A cost effective approach to the design and analysis of multiple experimental groups: a useful methodology for comparing potential treatments for COVID-19

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Scientific research often requires the comparison of two or more experimental groups. The successful conduct of such investigations requires a study design appropriate for the scientific question at hand, a valid testing procedure for the hypothesis of interest, and an adequate sample size which guarantees suitable power. Sample size determination, or equivalently power calculations, are usually based on two-sample and two-sided alternative hypotheses designed to test whether the mean response of the treatment group is different from that of the control group (1). Such calculations are simple and very widely used and numerous software packages, such as SAS and SPSS, have built-in routines for such tasks. As discussed in this article, studies designed for assessing two-sided hypotheses are often grossly inefficient in terms of power and therefore may require a much larger than necessary number experimental units. Since in many experimental sciences a substantial portion of the budget is devoted to acquiring the sample, ill-designed studies incur increased costs. Of course, beyond the financial burden, ethical consideration arises when the subjects are animals and even more so when human. Here, we describe an alternative approach that, when appropriate, yields higher power per experimental unit and consequently substantially lowers the cost of experimentation.

In many applications, such as dose-response studies, time-course gene expressions studies or multi-drug trials, researchers may have a priori beliefs about the experimental groups. These beliefs are usually based on earlier studies or an understanding of the underlying scientific phenomenon and are often formulated as mathematical inequalities or constraints, known as order restrictions. For example, in a dose-response study, toxicologists may expect that the mean response increases (or decreases) with the dose of a chemical. This constraint is known as the simple order. Observational data are also often of this form. For example, in (2) the length of the ramus bone of 20 boys was measured at three equally spaced time points from age 8 to 9. The question of interest was: did a significant growth spurt occur during the observed period? In a time-course gene expression study, the mean expression of a gene may increase up to a certain point, reflecting its biological activity (3) and then decrease. This constraint is known as the umbrella order. In clinical trials, a researcher may be interested in demonstrating that the standard treatment is inferior to one of the new treatments, or, that a new treatment is at least as efficacious as the existing ones. This constraint is called the tree order. For example, (4) compared the effect of various doses of cytisine on a dysphoric–like state in rats. In some cases, the study design may include multiple control and multiple treatment groups. For example, the US National Toxicology Program (NTP) evaluates toxicity and carcinogenicity of chemicals using the concurrent control group as well as historical controls (which are controls collected from similar studies conducted by the NTP). This set up leads naturally to a bipartite order restriction (5, 6). The above-mentioned order relations are represented graphically in Figure 1 by their corresponding order graphs. In each of the Figures, a circle represents a group mean, or more generally any other statistical parameter, and a pointed arrow implies an inequality among the two means or parameters. The roots of the order graph are the nodes with the largest means, whereas the leaves are the nodes with the smallest means. A variety of other constraints, or order restrictions, arise in applications and there exist over six decades of literature on this subject (7).

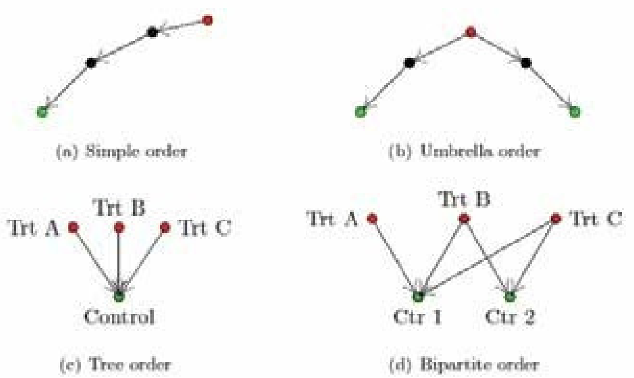

Figure 1. Order graphs for some common order restrictions. Circles represent group means and a pointed arrow indicates an inequality among the means. Green circles correspond to leaves of the order graph and red circles to their roots. We refer to the leaves and roots as the extreme groups. The intermediate groups are designated by a black circle

Research Diary

Standard methods for the above-mentioned analyses, often based on two-sided F or permutation tests, were not designed to address scientific problems in which ordering is inherent. Moreover, as mentioned earlier, their use typically results in a considerable loss of power. Thus, in this proposal, we emphasize that statistical methods which incorporate the underlying constraints are available, and should be used whenever appropriate. This collection of methods is known in the literature as constraint statistical inference (CSI). We illustrate the consequences of using such methodologies in both the design and the analysis of experiments. Doing so addresses the scientific questions motivating the study in a principled manner. Moreover, such methods may provide the power to uncover clinically important features in the data missed by standard methods. There is a current worldwide outbreak of a new type of coronavirus (COVID-19). There is no specific effective antiviral treatment available. However, some potential treatments based on drugs such as Remdesivir, Favipiravir, Lopinavir/ritonavir, and Hydroxychloroquine among others are actively used (8,9,10). Using the methods of the CSI and experimental designs, multiple comparisons among these treatments can be done effectively with a significantly reduced budget. Moreover, carefully designing and planning the experiment the using the methods such as a bipartite, tree, and umbrella order comparisons might result in the insightful in-depth interpretation of the study.

References and Notes:

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Design for the New World: Post COVID-19: A Disruptive Change in Context

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Originating from China to almost every country and every state, COVID-19 has spread to every habitable corner of this planet. It has brought significant damages and loss of lives across humanity. The world, as we know it, is a changed place now. The practices and behaviours which were considered normal and were even not noticeable are now disrupted. The world has become helpless to run its routine and it looks like we've ended up at the beginning of establishing civilizational traits for humanity. The biggest question is how to cope up in the No-Touch world!? Well, strange times. But the same 27