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STATISTICAL PROPERTIES OF RATIO  
MEASURES BASED ON THE PRE- AND  
POST-DATA

TAKAHARU YAMABE

MARCH 2012



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MEASURES BASED ON THE PRE- AND  
POST-DATA

A dissertation submitted to  
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BY  
TAKAHARU YAMABE

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# Abstract

In a clinical trial, we sometimes evaluate the treatment effect based on the ratio measures which requires pre- and post-data of treatment intervention. As a measure of ratio, percent change from baseline ( $PC$ ) which is defined as  $PC = (X_2 - X_1)/X_1$  is often used in a trial. And, symmetrized percent change ( $SPC$ ) which is defined as  $SPC = (X_2 - X_1)/(X_1 + X_2)$  is sometimes also used in trials (Berry, 1989). Though the statistical properties of  $PC$  were investigated on condition that pre- and post-data are assumed as bivariate normal distribution in past research,  $PC$  is said to have some difficulties to apply the statistical analysis based on the parametric methods (Asakura *et al.*, 2011; Senn & Julious, 2009). On the other hand,  $SPC$  is said to have good performance based on a limited simulation, but is said to have difficulties in interpretation (Berry, 1989; Berry & Ayers, 2006).

As I mentioned in the above paragraph,  $PC$  and  $SPC$  as the ratio measures are investigated in some aspects. However, past findings are based on limited research such as the investigations of  $PC$  assumed as the bivariate normal distribution in pre- and post-data. In a clinical trial, data follows not only normal distribution but also positive skew distribution such as log-normal distribution or more positive skew distribution than log-normal (Maruo *et al.*, 2008). Therefore, we need to investigate the statistical properties of two ratio measures,  $PC$  and  $SPC$ , in various distributions of pre- and post-data. In this paper, we declare the probability distribution function (pdf) of two ratio measures, percent change ( $PC$ ) and symmetrized percent change ( $SPC$ ), and evaluate the relationship between the skewness of two ratio measures and the distribution of pre- and post-data. Next, we evaluate the performance of two ratio measures to detect the treatment difference within pre- and post-data or between two groups based on the simulation and propose how to apply two measures in various situations. In addition, we declare the relationship between ratio measure ( $SPC$ ) and coefficient of variation ( $CV$ ).



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# Notations

notation	definition/example	explanation
general		
$E[\cdot]$	$E[X]$	expectation
$\text{Var}[\cdot]$	$\text{Var}[X]$	variance
$\xi_{\cdot}$	$\xi_{0.5}$	percentile
distribution		
$X_i$		random variable on pre- and post-data
$x_i$		observed value on pre- and post-data
$\lambda_i$		shape parameter (transformation parameter)
$\mu_i$		location parameter
$\sigma_i$		scale parameter
BN	$\text{BN}(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$	bivariate normal distribution
BLN	$\text{BLN}(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$	bivariate log normal distribution
BPN	$\text{BPN}(\lambda_1, \lambda_2, \mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$	bivariate power-normal distribution
$f(\cdot)$	$f_{\text{BPN}}(x_1, x_2)$	probability density function (pdf)
$F(\cdot)$	$F_{\text{BPN}}(x_1, x_2)$	cumulative distribution function (cdf)
$\phi(\cdot)$	$\phi(x)$	pdf of standardized normal distribution
$\Phi(\cdot)$	$\Phi(x)$	cdf of standardized normal distribution



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# Section 1

## Introduction

### 1.1 Background

The designs with pre- and post-data fall under the broad category of paired data analysis. Paired data arise when the same experimental unit, such as a person or laboratory animal, is measured on some variable in two different timings or at the same time under different testing conditions. A type of the design with pre- and post-data is when subjects receive a treatment intervention prior to the measurement of the post-data, after collecting the pre-data. And the question of interest is either that there are differences among groups or changes in an individual over time. For example, an object of a clinical trial is to compare the treatment groups with intervention, and it is said that pre-defined measures for evaluating the intervention is very important (Tsubaki, 1999).

In the case of a treatment evaluation of disease, and especially in the evaluation of the efficiency of a particular drug, we sometimes use an index based on the change seen in pre- and post-treatment data of the drug, specifically used in a certain disease area. Generally, the index (measure) is considered as a categorical scale, ordinal scale or interval scale. In particular, the measure of the continuous data is based on a difference or a ratio of pre- ( $X_1$ ) and post- ( $X_2$ ) data.

The appropriate measure is selected according to the balance of both the clinical and statistical points of view. The clinical point comes from ease of the interpretation and the statistical point comes from the ease of data analyses based on the normal distribution. In a particular experiment, a choice of difference or ratio as the primary measure of treatment effect may not be obvious. Statistically, the principal reasons to adjust for baseline, usually presented in relation to analysis of covariance, are to remove concomitant variation in the response and improve the precision of treatment comparisons (Steel & Torrie, 1980). Furthermore, summary statistics of an adjusted response should be independent response (Kaiser, 1989). Another relevant question is about the kind of effect anticipated. For example, is it additive, multiplicative or neither?

Compared with difference, ratio measures are not always investigated from the statistical point of view. Thus, this paper focuses on the statistical property of ratio measures. In later paragraphs of this section, firstly, we show the statistical properties of general ratio measures. Secondly, we review the past findings of two ratio measures. Lastly, we show some applicable examples of these two ratio measures in clinical trials and some examples of the difference often seen in clinical trials.

**Statistical properties of general ratio measures.** Relative change scores as ratio measure require the pre- and post-data to be continuous random variables. Thus ensuring the change score (difference) to be a continuous random variable, relative change scores also require the pre- and post-data to be the same type of measurement made using the same device and have equal units of measurement. Although pre- and post-data have the same units, relative change scores are often unitless or expressed as percentages.

Relative change scores convert the pre- and post-data into a proportional change score,  $C$ , expressed as either raw change (difference) or absolute change. The formula to convert pre- and post-data can be written as

$$C = \frac{X_2 - X_1}{X_1}$$

in the case of raw change, or

$$C = \frac{|X_2 - X_1|}{X_1}$$

in the case of absolute change, where  $C$  is the change score,  $X_2$  is the post-data and  $X_1$  is the pre-data (Bonate, 2000). Note that the numerator is a difference whereas the denominator scale is the pre-data. A variant of these equations is to multiply the proportional change scores by 100 thereby converting them to percent change scores. If  $C = 0$ , no change has occurred. A positive relative change score indicates that the post-data was greater than the pre-data, whereas a negative relative change indicates that the post-data was less than the pre-data. One criticism of relative change score is in the choice of the scaling term or denominator. Consider an individual whose initial score is 3 and whose final score is 7. Using Eq. 1.1, this represents a 133 % increase from baseline. However, if a patient scores a 7 initially and deteriorates to a 3, a -57 % decrease has occurred. Hence, different denominator terms result in different transformations and estimates of change.

Proportional and percent change score fall under a family of transformations known as change functions. Törnqvist, *et al.*, (1985) formally defined a change function as a real-value function  $C(X_1, X_2)$  of positive arguments,  $C : \mathbf{R}_2^+ \rightarrow \mathbf{R}$  with the following properties:

1.  $C(X_1, X_2) = 0$ , if  $X_1 = X_2$
2.  $C(X_1, X_2) > 0$ , if  $X_1 > X_2$
3.  $C(X_1, X_2) < 0$ , if  $X_1 < X_2$
4.  $C$  is a continuous increasing function of  $X_2$  when  $X_1$  is fixed.
5.  $\forall a : a > 0 \rightarrow C(aX_1, aX_2) = C(X_1, X_2)$

The last property merely states that the function is independent of units of measurement. The property  $C : \mathbf{R}_2^+ \rightarrow \mathbf{R}$  states that a two-dimensional vector  $(\mathbf{R}_2^+)$  is mapped into a one-dimensional vector  $(\mathbf{R})$  by the function  $C$ . It can be shown that both proportional percent change functions meet these requirements. It can also be shown that difference scores represent another valid type of change function.

By setting  $a = 1/X_1$  in property 5, Törnqvist, *et al.*, (1985) have shown that almost every indicator of relative change can be expressed as a function of  $X_2/X_1$  alone. Hence, the change function can be expressed as an alternate function dependent solely on  $X_2/X_1$ . Formally, there exists a function  $H$ , such that

$$C(X_1, X_2) = H\left(\frac{X_2}{X_1}\right) = C\left(1, \frac{X_2}{X_1}\right)$$

with properties:

1.  $H\left(\frac{X_2}{X_1}\right) = 0$ , if  $\frac{X_2}{X_1} = 1$
2.  $H\left(\frac{X_2}{X_1}\right) > 0$ , if  $\frac{X_2}{X_1} > 1$
3.  $H\left(\frac{X_2}{X_1}\right) < 0$ , if  $\frac{X_2}{X_1} < 1$
4.  $H$  is a continuous increasing function of its argument  $\frac{X_2}{X_1}$ .
5.  $H\left(\frac{aX_2}{aX_1}\right) = H\left(\frac{X_2}{X_1}\right)$  trivially

Table 1.1 shows a variety of other relative change functions proposed by Törnqvist, *et al.* (1985) and their simplification into functions of  $Y = (X_2/X_1)$ . Here,  $K(X_1, X_2)$  is any mean of  $X_1$  and  $X_2$ .

Table 1.1: Relative change functions and their simplification into functions of  $Y(= X_2/X_1)$  as presented by Törnqvist *et al.*(1985)

Mapping	Function	Mapping	Function
$\frac{X_2 - X_1}{X_1}$	$Y - 1$	$\frac{X_2 - X_1}{2(X_1^{-1} + X_2^{-1})^{-1}}$	$\frac{1}{2}(Y - 1)(1 + 1/Y)$
$\frac{X_2 - X_1}{X_2}$	$1 - \frac{1}{Y}$	$\frac{X_2 - X_1}{\min(X_1, X_2)}$	$\frac{Y - 1}{\min(1, Y)}$
$\frac{X_2 - X_1}{(X_1 + X_2)/2}$	$\frac{Y - 1}{(1 + Y)/2}$	$\frac{X_2 - X_1}{\max(X_1, X_2)}$	$\frac{Y - 1}{\max(1, Y)}$
$\frac{X_2 - X_1}{\sqrt{X_1 X_2}}$	$\frac{Y - 1}{\sqrt{Y}}$	$\frac{X_2 - X_1}{K(X_1, X_2)}$	$\frac{Y - 1}{K(1, Y)}$

**Statistical properties of two ratio measures.** In this paragraph, two ratio measures which has been applied in the clinical trial are shown. As a measure of ratio, percent change from baseline ( $PC$ ),  $PC = (X_2 - X_1)/X_1$ , is often used in a trial. In addition, symmetrized percent change ( $SPC$ ),  $SPC = (X_2 - X_1)/(X_1 + X_2)$ , are sometimes also used in trials(Berry,1989). Bonate(2000) and Törnqvistnqvist, *et al.* (1985) shows the modified  $SPC$  which is defined as the mean of two values for a numerator which is  $(X_2 - X_1)/\{\frac{1}{2} \times (X_1 + X_2)\}$ .

The  $PC$  means "the proportion of increase (or decrease) for pre-value", and is acceptable from the clinical point of view because of the easy interpretation. On the other hand, some statistical difficulties are pointed out to  $PC$ . Senn & Julious(2009) said that the statistical analysis based on the parametric are not recommended for  $PC$ , because  $PC$ (or ratio of two values) is not normal even if pre- and post-data are normal. Asakura *et al.*,(2011) investigated the statistical properties of ratio on condition that two values are normal, summarized the statistical issues of ratio and gave a warning for using the ratio to the estimation of effect. Pharm-Gia *et al.*(2006) gave the exact closed form expression of the density of  $X_2/X_1$ , where  $X_1$  and  $X_2$  are normal random variables, in terms of Hermite and confluent hypergeometric functions, and show the skewness distribution in some situation. On the other hand, Berry (1989) introduced the  $SPC$  as the modified percent change with good statistical properties in the medical field. Brouwers & Mohr(1989) argued that the advantage of using  $SPC$  over the  $PC$  is that the transformed variable dose not depend on the denominator used in the transformation and the resultant distribution is symmetrical about its mean. Berry & Ayers(2006) showed the simulation results under independent, additive and multiplicative correlation structures of pre- and post-data for parametric and nonparametric analyses. And Berry & Ayers(2006) concluded

that simple ANOVA on  $SPC$  had power equal or greater than alternative analysis methods except for independence structure. However, the interpretation of  $SPC$  may not be intuitive for those accustomed to thinking in terms of  $PC$ . For example, if  $SPC$  is  $-0.1$  or  $-0.2$ , then the post-data shows to reduce from pre-data, but it is difficult to interpret the value of  $-0.1$  or  $-0.2$ . Concerning this point, Koti(2001) suggested that  $SPC$  is obscurant in nature. However, the same can be said for many statistical methods that are valuable in making inferences, such as taking the logarithm and most nonparametric tests(Berry & Ayers, 2006). For interpretability of analysis results, Berry (1989) suggested transforming  $SPC$  to the  $PC$  scale using the inverse transformation: robust percent change  $RPC = 2 \times SPC / (1 - SPC)$ . For example, if  $SPC$  is equal to  $-0.25$  for a particular treatment arm, then  $RPC = -0.4$ .

**Application example of difference or ratio measures in clinical trial.** As some example of measures, the difference which is defined as  $D = X_2 - X_1$  is used for the treatment evaluation for patients with high-blood pressure based on the diastolic blood pressure or systolic blood pressure (Adachi *et al.*, 2009), for patients with pain, such as neuropathic pain or pain of osteoarthritis of the knee, based on the 11-point rating scale or 100mm visual analog scale (Sato *et al.*, 2010; Lane *et al.*, 2010) and for patients with glaucoma based on the ocular pressure (Kitazawa *et al.*, 2009)

As the ratio measures, the percent change ( $PC$ ) which is defined as  $PC = (X_2 - X_1) / X_1 = (X_2 / X_1) - 1$  are often used for treatment evaluation. On the other hand, symmetrized percent change which is defined as  $SPC = (X_2 - X_1) / (X_1 + X_2) = \{(X_2 / X_1) - 1\} / \{1 + (X_2 / X_1)\}$  are sometimes used. As examples of clinical evaluation,  $PC$  are applied to the treatment evaluation of patients with high-density lipoprotein cholesterol (Adachi *et al.*, 2009), of patients with urge to urinate or urge incontinence based on the number of micturitions (Homma *et al.*, 2003), of patients with climacteric disorder based on the number of hot flush (Endrikat *et al.*, 2007).  $SPC$  is applied to the treatment evaluation of patients with partial epilepsy based on the seizure frequency(Yamauchi *et al.*, 2006) and evaluation of male patients with osteoporotic fracture based on the physical activity (Anney *et al.*, 2010).

## 1.2 Motivation

As I mentioned in the previous section,  $PC$  and  $SPC$  as the ratio measures are investigated in some aspects. However, past findings are based on limited researches such as the investigations of  $PC$  assumed as the bivariate normal distribution in pre- and post-data. In a clinical trial, data follows not only normal distribution but also positive skew distribution such as log-normal distribution or more positive skew distribution than log-normal(Maruo *et al.*, 2008). Therefore,

we need to investigate the statistical properties of two ratio measures,  $PC$  and  $SPC$ , in various distributions of pre- and post-data. In this paper, we show more deeply investigation of two ratio measures as follows,

- We derive the probability distribution function (pdf) of two ratio measures, percent change ( $PC$ ) and symmetrized percent change ( $SPC$ )
- We evaluate the relationship between the skewness of two ratio measures and the distribution of pre- and post-data
- We evaluate the performance of two ratio measures to detect the treatment difference within pre- and post-data or between two groups based on the simulation
- We propose how to apply the two measures in various situations
- We show the relationship between ratio measure ( $SPC$ ) and coefficient of variation ( $CV$ )

### 1.3 Components of this paper

In section 2, we define the three kinds of distributions of the pre- and post-data, which are bivariate normal, bivariate log-normal and bivariate power normal distribution, and review some statistical properties of the distributions. In section 3, we derive the probability density function (pdf) of ratio measures and evaluate the skewness of distribution in each condition. In addition, we declare the relationship between ratio measures and coefficient of variation between pre- and post data with correlation. In section 4, we conduct simulations to evaluate the performance to detect the treatment difference within pre- and post-data or between two groups based on the simulations. In addition, we show a case example to apply  $SPC$ . In section 5, we describe the summary results, findings of this research and future investigation plan.

## Section 2

# Definition of the distributions for pre- and post-data

In this chapter, firstly, we introduce bivariate normal distribution and bivariate log-normal distribution assumed as pre- and post-data distribution generally used. However, distributions of pre- and post-data in real situations such as in clinical trials are sometimes not based on these two distributions. Therefore, we also introduce the bivariate power normal distribution and will evaluate properties of ratio measures comprehensively in a later chapter.

### 2.1 Commonly used distributions for pre- and post-data

**Bivariate normal distribution (BN).** Let the random variables  $X_i (i = 1, 2)$  denote the response of pre- and post-data following bivariate normal distribution, and the variables satisfy  $(X_1, X_2) \sim \text{BN}(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$ , where  $\mu_i$  is the location parameters,  $\sigma_i$  is the scale parameters and  $\rho$  is the correlation parameter between two random variables of pre- and post-data. Then, the probability density function (pdf) of random variable  $X_i (i = 1, 2)$  which follows a bivariate normal distribution is,

$$f_{BN}(x_1, x_2) = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}} \times \exp \left[ -\frac{1}{2(1-\rho^2)} \left\{ \left( \frac{x_1 - \mu_1}{\sigma_1} \right)^2 - 2\rho \left( \frac{x_1 - \mu_1}{\sigma_1} \right) \left( \frac{x_2 - \mu_2}{\sigma_2} \right) + \left( \frac{x_2 - \mu_2}{\sigma_2} \right)^2 \right\} \right].$$

**Bivariate log-normal distribution (BLN).** Let the positive random variables  $X_i (i = 1, 2)$  denote the response of pre- and post-data following bivariate log-normal distribution, and the



variables satisfy  $(X_1, X_2) \sim \text{BLN}(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$ . Then, the pdf of random variable  $X_i (i = 1, 2)$  which follows a bivariate log-normal distribution is,

$$f_{BLN}(x_1, x_2) = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}x_1x_2} \times \exp \left[ -\frac{1}{2(1-\rho^2)} \left\{ \left( \frac{\log x_1 - \mu_1}{\sigma_1} \right)^2 - 2\rho \left( \frac{\log x_1 - \mu_1}{\sigma_1} \right) \left( \frac{\log x_2 - \mu_2}{\sigma_2} \right) + \left( \frac{\log x_2 - \mu_2}{\sigma_2} \right)^2 \right\} \right]$$

## 2.2 Comprehensive distribution for pre- and post-data

**Bivariate power normal distribution(BPN).** Bivariate power normal distribution is a parametric class of probability distributions which includes the bivariate truncated normal and the bivariate log-normal as a special case. The bivariate power normal distribution is on the basis of the Box and Cox power-transformation which is defined by positive random variables  $X_i (i = 1, 2)$

$$X_j^{(\lambda_j)} = \begin{cases} \frac{X_j^{\lambda_j} - 1}{\lambda_j} & \lambda_j \neq 0 \\ \log X_j & \lambda_j = 0 \end{cases} \quad (2.1)$$

where the range of  $X_j^{(\lambda_j)}$  is  $-1/\lambda_j < X_j^{(\lambda_j)} < +\infty$  when  $\lambda_j > 0$  and is  $-\infty < X_j^{(\lambda_j)} < -1/\lambda_j$  when  $\lambda_j < 0$ .

Let a power transformed variables  $X_i^{(\lambda_i)}$  of  $X_i$  denote the truncated bivariate normal distribution with mean vector  $\mu = (\mu_1, \mu_2)^T$  and variance covariance matrix

$$\Sigma = \begin{bmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}. \quad (2.2)$$

Then,  $(X_1, X_2)$  is to have the bivariate power-normal distribution if the marginal pdf is

$$f_{BPN}(x_1, x_2) = \frac{x_1^{\lambda_1-1} x_2^{\lambda_2-1}}{A(\mathbf{K})} g_{BPN}(x_1^{\lambda_1-1}, x_2^{\lambda_2-1}), \quad x_1, x_2 > 0 \quad (2.3)$$

where

$$g_{BPN}(x_1^{\lambda_1-1}, x_2^{\lambda_2-1}) = \frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}} \exp \left\{ -\frac{Q(x_1^{(\lambda_1)}, x_2^{(\lambda_2)})}{2} \right\} \quad (2.4)$$

and

$$Q(x_1^{(\lambda_1)}, x_2^{(\lambda_2)}) = \frac{1}{1-\rho^2} \times \left\{ \left( \frac{x_1^{(\lambda_1)} - \mu_1}{\sigma_1} \right)^2 - 2\rho \left( \frac{x_1^{(\lambda_1)} - \mu_1}{\sigma_1} \right) \left( \frac{x_2^{(\lambda_2)} - \mu_2}{\sigma_2} \right) + \left( \frac{x_2^{(\lambda_2)} - \mu_2}{\sigma_2} \right)^2 \right\}$$

where  $\lambda_j$ ,  $\mu_j$  and  $\sigma_j$  are shape, location and scale parameters and  $\rho$  is a correlation parameter between  $X_1^{(\lambda_1)}$  and  $X_2^{(\lambda_2)}$  (Goto & Hamasaki, 2002 : Hamasaki & Goto, 2002).  $A(\mathbf{K})$  is the probability proportional constant term and is given by,

$$A(\mathbf{K}) = \int_{a_2}^{b_2} \int_{a_1}^{b_1} \phi(x_1, x_2 : \rho) dx_1 dx_2, \quad (2.5)$$

in terms of the joint pdf of the bivariate standard normal distribution

$$\phi(x_1, x_2 : \rho) = \frac{1}{2\pi\sqrt{1-\rho^2}} \exp \left\{ -\frac{x_1^2 - 2\rho x_1 x_2 + x_2^2}{2(1-\rho^2)} \right\}, \quad (2.6)$$

with the values of  $a_j$  and  $b_j$  given by in the following,

- $a_j = -k_j$ ,  $b_j = +\infty$  when  $\lambda_j > 0$
- $a_j = -\infty$ ,  $b_j = +\infty$  when  $\lambda_j = 0$
- $a_j = -\infty$ ,  $b_j = -k_j$  when  $\lambda_j < 0$

and the standardized truncation point  $k_j$  is given by

$$k_j = \frac{\lambda_j \mu_j + 1}{\lambda_j \sigma_j}, \quad j = 1, 2. \quad (2.7)$$

The power normal distribution fits a large variety of distributions, because it has the shape parameter. Goto *et al.* (1983) mentioned four considering points about the inclusive model.

1. The consistency of logic about statistical analyses process.
2. The flexibility of the model.
3. The ease of the model fitting evaluation.
4. The ease of computation.

**Parameter Setting of BPN.** In the previous paragraph, a bivariate power normal distribution,  $BPN(\lambda_1, \lambda_2, \mu_1, \mu_2, \sigma_1, \sigma_2, \rho)$  is introduced as a distribution of pre- and post-data. In this paragraph, we consider the reduction of location parameter from pre- to post-data ( $\mu_1 > \mu_2$ ) with same shape and scale parameters between pre- and post-data ( $\lambda_1 = \lambda_2 = \lambda$ ,  $\sigma_1 = \sigma_2 = \sigma$ ). This means  $(X_1, X_2) \sim BPN(\lambda, \lambda, \mu_1, \mu_2, \sigma, \sigma, \rho)$ .

However, it is difficult to set these location ( $\mu_i$ ) and scale ( $\sigma_i$ ) parameters for simulations, since

it is difficult to interpret the values of these parameters which vary greatly depending on the value of  $\lambda_i$ . Therefore, we use the median of original scale ( $\xi_{0.5}$ ) as location-related parameter and the  $\tau = (\xi_{0.75} - \xi_{0.25})/\xi_{0.5}$  as scale-related parameter for easiness of parameter setting and interpretation (Maruo & Goto, 2012; Maruo, *et al.*, 2011).  $\xi_p$  is the 100 $p$  percentile of power normal distribution and is given by

$$\xi_p = \begin{cases} \{\lambda(\mu + \sigma z_{p^*}) + 1\}^{\frac{1}{\lambda}}, & \lambda \neq 0, \\ \exp(\mu + \sigma z_p), & \lambda = 0, \end{cases}$$

where  $z_p$  and  $z_{p^*}$  are the  $p$  and  $p^*$  percentile of standard normal distribution, and  $p^*$  is given by

$$p^* = \begin{cases} 1 - A(K)(1 - p), & \lambda > 0, \\ A(K)p, & \lambda < 0. \end{cases}$$

Moreover, the change of location parameter between pre- and post-data defines from percent change from pre-data of original scale ( $R$ ), and the relationship is defined as {the median of post-data original scale} =  $\xi_{0.5} \times (100 - R)/100$  ( $0 < R < 100$ ). In summary, the distributions are identified based on reparametrization method  $\{\lambda, \xi_{0.5}, \tau, R, \rho\}$  instead of  $\{\lambda, \mu_1, \mu_2, \sigma, \rho\}$ . The detail of reparametrization method is shown in appendix (Maruo, *et al.*, 2011; Maruo & Goto, 2012).

Figure 2.1 shows the pdf of BPN with the parameters of reparametrization method. In the figure, shape parameters are from -1 to +1 by 1 ( $\lambda = -1, 0, +1$ ), scale-like parameters are from 0.2 to 0.8 by 0.2 ( $\tau = 0.2, 0.4, 0.6, 0.8$ ), median of pre-data is 100 ( $\xi_{0.5} = 100$ ), percent change from pre-data is 0 ( $R = 0$ ) and correlation parameter is  $\rho = 0.8$ . The distribution is positive skewed when  $\lambda$  is less than 1, and the scale becomes large when the value of  $\tau$  increases.

**Applications of BPN to clinical data.** It is expected that BPN is applicable to distributions of various clinical data, because BPN includes the shape parameters ( $\lambda$ ) and can set the various distributions including more skewed distributions. For example, Goto & Uesaka (1980) presented the  $\hat{\lambda}$  of blood serum component of laboratory test. Maruo *et al.*(2008) applied the univariate power normal distribution to various laboratory test data and estimated the shape parameter  $\hat{\lambda}$  with the range between  $-1$  and  $0.25$  as shown in figure 2.1 and evaluated the loss of information when we assume the normal or log-normal distribution to laboratory data. Hamasaki & Goto (2002) applied the BPN to the clinical data in both diastolic blood pressure (DBP) and systolic blood pressure (SBP) of the clinical trial to evaluate the treatment effect of calcium blocker, and said that SBP would be more positive skewed distribution than log-normal distribution because of  $\hat{\lambda} < 0$  and DBP would be normal distribution because of  $\hat{\lambda} \approx 1$  in the data. Goto *et al.*(2007) applied the power normal distribution to partial epilepsy data and estimated  $\hat{\lambda} \approx 0$ ,

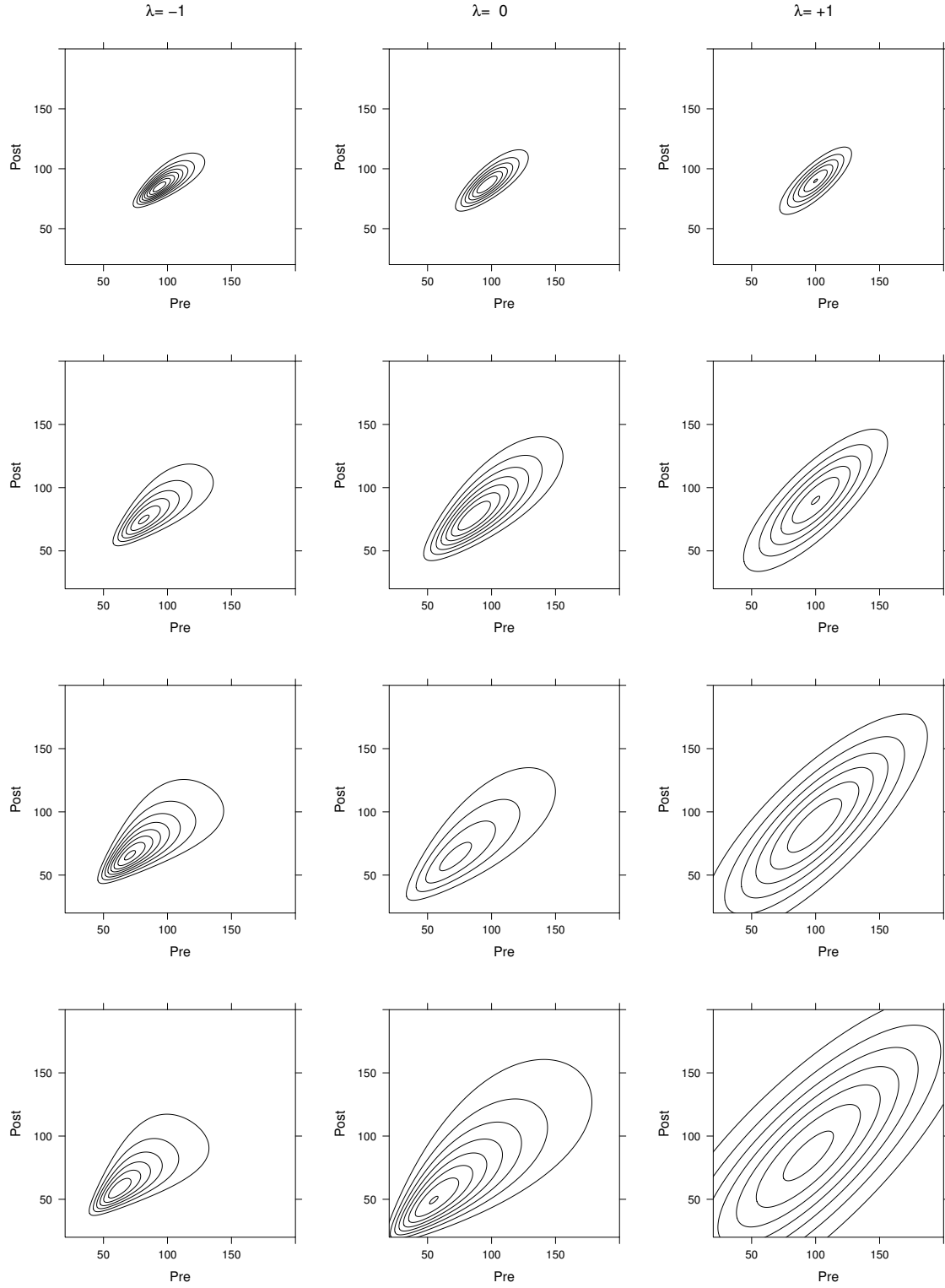


Figure 2.1: PDF of BPN with  $\lambda = -1, 0, +1$  and  $\tau = 0.2$ (upper) ,  $\tau = 0.4$ ,  $\tau = 0.6$ ,  $\tau = 0.8$ (bottom) )

which means that it is appropriate to analyze the data based on the log-normal distribution.

Table 2.1:  $\hat{\lambda}$  of laboratory test: the modification of table 2 in Maruo *et al.*(2008)

Laboratory test	$\hat{\lambda}$	Laboratory test	$\hat{\lambda}$
ALP	0.25	TC	0.25
GOT	-1	TG	-0.25
GPT	-0.5	HDL-C	0
$\gamma$ -GTP	-0.5		

## Section 3

# Statistical properties of ratio measures

### 3.1 Evaluation based on the bivariate normal distribution

**Probability density function of  $PC$  and  $SPC$ .** Pham-Gia *et al.* (2006) gave the exact closed form expression of the density of  $X_1/X_2$ , where  $X_1$  and  $X_2$  are normal random variables, in terms of Hermite and confluent hypergeometric functions. In this section, we give the probability density function of  $PC$  and  $SPC$  based on Pham-Gia *et al.* (2006).

Let  $X_1$  and  $X_2$  be the two random variables of bivariate normal distribution with parameters  $\text{BN}(\mu_1, \mu_2, \sigma, \sigma, \rho)$ . Strictly speaking, suppose that truncated bivariate normal distribution,  $\text{TBN}(\mu_1, \mu_2, \sigma, \sigma, \rho)$ , for  $X_1$  and  $X_2$ , because we consider the data which is  $X_1 \geq 0, X_2 \geq 0$ . Then the distribution of  $PC$  is

$$h_{\text{BN(PC)}}(v) = \frac{K_1}{2(1-\rho)(1+v) + v^2} H_{-2}(\xi_1(v)), \quad (3.1)$$

where  $H_{-2}(\cdot)$  is the Hermite function,

$$H_{-2}(z) = \int_0^\infty t e^{-t^2 - 2tz} dt$$

and

$$\xi_1(v) = -\frac{(1-\rho)(\mu_1 + \mu_2) + (\mu_2 - \rho\mu_1)v}{\sigma\sqrt{2(1-\rho^2)\{2(1-\rho)(1+v) + v^2\}}},$$

$$K_1 = \frac{\sqrt{1-\rho^2}}{\pi\Phi_2(0, 0; -\mu_1, -\mu_2, \sigma, \sigma, \rho)} \\ \times \exp\left\{-\frac{\mu_1^2 - 2\rho\mu_1\mu_2 + \mu_2^2}{2(1-\rho^2)\sigma^2}\right\}.$$

And the pdf of *SPC* is

$$h_{\text{BN}(\text{SPC})}(w) = \frac{K_2}{1-\rho + (1+\rho)w^2} H_{-2}(\xi_2(w)) \quad (3.2)$$

where  $H_{-2}(\cdot)$  is also the Hermite function as well as the case of  $h_{\text{BN}(\text{PC})}(v)$  and

$$\xi_2(w) = -\frac{1}{2\sigma\sqrt{(1-\rho^2)\{1-\rho + (1+\rho)w^2\}}} \\ \times \{(1-\rho)(\mu_1 + \mu_2) + (1+\rho)(\mu_2 - \mu_1)w\}, \\ K_2 = \frac{\sqrt{1-\rho^2}}{\pi\Phi_2(0, 0; -\mu_1, -\mu_2, \sigma, \sigma, \rho)} \times \exp\left\{-\frac{\mu_1^2 - 2\rho\mu_1\mu_2 + \mu_2^2}{2(1-\rho^2)\sigma^2}\right\},$$

where  $\Phi_2(\cdot)$  is the cumulative distribution function of standard normal distribution.

Consider the situation with small coefficients of variation which are  $(\sigma/\mu_1$  or  $\sigma/\mu_2)$  to ignore the affect of truncation. Then,  $\Phi_2(0, 0; -\mu_1, -\mu_2, \sigma, \sigma, \rho)$  is approximated by 1, and we can assume the situation that  $X_1, X_2 \geq 0$ . Figure 3.1 shows the pdf of *PC* and *SPC* with the parameters that  $\mu_2 - \mu_1 = 0, -0.3, -1, \sigma = 5, 10$  and  $\rho = 0, 0.4, 0.8$  to figure out the shapes of the pdf. The pdf of *SPC* is symmetrical comared to the pdf of *PC* based on this figure.

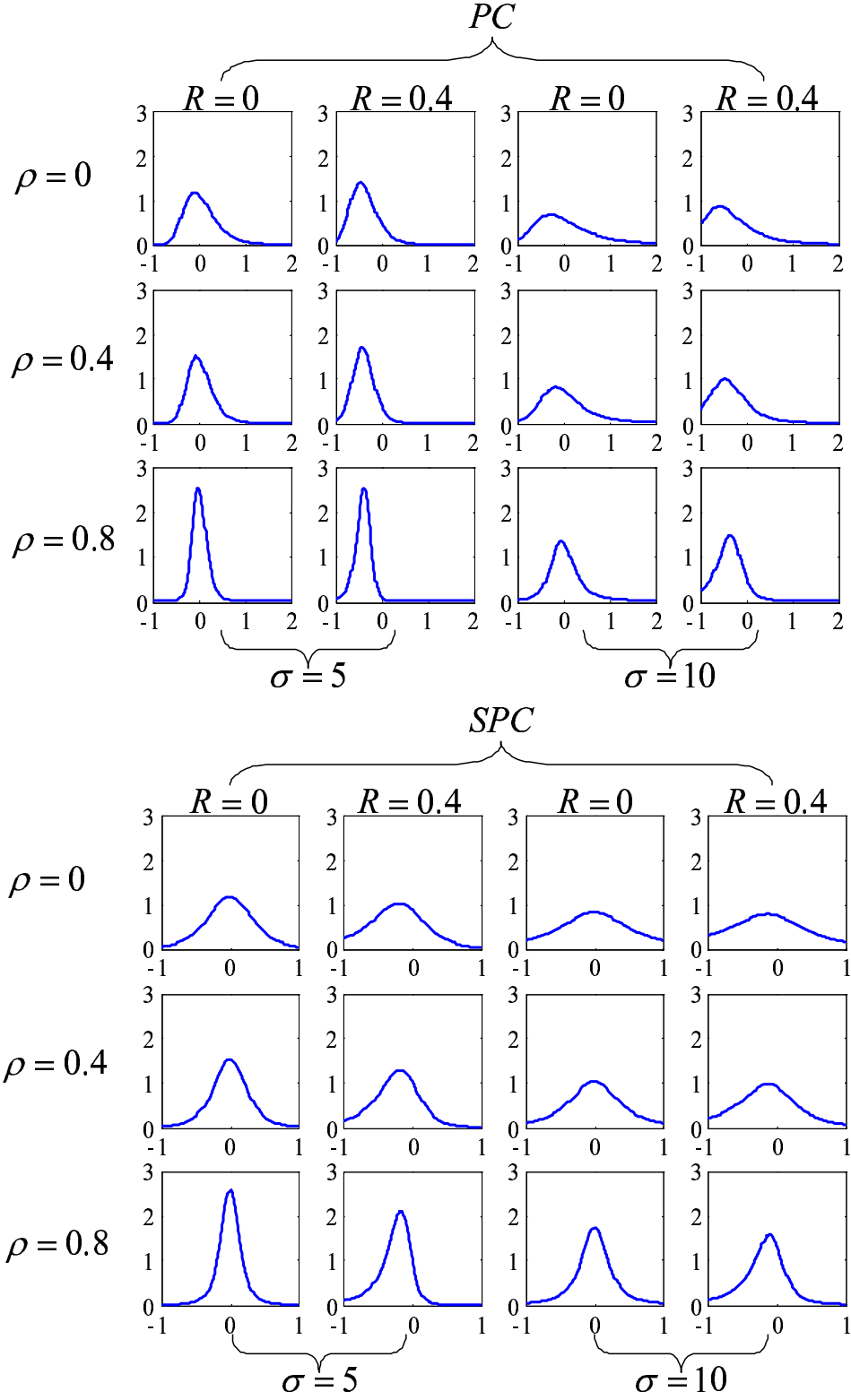


Figure 3.1: The pdf of *PC* and *SPC* based on bivariate normal distribution



**Skewness of  $PC$  and  $SPC$ .** Figure 3.2 shows the skewness of  $PC$  or  $SPC$  calculated based on each pdf. We assume that two random variables,  $X_1, X_2$ , are based on the bivariate normal distribution with the parameters  $BN(\mu_1, \mu_2, \sigma^2, \sigma^2, \rho)$  which are set within the range of  $\mu_1 = 10$ ,  $\mu_2 = 9$ ,  $\sigma = 1$  and  $\rho = 0 \sim 0.9$ . The  $PC$  do not skew so much and so the difference of skewness between  $PC$  and  $SPC$  became small.

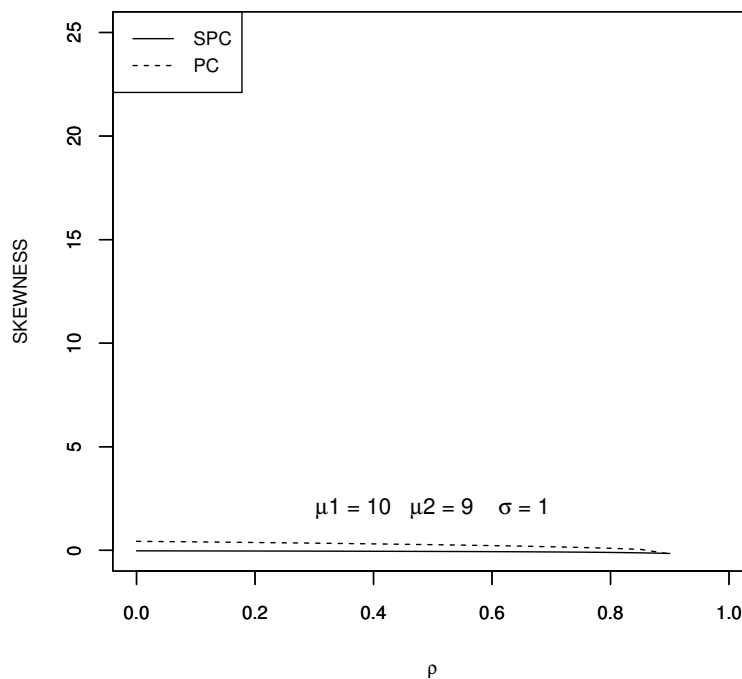


Figure 3.2: The relationship between  $\rho$  and skewness of  $PC$  and  $SPC$  based on bivariate normal distribution

### 3.2 Evaluation based on the bivariate log-normal distribution

**Probability density function of  $PC$  and  $SPC$ .** Let  $X_1$  and  $X_2$  be two random variables of bivariate log-normal distribution with parameters  $BLN(\mu_1, \mu_2, \sigma, \sigma, \rho)$ . Then, we define the pdfs of  $PC$  is  $h_{BLN(PC)}(v)$  and the pdfs of  $SPC$  is  $h_{BLN(SPC)}(w)$ , and these pdfs are

$$\begin{aligned}
h_{\text{BLN(PC)}}(v) &= \frac{1}{2\sigma(1+v)\sqrt{\pi(1-\rho)}} \\
&\times \exp\left[-\frac{1}{4\sigma^2(1-\rho)}\{\log(1+v) - (\mu_2 - \mu_1)\}^2\right], \quad (3.3)
\end{aligned}$$

$$\begin{aligned}
h_{\text{BLN(SPC)}}(w) &= \frac{1}{\sigma(1-w^2)\sqrt{\pi(1-\rho)}} \\
&\times \exp\left[-\frac{1}{4\sigma^2(1-\rho)}\left\{\log\left(\frac{1-w}{1+w}\right) + \mu_2 - \mu_1\right\}^2\right], \quad (3.4)
\end{aligned}$$

where  $\mu_1$  and  $\mu_2$  are the mean of log-transformed two variables ( $X_1$  and  $X_2$ ),  $\sigma^2$  is the variance and  $\rho$  is the correlation.

Figure 3.3 shows the pdf of *SPC* and *PC* with the parameters that  $R = 0, 0.4$ ,  $\sigma = 0.5, 1$ ,  $\rho = 0, 0.4, 0.8$  to figure out the shapes of the pdf. The  $R$  is the median of percent change about post-data which is calculated by the  $\exp(\mu_2) = (1 - R)\exp(\mu_1)$ .  $R = 0$  means that the median of pre-data is same as the median of post-data, and  $R = 0.4$  means the median of post-data had the 40 % reduction from pre-data. In these figures, all *PC* shows the positive skew distribution. On the other hand, *SPC* shows the symmetrized distributions.

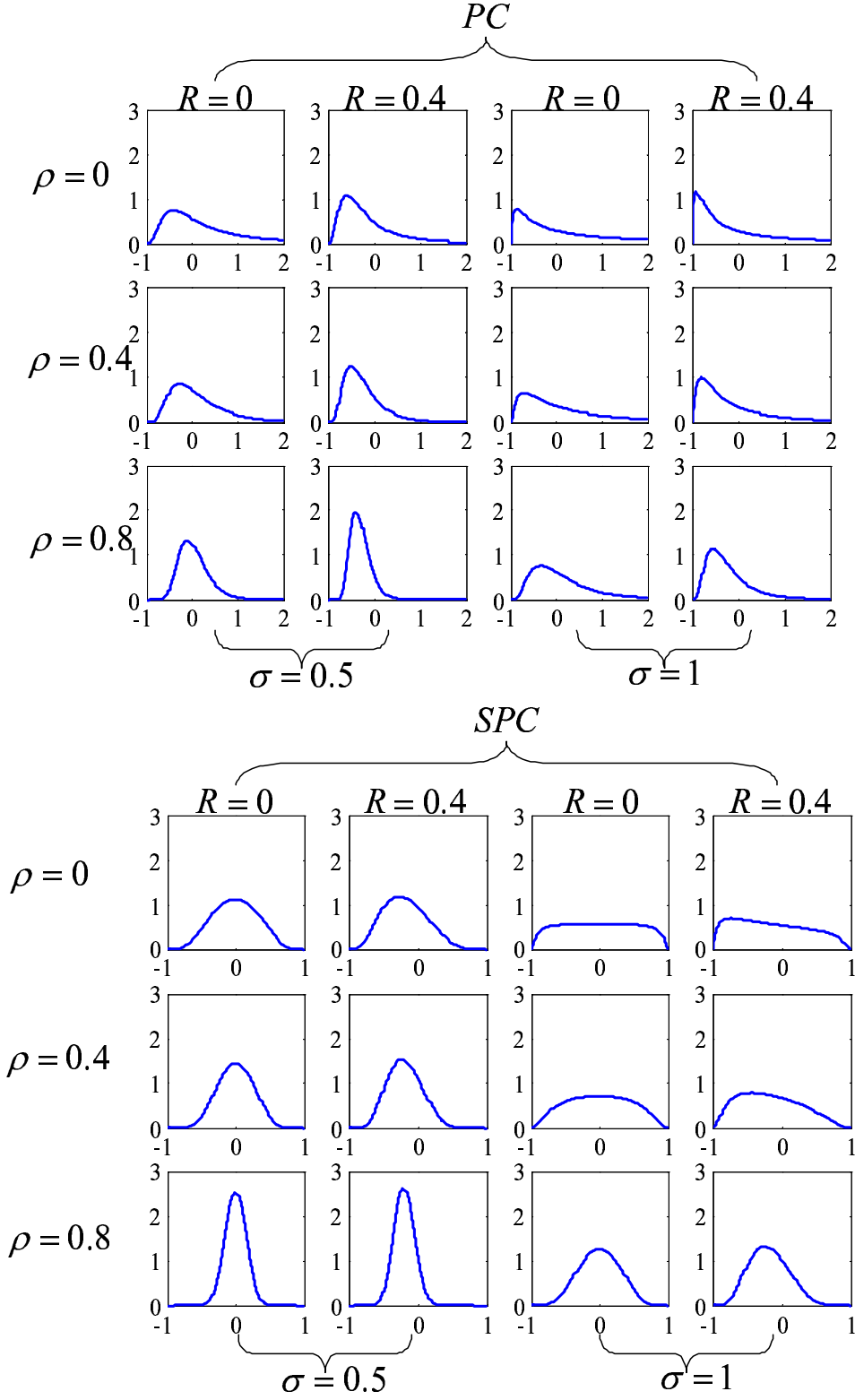


Figure 3.3: The pdf of *PC* and *SPC* based on bivariate log-normal distribution

**Skewness of  $PC$  and  $SPC$ .** In this paragraph, we evaluated the skewness of  $PC$  and  $SPC$  calculated by numerical integration method based on the pdfs, quantitatively. Figure 3.4 shows the relationship between correlation and skewness of  $PC$  and  $SPC$ . The parameter combinations used for the skewness calculation in this figure are that  $\mu_1 = 1$ ,  $\mu_2 = 0.9$ ,  $\sigma = 1$  and  $\rho = 0 \sim 0.9$ . The skewness of  $SPC$  is smaller than  $PC$  without regard to correlation.

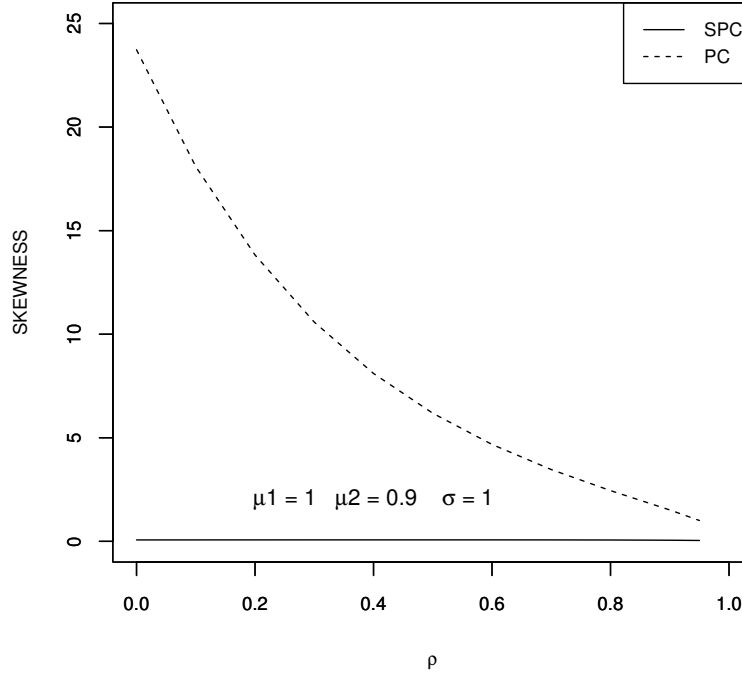


Figure 3.4: The relationship between  $\rho$  and skewness of  $PC$  and  $SPC$  based on bivariate log-normal distribution

### 3.3 Evaluation based on the bivariate power-normal distribution

**Probability density function of  $PC$  and  $SPC$ .** Let  $X_1$  and  $X_2$  be the two positive random variables of bivariate power normal distribution with parameters  $\text{BPN}(\lambda, \lambda, \mu_1, \mu_2, \sigma, \sigma, \rho)$ . The pdfs of  $PC$  or  $SPC$  are calculated by using the variable transformation method. The two random variables,  $X_1$  and  $X_2$ , of BPND in section 2 are transformed to  $X_1 = U$  and  $X_2 = U(1 + V)$  for  $PC$ , which is equal to  $U = X_1$  and  $V = (X_2 - X_1)/X_1$ . On the other hand, the two variables are also transformed to  $X_1 = U$  and  $X_2 = U \times (1 + W)/(1 - W)$  for  $SPC$ , which is equal to

$U = X_1$  and  $W = (X_2 - X_1)/(X_1 + X_2)$ . Then, the pdfs of  $PC$  as  $h_{\text{BPN(PC)}}(v)$  is given by,

$$\begin{aligned} h_{\text{BPN(PC)}}(v) &= \int u \times \frac{u^{2\lambda-2}(1+v)^{\lambda-1}}{2\pi\sigma^2\sqrt{1-\rho^2}A(\mathbf{K})} \\ &\quad \times \exp\left[-\frac{1}{2}\left(\mathbf{M}^{(\lambda)} - \boldsymbol{\mu}\right)^T \boldsymbol{\Sigma}^{-1} \left(\mathbf{M}^{(\lambda)} - \boldsymbol{\mu}\right)\right] du \end{aligned} \quad (3.5)$$

where  $A(\mathbf{K})$  is the probability proportional constant term shown in section 2 and

$$\mathbf{M}^{(\lambda)} = \left(u^{(\lambda)}, \{u(1+v)\}^{(\lambda)}\right),$$

$$\boldsymbol{\mu} = (\mu_1, \mu_2),$$

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 \end{pmatrix}.$$

And the components of  $\mathbf{M}^{(\lambda)}$  are

$$u^{(\lambda)} = \begin{cases} \frac{u^\lambda - 1}{\lambda} & \lambda \neq 0 \\ \log u & \lambda = 0 \end{cases}$$

and

$$\{u(1+v)\}^{(\lambda)} = \begin{cases} \frac{u^\lambda(1+v)^\lambda - 1}{\lambda} & \lambda \neq 0 \\ \log \{u(1+v)\} & \lambda = 0. \end{cases}$$

Next, the pdf of  $SPC$  as  $h_{\text{BPN(SPC)}}(w)$  is given by

$$\begin{aligned} h_{\text{BPN(SPC)}}(w) &= \int \frac{u}{(1-w)^2} \times \frac{u^{\lambda-1} \left\{ \frac{1+w}{1-w} \times u \right\}^{\lambda-1}}{\pi\sigma^2\sqrt{1-\rho^2}A(\mathbf{K})} \\ &\quad \times \exp\left[-\frac{1}{2}\left(\mathbf{N}^{(\lambda)} - \boldsymbol{\mu}\right)^T \boldsymbol{\Sigma}^{-1} \left(\mathbf{N}^{(\lambda)} - \boldsymbol{\mu}\right)\right] du \end{aligned} \quad (3.6)$$

where

$$\mathbf{N}^{(\lambda)} = \left(u^{(\lambda)}, \left(\frac{1+w}{1-w} \times u\right)^{(\lambda)}\right)$$

and  $A(\mathbf{K})$  is also the probability proportional constant term shown in section 2,  $\boldsymbol{\mu}$  and  $\boldsymbol{\Sigma}$  is the same as ones of  $PC$ . The components of  $\mathbf{N}^{(\lambda)}$  are

$$u^{(\lambda)} = \begin{cases} \frac{u^\lambda - 1}{\lambda} & \lambda \neq 0 \\ \log u & \lambda = 0 \end{cases}$$

and

$$\left(\frac{1+v}{1-v} \times u\right)^{(\lambda)} = \begin{cases} \frac{\left(\frac{1+v}{1-v} \times u\right)^\lambda - 1}{\lambda} & \lambda \neq 0 \\ \log \left(\frac{1+v}{1-v} \times u\right) & \lambda = 0. \end{cases}$$

### 3.3.1 Definition of the distribution of skewness

When the shape parameter of power normal distribution is equal to or larger than 0 generally, it is possible to calculate any moment and skewness. However, skewness cannot be calculated in  $-3 \leq \lambda < 0$ , because three order moment does not exist (Goto *et al.*, 1983). In this section, we define the alternative criterion about skewness, which is

$$\eta = \frac{\xi_{0.975} - \xi_{0.5}}{\xi_{0.5} - \xi_{0.025}}.$$

When the distributions become more symmetrical,  $\eta$  will become nearer one. And, when  $\eta$  is larger than one, the distributions become more positively skewed. On the other hand, the distributions become negative skew, when  $\eta$  is less than 0.

### 3.3.2 Detection of factors to affect the skewness of distributions

Factors to affect the distribution of skewness of  $PC$  or  $SPC$  were investigated based on ANOVA. In this analysis,  $\eta$  of  $PC$  or  $SPC$  is set as response value, shape( $\lambda$ ), scale-like( $\tau$ ), percent change from pre-data ( $R$ ) and correlation ( $\rho$ ) were included as factor. In addition, the interactions between two factors of four parameters were also included in the model. In the clinical data, such as epilepsy (Goto *et al.*, 2007) and laboratory data (Uesaka & Goto:1980, Maruo *et al.*: 2007) are based on the positive skew distribution in many cases, therefore shape parameters are set from -1 to 1 by 0.5 ( $\lambda = -1, -0.5, 0, 0.5, +1$ ). Percent change from pre-data are set from 10 to 40 by 10 ( $R = 10, 20, 30, 40$ ). Scale-like parameter are set from 0.2 to 1.0 by 0.2 ( $\tau = 0.2, 0.4, 0.6, 0.8, 1.0$ ). Correlation parameter are set from 0.2 to 0.8 by 0.2 ( $\rho = 0.2, 0.4, 0.6, 0.8$ ). The  $\eta$  of  $PC$  or  $SPC$  were calculated based on the numerical integral for all combinations of

Table 3.1: Sum of square, F value and contribution rate of *PC* or *SPC* based on the ANOVA

	The $\eta$ of <i>PC</i> is response.			The $\eta$ of <i>SPC</i> is response.		
Factor	Sum of square	F value	Cont. Rate (%)	Sum of square	F value	Cont. Rate (%)
$\lambda$	52.573	273.359	9.94	0.316	258.289	38.97
$\tau$	315.690	1641.466	59.70	0.091	74.131	11.18
$\rho$	106.838	555.514	20.20	0.238	193.977	29.27
$R$	9.605	49.941	1.82	0.013	10.693	1.61
$\lambda \times \tau$	17.868	92.904	3.38	0.021	16.852	2.54
$\lambda \times \rho$	3.266	16.979	0.62	0.009	7.729	1.17
$\lambda \times R$	1.993	10.365	0.38	0.059	48.415	7.30
$\tau \times \rho$	19.814	103.026	3.75	0.007	5.660	0.85
$\tau \times R$	1.126	5.854	0.21	0.015	12.637	1.91
$\rho \times R$	0.006	0.031	near 0	0.042	34.439	5.20

these four parameter, which were 400 combination cases (= 5 levels of  $\lambda \times 4$  levels of  $R \times 5$  levels of  $\tau \times 4$  levels of  $\rho$ ) as total.

Table 3.1 shows the sum of squares, F value and contribution rate which is defined as the sum of squares in each factor is divided by the sum of squares in total factors  $\times 100$ . For *PC*, the  $\tau$  was the largest contribution to distribution of skewness (59.70 %). The second largest contribution was  $\rho$  (20.20 %), and the third was  $\lambda$  (9.94 %). However, the  $R$  did not have a high contribution to the distribution of skewness (1.82 %). For interactions between two factors of *PC*,  $\lambda \times \tau$  (3.38 %) and  $\tau \times \rho$  (3.75 %) had more contribution than others. On the other hand, the contribution rate of  $\tau$ ,  $\rho$  and  $\lambda$  for *SPC* which had high contribution for *PC* were 11.18 %, 29.27 % and 38.97 % respectively. These three factors of *SPC* were also contributed highly as well as *PC*. The contribution of  $R$  for *SPC* was also low (1.61 %). For interactions, *SPC* had a different trend to *PC*, and the contribution of  $\lambda \times R$  (7.30 %) and  $\rho \times R$  (5.20 %) was high. However, the sum of squares of *SPC* in each factor was much smaller than *PC*, and it was shown that each factor of *SPC* was contribution less to skewness of distributions.

### 3.3.3 Graphical evaluation of skewness of distribution

In this section, we evaluated the effect of three parameters which had a high contribution to skewness of *PC*, graphically. The three parameters were  $\lambda$ ,  $\tau$  and  $\rho$ , and the  $R$  which had less contribution to the skewness of *PC* were fixed as 10 %. Figure 3.5 to 3.8 shows the relationship

between the skewness of the distribution ( $\eta$ ) of  $PC$  or  $SPC$  and the three parameters of BPN ( $\lambda$ ,  $\tau$  and  $\rho$ ). The  $\lambda$  set 5 levels which are -1, -0.5, 0, +0.5 and +1. The  $\tau$  set 4 levels which were 0.2, 0.4, 0.6 and 0.8. The  $\rho$  set 4 levels which were 0.2, 0.4, 0.6 and 0.8.

For  $PC$ , the  $\eta$  increased with the absolute value of  $\lambda$  ( $\lambda = 1$  or  $-1$ ) and this trend became remarkable especially when  $\tau$  was equal to or more than 0.6. And the  $\eta$  increased with  $\tau$  increasing or decreases with  $\rho$  increasing. When  $\lambda < 0$ , the distribution of pre- and post-data became more positively skewed than log-normal distribution, and might have the case that post-value ( $X_1$ ) was much larger than post-value ( $X_2$ ). Then, the  $\eta$  of  $PC$  was larger than one and the  $\eta$  increased with increasing  $\tau$ . When  $\lambda > 0$ , the distribution of pre- and post-data became more negative skew and occurred the value near 0. Especially, when  $\tau$  was large, the truncation in the left side occurred ( $A(\mathbf{K}) < 1$ ) and a lot of values near  $X_1 = 0$  generated. Then, the  $\eta$  of  $PC$  increased. For  $\rho$ , the  $\eta$  of  $PC$  increased with decreasing  $\rho$ , because the difference between  $X_1$  and  $X_2$  became large.

For  $SPC$ , the skewness of the distribution ( $\eta$ ) was almost one in all conditions, and this means that all distributions of  $SPC$  show almost all symmetry in all combinations of the BPN parameters.



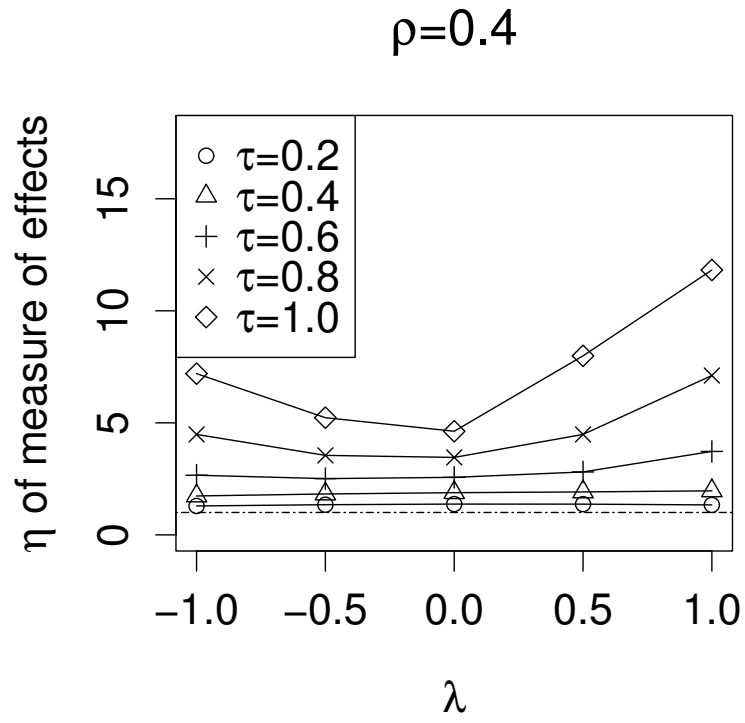
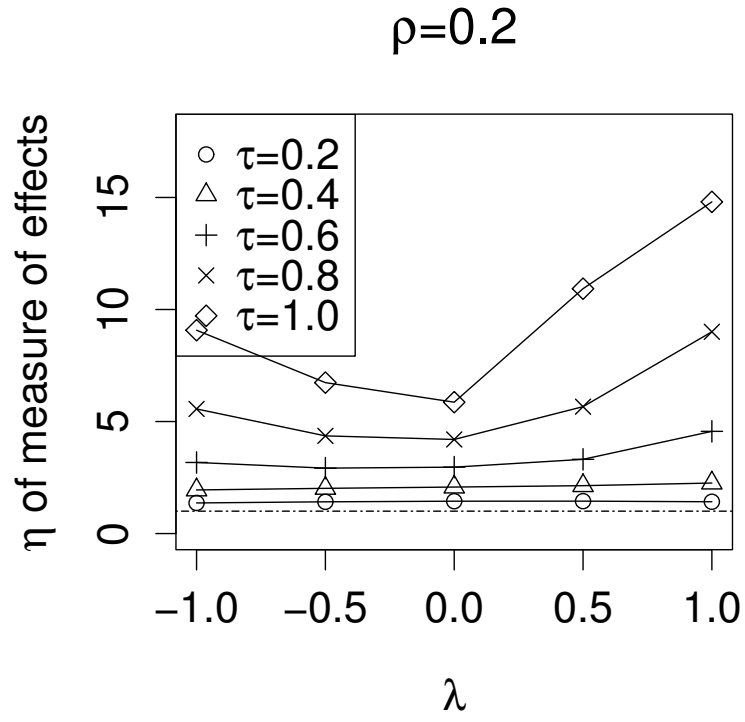


Figure 3.5: Relationship between  $\eta$  of  $PC$  and  $\lambda$  of BPN ( $\rho = 0.2, 0.4$  and  $R = 10\%$ )

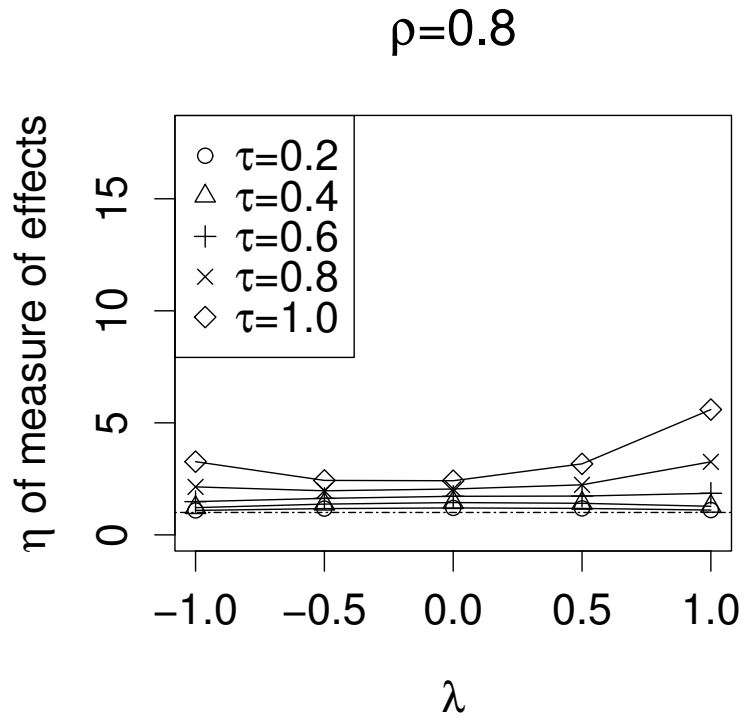
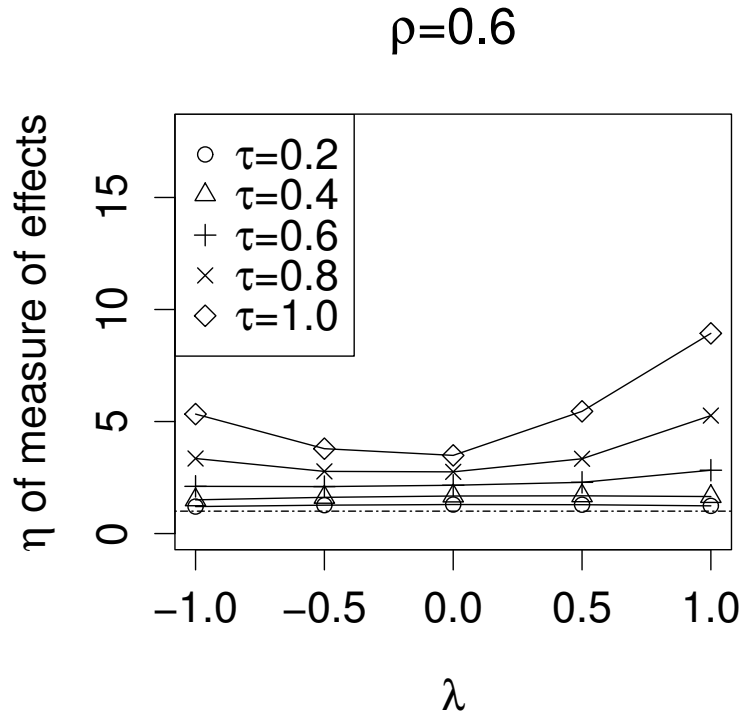


Figure 3.6: Relationship between  $\eta$  of  $PC$  and  $\lambda$  of BPN ( $\rho = 0.6, 0.8$  and  $R = 10\%$ )

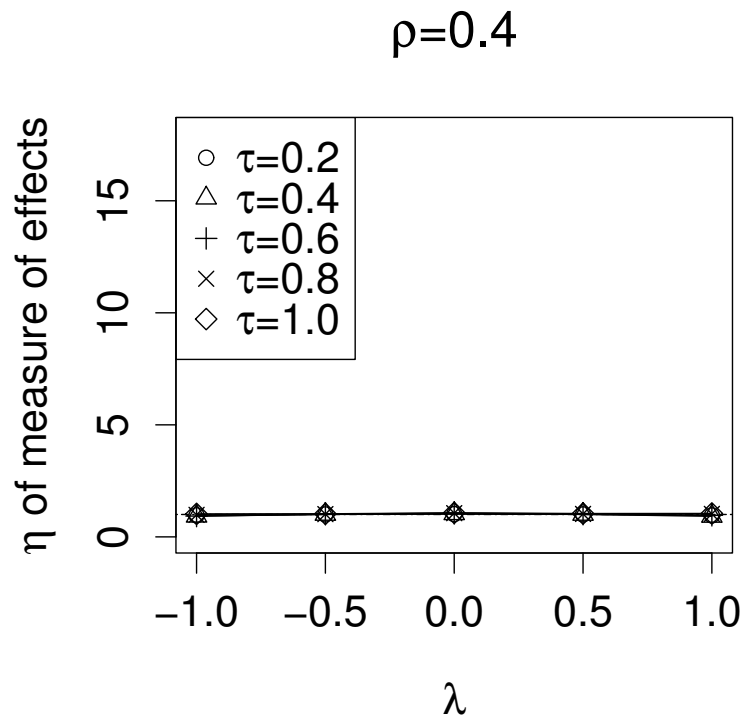
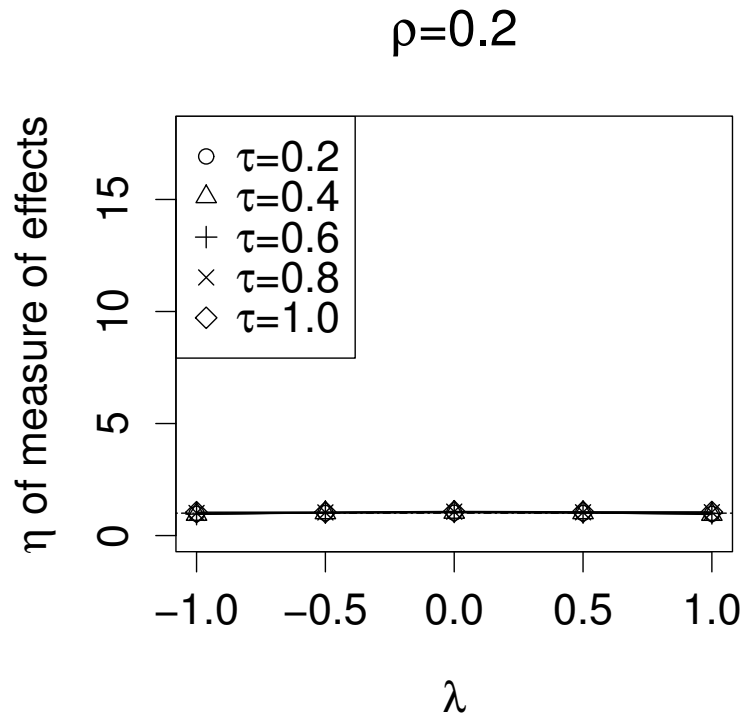


Figure 3.7: Relationship between  $\eta$  of *SPC* and  $\lambda$  of BPN ( $\rho = 0.2, 0.4$  and  $R = 10\%$ )

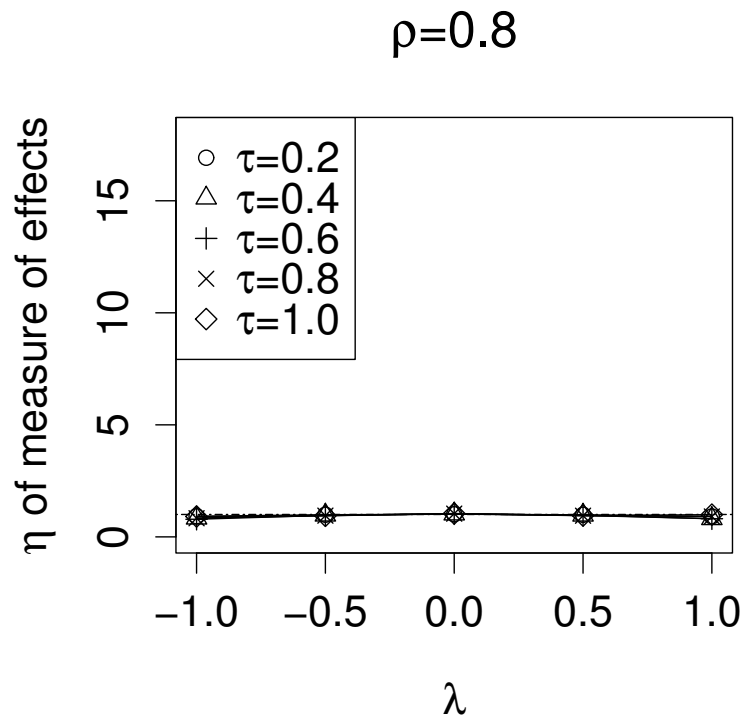
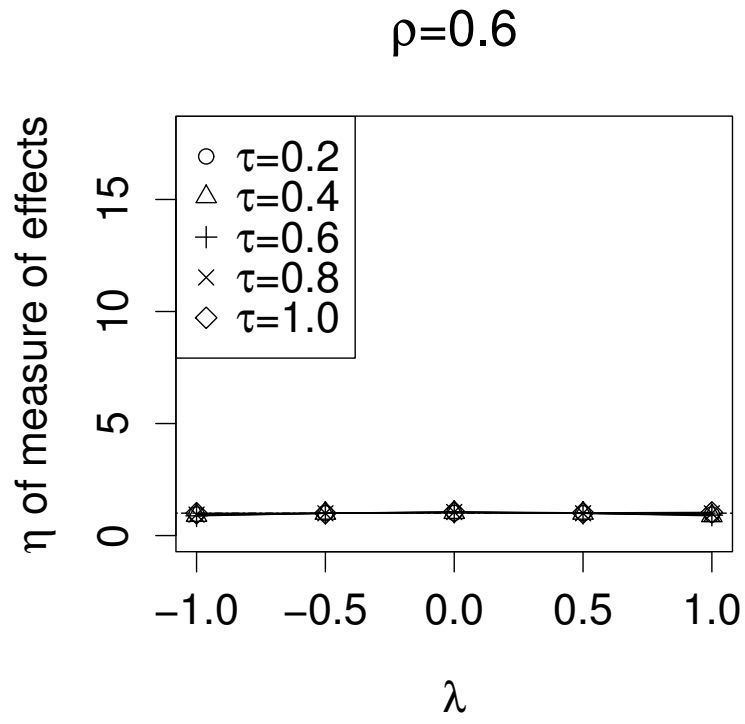


Figure 3.8: Relationship between  $\eta$  of *SPC* and  $\lambda$  of BPN ( $\rho = 0.6, 0.8$  and  $R = 10\%$ )

### 3.4 Relationship between symmetrized percent change and coefficient of variation

On the other hand, we considered another measure which is defined as  $(X_2 - X_1)/\frac{1}{2}(X_2 + X_1)$ . The numerator of the measure is a difference of two data and the denominator is a mean. When we regard the difference of denominator as an index of variation, the measure may be considered as a variation standardized by mean, such as a coefficient of variation. In fact, this measure is called Variability (%) in the bioanalytical field and is used for evaluating the level of reproducibility of assay results using incurred samples (Mario *et al.*, 2007 and Douglas *et al.*, 2009). The variability is used in a fixed error limit method and a model similar to the familiar 4-6-X QC criteria can be applied. For small molecules (non-ligand binding) two thirds of the repeat samples ( $X_2$ ) should agree within 20 % and for ligand-binding assay, two thirds of the repeat samples should agree within 30 %. The variability (% difference) should be calculated using the mean of the original and repeat results as described by the following formula:

$$\text{Variability}(\%) = \frac{\text{Repeat}(X_2) - \text{Original}(X_1)}{\frac{1}{2}(X_1 + X_2)} \times 100$$

**Graphical comparison of pdf.** In this paragraph, we investigate the relationship between *SPC* (Variability) and *CV* of two samples. Figure 3.9 shows the relationship between *SPC* and *CV*. The *CV* of two samples is given by  $|X_2 - X_1|/(X_1 + X_2)$  and the numerator of this formula is replaced by the difference of two samples with absolute value.

To figure out the distribution of *SPC* and *CV* graphically, we show the histogram of *SPC* and *CV* in figure 3.10 on condition that two samples follows the bivariate normal distribution (BN) and bivariate log-normal distribution (BLN). The upper graph is based on the BN with parameters of  $\text{BN}(10, 9, 1, 1, \rho)$  and the bottom is on the BLN with parameters of  $\text{BLN}(10, 9, 1, 1, \rho)$ . The  $\rho$  is from 0.2 to 0.8 by 0.2 in all graphs. We generate the 10,000 random samples with each parameters and create histograms. From these figures, the distribution of *CV* is the distributions folded back negative value of *SPC* to positive, because of the formula of absolute value of numerator.

### Relationship between *SPC* and *CV*

$$SPC = \frac{X_2 - X_1}{X_1 + X_2} \longleftrightarrow CV = \frac{\sqrt{V(X)}}{\bar{X}},$$

where  $\bar{X} = \frac{1}{2}(X_1 + X_2),$

$$V(X) = \frac{1}{2} \sum_{i=1}^2 (X_i - \bar{X})^2$$

$$CV = \frac{\sqrt{V(X)}}{\bar{X}} = \frac{\sqrt{\frac{1}{2} \sum_{i=1}^2 (X_i - \bar{X})^2}}{\frac{1}{2}(X_1 + X_2)} = \frac{\sqrt{\frac{1}{4}(X_2 - X_1)^2}}{\frac{1}{2}(X_1 + X_2)} = \frac{|X_2 - X_1|}{X_1 + X_2}.$$

Figure 3.9: The relationship between *SPC* and *CV* of two samples

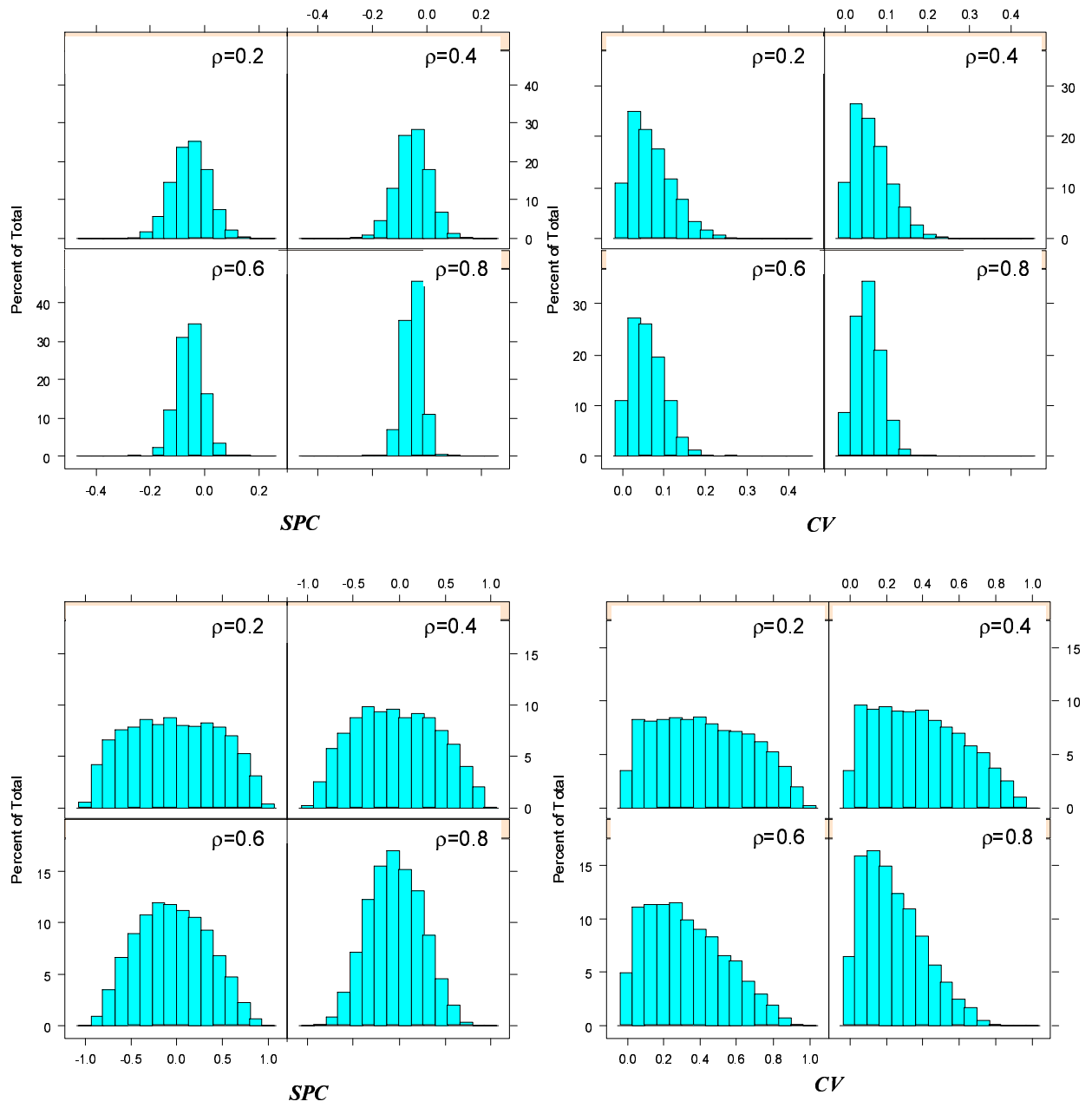


Figure 3.10: The distribution of  $SPC$  and  $CV$  (upper is BN and bottom is BLN)

## Section 4

# Simulations and case studies

In this section, we evaluate the effect of the statistical test results based on the simulation in case the distributions of *PC* or *SPC* do not follow the assumed distribution in each test, such as normal. In addition, we also show the case example to apply the power normal distribution to *SPC*.

### 4.1 Simulation 1: One sample comparison

#### 4.1.1 Design of simulation 1

We consider the situation where treatment effect is to reduce the post-data from pre-data, which is  $R > 0$ , and then we investigate the power of one-sample test for *PC* or *SPC*. The objective of this simulation is to evaluate the relationship between the distribution of pre- and post data based on the BPN and the power of the one-sample test about *PC* or *SPC*.

**Hypothesis of the statistical test.** In this simulation, the following hypotheses with 0.05 of significance level are set for three measures *PC*, *SPC*, *DTS*. The *DTS* is called "Difference on Transformed Scale" and is defined as  $X_2^{(\lambda)} - X_1^{(\lambda)}$ . One-sample t-test is used for *PC*, *SPC* and *DTS* and Wilcoxon Signed Rank Test (WSRT) are also used for *PC* and *SPC*. The hypotheses of interest are based on one-side and are as follows,

$$\begin{aligned} & H_0 : \theta = 0, \\ \text{vs} \quad & H_1 : \theta < 0, \end{aligned}$$

where  $\theta$  is the expected value or median of *PC*, *SPC* and *DTS*(expected value only) in one sample test. In addition, we evaluate the hypotheses based on the two sides,

$$\begin{aligned} & H_0 : \theta = 0, \\ \text{vs} \quad & H_1 : \theta \neq 0. \end{aligned}$$



**Parameter setting.** Table 4.1, 4.2 and 4.3 shows the parameters combination of BPN assumed as pre- and post-data distribution. We set the 5 levels  $\lambda$  ( $= -1, -0.5, 0, 0.5, 1$ ), 4 levels  $\tau$  ( $= 0.2, 0.4, 0.6, 0.8$ ), 4 levels  $\rho$  ( $= 0.2, 0.4, 0.6, 0.8$ ) and  $R$  ( $= 0, 10\%$ ), and then calculate the  $\mu_1, \mu_2, \sigma_1$  and  $\sigma_2$  based on the reparametrization method (Maruo, *et al.*, 2011; Maruo & Goto, 2012). Sample size is calculated based on the  $DTS$ (t-test), because  $DTS$  is normal in many cases and has highest power. Minimum sample size to exceed the power of 0.8 for  $DTS$ (t-test) sets in both hypotheses.

We calculate the proportion of significance per total numbers of simulations about  $DTS$ ,  $PC$  and  $SPC$ , when one-sample t-test or Wilcoxon Signed Rank Test ( $PC$  and  $SPC$  only) are applied. Total numbers of simulation is 100,000 times. The (tentative) type I error rate is defined as the proportion of significance when  $R = 0$ , and the (tentative) power is defined as the proportion of significance when  $R = 10$ . We can evaluate the loss of information based on the difference from the power of  $PC$  or  $SPC$  to 0.8, because sample size sets near the value of 0.8 for power of  $DTS$ .

Table 4.1: The combination of parameters for simulation and sample size ( $\lambda = -1$  and  $-0.5$ )

$\lambda$	med1	$R$	$\tau$	$\rho$	$\mu_1$	$\mu_2$	$\sigma_1$	$\sigma_2$	$n(\text{one side})$	$n(\text{two sides})$
-1	100	10	0.2	0.2	0.990	0.989	0.00147	0.00147	18	44
-1	100	10	0.2	0.4	0.990	0.989	0.00147	0.00147	13	34
-1	100	10	0.2	0.6	0.990	0.989	0.00147	0.00147	9	24
-1	100	10	0.2	0.8	0.990	0.989	0.00147	0.00147	5	12
-1	100	10	0.4	0.2	0.990	0.989	0.00286	0.00286	66	166
-1	100	10	0.4	0.4	0.990	0.989	0.00286	0.00286	49	126
-1	100	10	0.4	0.6	0.990	0.989	0.00286	0.00286	33	84
-1	100	10	0.4	0.8	0.990	0.989	0.00286	0.00286	17	42
-1	100	10	0.6	0.2	0.990	0.989	0.00415	0.00415	143	368
-1	100	10	0.6	0.4	0.990	0.989	0.00415	0.00415	106	270
-1	100	10	0.6	0.6	0.990	0.989	0.00415	0.00415	71	180
-1	100	10	0.6	0.8	0.990	0.989	0.00415	0.00415	36	90
-1	100	10	0.8	0.2	0.990	0.989	0.00549	0.00549	288	726
-1	100	10	0.8	0.4	0.990	0.989	0.00549	0.00549	208	534
-1	100	10	0.8	0.6	0.990	0.989	0.00549	0.00549	134	340
-1	100	10	0.8	0.8	0.990	0.989	0.00549	0.00549	65	166
-0.5	100	10	0.2	0.2	1.80	1.79	0.0148	0.0148	19	48
-0.5	100	10	0.2	0.4	1.80	1.79	0.0148	0.0148	14	36
-0.5	100	10	0.2	0.6	1.80	1.79	0.0148	0.0148	10	24
-0.5	100	10	0.2	0.8	1.80	1.79	0.0148	0.0148	5	12
-0.5	100	10	0.4	0.2	1.80	1.79	0.0291	0.0291	72	182
-0.5	100	10	0.4	0.4	1.80	1.79	0.0291	0.0291	53	136
-0.5	100	10	0.4	0.6	1.80	1.79	0.0291	0.0291	36	92
-0.5	100	10	0.4	0.8	1.80	1.79	0.0291	0.0291	18	46
-0.5	100	10	0.6	0.2	1.80	1.79	0.0427	0.0427	157	396
-0.5	100	10	0.6	0.4	1.80	1.79	0.0427	0.0427	115	290
-0.5	100	10	0.6	0.6	1.80	1.79	0.0427	0.0427	77	194
-0.5	100	10	0.6	0.8	1.80	1.79	0.0427	0.0427	39	100
-0.5	100	10	0.8	0.2	1.80	1.79	0.0553	0.0553	260	658
-0.5	100	10	0.8	0.4	1.80	1.79	0.0553	0.0553	192	492
-0.5	100	10	0.8	0.6	1.80	1.79	0.0553	0.0553	130	328
-0.5	100	10	0.8	0.8	1.80	1.79	0.0553	0.0553	66	166

Table 4.2: The combination of parameters for simulation and sample size ( $\lambda = 0$  and  $+0.5$ )

$\lambda$	med1	$R$	$\tau$	$\rho$	$\mu_1$	$\mu_2$	$\sigma_1$	$\sigma_2$	$n(\text{one side})$	$n(\text{two sides})$
0	100	10	0.2	0.2	4.61	4.50	0.148	0.148	20	50
0	100	10	0.2	0.4	4.61	4.50	0.148	0.148	15	38
0	100	10	0.2	0.6	4.61	4.50	0.148	0.148	10	26
0	100	10	0.2	0.8	4.61	4.50	0.148	0.148	5	14
0	100	10	0.4	0.2	4.61	4.50	0.295	0.295	78	198
0	100	10	0.4	0.4	4.61	4.50	0.295	0.295	59	148
0	100	10	0.4	0.6	4.61	4.50	0.295	0.295	39	100
0	100	10	0.4	0.8	4.61	4.50	0.295	0.295	20	50
0	100	10	0.6	0.2	4.61	4.50	0.438	0.438	172	436
0	100	10	0.6	0.4	4.61	4.50	0.438	0.438	129	328
0	100	10	0.6	0.6	4.61	4.50	0.438	0.438	86	218
0	100	10	0.6	0.8	4.61	4.50	0.438	0.438	43	110
0	100	10	0.8	0.2	4.61	4.50	0.578	0.578	299	758
0	100	10	0.8	0.4	4.61	4.50	0.578	0.578	224	570
0	100	10	0.8	0.6	4.61	4.50	0.578	0.578	150	380
0	100	10	0.8	0.8	4.61	4.50	0.578	0.578	75	190
0.5	100	10	0.2	0.2	18.0	17.0	1.48	1.48	21	54
0.5	100	10	0.2	0.4	18.0	17.0	1.48	1.48	16	40
0.5	100	10	0.2	0.6	18.0	17.0	1.48	1.48	11	28
0.5	100	10	0.2	0.8	18.0	17.0	1.48	1.48	6	14
0.5	100	10	0.4	0.2	18.0	17.0	2.97	2.97	84	208
0.5	100	10	0.4	0.4	18.0	17.0	2.97	2.97	63	160
0.5	100	10	0.4	0.6	18.0	17.0	2.97	2.97	42	106
0.5	100	10	0.4	0.8	18.0	17.0	2.97	2.97	21	54
0.5	100	10	0.6	0.2	18.0	17.0	4.45	4.45	185	478
0.5	100	10	0.6	0.4	18.0	17.0	4.45	4.45	141	352
0.5	100	10	0.6	0.6	18.0	17.0	4.45	4.45	94	240
0.5	100	10	0.6	0.8	18.0	17.0	4.45	4.45	47	118
0.5	100	10	0.8	0.2	18.0	17.0	5.93	5.93	337	860
0.5	100	10	0.8	0.4	18.0	17.0	5.93	5.93	253	628
0.5	100	10	0.8	0.6	18.0	17.0	5.93	5.93	167	424
0.5	100	10	0.8	0.8	18.0	17.0	5.93	5.93	83	210

Table 4.3: The combination of parameters for simulation and sample size ( $\lambda = +1$ )

$\lambda$	med1	$R$	$\tau$	$\rho$	$\mu_1$	$\mu_2$	$\sigma_1$	$\sigma_2$	$n(\text{one side})$	$n(\text{two sides})$
1	100	10	0.2	0.2	99.0	89.0	14.8	14.8	22	56
1	100	10	0.2	0.4	99.0	89.0	14.8	14.8	17	42
1	100	10	0.2	0.6	99.0	89.0	14.8	14.8	11	28
1	100	10	0.2	0.8	99.0	89.0	14.8	14.8	6	14
1	100	10	0.4	0.2	99.0	89.0	29.7	29.7	89	226
1	100	10	0.4	0.4	99.0	89.0	29.7	29.7	66	166
1	100	10	0.4	0.6	99.0	89.0	29.7	29.7	45	112
1	100	10	0.4	0.8	99.0	89.0	29.7	29.7	22	56
1	100	10	0.6	0.2	98.2	88.2	45.2	45.2	232	590
1	100	10	0.6	0.4	98.2	88.2	45.2	45.2	169	436
1	100	10	0.6	0.6	98.2	88.2	45.2	45.2	112	280
1	100	10	0.6	0.8	98.2	88.2	45.2	45.2	54	138
1	100	10	0.8	0.2	93.3	83.3	64.2	64.2	628	1560
1	100	10	0.8	0.4	93.3	83.3	64.2	64.2	440	1100
1	100	10	0.8	0.6	93.3	83.3	64.2	64.2	271	696
1	100	10	0.8	0.8	93.3	83.3	64.2	64.2	128	322

#### 4.1.2 Results of simulation 1

Figure 4.1 shows the (tentative) type I error rate with one side in each parameter combination. Tentative type I error rate of three measures were nearly equal to or less than significance level (0.05) in all parameter combinations. Especially, the (tentative) type I error rate of  $PC(\text{t-test})$  and  $PC(\text{WSRT})$  were much less than 0.05. This was because the absolute value order of positive value was larger than negative value order because of positive skew distribution and expectation of  $PC$  was more than 0, even if  $\mu_1 > \mu_2$  ( $R > 0$ ).

On the other hand, figure 4.3 shows the (tentative) type I error rate with both sides hypothesis ( $H_1 : \theta \neq 0$ ) in each parameter combination. From these figures, the (tentative) type I error rate of  $PC$  was much larger than 0.05 when  $\rho$  was small and  $\tau$  was large, because  $PC$  had significance in the positive expectation value ( $\theta > 0$ ).

Next, we show the results of (tentative) power with one side hypothesis in figure 4.2. The (tentative) power of  $DTS(\text{t-test})$  was nearly equal to 0.8. The (tentative) powers of  $PC$  which was  $PC(\text{WSRT})$  and  $PC(\text{t-test})$  were less than 0.7 in all parameters combination. This trend became larger when  $\tau$  was large or  $\rho$  was small. Especially, the (tentative) power of  $PC(\text{t-test})$

was nearly equal 0 when  $\tau$  was equal to or larger than 0.6 and  $\rho$  was equal to or less than 0.4. The condition to decrease the (tentative) power of  $PC$  depended on the skewness of distribution. The larger the distribution of skewness was (The larger the  $\eta$  is), the less the (tentative) power became. The (tentative) power of  $SPC$  which are  $SPC(WSRT)$  and  $SPC(t\text{-test})$  was nearly equal to 0.8 when  $\tau = 0.4$ , and was a little less than 0.8 in  $\lambda = -1, 1$  when  $\tau \geq 0.6$ . Regarding the (tentative) power with both sides hypothesis ( $H_1 : \theta \neq 0$ ) in figure 4.4, the (tentative) power of  $PC(t\text{-test})$  or  $PC(WSRT)$  was less than other measures ( $DTS$  or  $SPC$ ), because of the skewness of the distributions.

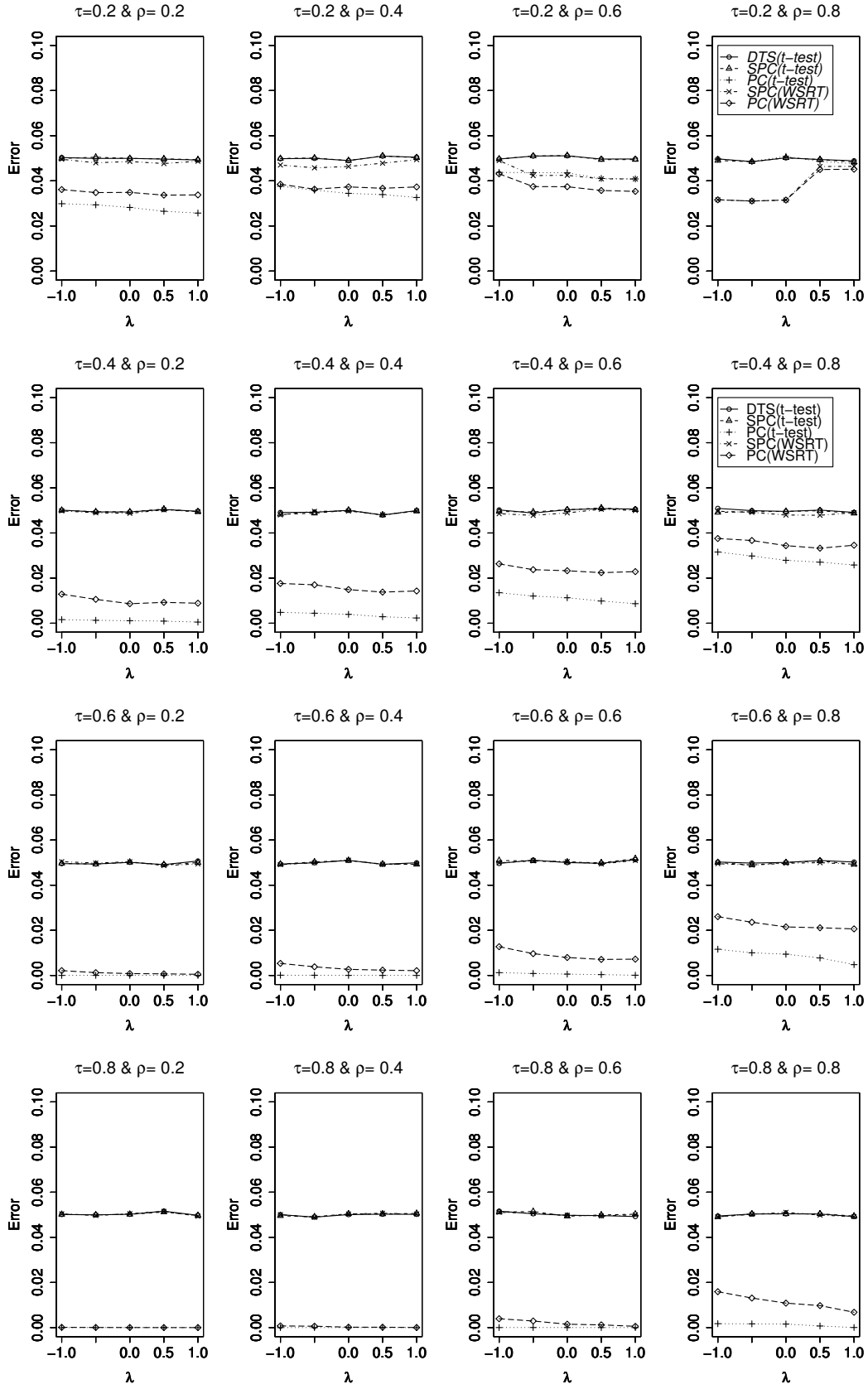


Figure 4.1: The relationship b/w type I error and  $\lambda$  (One sample & Set the 0.05 in one side)

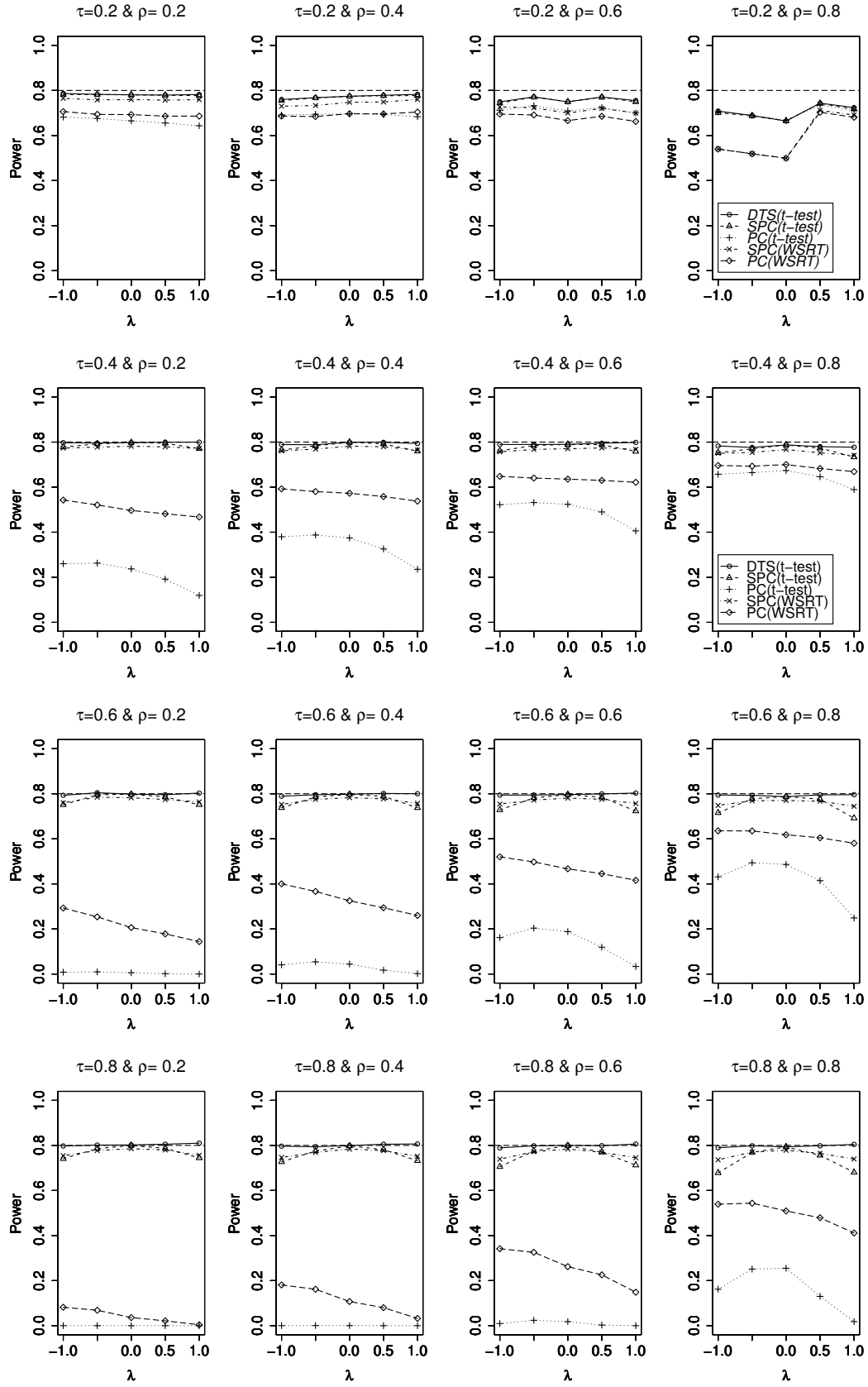


Figure 4.2: The relationship b/w power and  $\lambda$  (One sample & Set the 0.05 in one side)

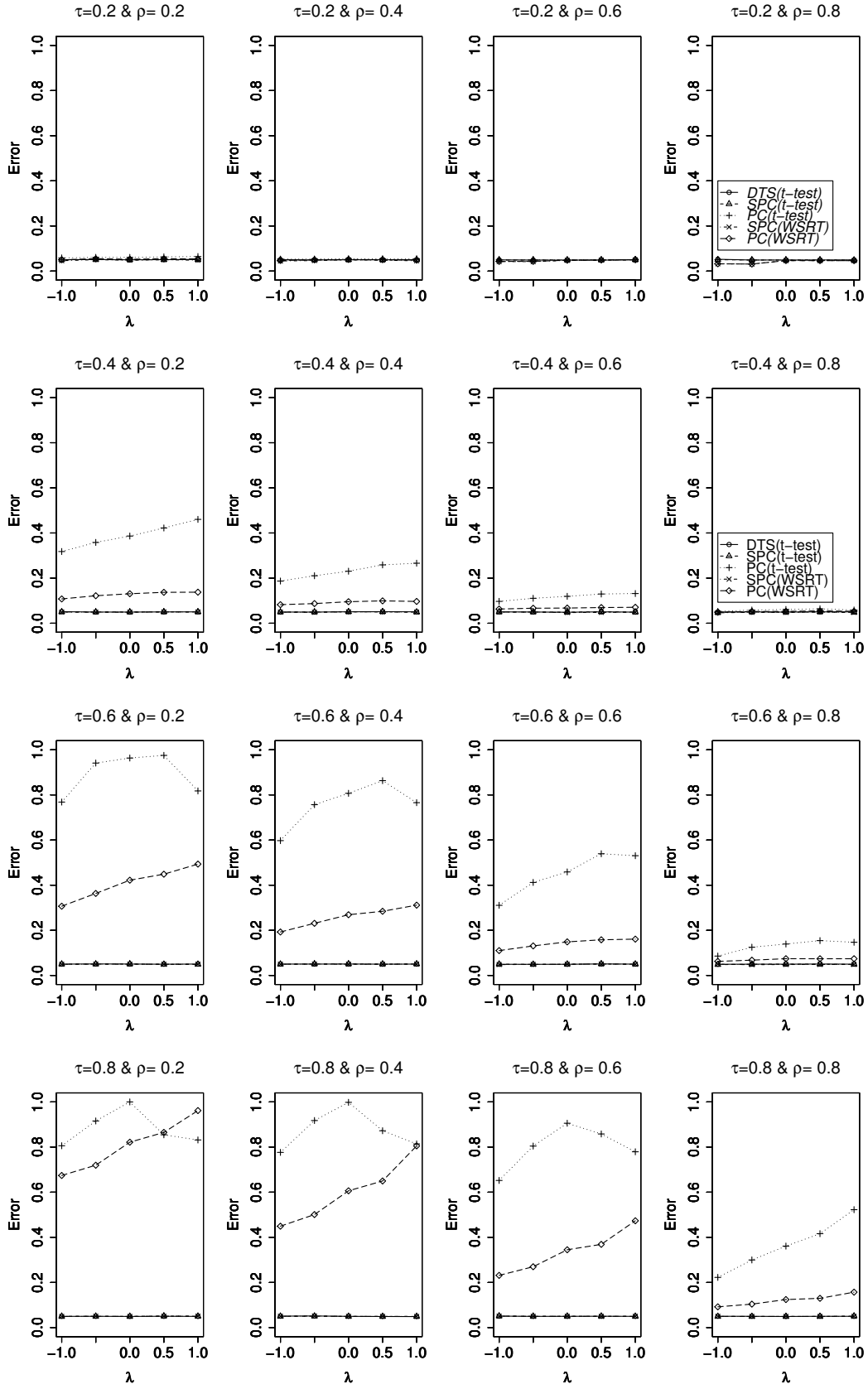


Figure 4.3: The relationship b/w type I error and  $\lambda$  (One sample & Set the 0.05 in both sides)



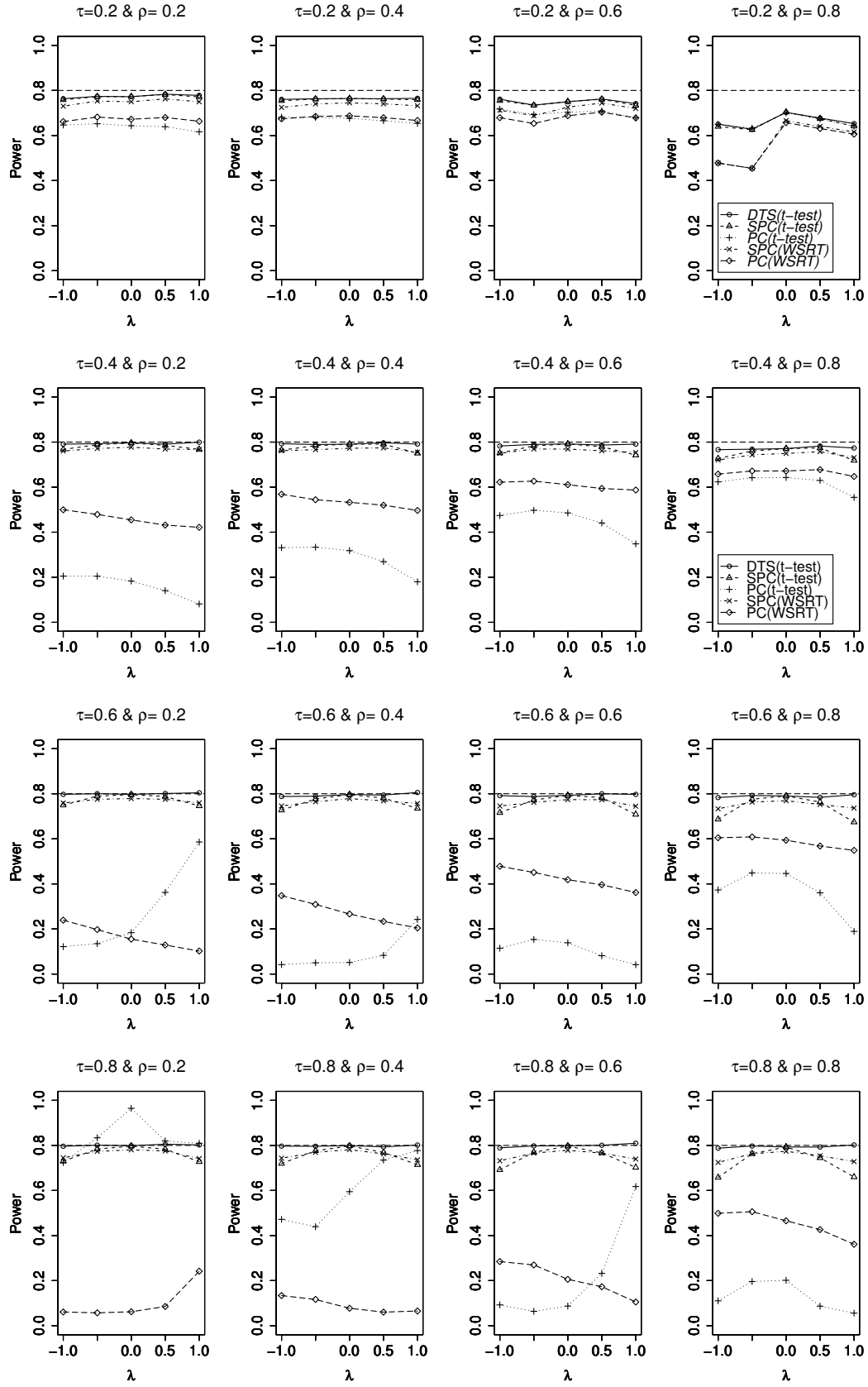


Figure 4.4: The relationship b/w power and  $\lambda$  (One sample & Set the 0.05 in both sides)

## 4.2 Simulation 2: Two samples comparison

### 4.2.1 Design of simulation 2

In this section, we evaluate the effect on statistical test of two samples which are treatment and control groups, when the distribution of  $PC$  or  $SPC$  has skewness. Pre- and post-data are assumed as BPN and the  $PC$  and  $SPC$  are calculated from pre- and post-data. And we also consider the situation that some effect is to reduce the post-data from pre-data as well as one sample comparison in previous section.

**Hypothesis of the statistical test.** In this simulation, the following hypotheses with 0.05 of significance level are set for three measures  $PC$ ,  $SPC$ ,  $DTS$ . Two-samples t-test is applied to  $PC$ ,  $SPC$  and  $DTS$  and Wilcoxon Rank Sum Test (WRST) is also applied to  $PC$ . The  $PC$  and  $SPC$  has the same order because these two measures are functions of pre- and post-data and can show a relational expression( $PC = 2 \times SPC/(1 - SPC)$ ). Therefore, the statistical results of  $PC$ (WRST) are the same as  $SPC$ (WRST). The hypotheses of interest are based on the one-side and are as follows,

$$\begin{aligned} & H_0 : \theta_T = \theta_C, \\ \text{vs} \quad & H_1 : \theta_T < \theta_C, \end{aligned}$$

where  $\theta_T$  or  $\theta_C$  are the expected value or median of treatment or control for  $PC$ ,  $SPC$ (expected value only) and  $DTS$ (expected value only) in two samples test. In addition, we also evaluate the hypotheses based on the two sides,

$$\begin{aligned} & H_0 : \theta_T = \theta_C, \\ \text{vs} \quad & H_1 : \theta_T \neq \theta_C. \end{aligned}$$

**Parameter setting.** We set the 5 levels  $\lambda$  ( $= -1, -0.5, 0, 0.5, 1$ ), 4 levels  $\tau$  ( $= 0.2, 0.4, 0.6, 0.8$ ), 4 levels  $\rho$  ( $= 0.2, 0.4, 0.6, 0.8$ ) and  $R$ ( $=0, 10\%$ ), and then calculate the  $\mu_1$ ,  $\mu_2$ ,  $\sigma_1$  and  $\sigma_2$  based on the reparametrization method in each treatment group(Maruo, *et al.*, 2011; Maruo & Goto, 2012). Sample size is calculated based on the  $DTS$ (t-test), because  $DTS$  is normal in many cases and has highest power. Minimum sample size to exceed the power of 0.8 for  $DTS$ (t-test) sets in both hypotheses, and this size is double of one simulation 1.

We calculate the proportion of significance per total numbers of simulations about  $DTS$ ,  $PC$  and  $SPC$ , when two-samples t-test or WRST ( $PC$  only) are applied. Total numbers of simulation is 100,000 times. The (tentative) type I error rate is defined as the proportion of significance when  $R = 0$ , and the (tentative) power is defined as the proportion of significance

when  $R = 10$ . We can evaluate the loss of information based on the difference from the power of  $PC$  or  $SPC$  to 0.8, because sample size sets near the value of 0.8 for power of  $DTS$ .

#### 4.2.2 Results of simulation 2

Figure 4.5 shows the (tentative) type I error rate for one side hypothesis. The (tentative) type I error rate of  $DTS(t\text{-test})$ ,  $SPC(t\text{-test})$ ,  $PC(WRST)$  were nearly equal to 0.05 in all parameter combinations.  $PC(t\text{-test})$  was also nearly equal to 0.05 when  $\tau = 0.2$  and  $\tau = 0.4$ . However,  $PC(t\text{-test})$  was less than 0.05, when  $\tau=0.6$  and  $\lambda = -1, +1$  or when  $\tau=0.8$  and  $\lambda = -1, -0.5, +0.5, +1$ .

On the other hand, figure 4.7 shows the (tentative) type I error rate for both side hypothesis. The trends of all measures were the same as the trends for one side hypothesis of figure 4.5. This was different from one sample results with both sides hypothesis and it was not shown that there was  $\theta_T > \theta_C$ .

Next, we show the results of (tentative) power of two sample test with one side hypothesis in figure 4.6.  $DTS(t\text{-test})$  had the highest (tentative) power and the (tentative) power was nearly equal to 0.8. The (tentative) power of  $PC(WRST)$  and  $SPC(t\text{-test})$  was almost same and  $PC(t\text{-test})$  had the lowest (tentative) power. The (tentative) power of  $PC(WRST)$ ,  $SPC(t\text{-test})$  and  $PC(t\text{-test})$  decreased with increasing the absolute values of  $\lambda$  ( $\lambda=-1$  or  $+1$ ) when  $\rho$  and  $\tau$  were constant. The reason why the (tentative) power of  $PC(t\text{-test})$  became small was considered based on increasing the standard error of difference with increasing the distribution of skewness of  $PC$ . The (tentative) power of  $SPC(t\text{-test})$  and  $PC(WRST)$  was nearly equal to 0.8 without regard to  $\rho$  and  $\lambda$  when  $\tau=0.2$  and  $0.4$ . These two measures,  $SPC(t\text{-test})$  and  $PC(WRST)$ , had less (tentative) power than 0.8 when  $\lambda = -1$  and  $+1$ . And the (tentative) power about two sample test with both sides in figure 4.8 were same trend as the (tentative) power with one side in figure 4.6.

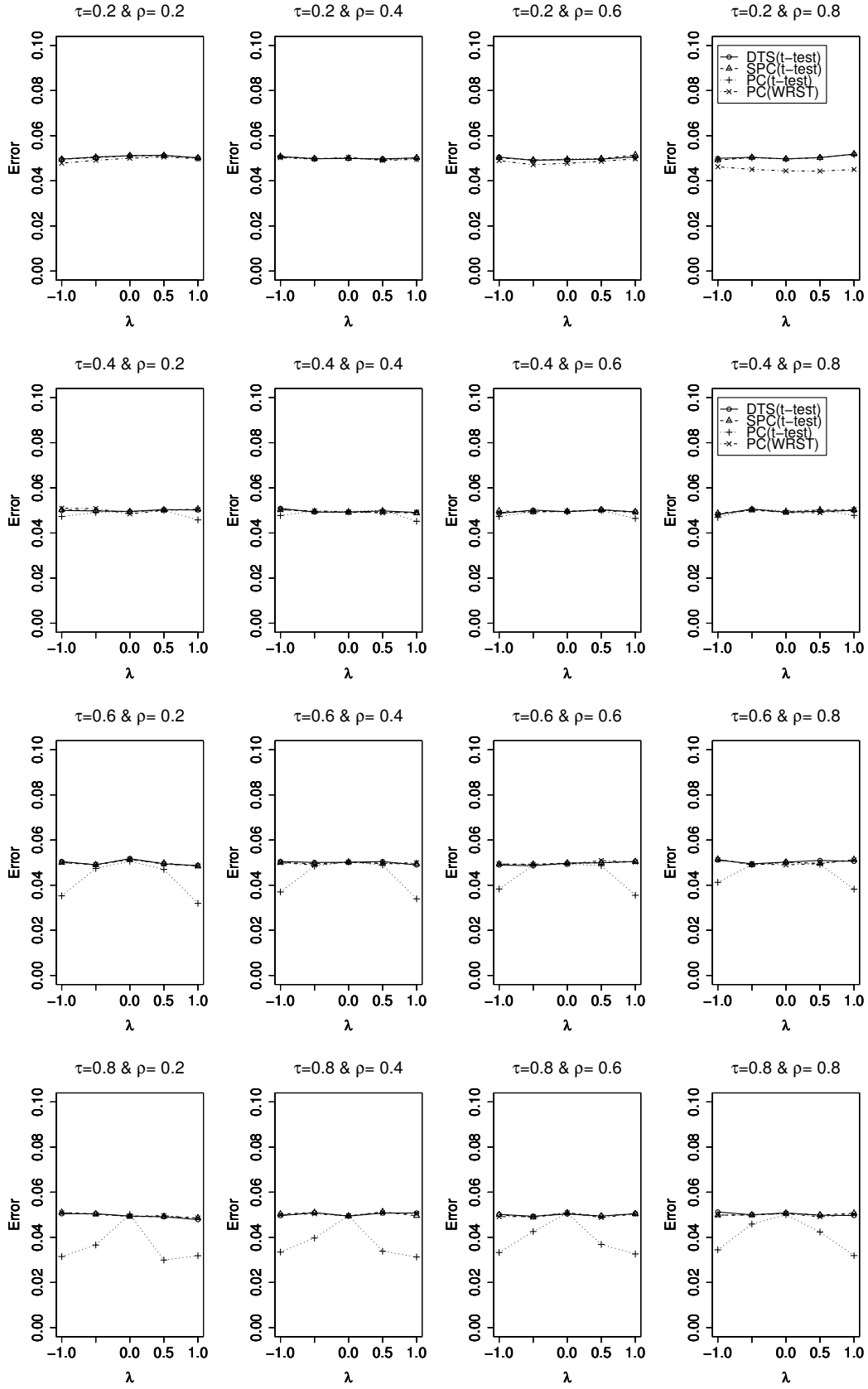


Figure 4.5: The relationship b/w type I error and  $\lambda$  (Two samples & Set the 0.05 in one sides)

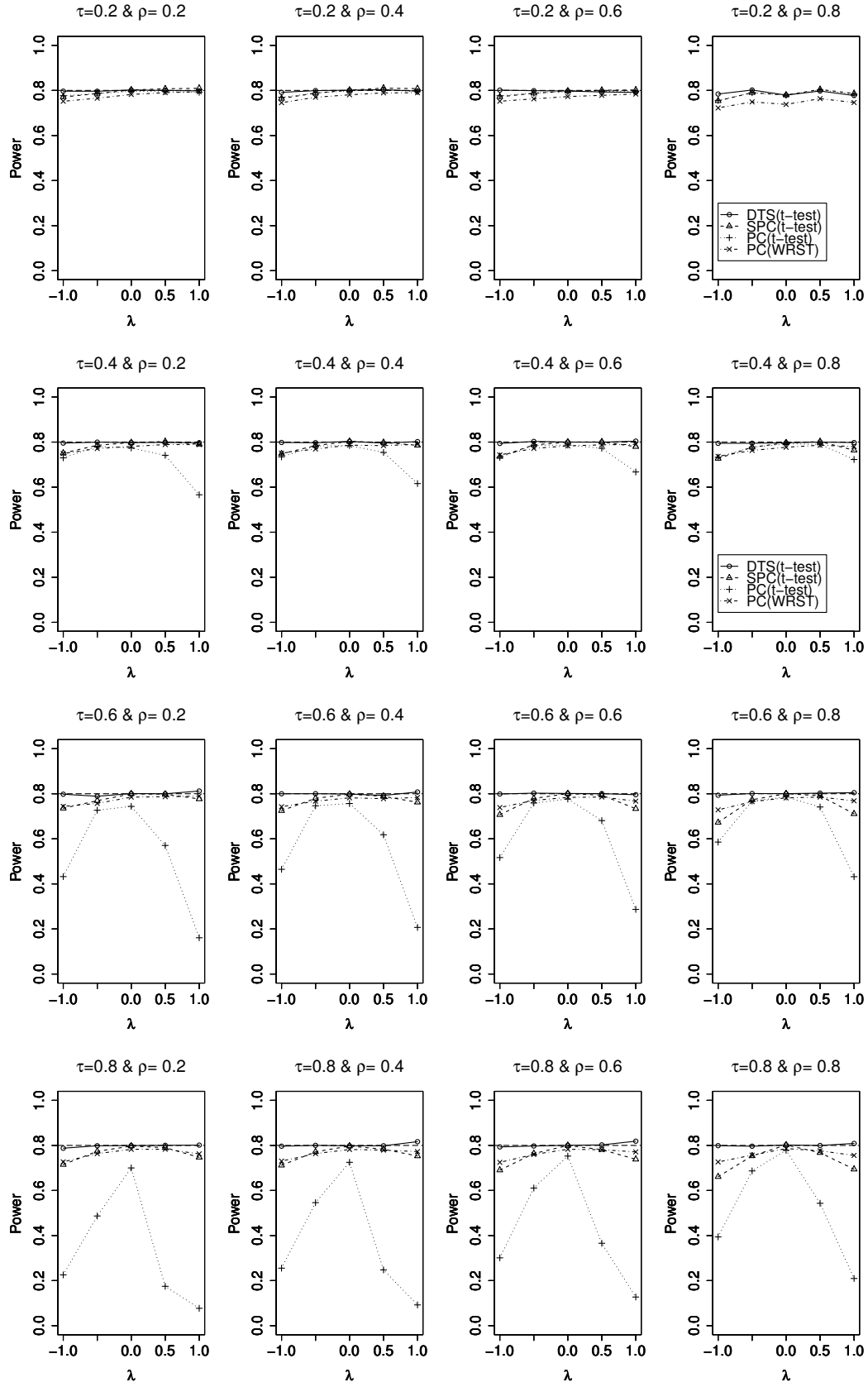


Figure 4.6: The relationship b/w Power and  $\lambda$  (Two samples & Set the 0.05 in one sides)

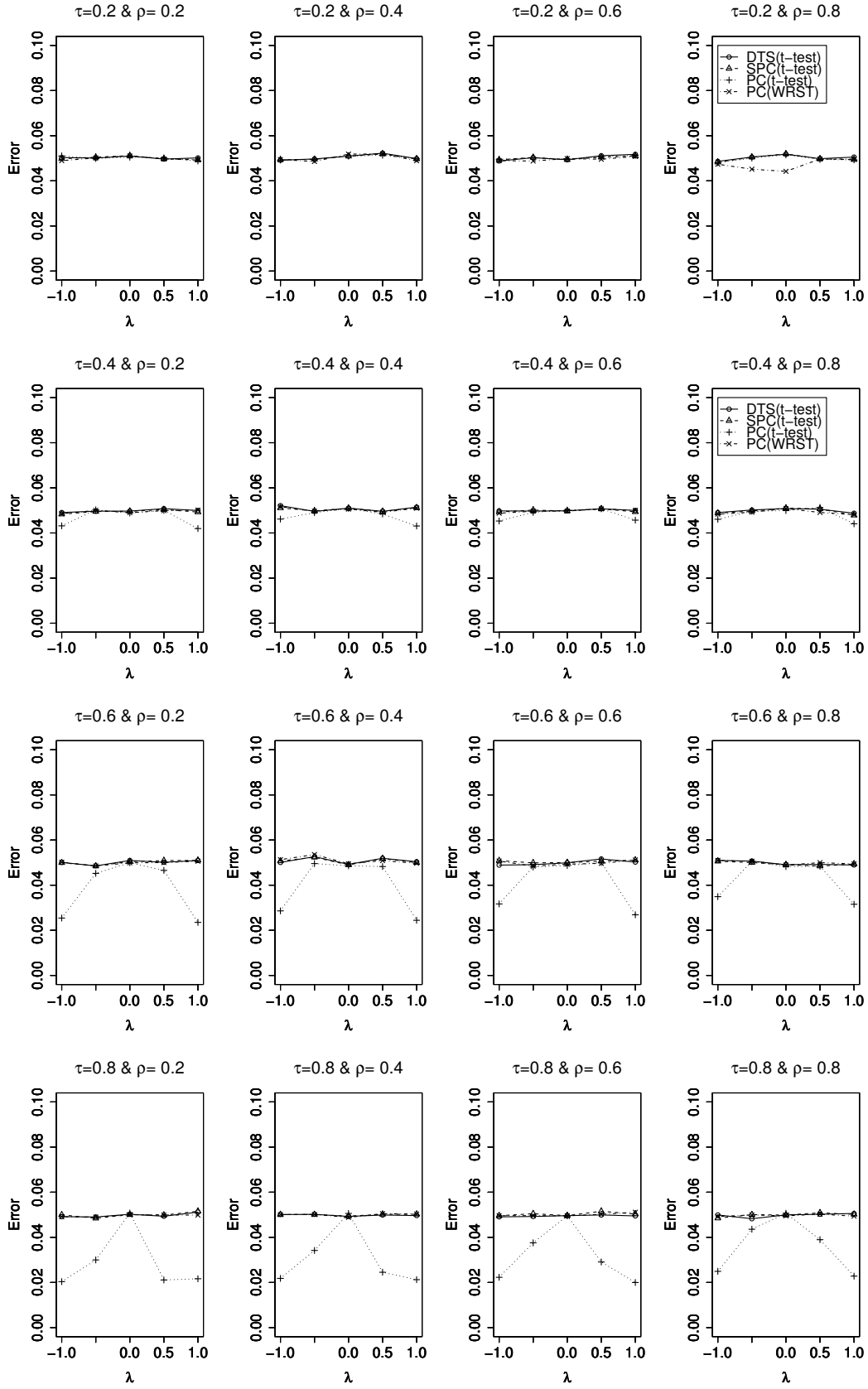


Figure 4.7: The relationship b/w type I error and  $\lambda$  (Two samples & Set the 0.05 in both sides)

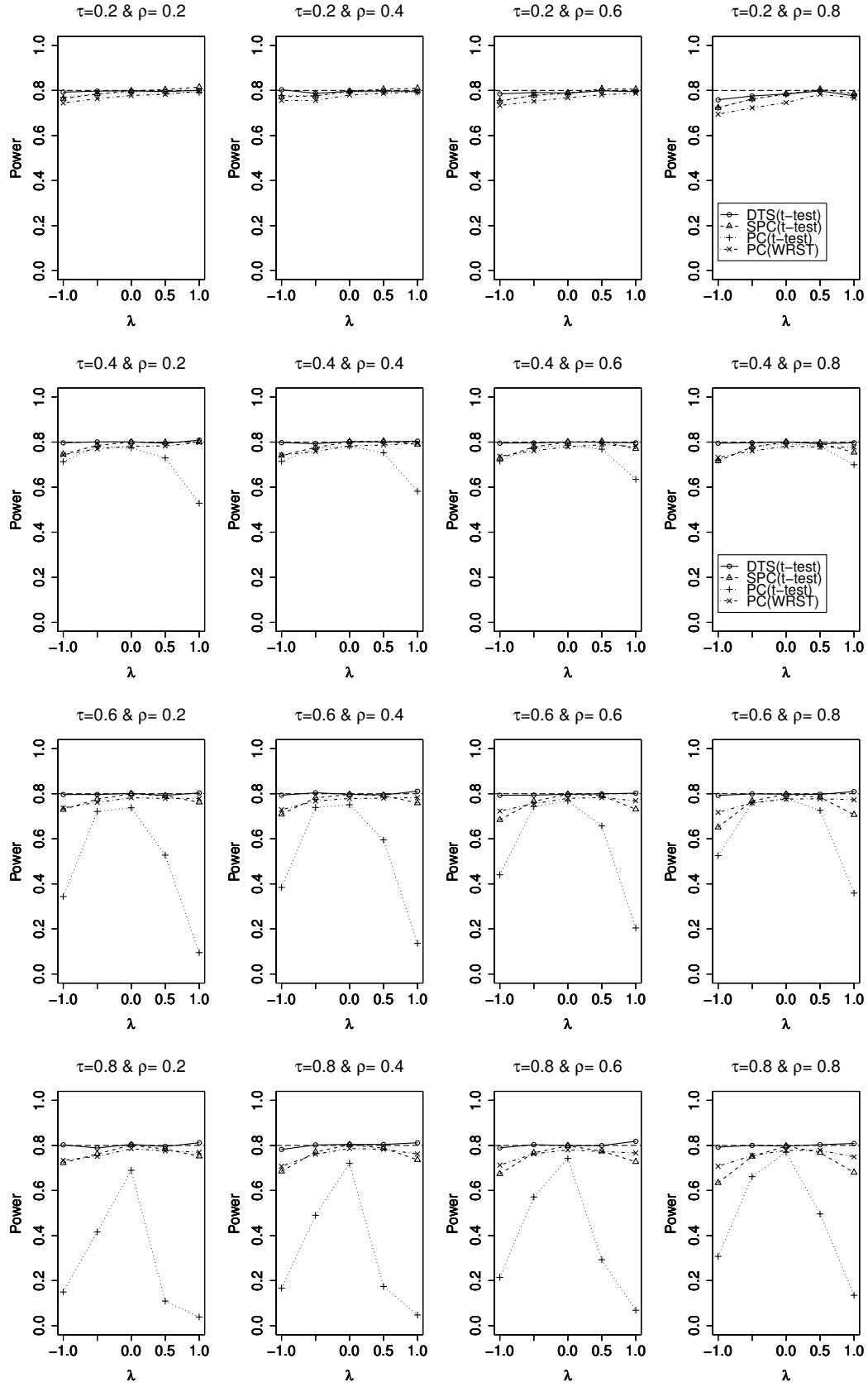


Figure 4.8: The relationship b/w Power and  $\lambda$  (Two samples & Set the 0.05 in both sides)

## 4.3 Case example

### 4.3.1 The application of symmetrized percent change to epilepsy data

In this section, we introduce the case example of *SPC* application as an example of the data analysis in phase III study of Gabapentin which is treated as an add-on therapy for refractory epilepsy. In this trial, *SPC* was named "Response Ratio (*RR*)".

The main objective of epilepsy treatment is to reduce the seizure frequency of each patient. Therefore, we evaluate the treatment effect to compare the seizure frequency of pre- and post-data in the clinical development of an antiepileptic drug. The evaluation of efficacy is based on the percent change from baseline in this field (French, 2001), because seizures are large variability in both intra- and inter-subjects and are skewness distribution for pre- and post-data. Additionally, when we evaluate seizure frequency (count data), the count data sometimes increase dramatically, such as from 10 counts of pre-data to more than 100 of post-data, if there are no treatment effects. For example, if a patient has 10 seizures of pre-data and 110 of post-data, then *PC* is 1000 %, and this value is too large. On the other hand, then *SPC* is 0.909 and is not too large. From this example, we consider *SPC* does not have less skew distribution than *PC*, because *SPC* does not give the too large value and shows robustness to outliers.

The 12-weeks, placebo controlled, double-blind study was conducted to evaluate the efficacy and safety of Gabapentin (Yagi & Sase, 2007 : Yamauchi *et al.*, 2006). This study set three treatment arms, 1200mg/day, 1800mg/day and placebo, and target population is the patients who had more than eight seizures in baseline period (pre-data) of 12 weeks. The 209 patients (86 patients in 1200mg/day, 41 patients in 1800mg/day and 82 patients in placebo) were included in the study, and per protocol set (PPS) was defined as the primary efficacy population. Table 4.4 shows the efficacy results of *SPC* about the comparison between 1200mg/day and placebo for PPS. The p-value was 0.0032 and statistical significance was shown for the comparison between 1200mg/day and placebo about 0.05 significance level.



Table 4.4: Efficacy Results of Gabapentin(From Goto *et al.*, 2007).

$SPC(RR)$	Placebo $n = 75$	Gabapentin (1,200mg/day) $n = 80$
Mean	-0.037	-0.144
SD	0.214	0.230
95%CI	[-0.086, 0.012]	[-0.195, -0.093]
Dif. b/w two groups	-0.107	
95%CI	[-0.176, -0.038]	
p value(t-test)	0.0032	

Next, we evaluate the shape of the sample distribution about the seizure data in the above study. Figure 4.9 shows the histogram of pre- and post-seizure data in 1200mg/day and placebo and shows the data driven power normal distribution(Goto *et al.*, , 2007; Goto *et al.*, 1979; Goto *et al.*, 1983). The estimate value of shape parameter ( $\lambda$ ) is follows.

	1,200mg/day	Placebo
Pre-data	-0.38	-0.37
Post-data	-0.14	-0.23

These estimated values of  $\lambda$  are negative near 0, and this result shows that the distribution of the seizure data in this study can approximate the log-normal distribution.

Figure 4.10 shows the histogram of  $SPC$  data in 1200mg/day and placebo and shows the distribution given by expression (3.4). In addition, we show the estimated value of  $\lambda$  as follows. From these results, it was shown that the distribution of  $SPC$  was nearly equal to a normal distribution.

	1,200mg/day	Placebo
$SPC$	1.45	0.94

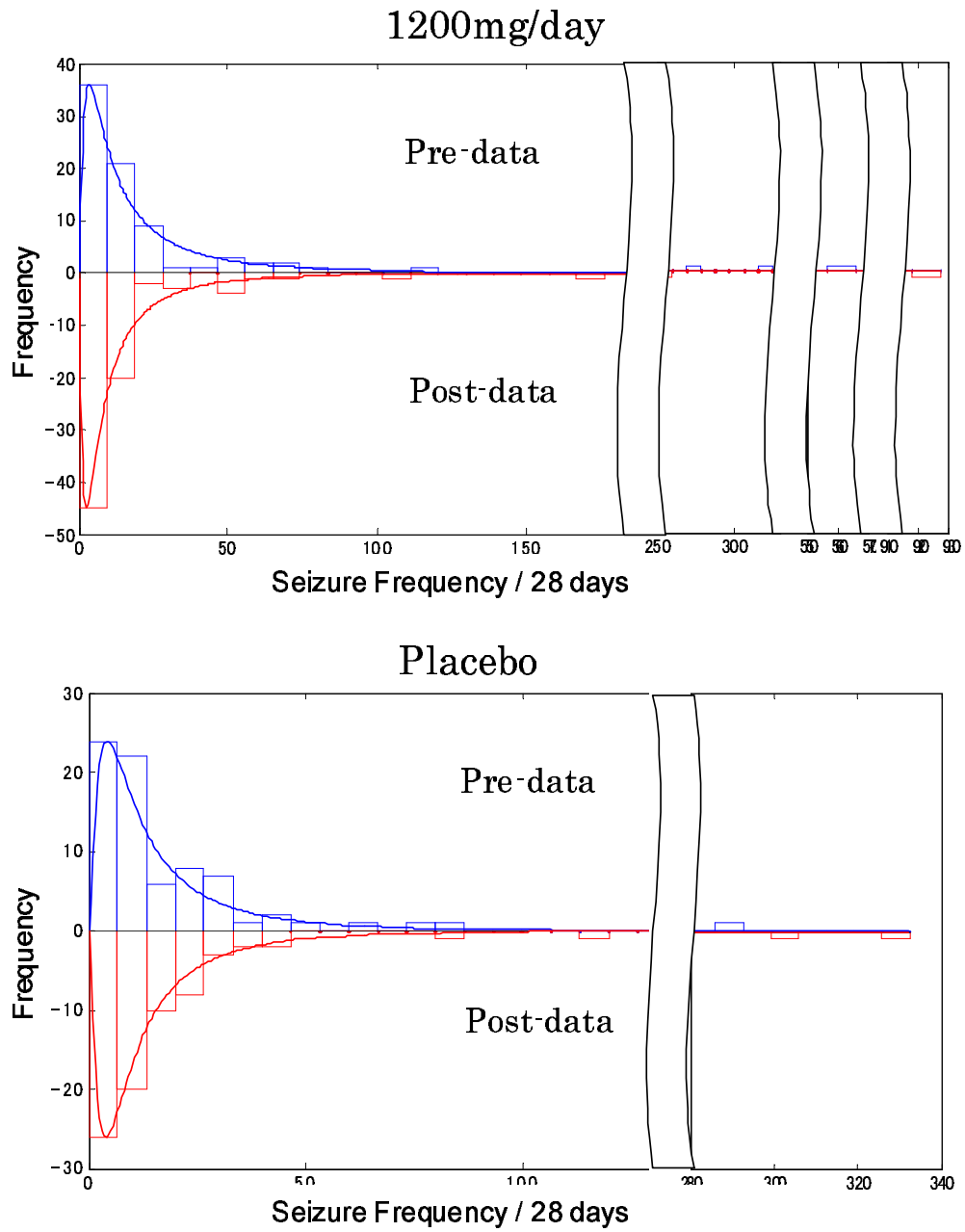


Figure 4.9: The histogram and applied power-normal distribution to seizure frequency (log-normal distribution): From Goto *et al.*, (2007)

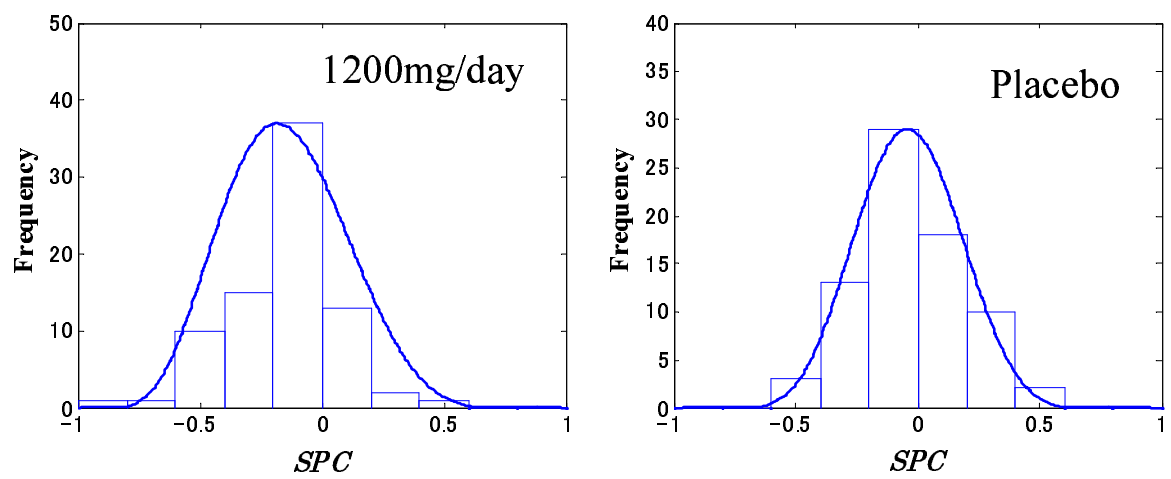


Figure 4.10: The histogram and applied distribution to  $SPC$  (given by expression (3.4)): From Goto *et al.*, (2007)

## Section 5

# Conclusion

### 5.1 Results and productive findings of this study

Both  $PC$  and  $SPC$  are used as ratio measures in a clinical trial in which a treatment effect is evaluated. However,  $PC$  was shown to have some difficulty to apply the statistical methodology based on the parametric methodology (Asakura *et al.*, 2011; Pharm-Gia *et al.*, 2006; Senn & Julious, 2009), and  $SPC$  was not clear in the statistical properties. In this paper, we investigated statistical properties of  $PC$  and  $SPC$  in which declaration of pdf, evaluation of skewness and evaluation to statistical power are included. And we propose how to apply the two measures in various situations in later paragraphs. In addition, we declared the relationship between  $SPC$  and coefficient of variation ( $CV$ ).

**Statistical properties of  $PC$ .** The distribution of  $PC$  was positively skewed when post-data was much larger than pre-data. This condition arises in the combinations of the following points.

1. The scale like parameter ( $\tau$ ) of pre- and post-data became large.
2. The correlation parameter ( $\rho$ ) between pre- and post-data became small.
3. The distribution of pre- and post-data became far from bivariate log-normal distribution, which means that the distribution becomes more positively skewed than log-normal distribution ( $\lambda$  becomes close to  $-1$ ) or that the distribution is close to normal and becomes negative skew ( $\lambda$  becomes close to  $+1$ ).

The  $\tau$  gave the largest contribution to a skewness of distribution for  $PC$ . The second largest contribution was  $\rho$  and third was  $\lambda$ . It is difficult to identify the condition to symmetrize the distribution, because the cause of distribution skewness exists more than one component and is from the combination of the components. Therefore, we recommend to confirm each distribu-

tion skewness in each situation taking the above results into consideration before applying the statistical methodology.

From results of comparison between pre- and post-data based on one sample statistical test, the (tentative) type I error of  $PC(t\text{-test})$  and  $PC(WSRT)$  became extremely low from the pre-defined significance level and the (tentative) power decreased more 0.1 (10 %) than  $DTS$ , which means that the (tentative) power was less than 0.7 in all conditions. From results of two group comparisons based on the two samples statistical test, the (tentative) type I error of  $PC(t\text{-test})$  became nearly equal to or slightly less than the pre-defined significance level and the (tentative) power decreased extremely when the scale like parameter ( $\tau$ ) became large or the distribution became far from log-normal (absolute value of  $\lambda$  is  $+1$ ). On the other hand, the (tentative) type I error of  $PC(WSRT)$  became nearly equal to pre-defined significance level and the (tentative) power was only slightly smaller than  $DTS$ .

**Statistical properties of  $SPC$ .** The distribution of  $SPC$  kept symmetry without regard to shape, scale like and correlation parameters of the distribution for pre- and post-data. Therefore, we can consider the application of statistical analysis based on the parametric methodology. From results of comparison between pre- and post-data based on one-sample test, the (tentative) type I error of  $SPC(t\text{-test})$  became nearly equal to pre-defined significance level and the (tentative) power of  $SPC(t\text{-test})$  slightly decreased when scale like parameter was large (especially  $\tau \geq 0.6$ ) and the distribution of pre- and post-data was far from log-normal. However, the (tentative) power of  $SPC(t\text{-test})$  was larger than  $PC(t\text{-test})$  or  $PC(WSRT)$ . From results of two groups comparison based on the two samples statistical test, the (tentative) type I error of  $SPC(t\text{-test})$  became nearly equal to pre-defined significance level and the (tentative) power was also nearly equal to or slightly less than  $DTS$ . In addition, the (tentative) power of  $SPC(t\text{-test})$  was also same as  $PC(WRST)$  in all conditions.

**Proposal how to apply two measures.** We can use the  $PC(WRST)$  when the objective is to evaluate the two groups comparison based on the ratio measures. Because  $PC$  is easy to interpret and  $PC(WRST)$  can keep high power. However, it is necessary to investigate the possibility of application carefully, if we know the factors to affect the treatment effect, if we estimate the effect based on the statistical methodology such as analysis of covariance(ANCOVA) and if we apply the  $PC(t\text{-test})$  for groups comparison. We need to make sure preliminarily whether or not the assumption to apply the  $PC(t\text{-test})$  are satisfied. If assumptions are not satisfied or if assumptions cannot be confirmed, then we can analyze the data to apply the  $SPC$  and can interpret the results after transforming the robust percent change ( $RPC$ ) proposed by Berry(1989).

In addition, we consider the statistical analysis should be done based on the *SPC*, when the objective is to compare the one-group comparison. Because the type I error keeps significance level and the power became large. The *SPC* is necessary to re-transformation for interpretation of the results. However, we consider that *SPC* is one of the favorable options for ratio measures, because we can use *SPC* in various shape of distributions. For example, when we analyze the change between pre- and post data of laboratory items, difference or percent change are only applied based on the past experience. We think laboratory items such as triglyceride (TG), which has positive skew distribution and becomes primary or secondary efficacy endpoint, should be applied *SPC*.

When we select a measure of effect in a clinical trial, a difference or a percent change are only applied based on the past experience without investigating the statistical properties so much. The important thing when selecting the measures of effect is to define the goal of statistical analysis definitely, and is to evaluate statistical properties, such as a skewness of distribution or a power in addition to evaluation from the clinical points of view.

**Relationship between *SPC* and *CV*.** There is the relationship between *SPC* and *CV* which is that the numerator of *CV* is replaced by the numerator of *SPC* with absolute value. Therefore, the distribution of *CV* is the distribution folded back negative value of *SPC* to positive.

## 5.2 Subjects for future investigation

As we mentioned in the previous section, *SPC* needs to be transformed into appropriate measures such as *RPC* proposed by Berry (1989) for interpretation. And Berry & Ayers (2006) also mentioned that the investigator would report an estimated *RPC* with an appropriately calculated standard error or confidence interval. However, there is no research about the standard error or the confidence interval. Therefore, it would be desirable to propose these in future research.



# Appendix A

## Reparametrization.

We show the reparametrization method to apply in section 2 of this paper (Maruo & Goto, 2008; Maruo, *et al.* 2010; Maruo & Goto, 2012). The  $\tau$  is defined as the scale parameter. When  $\lambda \neq 0$ ,  $\mu$  and  $\sigma$  cannot be obtained from  $\lambda, \xi_{0.5}$ , and  $\tau$  explicitly. Thus, they have to be calculated based on the grid search method. The calculation process for  $\mu$  and  $\sigma$  is given as follows:

- S1. Give  $\lambda, \xi_{0.5}$ , and  $\tau$ , and set  $K^{(\tau)} = \{-100, -99.9, \dots, 99.9, 100\}$ .  $K_i^{(\tau)}$  is the  $i$ th factor of  $K^{(\tau)}$  ( $i = 1, \dots, 2000$ ).
- S2. Calculate  $\mu_i^{(\tau)}$  and  $\sigma_i^{(\tau)}$  for all  $K_i^{(\tau)}$  based on (A.1). Then evaluate  $\delta_i^{(\tau)} = \xi_{0.75i}^{(\tau)} - \xi_{0.25i}^{(\tau)} - \xi_{0.5}\tau$  and replace  $\delta_i^{(\tau)}$  that can not be evaluated for some reason (e.g., obtained as NaN or infinity because of calculation precision of computers) and seven values on both sides of it by sufficiently large values, where  $\xi_{pi}^{(\tau)}$  is the percentile of the power-normal distribution with parameters:  $\lambda, \mu_i^{(\tau)}$ , and  $\sigma_i^{(\tau)}$ .

$$\mu = \begin{cases} \left(1 + \frac{z_{0.5^*}}{K}\right)^{-1} \left(\frac{\xi_{0.5}^\lambda - 1}{\lambda - \frac{z_{0.5^*}}{\lambda K}}\right), & K \neq 0, \\ -\frac{1}{\lambda}, & K = 0, \end{cases} \quad \sigma = \begin{cases} \frac{1 + \lambda\mu}{\lambda K}, & K \neq 0, \\ \frac{\xi_{0.5}^\lambda}{\lambda z_{0.5^*}}, & K = 0, \end{cases} \quad (\text{A.1})$$

- S3. Set  $i_{min} = \arg \min_i \text{abs}(\delta_i^{(\tau)})$ . If  $\delta_i^{(\tau)} < 0$ , divide  $\{K_{i_{min}}^{(\tau)}, K_{i_{min}+1}^{(\tau)}\}$ , else divide  $\{K_{i_{min}-1}^{(\tau)}, K_{i_{min}}^{(\tau)}\}$  into required accuracy of intervals (e.g., 0.0001) and replace  $K^{(\tau)}$  by this set. Repeat S1 and S2.
- S4. Set  $i_{min} = \arg \min_i \text{abs}(\delta_i^{(\tau)})$ . Calculate  $\mu$  and  $\sigma$  from  $K_{i_{min}}^{(\tau)}$ .

This calculation process can be performed by any programming language capable of parallel computation. The range  $[-100 \leq K \leq 100]$  covers almost any realistic situations, but cannot be calculated because  $K$  tends to become too large in the neighborhood of  $\lambda = 0$ . When  $\lambda = 0$ ,



$\mu$  and  $\sigma$  can be calculated explicitly:

$$\mu = \log(\xi_{0.5}), \sigma = \frac{\log\{(\tau + \sqrt{\tau^2 + 4})/2\}}{z_{0.75}}.$$

Fig.A.1 illustrates the relations between  $A(K)$  and  $\lambda$  for  $\xi_{0.5} = 100$  and  $\tau = 0.1, 0.3$ , and  $0.5$ . Simulations where the truncation is ignored should be run for  $\tau < 0.5$ . In addition, this relationship is invariant for  $\xi_{0.5}$  though we set  $\xi_{0.5} = 100$  in this figure.

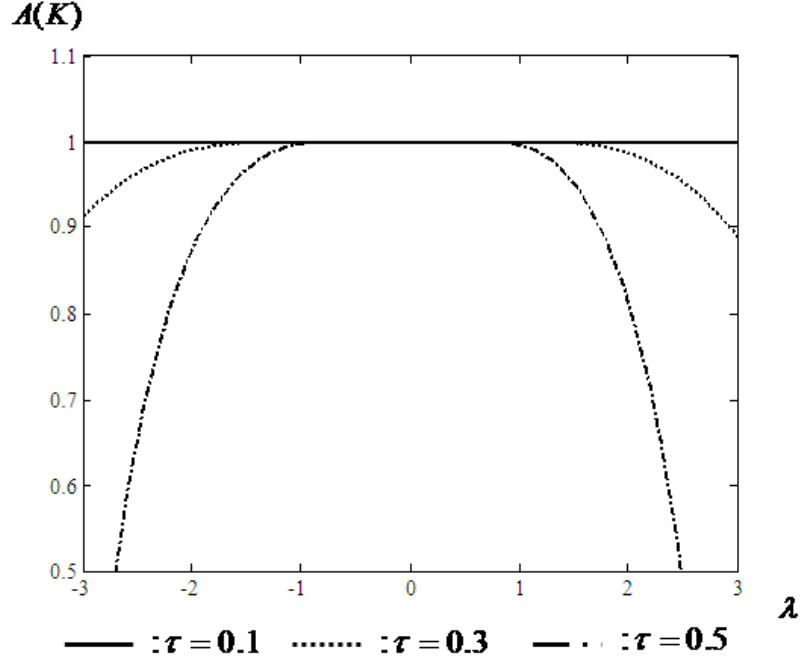


Figure A.1: The relationship b/w  $A(K)$  and  $\lambda$  for  $\xi_{0.5} = 100$ , and  $\tau = 0.1, 0.3$  and  $0.5$ .

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