國 立 交 通 大 學

統計學研究所

碩 士 論 文

參考曲線相等性之假設檢定

Hypothesis Testing for Equality of Reference Charts

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摘要

驗證兩個母體的參考曲線是否具有相同型態的比較在過去的文獻上得到一些注意，例如探討迴歸參數或迴歸函數的相等性皆有文章予以討論。在公共衛生的目的上，我們在參考曲線的相等性中考慮了較具一般性理論之研究，來比較兩個國家的成長型態，並且建立了成長模型參數的相等關係。這個方法可以讓我們描繪多種有趣的長期資料追蹤模型的參考曲線，並證明用檢定迴歸參數或函數的相等性的方式來比較參考曲線是不適當的。最後我們對於比較參考曲線提出來一個正確的檢定方法。

Hypothesis Testing for Equality of Reference Charts

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Abstract

Comparisons of reference charts for verifying if two populations of subjects have the same growth pattern have received some attention in literature. However, the proposals of comparison are restricted on equalities of regression parameters or regression functions. For public health purpose of comparing growth countries, we consider general theory of equalities of reference charts and establish its relations to equalities of growth model parameters. This approach allows us to display these relations for several interesting longitudinal growth models and these relations show that it is in-appropriate in comparing reference charts by testing equality of regression parameters or regression functions. Finally, we propose an exact test for comparisons of reference charts.

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張妙如 於交通大學統計學研究所

中華民國九十九年四月

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Abstract

Comparisons of reference charts for verifying if two populations of subjects have the same growth pattern have received some attention in literature. However, the proposals of comparison are restricted on equalities of regression parameters or regression functions. For public health purpose of comparing growth patterns of two countries, we consider general theory of equalities of reference charts and establish its relations to equalities of growth model parameters. This approach allows us to display these relations for several interesting longitudinal growth models and these relations hsow that it is in-appropriate in comaparing reference charts by testing equality of regression parameters or regression functions. Finally, we propose an exact test for comparisons of reference charts.

1. Introduction

Growth is a fundamental property of biological systems, occurring at the level of populations, individual animals and plants, as well as within organisms while the growth of a subject depends on nutritional, health, and environmental conditions. Typically the growth pattern for a treatment group depicts a family of symmetric quantile curves, called reference charts, as a function of some covariates (age or time). One difficulty in reference charts problem is that the measurement variables taken over time are generally not independent.

Much research has been devoted to modelling growth function and constructing growth charts in parametric or nonparametric way. For overview of parametric methodology, linear or nonlinear growth models, see Cole and Green (1992) and Laird and Ware (1982). When the measurements can be formulated as parametric regression model, the reference charts may be expressed as simple functions of parameters involved in the regression model so that its estimation may be done through estimations of these parameters. For example, the reference charts of a regression with normal errors model are linear functions of the mean and standard deviation. For

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growth characteristics that are approximately normal, proposals are available for transformations to normal where, among them, the most successful proposal is the LMS by Cole (1988). However, the Exponential-Normal distribution method by Wright and Royston (1997) has the advantage of being parametric with explicit expressions for estimating parameters and quantiles.

Verifying the similarity of two growth patterns through comparing the reference charts is an important topic in application. Basically the use of growth charts tries to summarize individual differences in the growth pattern and it is commonly known that the comparison of reference charts is done by studying the determinants of these differences. The most common method of comparison considers parametric growth model that the determinals of growth pattern can be represented by a few model parameters so that the job can be done by comparison of these parameters. However, the reference charts comparison considered in literature mainly restrcited on the comparison of growth regression functions. For example, it is seen that most parametric comparison methods consider only those parameters involved in regression function such as testing equality of two or several regression parameter vectors (see, Hoel (1964), Chi and Weerahandi (1998) and Pan and Cole (2004)) or comparing relations between regression slope parameters and (or) intercept parameters (see Zucker, Zerbe and Wu (1995)). Instead of parametric reference charts comparison, there are nonparametric methods comparing the unknown regression functions (see, for examples, Scheike and Zhang (1998), Scheike, Zhang and Juul (1999), Richard, et al. (1989) and Griffiths, Iles et al. (2004)). Hoel (1964) showed that such methods are less efficient than those to compare values of regression parameters.

For any comparison exercise, there needs to be clarity its precise objectives. For that assessment of growth pattern by charts is the single tool for defining health and nutritional status at both individual and population (country) level, there needs more general study for public health purpose in verifying if two or several countries display in the same or similar growth pattern. In light of this, we may ask: Do two populations (countries) have the same reference charts? This is an objective important to be answered in public health, espectially, for studying the developing countries. However, little research has been performed in reference charts comparison truely investigated in this purpose. It can be seen that comparisons of mean regression functions or few regression parameters can not achieve this public health problem (see Henry (1992)). One exception of a closer study is that Heckman and Zamar (2000) discussed the concepts of similarity and grouping in growth pattern based on rank correlation coefficient between regression functions. However, besides this is an estimation procedure that it is difficult to extend to hypothesis testing of comparison, regression function comparison is not enough to interprete the similarity or equality of growth patterns characterized by the reference charts. We consider the unknown population reference charts as parameters and study the differnces of two sets of unknown reference charts for comparison. This generalizes the comparison problem to a more general growth patterns comparison.

In this paper we develop the analytic relationships between model parameters of growth models achieving the fact of equality of population reference charts. This relationships provides exact test for comparison of reference charts and this observation indicates that testing equalities of regression parameters or regression mean functions often provides only a crude approximation to reality so that the conclusions for growth pattern comparison are very questionable. This approach is heading in a right direction in a general investigation if two growth models are with the same growth pattern.

In Section 2, we develop parameter relations for equality of reference charts constructed for two linear growth models that covers most linear mixed effects models. In Section 3, we select several interesting longitudinal linear models as examples to display these relations. These results will show that all existed studies of comparisons of regression parameters even without assuming known structure of covariance matrix of error variables are in-appropriate. In Section 4, we propose an exact test for conducting comparison of reference charts.

2. Characterization of Reference Charts

One reason for fitting models to growth data is that an appropriate curve will conveniently summarize the information provided by the observations of a individual subject. Thus the response variable $y(t)$ (height, weight, circumferences) with age or time t for disease group of subjects may be formulated (after an appropriate transformation) in a regression model with a vector $x(t)$ (age) in terms of few parameters. We consider the linear regression model

$$y(t) = x(t)'\beta_y + \epsilon_y(t), t \in (0,1) \tag{2.1}$$

where $\epsilon_y(t)$ is error variable with mean zero. Suppose that for another group of subjects there is also a response variable $z(t)$ that follows the same linear regression model with ossibly different parameters as

$$z(t) = x(t)'\beta_z + \epsilon_z(t) \tag{2.2}$$

where $\epsilon_z(t)$ is also error variable independent of $\epsilon_y(t)$ with mean zero. Using the same explanatory variables $x(t)$ indicates the balanced design that all the subjects in two groups are measured on the same set of time points. This design is for simplicity of discussion for our purpose while the theory and method developed in this paper are valid for the unbalance design. The interest of the comparison of reference charts is that the two sets of reference charts, respectively, constructed by these two regression models are identical. The parametric approaches of reference charts comparison consider to test equality of regression parameters as

$$H_\beta : \beta_y = \beta_z. \tag{2.3}$$

The general form of the reference charts is a series of smoothed curves, selected quantiles of the distribution of the response variable, plotted against the covariate (age or time). For $\gamma \in (0,1)$, the conditional quantile of y given age t is denoted by $F_y^{-1}(\gamma|t)$. The γth reference curve is the plot of the function $F_y^{-1}(\gamma|t)$ against t in S, set of ages, that can be reprented as

$$C_y(\gamma) = \{F_y^{-1}(\gamma|t) : t \in S\}$$

where S is the set of age. The reference curves of 7 percentages, $\gamma = 0.05, ..., 0.95$, symmetrical above and below the median, are used in North American and Europe. It is no loss of generality to consider all percentages in $(0,1)$. Without specifying the quantile percentages $\gamma's$, we consider the reference curves for a population of variable y as

$$\{C_y(\gamma) : \gamma \in (0,1)\}. \tag{2.4}$$

For response variable $z(t)$, the γth reference chart may be analogously represented as

$$C_z(\gamma) = \{F_z^{-1}(\gamma|t) : t \in S\}$$

where $F_z^{-1}(\gamma|t)$ is the γth quantile of z at time t and the reference charts for the population of variable z is $\{C_z(\gamma) : \gamma \in (0,1)\}$. The general hypothesis for comparison of reference charts then is

$$H_0 : C_y(\gamma) = C_z(\gamma), \gamma \in (0,1). \tag{2.5}$$

With linear model assumption of (2.1), it is seen that the γth reference charts may be written as $F^{-1}_{y(t)|x(t)}(\gamma) = x(t)'\beta_y + F^{-1}_{\epsilon_y}(\gamma) = x(t)'\beta_{y\gamma}$ where $\beta_{y\gamma} = \beta_y + \begin{pmatrix} F^{-1}_{\epsilon_y}(\gamma) \\ 0_{p-1} \end{pmatrix}$ is called the regression quantile (see Koenker and Bassett (1978)). The $100\gamma\%$th reference chart then is

$$C_y(\gamma) = \{x(t)'\beta_{y\gamma} : t \in S\}. \tag{2.6}$$

As pointed out by Hoel (1964), the estimation of reference charts is reduced to estimating the regression quantile β_γ.

The γth regression quantile for model (2.2) is $F^{-1}_{z(t)}(\gamma) = x(t)'\beta_z + F^{-1}_{\epsilon_z}(\gamma) = x(t)'\beta_{z\gamma}$ with $\beta_{z\gamma} = \beta_z + \begin{pmatrix} F^{-1}_{\epsilon_z}(\gamma) \\ 0_{p-1} \end{pmatrix}$. Then the γ reference chart for response variable z is

$$C_z(\gamma) = \{x(t)'\beta_{z\gamma} : t \in S\}. \tag{2.7}$$

and then the reference charts for regression model (2.2) is

$$\{C_z(\gamma) : \gamma \in (0,1)\}.$$

It is agreed, as investigated by Hoel (1864), that comparison of reference charts is more efficient conducted by comparing model parameters. It is then desired to verify when equality of reference charts in hypothesis (2.5) can be re-written into equations in terms of model parameters. The following theorem guides us a direction for these two problems.

Theorem 2.1. (a) The hypothesis of equal reference charts may be formulated as

$$H_{ref} : \beta_y = \beta_z, F_{\epsilon_y}^{-1}(\gamma) = F_{\epsilon_z}^{-1}(\gamma),\ \gamma \in (0,1). \tag{2.8}$$

(b) If we further assume that $F_{\epsilon_y}^{-1}(\gamma) = \sigma_y F_0^{-1}(\gamma)$ and $F_{\epsilon_z}^{-1}(\gamma) = \sigma_z F_0^{-1}(\gamma)$ where σ_y and σ_z are two unknown constants not dependent of time t. Then the hypothesis reduces to

$$H_{ref} : \beta_y = \beta_z, \sigma_y = \sigma_z. \tag{2.9}$$

Proof. From (2.6) and (2.7), identities of reference charts indicates

$$x(t)'\beta_{y\gamma}(t) = x(t)'\beta_{z\gamma}(t), t \in (0,1), \text{ for } 0 < \gamma < 1, t \in (0,1),$$

equalities holding for all covariates $x(t)$ which is equivalent to the follwoings

$$\beta_{y\gamma}(t) = \beta_{z\gamma}(t), \text{for } t \in S \text{ and } \gamma \in (0,1).$$

that reduces to

$$\begin{cases} \beta_y = \beta_z \text{ and} \\ F_{\epsilon_y}^{-1}(\gamma) = F_{\epsilon_z}^{-1}(\gamma),\ \gamma \in (0,1) \end{cases}$$

The result of (b) is obvious by the fact that $(\sigma_y - \sigma_z)F_0^{-1}(\gamma)$ for $\gamma \in (0,1)$ indicates $\sigma_y - \sigma_z = 0$. □

Result of (b) in Theorem 2.1 tells us that solving a comparison of reference charts is valid to be treated as a problem of testing hypothesis for equalities of some model parameters. However, different growth models lead to varying hypothesis testing problems. It is then interesting to see if the hypothesis in Theorem 2.1 is exactly done by testing equalities of all model parameters. For this, we know that each individual practically is repeated measured with n-observations $y_1, ..., y_n$ and $x_1, ..., x_n$ available from model (2.1). Let us define vectors $y = (y_1, ..., y_n)'$, $X' = (x_1, ..., x_n)$ and $\epsilon_y' = (\epsilon_y(t_1), ..., \epsilon_y(t_n))$. A matrix form of this regression model for this individual is

$$y = X\beta_y + \epsilon_y \tag{2.10}$$

where we consider that $\epsilon_y(t_i)'s$ are not independent with means $0s$ and ϵ_y has covariance matrix as Σ_y. The difficulty in reference chart problem of estimation and hypothesis testing is that the measurement variables taken over time are not statistically independent. Hence, generally the variables in $\{\epsilon_y(t) : t \in S\}$ have a complicated structure including correlation. In this consideration, we may test equalities of all model parameters as

$$H_{\beta,\Sigma} : \beta_y = \beta_z, \Sigma_y = \Sigma_z. \tag{2.11}$$

3. Formulation of Equal Reference Charts for Some Models

In this section, we consider several interesting repeated measurements regression models as examples to formulate specification of hypothesis in (2.5) for verifying if the classical hypothesis (2.3) of equalities of regression parameters is valid for general hypothesis of equal reference charts.

The random intercept model

The random intercept model for one individual is of the form

$$y(t_j) = \beta_{0y} + V_y + \beta_{1y}x_1(t_j) + \delta_y(t_j), j = 1, ..., n$$

where V_y has normal distributions $N(0, \sigma_{vy}^2)$ and $\delta_y(t_j)'s$ are independent normal distributions $N(0, \sigma_y^2)$. Also, variables V_y and $\delta_y(t_j)$ are assumed to be independent. This is a model of (2.1) with $x(t)'\beta_y = \beta_{0y} + \beta_{1y}x_1(t)$ and $\epsilon_y(t) = V_y + \delta_y(t)$. This random intercept model allows each individual to have its own intercept term and then the starting level for this individual is $\beta_{0y} + v_y$ where various subjects may have different observations $v_y's$ of V_y. This random intercept regression model has the form of (2.10) with designed matrix X and parameter vector β_y as

$$X = \begin{pmatrix} 1 & x_1 \\ 1 & x_2 \\ \vdots & \\ 1 & x_n \end{pmatrix}, \beta_y = \begin{pmatrix} \beta_{0y} \\ \beta_{1y} \end{pmatrix}, \Sigma_y = \sigma_y^2 I_n + \sigma_{vy}^2 J \tag{3.1}$$

with $x_j = x(t_j)$ and J is $n \times n$ matrix of 1's. In this model, the hypothesis of equality of all parameters is

$$H_{\beta,\Sigma} : \beta_y = \beta_z, \sigma_y = \sigma_z, \sigma_{vy} = \sigma_{vz}. \tag{3.2}$$

The set of reference charts of (2.4) for this random intercept model is

$$C_y(\gamma) = \{\beta_{0y} + \beta_{1y} x_1(t) + \sqrt{\sigma_{vy}^2 + \sigma_y^2} z_\gamma : t \in S\} \tag{3.3}$$

where z_γ is the γth quantile point for the standard normal distribution. Since the covariances are identical, this random intercept model is also called the uniform correlation model.

The equality of reference charts indicates

$$\beta_{0y}+\beta_{1y}x_1(t)+\sqrt{\sigma_{vy}^2 + \sigma_y^2}z_\gamma = \beta_{0z}+\beta_{1z}x_1(t)+\sqrt{\sigma_{vz}^2 + \sigma_z^2}z_\gamma \text{ for all } x_1(t) \text{ and } \gamma \in (0,1)$$

which indicates that testing equalities of reference charts is equivalent to test the following hypothesis

$$H_{ref} : \beta_y = \beta_z, \sqrt{\sigma_y^2 + \sigma_{vy}^2} = \sqrt{\sigma_z^2 + \sigma_{vz}^2}. \tag{3.4}$$

When we test the hypothesis H_β, acceptance of $\beta_y = \beta_z$ obviously does not indicate equality of reference charts since $\sqrt{\sigma_y^2 + \sigma_{vy}^2} = \sqrt{\sigma_z^2 + \sigma_{vz}^2}$ may not be guaranteed. Since $\sigma_y = \sigma_z$ and $\sqrt{\sigma_{vy}^2} = \sqrt{\sigma_{vz}^2}$ indicates that $\sigma_y^2 + \sigma_{vy}^2 = \sigma_z^2 + \sigma_{vz}^2$ is true, so, when we test hypothesis $H_{\beta,\Sigma}$ and the hypothesis is accepted then we are sure that the two reference charts are equal. However, there is a risk that these two reference charts are really equal when we reject $H_{\beta,\Sigma}$ since $\sqrt{\sigma_y^2 + \sigma_{vy}^2} = \sqrt{\sigma_z^2 + \sigma_{vz}^2}$ doesn't indicate that $\sigma_y = \sigma_z$ and $\sigma_{vy} = \sigma_{vz}$ are true.

When we are allowed to assume that $\sigma_y = \sigma_z$. The hypotsheis is reduced to the following

$$\beta_y = \beta_z, \sigma_y = \sigma_z, \sigma_{vy} = \sigma_{vz} \tag{3.5}$$

and then testing hypothesis $H_{\beta,\Sigma}$ is then appropriate.

The autoregressive model

The sample autoregressive model is model of (2.1) with error variables of the form

$$y(t_j) = \beta_{0y} + \beta_{1y}x_1(t_j) + \epsilon_y(t_j), j = 1, ..., n$$
$$\epsilon_y(t_j) = \rho_y \epsilon_y(t_{j-1}) + \delta_y(t_j)$$

where $\delta_y(t_j)$'s are iid random variables with normal distribution $N(0, \sigma_y^2)$. The autoregressive model may be re-formulated as is

$$y(t_j) = \beta_{0y} + \beta_{1y}x_1(t) + \epsilon_y(t_j), j = 1, ..., n$$
$$\epsilon_y(t_j) = \sum_{s=0}^{\infty} \rho_y^s \delta_y(t_{j-s}).$$

The measurement vector y is model of (2.10) with the same design of (3.1) except the covariance matrix as

$$\Sigma_y = \sigma_y^2 \Omega_y \text{ with } \Omega_y = \frac{1}{1-\rho_y^2} \begin{pmatrix} 1 & \rho_y & \cdots & \rho_y^{n-1} \\ \rho_y & 1 & \cdots & \rho_y^{n-2} \\ \vdots & \vdots & \vdots & \vdots \\ \rho_y^{n-1} & \rho_y^{n-2} & \cdots & 1 \end{pmatrix}.$$

The hypothesis of all parameters is the follwoing

$$H_{\beta,\Sigma} : \beta_y = \beta_z, \rho_y = \rho_z, \sigma_y = \sigma_z.$$

Then the set of reference charts is

$$C_y(\gamma) = \{\beta_{0y} + \beta_{1y}x_1(t) + \sqrt{\frac{\sigma_y^2}{1-\rho_y^2}} z_\gamma : t \in S\}.$$

From (2.5), the equality of reference charts indicates

$$\beta_{0y} + \beta_{1y}x_1(t)\sqrt{\frac{\sigma_y^2}{1-\rho_y^2}} z_\gamma = \beta_{0z} + \beta_{1z}x_1(t) + \sqrt{\frac{\sigma_z^2}{1-\rho_z^2}} z_\gamma \text{ for all } x_1(t) \text{ and } \gamma \in (0,1)$$

which requires to test the following hypothesis

$$H_{ref} : \beta_y = \beta_z, \sqrt{\frac{\sigma_y^2}{1-\rho_y^2}} = \sqrt{\frac{\sigma_z^2}{1-\rho_z^2}}.$$

In this model the acceptance of hypothesis H_β does not indicate the equality of reference charts. However, testing hypothesis $H_{\beta,\Sigma}$ has the risk that when the null hypothesis of equal reference charts is rejected the true fact is that the reference charts are in fact equal.

Random slope model

A simple random slope effects model is

$$y(t_j) = \beta_{0y} + (\beta_{1y} + B_y)x_1(t_j) + a_y(t_j), j = 1, ..., n$$

where B_y is a random variable with mean zero and variance $\sigma^2_{\delta y}$ and $a_y(t)$'s are iid random variables with mean zero and variance σ^2_y. This model allows the slope $\beta_{1y} + B_y$ being varied in individuals. This is a model of (2.1) with $\epsilon_y(t) = B_y x_1(t) + a_y(t)$.

This is a model of (2.1) with $x(t)'\beta_y = \beta_{0y} + \beta_{1y}x_1(t)$ and $\epsilon_y(t) = B_y x_1(t) + a_y(t)$ and the measurement vector y has covariance matrix as

$$\Sigma_y = \begin{pmatrix} \sigma^2_{\delta y}x(t_1)^2 + \sigma^2_y & \sigma^2_{\delta y}x(t_1)x(t_2) & \dots & \sigma^2_{\delta y}x(t_1)x(t_n) \\ \sigma^2_{\delta y}x(t_2)x(t_1) & \sigma^2_{\delta y}x(t_2)^2 + \sigma^2_y & \dots & \sigma^2_{\delta y}x(t_2)x(t_n) \\ \vdots & \vdots & & \vdots \\ \sigma^2_{\delta y}x(t_n)x(t_1) & \sigma^2_{\delta y}x(t_n)x(t_2) & \dots & \sigma^2_{\delta y}x(t_n)^2 + \sigma^2_y \end{pmatrix}$$

The hypothesis of equal parameters is

$$H_{\beta,\Sigma} : \beta_y = \beta_z, \sigma_{\delta y} = \sigma_{\delta z}, \sigma_y = \sigma_z. \tag{3.6}$$

The the set of reference charts is

$$C_y(\gamma) = \{\beta_{0y} + \beta_{1y}x_1(t) + \sqrt{\sigma^2_{\delta y}x_1(t)^2 + \sigma^2_y} z_\gamma : t \in S\}.$$

Then, the equality of reference charts indicates

$$\beta_{0y} + \beta_{1y}x_1(t) + \sqrt{\sigma^2_{\delta y}x_1(t)^2 + \sigma^2_y} z_\gamma = \beta_{0z} + \beta_{1z}x_1(t) + \sqrt{\sigma^2_{\delta z}x_1(t)^2 + \sigma^2_z} z_\gamma \text{ for all } x_1(t) \text{ an d } \gamma \in (0,$$

which requires to test the following hypothesis

$$H_{ref} : \beta_y = \beta_z, \sigma_{\delta y} = \sigma_{\delta z}, \sigma_y = \sigma_z. \quad \square$$

Two comments may be drawn from the results developed in the above example.

(a) For being able in detection of differences of reference charts, tests for equalities of regression parameters is not sufficient to achieve this aim. The approaches in comparisons of reference charts for the public health purpose mainly considered in verifying if main effects (regression parameters in parametric study and regression function in nonparametric study (see Scheike, Zhang and Juul (1999))) in regression models for two population groups are equal. This, from our investigation, generally does not fit the purpose of verifying the equality of reference charts that are accepted to represent the pattern of human growth.

(b) If we test hypothesis of equalities of all parameters such as random intercept or AR(1) errors models, then rejection of null hypothesis is not appropriate to conclude that the two reference chartes sets are identical.

Random intercept and random slope model

We consider a random effects model as

$$y(t_j) = \beta_{0y} + V_y + (\beta_{1y} + B_y)x_1(t_j) + a_y(t_j), j = 1, ..., n$$

where we further assume that V_y and B_y are independent normal random variables with distributions, respectively, as $N(0, \sigma^2_{vy})$ and $N(0, \sigma^2_{\delta y})$. We also assume that $a_y(t_j), j = 1, ..., n$ are iid random variables with distribution $N(0, \sigma^2_y)$. This is a model of (2.1) with $\epsilon_y(t) = V + Bx_1(t) + a(t)$. The covariance matrix of error vector is $\Sigma_y = (\sigma_{yjk})_{j,k=1,\ldots,n}$ with

$$\sigma_{yjj} = Var(\epsilon_y(t_j)) = \sigma^2_{vy} + \sigma^2_{\delta y} x_1(t)^2 + \sigma^2_y$$
$$\sigma_{yjk} = Cov(\epsilon_y(t_j), \epsilon_y(t_k)) = \sigma^2_{vy} + \sigma^2_{\delta y} x_1(t)^2.$$

The equality of all parameters hypothesis is

$$H_{\beta,\Sigma} : \beta_y = \beta_z, \sigma_{vy} = \sigma_{vz}, \sigma_{\delta y} = \sigma_{\delta z}, \sigma_y = \sigma_z.$$

The reference charts is the following set

$$C_y(\gamma) = \{\beta_{0y} + \beta_{1y} x_1(t) + \sqrt{\sigma^2_{vy} + \sigma^2_{\delta y} x_1(t)^2 + \sigma^2_y} z_\gamma : t \in S\}.$$

The equality of reference charts gives the hypothesis

$$H_{ref}:\beta_y=\beta_z,\sqrt{\sigma_{vy}^2+\sigma_y^2}=\sqrt{\sigma_{vz}^2+\sigma_z^2},\sigma_{\delta y}=\sigma_{\delta z}. \tag{3.7}$$

Our interest for the rest of this paper is introducing statistical methods to deal with exact test of reference charts comparison while Wright and Roysten (1997) indicated that this is a topic received little attention in the literature.

4. Comparison of Two Unknown Reference Charts

When the reference chart is used for public health purposes, it is to compare general health and nutrition of two or more populations (developed and developing world). In this situation, exact test for reference charts comparison for populations is desired to be proposed and evaluated.

The fact in statistical inferences is that we have m individuals and there are n observations for each individual. For jth individual, there are y_j and ϵ_j follow model of (2.1) as $y_j=X\beta_j+\epsilon_j$ for $j=1,...,m$. By setting vertical joinings y with $y'=(y'_1,y'_2,...,y'_m)$ and ϵ_y with $\epsilon'_y=(\epsilon'_{y1},...,\epsilon'_{ym})$, vector y has linear regression model of matrix form as

$$y=(1_m\otimes X)\beta_y+\epsilon_y,E(\epsilon_y)=1_m\otimes 0_n,cov(\epsilon_y)=I_m\otimes\Sigma_y \tag{4.1}$$

where $\otimes$ represents the Kronecker product, 1_m is m-vector of values $1's$ and I_m is $m\times m$ identity matrix. Models of this type is interesting since the covariance matrices for various subjects are identical. Suppose that for reference group of k subjects that response variable $z(t)$ following regression model (2.2) we also have n-observations $z_{ij},x_j,j=1,...,n,j=1,...,k$ available from model (2.2). Let vectors z_i and ϵ_{zi} satisfies $z'_i=(z_{i1},...,z_{in})$ and $\epsilon'_{zi}=(\epsilon_{zi1},...,\epsilon_{zin})$. A matrix form of this regression model for ith individual is

$$z_i=X\beta_z+\epsilon_{zi},i=1,...,k$$

where $\epsilon'_{zi}s$ are iid with mean 0_n and common covariance matrix Σ_z. By setting vertical joinings z with $z'=(z'_1,z'_2,...,z'_k)$ and ϵ with $\epsilon'_z=(\epsilon'_{z1},...,\epsilon'_{zk})$, vector z has linear regression model

$$z=(1_k\otimes X)\beta_z+\epsilon_z,E(\epsilon_z)=1_k\otimes 0_n,cov(\epsilon_z)=I_k\otimes\Sigma_z. \tag{4.2}$$

With this setting, the advanced joining $\begin{pmatrix} y \\ z \end{pmatrix}$ has the following model

$$\begin{pmatrix} y \\ z \end{pmatrix} = \begin{bmatrix} (1_m \otimes X)\beta_y \\ (1_k \otimes X)\beta_z \end{bmatrix} + \begin{pmatrix} \epsilon_y \\ \epsilon_z \end{pmatrix}$$

where $\begin{pmatrix} \epsilon_y \\ \epsilon_z \end{pmatrix}$ has mean $0_{(m+k)n}$ and covariance matrix $\begin{pmatrix} I_m \otimes \Sigma_y & 0 \\ 0 & I_k \otimes \Sigma_z \end{pmatrix}$. We now further consider the random intercept regression model, we have the likelihood function as

$$L(\beta_y,\beta_z,\sigma_y,\sigma_{vy},\sigma_z,\sigma_{vz}) = (2\pi)^{-(m+k)n/2} \begin{vmatrix} I_m \otimes (\sigma_{vy}^2 J + \sigma_y^2 I_n) & 0 \\ 0 & I_k \otimes (\sigma_{vz}^2 J + \sigma_z^2 I_n) \end{vmatrix}^{-1/2}$$
$$exp\{-1/2(\begin{pmatrix} y \\ z \end{pmatrix} - \begin{bmatrix} (1_m \otimes X)\beta_y \\ (1_k \otimes X)\beta_z \end{bmatrix})'$$
$$\begin{pmatrix} I_m \otimes (\sigma_{vy}^2 J + \sigma_y^2 I_n)^{-1} & 0 \\ 0 & I_k \otimes (\sigma_{vz}^2 J + \sigma_z^2 I_n)^{-1} \end{pmatrix} (\begin{pmatrix} y \\ z \end{pmatrix} - \begin{bmatrix} (1_m \otimes X)\beta_y \\ (1_k \otimes X)\beta_z \end{bmatrix})\} \quad (4.3)$$

he problem of comparison of reference charts is to verify based on these two sample regression models if the patterns of these two regression models are the same. Let us assume that $\sigma_y^2 = \sigma_z^2$ so that the hypothesis of equal reference charts is equivalent to test the following hypothesis of equal parameters

$$H_{\mu,\Sigma} : \beta_y = \beta_z, \sigma_y = \sigma_z, \sigma_{vy} = \sigma_{vz}$$

and the likelihood function under $H_{\mu,\Sigma}$ is

$$L(\beta,\sigma,\sigma_v) = (2\pi)^{-(m+k)n/2} |I_{m+k} \otimes (\sigma_v^2 J + \sigma^2 I_n)|^{-1/2} exp\{-1/2(\begin{pmatrix} y \\ z \end{pmatrix} - (1_{m+k} \otimes X)\beta)$$
$$(I_{m+k} \otimes (\sigma_v^2 J + \sigma^2 I_n)^{-1}(\begin{pmatrix} y \\ z \end{pmatrix} - (1_{m+k} \otimes X)\beta)\} \quad (4.4)$$

The generalized likelihood ratio is defined as

$$\Lambda = \frac{\sup_{\beta,\sigma,\sigma_v} L(\beta,\sigma,\sigma_v)}{\sup_{\beta_y,\beta_z,\sigma_y,\sigma_{vy},\sigma_z,\sigma_{vz}} L(\beta_y,\beta_z,\sigma_y,\sigma_{vy},\sigma_z,\sigma_{vz})}$$

A test based on this generalized likelihood ratio is:

$$\text{rejecting } H_0 \text{ if } \Lambda \leq q \quad (4.5)$$

where q satisfies $\alpha = P_{H_0}\{\Lambda \leq q\}$.

Let us denote the followings:

$$\bar{y}_{i.} = \frac{\sum_{j=1}^{n} y_{ij}}{n}, \bar{y}_{.j} = \frac{\sum_{i=1}^{m} y_{ij}}{m}, \bar{y}_{..} = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n} y_{ij}}{nm}, \bar{x} = \frac{\sum_{j=1}^{n} x_j}{n}$$

$$S_{yx} = \sum_{j=1}^{n}(\bar{y}_{.j} - \bar{y}_{..})(x_j - \bar{x}), S_{xx} = \sum_{j=1}^{n}(x_j - \bar{x})^2,$$

$$S_{zx} \sum_{j=1}^{n}(\bar{z}_{.j} - \bar{z}_{..})(x_j - \bar{x}).$$

The maximum likelihood estimates involved in likelihood function of (4.3) are

$$\hat{\beta}_{0y} = \bar{y}_{..} - \hat{\beta}_{1y}\bar{x}, \hat{\beta}_{1y} = \frac{S_{yx}}{S_{xx}}, \hat{\sigma}_y^2 = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n}(y_{ij} - (\bar{y}_{..} + \hat{\beta}_1(x_j - \bar{x})))^2}{m(n-1)}$$

$$\hat{\sigma}_{vy}^2 = \frac{1}{n}\left(\frac{n\sum_{i=1}^{m}(\bar{y}_{i.} - \bar{y}_{..})^2}{m} - \hat{\sigma}_y^2\right),$$

$$\hat{\beta}_{0z} = \bar{z}_{..} - \hat{\beta}_{1z}\bar{x}, \hat{\beta}_{1z} = \frac{S_{zx}}{S_{xx}}, \hat{\sigma}_z^2 = \frac{\sum_{i=1}^{k}\sum_{j=1}^{n}(z_{ij} - (\bar{z}_{..} + \hat{\beta}_{1z}(x_j - \bar{x})))^2}{k(n-1)}$$

$$\hat{\sigma}_{vz}^2 = \frac{1}{n}\left(\frac{n\sum_{i=1}^{k}(\bar{z}_{i.} - \bar{z}_{..})^2}{k} - \hat{\sigma}_z^2\right)$$

By letting $u_{ij} = \begin{cases} y_{ij} & \text{if } i = 1, ..., m \\ z_{i-mj} & \text{if } i = m+1, ..., m+k \end{cases}$, we further denote the followings

$$\bar{u}_{i.} = \frac{\sum_{j=1}^{n} u_{ij}}{n}, \bar{u}_{.j} = \frac{\sum_{i=1}^{m+k} u_{ij}}{m+k}, \bar{u}_{..} = \frac{\sum_{i=1}^{m+k}\sum_{j=1}^{n} u_{ij}}{n(m+k)}, S_{ux} = \sum_{j=1}^{n}(\bar{u}_{.j} - \bar{u}_{..})(x_j - \bar{x}).$$

The maximum likelihood estimates involved in likelihood function of (4.4) are

$$\hat{\beta}_0 = \bar{u}_{..} - \hat{\beta}_1\bar{x}, \hat{\beta}_1 = \frac{S_{ux}}{S_{xx}}, \hat{\sigma}^2 = \frac{\sum_{i=1}^{m+k}\sum_{j=1}^{n}(u_{ij} - (\bar{u}_{..} + \hat{\beta}_{u1}(x_j - \bar{x})))^2}{(m+k)(n-1)}$$

$$\hat{\sigma}_v^2 = \frac{1}{n}\left(\frac{n\sum_{i=1}^{m+k}(\bar{u}_{i.} - \bar{u}_{..})^2}{m+k} - \hat{\sigma}_{u1}^2\right).$$

We consider the random intercept model for simulating the performance of the likelihood ratio test. How to get appropriate cutoff point q for rule

(4.5)? The classical theory for likelihood ratio test suggests the test statistic $-2ln\Lambda$ using the chi-squares distribution. For evaluation, let us restrict $k = m = 2$ and setting $\beta_{1y} = \beta_{1z} = \beta_{0y} = \beta_{0z} = \sigma_y^2 = \sigma_z^2 = \sigma_{vy}^2 = \sigma_{vz}^2 = 1$. In this design, it is $\chi^2_{1-\alpha}(4)$ that they are $9.488, 11.143$ and 13.277 when we consider $\alpha = 0.01, 0.025$ and 0.05. We perform a simulation under sample sizes $n_1 = n_2 = 30$ for evaluation of this theoretical results of the type I error probabilities. With replications $100,000$, the simulated results of type I error probabilities are, respectively,

$$0.00409, 0.01061, 0.02371. \tag{4.6}$$

They are too far below the theoretical values, $0.01, 0.025, 0.05$. Hence, applying the chi-squares approximation for likelihood ratio statistic Λ in this reference charts comparison problem is too conservative so that this cutoff point is not appropriate.

We proprose, for this problem, the simulation method. With designing all parameters being values 1, sample sizes $n_1 = n_2 = 30$ and setting the level $\alpha = 0.05$, we generate the observations and compute the likelihood ratio Λ. With replication 100 thousands, we order the values of the computed likelihood ratios, the cutoff point is chosed as the lower 5% order statistic which is 0.019214. We then apply the following rule

$$\text{rejecting } H_0 \text{ if } \Lambda \leq 0.019214. \tag{4.7}$$

Is this test robust in determination of cutoff point? We let $\beta_{1y} = \beta_{1z} = 2, \beta_{0y} = \beta_{0z} = 2$

Case 1: $\sigma_y^2 = \sigma_z^2 = 1$

Case 2: $\sigma_y^2 = \sigma_z^2 = 2$

Case 3: $\sigma_y^2 = \sigma_z^2 = 5$

Case 4: $\sigma_y^2 = \sigma_z^2 = 10$

Table 1. Type I error probabilities comparison

$\sigma_v^2 = \sigma_{vb} = c$	Case 1	Case 2	Case 3	Case 4
$c = 2$	0.0499	0.0515	0.0588	0.0795
$c = 5$	0.0511	0.0471	0.0447	0.0578
$c = 10$	0.0477	0.0474	0.0456	0.0522

Comparing the above results with the ones in (4.6), this simulation method seems to be quite robust and we will study this test by evaluating its power performance. We let

$$n_y = n_z = 30, \beta_y = (1, 1), (\sigma_{vy}^2, \sigma_y^2) = (1, 1)$$

We design $\beta_z = (\beta_{0z}, \beta_{1z})', (\sigma_{vz}^2, \sigma_z^2)$ for power study. If parameters for model of z are not specified, they are identical to the corresponding ones of y.

Table 2. Power performance presentation

Parameters	Power	Parameters	Power
$\beta_{1z} = 1.2$	1	$\begin{pmatrix} \beta_{0z} \\ \sigma_z^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 1.2 \end{pmatrix}$	0.604
$\begin{pmatrix} \beta_{1z} \\ \beta_{0z} \end{pmatrix} = \begin{pmatrix} 1.2 \\ 1.2 \end{pmatrix}$	1	$\begin{pmatrix} \beta_{0z} \\ \sigma_z^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 1.5 \end{pmatrix}$	0.680
$\begin{pmatrix} \beta_{1z} \\ \sigma_z^2 \end{pmatrix} = \begin{pmatrix} 1.2 \\ 1.2 \end{pmatrix}$	1	$\begin{pmatrix} \beta_{0z} \\ \sigma_z^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 2 \end{pmatrix}$	0.772
$\begin{pmatrix} \beta_{1z} \\ \sigma_{vz}^2 \end{pmatrix} = \begin{pmatrix} 1.2 \\ 1.2 \end{pmatrix}$	1	$\begin{pmatrix} \beta_{0z} \\ \sigma_z^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 2.5 \end{pmatrix}$	0.842
$\beta_{0z} = 1.5$	0.479	$\sigma_z^2 = 1.2$	0.541
$\begin{pmatrix} \beta_{0z} \\ \sigma_{vz}^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 1.2 \end{pmatrix}$	0.575	$\sigma_z^2 = 1.5$	0.650
$\begin{pmatrix} \beta_{0z} \\ \sigma_{vz}^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 1.5 \end{pmatrix}$	0.905	$\sigma_z^2 = 2$	0.755
$\begin{pmatrix} \beta_{0z} \\ \sigma_{vz}^2 \end{pmatrix} = \begin{pmatrix} 1.5 \\ 2 \end{pmatrix}$	0.998	$\sigma_z^2 = 2.5$	0.833
$\beta_{0z} = 2.0$	0.985		
$\sigma_{vz}^2 = 1.5$	0.742		
$\sigma_{vz}^2 = 2$	0.997		

We have several comments on the results in Table 2:

(1). This test is very sensitive for a change in slope parameter β_1 since the powers all cases involve a change in this parameter is as high as values 1.
(2) This test is also satisfactory for a change in location parameter β_0 as it is showing the cases with $\beta_0^a = 1.5$.

How much price should we pay to use test (4.7) when $\sigma_y^2 = \sigma_z^2$ is not true when the reference charts are actually equal? We design some alternative cases to verify the probabilities of type I error for test (4.7) when $\sigma_y^2 + \sigma_{vy}^2 = \sigma_z^2 + \sigma_{vz}^2$.

Table 3. Performance of type I error probabilities

Parameters	Power	Parameters	Power
$\sigma_y^2 = 1.2, \sigma_{vz}^2 = 1.2$	0.5739	$\sigma_y^2 = 1.5, \sigma_{vz}^2 = 2$	0.9958
$\sigma_y^2 = 1.2, \sigma_{vz}^2 = 1.5$	0.7527	$\sigma_y^2 = 2, \sigma_{vz}^2 = 1.2$	0.1949
$\sigma_y^2 = 1.5, \sigma_{vz}^2 = 1.2$	0.1941	$\sigma_y^2 = 2, \sigma_{vz}^2 = 1.5$	0.7489
$\sigma_y^2 = 1.5, \sigma_{vz}^2 = 1.5$	0.7337	$\sigma_y^2 = 2, \sigma_{vz}^2 = 2$	0.9976
$\sigma_y^2 = 1.2, \sigma_{vz}^2 = 2$	0.9967	$\sigma_y^2 = 3, \sigma_{vz}^2 = 3$	1

Table 3 give the results showing that this test is not appropriate to test when the assumption that σ^2 and σ_z^2 are assumed to be equal.

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