Estimating Relative Potency Based on Multivariate Risk/Benefit Assessment

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Relative potency plays a key role in understanding the relationship between the doses of two treatments. Defined as the ratio of equally effective doses, it is central to communicating the relationship between a new drug entering the market and older medications. Because doses are tested and collected at discrete points in clinical trials, estimation in direct assays is hampered by the fact that clinical responses and tolerances are usually only available as grouped data which is frequently left- or right-censored information or both. This problem was considered in Bonzo and Laska (2004), which modeled premature discontinuation of treatment. However, further difficulties arise when the risk/benefit assessment is multivariate in dimension. This paper proposes an extension of the author's previous work for estimating relative potency in the multivariate setting utilizing dimension reduction and generalized mixed data model (GMDM) approaches. Large sample approximation and an analogue of Fieller's theorem are used to construct confidence interval estimates. Simulated data and data from a clinical trial are used to illustrate the methods' use.

Key Words: left-/right-censored information, grouped data, generalized mixed data model, fiducial limits

1. Introduction

Direct assays have been used as one of the primary methods in drug formulation. They are characterized by the application of doses of a test and standard drug formulations (stimuli) to subjects (usually humans) to produce a directly measurable response. The dose that produces the desired response is called the subject's tolerance dose. Central to their analysis is the estimation of relative potency, a ratio of two equally effective doses. As used in pharmacological studies, relative potency helps gauge how the recommended dose of a test drug is formulated using an established drug as a base comparator. In switching studies, it is used to communicate the relationship between a new drug entering the market and older medications in the same pharmacologic class.

The construct for estimating relative analgesic potency using the direct assay approach when the only available information is the dose interval in which the drug's desired effect took place is as follows (Bonzo and Laska, 2004). Let $(Y_1,...,Y_n)$ be IID with distribution F and consider fixed points $a_1,...,a_k$ in the support of F such that $a_{i-1} < a_i$, i = 1, . . ., k, where $a_0 = -\infty$ and $a_k = +\infty$. We then use the a_i's to define intervals $(a_{i-1}, a_i]$ and let X_i represent the count of Y_i's in $(a_{i-1}, a_i]$, i = 1, . . . , k. Note that the count for the right-censored interval (a_{k-1}, ∞) is assumed to contain non-responders.

If $(Y_1,...,Y_n)$ is IID from $F(y;\theta)$ where $\theta \in \Theta \subset R^k$ and the Y_i's are observed at intervals defined by fixed points $a_1,...,a_k$ such that $a_{i-1} < a_i$, i = 1, . . ., k, where $a_0 = -\infty$ and $a_k = +\infty$. Estimation of the unknown parameter θ can be done by maximizing the likelihood $L(\theta) = \prod_{i=1}^{k} \left(F(a_i;\theta) - F(a_i;\theta)\right)^{X_i}$, or equivalently by maximizing the log-likelihood given by $l(\theta) = \sum_{i=1}^{k} X_i \log[F(a_i;\theta) - F(a_{i-1};\theta)]$. The value of the maximum likelihood estimator (MLE) $\hat{\theta}$, can be extracted using an iterative approach such as the Newton-Raphson method. At the (m+1)th iteration the estimate is given by

$$\theta^{(m+1)} = \theta^{(m)} - H^{-1}(\theta)S(\theta)\Big|_{\theta=\theta^{(m)}}$$

where $S(\theta) = \frac{\partial}{\partial\theta} l(\theta)$ is the Fisher score function and $H(\theta) = \frac{\partial^2}{\partial\theta\partial\theta'} l(\theta)$ is the Hessian matrix. Iteration is terminated when $|\theta^{(m+1)} - \theta^{(m)}| \leq \in$, for some pre-specified tolerance $\in$.

Since $\hat{\theta}$ is MLE, it follows that $\hat{\theta} \xrightarrow[L]{} N(\theta, I^{-1}(\theta))$. Hence the standard error of $\hat{\theta}$ is given by $se(\hat{\theta}) = diag(I^{-1/2}(\theta))$ and the approximate 95% confidence interval for θ_i is given by $\hat{\theta}_i \pm 1.96 se(\hat{\theta}_i)$.

The paper is organized as follows. Section 1 discusses the general estimation approach for relative potency using interval information. Section 2 presents the multivariate extension of the problem utilizing dimension reduction and generalized mixed data model (GMDM) approaches. Section 3 shows the large sample approximation results for the inference of relative potency in the multivariate setting, as well as an analogue of Fieller's theorem. Application of the method using simulated data is presented in Section 4. Finally, Section 5 gives some concluding remarks.

2. Multivariate Extension

Consider a set of mixed data observations $\{(u_j, y_{2j}, y_{3j}), j = 1,...,M\}$. Let $\{(y_{i1},...,y_{in_i}), i = 1,...,N\}$, denote the state-induced data where the 1x(1+d_2+d_3) vector y_{ij} denotes the jth data observation in the ith state. Alternatively, we can represent the same data as $\{(y_{1ij}, y_{2ij}, y_{3ij}), j = 1,...,n_i; i = 1,...,N\}$ where y_{1ij} is equal to 1; y_{2ij} is a $1xd_2$ vector of continuous observations; and y_{3ij} is a $1xd_3$ vector of ordinal observations.

We assume that each observation y_{ij} in the ith state follow some generalized linear model (GLIM) specification given by $\eta_{ij} = h(E(y_{ij}))$ for some natural link function h where the natural parameter η_{ij} is linear with respect to a px(1+d_2+d_3) vector of common regression coefficients β, i.e., $\eta_{ij} = x_{ij}\beta$ for some 1xp vector of regressors x_{ij}. Instead of working directly with the GLIM specification above to make an inference on β, we follow the conditioning approach used by Fitzmaurice and Laird (1995) and extend it to include the ordinal variables. This approach structurally conforms with the generalized mixed data model (GMDM) introduced by de Leon and Carriere (2007) without the burden of specifying the actual joint distribution of the vector of mixed random variables.

We assume that the GLIM specification is equivalent to the conditional specification given by

$$\eta_{1ij} = h_1(E(y_{1ij})) = x_{ij}\beta_{(1)}$$
$$\eta_{2ij|1} = h_2(E(y_{2ij} \mid y_{1ij})) = x_{ij}\beta_{(2)} + (y_{1ij} - \eta_{1ij})\gamma_1 \qquad (2.1)$$

and

$$\eta_{3ij|21}{}^* = h_3(E(y_{3ij}{}^* \mid y_{2ij}, y_{1ij})) = x_{ij}\beta_{(3)} + (y_{2ij} - \eta_{2ij|1})\gamma_2 + (y_{1ij} - \eta_{1ij})\gamma_3$$

where $\{y_{3ij}{}^*, j = 1,...,n_i; i = 1,...,N\}$ is a set of continuous latent variables related to the ordinal measurements $\{y_{3ij}, j = 1,...,n_i; i = 1,...,N\}$.

Following de Leon and Carriere (2007), we assume that the latent relationship between $y_{3ij}{}^*$ and y_{3ij} given y_{2ij} and y_{1ij} is defined by the threshold model:

$$y_{3dij} = l \Leftrightarrow \Delta_{d,l-1} < y_{3dij}{}^{*} - \eta_{3dij|21} \le \Delta_{d,l}$$

where $y_{3dij}{}^{*}$ and y_{3dij} are the dth components of $y_{3ij}{}^{*}$ and y_{3ij}, respectively, d = 1, … , d_2; $\eta_{3dij|12}$ is the dth component of $\eta_{3ij|12}$; $l = 1,...,m_d$ are the ordinal scores for y_{3dij}; and $\{\Delta_{d,0} = -\infty, \Delta_{d,1},...,\Delta_{d,m_d-1}, \Delta_{d,m_d} = +\infty\}$ are the unknown cutpoints.

To facilitate the estimation of the regression coefficients β, we propose the use of the generalized estimating equation (GEE) approach by suitably assuming working covariances for y_{1ij}, y_{2ij} given y_{1ij} and y_{3ij} given y_{2ij} and y_{1ij}. We let $\text{cov}(y_{1ij}) = v_{1ij} \approx \sigma_{1i}^2$; $\text{cov}(y_{2ij} \mid y_{1ij}) = v_{2i} \approx \Sigma_{2i}$; and $\text{cov}(y_{3ij} \mid y_{2ij}, y_{1ij}) = v_{3i} \approx \Sigma_{3i}$.

Given the specification in (2.1), let $\alpha_1 = \beta_{(1)}$, $\alpha_2 = (vec(\beta_{(2)})', vec(\gamma_1)')'$ and $\alpha_3 = (vec(\beta_{(3)})', vec(\gamma_2)', vec(\gamma_3)')'$ where vec(A) stacks the column of any $m \times n$ matrix A into an $mn \times 1$ vector. Similarly, define $w_{1ij} = x_{ij}$; $w_{2ij} = (I_{d_2} \otimes x_{ij}, I_{d_2} \otimes (y_{1ij} - \eta_{1ij}))$; and $w_{3ij} = (I_{d_3} \otimes x_{ij}, I_{d_3} \otimes (y_{2ij} - \eta_{2ij|1}), I_{d_3} \otimes (y_{1ij} - \eta_{1ij}))$, where $\otimes$ denotes the Kronecker product.

This re-definition, gives an alternative form to (2.1) given by $\eta_{1ij} = w_{1ij}\alpha_1$; $vec(\eta_{2ij|1}) = w_{2ij}\alpha_2$; and $vec(\eta_{3ij|12}{}^{*}) = w_{3ij}\alpha_3$. The set of GEE's for $\alpha = (\alpha_1', \alpha_2', \alpha_3')'$ is given by the set of $p(1+d_2+d_3)+d_2+d_2d_3+d_2$ equations

$$\sum_{i=1}^{N}\sum_{j=1}^{n_i} u_{ij}(\alpha, \Sigma_i, \Delta) = \sum_{i=1}^{N}\sum_{j=1}^{n_i} z_{ij}(\alpha)' d_{ij}(\alpha, \Delta) v_{ij}^{-1}(\Sigma_i) r_{ij}(\alpha, \Delta) = 0 \qquad (2.2)$$

where $z_{ij}(\alpha)$ is a $(1+d_2+d_3) \times p(1+d_2+d_3) + d_2 + d_2d_3 + d_3$ matrix of constants; $v_{ij}(\Sigma_i)$ is the matrix of covariances; $r_{ij}(\alpha, \Delta)$ is the vector of errors; $d_{ij}(\alpha, \Delta)$ is a $(1+d_2+d_3) \times (1+d_2+d_3)$ block-diagonal matrix; and Δ represents the set of unknown cutpoints $\{\Delta_{d,l}, l = 1,..., m_d - 1; d = 1,..., d_3\}$.

3. Estimation of Relative Potency Using the Direct Assay Approach

Consider the problem of a multivariate parallel-line bioassay in which the outcomes of interest are of a mixed data structure. Suppose we stratify observations $\{y_{ij}, j = 1,..., n_i\}$ in the ith state as $\{y_{it}, t = 1,..., T_i\}$ and $\{y_{is}, s = 1,..., S_i\}$ where y_{it} represents observation from a unit exposed to the test drug and y_{is} represents observation from a unit exposed to the standard drug, $n_i = T_i + S_i$. The parametric form of the dose-response lines for the test and standard drugs in the ith state is given by

$$\eta_{it} = \beta_{10} + \beta_{11}x_{it},\ t = 1,..., T_i \quad \text{and} \quad \eta_{is} = \beta_{20} + \beta_{21}x_{is},\ s = 1,..., S_i \qquad (3.1)$$

where $\eta_i = h(E(y_i))$ is a natural link function, β_{ij}'s are $1x(1+d_2+d_3)$ vector of regression coefficients and x_i represents log dose levels. The fundamental condition of similarity between standard and test drugs in (3.1) requires that $\eta_{it} = \eta_{is}$ when $x_{it} = \mu + x_{is}$, $\mu = \log \rho$, ρ being a measure of common relative potency of the test drug relative to the standard drug.

This condition of similarity can be broken down into two hypotheses, namely:

(i) $H_m:\ \beta_{11} = \beta_{21} = \beta_{.1}$ and (ii) $H_s:\ \beta_{10} = \beta_{20} + \beta_{.1}\mu$.

H_m is called the hypothesis of marginal parallelism while H_s is called the hypothesis of (main) similarity condition. These two hypotheses are tested sequentially with H_m tested first and then H_s next if H_m is rejected.

Clearly, the set of equations in (3.1) can be represented in multivariate regression form

$$\eta_i = X_i\beta. \qquad (3.2)$$

Similarly, the fundamental condition of similarity can be represented in terms of a general linear hypothesis form with (i) given by $H_m:\ C_m\beta = 0$ and (ii) given by $H_s:\ C_s(\mu)\beta = 0$ where $C_m = \begin{pmatrix}0 & 1 & 0 & -1\end{pmatrix}$ and $C_s(\mu) = \begin{pmatrix}1 & -\mu & -1 & 0\\ 0 & 1 & 0 & -1\end{pmatrix}$. Our suggested approach to treating this problem when data is of the mixed type proceeds from utilizing the X matrix structure given in (3.2) for use in a conditional model given by (2.1).

Partitioning β as $\beta = (\beta_{(1)}, \beta_{(2)}, \beta_{(3)})$ where $\beta_{(j)} = (\beta_{10(j)}', \beta_{11(j)}', \beta_{20(j)}', \beta_{21(j)}')'$, j = 1, 2, 3 and $\beta_{(1)}$, $\beta_{(2)}$ and $\beta_{(3)}$ represent the coefficients for the nominal, continuous and ordinal outcomes, respectively. Based on this partition, the hypothesis of marginal parallelism is given by $H_m:\ C\beta^* = 0$ where

$$C = \begin{pmatrix}1 & 0 & 0\\ 0 & I_{d_2} & 0\\ 0 & 0 & I_{d_3}\end{pmatrix} \otimes C_m.$$

Using the asymptotic result for $\hat{\beta}^*$, H_m can be tested using the Wald-type chi-square given by

$$\chi^2_W = (C\hat{\beta}^*)'(\hat{H}_1^{-1}\hat{G}_1^{-1}\hat{H}_1^{-1})^{-1}(C\hat{\beta}^*)$$

where H_1 and G_1 are obtained from the alternative representation of (2.1) using the X matrix in (3.2) and $\hat{\beta}^*$ is the corresponding GEE estimator obtained from (2.2). Under H_m, $\chi^2_W \to_L \chi^2_{1+d_2+d_3}$.

Testing the hypothesis of similarity is equivalent to testing $H_s:\ C(\mu)\beta^* = 0$ where

$$C(\mu) = \begin{pmatrix}1 & 0 & 0\\ 0 & I_{d_2} & 0\\ 0 & 0 & I_{d_3}\end{pmatrix} \otimes C_s(\mu) \qquad (3.3)$$

for some constant $\mu = \log\rho$, ρ being a measure of common relative potency. Using the same approach as that for H_m, H_s can be tested using the Wald-type chi-square given by

$$\chi^2_W = (C(\mu)\hat{\beta}^*)'(\hat{H}_1^{-1}\hat{G}_1^{-1}\hat{H}_1^{-1})^{-1}(C(\mu)\hat{\beta}^*)$$

where H_1, G_1 are obtained from the alternative representation of (2.1) using the X matrix in (3.2) and $\hat{\beta}^*$ is the corresponding GEE estimator obtained from (2.2). Under H_s, $\chi^2_W \to_L \chi^2_{2(1+d_2+d_3)}$.

If we let $a = (a_{11}, a_{21}, ..., a_{2d_2}, a_{31}, ..., a_{3d_3})'$ and $b = (b_{11}, b_{21}, ..., b_{2d_2}, b_{31}, ..., b_{3d_3})'$ where $a_{ij} = \hat{\beta}_{10(ij)} - \hat{\beta}_{20(ij)}$ and $b_{ij} = \hat{\beta}_{110(ij)}$, respectively. Also, let $F = \left(\hat{H}_1^{-1}\hat{G}_1\hat{H}_1^{-1}\right)^{-1} = (f_{ij})$. Assuming that H_m and H_s are not rejected, an asymptotic Fieller-type fiducial limits for μ can be obtained by solving the inequality

$$(a + b\mu)'F(A + b\mu) \le \chi^2_{\alpha,(1+d_2+d_3)} \qquad (3.4)$$

for μ where $\chi^2_{\alpha,(1+d_2+d_3)}$ is the upper α percentage point of the chi-square distribution with $1 + d_2 + d_3$ degrees of freedom. Solving (3.4) yields the limits

$$(\mu_L, \mu_U) = \hat{\mu} \pm \sqrt{\hat{\mu}^2 + \frac{1}{b'Fb}(\chi^2_{\alpha,1+d_2+d_3} - a'Fa)}$$

where $\hat{\mu} = \dfrac{a'Fb}{b'Fb}$. Thus, $\dfrac{a'Fb}{b'Fb}$ is a logical choice for the value of μ in (3.3) above.

4. Some Simulation Results

The data for this application were simulated from a clinical trial evaluating interval dose information. A total of four levels were used for the study drug (standard), active comparator (test) and placebo. Dose intervals provided here represent the dose range at which subjects attained stable pain. Table 1 shows the interval counts for both the study drug and active comparator. Counts for placebo were not included. Within the intent-to-treat population, a total of 32 subjects were exposed to the active comparator, while 33 subjects were exposed to the study drug. The dose levels used for the active comparator were 20, 40, 60, and 80 dose units. The corresponding dose levels for the study drug were 12.5, 25, 37.5, and 50 dose units.

Table 1. Stable Dose Interval information for Study and Active Comparator Drugs (Intent-to-Treat Population)

Active Comparator		Study Drug	
Interval	Count	Interval	Count
$(-\infty, 20]$	3	$(-\infty, 12.5]$	7
$(20, 40]$	6	$(12.5, 25]$	3
$(40, 60]$	11	$(25, 37.5]$	10
$(60, 80]$	4	$(37.5, 50]$	3
$(80, \infty)$	8	$(50, \infty)$	10
Total	32	Total	33

Estimation and test results are given in Table 2. Results show that for the active comparator group, the maximum likelihood estimate of the model parameters is given by (0.2219, 44.7935, 383.6393). For the study drug group, the maximum likelihood estimate of the parameters is given by (0.2130, 26.1795, 391.6922).

Hypothesis testing results show that the joint hypothesis given by H_1 is rejected in the active comparator group (p = 0.0102). However, the same hypothesis was not rejected in the study drug group (p = 0.01246). Test results for H_2 showed that both groups contain non-responders (p = 0.0030 for active comparator and p = 0.0466 for study drug). The hypothesis $H_3 : \mu = 50$ was not rejected in the active comparator group (p = 0.2093), while the hypothesis $H_3 : \mu = 30$ was not rejected in the study drug group (p = 0.4614). Hence, if

non-responders are excluded, we can view the active comparator and study drug groups as having mean tolerance doses of 45 dose units and 26 dose units, respectively.

Table 2. Estimation and Test Results for Mixture Distribution

Statistic/Hypothesis	Active Comparator (N = 32)	Study Drug (N = 33)
Parameter Estimate		
Alpha (SE)	0.2219 (0.0749)	0.2130 (0.1070)
Mean (SE)	44.7935 (4.1464)	26.1795 (5.1868)
Variance (SE)	383.6393 (151.3384)	391.6922 (234.3714)
Median	51.9504	33.0270
Hypothesis		
$\alpha = 0$ and $\mu = 50 / \mu = 30$	9.1728 (0.0102)	4.1660 (0.1246)
$\alpha = 0$	8.7771 (0.0030)	3.9609 (0.0466)
$\mu = 50 / \mu = 30$	1.5765 (0.2093)	0.5425 (0.4614)
Relative Potency (Comparator/Study)	1.5730	
Standard Error	0.2771	
Delta Method	(1.0298, 2.1161)	
Fieller's Method	(1.435, 2.3317)	

Relative potency calculation yielded an estimate of 1.57. This indicates that 1.57 dose units of the active comparator is equivalent to 1 dose unit of the study drug. The standard error estimate is 0.2771 which indicates an adequate precision level. The delta method yielded an approximate 95% CI given by (1.0298, 2.1161), while Fieller's method yielded an approximate 95% fiducial limits of (1.435, 2.3317). Examination of the interval widths shows that Fieller's method yielded a relatively tighter interval compared to the delta method.

5. Conclusions

The preceding section demonstrated that valid relative potency estimates can be formulated using the direct assay approach even if the effective dose information is represented in interval form. In the application demonstrated, stable pain was defined as achievement of a pre-specified pain level within n-1 out of a rolling window of n days. One can argue that the definition, though operational, does not equate to adequate pain control. One can argue that such concerns can be addressed more adequately through an indirect assay where the response can be represented by a mixed-data structure. Analysis of such data types can be done using the extension results presented in Sections 3 and 4.

References

Bonzo, D.C. and Laska, E. (2004). Estimating Relative Potency in Direct Assays Containing Nonresponders, Proceedings of the 2004 Joint Statistical Meeting.

De Leon, A.R. and Carriere, K.C. (2007). General mixed-data model: extension of general location and continuous models, Can. J. of Statist. 35:4, pp.533-548.

Fitzmaurice, G. and Laird, N. (1995). Regression models for a bivariate discrete and continuous outcome with clustering, J. Amer. Statist. Asso. 90, pp. 845-852.