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Randomized Blocks Designs: Omnibus *vs.* Pairwise Comparison, Fixed *vs.* Relative Optimal Discriminant Threshold, and Raw *vs.* Ipsative *z*-Score Measures

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This study extends recent research assessing the use of relative thresholds in matched-pairs designs, for a randomized blocks design in which four treatments are randomly assigned to blood samples drawn from each of eight people (each person treated as a block[1]). Both raw and ipsatively standardized plasma clotting times are compared between treatments.

For applications that involve ordered attributes ("dependent variables"), optimal discriminant (or data) analysis (ODA) compares the values of one or more attributes between two or more groups of observations with respect to a *fixed* discriminant threshold which maximizes the models predictive accuracy, normed *vs*. chance, for the sample.[2-30] However, recent research with matched-pairs designs found that using a *relative* discriminant threshold to evaluate an alternative hypothesis *separately for each of the matched pairs* of subjects can find inter-group differences otherwise too small to be identified vis-à-vis fixed thresholds.[31,32]

Fleiss gives an example of a randomized blocks experiment in which four treatments are randomly assigned to blood samples which were drawn from each of eight different people (each person is treated as a block), and plasma clotting time is compared between treatments.[1] In Figure 1 (raw minutes) and Figure 2 (ipsative $z_{minutes}$) treatments are color-coded (in the Figures) as **blue**, **red**, **green** and **purple** for treatments 1, 2, 3 and 4, respectively.

Figure 1: Clotting Time in Minutes (Vertical Axis) by Four Different Treatments (Colors), Separately for Each of Eight Patients[1]

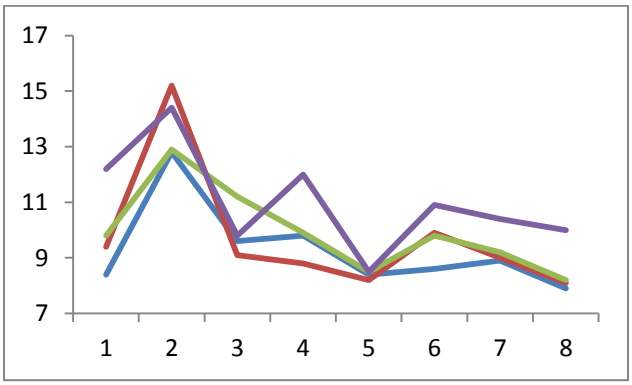

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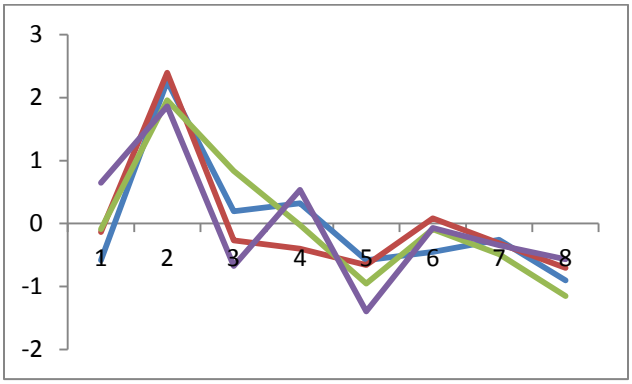
Figure 2: Ipsatively Standardized Clotting Time (Vertical Axis) by Four Different Treatments (Colors), Separately for Each of Eight Patients



Classic Analytic Approaches

Raw Data

For comparison *vs*. ODA methodology, we first replicated the ANOVA described by Fleiss[1] in which a statistically significant *F* value was estimated for the overall model: F=6.62, p<0.025. However, when applying the Sheffe adjustment for multiple hypothesis testing, the only statistically significant treatment effect was between the first and fourth treatments (p<0.037).

One can argue that using a parametric model to conduct a treatment effects analysis with four treatments and a sample size of eight is inappropriate given that the assumptions required of such a model are easily violated (e.g., sample size, normality of the data, etc.). As a more appropriate alternative, we perform a Skillings-Mack test[33]—a generalization of the Friedman non-parametric test which is a suitable alternative to repeated measures ANOVA for small samples and possibly non-normally distributed data. The overall model was statistically significant (p<0.0001), and four of the pairwise comparisons between treatments achieved significant *p* values (at the conventional p<0.05 level) derived using 1,000 simulations (1 *vs*. 3: p<0.0001; 1 *vs*. 4: p<0.0001; 2 *vs*. 4: p<0.0070; 3 *vs*. 4: p<0.0190).

Ipsative Standard Data

The replication of Fleiss' ANOVA using the standardized data was not statistically significant (p=1.00). Similarly, the Skillings-Mack test using the standardized data was not statistically significant (p<0.79).

ODA Fixed Discriminant Threshold

Raw Data

Raw clotting times of all four groups (Figure 1) were compared by omnibus four-class-category ODA analysis. Training analysis identified a model with a moderate effect size (ESS=37.5) which wasn't statistically significant (p<0.28).

All six possible pairwise comparisons of raw clotting times among the four groups were conducted by two-class-category ODA: none were statistically significant (all p>0.08).

Ipsative Standard Data

Ipsatively standardized clotting times of all four groups (Figure 2) were compared by omnibus four-class-category ODA analysis. Training analysis identified a model with a moderate effect size (ESS=25.0) which wasn't statistically significant (p<0.99).

All six possible pairwise comparisons of ipsatively standardized clotting times among the four groups were conducted using ODA: none were statistically significant (all p>0.66).

ODA Relative Discriminant Threshold

Raw Data

No multiclass omnibus relative threshold model yet exists.[31,32] Pairwise comparisons of corresponding raw clotting times (Figure 1) between pairs of treatments assessed if time for treatment X is *strictly less than* time for treatment Y, for each subject considered separately. Results showed treatment 1 had 100% lower clotting time when considered on a pairwise basis *vs*.

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treatments 3 or 4: for each, binomial $p<0.00391$. Treatment 2 had 82.5% lower clotting time *vs*. treatment 4 (binomial $p<0.032$). Finally, under the strictly-less-than ("always lower") criterion the pairwise comparison of treatments 3 and 4 was not statistically significant (75% difference in clotting times, $p<0.11$), however under the *less-than-or-equal* ("never higher") criterion the difference was statistically significant (82.5% difference in clotting times, $p<0.032$). Other pairwise comparisons were not statistically significant.

Ipsative Standard Data

Pairwise comparisons of corresponding ipsative *z*-scores (Figure 2) within pairs of treatments assessed if the *z*-score for treatment X is strictly less than the *z*-score for treatment Y (there were no equivalent *z*-scores), considered separately for each subject in the sample: none were statistically significant (all $p>0.21$).

Comments

As occurred herein, different statistical methods may generate consistent as well as inconsistent analytic conclusions.[34,35]

For example highly inconsistent findings were obtained herein for *omnibus* comparisons of *raw* clotting times (Figure 1): Skillings-Mack identified a training analysis effect that yielded lowest Type I error ($p<0.0001$); ANOVA found a training analysis effect which met the criterion for per-comparison (not for experimentwise[35]) statistical significance ($p<0.025$); and ODA using a fixed discriminant threshold found no effect ($p<0.28$). No multiclass optimal omnibus relative discriminant threshold methodology is yet available: a novometric procedure to identify and evaluate all possible omnibus models is thus needed.[2,30,36-38]

Inconsistent findings also emerged for *pairwise* comparisons of *raw* clotting times. ANOVA with a Sheffe post-estimation adjustment found a statistically significant ($p<0.037$) treatment effect only in the comparison between treatments 1 and 4; Skillings-Mack identified significant pairwise differences between treatments 1 *vs*. 3 and 1 *vs*. 4 (p's<0.0001), 2 *vs*. 4 ($p<0.007$), and 3 *vs*. 4 ($p<0.019$); ODA using a *fixed* discriminant threshold found no statistically significant pairwise differences (p's>0.08); ODA using a *strictly-less-than relative* discriminant threshold identified significant pairwise differences between treatments 1 *vs*. 3 and 1 *vs*. 4 (p's<0.00391), and 2 *vs*. 4 ($p<0.032$); and ODA using a *less-than-or-equal relative* discriminant threshold identified a pairwise difference between treatments 3 *vs*. 4 ($p<032$).

In stark contrast to inconsistent findings obtained between methods in analysis of raw clotting time data, a *uniformly consistent* finding of *no effect* emerged in analyses of *ipsatively standardized* data vis-à-vis ANOVA ($p=1.00$), Skillings-Mack ($p<0.79$); ODA using a *fixed* discriminant threshold in *omnibus* ($p<0.99$) or *pairwise* (p's>0.66) comparisons; and ODA using *relative* discriminant thresholds in pairwise analyses (p's>0.21).

What explanation underlies the different findings which were obtained by analyzing raw *vs*. ipsatively standardized data? Quite simply, this is a classical form of Simpson's Paradox (i.e., paradoxical confounding) whereby pooling raw clotting times of different people ignored existing baseline interpersonal differences and yielded invalid and inconsistent results—which vanish once interpersonal baseline differences in mean and variance are eliminated using separate (ipsative) standardizations.[39] The present study is yet another example of a ubiquitous problem permeating all quantitative sciences—the use of inappropriate measurement metrics[39-47] and/or suboptimal statistical methods[48-51] may fail to identify true underlying effects and instead find confounded effects—which in reality simply *don't* exist.

Two fundamental weaknesses underlie the experimental methodology used presently. One weakness is the inadequate sample size: the

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first axiom of novometric statistical theory is the sample must yield adequate statistical power to test the *a priori* alternative hypothesis.[36-38] The second design weakness lies in the sample of observations itself, in light of the evidence of paradoxical confounding attributable to baseline differences. Because outcome analysis may be biased by confounding, it is imperative to use an appropriate matching/blocking process to eliminate possible confounding which is attributable to observed covariates that exert influence on the outcome. For example, in studies with small (sufficiently large) samples and few covariates, matching directly on the covariates may suffice. However, as the number of covariates increases and the distributions differ increasingly between the treatment and control conditions, methods to stratify and weight individuals into blocks (of the propensity score) and thereby to adjust for observed confounding should be considered.[52]

These techniques are incorporated in the ODA, CTA and novometric frameworks.[53-55] In any substantive analytic application, optimal ("maximum-accuracy") methods are available to assist researchers to obtain a clear understanding of the factors which must be considered to be potential threats to causal inference: to identify variables characterizing participation in both discretionary treatment[56] and observational[27] research (to identify possible confounding variables), and to find structural breaks in single[57,58] and multiple-group[59] interrupted time series analysis, dose-response studies[47,60] and in research investigating mediating processes.[61] Optimal ODA and CTA methods are available to assist researchers to identify and correct (in real time) covariate interactions which exist in data from matched[53] and randomized trials[62] to remove otherwise undetected threats to causal inference. Globally-optimal ("novometric") analysis is available to identify all statistically unique propensity score models that maximize classification accuracy and vary as a function of complexity, which exist within a sample: this makes model misspecification impossible, and is used in both time-to-event and single-case precision forecasting.[63-66] The present findings further illustrate why we strongly advocate using ODA, CTA and novometric frameworks to draw causal inferences about treatment effects in observational data and in data from randomized controlled trials. Clearly, changes are needed in guidelines concerning how health care interventions and policy changes are evaluated.[67,68]

Finally, several new tantalizing research directions are indicated by our recent studies of the use of relative discriminant thresholds in maximum-accuracy models. First, an enhanced incarnation of novometric CTA is needed, that combines fixed and relative thresholds—always using the fixed threshold first. And, application of these methods should be extended to research designs involving dyads, couples, and "self *vs*. other" configurations, as well as to designs that involve temporal comparisons.

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