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Unit–Treatment Interaction and Its Practical Consequences

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SUMMARY. Most statistical characterizations of a treatment effect focus on the average effect of the treatment over an entire population. However, average effects may provide inadequate information, sometimes misleading information, when a substantial unit–treatment interaction is present in the population. It is even possible that a nonnegligible proportion of the individuals in the population experience an unfavorable treatment effect even though the treatment might appear to be beneficial when considering population averages. This paper examines the extent to which information about unit–treatment interaction can be extracted using observed data from a two-treatment completely randomized experiment. A method for utilizing the information from an available covariate is proposed. Although unit–treatment interaction is a nonidentifiable quantity, we show that mathematical bounds for it can be estimated from observed data. These bounds lead to estimated bounds for the probability of an unfavorable treatment effect. Maximum likelihood estimators of the bounds and their corresponding large-sample distributions are given. The use of the estimated bounds is illustrated in a clinical trials data example.

KEY WORDS: Additivity; Clinical trial; Counterfactual; Heterogeneity; Potential response; Subject–treatment interaction.

1. Introduction

We begin by considering a clinical trial where a new treatment, T_1, is being compared with a standard treatment, T_2. An example of such a trial is discussed in Section 4. Let X denote what the response would be if a randomly chosen individual from the population is subjected to treatment T_1 and Y denote what the response of this individual would be if subjected to treatment T_2. X and Y are called potential responses, and the quantity $D = X - Y$ may be defined as the effect of treatment T_1 relative to T_2 for the chosen individual. What is generally estimated in clinical trials is an average effect, $\mathrm{E}(X - Y)$, where the expectation $\mathrm{E}(\cdot)$ is with respect to the population of interest.

It is not always the case that every subject in the population will experience a beneficial effect due to treatment T_1. We will interpret the phrase "T_1 has a beneficial effect" to mean $X - Y \geq \tau$, where τ is some specified constant. Without loss of generality, we take τ to be zero. It is important to note that the effect of T_1 relative to T_2 could appear beneficial when considering the average effect even though a nonnegligible proportion of individuals could be experiencing an unfavorable effect. In fact, Longford (1999) suggested that the validity of current clinical trial design and analysis is greatly eroded when treatment effects are heterogeneous. A key parameter, the value of which should be considered when making decisions concerning the use of a new treatment T_1, is the proportion of the individuals in the population for whom the value of $D = X - Y$ is negative. We denote this proportion as $P_- = P(D < 0)$. If P_- is nonnegligible, it becomes important to identify the subset of individuals in the population who actually benefit from T_1. For instance, in our discussion of a clinical trials data set in Section 4 involving epilepsy patients, we show that the maximum likelihood estimates for lower and upper bounds for P_- are 5 and 36%, respectively. We also show how to obtain approximate confidence intervals for these bounds, which then allows us to test the statistical significance of these estimates. We then obtain similar bounds and confidence intervals for P_- conditioned on the value of a suitable covariate. This latter procedure is particularly useful in identifying the range of values of the covariate for which the treatment may be safely recommended.

We will assume that the random vector $\{(X, Y)\}$ of potential responses follows a bivariate normal distribution (possibly after a suitable monotonic transformation). The value of P_- is then nonzero when $\sigma_D^2 = \mathrm{var}(X - Y)$ is nonzero, i.e., when unit–treatment interaction is present. The problem of estimating P_- is tied to the problem of estimating σ_D^2. If the treatments T_1 and T_2 are assigned to a random sam-

ple of subjects using a two-treatment completely randomized design, then it is easily seen that neither σ_D^2 nor P_- is identifiable. This is due to the fundamental problem of causal inference (Holland, 1986) since, for each individual unit, we can observe only one of the two potential responses X or Y during any single instance.

Issues relating to unit–treatment interaction in the context of clinical trials have been recognized and reported in the literature in bioequivalence studies. Bioequivalence between two formulations of a drug is often determined by estimating the mean difference in bioavailability using a crossover design. Ekbohm and Melander (1989) proposed that the focus on the mean difference is insufficient since a small mean difference and a narrow confidence interval might be obtained even though the effects vary considerably among subjects. Sheiner (1992) has proposed a method of assessing individual bioequivalence for a patient that switches from the standard formulation to the new formulation, and Schall (1995) developed alternative criteria for assessing individual bioequivalence.

The above methods for assessing individual bioequivalence make use of crossover designs and restrictive assumptions about time effects. In a crossover design, even if we can safely assume absence of carryover effects, there are four potential responses, $(X^{(j)}, Y^{(j)})$, where $j = 1, 2$ denotes the time period at which one would observe a response. Only one of the two pairs, $(X^{(1)}, Y^{(2)})$ or $(X^{(2)}, Y^{(1)})$, can be observed for an individual, depending on which sequence of treatment assignments the individual received. Similarly, if there are three periods, then there are six potential responses, two for each period. Proceeding with an analysis of unit–treatment interaction generally requires an additional assumption that the time effects are zero or, at least, that they are constant across all units in the population. Further details on this topic can be found in Gadbury (1998).

In this paper, we propose a method to obtain bounds for σ_D^2 and P_- based on data from a two-treatment completely randomized design where a suitable covariate is also measured. In the next section, we use the potential response framework (Rubin, 1974; Holland, 1986) to obtain mathematical bounds for P_-. In Section 3, we present maximum likelihood estimators for these mathematical bounds along with their large-sample distributions. Results are also provided for bounds on the probability $P_{-\cdot z}$ of an unfavorable treatment effect given that the value of the covariate is equal to z. We illustrate our method using a previously published clinical trials data set and then conclude with a discussion.

2. Bounds for σ_D^2 and $P_- = P(D < 0)$

Suppose an i.i.d. sample of potential responses, (X_i, Y_i) $i = 1, \ldots, N$, is available from a bivariate population of potential responses with mean $(\mu_X, \mu_Y)^{\mathrm{T}}$, variances σ_X^2 and σ_Y^2, and correlation parameter ρ_{XY}. We assume throughout that there is no interference between units (Cox, 1958, p. 19). The distribution of treatment effects has mean $\mu_D = \mu_X - \mu_Y$ and variance $\mathrm{var}(X - Y) = \sigma_D^2 = \sigma_X^2 + \sigma_Y^2 - 2\sigma_X\sigma_Y\rho_{XY}$. The difference between the sample means of the two treatments is easily shown to be an unbiased estimator of μ_D. As stated earlier, σ_D^2 and P_- are nonidentifiable. However, when covariate information is available for each unit in the sample, useful bounds for these parameters may be computed.

Consider the situation where a covariate, Z, can be observed on the population units. The population of potential responses may now be viewed as a trivariate population represented by the random vector (X, Y, Z) with mean $(\mu_X, \mu_Y, \mu_Z)^{\mathrm{T}}$ and variance matrix

$$\begin{pmatrix} \sigma_X^2 & \rho_{XY}\sigma_X\sigma_Y & \rho_{XZ}\sigma_X\sigma_Z \\ \rho_{XY}\sigma_X\sigma_Y & \sigma_Y^2 & \rho_{YZ}\sigma_Y\sigma_Z \\ \rho_{XZ}\sigma_X\sigma_Z & \rho_{YZ}\sigma_Y\sigma_Z & \sigma_Z^2 \end{pmatrix}. \tag{1}$$

Let (X_i, Z_{1i}), $i = 1 \cdots n_1$, denote the observed responses to treatment T_1 and the value of the covariate for the n_1 units assigned to the new treatment group. Then (Y_j, Z_{2j}), $j = 1 \cdots n_2$, are the observed responses to T_2 and the value of the covariate for the n_2 units assigned to the standard treatment group.

The positive definiteness of the correlation matrix (1) implies that ρ_{XY} must lie in the interior of the interval bounded by the two numbers $\rho_{XZ}\rho_{YZ} \pm [(1-\rho_{XZ}^2)(1-\rho_{YZ}^2)]^{1/2}$. This observation leads to the following lower bound, L, and upper bound, U, for σ_D^2:

$$L = \sigma_X^2 + \sigma_Y^2 - 2\sigma_X\sigma_Y \left\{ \rho_{XZ}\rho_{YZ} + \sqrt{\left(1-\rho_{XZ}^2\right)\left(1-\rho_{YZ}^2\right)} \right\} \tag{2}$$

$$U = \sigma_X^2 + \sigma_Y^2 - 2\sigma_X\sigma_Y \left\{ \rho_{XZ}\rho_{YZ} - \sqrt{\left(1-\rho_{XZ}^2\right)\left(1-\rho_{YZ}^2\right)} \right\}. \tag{3}$$

If the trivariate distribution of potential responses is normal, then bounds for P_- are given by $P_L = \Phi(-\mu_D/L^{1/2})$ and $P_U = \Phi(-\mu_D/U^{1/2})$, where $\Phi(a)$ is the standard normal cumulative distribution function evaluated at a. In the next section, we give the maximum likelihood estimators (MLEs) of L, U, P_L, and P_U along with their large-sample distributions using a trivariate normal population.

3. Maximum Likelihood Estimation

The likelihood function of observed data is of the form $\Pi_{i=1}^{n_1} f(x_i, z_{1i}) \Pi_{j=1}^{n_2} f(y_j, z_{2j})$, which involves eight unknown parameters. It is convenient to consider the set of parameters (Lord, 1955b) $\mu_X, \mu_Y, \mu_Z, \sigma_Z, \sigma_{X\cdot Z}, \sigma_{Y\cdot Z}, \beta_X, \beta_Y$, where

$$\begin{aligned} \sigma_{X\cdot Z}^2 &= \sigma_X^2\left(1-\rho_{XZ}^2\right), \\ \sigma_{Y\cdot Z}^2 &= \sigma_Y^2\left(1-\rho_{YZ}^2\right), \\ \beta_X &= \sigma_X\rho_{XZ}/\sigma_Z, \\ \beta_Y &= \sigma_Y\rho_{YZ}/\sigma_Z. \end{aligned}$$

The MLEs of these eight parameters are given in Lord (1955a, 1955b). Rewriting the lower and upper bounds given by equations (2) and (3) as

$$\begin{aligned} L &= (\sigma_{X\cdot Z} - \sigma_{Y\cdot Z})^2 + (\beta_X - \beta_Y)^2\sigma_Z^2 \\ U &= (\sigma_{X\cdot Z} + \sigma_{Y\cdot Z})^2 + (\beta_X - \beta_Y)^2\sigma_Z^2 \end{aligned}$$

and using Lord's results, it follows that the MLEs of L and U are given by

$$\hat{L} = (s_{X\cdot Z} - s_{Y\cdot Z})^2 + (b_X - b_Y)^2 s_Z^2$$

$$\hat{U} = (s_{X\cdot Z} + s_{Y\cdot Z})^2 + (b_X - b_Y)^2 s_Z^2,$$

where $s_{X\cdot Z}^2 = s_X^2(1 - r_{XZ}^2)$ and $s_{Y\cdot Z}^2 = s_Y^2(1 - r_{YZ}^2)$. The statistics s_X, r_{XZ}, and b_X are the usual sample standard deviations, correlation, and regression coefficient for the n_1 observations in the treatment group; s_Y, r_{YZ}, and b_Y are the corresponding quantities for the n_2 observations in the control group; and s_Z is the sample standard deviation of the observed covariate values over all N individuals in the study. The MLE for μ_D is $\hat{\mu}_D = \bar{x} - \bar{y} - b_X(\bar{z}_1 - \bar{z}) + b_Y(\bar{z}_2 - \bar{z})$, where $\bar{x}$ and $\bar{z}_1$ are observed sample means of the response and the covariate for the n_1 individuals in the treatment group and $\bar{y}$ and $\bar{z}_2$ are the corresponding quantities for the control group.

The MLEs for P_L and P_U are $\hat{P}_L = \Phi(-\hat{\mu}_D/\hat{L}^{1/2})$ and $\hat{P}_U = \Phi(-\hat{\mu}_D/\hat{U}^{1/2})$. The asymptotic joint distribution of $(\hat{P}_L, \hat{P}_U)^{\mathrm{T}}$ is normal with mean equal to $(P_L, P_U)^{\mathrm{T}}$ and variances and covariances given by

$$\mathrm{var}(\hat{P}_L) = \frac{\left(\phi\left(-\mu_D/\sqrt{L}\right)\right)^2}{L}\left\{\mathrm{var}(\hat{\mu}_D) + \frac{\mu_D^2 \mathrm{var}(\hat{L})}{4L^2}\right\}$$

$$\mathrm{var}(\hat{P}_U) = \frac{\left(\phi\left(-\mu_D/\sqrt{U}\right)\right)^2}{U}\left\{\mathrm{var}(\hat{\mu}_D) + \frac{\mu_D^2 \mathrm{var}(\hat{U})}{4U^2}\right\}$$

$$\mathrm{cov}(\hat{P}_L, \hat{P}_U) = \frac{\phi\left(-\mu_D/\sqrt{L}\right)\phi\left(-\mu_D/\sqrt{U}\right)}{\sqrt{LU}} \times \left\{\mathrm{var}(\hat{\mu}_D) + \frac{\mu_D^2 \mathrm{cov}(\hat{L}, \hat{U})}{4LU}\right\},$$

where $\phi(a)$ is the standard normal density evaluated at a and

$$\begin{aligned}
\mathrm{var}(\hat{L}) &= \frac{2}{N}(\beta_X - \beta_Y)^4 \sigma_Z^4 \\
&\quad + 2(\sigma_{X\cdot Z} - \sigma_{Y\cdot Z})^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right) \\
&\quad + 4(\beta_X - \beta_Y)^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right)\sigma_Z^2 \\
\mathrm{var}(\hat{U}) &= \frac{2}{N}(\beta_X - \beta_Y)^4 \sigma_Z^4 \\
&\quad + 2(\sigma_{X\cdot Z} + \sigma_{Y\cdot Z})^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right) \\
&\quad + 4(\beta_X - \beta_Y)^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right)\sigma_Z^2 \\
\mathrm{cov}(\hat{L}, \hat{U}) &= \frac{2}{N}(\beta_X - \beta_Y)^4 \sigma_Z^4 \\
&\quad + 2\left(\sigma_{X\cdot Z}^2 - \sigma_{Y\cdot Z}^2\right)\left(\sigma_{X\cdot Z}^2/n_1 - \sigma_{Y\cdot Z}^2/n_2\right) \\
&\quad + 4(\beta_X - \beta_Y)^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right)\sigma_Z^2 \\
\mathrm{var}(\hat{\mu}_D) &= \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right) + \frac{1}{N}(\beta_X - \beta_Y)^2 \sigma_Z^2.
\end{aligned}$$

These expressions are derived using the results in Lord (1955a). They are useful for computing asymptotic standard errors and approximate confidence intervals for P_L and P_U.

If observed data provide some evidence that $\beta_X \neq \beta_Y$, one might argue that this information could be used to predict positive (or negative) treatment effects on the basis of covariate values. What is actually predicted in such a case is the mean treatment effect conditioned on the covariate value. For a given covariate value, say $Z = z$, there is a subpopulation of individual treatment effects at $Z = z$ with mean equal to $\mu_{D\cdot z} = \mu_X - \mu_Y + (\beta_X - \beta_Y)(z - \mu_Z)$ and variance equal to $\sigma_{D\cdot z}^2 = \sigma_{X\cdot Z}^2 + \sigma_{Y\cdot Z}^2 - 2\sigma_{X\cdot Z}\,\sigma_{Y\cdot Z}\,\rho_{XY\cdot Z}$. The partial correlation coefficient, $\rho_{XY\cdot Z}$, cannot be estimated from observed data, but it must lie in the interval $[-1, 1]$. A lower bound L_z and an upper bound U_z for $\sigma_{D\cdot z}^2$ are then $L_z = (\sigma_{X\cdot Z} - \sigma_{Y\cdot Z})^2$ and $U_z = (\sigma_{X\cdot Z} + \sigma_{Y\cdot Z})^2$, and corresponding MLEs are given by $\hat{L}_z = (s_{X\cdot Z} - s_{Y\cdot Z})^2$ and $\hat{U}_z = (s_{X\cdot Z} + s_{Y\cdot Z})^2$.

Lower and upper bounds for the conditional probability $P_{-\cdot z} = P(D < 0 \mid Z = z)$ are $P_{L\cdot z} = \Phi(-\mu_{D\cdot z}/L_z^{1/2})$ and $P_{U\cdot z} = \Phi(-\mu_{D\cdot z}/U_z^{1/2})$. The MLEs of $P_{L\cdot z}$ and $P_{U\cdot z}$ are $\hat{P}_{L\cdot z} = \Phi(-\hat{\mu}_{D\cdot z}/\hat{L}_z^{1/2})$ and $\hat{P}_{U\cdot z} = \Phi(-\hat{\mu}_{D\cdot z}/\hat{U}_z^{1/2})$. The asymptotic joint distribution of $(\hat{P}_{L\cdot z}, \hat{P}_{U\cdot z})^{\mathrm{T}}$ is normal with mean equal to $(P_{L\cdot z}, P_{U\cdot z})^{\mathrm{T}}$ and variance and covariance given by

$$\mathrm{var}(\hat{P}_{L\cdot z}) = \frac{\left(\phi\left(-\mu_{D\cdot z}/\sqrt{L_z}\right)\right)^2}{L_z} \times \left\{\mathrm{var}(\hat{\mu}_{D\cdot z}) + \frac{\mu_{D\cdot z}^2 \mathrm{var}(\hat{L}_z)}{4L_z^2}\right\}$$

$$\mathrm{var}(\hat{P}_{U\cdot z}) = \frac{\left(\phi\left(-\mu_{D\cdot z}/\sqrt{U_z}\right)\right)^2}{U_z} \times \left\{\mathrm{var}(\hat{\mu}_{D\cdot z}) + \frac{\mu_{D\cdot z}^2 \mathrm{var}(\hat{U}_z)}{4U_z^2}\right\}$$

$$\mathrm{cov}(\hat{P}_{L\cdot z}, \hat{P}_{U\cdot z}) = \frac{\phi\left(-\mu_{D\cdot z}/\sqrt{L_z}\right)\phi\left(-\mu_{D\cdot z}/\sqrt{U_z}\right)}{\sqrt{L_z\,U_z}} \times \left\{\mathrm{var}(\hat{\mu}_{D\cdot z}) + \frac{\mu_{D\cdot z}^2 \mathrm{cov}(\hat{L}_z, \hat{U}_z)}{4\,L_z\,U_z}\right\},$$

where

$$\begin{aligned}
\mathrm{var}(\hat{L}_z) &= 2(\sigma_{X\cdot Z} - \sigma_{Y\cdot Z})^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right) \\
\mathrm{var}(\hat{U}_z) &= 2(\sigma_{X\cdot Z} + \sigma_{Y\cdot Z})^2 \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right) \\
\mathrm{cov}(\hat{L}_z, \hat{U}_z) &= 2\left(\sigma_{X\cdot Z}^2 - \sigma_{Y\cdot Z}^2\right)\left(\sigma_{X\cdot Z}^2/n_1 - \sigma_{Y\cdot Z}^2/n_2\right) \\
\mathrm{var}(\hat{\mu}_{D\cdot z}) &= \left(\sigma_{X\cdot Z}^2/n_1 + \sigma_{Y\cdot Z}^2/n_2\right)\left(1 + \frac{(z - \mu_Z)^2}{\sigma_Z^2}\right).
\end{aligned}$$

We now illustrate the computation and use of the bounds in an example.

4. Example

We consider data from a clinical trial of 59 individuals with epilepsy (Thall and Vail, 1990). Patients were randomized into two groups receiving either the antiepileptic drug progabide or a placebo as an adjuvant to standard chemotherapy. Seizure rates were recorded for each subject at 2-week intervals over an 8-week period. The response that we use for illustrative purposes is the total seizure count over the 8-week period. The covariate Z is a baseline seizure rate over the 8-week period prior to treatment assignment. Thall and Vail (1990) omitted one patient in the treatment group as an outlier and we do the same.

We analyzed these data using analysis of covariance, and diagnostics suggested transforming the seizure count data by taking logarithms (after first adding one to accommodate an individual with a zero response). Therefore, all results in this example are reported in transformed units. Analysis of covariance produces a point estimate for a mean treatment effect equal to -0.414 and a 95% confidence interval of

$(-0.733, -0.095)$, suggesting a beneficial decrease in average number of seizures due to the progabide treatment.

The MLEs of the relevant parameters are $\hat{\mu}_D = -0.415$, $\hat{\sigma}_Z = 0.709$, $\hat{\sigma}_{X.Z} = 0.687$, $\hat{\sigma}_{Y.Z} = 0.460$, $\hat{\beta}_X = 0.995$, and $\hat{\beta}_Y = 0.839$. MLEs of the bounds for σ_D are $\hat{L}^{1/2} = 0.253$ and $\hat{U}^{1/2} = 1.152$. The proportion of the population experiencing an unfavorable effect (i.e., an increase in the number of seizures) due to the new treatment is estimated to be between $\hat{P}_L = 0.051$ and $\hat{P}_U = 0.359$.

Assuming (X, Y, Z) is normal and that there were no measurement errors in observed responses, the MLE of P_L suggests at least 5% of the population will experience an increase in seizures due to the progabide treatment and the MLE for P_U suggests this percentage could be as high as 36%. Approximate 90% confidence intervals for P_L and P_U are $(-0.116, 0.218)$ and $(0.275, 0.444)$, respectively. The confidence interval for P_L indicates that there is insufficient evidence in the data to conclude P_- is positive. On the other hand, the interval for P_U indicates that P_- could be as high as 0.275 to 0.444 with 90% confidence.

There is no evidence in the transformed data that $\beta_X \neq \beta_Y$, but for illustration, we estimated the conditional bounds for $P_{-\cdot z}$ evaluated at the MLE for μ_Z, i.e., at $\bar{z} = 3.12$. The MLEs of the two bounds are $\hat{P}_{L.z} = 0.034$ and $\hat{P}_{U.z} = 0.358$, and 90% confidence intervals for $P_{L.z}$ and $P_{U.z}$ are given by $(-0.102, 0.171)$ and $(0.274, 0.443)$, respectively. Again, there is insufficient evidence in the data to suggest that $P_{-\cdot\bar{z}}$ is positive, yet the proportion experiencing a negative effect in this subpopulation could be as high as 0.274 to 0.443 with 90% confidence. These calculations can be repeated for any other specified value of Z.

The bounds σ_D and P_- were estimated from the existing clinical trial data and approximate confidence intervals for them were easily computed. The practitioner could now use this additional information together with available subject-matter knowledge to decide whether or not the treatment could be recommended for any given individual.

5. Discussion and Future Work

We proposed that, when individual treatment effects are the quantities of primary importance rather than a population average treatment effect, attention should be given to the estimation of $P_- = P(D < 0)$. This probability is invariant to data transformations as long as the original measurements were made on a meaningful scale and the allowable transformations are monotonic.

It is well known that unit–treatment interaction has consequences that can be checked using sample data (Cox, 1992). Observe that σ_D^2 can be written as

$$\sigma_D^2 = (\sigma_{X.Z} - \sigma_{Y.Z})^2 + 2\sigma_{X.Z}\sigma_{Y.Z}(1 - \rho_{XY.Z}) + (\beta_X - \beta_Y)^2\sigma_Z^2, \quad (4)$$

where $\rho_{XY.Z}$ is the conditional correlation of X and Y, given Z. This correlation cannot be estimated using observed data, but the other terms in equation (4) can be. The three conditions, $\sigma_{X.Z} = \sigma_{Y.Z}$, $\beta_X = \beta_Y$, and $\rho_{XY.Z} = 1$, are all required for σ_D^2 to equal zero. The two bounds for σ_D^2 that we used to derive MLEs for P_L and P_U result from letting $\rho_{XY.Z}$ equal 1 and -1, respectively. This suggests that a Bayesian approach using appropriate prior distributions for $\rho_{XY.Z}$ might lead to tighter bounds. Bounds for P_- using a Bayesian framework will be reported elsewhere.

Finally, the only unfavorable treatment effects that we considered in this paper were negative effects with respect to the primary response variable. Adverse treatment effects could occur in one or more secondary response variables as well. A study of unfavorable individual effects in multivariate response data will be discussed in future work.

Résumé

La plupart des estimations statistiques de l'effet d'un traitement porte sur l'effet moyen du traitement sur une population. Cependant, des effets moyens peuvent fournir une information inappropriée et parfois trompeuse quand existe dans la population une importante interaction traitement—unité expérimentale. Il est même possible qu'une proportion non négligeable des individus subisse un effet défavorable du traitement même si le traitement peut paraître bénéfique lorsque l'on considère les moyennes sur la population. Ce papier examine dans quelle mesure une information sur l'interaction traitement—unité peut être extraite des données d'un essai randomisé de deux traitements. Une méthode pour utiliser l'information sur une covariable disponible est proposée. Bien que l'interaction traitement—unité soit non-mesurable, nous montrons que des bornes mathématiques peuvent être estimées à partir des données observées. Ces bornes amènent à des bornes estimées pour la probabilité d'un effet défavorable du traitement. Des estimations du maximum de vraisemblance de ces limites et de leur distribution sur grands échantillons sont données. L'utilisation de ces bornes estimées est illustrée à partir de l'exemple d'un essai clinique.

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