THE JONCKHEERE-TERPSTRA NONPARAMETRIC TEST FOR TREND UTILIZING SAS MACROS

Robert S. Hoop, Warner-Lambert/Parke-Davis Pharmaceutical Research
Iraj Mohebalian, Warner-Lambert/Parke-Davis Pharmaceutical Research

ABSTRACT

When the apriori research interest is testing for trend in a completely randomized design, the Jonchkheere-Terpstra non-parametric test is useful. It is used to test the hypothesis that three or more treatments are in a definite order, e.g., the second is better than the first, the third better then the second.

A SAS MACRO has been written to produce

1. Hypothesis tests for small or large sample sizes
2. Estimates of treatment differences
3. Confidence intervals of estimates of treatment differences
4. Estimates of treament differences weighted by sample size
5. A graph of the medians for the treatment groups

INTRODUCTION

Often a researcher is interested in testing a hypothesis that three or more treatments are equally effective against an alternative hypothesis that the treatment effects are a definite order, e.g., the second is better then the first, the third better than the second.

Examples of such research topics include

1. Do increased doses of a drug produce increased therapeutic effect?
2. Are increases in the concentration of a chemical compound associated with increased mutations in mice?[1]
3. Is there a trend toward increased weight loss during successive days of exposure to ionizing radiation?[2]

A distribution-free test for trend may be advisable if the

1. Sample sizes are small.
2. Data, even after transformation, are substantially non-normal.
3. Research interest is primarily in testing for trend, keeping in mind that a global analysis of variance may be less powerful in detecting a pre-specified trend.

When the research interest is not in detecting a trend among three or more treatments in a completely randomized design, the usual omnibus test is the Kruskal-Wallis. In the same situation, but when the research interest is testing for trend, a useful test is the one proposed by Jonckheere[3] and Terpstra.[4]

JONCKHEERE-TERPSTRA TEST FOR TREND

Let X_{ij} be observations
μ be the overall mean
T_j be the treatment effect of jth population
E_{ij} be the error term

The assumption is that the observations are independently sampled from the same continuous distribution.

Model: $X_{ij} = \mu + T_j + E_{ij}$ with $n_1 + n_2 + \ldots + n_j = n$
HO: Treatment effects are equal:
$T_1 = T_2 \ldots = Tk$
Ha: Treatment effects are ordered,
$T_1 \leq T_2 \ldots \leq TK$
Where at least one of the $\leq$ is really $<$
The test applies, as well, to Ha of
$T_1 \geq T_2 \geq \ldots \geq T_k$.

THE CALUCATION

1. Arrange sample data by treatment group in the order of increasing magnitude suggested by Ha (for conceptual purposes, not in the actual SAS data set).
2. Rank all responses across treatments (not within) from 1, ... n
3. For each sample, compare every rank in each successive sample. If the comparison supports Ha, record one, zero otherwise, i.e.,

   W_{ij}: $X_{i\alpha} < X_{j\beta}$ where

   $\alpha = 1, 2, 3, \ldots n_j$
   $\beta = 1, 2, 3, \ldots n_j$

   $= 1$ if $X_{i\alpha} < X_{j\beta}$
   $= 0$ otherwise

   That is, $W_{ij} = \sum_{\alpha\beta} (X_{i\alpha} < X_{j\beta})$

   These are Mann-Whitney statistics
4. $W = \sum_{i<j} W_{ij}$ is the test statistic

A presentation of this topic appears in Hollander and Wolfe[5] and in Lehman.[6]

LARGE SAMPLE THEORY

The normal distribution is the limiting form for the Jonckheere-Terpstra test statistic.[3,4]

EFFICIENCY

The asymptotic relative efficiency (ARE) of Jonkheere's test with respect to a suitable normal t-test for ordered alternatives

is $\geq$ 0.864 for all distributions; for normal distributions, the ARE = 0.955.[7]

The test's ARE is nearly identical to that of the Wilcoxon (Mann-Whitney) rank sum test.

SAS APPLICATION

The SAS program described below can be used by statisticians or other scientists. It functions with three or more treatment groups and one or more dependent variables. The program requires no upper limit on the number of treaments, on the sample size, nor on the number of dependent variables. The output automatically provides

1. A graph of the median of each treatment group.
2. An hypothesis test for small or large sample sizes depending on sample size and number of treatment groups.
3. Estimates of the shift in location due to treatment, computed using the Hodges-Lehman[8] estimator of median differences between each pair of treatments.
4. A confidence interval for this estimate of treatment differences[5] (identical to the procedure with Wilcoxon's rank sum test.
5. Spjotvoll's estimator of linear contrasts, which are the Hodges-Lehman estimator weighted by each treatment's sample size.[9]

This SAS ouput differs from other distribution-free statistical software in that it goes beyond hypothesis testing, to a graphical presentation of descriptive statistics, to estimation and confidence intervals, which are often overlooked.

COMPUTER PROGRAMMING

A combination of SAS and SAS MACRO language is used for the Jonckheere-Terpstra test program. It has been implemented on an IBM 3033 with MVS Operating Systems, and can be adapted to others.

In order to invoke Jonckheere's test the following syntax is required:

```
%JONCK(<list of dependent variables>,
[<treatment variable][<list of class
variables>), [<Confidence Interval>],
[decreasing/increasing],[debug=true])
```

.<list of dependent variables>: separate analyses will be performed on each continuous variable listed.

.<treatment variable>: the alternative hypothesis contends that there is an increasing or decreasing trend across the categories of this variable.

.<list of class variables>: an optional parameter provides class variables, so that separate analyses will be performed for each category of the variable, if one such variable is listed. For example, if sex is specified, then analyses will be performed separately for females and males. If race is to be analyzed separately from sex, then the program must be invoked twice. If, however, (sex race) is specified, then analyses will be computed for females blacks, female whites, male blacks, male whites.

.<Confidence Interval>: an optional parameter with the default set to 90 percent. Specify the numerical value of the percent without "%" or "percent". Confidence intervals are computed based upon large sample approximations.

.<decreasing/increasing>: an optional parameter to indicate the order specified in the alternative hypothesis. The default is set to "increasing".

.debug: an optional parameter. By assigning debug=true the program prints the macro expansions.

NOTE: Input data for Jonckheere's test has to be in SAS dataset format.

EXAMPLE:

```
%include jonck;
data;
   input dose response;
   cards;

      :
    <data>
      :

%jonck(response, dose,, decreasing)
```

The Jonckheere-Terpstra program will be invoked to test whether or not there is a trend for the response variable to decrease as dose increases. No class variables are specified and the confidence interval will be the default value of 90%.

ILLUSTRATION

Jonchkheere-Terpstra's test and the SAS program described above are useful in a pharmaceutical research study of the effect of "Drug X" on swelling in arthritic rats. The efficacy parameter (dependent variable) of interest is the change from baseline in paw volume. Thirty-seven arthritic rats were randomly assigned to treatment groups consisting of the following doses: 2, 6, 20, and 50 mg. One research question asks whether or not increased doses of Drug X produces decreases in swelling (paw volume), that is, does a dose-response relationship exist.

The code specified in the previous section (with the variable name "VOL_CHG" replacing "response") produced the output seen below. First, a listing of the raw data appears, then a bar chart displays the median of each treatment group. Results of the hypothesis test indicate rejection of the null hypothesis in favor of a decreasing trend, that is, a dose-response relationship ($p = .013$). Estimates of treatment effect for each pair of doses is provided, as well as 90% confidence intervals for the estimates.

ALTERNATIVE TECHNIQUES

For a completely randomized design, a variety of statistical tests for trend exist, in addition to Jonckheere-Terpstra's. These include

1. Parametric
   a. ANOVA followed by posterior comparison for trend
   b. Linear regression
   c. Bartholomew's E^2 test
   d. Abelson-Tukey's optimal contrasts
2. Nonparametric
   a. Chacko's H
   b. Puri's expected normal scores
   c. Modified Cox-Stuart weighted sign test
   d. Sen-Boyd's union intersection
   e. Podmanabham-Puri-Salek
   f. K. S. M. Rao

ACKNOWLEDGMENT

The authors appreciate the contributions of 1) C. A. Seng for her patience and word processing skill, 2) E. R. Heyman and W. E. Ewy for providing insightful editorial comments, and 3) S. C. Wu for guidance and encouragement in the early stages of the project.

REFERENCES

1. Boyd, Michael N. Examples of testing against ordered-alternatives in the analysis of mutagenicity data. Mutation Research, V 97, N 2, 1982, pp 147-152.

2. Gralla, Edward J., Sabo, John P., et at. The effect of selected drugs on first stage radioemesis in Beagle dogs. Radiation Research, V 78, 1979, pp 286-295.

3. Jonckheere, A. R. A distribution-free k-sample test against ordered alternatives. Biometrika, V 41, 1954, pp 133-145.

4. Terpstra, T. J. The asymptotic normality and consistency of Kendall's test against trend, when ties are present in one ranking. INDAGATIONES MATH. Vol 14, 1952, pp 327-333.

5. Hollander, Myles, and Wolfe, Douglas A. Nonparametric Statistical Methods. John Wiley and Sons, 1973, pp 78-79, 120-123, 136.

6. Lehman, E. L., and D'Abrera, H. J. M. Nonparametrics: Statistical Methods Based on Ranks. McGraw Hill, 1975, pp 232-233.

7. Puri, Madan L. Some distribution-free k-sample rank tests of homogeneity against ordered alternatives. Communications on Pure and Applied Mathematics, V 18, 1965, pp 51-53.

8. Hodges, J. L., Lehman, E. L. Estimates of location based on rank tests. Annal of Mathematical Statistics, V 34, 1963, pp 598-611.

9. Spjotvoll, E. A note on robust estimation in analysis of variance. Annals of Mathematical Statistics. V 39, 1968, pp 1486-92.

For either a copy of this SAS program or additional information, contact one of the authors:

Robert S. Hoop, Statistician
Warner-Lambert/Parke-Davis
2800 Plymouth Road
Ann Arbor, Michigan 48105
(313) 996-7526

Iraj Mohebalian, Programmer
Warner-Lambert/Parke-Davis
2800 Plymouth Road
Ann Arbor, Michigan 48105
(313) 996-7367

JONCKHEERE - TERPSTRA NONPARAMETRIC TEST FOR TREND

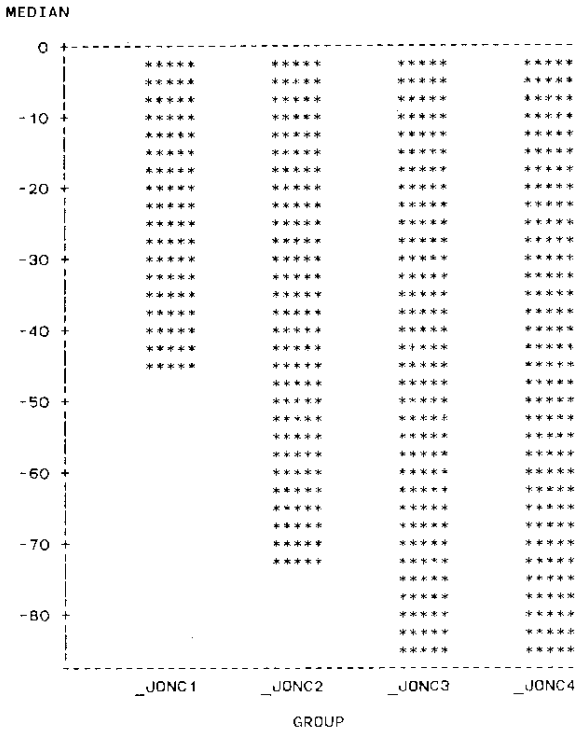
DEPENDENT VARIABLE(S): VOL_CHG
CLASS VARIABLE(S): DOSE
COMPUTAION FOR DEPENDENT VARIABLE VOL_CHG

OBS	_JONC1	_JONC2	_JONC3	_JONC4
1	-263	-184	-175	-290
2	-53	-132	-182	-218
3	-129	-120	-147	-158
4	-128	-133	-138	-130
5	75	-72	-59	-85
6	-48	21	-86	-63
7	-8	-71	-84	-70
8	-42	-23	-42	-56
9	-26	-53	-47	-65
10	7	.	.	.

JONCKHEERE - TERPSTRA NONPARAMETRIC TEST FOR TREND

DEPENDENT VARIABLE(S): VOL_CHG
CLASS VARIABLE(S): DOSE
COMPUTAION FOR DEPENDENT VARIABLE VOL_CHG

BAR CHART OF MEDIAN



HYPOTHESIS TEST FOR INCREASING TREND:

W=172 X=2.2903

NORMAL APPROXIMATION, LARGE SAMPLE SIZE: P=0.9890

OF TREATMENT GROUPS: 4
OF OBSERVATIONS IN TREATMENT GROUP _JONC1 =10
OF OBSERVATIONS IN TREATMENT GROUP _JONC2 =9
OF OBSERVATIONS IN TREATMENT GROUP _JONC3 =9
OF OBSERVATIONS IN TREATMENT GROUP _JONC4 =9

MEDIAN FOR EACH LEVEL OF TREATMENT GROUP:

MEDIAN FOR TREATMENT _JONC1 = -45
MEDIAN FOR TREATMENT _JONC2 = -72
MEDIAN FOR TREATMENT _JONC3 = -86
MEDIAN FOR TREATMENT _JONC4 = -85

ESTIMATE (HODGES - LEHMAN) OF MEDIAN TREATMENT DIFFERENCES:

	ESTIMATE	90% CONFIDENCE INTERVAL
Z(_JONC1 ,_JONC2)	=29.5	(-29 ,90)
Z(_JONC1 ,_JONC3)	=48	(5 ,121)
Z(_JONC1 ,_JONC4)	=58	(14 ,137)
Z(_JONC2 ,_JONC3)	=15	(-34 ,68)
Z(_JONC2 ,_JONC4)	=26	(-26 ,91)
Z(_JONC3 ,_JONC4)	=11	(-45 ,72)

NOTE: THIS CONFIDENCE INTERVAL IS A LARGE SAMPLE APPROXIMATION

ESTIMATE (SPJOTVOLL) WEIGHTED BY SAMPLE SIZE; FOR USE WITH CONTRASTS:

(_JONC1 ,_JONC2)	=30.95946
(_JONC1 ,_JONC3)	=46.90541
(_JONC1 ,_JONC4)	=57.63514
(_JONC2 ,_JONC3)	=15.94595
(_JONC2 ,_JONC4)	=26.67568
(_JONC3 ,_JONC4)	=10.72973