SYSTAT Application Notes

Biostatistics In Medical Research Using SYSTAT

Introduction

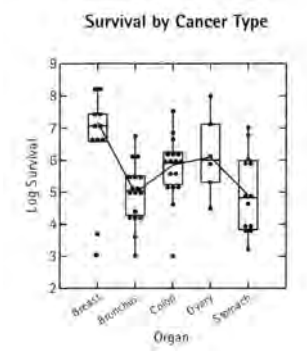
A brief glance through almost any recently published medical journal will show that statistical methods are playing an increasingly visible role in modern medical research. At the very least, most research papers quote at least one 'p-value' to communicate. At the same time, a growing number of papers are now presenting the results of relatively sophisticated, statistical analyses of complex sets of medical data (Matthews and Farewell (1996)).

This proliferation in the use of statistical methods has also been paralleled by the increased involvement of professionally trained statisticians in medical research as well as the use of statistical softwares like SYSTAT.

Design of Experiments

Medical researchers have long understood the importance of carefully designed experiments and have been using them. Properly designed and executed experiments will generate more-precise data while using substantially fewer experimental runs than alternative approaches.

They will lead to results that can be interpreted using relatively simple statistical techniques, in contrast to the information gathered in observational studies, which can be exceedingly difficult to interpret.



SYSTAT offers three methods for generating experimental designs: Classic DOE, the DOE Wizard, and the DESIGN command.

Classic DOE provides a standard dialog interface for generating the most popular complete (full) and incomplete (fractional) factorial designs. Complete factorial designs can have two or three levels of each factor, with two-level designs limited to two to seven factors, and three-level designs limited to two to five factors. Incomplete designs include: Latin square designs with 3 to 12 levels per factor; selected two-level designs with 3 to 11 factors and from 4 to 128 runs; 13 of the most popular Taguchi designs; all of the Plackett and Burman two-level designs with 4 to 100 runs; the 6 three-, five-, and seven-level designs described by Plackett and Burman; and the set of 10 three-level designs described by Box and Behnken in both their blocked and unblocked versions. In addition, the Lattice, Centroid, Axial, and Screening mixture designs can be generated.

The DOE Wizard provides an alternative interface consisting of a series of questions defining the structure of the design. The wizard offers more designs than Classic DOE, including response surface and optimal designs. Optimization methods include the Federov, k-exchance, and coordinate exchange algorithms with three optimally criteria available. The coordinate exchange algorithms accommodate both continuous and categorical variables. The search algorithms for fractional factorial designs allow any number of levels for any factor and search for orthogonal, incomplete blocks if requested. The DESIGN command generates all designs found in Classic DOE using SYSTAT's command language.

Power Analysis

The question of sample size is a technical consideration comprising one aspect of the general problem of design. Although, in general terms, it is difficult to specify how many subjects are required to make a clinical trial worthwhile, to embark on any study without considering the sample size which is adequate is unwise, and may even be unethical.

It is important to realize, right from the start, that sample size calculations will always be approximated. It is clearly impossible to predict the exact outcome of any particular clinical trial or laboratory experiment.

Nevertheless, the importance of sample size calculations is demonstrated by the fact that they provide information about two important design questions:

- ❑ How many subjects should participate in the intended experiment?

- ❑ Is this study worth doing if only n subject (a fixed number) participate?

For a specific experimental design, SYSTAT's power analysis (POWER) explores the relationship between sample size and the probability of achieving statistical significance. Available experimental designs include:

- ❑ comparing a single proportion to a value
- ❑ equality of two independent proportions
- ❑ comparing a correlation coefficient to a value
- ❑ equality of two correlation coefficients
- ❑ z- tests (one sample and two sample)
- ❑ t-tests (one sample, paired, and two sample)
- ❑ one-way ANOVA
- ❑ two-way ANOVA

Power calculations for other designs can be performed using generic power analysis. In this case, specify the degrees of freedom and the non-centrality parameter to perform the analysis.

This approach can be used for general factorial designs, randomized block designs, and fixed effect regression, as well as many other designs. In general, power depends on the parameters of the population(s) involved, the probability of making an error, and the size of the sample(s).
For a fixed error rate and set of population parameters, you can either find the sample size needed to achieve a specific power level or find the power corresponding to a specific sample size. You can also find the power for each sample in a range of sample sizes.

Applications

The visual loss secondary to diabetic macular oedema can be controlled to some extent by photocoagulation, though the mechanism of action is largely unknown. The purpose of a study by Sander et al. (2002) was to quantitate the effect of photocoagulation on the blood-retinal barrier using fluorescein as a tracer of passive and active transport.

A prospective 46 eyes in 34 patients with clinically significant macular oedema (CSMO) were examined by vitreous fluorometry before and 6 months after macular photocoagulation treatment. All calculations were performed with SYSTAT; the test was used to test for significance.

With reference to the presence or absence of CSMO at follow up, the passive transport (permeability) for responding eyes decreased after photocoagulation in contrast with an increase in non-responding eyes the difference between the groups at follow up was significant (p=O.O3). The active transport for responding eyes decreased slightly at follow up, while it increased for non-responding eyes; the difference between the groups at follow up was not significant (p=0.09).

One hundred and thirty one consultant pathologists in two English Regions were sent a questionnaire by Silcocks and Page (2001) containing 37 phrases used in pathology reports, including those indicating cancer and those not.

The aim was to compare interpretation by cancer registries and histopathologists of phrases that might confirm a diagnosis of cancer. Pathologists were asked to indicate whether each phrase confirmed the disease, ruled it out, or was uncertain, together with a subjective estimate of how frequently they used the phrase.

Comparisons of the responses in each region were performed by x2 tests on the two 2 x 3 tables corresponding to each phrase using SYSTAT. They concluded that the cancer registry should consider ignoring four of the 13 terms currently regarded as confirmatory.

Terminology used in pathology reports should be standardized across registries. Registries and coding departments should use empirical evidence to assess which phrases confirm a diagnosis.

The mechanisms by which glucocorticosteroids promote osteoclastogenesis in vitro are uncertain.

As macrophage colony-stimulating factor (MCSF) is critical for osteoclastogenesis, Rubin et al. (1998) hypothesized that glucocorticosteroids might regulate membrane-bound MCSF (mMCSF) and soluble MCSF (sMCSF) production by stromal cells or osteoblasts. ST2 cells or murine calvarial osteoblasts (MOBS) were treated with dexamethasone (Dex; 100 nM) and/or 1, 25-dihydroxyvitamin [1, 25(OH)2D; 10 nM] for 3 days.

Significance between groups was assessed with ANOVA followed by Bonferroni post-hoc test using SYSTAT. Their results suggested that Dex influences osteoclastogenesis by increasing the expression of mMCSF by accessory cells in culture.

The symptoms of women with premenstrual syndrome improve in response to suppression of ovarian function, although these women have no evidence of ovarian dysfunction. Schmidt et al. (1998) undertook a study to determine the role of estrogen and progesterone in this syndrome.

The daily ratings for each symptom were averaged for each of the four weeks preceding the leuprolide or saline injections and for the four weeks of estradiol and progesterone replacement in the hormone-replacement study.

In the leuprolide study the means of the daily symptom ratings were compared by analysis of variance with repeated measures (SYSTAT), with treatment (leuprolide vs. placebo) as the variable between groups and study phase (base line vs. treatment), month, and week as the variables within groups.

The efficacy of leuprolide as compared with placebo was further determined in post hoc comparisons of symptoms during weeks 2 and 4 ,which were the weeks with maximal variation in symptoms (postmenstrual vs. premenstrual) during base line.

Since the blinding could not be maintained in those receiving placebo for more than two months, we selected the last two months of treatment to compare the effects of leuprolide and placebo. They showed that in women with premenstrual syndrome, the occurrence of symptoms represents an abnormal response to normal hormonal changes.

Folate status is inversely related to the risk of colorectal cancer. Whether conventional blood measurements of folate status accurately reflect folate concentrations in the colorectal mucosa has been a controversial topic.

This is an important issue because accurate measures of folate status in the colorectal mucosa are important for ascertaining the risk of colorectal cancer in epidemiological studies and for determining the effects of folate supplementation in clinical trials.

Kim et al. (2001) examined whether conventional blood measurements of folate and a more sensitive, inverse indicator of systemic folate status, serum homocysteine, accurately reflect folate concentrations in human colonic mucosa obtained by endoscopic biopsy.

Linear regression analysis using SYSTAT was used to assess the correlation between variables. Their observations indicated that colonic mucosal concentrations of folate might be predicted accurately by blood measurements of folate status only among individuals not ingesting supraphysiological quantities of folate.

Cord blood hemoglobin Barts (HbBarts) and hemocytometric indices may be used for classification of newborns into those without a thalassemia-2 (aa/aa) and with heterozygous a-thalassemia-2 (-a37/aa).

Dijs et al. (1999) investigated by SYSTAT's logistic regression analysis whether the combination of HbBarts and hemocytometric indices improves classification compared with classification based on a single analyte.

HbBarts percentages and hemocytometric indices were determined in cord blood of 208 consecutive newborns in Curacao (Netherlands Antilles). Of these, 157 had aa/aa and 51 had -a37/aa, as established by DNA analysis.

Between-group differences were significant for erythrocytes, mean cell volume, mean cell hemoglobin (MCH), mean cell hemoglobin concentration, platelets, hemoglobin F0, (HbF0), and HbBarts.

The Logit equation of the logistic regression model, using MCH (pg) and HbBarts (%), was: 42.7164 + 5.7916(HbBarts) - 1.3110(MCH). A sensitivity of 100% was reached at a Logit value of -3.70.

The corresponding specificity was 62.2%, and the predictive value of a positive test (PV+) was 46.3% (95% confidence interval, 37.055.7%). The relative information gains were as follows: 88% for the HbBarts-MCH combination, 26% for MCH (not significant), and 0% for HbBarts compared with the 24.6% -a37/aa prevalence.

They concluded that combined use of cord blood HbBarts and MCH improves classification compared with classification based on single hemocytometric indices.

Left ventricular or biventricular pacing/stimulation can acutely improve systolic function in patients with dilated cardiomyopathy (DCM) and intraventricular conduction delay by resynchronizing contraction. Most heart failure therapies directly enhancing systolic function do so while concomitantly increasing myocardial oxygen consumption (MVO,).

Nelson et al. (2000) hypothesized that pacing/stimulation, in contrast, incurs systolic benefits without raising energy demand.
Ten DCM patients with left bundle-branch block (ejection fraction 20 +/- 3%, QRS duration 179 +/- 3 ms, mean+SEM) underwent cardiac catheterization to measure ventricular and aortic pressure, coronary blood flow, arterial coronary sinus oxygen difference (AAVO2), and MuO2. Data were measured under normal sinus rhythm (NSR) or with left ventricular or biventricular pacing/stimulation at the same heart rate.

Statistical analysis was performed using SYSTAT. Comparisons of data measured during NSR versus pacing/stimulation or between predobutamine and postdobutamine infusion were performed by use of a Wilcoxon nonparametric test. Comparisons between these interventions were performed by a Kruskal-Wallis nonparametric test.

They concluded that, ventricular resynchronization by left ventricular or biventricular pacing/stimulation in DCM patients with left bundle-branch block acutely enhances systolic function while modestly lowering energy cost. This should prove valuable for treating DCM patients with basal dyssynchrony.

Despite numerous reports of short-term response to lung volume reduction surgery (LVRS) for treatment of emphysema, longer-term survival has not been reported (Brenner et al. (1999)).

They describe survival following LVRS in a large cohort of 256 patients treated with bilateral staple LVRS (n = 236 video-assisted thoracic surgery [VATS] approaches, n = 20 median sternotomy) by a single group of physicians over a 3 1/2- year period from April1994 to November 1997.

The overall survivor function is estimated using the Kaplan-Meier method. Differences in survival after stratification by preoperative and postoperative variables were tested using the log-rank test. The simultaneous importance of preoperative and postoperative variables on survival was investigated using Cox proportional hazards regression.

Covariate analysis was performed, including variables found to be significant in univariate survival. Analyses were conducted using SYSTAT.

Conclusions

The description above just gave a bird's eye view of SYSTAT's capabilities. But SYSTAT provides a powerful statistical and graphical analysis system in a graphical environment

using descriptive menus and simple dialog boxes. SYSTAT's command language provides functionality not available in the dialog box interface in addition to complete coverage of menu-based functionality.

Robust algorithms from leading statisticians give meaningful results-even with extreme data. Create missing value estimates using regression based point estimation or an EM algorithm.

Matrix procedure allows you to use matrix algebra to specify statistical analyses and perform data management tasks. Create compelling reports by combining formatted statistical output with publication-quality graphs in SYSTAT's rich text output window.

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