國 立 交 通 大 學

統計學研究所

碩士論文

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A Statistical Study of Interactions

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中華民國一百零一年六月

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摘要

我們引入統計觀點來制訂 isobole，並用它來制訂正(synergistic)效果和負(antagonistic)效果。isobole 的點估計也被引入，且通過點估計鑑定交互作用檢定力的模擬研究已經完成。模擬結果顯示該方法是統計上的滿意。

關鍵字：協同作用; 交互作用; isobole

A Statistical Study of Interactions

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SUMMARY

We introduce the statistical formulation of isobole and use it to formulate synergistic interaction effect and antagonistic interaction effect. Point estimation of isobole is also introduced and simulation study for power of identification of interaction through this point estimator has been performed.
The simulation results show that this approach is statistically satisfactory.

Key words: Antagonistic effect; interaction effect; isobole; synergistic effect

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本論文的完成承蒙指導教授陳鄰安老師的諄諄教誨與指導，在此致上最誠摯的謝意。從一開始老師就很有耐心的指導，一步一步帶領著我們去完成這未知的論文，遇到問題時老師總是不厭其煩的為我解惑。不但如此，老師更是常告誡我們一些人生道理，教導我們人生要有目標和態度，非常榮幸自己能成為陳鄰安教授的學生。

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張家榕 謹誌于

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1. Introduction

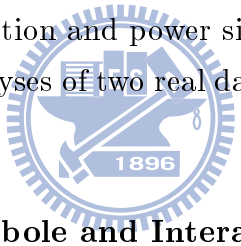
The toxicological research has long been devoted to assess the risk with exposure to single chemicals in the environment. However, organisms are rarely environmentally exposed to single chemicals in isolation. More typically, exposures occur to multiple chemicals simultaneously. It has long understood that the behavior of one chemical in the body is affected by other chemicals. Recently most researches in the literature have 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.

There is widespread confusion about the concept and methods for evaluating a possible interaction in biological or environmental system. Among the popular approaches, analysis of variance (ANOVA) is designed with restriction of zero sum interactions between levels. This technique can detect the existence of interactions, however, there are no descriptions of signs and magnitudes of the interaction to be given. The linear regression approach considers the presence of interactions when product terms $x_1^{c_1}x_2^{c_2}$ existed in the statistical model that is criticized for several grounds (see Rothman (1974), Rothman, Greenland and Walker (1980) and Geenland (1993)). For one concern, the presence or absence of interaction with the usage of linear regression practically depends on the model one chooses. Hence, it often happen in analyzing one real data that interaction exists when one model is applied but not exist when the others are used. For another concern, Mauderly and Samet (2009) pointed out that statistical tests for the presence of interaction have low statistical power.

The isobologram, popularized by Loewe (1928, 1953), is presently the most widely used method as an alternative method for the study of chemical or biological interactions. An isobole forms a dose-response relation for chemical mixtures to obtain the same effect. Results of chemical mixtures are considered to be performed through deterministic experiment (Berenbaum (1981), Rider and LeBlane (2005), Ei-Masri, Reardon and Yang (1997)).

Unfortunately this very convincing technique require experimental iterations which is not only labor extensive and require a large number of animal experiments. Efforts of mathematical formulation for isobole has been done by many authors (see, for examples, Ei-Masri, Reardon and Yang (1997), Lam (1993) and Suhnel (1992)). Incorporating the experimental variation, response surface model has widely been applied for isobole study (Greco, Bravo and Parsons (1995), Sorensen et al. (2007)). This requires models for various chemical mixtures again sharing the disadvantage of experimental labor cost. To get rid of these disadvantages, we consider an isobole of interest as an unknown (unique) curve in terms of parameters of distribution of response and independent variables.

The aim in this paper is modeling the isobole from a probability distribution involving the chemical variables and response variable. This draws us a mechanism to define the so-called zero interaction through concept of statistical independence and use it to present interactions. Modeling the interaction under the normal distribution is introduced in Section 2 and methods of detection of interaction and power simulation of these methods are provided in Section 3. Analyses of two real data sets are given in Section 4.



2. Statistical Model for Isobole and Interaction Analysis

We consider two chemicals A and B for study of their combined effect. In experiment, each combination (x_1, x_2) of dosages of A and B generates a combined effect y_{x_1,x_2}. The plot of magnitude of combined effect as a function of dosages of two chemicals is a three dimensional surface. The plot of dosages of two chemicals that produces a fixed single point of effect magnitude (effect level) is a two dimensional curve, called an isobole. Isobole may forms a straight line or other curves. Given an effect level ℓ and choosing the two end points $(x_{1\ell}, 0)$ and $(0, x_{2\ell})$ such that $y_{x_{1\ell},0} = y_{0,x_{2\ell}} = \ell$, the following straight line

$$IB_0(\ell) = \{\begin{pmatrix} ax_{1\ell} \\ (1-a)x_{2\ell} \end{pmatrix} : 0 \le a \le 1\} \tag{2.1}$$

is called the "line of additivity" or the no-interaction isobole. Now, an isobole is the curve of combination (x_1, x_2)'s of equl effect ℓ as

$$IB(\ell) = \{\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} : y_{x_1,x_2} = \ell, x_1 > 0, x_2 > 0\}, \tag{2.2}$$

the sizes (x_1, x_2) of chemicals A and B that produce equal effect ℓ. Roughly it is conjectured that there are three types of isoboles showing in Figure 1.

Figure 1 is here

We say that there is synergistic effect if the isobole lies below the line of no-interaction and there is antagonistic effect if the isobole lies above the line of no-interaction.

Systematic effect investigation of chemical mixtures is usually done through laboratory study to control the combined effect without uncertainty. This suffers the construction of isobole with requiring a very large number of combinations in experiment and is not practical to investigate interaction effect when uncertainty through other uncontrolled factors exists in the environment or workplace (Ei-masri, Reardon and Yang (1997)).

We consider statistical approach of isobole that allows the combined effect with uncertainty from uncontrolled factors. Let X_1 and X_2 be independent variables representing magnitudes of chemicals and Y be the response variable with normal distribution as

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

With statistical model, the mean combined effect is represented as the conditional mean given $X_1 = x_1$ and $X_2 = x_2$ as

$$\mu(x_1, x_2) = \mu_y + (\sigma_{y1}, \sigma_{y2}) \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}^{-1} \begin{pmatrix} x_1 - \mu_1 \\ x_2 - \mu_2 \end{pmatrix}. \tag{2.3}$$

Given value ℓ, the effect level ℓ isobole is defined as

$$IB(\ell) = \{\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} : \mu(x_1, x_2) = \ell\}.$$

In the classical isobole study, effect level ℓ may be determined by the analyst when the experiment of sampling is done in laboratory. But in environment study, it is determined by distributional parameters, generally unknown. Extended from the classical isobole of (2.1), we solve statistical isobole's endpoints by solving $x_{1\ell} = x_1$ and $x_{2\ell} = x_2$ from $\mu(x_1, 0) = \mu(0, x_2) = \ell$ for x_1 and x_2 given that

$$x_{1\ell} = \frac{\sigma_{y2}\sigma_1^2 - \sigma_{y1}\sigma_{12}}{\sigma_{y1}\sigma_2^2 - \sigma_{y2}\sigma_{12}}\mu_2 + \frac{\sigma_1^2\sigma_2^2 - \sigma_{12}^2}{\sigma_{y1}\sigma_2^2 - \sigma_{y2}\sigma_{12}}(\ell - \mu_y) + \mu_1$$

and (2.4)

$$x_{2\ell} = \frac{\sigma_{y1}\sigma_2^2 - \sigma_{y2}\sigma_{12}}{\sigma_{y2}\sigma_1^2 - \sigma_{y1}\sigma_{12}}\mu_1 + \frac{\sigma_1^2\sigma_2^2 - \sigma_{12}^2}{\sigma_{y2}\sigma_1^2 - \sigma_{y1}\sigma_{12}}(\ell - \mu_y) + \mu_2.$$

We then have derived a statistical isobole.

Theorem 2.1. With $x_{1\ell}$ and $x_{2\ell}$ in (2.4), an isobole is a straight line that may be represented as

$$IB(\ell) = \{\begin{pmatrix} ax_{1\ell} \\ (1-a)x_{2\ell} \end{pmatrix} : 0 \le a \le 1\}. \tag{2.5}$$

We say that this isobole contains combinations $\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} ax_{1\ell} \\ (1-a)x_{2\ell} \end{pmatrix}, 0 \le a \le 1$.

The definition of synergism and antagonism depends on how the concept of no-interaction is defined. Among the three basic criteria (summation, independence and isobole) of interaction evaluation (Suhnel (1992)), we are allowed to joining with this isobole approach with the independence approach that, under the normal assumption, the no-interaction (zero interaction) isobole is the one with $\sigma_{12} = 0$. By letting $x_{1\ell 0} = x_{1\ell}$ and $x_{2\ell 0} = x_{2\ell}$ in (2.4) subjected to $\sigma_{12} = 0$, then we have the following theorem.

Theorem 2.2.. The no-interaction line may be formulated as

$$\begin{aligned} IB_0(\ell) &= \{\begin{pmatrix} ax_{1\ell 0} \\ (1-a)x_{2\ell 0} \end{pmatrix} : 0 \le a \le 1\} \\ &= \{\begin{pmatrix} a[\frac{\sigma_{y2}\sigma_1^2}{\sigma_{y1}\sigma_2^2}\mu_2 + \frac{\sigma_1^2}{\sigma_{y1}}(\ell - \mu_y) + \mu_1] \\ (1-a)[\frac{\sigma_{y1}\sigma_2^2}{\sigma_{y2}\sigma_1^2}\mu_1 + \frac{\sigma_2^2}{\sigma_{y2}}(\ell - \mu_y) + \mu_2] \end{pmatrix} : 0 \le a \le 1\} \end{aligned} \tag{2.6}$$

We follow the definition of interaction effect for classical isobole to this statistical model.

Definition 2.3. We say that there is synergistic effect if $IB(\ell)$ lies below $IB_0(\ell)$ and there is antagonistic effect if $IB(\ell)$ lies above $IB_0(\ell)$.

However, Both isoboles $IB(\ell)$ and $IB_0(\ell)$ are generally unknown since they involve unknown distributional parameters. Hence statistical inferences should be done for detection of interaction that require observation from the underlying distribution.

For observations $\begin{pmatrix} y_i \\ x_{1i} \\ x_{2i} \end{pmatrix}, i = 1, ..., n$, we denote mean estimate $\begin{pmatrix} \hat{\mu}_y \\ \hat{\mu}_1 \\ \hat{\mu}_2 \end{pmatrix} = \begin{pmatrix} \bar{y} \\ \bar{x}_1 \\ \bar{x}_2 \end{pmatrix}$ where $\bar{y}, \bar{x}_1$ and $\bar{x}_2$ are, respectively, the sample means of variables y, x_1 and x_2 and covariance matrix estimate $\begin{pmatrix} \hat{\sigma}_y^2 & \hat{\sigma}_{y1} & \hat{\sigma}_{y2} \\ \hat{\sigma}_{1y} & \hat{\sigma}_1^2 & \hat{\sigma}_{12} \\ \hat{\sigma}_{2y} & \hat{\sigma}_{21} & \hat{\sigma}_2^2 \end{pmatrix} = \begin{pmatrix} s_y^2 & s_{y1} & s_{y2} \\ s_{1y} & s_1^2 & s_{12} \\ s_{2y} & s_{21} & s_2^2 \end{pmatrix} = \frac{1}{n-1}\sum_{i=1}^{n} \begin{pmatrix} y_i - \bar{y} \\ x_{1i} - \bar{x}_1 \\ x_{2i} - \bar{x}_2 \end{pmatrix} \begin{pmatrix} y_i - \bar{y} \\ x_{1i} - \bar{x}_1 \\ x_{2i} - \bar{x}_2 \end{pmatrix}'$. We then estimate the conditional mean by

$$\hat{\mu}(x_1, x_2) = \bar{y} + (s_{y1}, s_{y2}) \begin{pmatrix} s_1^2 & s_{12} \\ s_{21} & s_2^2 \end{pmatrix}^{-1} \begin{pmatrix} x_1 - \bar{x}_1 \\ x_2 - \bar{x}_2 \end{pmatrix}.$$

We define estimates of $x_{1\ell}$ and $x_{2\ell}$, respectively, as

$$\hat{x}_{1\ell} = \frac{s_{y2}s_1^2 - s_{y1}s_{12}}{s_{y1}s_2^2 - s_{y2}s_{12}}\bar{x}_2 + \frac{s_1^2 s_2^2 - s_{12}^2}{s_{y1}s_2^2 - s_{y2}s_{12}}(\ell - \bar{y}) + \bar{x}_1$$

and (2.7)

$$\hat{x}_{2\ell} = \frac{s_{y1}s_2^2 - s_{y2}s_{12}}{s_{y2}s_1^2 - s_{y1}s_{12}}\bar{x}_1 + \frac{s_1^2 s_2^2 - s_{12}^2}{s_{y2}s_1^2 - s_{y1}s_{12}}(\ell - \bar{y}) + \bar{x}_2$$

Then the estimator of population isobole IB is

$$\hat{IB}(\ell) = \{ \begin{pmatrix} a\hat{x}_{1\ell} \\ (1-a)\hat{x}_{2\ell} \end{pmatrix} : 0 \le a \le 1 \}. \tag{2.8}$$

and the no-interaction line may be formulated as

$$\begin{aligned} \hat{IB}_0(\ell) &= \{\begin{pmatrix} a\hat{x}_{1\ell 0} \\ (1-a)\hat{x}_{2\ell 0} \end{pmatrix} : 0 \le a \le 1\} \\ &= \{\begin{pmatrix} a[\frac{s_{y2}s_1^2}{s_{y1}s_2^2}\bar{x}_2 + \frac{s_1^2}{s_{y1}}(\ell-\bar{y}) + \bar{x}_1] \\ (1-a)[\frac{s_{y1}s_2^2}{s_{y2}s_1^2}\bar{x}_1 + \frac{s_2^2}{s_{y2}}(\ell-\bar{y}) + \bar{x}_2] \end{pmatrix} : 0 \le a \le 1\} \end{aligned} \tag{2.9}$$

where $\hat{x}_{1\ell 0} = \hat{x}_{1\ell}$ and $\hat{x}_{2\ell 0} = \hat{x}_{2\ell}$ by setting $s_{12} = 0$.

3. Isobole based Interaction Identification

With statistical formulation of isobole, three interaction detection problems may be considered. First, given an effect level ℓ, is the unknown isobole $IB(\ell)$ synergistic or antagonistic? Unlike the laboratory test, the effect level ℓ is determined in practical environment that is altered not only in location but also in time. This leads to the second problem of prediction at mean (μ_1, μ_2) and the third problem of prediction at sample point (x_1, x_2).

We start from the first problem. Since isoboles $IB(\ell)$ and $IB_0(\ell)$ are straight lines, differences of two end points as $c_{1\ell} = x_{1\ell} - x_{1\ell 0}$ and $c_{2\ell} = x_{2\ell} - x_{2\ell 0}$ may be used to detect interaction. With careful re-arrangements, we have

$$c_{1\ell} = \frac{\sigma_{12}(\sigma_{y2}^2\sigma_1^2 - \sigma_{y1}^2\sigma_2^2)}{(\sigma_{y1}\sigma_2^2 - \sigma_{y2}\sigma_{12})\sigma_{y1}\sigma_2^2}\mu_2 + (\frac{\sigma_1^2\sigma_2^2 - \sigma_{12}^2}{\sigma_{y1}\sigma_2^2 - \sigma_{y2}\sigma_{12}} - \frac{\sigma_1^2}{\sigma_{y1}})(\ell - \mu_y)$$

and (3.1)

$$c_{2\ell} = \frac{\sigma_{12}(\sigma_{y1}^2\sigma_2^2 - \sigma_{y2}^2\sigma_1^2)}{(\sigma_{y2}\sigma_1^2 - \sigma_{y1}\sigma_{12})\sigma_{y2}\sigma_1^2}\mu_1 + (\frac{\sigma_1^2\sigma_2^2 - \sigma_{12}^2}{\sigma_{y2}\sigma_1^2 - \sigma_{y1}\sigma_{12}} - \frac{\sigma_2^2}{\sigma_{y2}})(\ell - \mu_y).$$

We call $c_{1\ell}$ and $c_{2\ell}$ the interaction indices. In case that $c_{1\ell} = c_{2\ell}$, two isoboles $IB(\ell)$ and $IB_0(\ell)$ are parallel.

Based on Definition 2.3 and (3.1), interaction detection for combinations of x_1 and x_2 in isobole $IB(\ell)$ can be described below:

(a) Isobole $IB(\ell)$ contains combinations with synergistic effects if $c_{1\ell} < 0$ and $c_{2\ell} < 0$.

(b) Isobole $IB(\ell)$ contains combinations with antagonistic effects if $c_{1\ell} > 0$ and $c_{2\ell} > 0$.

When it ocuurs that $c_{1\ell} > 0$ and $c_{2\ell} < 0$ or $c_{1\ell} < 0$ and $c_{2\ell} > 0$, interactions exist for all combinations of x_1 and x_2 on the isobole besides the single intersection point. However, each combination (x_1, x_2) to be synergistic or antagonistic requires to be further verified.

Pictures of isoboles are displayed in the following figure.

Figure 2 of synergistic effect and antagonistic effect

The above procedure can detect the case that $IB(\ell)$ is above or below $IB_0(\ell)$. When the isobole $IB(\ell)$ and $IB_0(\ell)$ intersect somewhere, the detection is slightly complicated and we suggest to conduct the detection through the next approach.

With modeling the interactions through probability distribution, it is the interesting to propose statistical methods for interaction of identification. Among the statistical inferences, the point estimation is the basic technique and can be derived straight forward through the formulas in (3.1).

With efficient estimator of conditional mean $\mu(x_1, x_2)$, we expect that corresponding estimates of interaction indices $c_{1\ell}$ and $c_{2\ell}$ defined as

$$\begin{aligned}\hat{c}_{1\ell} =& \frac{s_{12}(s_{y2}^2 s_1^2 - s_{y1}^2 s_2^2)}{(s_{y1}s_2^2 - s_{y2}s_{12})s_{y1}s_2^2}\bar{x}_2 + (\frac{s_1^2 s_2^2 - s_{12}^2}{s_{y1}s_2^2 - s_{y2}s_{12}} - \frac{s_1^2}{s_{y1}})(\ell - \bar{y}) \\ \hat{c}_{2\ell} =& \frac{s_{12}(s_{y1}^2 s_2^2 - s_{y2}^2 s_1^2)}{(s_{y2}s_1^2 - s_{y1}s_{12})s_{y2}s_1^2}\bar{x}_1 + (\frac{s_1^2 s_2^2 - s_{12}^2}{s_{y2}s_1^2 - s_{y1}s_{12}} - \frac{s_2^2}{s_{y2}})(\ell - \bar{y}).\end{aligned} \tag{3.2}$$

may provide efficient tool in interaction detection. Induced rule for identification of interactions based on interaction index estimates is as follows:

(a) There is synergistic effect if $\hat{c}_{1\ell} < 0$ and $\hat{c}_{2\ell} < 0$.

(b) There is antagonistic effect if $\hat{c}_{1\ell} > 0$ and $\hat{c}_{2\ell} > 0$.

The advantage of interpreting the isobole's concept of interaction through statistical model is that it requires only a data for estimation of distributional parameters.

With the above rule of interaction identification, there are four categories for the result computed from one data set that are displayed in Table 1.

Table 1. Correctness and Errors in interaction detection

	$\text{sign}(\hat{c}_{1\ell}) = \text{sign}(c_{1\ell})$	$\text{sign}(\hat{c}_{1\ell}) \neq \text{sign}(c_{1\ell})$
$\text{sign}(\hat{c}_{2\ell}) = \text{sign}(c_{2\ell})$	Correct	Error I
$\text{sign}(\hat{c}_{2\ell}) \neq \text{sign}(c_{2\ell})$	Error I	Error II

Error II is the most serious one since two signs of interactions are predicted with error.

To evaluate the power of correctness in detection, we consider the following setting of joint distribution:

$$\begin{pmatrix} Y \\ X_1 \\ X_2 \end{pmatrix} \sim N_3\left(\begin{pmatrix} 1 \\ 2 \\ 3 \end{pmatrix}, \begin{pmatrix} 2 & 0.7 & 0.7 \\ 0.7 & 2 & \sigma_{12} \\ 0.7 & \sigma_{12} & 2 \end{pmatrix}\right)$$

and set $c_{1\ell} = c_{2\ell} = c$ for some values c, positive and negative for being, respectively, antagonistic and synergistic. With replication number m, the power of identification of interaction is defined as

$$\pi = \frac{1}{m}\sum_{j=1}^{m} I(\text{sign}(\hat{c}_{1\ell}) = \text{sign}(c_{1\ell}), \text{sign}(\hat{c}_{2\ell}) = \text{sign}(c_{2\ell})).$$

With $m = 1,000$ and some sample sizes, the simulated results of power π are displayed in Tables 2 and 3.

Table 2. Power performance for interaction detection through estimation

	$c = -1.029$	$c = -1.286$	$c = -1.929$
$\sigma_{12} = -0.9$			
$n = 30$	0.517	0.601	0.736
$n = 50$	0.635	0.748	0.860
$n = 100$	0.816	0.875	0.959
$\sigma_{12} = 0.9$			
$n = 30$	0.641	0.695	0.774
$n = 50$	0.679	0.775	0.899
$n = 100$	0.829	0.918	0.977

Table 3. Power performance for interaction detection through estimation

	$c = 0.286$	$c = 0.571$	$c = 0.857$	$c = 1.143$
$\sigma_{12} = -0.4$				
$n = 30$	0.398	0.690	0.791	0.805
$n = 50$	0.506	0.806	0.892	0.904
$n = 100$	0.651	0.945	0.971	0.974
$\sigma_{12} = 0.4$	$c = -0.286$	$c = -0.571$	$c = -0.857$	$c = -1.143$
$n = 30$	0.350	0.630	0.747	0.790
$n = 50$	0.428	0.771	0.866	0.902
$n = 100$	0.594	0.907	0.975	0.970

We conclude the following from Tables 2 and 3:

(a) The results show that the detection power is increasing when sample size increases.

(b) It also shows that the power increases when value c lies away of zero.

(c) The power performance showing in these two tables is satisfactory.

Let (t_1, t_2) be fixed values for (X_1, X_2). We consider a process below for detection of interaction at this obaservation:

(a) The predicted interaction level of the isobole that this sample point lies is $\ell = \hat{\mu}(t_1, t_2)$.

(b) Given this predicted effect level ℓ, a combination $(X_1, X_2) = (t_1, t_{20})$ lying on no-interaction isobole of level ℓ may be solved as

$$t_{20} = -\frac{s_{y1}s_2^2}{s_{y2}s_1^2}(t_1 - \bar{x}_1) + \bar{x}_2 + \frac{s_2^2}{s_{y2}}(\ell - \bar{y}). \tag{3.3}$$

(c) Rule for predicting the interaction effect on this isobole:

There is synergistic effect at (t_1, t_2) if $t_2 < t_{20}$

There is no-interaction effect at (t_1, t_2) if $t_2 = t_{20}$

There is antagonistic effect at (t_1, t_2) if $t_2 > t_{20}$

For mean interaction detection, let $(t_1, t_{20}) = (\bar{x}_1, \bar{x}_2)$. The rule in (c) above predicts the interaction effect when $(X_1, X_2) = (\mu_1, \mu_2)$. For interaction detection at an observation, let $(t_1, t_{20}) = (x_1, x_2)$. The rule in (c) above predicts the interaction effect when $(X_1, X_2) = (x_1, x_2)$.

4. Data Analyses

A data of size $n = 20$ for studying blood pressure with some explanatory variables has been considered in Daniel (1999, p484-485) where variables in this data are listed below:

$$
\begin{aligned}
Y &= \text{ mean arterial blood pressure (mm Hg)} \\
X_1 &= \text{ age (years)} \\
X_2 &= \text{ weight (kg)} \\
X_3 &= \text{ body surface area (sq m)} \\
X_4 &= \text{ duration of hypertension (years)} \\
X_5 &= \text{ basal pulse (beats/ min)} \\
X_6 &= \text{ measure of stress.}
\end{aligned}
$$

The sample mean and covariance matrix are displayed below:

$$
\begin{pmatrix} \hat{\mu}_y \\ \hat{\mu}_3 \\ \hat{\mu}_5 \end{pmatrix} = \begin{pmatrix} 114.0 \\ 1.998 \\ 69.6 \end{pmatrix}, \hat{\Sigma} = \begin{pmatrix} 31.02 & 0.675 & 15.67 \\ 0.675 & 0.019 & 0.253 \\ 15.67 & 0.253 & 15.22 \end{pmatrix}
$$

Next, we display the estimated interaction indices $\hat{c}_{1\ell}$ and $\hat{c}_{2\ell}$ as functions of ℓ in Figure 3.

Figure 3 is here

For $\ell > 185.4352$, there are antagonistic effect since $\hat{c}_{1\ell} > 0$ and $\hat{c}_{2\ell} > 0$. However, we can not conclude the effect for that $\ell < 185.4352$ since signs of $\hat{c}_{1\ell}$ altered. We then draw a picture of $I\hat{B}$ and $I\hat{B}_0$ for $\ell = 160$ and 200 in Figure 4.

Figure 4 is here

Both level $\ell = 160$ and 200 correspond to isobole of antagonistic effect that may not be seen in Figure 3 based on $\hat{c}_{1\ell}$ and $\hat{c}_{2\ell}$.

We consider the problem of interaction prediction(detection) when an observation (x_3, x_5) of independent variables (X_3, X_5) is given. For this example, we evaluate all observations of $n = 20$ samples. So, for each observation point (x_3, x_5), we conduct the process of interaction prediction and

we display in Table 4 the predicted interaction level ℓ and the quantity x_{50} such that (x_3, x_{50}) lies on the level ℓ no-interaction isobole. The results (S for synergistic effect and A for antagonistic effect) of interaction detections for all sample points (X_3, X_5) are also displayed.

Table 4. Interaction study for arterial blood pressure data

prediction	ℓ	$x_3(x_5)$	$x_5(x_3)$	Effect
(x_3, x_5)				
$1.75, 63$	103.49	1.890	67.68	S
$2.1, 70$	116.9	2.072	69.08	A
$1.98, 72$	114.9	1.952	71.08	A
$2.01, 73$	116.2	1.963	71.42	A
$1.89, 72$	112.4	1.882	71.74	A
$2.25, 71$	121.5	2.176	68.54	A
$2.25, 69$	120.4	2.202	67.42	A
$1.9, 66$	109.2	1.968	68.28	S
$1.83, 69$	109.1	1.874	70.48	S
$2.07, 64$	112.6	2.127	65.91	S
$2.07, 74$	118.4	1.996	71.55	A
$1.98, 71$	114.3	1.965	70.52	A
$2.05, 68$	114.4	2.059	68.31	S
$1.92, 67$	110.3	1.970	68.70	S
$2.19, 76$	122.8	2.064	71.80	A
$1.98, 69$	113.1	1.991	69.39	S
$1.87, 62$	106.1	1.997	66.24	S
$1.9, 70$	111.5	1.916	70.54	S
$1.88, 71$	111.6	1.887	71.25	S
$2.09, 75$	119.6	1.999	71.97	A
$(\bar{x}_3, \bar{x}_5)$		$\bar{x}_3$	$\bar{x}_{50}$	
$1.998, 69.6$	114	1.998	69.6	N

We have several comments for the displayed results:

(a) The predicted interaction levels ℓ (column 2) for all observations (x_3, x_5) are larger than the sample mean, 114.0, of response variable y indicates that independent variables X_3 and X_5 make significant contribution on the mean conditional effect of y given (x_3, x_5). Their differences between ℓ's and 4978.4 give the sizes of contributions.

(b) Some observations show synergistic effects and some show antagonistic effects. However, the sample mean $(\bar{x}_1, \bar{x}_2)$ gives no-interaction effect.

In concerning the need for hospital labor, Bowerman and O'Connell (1990) conduct this analysis on a data set of size $n = 17$ through linear regression model. The response variable Y represents the monthly labor hours. Among the explanatory variables, we first choose X_1, the average daily patient load, and X_5, the average length of patients' stay in days for analysis. We first consider explanatory variables X_1 and X_5. The mean estimate and covariance estimate are, respectively,

$$\begin{pmatrix} \hat{\mu}_y \\ \hat{\mu}_1 \\ \hat{\mu}_5 \end{pmatrix} = \begin{pmatrix} 4978.4 \\ 148.27 \\ 5.89 \end{pmatrix}, \hat{\Sigma} = \begin{pmatrix} 32852004 & 937770 & 5414 \\ 937770 & 27554 & 181.92 \\ 5414 & 181.92 & 2.666 \end{pmatrix}$$

For this set of observations, we also compute their corresponding predicted interaction effects that are displayed in Table 5.

Table 5. Interaction study for monthly labor hours data

prediction	ℓ	$x_1(x_5)$	$x_5(x_1)$	Effect
(x_1, x_5)				
$15.57, 4.45$	762.7	110.5	6.041	S
$44.02, 6.92$	521.2	−43.94	5.445	A
$20.42, 4.28$	1034	128.6	6.094	S
$18.74, 3.9$	1173	155.4	6.190	S
$49.2, 5.5$	1468	68.62	5.825	S
$44.92, 4.6$	1784	131.6	6.053	S
$55.48, 5.62$	1640	66.52	5.085	S
$59.28, 5.15$	2032	106.0	5.934	S
$94.39, 6.18$	2804	67.29	5.725	A
$128.0, 6.15$	4082	106.6	5.791	A
$96, 5.88$	3023	91.64	5.806	A
$131.4, 4.88$	4883	205.9	6.129	S
$127.2, 5.5$	4396	154.6	5.959	S
$252.9, 7.0$	8318	180.3	5.785	A
$409.2, 10.78$	12181	68.31	5.067	A
$463.7, 7.05$	16204	409.1	6.135	A
$510.2, 6.35$	18321	513.0	6.398	S
$(\bar{x}_1, \bar{x}_5)$		$\bar{x}_1$	$\bar{x}_{50}$	
$148.27, 5.89$	4978	148.2	5.893	N

This analysis shows that most observations give synergistic effects and only a few give antagonistic effects.

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Figure 1. Classical interaction by isobole

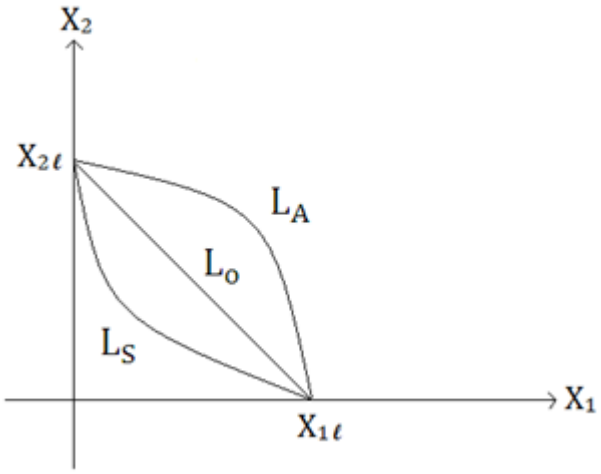

Figure 2. Possible statistical isoboles

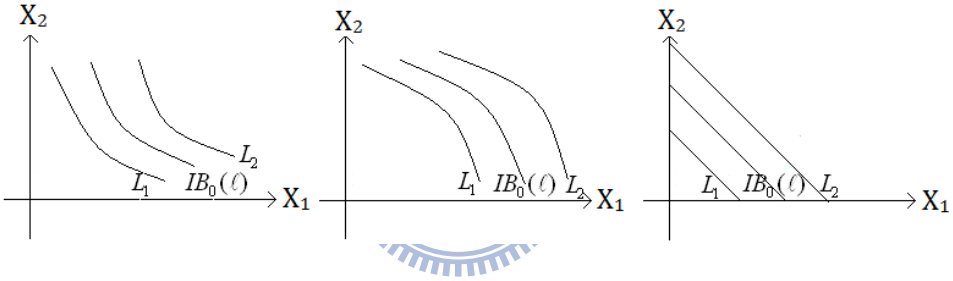

Figure 3. Lines $\hat{c}_{1\ell}$ and $\hat{c}_{2\ell}$

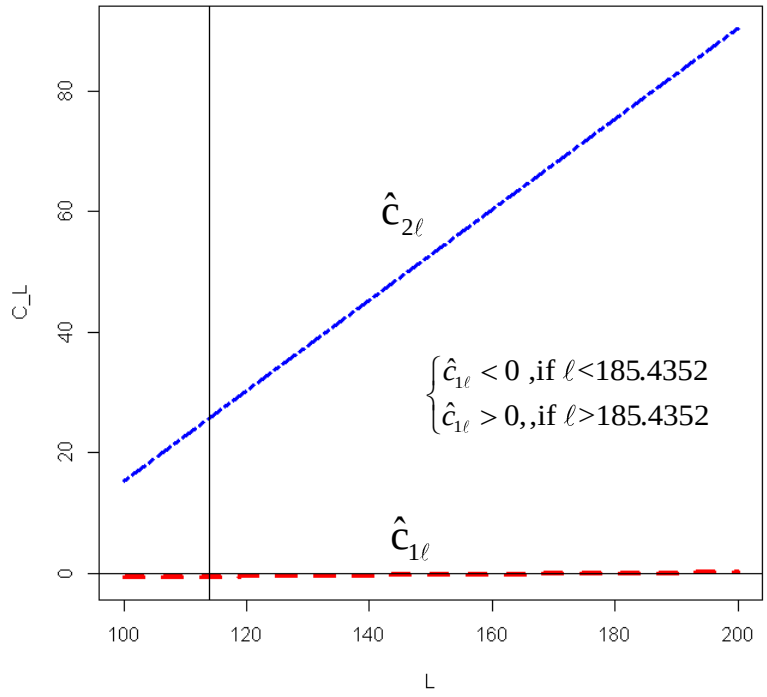

Figure 4. Isobole $\hat{IB}$ and $\hat{IB}_0$

(a) ℓ =160 (b) ℓ =200