Statistical properties of symmetrized percent change and percent change based on the bivariate power normal distribution

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1 Introduction

One of the most popular measure of effects for continuous data is percent change from baseline (PC) in a clinical trial, however it is said that PC may skew empirically. Thus, some tests in the framework of nonparametric methodology, such as Wilcoxon rank sum test will be applied for two group comparison. In this paper, we investigate the factors that affect the skewness of two measure of effects, which are PC and symmetrized percent change (SPC) (Berry, 1989: Berry and Ayers, 2006: Goto *et. al*, 2007), and also evaluate the factors that affect the power. First, we investigate the relationship between distribution of skewness for two measure of effects and parameters of pre- and post-data based on bivariate power normal distribution (BPND), and identify the factors that affect the distribution of skewness. Second, we evaluate the relationship between the factors and power for two group comparison quantitatively.

In Section 2, we introduce the BPND for pre- and post-data, and define the parameters for evaluation of skewness based on a percentile. In Section 3, we evaluate the relationship between the skewness of PC/SPC and the parameters of pre- and post-data. In Section 4, we calculate the power for two treatment group comparisons in each shape of distribution based on the simulation and evaluate the relationship between skewness and power. Finally, we summarize our findings in section 5.

2 Bivariate Power Normal Distribution (BPND)

In this section, we introduce the BPND to apply the pre- and post-data and show the identification of parameters for pre- and post-data. In addition, we define the index to evaluate the skewness of measure of effects based on the percentile.

2.1 BPND for pre-and post-data

Let $X_j (j = 1, 2)$ be the positive random variable and power transformation of X_j is defined as,

$$X_j^{(\lambda_j)} = \begin{cases} \dfrac{X^{\lambda_j} - 1}{\lambda_j} & \lambda_j \neq 0 \\ \log X_j & \lambda_j = 0 \end{cases}$$

where λ_j is the transforming parameter (Box and Cox, 1964). The ranges for the power transformed variable $X_j^{(\lambda)}$ are $-1/\lambda_j < X_j^{(\lambda)} < +\infty$ for $\lambda_j > 0$ and $-\infty < X_j^{(\lambda)} < -1/\lambda_j$ for $\lambda_j < 0$.

The distribution of $(X_1^{(\lambda_1)}, X_2^{(\lambda_2)})$ is based on the truncated bivariate normal distribution with mean vector $\mu = (\mu_1, \mu_2)^T$ and variance covariance matrix

$$\Sigma = \begin{bmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}$$

where ρ is the correlation coefficient between $X_1^{(\lambda_1)}$ and $X_2^{(\lambda_2)}$(association parameter). Then, two observed values, (X_1, X_2), are based on the bivariate power normal distribution and the joint pff is as (Goto and Hamasaki, 2002),

$$g(x_1, x_2) = \frac{x_1^{\lambda_1 - 1} x_2^{\lambda_2 - 1}}{A(\boldsymbol{K})} f\left(x_1^{(\lambda_1)}, x_2^{(\lambda_2)}\right), \quad x_1, x_2 > 0$$

where

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

and

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

$A(\boldsymbol{K})$ is the probability proportional constant term given by

$$A(\boldsymbol{K}) = \int_{a2}^{b2}\int_{a1}^{b1} \phi_2(x_1, x_2 : \rho)\, dx_1 dx_2$$

where $\phi_2(x_1, x_2 : \rho)$ is the joint pdf of the BPND and $\boldsymbol{K}$ is $(k_1, k_2)^T$. When k_j $(j = 1, 2)$ is said to the standarized truncation point and is defined as $k_j = (\lambda_j\mu_j + 1)/(\lambda_j\sigma_j)$, a_j and b_j are given as follows. First, when $\lambda_j > 0$, $a_j = -k_j$ and $b_j = -\infty$. Second, when $\lambda_j = 0$, $a_j = -\infty$ and $b_j = \infty$. And, third, when $\lambda_j < 0$, $a_j = -\infty$ and $b_j = -k_j$.

The BPND is identified by four kind of parameters, which are shape(λ_j), location(μ_j), scale(σ_j) and association(ρ) parameters. Especially, we can obtain various distributions with different shape associated λ_j. For example, a distribution is the normal, square-root transformed normal and lognormal distributions associated with λ_j of 1, 0.5 and 0, correspondengly. The power normal distribution can be fitted to real data including the various shape of distribution, thus we can use the traditional statsitical approach based on the normal distribution more easliy and widely.

2.2 Identification of parameters for pre- and post-data

It is difficult to interpret the properties of distribution for observed response based on the transformed paramters. Thus, we define the distributions based on the three paramters which are median ($\xi_{0.5}$) and variation of distribution(τ) and λ in this paper. τ is defined as,

$$\tau = \frac{\xi_{0.75} - \xi_{0.25}}{\xi_{0.5}}.$$

The 100p percentile (ξ_p) of the power normal distribution is given by

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

where z_p and z_{p*} are the percentile of $100p$ and $100p^*$ for standard normal distribution respectively(Maruo and Goto,2008). In addition, the combination of three parameters, (λ,$\xi_{0.5}$,τ) is connected with (μ,σ,K) by using the grid research and the following two equations, and Maruo and Goto(2008) have called this approach as reparametrization method.

$$\mu = \left(1 + \frac{z_{0.5*}}{K}\right)^{-1} \times \left(\frac{\xi_{0.5}^{\lambda} - 1}{\lambda - z_{0.5*}/(\lambda K)}\right), \qquad \sigma = \frac{1 + \lambda\mu}{\lambda K}$$

2.3 Index for evaluation of skewness

In the power normal distribution, some summary statistics such as skewness may not be able to be calculated when λ is less than 0, because more than p-ordered moment do not exist. To overcome this problem, we define the variation of skewness (η) based on the percentile as follows

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

The distribution of measures of effect is symmetry, when η is equal to 1. Thus, the distribution has positively skew(or negatively skew) when η is larger (or less) than 1.

3 Statistical Properties for SPC and PC

In this section, we evaluate the skewness of distribution for PC and SPC to use the η. Pre- (X_1) and post-data (X_2) are assumed as BPND to evaluate the various distribution. We set the following conditions about parameters of BPND, and identify the distribution based on the combination of parameters.

- We consider that pre- and post-data are positively skewed distribution, and shape parameter ($\lambda_j, j = 1, 2$) set from -1 to 1 by 0.5.
- Shape parameters of pre- and post-data are same($\lambda = \lambda_1 = \lambda_2$).
- Scale parameters of pre- and post-data are same ($\sigma = \sigma_1 = \sigma_2$).
- Median ($\xi_{0.5}$) of pre-data is 100 and median ($\xi_{0.5}$) of post-data is 10 % reduction from pre-value, which is 90.
- Variation of distribution (τ_1) for pre-data is from 0.2 to 0.8 by 0.2.
- Association parameter (ρ) between pre- and post-data is 0.4 and 0.8.

After identifying three parameters of pre-data, which are median ($\xi_{0.5}$), variation and distribution (τ_1), and shape (λ_1) parameters, we transformed three parameters, location (μ_1), scale (σ_1) and K are calculated from these parameters by using reparametrization method. And, we set σ_2 of post-data, and set the association parameter (ρ). Then, we calculate the percentile of PC and SPC by using the Monte-Carlo integration, and also calculate the skewness of distribution (η).

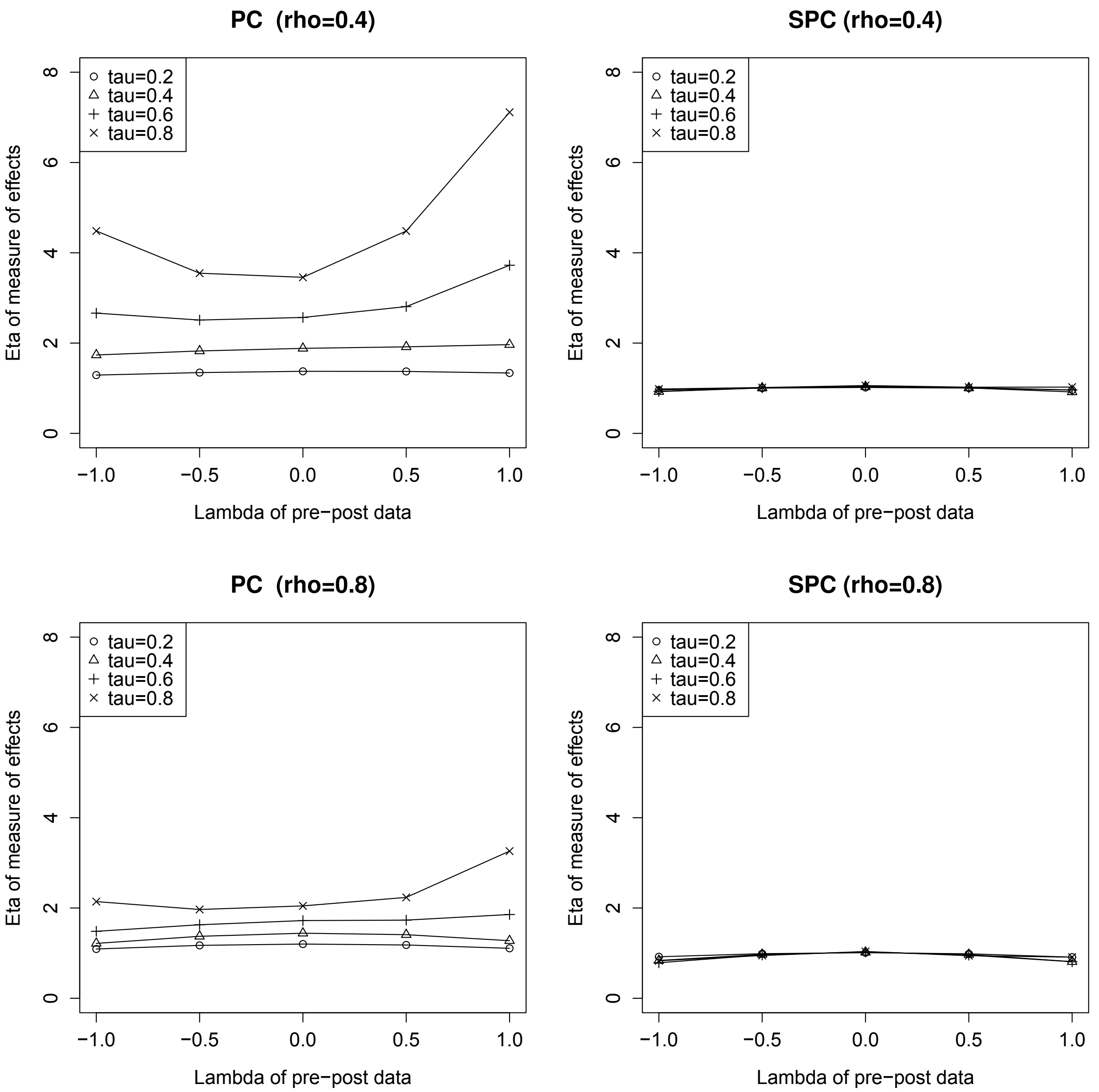

Figure 1: Relationship between λ of pre-post data and η of measure of effects (post-data is 10 percent reduction)

The relationship between $\lambda(= \lambda_1 = \lambda_2)$ and η are shown in Fig. 1 to investigate the shape of distribution for PC and SPC. The η of PC increased with increasing τ_1 and without depending on λ until τ_1 is 0.4. However, the η of PC is more increased in -1 or +1 of λ when τ_1 is more than 0.4. In addition, η of PC increased with ρ decreasing. The reason to skew the distribution is as follows in case that τ_1 increases or ρ decreases, (1) when λ is -1, the maximum of observed post-data increases because of positively skewed distribution, and (2) when λ is +1, the pre-value near 0 increase because this distribution is truncated normal distribution. On the other hand, η of SPC is almost 1, and is not depend on λ, ρ and τ_1.

4 Simulation

Objective : Generally, the distribution is assumed as normal, when the statistical tests on the parametric framework are applied. However, real data may differ from normal. In this simulation, the power of PC and SPC are calculated in various shape of distribution based on t-test. The difference of the power normal transformed value for pre- and post-data is approximately normal, and we compare the power between the difference based on the power transformed pre- and post-data and two measure of effects (PC and SPC). Then, we evaluate the loss of information which is impact to power between normal and other distributions. In addition, Wilcoxon rank sum test is included as reference in this simulation.

Design and results : We consider clinical trials with continuous endpoint to compare treatment and reference group. The pre- and post-data are collected, and reduction of post-data means the effect. The distributions of pre- and post-data about treatment and reference groups are assumed as BPND, and λ sets from -1 to +1 by 0.5. The $\xi_{0.5}$ of pre- and post-data for reference group sets as 100. The $\xi_{0.5}$ of pre-data for treatment group set 100, and the $\xi_{0.5}$ of post-data for treatment group sets 90 (10 % reduction from pre-data). The τ of pre-data of both groups sets 0.2, 0.4 and 0.8. Post-data sets same scale parameter (σ) as pre-data. And the ρ sets 0.8. Sample size sets to keep 0.8 of power for t-test about the difference of power normal transformed pre- and post-data. Number of simulation is 50000 times and we calculated the power and type I error, which are defined as the proportion of the number of significance per simulation number, when t-test is applied. Null hypothesis is defined as "true mean of treatment group is equal to reference group", and alternative hypothesis is defined as "true mean of treatment group is not equal to reference group". Power and type I error are also calculated on Wilcoxon rank sum test.

First, the relationship between λ and type I error were shown in Fig. 2. All simulations kept 0.05 about type I error. Next, the relationship between λ and power were also shown in Fig. 2, and our findings are, (1) the power was almost same in all λ when τ_1=0.2, (2) when τ_1=0.3, power was almost same in all methods from λ= -1 to 0.5, and was $Dif(t) = SPC(t) = PC(w) > PC(t)$ in λ=1. and (3) power was $Dif(t) > PC(w) \approx SPC(t) > PC(t)$ in all λ, when τ_1=0.8.

5 Conclusion Remarks

We investigated the factors that affect the skewness of two measure of effects (PC and SPC), and also evaluated the factors that affect the power. Then we summarized the findings obtained by our investigations and simulations as follows:

The η of PC increased with increasing τ_1 and without depending on λ until τ became 0.4. However, the η of PC was more increased in -1 or +1 of λ, when τ was more than 0.4. In addition, η of PC increased with ρ decreasing. The reason to skew the distribution is as follows in case that τ_1 increases or ρ decreases. When λ is -1, the maximum value of observed post-data increases because of positively skewed distribution. When λ is +1, the pre-value near 0 increases because this distribution is truncated normal distribution. On the other hand, η of SPC is almost 1, and dose not depend on λ, ρ and τ_1.

The power is almost all the same in all λ when τ_1=0.2. When τ_1=0.4, power is almost the same in all methods from λ= -1 to 0.5, and is $Dif(t) = PC(w) \approx SPC(t) > PC(t)$ in λ=1. Power is $Dif(t) > SPC(t) = PC(w) > PC(t)$ in all λ, when τ=0.8.

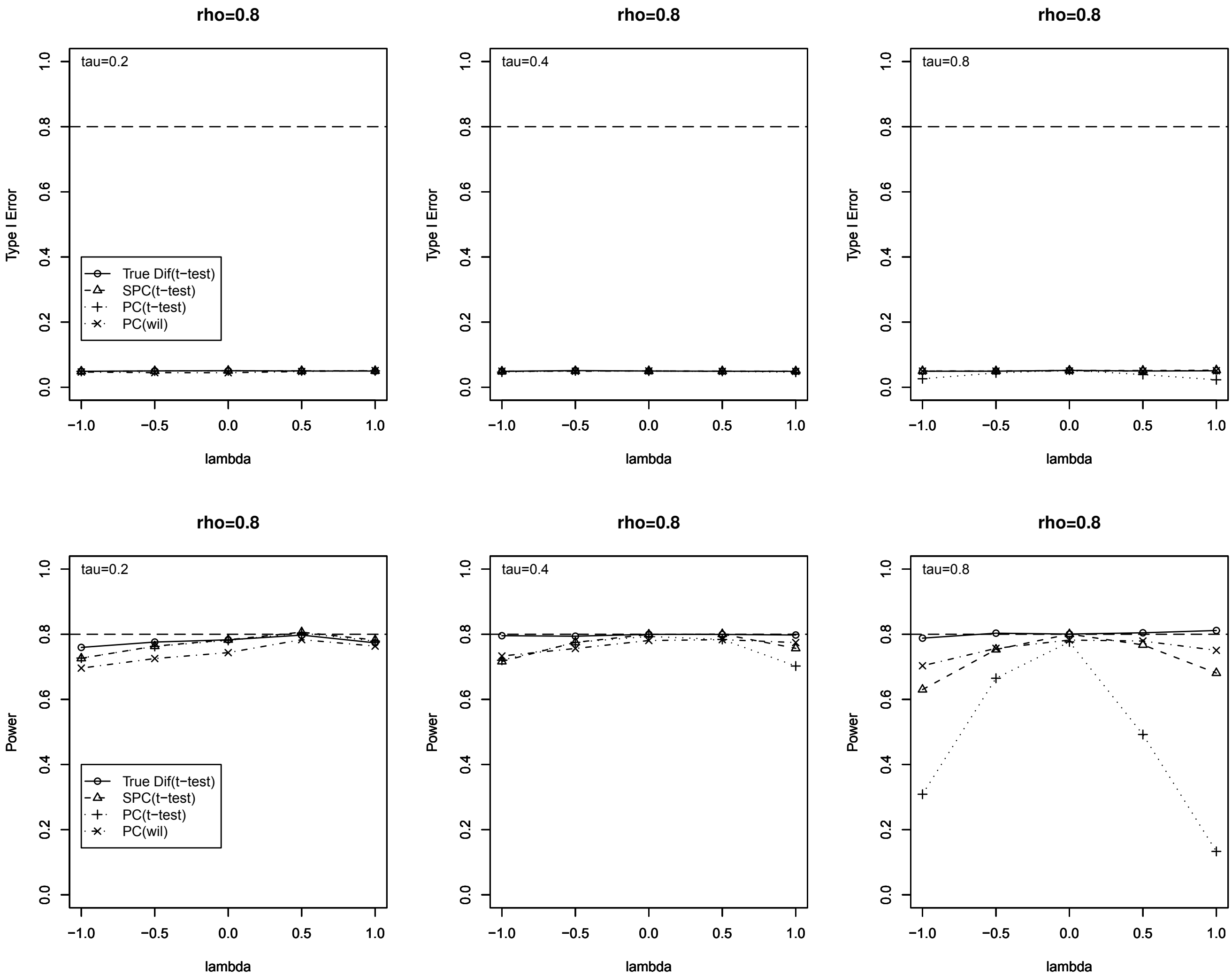

Figure 2: Relationship between λ and type I error or between λ ans Power

References

[1] Berry, D. A.(1989). *Statistical Methodology in the Pharmaceutical Sciences.*Marcel Dekker, New York.

[2] Berry, D. A. & Ayers, G. D.(2006). Symmetrized percent change for treatment comparisons. *The American Statistician*, **60** : 27-31.

[3] Box, G.E.P. & Cox, D.R. (1964). An analysis of transformations (with discussion). *J. Roy. Statist. Soc.*,, **B26(2)**: 211-246.

[4] Goto M. & Hamasaki T. (2002). The bivariate power normal distribution. *Bulletin of Informatics and Cybernetics*, **34(1)**: 29-49.

[5] Goto M., Yamabe T., Maruo K. & Kawai N. (2007), Statistical data analysis based on response ratio. *Japanese Journal of Clinical Psychopharmacology*, **10**: 667-676.

[6] Maruo K. & Goto M. (2008). On estimation of parameters in power-normal distribution. *Joint Meeting of 4th World Conference of the IASC and 6th Conference of the Asian Regional Section of the IASC on Computational Statistics and Data Analysis.*