DR ELLINOR FACKLE-FORNIUS

Design for disparate disciplines

From patient treatment groups to assessment of environmental values, algorithms perform essential calculations across myriad subjects. **Dr Ellinor Fackle-Fornius** of the Department of Statistics at Stockholm University tells us about her team and how their work in experimental design will make a difference

Whom does your research group comprise and what expertise is represented?

I have a PhD in Statistics and my research area is optimal design of experiments, including sequential designs and the design of experiments where the outcome is binary. The research group comprises other experienced statisticians. Professor Hans Nyquist has 20 years of experience within the field of optimal experimental design. His expertise also covers statistical theory as well as statistical methods in forestry and economics. Linda Wänström PhD's expertise is in both statistics and psychology. Among other things she has worked with models for cognitive development. In addition, a PhD from the pharmaceutical industry and two PhD students are connected to our research group.

What is design methodology? How has it emerged and what needs does it respond to?

The design methodology offers theories for designing an experiment from which valid conclusions can be drawn from the observations and where resources are used efficiently. It was first developed in connection with agricultural research in the 1930s by the pioneer, Sir Ronald A Fisher. The outcomes of agricultural experiments are affected by weather conditions such as rainfall and temperature. Fisher showed how to use statistical methods to plan experiments such that valid conclusions can be drawn under varying conditions. Many applications were also found in biology and medicine. The experimental design methodology then evolved to military and industrial applications, especially within quality improvement and process optimisation. It is now common in many research disciplines, including social sciences and economics.

Have you sought out any collaborators over the course of your study, and if so, what value have they added?

One of the aims of the project was to apply the minimax design approach to practical, real-world problems. This has led us to collaborations with Stockholm Resilience Centre concerning the estimation of the value of environmental goods, and Astra Zeneca concerning issues in drug development. Applying the methodology to real problems has resulted in useful insights, which in turn have resulted in further refinements of the methods.

What progress has been made in applying the knowledge gained over the course of the project to practical problems?

We have learned how minimax designs can be useful for different applications. One application is to plan a contingent valuation experiment (CVE) for estimation of indivdiuals' willingness to pay for clothes made from ecologically produced cotton. Another example is the minimax allocation of patients to treatment groups under variance heterogeneity; the minimax allocation is often better than allocating an equal number of patients to each treatment. We have also worked with a dose-finding study in a phase II clinical trial where we learned that the minimax design offers an improvement over the standard design, being at least 15 per cent more efficient.

By what means are you examining the effectiveness of minimax designs in comparison with other design methods? Do you have any findings to report here?

Comparisons of minimax design with other design methods have been done through simulations. The efficiency of a design is defined by the number of further observations that are needed in order for the design to be equivalent to the best possible design, ie. that which one would use if one knew the true model parameters. The efficiency is computed and evaluated under different scenarios. In summary, our results indicate that the minimax designs can do well in terms of efficiency even outside the a priori specified range of plausible parameter values.

Your research project is set to continue until the end of the year. What do you hope to achieve between now and then?

We are currently working on extensions of some of our results. For example, we have results for minimax allocation of patients to treatment groups where the variability is different in the treatment groups. The next step is to allow the costs to vary between the groups, which is a common situation in practice. We also hope to further improve the programme codes that implement our algorithm to construct minimax designs. Furthermore, we will continue with the efficiency evaluations.

Maximising success, minimising failure

A poorly designed experiment can lead to useless results and wasted resources. However, by carefully designing an experiment, it should be possible to minimise information losses and increase the amount of information gained from data. Minimax aims to do just that

WHEN GATHERING INFORMATION from experiments, it is crucial to think about the means of doing so. Known as experimental design, the choices made are shaped by the decisions on what variables to examine, the level at which they should be examined and how they should be examined in relation to other variables. Each decision is made with the aim of finding the optimal design for the experiment. This will maximise the information gathered within the limitations of the resources available. Experimental design is central to the success and validity of any experiment, and is therefore crucial. Nonetheless, there are numerous examples of experiments where better planning could have doubled the precision in the parameter estimation (measured in terms of halved error of estimation). There are also examples of where a poorly planned experiment results in a situation where it is not possible to draw any conclusions at all.

EXPERIMENTAL DESIGN

A problem with the construction of optimal designs arises from the fact that, for many experiments, these designs depends on unknown model parameters. Various strategies have been proposed to circumvent this problem. The simplest option is to use locally optimal design, which relies on guess work; poor guesses will lead to a poor experimental design. Another option is to use the optimum on-the-average design based on several guesses. Alternatively, sequential designs can be used, but this might be time-consuming. A further option is minimax design, which involves the optimisation of the worst value of the criterion when the unknown parameters are allowed to vary in a specified range. However, construction of the minimax design is incredibly difficult when using conventional analysis. As such, Dr Ellinor Fackle-Fornius from the Department of Statistics at Stockholm University has led a team to develop the role that minimax can play in experimental design. The important research means that it will now be possible to apply minimax design routinely in experiments across various disciplines.

CUTTING LOSSES

Working alongside Dr Linda Wänström and Professor Hans Nyquist, Fackle-Fornius started the three-year project by attempting to build an algorithm for the construction of minimax designs. Minimax has been held back by the fact that it is extremely difficult to compute. The team therefore attempted to eradicate this problem by building an algorithm based on the relationship between optimum on-the-average designs and minimax designs. The minimax design offers a solution to the issue of the

INTELLIGENCE

MINIMAX DESIGN – CONSTRUCTION, EFFECTIVENESS COMPARISONS, AND PRACTICAL APPLICATIONS

OBJECTIVES

The project aims to develop a new algorithm to handle the computational difficulties involved in the construction of minimax designs. The main objectives are to develop the algorithm and evaluate its convergence properties, examine the efficiency of minimax designs in comparison with other design methods, and apply the algorithm to practical problems.

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optimal design's dependence upon unknown model parameters. As such, the design relies on specifying a model and indicating a range of plausible parameter values. These values give minimax its main advantage: robustness. An experiment designed using minimax is protected against the worst case within a specified range of plausible parameter values. As its name suggests, minimax minimises the maximum loss of information.

MAXIMISING EFFICIENCY

Having spent a year working to build the algorithm, the team spent the second year of the project testing how effective the minimax design is against other design methods. Using simulation models, the efficiency of each design was measured by the number of observations needed in order for the design to match the best possible design. The findings came from a calculation of the design's efficiency which was then evaluated in different scenarios. Results showed that the algorithm worked well, indicating that the minimax designs can show high levels of efficiency even when the previous information is incorrect.

DEVELOPING THE DESIGN

In the final year of the project the team has further developed the algorithm and used the minimax design in a number of applications. They showed that the design could be used in contingent valuation experiments (CVE), which are frequently used to calculate the value of non-market goods and services such as environmental resources. To measure the value, CVE respondents are presented with a hypothetical scenario in which the goods or services are offered and then bid upon. Part of the planning process of CVE involves deciding upon the number and size of bids, and how many respondents to allocate to each bid.

Information is needed on people's willingness to pay for the goods or services. The team therefore applied their algorithm to construct a minimax design for various scenarios of the trinomial spike model, a particular version of the logistic model that only supports positive bid values. This model allowed for the possibility that the respondents may be unwilling to pay, by explicitly asking them whether they were happy to pay anything at all. Findings revealed that the optimal design often consists of one bid, therefore suggesting that it is optimal to present the same cost to all the respondents.

To further test the algorithm, the researchers applied it to find the optimal allocation of patients to treatment groups; such experiments are common in medical trials involving a placebo. The optimal design is that which allows allocation based on the group's variances. The team found that the minimax design worked well when compared to the traditional experimental design. Furthermore, it was shown to be robust even outside the specified range of plausible values.

A third test involved the application of the algorithm to a dose-finding study in phase II clinical trials. The optimal design for studying the effect of a drug concerns three aspects: the number of doses, the choice of doses and the allocation of patients to doses. Practical differences can also play a part; the choice of doses are at times restricted to certain levels. Results indicate that the minimax was 15-62 per cent more efficient than the standard design. The advantages of the methodology are clear: "Since clinical trials often involve high investments it is very important to optimise the use of resources," Fackle-Fornius notes.

FUTURE PLANS

The Swedish researchers intend to continue testing minimax's efficiency, further pushing its ability to optimise experimental designs. They are already turning their thoughts to applying their design to more complex models in order to develop the design methodology. This could include using the minimax design for a generalised linear model with random effects. Such models are very flexible, and include elements found in psychology, pharmacology and economics, among others. In particular, the team is collaborating with pharmacologists on treatments of tubercolosis. The team is working towards making the algorithm as efficient as possible, whilst showing just how valuable a design it can be.

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