	0.7219	0.7236	0.7623
$n=500$	0.8003	0.9363	0.9358	0.9664
$r=-0.33(c)$	(0.8521)	(0.9587)	(0.9771)	(1.0175)
$n=30$	0.6244	0.6951	0.6966	0.7140
$n=50$	0.7049	0.7782	0.7782	0.8028
$n=100$	0.8159	0.8908	0.8912	0.9161
$n=500$	0.9861	0.9986	0.9986	0.9996
$r=-0.43(c)$	(1.2864)	(1.4728)	(1.4949)	(1.5593)
$n=30$	0.8022	0.8072	0.8574	0.8724
$n=50$	0.8951	0.9350	0.9349	0.9457
$n=100$	0.9742	0.9901	0.9896	0.9932
$n=500$	1	1	1	1

The simulated results show that the estimation technique is satisfactory for observing that the interaction estimate reaches the risk point.

In the next, we consider a hypothesis testing $H_0 : \eta_{jg} = \eta_0$ vs $H_1 : \eta_{jg} > \eta_0$. Suppose that we have observation $\begin{pmatrix} y_i \\ x_{1i} \\ x_{2i} \end{pmatrix}$ from a normal distribution of (4.1). We consider a test for this hyppothesis as

$$\text{rejecting } H_0 \text{ if } \frac{\hat{\eta}_{jg} - \eta_0}{s_{jg}} \geq h_\alpha$$

where $\hat{\eta}_{jg}$ is an estimate of η_{jg}, s_{jg} is scale estimate of $\hat{\eta}_{jg}$ for standardization and h_α is the level α critical point. For power performance evaluation, we conduct this data generation m times and we have corresponding estimates $\hat{\eta}^c_{jg}$ and $s^c_{jg}, c = 1, ..., m$, the power is estimated as

$$p = \frac{1}{m} \sum_{c=1}^{m} I(\frac{\hat{\eta}^c_{jg} - \eta_0}{s^c_{jg}} \geq h_\alpha). \tag{5.2}$$

We then need to decide scale estimate s_{jg} and level α critical point h_α. The distribution theory of interaction estimator of interaction η_{jg} does not support in using normal distribution to construct h_α.

We propose the following bootstrapping process technique:

(a) We resample $k = 1000$ times from this data set and compute the resulted estimates $\hat{\eta}^c_{jg}$.
(b) The scale parameter estimate is defined as $s^2_{jg} = \frac{1}{1000}\sum_{c=1}^{1000}(\hat{\eta}^c_{jg} - \bar{\eta}_{jg})^2$.
(c) The level α critical point h_α is defined as $k100(1-\alpha)\%$ order statistic of $\frac{\hat{\eta}^c_{jg}-\eta_0}{s_{jg}}$.
(d) We resample 2000 samples from (4.1) and we denote the interaction estimates be denoted as $\hat{\eta}^c_{jg}, c = 1, ..., 2000$. The simulated power is

$$p = \frac{1}{2000}\sum_{c=1}^{2000} I(\frac{\hat{\eta}^c_{jg} - \eta_0}{s^c_{jg}} \geq h_\alpha).$$

Unfortunately there is no fixed value h_α making the probabilities of type I error for different sample sizes equal. Hence, we search h_α for each size n so that the level of significance is fixed to be 0.05 and then we evaluate the powers when H_1 is true with some given values of η_{jg}. The simulated results are displayed in Table 7 where the true value is $\eta_0 = 0.49778$.

Table 7. Power performance when significance level is fixed

sample size	H_0	$\eta_0^* = 0.8626$	$\eta_0^* = 1.3255$	$\eta_0^* = 2.0048$	$\eta_0^* = 3.0169$
$n = 50$	$0.0512(h_\alpha = 1.2815)$	0.154	0.3796	0.656	0.8845
$n = 100$	$0.049(h_\alpha = 1.3105)$	0.244	0.635	0.918	0.995
$n = 500$	$0.049(h_\alpha = 1.645)$	0.623	0.995	1	1

The results are not very satisfactory. But this is the first step in developing interaction detection for ANOVA like model.

6. ANOVA Analysis for Unknown Quantiles

It is desired to develop the large sample theory for the estimator of the interactions so that we may construct distribution based test for hypothesis of interactions. However, we have tried but it is difficult to accomplish this task. In the following, we display a result on the asymptotic distribution for the group means that will help in deriving asymptotic distributions of main effects.

Practically the quantile functions $F_x^{-1}(\alpha_j)'s$ are unknown and then the interval levels $A_j's$ need to be estimated. We also assume that there is a

random sample $\begin{pmatrix} Y_1 \\ X_1 \end{pmatrix}, ..., \begin{pmatrix} Y_N \\ X_N \end{pmatrix}$ is available from this distribution. It is generally define the cutoff points as quantiles of the observations of grouping variable X and a monotone and disjoint interval levels as

$$\hat{A}_0 = (-\infty, \hat{F}_x^{-1}(\alpha_1)], \hat{A}_1 = (\hat{F}_x^{-1}(\alpha_1), \hat{F}_x^{-1}(\alpha_2)], ..., \hat{A}_k = (\hat{F}_x^{-1}(\alpha_k), \infty). \tag{6.1}$$

By letting $\bar{Y} = \frac{\sum_{i=1}^n Y_i}{n}, \bar{Y}_j = \frac{\sum_{i=1}^n Y_i I(\hat{F}_x^{-1}(\alpha_j) \le X_i \le \hat{F}_x^{-1}(\alpha_{j+1}))}{\sum_{i=1}^n I(\hat{F}_x^{-1}(\alpha_j) \le X_i \le \hat{F}_x^{-1}(\alpha_{j+1}))}, j = 0, 1, ..., k,$ we define two parameters estimates $\hat{\mu}_y = \bar{Y}$ and $\hat{\mu}_j^a = \bar{Y}_j$, the main effect estimate is setting as

$$\hat{\eta}_j^a = \bar{Y}_j - \hat{\mu}_y. \tag{6.2}$$

The following theorem provides a step for constructing tests for testing the main effects.

Theorem 6.1.

$$\sqrt{n}(\bar{Y}_j - \mu_{A_j}) = \frac{1}{\alpha_{j+1} - \alpha_j} n^{-1/2} \sum_{i=1}^{n} (\gamma_j(Y_i, X_i) - E[\gamma_j(Y, X)]) + o_p(1)$$

with $\gamma_j(Y, X) = \begin{cases} E(Y - \mu_y | F_X^{-1}(\alpha_j)) & \text{if } X \le F_X^{-1}(\alpha_j) \\ Y - \mu_y & \text{if } F_X^{-1}(\alpha_j) < X < F_X^{-1}(\alpha_{j+1}) \\ E(Y - \mu_y | F_X^{-1}(\alpha_{j+1})) & \text{if } X \ge F_X^{-1}(\alpha_{j+1}) \end{cases}$

and $\mu_{A_j} = \mu_y + \frac{1}{\alpha_{j+1} - \alpha_j} E[Y - \mu_y I(F_X^{-1}(\alpha_j) \le X \le F_X^{-1}(\alpha_{j+1}))]$.

Corollary 6.2. $\sqrt{n}(\bar{Y}_j - \mu_{A_j})$ is asymptotically normal with distribution $N(0, \sigma^2(\alpha_j, \alpha_{j+1}))$ where

$$\sigma^2(\alpha_j, \alpha_{j+1}) = \frac{1}{(\alpha_{j+1} - \alpha_j)^2} \{\alpha_j [E(Y - \mu_y | F_X^{-1}(\alpha_j))]^2 + (1 - \alpha_{j+1}) [E(Y - \mu_y | F_X^{-1}(\alpha_{j+1}))]^2$$
$$+ E[(Y - \mu_y)^2 I(F_X^{-1}(\alpha_j) \le X \le F_X^{-1}(\alpha_{j+1})] + (\alpha_j E[Y - \mu_y | F_X^{-1}(\alpha_j)]$$
$$+ (1 - \alpha_{j+1}) E[Y - \mu_y | F_X^{-1}(\alpha_{j+1})] + E[(Y - \mu_y) I(F_X^{-1}(\alpha_j) \le X \le F_X^{-1}(\alpha_{j+1}))])^2\}.$$

From this theory, we may expect that the main effects are asymptotically normal that help in constructing tests for hypotheses of main effects. However, in our try, we found that the estimators of interactions are quite like products of two correlated normal variables so that their asymptotic distributions are unable to develop since the correlations are two complicated.

7. Appendix

The following proof is rewritten from Chan, et. al. (2008).

Proof of Theorem 3.1: From the well known property $E(y|x_1) = \mu_y + \frac{\rho_{y1}\sigma_y}{\sigma_1}(x_1 - \mu_1)$ where x_1 is a given value, we have

$$\begin{aligned}
\mu_1^a &= \int_{-\infty}^{\infty} y f_{y|A_1}(y)dy \\
&= \int_{-\infty}^{\infty} y \frac{1}{P(X_1 \le a_1)} \int_{-\infty}^{a_1} f(y, x_1)dx_1 dy \\
&= \frac{1}{P(X_1 \le a_1)} \int_{-\infty}^{a_1} [\int_{-\infty}^{\infty} y f(y|x_1)dy] f_{x_1}(x_1)dx_1 \\
&= \frac{1}{P(X_1 \le a_1)} \int_{-\infty}^{a_1} [\mu_y + \frac{\rho_{y1}\sigma_y}{\sigma_1}(x_1 - \mu_1)] f_{x_1}(x_1)dx_1 \\
&= \frac{1}{P(X_1 \le a_1)} \{\mu_y P(X_1 \le a_1) + \frac{\rho_{y1}\sigma_y}{\sigma_1}[\int_{-\infty}^{a_1} x_1 f_{x_1}(x_1)dx_1 - \mu_1 P(X_1 \le a_1)]\} \\
&= \mu_{y1} + \rho_{y1}\frac{\sigma_y}{\sigma_1}\mu_1 - \frac{1}{\Phi(\frac{a_1-\mu_1}{\sigma_1})}\frac{\rho_{y1}\sigma_y}{\sqrt{2\pi}} e^{-\frac{1}{2}(\frac{a_1-\mu_1}{\sigma_1})^2}
\end{aligned}$$

from the fact that $\int_{-\infty}^{a_1} x f_x(x)dx = \mu_x P(x \le a_1) - \frac{\sigma_x}{\sqrt{2\pi}} e^{-\frac{1}{2}(\frac{a_1-\mu_x}{\sigma_x})^2}$. The other μ_{A_j}'s may be derived analogously and are skipped. We here note that the main effects, showing in this proof, may also be represented as $\eta_j^a = \frac{\sigma_{y1}}{\sigma_1^2}\frac{\int_{A_j} x_1 f_1(x_1)dx_1}{P(X_1 \in A_j)}$ and $\eta_g^b = \frac{\sigma_{y2}}{\sigma_2^2}\frac{\int_{B_g} x_2 f_2(x_2)dx_2}{P(X_2 \in B_g)}$. □

Proof of Theorem 3.2: Next, from the proof of Theorem 3.1, we may see that the group means for this interval grouping ANOVA model have an alternative form that can be expressed as the followings:

$$\begin{aligned}
\eta_1^a &= \rho_{y1}\frac{\sigma_y}{\sigma_1}\int_{A_1} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_1)}dx_1 \\
\eta_2^a &= \rho_{y1}\frac{\sigma_y}{\sigma_1}\int_{A_2} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_2)}dx_1 \\
&\vdots \\
\eta_{m-1}^a &= \rho_{y1}\frac{\sigma_y}{\sigma_1}\int_{A_{m-1}} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_{m-1})}dx_1 \\
\eta_m^a &= \rho_{y1}\frac{\sigma_y}{\sigma_1}\int_{A_m} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_m)}dx_1
\end{aligned}$$

where $A_1, ..., A_m$ is a monotone sequence of intervals forming a partition on the support of the grouping variable. Since $\frac{f_{x_1}(x_1)}{P(X_1 \in A_j)}$ is a truncated pdf on space A_j, then we have

$$\int_{A_1} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_1)} dx_1 < \int_{A_2} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_2)} dx_1 < ... < \int_{A_m} x_1 \frac{f_{x_1}(x_1)}{P(X_1 \in A_m)} dx_1$$

and possible values of ρ_{y1} must fall in one of the 3 sets $[-1, 0), \{0\}$, or $(0, 1]$ which leads to the theorem. □

Proof of Theorem 4.1:

$$\mu_{jg} = \int_{-\infty}^{\infty} y f_{y|A_j \times B_g}(y) dy$$

$$= \int_{-\infty}^{\infty} y \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} \int_{B_g} \int_{A_j} f(y, x_1, x_2) dx_1 dx_2 dy$$

$$= \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} \int_{B_g} \int_{A_j} [\int_{-\infty}^{\infty} y f(y|x_1, x_2) dy] f_{x_1, x_2}(x_1, x_2) dx_1 dx_2$$

$$= \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} \int_{B_g} \int_{A_j} [\mu_y + (\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}^{-1} (\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} - \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix})]$$

$$f_{x_1, x_2}(x_1, x_2) dx_1 dx_2$$

$$= \mu_{y12} + \frac{1}{P(\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \in A_j \times B_g)} (\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}^{-1}$$

$$\begin{pmatrix} \int_{B_g} \int_{A_j} x_1 f_{x_1, x_2}(x_1, x_2) dx_1 dx_2 \\ \int_{B_g} \int_{A_j} x_2 f_{x_1, x_2}(x_1, x_2) dx_1 dx_2 \end{pmatrix}$$

which leads to the result in Theorem 4.1. □

Proof of Theorem 4.4: Assuming that X_1 and X_2 are uncorrelated, they are independent in this normal case and the formula is derived from the

followings:

$$\mu_{jg} = \mu_y + \frac{1}{P(X_1 \in A_j)P(X_2 \in B_g)}(\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}^{-1} \begin{bmatrix} \int_{A_j}\int_{B_g} x_1 f_1(x_1) f_2(x_2) dx_1 dx_2 \\ \int_{A_j}\int_{B_g} x_2 f_1(x_1) f_2(x_2) dx_1 dx_2 \end{bmatrix}$$

$$- (\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}^{-1} \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}$$

$$= \mu_y + \frac{1}{P(X_1 \in A_j)P(X_2 \in B_g)}(\sigma_{y1}, \sigma_{y2}) \begin{bmatrix} \frac{1}{\sigma_1^2} P(X_2 \in B_g) \int_{A_j} x_1 f_1(x_1) dx_1 \\ \frac{1}{\sigma_2^2} P(X_1 \in A_j) \int_{B_g} x_2 f_2(x_2) dx_2 \end{bmatrix}$$

$$- [\frac{\sigma_{y1}}{\sigma_1^2}\mu_1 + \frac{\sigma_{y2}}{\sigma_2^2}\mu_2]$$

$$= \mu_y + \frac{\sigma_{y1}}{\sigma_1^2}(\frac{\int_{A_j} x_1 f_1(x_1) dx_1}{P(X_1 \in A_j)} - \mu_1) + \frac{\sigma_{y2}}{\sigma_2^2}(\frac{\int_{B_g} x_2 f_2(x_2) dx_2}{P(X_2 \in B_g)} - \mu_2)$$

$$= \mu_{y12} + \eta_j^a + \eta_g^b. \quad \square$$

Proof of Theorem 6.1. Sample group mean may formulated as $\bar{Y}_j = \mu_y + \frac{\sum_{i=1}^n (Y_i - \mu_y) I(\hat{F}_x^{-1}(\alpha_j) \le X_i \le \hat{F}_x^{-1}(\alpha_{j+1}))}{\sum_{i=1}^n I(\hat{F}_x^{-1}(\alpha_j) \le X_i \le \hat{F}_x^{-1}(\alpha_{j+1}))}$. The trimmed mean $\bar{Y}_j$ may be re-written as

$$\sqrt{n}(\bar{Y}_j - \mu_y) = [n^{-1}\sum_{i=1}^n I(\hat{F}_x^{-1}(\alpha_j) \le X_i \le \hat{F}_x^{-1}(\alpha_{j+1}))]^{-1}[n^{-1/2}\sum_{i=1}^n (Y_i - \mu_y)$$

$$(I(X_i \le \hat{F}_x^{-1}(\alpha_{j+1})) - I(X_i \le F_x^{-1}(\alpha_{j+1}))) - n^{-1/2}\sum_{i=1}^n (Y_i - \mu_y)(I(X_i \le$$

$$\hat{F}_x^{-1}(\alpha_j)) - I(X_i \le F_x^{-1}(\alpha_j))) + n^{-1/2}\sum_{i=1}^n (Y_i - \mu_y) I(F_x^{-1}(\alpha_j) \le X_i \le F^{-1}(\alpha_{j+1}))] \tag{7.1}$$

By letting $T_x = \sqrt{n}(\hat{F}_x^{-1}(\alpha) - F_x^{-1}(\alpha))$, we see that $I(X_i \le \hat{F}_x^{-1}(\alpha)) = I(X_i \le F_X^{-1}(\alpha) + n^{-1/2}T_x)$ with $T_x = \sqrt{n}(\hat{F}_x^{-1}(\alpha) - F_x^{-1}(\alpha))$.

$$n^{-1/2}\sum_{i=1}^n (Y_i - \mu_y)[I(X_i \le F_X^{-1}(\alpha) + n^{-1/2}T_n) - I(X_i \le F_X^{-1}(\alpha)]$$
$$= E(Y - \mu_y | F_X^{-1}(\alpha)) f_X(F_X^{-1}(\alpha)) T_n + o_p(1) \tag{7.2}$$

for any sequence $T_n = O_p(1)$.

$$\sqrt{n}(\hat{F}_x^{-1}(\alpha) - F_x^{-1}(\alpha)) = f_X^{-1}(F_X^{-1}(\alpha)) n^{-1/2} \sum_{i=1}^n (\alpha - I(X_i \le F_X^{-1}(\alpha))) + o_p(1). \tag{7.3}$$

Moreover, we also have

$$n^{-1}\sum_{i=1}^{n} I(\hat{F}_x^{-1}(\alpha_j) \le X_i \le \hat{F}_x^{-1}(\alpha_{j+1})) = \alpha_{j+1} - \alpha_j + o_p(1). \qquad (7.4)$$

Imposing the results in (7.2)-(7.3) into (7.1), we have the theorem. □

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