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Stockholm University
Department of Statistics

Festschrift in Honor of Hans Nyquist on the Occasion of His 65th Birthday

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Stockholm University

$\mathbf{R}_j^{\mathrm{T}}\beta = r_j \qquad f(y_i;\theta_i) = c(y_i)\exp\{\theta_i y_i - b(\theta_i)\}$

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$b^{c} = \lim_{\lambda_1,\ldots,\lambda_q \to \infty} b(\lambda)$

$b^{c\,(m+1)} = \tilde{b}^{(m+1)} + (X^{\mathrm{T}}WX)^{-1}R^{\mathrm{T}}\{R(X^{\mathrm{T}}WX)^{-1}R^{\mathrm{T}}\}^{-1}(r - R\tilde{b}^{(m+1)}).$

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Preface

In a small village called Gryttje in Gnarp, Hälsingland, in the north of Sweden on December 11, 1950, Hans Nyquist was born. Now, 65 years later, we have joined to create this festschrift in celebration of the life and career of a great scientist, teacher, colleague and friend.

Hans Nyquist started his academic journey in Umeå where he obtained a BStat in 1975 and a PhD in statistics in 1980 for the thesis entitled "Recent Studies on Lp-Norm Estimation". He immediately got a position as a lecturer in statistics at Umeå University where he stayed until 1983, when he also gained his docent title (associate professor) in statistics. Next followed two periods of postdoc positions, first at University of Sydney, Australia, and then at Imperial College London, UK. In 1993 he accepted a position as a lecturer in Biometry at the Swedish University of Agricultural Sciences. From 1995 to 2003 he was Professor in Statistics at Umeå University. During these years he had another postdoc period, this time at University of South Carolina, Columbia, USA. From 2003 until present time he holds a professorship here at the Department of Statistics, Stockholm University. In 2013 he stayed as a guest professor at University of Riverside, California, USA.

During the last decades Hans Nyquist has made significant contributions to several fields of statistics. Starting with his thesis on robust statistical inference his research interests include robust estimation of linear and non-linear models, sensitivity analysis and optimal design of experiments. Over the years he has been working with applications from forestry, economics, medicine, and educational measurements. His research has resulted in more than thirty articles published in peer reviewed journals. A creative and analytical mind, curiosity, diligence, and ability to communicate with anyone, are among the qualities making him a successful researcher. He is a popular collaborator in research and also a much appreciated speaker at conferences, always eager to interact with his audience.

Hans Nyquist has served science in many ways. He has been Associate Editor for several journals, including Journal of Statistical Planning and Inference, Journal of Official Statistics and Electronic Journal of Applied Statistical Analysis, reviewer for Zentralblatt für Mathematik and referee for a multitude of journals, such as Annals of Statistics, Biometrics, Journal of American Statistical Association, Review of Economics and Statistics and Scandinavian Journal of Statistics, to name just a few. He has acted as external reviewer of applications for research projects for Riksbankens Jubileumsfond, DESMI (co-funded by the Republic of Cyprus and the European Regional Development Fund), and CONICYT (Chile) as well as been a member of the reviewer group at the Swedish Research Council. In addition, Hans Nyquist is devoted to the promotion and development of statistical research and education. He has continuously supported the Swedish Statistical Association, where he was elected president for two periods (1997-1999, 2010-2012). He was also president of the European Courses of Advanced Statistics between 2006 and 2009, and head of the Department of Statistics, Stockholm University, for a period of six years (2005-2011).

Besides this, Hans Nyquist serves society as reserve officer (major) in the Swedish Air Force. He is also a keen orienteer, both as practitioner and organizer of orienteering events.

Hans Nyquist is a highly esteemed teacher at all levels, mastering teaching at the most basic introductory course as well as any graduate course. Numerous students over the years have had the opportunity to experience his dedication, enthusiasm and lucid explanations. Moreover, he has written a comprehensive introductory compendium for students. To date, he has successfully supervised ten PhD students (including myself). As supervisor he is committed, encouraging and willing to help at all times.

Those of us who have had the chance to collaborate with Hans Nyquist know that he is not only passionate about research but also truly friendly and humorous. Therefore it was no surprise to me that all of you gladly accepted my invitation to contribute to this festschrift. My apologies to those I did not manage to contact and who would also have liked to be a part of this celebration.

I would like to sincerely thank all of the authors for generously giving your time and ideas, and for adhering to the (often tight) deadlines. It has been a pleasure and a privilege to be the editor of this festschrift and you all have made the editing process so easy for me. I am also very grateful to Bergrún Magnúsdóttir, Jessica Franzén and Sofia Normark for editorial assistance, to Michael Carlson for sharing his experiences about editing a festschrift and to Siv Nyquist for providing me with background information and keeping this whole project a secret.

November 2015 Ellinor Fackle-Fornius

Professor Hans Nyquist, 2010

From optimal design theory to optimizing designs of clinical trials

Carl-Fredrik Burman[1]

Abstract

Optimal design theory is applicable to certain aspects of the design of clinical trials. In this article, we will discuss *D*-optimal designs for Emax models in particular. However, several important design features are outside the scope of classic optimal design theory. One example is optimisation of the sample size. Solving this type of problems requires us to move from a narrow view of statistics to an appreciation of the design as part of a wider scientific context. This may be especially important when considering trials in rare diseases where few patients are available for trial inclusion, the cost is relatively large compared to potential drug sales and where much is at stakes for future patients and patients in the trial. A particularly challenging problem is that of programme optimisation, where a dose-finding trial is to be optimised, not based on a function of its Fisher information matrix, but based on the expected utility for the optimal design of the following confirmatory trial.

Key words: D-optimal designs, clinical trials, small population groups, decision theory

1 Introduction

Since I became docent in "Biostatistik", I have felt some obligation to be able to answer simple questions from lay-men within that field. While the standard English translation of "Biostatistik" is Biostatistics, an alternative translation is "Cinema Statistics". I found the latter area more challenging, and therefore forced myself to study the sales statistics at BoxOfficeMojo.com and watch the lion part of the best-selling films. In one of them, *Mission Impossible - Ghost*

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Protocol, the excellent Swedish actor Nyquist played a professor at Stockholm University with IQ 190, specialising in game theory. His research centres on critical decisions and he designs a scenario that he thinks is optimal for the future of mankind. Such topics, like optimal design and decision-making will be the subject of this paper. The stakes will not be quite as high as in the film, but we will still be talking about lives and deaths, as we consider the development of new pharmaceuticals for serious diseases.

We will start, in Section 2, by outlining some concepts and results from optimal design theory as it relates to clinical trials. As an example, D-optimal designs for the Emax model will be provided. In Section 3, we will consider the design of clinical trials from a more practical point of view, and also discuss optimisation of design features that are normally not included in optimal design theory. We will then expand from the level of an individual experiment and sketch a problem of optimisation of a programme of trials (Section 4). This problem is especially mathematically challenging as the optimal design of a dose-finding trial does not depend on a function of the information matrix, but on what will be the optimal design of confirmatory phase III, and on how this optimisation will result in an expected value of the goal function. On the other hand, the optimisation of the confirmatory trial will depend on the dose-finding trial design and the stochastic outcome of that trial. Finally, Sections 5 and 6 provide a discussion and conclusions.

2 Optimal design theory relating to clinical trials

In this article, we define optimal design theory as the theory of optimising a function of the (asymptotic) Fisher information matrix for the parameter vector. This theory is described in, for example, Atkinson et al. (2007); Fedorov and Leonov (2013). Optimal design theory has been applied to a number of clinical trial design problems, for example: the choice of doses in phase IIB dose-finding trials (e.g. Miller et al. (2007)), adaptive dose-finding (e.g. Bornkamp et al. (2007); Bretz et al. (2010)), sequential designs to estimate the highest dose with acceptable toxicity (e.g. Haines et al. (2003)), the choice of sample times for longitudinal modelling (e.g. Bazzoli et al. (2009)), and covariate-balancing allocations (e.g. Atkinson (1982); Burman (1996); Atkinson (2014)). The most important application is arguably dose-finding and that is the topic of most of this section.

2.1 The Emax model

We will consider the following Emax model, which is the most important model for dose-response,

$$\eta(x,\theta) = \theta_1 + \theta_2 \frac{x^{\theta_4}}{x^{\theta_4} + \theta_3^{\theta_4}}, \tag{1}$$

where $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$ is the vector of parameters, η is the expected response, and the residuals are assumed to be additive and independent normally distributed with constant variance. The 4-parameter Emax model predicts that the response is a sigmoid function of the logarithm of the dose. The parameter θ_1 can be interpreted as the expected response in the placebo group, and θ_2 is the maximal expected additional efficacy. The potency parameter, θ_3, corresponds to the dose where half of the maximal additional efficacy is attained. The shape parameter θ_4, often called the Hill coefficient, is related to the steepness of the function around θ_3. In addition to the full 4-parameter model, we will also consider all models resulting when some of the four parameters are taken to be known. If the value of θ_1 is known to be θ_1^C we can subtract the constant θ_1^C from the response. The new response will then have expectation as in equation 1 with $\theta_1 = 0$. Thus, without loss of generality, we may set $\theta_1 = 0$. With similar arguments, we take $\theta_2 = 1$, $\theta_3 = 1$ and $\theta_4 = 1$ in the expected response $\eta(x,\theta)$ whenever they are known.

Some of the sub-models have their own names in specific areas of biosciences. One example is the Michaelis-Menten model, which we can regard as an Emax model where θ_1 and θ_4 are known. Thus, the Michaelis-Menten model includes only θ_2 and θ_3 as unknown parameters. Another model is named after Hill (1910). It is an extension of the Michaelis-Menten model including also θ_4 as unknown parameter. Examples of applications of Emax models in other areas than dose-finding clinical trials include biochemical engineering using enzyme reactors (Kumar and Nath (1997)), surface adsorption processes (Naidja and Huang (2002)), population dynamics (Xu and Chaplain (2002)), and biosensors (Liu et al. (2003)).

2.2 Locally D-optimal designs

A key aspect of designing the experiment consists in choosing the number of doses, n, the dose levels, $x_i, (i = 1, \ldots, n)$, and the proportion, $w_i, (i = 1, \ldots, n)$, of experimental units (patients) allocated to each dose in order to gain as much information as possible about the parameters in the model. Optimal designs for non-linear models are especially complicated since they

depend on the true parameter values. A common approach in this case is to make a Taylor expansion of the model to make it linear around the true, but unknown value, $\theta^\star = (\theta_1^\star, \theta_2^\star, \theta_3^\star, \theta_4^\star)$, of the parameter vector.

If we denote by $m(x_i, \theta)$ the contribution to the information matrix by one observation, with dose x_i, we have $m(x_i, \theta) = [\frac{\partial \eta(x_i,\theta)}{\partial \theta}][\frac{\partial \eta(x_i,\theta)}{\partial \theta}]^T$, where $[\frac{\partial \eta(x_i,\theta)}{\partial \theta}]$ is a column vector with the jth element equal to the partial derivative $\partial \eta(x_i, \theta)/\partial \theta_j$. The Fisher information matrix for a design ξ with n doses $x_1, \ldots, x_n$ and $Nw_1, \ldots, Nw_n$ observations per dose is $NM(\xi, \theta)$, where

$$M(\xi, \theta) = \sum_{i=1}^{n} w_i m(x_i, \theta)$$

is called the standardised information matrix. We will focus on the construction of a locally D-optimal design, which minimises

$$\psi(\xi, \theta) = \ln(\det M^{-1}(\xi, \theta)) = -\ln(\det M(\xi, \theta)).$$

It is crucial to be able to check a proposed design for optimality. This can be done using the General Equivalence Theorem by Kiefer and Wolfowitz (1960). Let ξ_x be the one-point design assigning unit mass to the point x. Define the directional derivative of $\psi(\xi, \theta)$ towards ξ_x as

$$\phi(x, \xi, \theta) = \lim_{\alpha \to 0^+} \frac{1}{\alpha}[\psi((1-\alpha)\xi + \alpha\xi_x, \theta) - \psi(\xi, \theta)].$$

A sufficient condition according to the General Equivalence Theorem for the design ξ to be optimal is that $\phi(x, \xi, \theta) \geq 0$ for all x. The theorem also states that equality is fulfilled at the support points of the optimal design. If we denote by p the number of parameters, the well known theorem by Caratheodory says that there exists a D-optimal design with $n \leq p(p+1)/2$ design points. In many models only p design points are needed. In this case equal weight should be given to each design point. This is the case in 13 of the 15 Emax models we study here. However, for the two models with $\{\theta_2, \theta_4\}$ and $\{\theta_1, \theta_2, \theta_4\}$ as unknown parameters, the number of design points in the optimal design exceeds the number of parameters in the model.

2.3 Locally D-optimal designs for the Emax models

Locally D-optimal designs are given in Table 1 for the 4-parameter model and for models with only a subset of the parameters. (For clarity, we will in the table use general values of known parameters, not assuming $\theta_1 = 0$,

$\theta_2 = 1$ etc.) The optimal designs have been deduced by direct studying of the criterion function and by applying the General Equivalence Theorem. Some of the results can be found in Hedayat et al. (1997); Duggleby (1979); Bezeau and Endrenyi (1986). Locally D-optimal designs for all cases are given in Sonesson and Burman (2004).

The parameters θ_1 and θ_2 enter the dose-response function linearly. In the optimal design, they call for design points in $x = 0$, to estimate θ_1, and formally in $x = \infty$, to estimate the sum $\theta_1 + \theta_2$, so that θ_2 can be estimated. In theory, we will allow a design point at infinite dose. In practise, the highest dose depends on previous information about toxicity and ethical considerations. The optimal design when the dose is constrained by $x \leq x_{\max}$ often needs to be determined numerically. Analytic results for the Michaelis-Menten model for this situation can be found in Duggleby (1979).

For a model with only θ_3, the absolute value of the derivative w.r.t. θ_3, is maximised when $x = \theta_3^\star$. Thus, that design point will give most information to estimate θ_3 and the one-point design is D-optimal.

For the model where the Hill coefficient, θ_4, is the only unknown parameter, a one-point design with dose x will have

$$\det(M(\xi, \theta_4)) \mid_{\theta_4=1} = \left(\frac{x^{\theta_4} \ln x^{\theta_4}}{(1 + x^{\theta_4})^2} \right)^2 .$$

Using the variable substitution $y = x^{\theta_4}$ the determinant is maximised when $(y-1)\ln y = y+1$. This equation has two roots: $y_1 = 1/A$ and $y_2 = A$ where $A \approx 4.6805$. The optimal design points x_1 and x_2 (where $x_i = y_i^{-\theta_4}$) are the doses where the additional efficacy, as compared with the placebo effect, is 17.6% and 82.4% of θ_2. Any of these two design points can be chosen in the optimal design. Furthermore, since linear combinations of D-optimal designs are also D-optimal, any 2-point design with x_1 and x_2 and arbitrary weights is also optimal. Figure 1 illustrates how the optimal design points are the ones that best discriminate between models with different values of θ_4. In order to simplify the text in the remainder of this sub-section, we assume that the problem is rescaled so that $\theta_4 = 1$ and $\theta_3 = 1$, also when these parameters are taken to be unknown. The summary table will, however, give solutions for general parameter values.

When including θ_1 in the model, in addition to θ_4, a kind of symmetry (in the logarithmic scale) is introduced in the problem. The optimal design consists of doses $x_1 = 1/A$ and $x_2 = A$ with equal weight.

The optimal design for the 2-parameter model with θ_3 and θ_4 have doses $\{1/B, B\}$ where $B \approx 2.84$. This design can be understood as a compromise

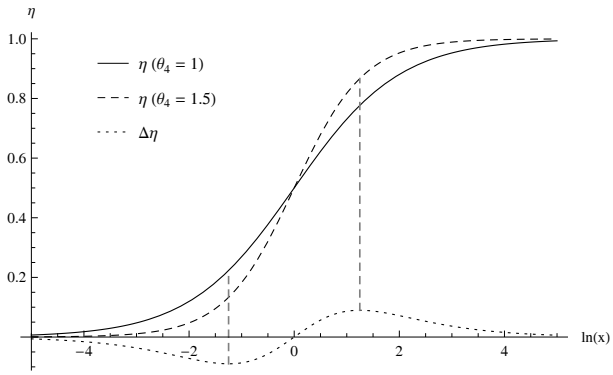

Figure 1: *The Emax model for the case of θ_4 being the only unknown parameter. As θ_4 approaches 1 from above, the vertical lines at the maximum and minimum of $\Delta\eta$ converge to $\pm\ln(A) = \pm 1.5434$.*

between the optimal designs with doses $\{1\}$ and $\{1/A, A\}$ for the two corresponding 1-parameter problems. The doses $1/B$ and B corresponds to 26.0% and 74.0% of the maximal efficacy compared to placebo.

For the model with unknown parameters θ_1, θ_2 and θ_4, there is an intrinsic (anti)symmetry in the model, which will appear clearly after a transformation. Let $z = \ln x$ and reparametrise the model by setting $\theta_{\text{diff}} = \theta_2/2$ and $\theta_{\text{aver}} = \theta_1 + \theta_2/2$.

The resulting expected value in the model is

$$\eta_z(z, \theta') = \theta_{\text{aver}} + \theta_{\text{diff}} \frac{\exp(\theta_4 z) - 1}{\exp(\theta_4 z) + 1} \tag{2}$$

where $\theta' = (\theta_{\text{diff}}, \theta_{\text{aver}}, \theta_4)$. The locally D-optimal design for this model will correspond in an obvious way to the optimal design of the original model. Note that for the model in formula 2,

$$\frac{1}{2}[\eta_z(z, \theta') + \eta_z(-z, \theta')] = \theta_{\text{aver}},$$

irrespective of z. This indicates that any symmetric design will lead to an estimator of θ_{aver} which is independent of the estimators of the two other parameters. Therefore, it is plausible that any non-symmetric 3-point design can be improved by making it symmetric by increasing the number of design

Table 1: *D-optimal designs for Emax models*

Unknown parameters	Optimal design points	Unknown parameters	Optimal design points	
		θ_4	θ_3/a	(Remark 1)
θ_1	0	θ_1, θ_4	θ_3/a, $a \cdot \theta_3$	
θ_2	∞	θ_2, θ_4	$c_1 \cdot \theta_3$, $c_2 \cdot \theta_3$, ∞	(Remark 2)
θ_3	θ_3	θ_3, θ_4	θ_3/b, $b \cdot \theta_3$	
θ_1, θ_2	0, ∞	θ_1, θ_2, θ_4	0, θ_3/a, $a \cdot \theta_3$, ∞	
θ_1, θ_3	0, θ_3	θ_1, θ_3, θ_4	0, θ_3/b, $b \cdot \theta_3$	(Remark 1)
θ_2, θ_3	θ_3, ∞	θ_2, θ_3, θ_4	θ_3/b, $b \cdot \theta_3$, ∞	
$\theta_1, \theta_2, \theta_3$	0, θ_3, ∞	$\theta_1, \theta_2, \theta_3$, θ_4	0, θ_3/b, $b \cdot \theta_3$, ∞	

Equal weight is given to each design point with one exception; see Remark 2.

$a = A^{1/\theta_4}$, *where* $A \approx 4.68$ *solves* $(A-1)\ln(A) = A+1$.

$b = B^{1/\theta_4}$, *where* $B \approx 2.84$ *solves* $2(B-1)\ln(B) = B+1$.

Remark 1: There is an alternative D-optimal design with the same number of design points.

Remark 2: The weights are unequal: 0.346, 0.342 *and* 0.312, *respectively. Constants are* $c_1 \approx 0.241$ *and* $c_2 \approx 5.640$.

points. Further, it is easy to see that a symmetric 3-point design cannot be optimal since the resulting information matrix is in fact singular.

Note that the model with only the two parameters θ_{diff} and θ_4, with θ_{aver} taken as a constant, has a 2-point optimal design with design points $\pm \ln A$ and $\pm\infty$. The plus or minus signs can be chosen arbitrarily due to the symmetry of the problem. In fact, the mass can be split arbitrarily between $+\ln A$ and $-\ln A$ and between $+\infty$ and $-\infty$. For the 3-parameter model, the optimal design for the 2-parameter problem can be applied directly with the only restriction of symmetry, which is caused by the inclusion of θ_{aver}. (Compare this situation with the inclusion of θ_1 to the model with only θ_4 above.) The optimal design is thus the 4-point design $-\infty$, $-\ln A$, $+\ln A$ and $+\infty$ with equal weights. It may be noted that this design is optimal also for the 2-parameter problem, that is, the inclusion of a third parameter does not make the estimation of θ_{diff} and θ_4 less precise. For the corresponding 3-parameter model using our original parameter setting, the optimal design thus consists of the design points $0, 1/A, A, \infty$, as presented in Table 1. (Recall that we have taken e.g. $\theta_3^\star = 1$ and $\theta_4^\star = 1$ in the discussion, while we give formulas for any parameter values in the table.)

Interestingly, there exists no 2-point optimal design for the 2-parameter model with unknown parameters θ_2 and θ_4. Turning to a 3 point design for

this model, one might expect that the optimal design would have doses $1/A$, A and ∞ with equal weights. However, this is not the case. Two of the design points in this design, as well as the weights, differ slightly from the optimal design. The optimal design in Table 1 for this model is found by numerical methods.

2.4 Some remarks

The minimisation of $\psi(\xi, \theta)$ as a design criterion is motivated by its connection to the variance of the estimated parameters. Assuming independent normally distributed residuals with constant variance σ^2 in the linear model $\eta = X\theta$, the variance-covariance matrix of the ordinary least squares estimates of θ equals $\sigma^2(X^TX)^{-1}$. The volume of the confidence ellipsoid of the estimated parameters depends on $\det(X^TX)$. The larger the determinant is the smaller will the volume be. For the non-linear models, we will get a similar result after a Taylor approximation around $\theta^\star$. This motivates the D-optimality criterion. However, for some of the Emax models, the maximum likelihood estimator has undefined variance. This critique often has limited practical importance, but care is recommended when the trial has a small sample size.

Another issue is that we have only considered continuous designs, where the design weights can be chosen in $(0, 1]$. However, all designs used in practice must be exact in the meaning that they are realisable for a specific number of observations, N. All design weights must thus be a multiple of $1/N$. This comment may be worth considering when the sample size is small.

Instead of focussing on all parameters, we may be particularly interested in some of them. A D_S-optimal design can then be considered. Often the interest lies in a function of the parameters to be estimated. In the case of a linear function of the parameters, the criterion is called local c-optimality. In dose-finding studies one might not be primarily interested in ED_{50}, the dose giving 50% of the maximum possible efficacy, but rather, for example, in ED_{90} or ED_{95}. Dette et al. (2010) gives local ED_p-optimal designs, together with D-optimal ones. One criterion for what is regarded as the optimal dose might be the dose where the response has a certain derivative w.r.t. the logarithm of the dose. This would be one way to balance efficacy and possible adverse effects of taking the drug.

Local D-optimality focuses on a single point estimate of the unknown parameters. As an alternative, optimal-on-average (a.k.a. Bayesian) optimal designs optimise the expectation over a prior for the parameter vector of the same criterion function as before (Atkinson et al. (2007); Pettersson and Nyquist (2003)). A review of Bayesian design can be found in Chaloner and Verdinelli

(1995). Results for the Michaelis-Menten model were obtained by Matthews and Allock (2004). An alternative to Bayesian designs is to focus on maximin designs (Dette and Biedermann (2003); Nyquist (2013); Fackle-Fornius et al. (2015); Fackle-Fornius and Nyquist (2015)). A way to extend the Emax model is to include random effects. Optimal design in that type of models has been studied in Mentré et al. (2001). Note that the Emax model is mathematically similar to logistic regression models for dichotomous data. Fackle-Fornius and Nyquist (2009) give c-optimal designs for this situation when the logit is a quadratic function of the independent variable, the dose, say. Magnusdottir and Nyquist (2015 (pre-published online) analyse Emax models with both efficacy and safety, and Burman et al. (2010) discuss the trade-off between them.

3 Optimising clinical trial designs

When a clinical trial is designed in practise, a multitude of design dimensions have to be considered. A natural first question is which treatments should be compared. We may know that a certain new drug under development should be tested but the choice of control group is not always obvious. Could placebo be used or is an active control needed for ethical reasons (Burman and Carlberg (2009)), and in that case which active control?

The choice of the dose or doses of the new drug is often important. Sometimes other dosing aspects are also of importance, such as how often the drug should be administered and through which route. Some designs have individualised doses, e.g. based on body weight, and can even use titration, that is, (usually) increasing doses over time. In many medical areas, one single dose has traditionally been tested in confirmatory phase III trials. However, this has been questioned by regulators and others. Lisovskaja and Burman (2013) therefore studied whether one or two doses would be optimal, and which dose(s) to choose. In that work, Bayesian decision theory was used rather than optimal design theory.

When discussing which treatment arms to include in a trial, the disease indication and population are often taken as given. However, the precise definition of inclusion and exclusion criteria for potential trial patients often requires considerable work. Other examples of design dimensions are sample size, the choice of (primary and secondary) variables, measurement time points, and the pre-specified analysis, including multiplicity adjustments. Cross-over designs can sometimes reduce the trial size and cost substantially. Adaptive designs, including group-sequential designs, allow pre-specified design modifi-

cations in response to interim data. This may help the trial to provide more informative information (after dose adaptations e.g.) or sufficient data for statistical conclusions.

Classical optimal design theory can readily attack some of the design problems, notably the choice of doses and relative sample sizes in a dose-response trial, where the optimality criterion is a function of the information matrix for a small number of parameters in a dose-response model. It has also been used for the timing of measurements when non-linear mixed effects models are used. Other design factors are perceived as less statistical in nature, and not suitable for optimal design theory. Some factors, like the choice of countries or centres, could possibly be addressed by the classic theory, but probably only to the price of forcing the problem into an awkward mathematical model. Arguably, the most important design parameter, the sample size, is normally ignored by standard optimal design theory.

3.1 Optimal sample size

One problem when optimising the sample size is that by intrinsic measures, an experiment becomes increasingly better, more informative, with an increased sample size. Thus, in the small world, larger is always better. Widening the perspective, however, the cost per patient is significant and there should be a trade-off between information gain and cost. Most of the literature on sample size calculations is, given a fixed type I error, focusing on obtaining a certain type II error for a certain one-point alternative θ_A. This may seem rational, but merely sweeps the problem under the carpet. How should the alternative hypothesis' value of the parameter be chosen? When designing clinical trials, it is common to use the so called "least clinically significant" difference as the alternative θ_A. But, I would argue, virtually any difference is clinically significant to the patients. A reduction in death risk of 1 in 10,000 is clearly valuable, at least in a situation where the new drug is as safe as the alternative treatment. If the new drug has larger safety problems, that should explicitly be factored into a benefit/risk assessment; it does not mean that a small reduction in mortality is clinically in-significant *per se*.

If optimal design theory is not applicable, and traditional sample size calculations are *ad hoc*, we should turn to an explicit analysis of the decision (Lindley (1997); Burman et al. (2007)). What is the value of the information generated by the trial, and what is the cost of experimentation? Assume that the cost $C(N)$ of a clinical trial is proportional to the trial size N, that is, $C(N) = cN$. The value of a trial can be modelled in many different ways, partly depending on which stakeholder perspective is taken. A patient who

will receive a new drug if it obtains regulatory approval would then have a benefit that depends on the drug's (placebo-adjusted) efficacy, θ. Assuming that the safety problems and cost of the new drug are ignorable, and that the patients' benefit is proportional to θ, the total benefit for a fixed future population could be modelled as

$$k\,\theta\,1_{\{\text{Regulatory approval}\}}.$$

For simplicity, we will assume that the drug is approved if and only if the efficacy is statistically significantly better than placebo at level $\alpha = 0.025$. Assume that the test statistic Z_N is normally distributed with mean $\theta\sqrt{N}$ and variance 1. The net utility, considering the benefits for future patients and the cost of the trial, could then be modelled as:

$$U(N,\theta) = k\,\theta\,1_{\{Z_N > C_\alpha\}} - c\,N,$$

where $C_\alpha = \Phi^{-1}(1-\alpha)$ is the critical limit for the test and Φ is the cumulative distribution function for the standard normal distribution. We are interested in optimising, over N, the expected utility

$$\mathrm{E}[U(N,\theta)] = k\,\theta\,p(N,\theta) - c\,N.$$

where $p(N,\theta) = \mathrm{Prob}(Z_N > C_\alpha) = \Phi(\theta\sqrt{N} - C_\alpha)$ is the statistical power of the trial. The optimisation could be made for a certain efficacy value, θ. However, as in non-linear optimal design theory, this kind of "local" optimisation appears somewhat artificial from a practical point of view. How can we assume that θ is known before the trial, when the purpose of the trial is to estimate this same parameter? Bayesian (or "optimal on average") decision theory moves one step further by explicitly modelling the prior uncertainty in the parameter. With π as the prior, the optimum sample size is then

$$\mathrm{argmax}_N\, k\,\mathrm{E}_\pi[\,\theta\;p(N,\theta)] - c\,N.$$

Figure 2 gives an example when θ is Normal$(0.2; 0.1)$ and $k\mathrm{E}_\pi[\theta]/c = 2000$. Optimal sample size have been discussed e.g. by Burman et al. (2007); Kikuchi et al. (2008). Note that the Bayesian decision theoretic approach described is Bayesian only with respect to the choice of design, not in the interpretation of trial data. This is the same as for Bayesian optimal design theory, where the prior is used only for design purposes, not to analyse data. The term optimal-on-average design theory reduces the risk that the method is perceived as fully Bayesian. The input to a decision theoretic model, as e.g. the commercial potential which depends partly on health care providers' willingness-to-pay, is important. Optimal design theory may be used e.g. to evaluate such willingness-to-pay (cf. Nyquist (1992)).

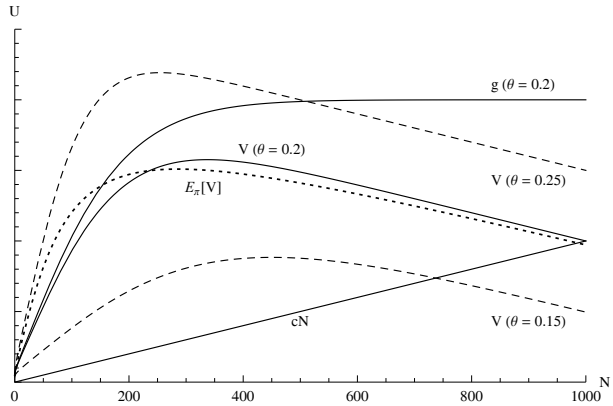

Figure 2: *The utility function for some specific values of θ, and when θ follows a Normal$(0.2; 0.1)$ prior. Solid lines show the cost, expected gain $g = k\,\theta\,p(N, \theta)$ and expected net utility $V = E[U(N, \theta)]$ when $\theta = 0.2$. Dashed lines indicate a higher/lower utility if θ is higher/lower. The dotted line gives the expected utility over the prior for θ.*

4 Adaptive programmes

In mathematics, we often generalise results from one dimension, to two, or infinitely many. As clinical development is a sequential process, where a new medicine has to be tested in a number of pre-clinical steps, followed typically by phase I, IIA, IIB and III clinical trials, it makes sense not only to study the optimal design of a single trial, but to consider also optimisation of a programme of trials. The intricate inter-dependence between the trials will lead to new and challenging problems. The cross-industry Adaptive Programme workstream, sponsored by the Drug Information Association (DIA), has been focussed on studying the design of phase IIB dose-finding in conjunction with phase III confirmatory trials. The publications Patel et al. (2012); Antonijevic et al. (2013b); Marchenko et al. (2013); Antonijevic et al. (2013a, 2015) from the Adaptive Programme workstream have often been relatively applied but more generic models have also been discussed. Some results are given by Jennison (2011).

Based on a prior π_1 for the parameter vector, we are to choose the design $\mathcal{D}_2$ for the phase IIB dose-finding study. Phase IIB will then generate random

data X_2. These data together with the prior π_1 gives the posterior π_2.

In similarity with phase IIB, we can then choose a design $\mathcal{D}_3$ for the confirmatory phase III, which will result in data X_3. However, while phase IIB was aimed at learning about the parameter vector, phase III is used for confirmation. The results from phase III, i.e. X_3, translates into a project value g. The value g may also depend on the total time duration of development, which depends on the design through the sample sizes or, more generally, $g = g(X_3, \mathcal{D}_2, \mathcal{D}_3)$. Let c be the cost of phase IIB and phase III. The generic problem is to maximise

$$\mathrm{E}_1[g - c] = \mathrm{E}_1\left[g(X_3, \mathcal{D}_2, \mathcal{D}_3) - c(\mathcal{D}_2, \mathcal{D}_3)\right]$$

with respect to the designs $\mathcal{D}_2$ and $\mathcal{D}_3 = \mathcal{D}_3(X_2)$ The expectation is taken over the distribution of the study results X_2 and X_3, which are governed by the prior for the parameter.

For our current purposes, a design will be characterised by the doses and related sample sizes. In this case, the design for stage i can be viewed as a counting measure ξ_i, where $n_i(d) = \xi_i(\{d\})$ is the sample size for dose d. The total sample size is $N_i = \xi_i([0, \infty])$ (including infinity for mathematical convenience).

To make the problem solvable, we have to further specify the relation between the model entities. Take all responses to be independent, normally distributed, with constant variance within each trial. Assume that the gain and cost depend only on the designs $\mathcal{D}_i$ through the sample sizes N_i. Thus, $c = c(N_2, N_3)$ and $g = g(X_3, N_2, N_3)$. The (main) reason that the gain depends on the sample sizes is that the commercial value depends on the total time duration T needed to complete the development program. We assume $T = T(N_2, N_3)$. Further, we assume a multiplicative structure, so that the gain is a product of one component v related to phase III efficacy and safety results, and one component t relating to time. Thus, $g = v(X_3) \cdot t(T(N_2, N_3))$.

In short, the generic model consists of the following components in temporal order,

1. Given: prior π_1 for the parameter vector θ
2. Choose: design $\mathcal{D}_2$ (based on π_1)
3. Random outcome: X_2 (depends on the design $\mathcal{D}_2$ as well as the parameter θ, which follows the prior distribution π_1).
4. Calculate: posterior π_2 (depending on prior π_1 and data X_2).
5. Choose: design $\mathcal{D}_3$ (based on X_2 and $\mathcal{D}_2$).
6. Random outcome: X_3 (depending on the design $\mathcal{D}_3$ and parameter θ).

7. Receive a utility $U = g(X_3, \mathcal{D}_2, \mathcal{D}_3) - c(\mathcal{D}_2, \mathcal{D}_3)$.

The objective is to estimate the expected utility.

Note that the parameter vector may govern both efficacy and safety, and potentially several correlated efficacy and safety variables. It makes sense, however, to start working with only one efficacy and (optionally) one safety variable. Note also that the response in phase IIB and in phase III may depend on different parameters. However, there has to be a dependence between the parameters for phase IIB and phase III, so that phase IIB data are informative about the best designs for phase III. The Adaptive Programme problem is still largely unexplored. However, Jennison (2011) has solved an example numerically and provided ideas for solutions of the more general problem.

5 Discussion

The decisions about designs of clinical trials are of fundamental importance to medical science, our society, and, in particular, the patients hoping for better treatments. For rare diseases in particular, we are in great need of methodological improvements to make trials more cost-effective, as the large drug development costs are hindering innovation. Whereas classic optimal design theory e.g. can guide the design of dose-finding trials and measurement times, Bayesian decision analysis is useful to optimally trade e.g. efficacy vs. safety, precision vs. bias, and trial costs vs. information. The combination of ideas from various areas of statistics, and beyond, may prove fruitful to further optimise clinical trial designs.

For late-stage designs in small population groups, some improvement areas are:

- Pooling data over multiple time points / longitudinal analysis
- Using continuous variables instead of dichotomised ones
- Choosing variables with relatively high signal-to-noise ratio
- Borrowing information from historic data or different populations
- Optimising regulatory requirements, based on a public health perspective
- Based on modelling and decision theory deciding whether one or two doses should be included in phase III, and when two doses are included making use of an optimal multiplicity correction (e.g. a pooled test).
- Utilising optimal design theory and similar methodology in design of dose-finding trials

- Adding interim analysis, and optimising group-sequential / adaptive designs
- Cross-over designs
- Optimising the sample size

6 Conclusions

I'd like to conclude by thanking professor Nyquist for his contributions to the progress of science, especially in the field of optimal design theory, and urge his followers to stand on his shoulders and go beyond the current scope of optimal design theory into the vast, mainly unexplored territory of optimisation of real-life (clinical) experiments.

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When is an adaptive design useful in clinical dose-finding trials?

Frank Miller[1]

Abstract

During the development process for new drugs, dose-finding trials have to be conducted and the choice of their design is an important issue. Traditionally, the standard design is a balanced design where equally large groups of patients are treated with different doses of the new drug or with a control. However, it has been identified that other innovative designs might be more efficient: Optimal designs which use non-balanced allocation to dose, and adaptive designs where the allocation to the doses can be changed during the study based on results collected earlier in the study. In a simulation study we will compare efficiencies of balanced non-adaptive, optimal non-adaptive, adaptive two-stage and fully sequential adaptive designs. In all situations considered one can gain from applying optimal design theory. However, when moving from the optimal non-adaptive design to an adaptive design, there are situations where the design is improved and other situations where there is only a minor or no gain. Based on our considered situations, we generalize our observations to answer when an adaptive design is useful.

Key words: Adaptive design; Clinical trial; Dose-finding; Efficiency; Fully sequential design; Interim analysis; Optimal design; Two-stage design.

1 Introduction

The development process of a new drug is divided into several phases: In Phase I, the tolerability of the drug is investigated in clinical trials and the aim is to identify a maximal tolerated dose. As the Phase I investigations often are conducted with healthy volunteers, no or limited information on the

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effect of the new drug is collected. In Phase II, patients are investigated. The objective in Phase II is to show that the drug has effect, and to obtain information about the dose-response profile. Often, a Phase II trial for dose-finding includes some hundred patients. In Phase III, trials are conducted comparing one chosen dose with placebo or with a control treatment (in some cases also two or rarely three doses of the new drug are investigated in Phase III). In Phase III trials, patients are usually treated during a longer time (if a chronic disease is to be treated) and patients come from a broader patient population than the Phase II trials. The dose-response profile estimated in Phase II is important such that the dose(s) for the expensive Phase III trials are chosen in the most adequate way.

It is therefore especially desirable to choose an efficient design for the Phase II dose-finding trial. With a more efficient design, there may be the opportunity to learn better about the new drug without increasing the number of patients needed (sample size). Traditionally, a common design for a dose-finding study allocates patients in a balanced way to placebo (or other control) and to 3-5 doses of the new drug. The same number of patients are therefore treated with each treatment out of 4-6 possible options. In recent years, the discussion about adaptive designs became popular. The trial may be started with a balanced design or with another design. After obtaining a certain number of results, the data is analysed (interim analysis) and the design for the remaining patients is chosen based on the results from the first patients. For example, it might turn out that the doses investigated in the first part (Stage 1) gave all similar and good effect such that the interest would be to investigate smaller doses after the interim analysis (in Stage 2).

In the first years when adaptive design ideas were discussed in this context, the usefulness of adaptivity had been overestimated. One reason was that no comprehensive simulation-based or analytical comparisons were available. Some small simulation studies which compared a non-adaptive design with an optimized adaptive design in a specific situation often showed great benefit of the adaptive design. However, a major shortcoming was that the adaptive design was optimized - but the non-adaptive design was suboptimal. This puts the non-adaptive design at a disadvantage but the interpretation was anyway that the large gain was due to the feature of adaptivity alone. A further shortcoming was the investigation of specific situations (sometimes assuming variances for observations much lower than usual in clinical trials) which turned out to be beneficial for the adaptation.

The organisation PhRMA (Pharmaceutical Research and Manufacturers of America) founded a working group on adaptive dose-ranging studies which

more comprehensively investigated these designs. They published their investigations in form of two white papers, see Bornkamp et al. (2007); Dragalin et al. (2010). They investigate several non-adaptive and adaptive designs for a variety of dose-response scenarios and compare different ways of analysing the data. Their work shows the potential of innovative methods applied to dose-finding. In some publications, situations were identified where the gain of adaptations was limited, see Miller et al. (2007); Dragalin et al. (2010); Jones et al. (2011); Dette et al. (2013); McCallum and Bornkamp (2015).

We will here in this simulation-based investigation quantify the gain of several innovative design features, namely we first improve the traditional balanced design as much as possible without using adaptations. When we then add on adaptivity, we want to figure out what the adaptivity itself contributes to the good properties of an adaptive design. Moreover, we consider two different adaptive designs: a two-stage design with a single interim analysis (as mentioned before) and a fully sequential design where each new patient is assigned to a treatment determined based on all available data from the ongoing study.

Consequently, we consider in this article the following four different types of designs:

1. Balanced (non-adaptive) design with k treatment arms (placebo and $k-1$ doses). The number of patients in each treatment arm is equal.

2. Optimal non-adaptive design. Optimal dose allocation is done according to knowledge prior to the study. Optimality is measured by a certain criterion, which will be specified in Section 2.

3. Adaptive two-stage design (with optimal allocation). Allocation ratios are updated once during the study. Two different optimal designs are used before and after the interim analysis.

4. Fully sequential adaptive design (with optimal dynamic allocation). Optimal allocation for each patient based on all information which is collected until the inclusion of this patient.

These four designs will be described with more details in Section 3.

In this article, we use a similar setting as considered by Miller et al. (2007); Fackle-Fornius et al. (2015) but investigate other, varying scenarios of prior knowledge. By this, we get a feeling in which situations an adaptive design is useful.

2 Model assumptions and objective of the trial

In our considered dose-finding trial we assume the possibility to use k treatment arms: $x_0 = 0$ (placebo) and $k-1$ doses of the new drug $0 < x_1 < \cdots < x_{k-1} \leq x_{\max}$. We use in this article five doses $x_1 = 20, x_2 = 40, x_3 = 60, x_4 = 80, x_5 = 100$ mg. A main aim of phase II in drug development is to obtain knowledge about the dose-efficacy and dose-safety profile of the drug. In this article, we focus on the dose-efficacy-profile, only. We assume that the primary outcome measuring the drug effect of patient i in dose group d is $Y_{di}, d = 0, \ldots, k-1$ following the $E_{\max}$-sigmoid model,

$$Y_{di} \sim N(f(x_d, \vartheta), \sigma^2)$$

with

$$\vartheta = (E_0, E_{\max}, ED_{50}, \alpha)^\top, \quad f(x, \vartheta) = E_0 + \frac{E_{\max} x^\alpha}{ED_{50}^\alpha + x^\alpha}.$$

For modelling of both efficacy and safety, we refer to Magnusdottir and Nyquist (2015) who consider a bivariate $E_{\max}$ model for simultaneous inference.

Here, we want to estimate the dose-efficacy in relation to placebo,

$$f(x, \vartheta) - f(0, \vartheta).$$

The placebo effect $f(0, \vartheta)$ is treated here as a nuisance parameter. However, not all parts of the dose-response curve are of equal importance. Especially, we do not need precision in estimates for the part of the curve with low effects below some threshold of clinical importance, δ. Therefore, Miller et al. (2007) used the following objective: if there exist doses within the dose range up to $x_{\max}$ with an effect of at least δ compared to placebo, we want to estimate

$$f(x, \vartheta) - f(0, \vartheta), \quad x \in [x_\delta, x_{\max}],$$

where x_δ is the dose with effect $= \delta$, i.e. $f(x_\delta, \vartheta) - f(0, \vartheta) = \delta$ or $x_\delta = (\delta/(E_{\max} - \delta))^{(1/\alpha)} ED_{50}$. If we have a drug without clinical relevant effect up to dose $x_{\max}$, we want to estimate the effect at the highest dose

$$f(x_{\max}, \vartheta) - f(0, \vartheta).$$

This objective is illustrated in Figure 1. We call this objective "estimation of the interesting part of the dose-response curve".

Given the described objective, we want to search for a good, or "optimal", design. To do this, we need to further formalize the objective and can then

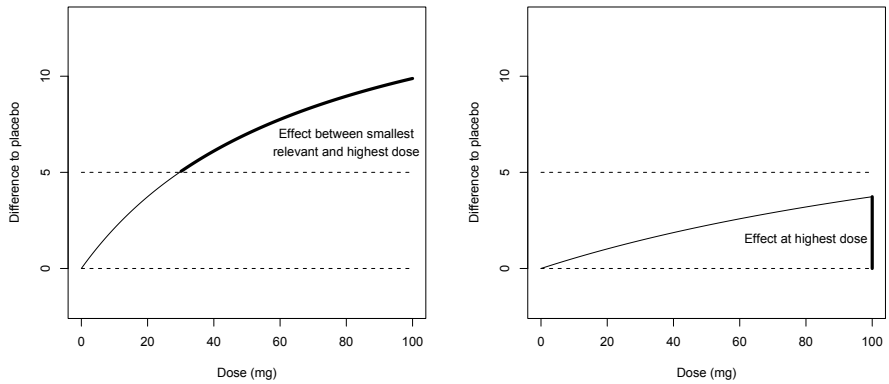

Figure 1: Objective of the trial: estimation of the placebo-adjusted effect between smallest relevant and highest dose (left picture) or – if no such relevant dose exists in the considered dose range – estimation of the effect at highest dose (right picture). The smallest relevant dose is the dose with effect $\delta = 5$.

apply optimal design theory. For a general background on optimal design of experiments, we refer to Silvey (1980); Atkinson et al. (2007).

Let us consider a non-adaptive design which is characterised by allocation ratios $w_d \geq 0, \sum_{j=0}^{k-1} w_j = 1$, for the dose $x_d, d = 0, \ldots, k-1$. We estimate the dose-response curve with the least square estimation in our assumed $E_{\max}$-sigmoid model. The variance of the estimated difference in the effect between a dose x and placebo (dose 0) is approximately proportional to

$$d(x, \xi, \vartheta) = (g(x, \vartheta) - g(0, \vartheta))^\top M^{-1}(\xi, \vartheta) (g(x, \vartheta) - g(0, \vartheta))$$

where

$$M(\xi, \vartheta) = \sum_{j=1}^{k} w_j g(x_j, \vartheta) g^\top(x_j, \vartheta)$$

is the information matrix, and

$$\begin{aligned} g(x, \vartheta) &= \left(\frac{\partial f(x, \vartheta)}{\partial E_0}, \frac{\partial f(x, \vartheta)}{\partial E_{\max}}, \frac{\partial f(x, \vartheta)}{\partial ED_{50}}, \frac{\partial f(x, \vartheta)}{\partial \alpha} \right)^\top \\ &= \left(1, \frac{x^\alpha}{ED_{50}^\alpha + x^\alpha}, \frac{-E_{\max} \alpha ED_{50}^{\alpha-1} x^\alpha}{(ED_{50}^\alpha + x^\alpha)^2}, \frac{E_{\max} ED_{50}^\alpha x^\alpha (\log x - \log ED_{50})}{(ED_{50}^\alpha + x^\alpha)^2} \right)^\top \end{aligned}$$

is the gradient of the dose-efficacy-function with respect to ϑ, see also Miller et al. (2007); Fackle-Fornius et al. (2015).

If there exists no dose within the dose range up to $x_{\max}$ with an effect of at least δ compared to placebo, we just have to maximise $1/d(x_{\max}, \xi, \vartheta)$. If there exist doses within this dose range with the required effect, we want to minimise the average variance of the estimates for $f(x, \vartheta) - f(0, \vartheta), x \in [x_\delta, x_{\max}]$, and use the I_L-criterion with $L = 1$, see Fedorov (1972); Dette and O'Brien (1999). Therefore we search a design ξ with large value of the following criterion function:

$$\Phi(\xi, \vartheta) = \begin{cases} \left\{ \frac{1}{x_{\max} - x_\delta} \int_{x_\delta}^{x_{\max}} d(x, \xi, \vartheta)\ dx \right\}^{-1}, & \text{if } f(x_{\max}, \vartheta) - f(0, \vartheta) > \delta, \\ 1/d(x_{\max}, \xi, \vartheta), & \text{if } f(x_{\max}, \vartheta) - f(0, \vartheta) \leq \delta. \end{cases} \tag{1}$$

We define the relative efficiency of an arbitrary design ξ with respect to the balanced design ξ_0 (used as reference design) by

$$\text{Eff}(\xi, \vartheta) = \Phi(\xi, \vartheta)/\Phi(\xi_0, \vartheta).$$

For example, an efficiency of 1.25 means that the balanced design would need 25% more patients than the design under consideration to obtain estimates with approximately the same precision.

Optimal designs for $E_{\max}$ dose-finding models based on other optimality criteria have been derived in the literature. Burman (2015) presents D-optimal designs for the $E_{\max}$-sigmoid model. Magnusdottir (2013) derives c-optimal designs for the bivariate $E_{\max}$ model. Dette et al. (2008) consider MED-optimal designs for estimation of the minimum effective dose.

Usually, there exists prior knowledge about possible dose-response scenarios before the study starts. Miller et al. (2007) have investigated an example based on an AstraZeneca study with seven possible dose-response scenarios. In this paper, we use as example three possible scenarios: an optimistic scenario, a pessimistic scenario, and a scenario with good effects only at high doses, see Table 1 and Figure 2. In Table 1, the parameter E_0 is not included, since we treat the placebo effect as nuisance parameter and our investigation does not depend on the value of E_0. Further, a standard deviation of $\sigma = 10$ is assumed leading to reasonable signal-to-noise ratios in clinical studies. With the knowledge before the study, we assume that the prior probabilities for the three scenarios are 0.35, 0.35, and 0.30, respectively.

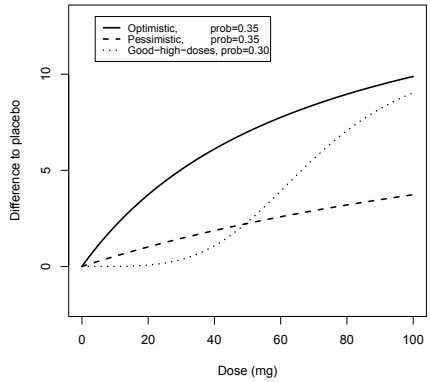

Figure 2: Prior knowledge about dose-efficacy scenarios (Example 1)

Table 1: Parameters for the dose-efficacy scenarios (Example 1)

Scenario	$E_{\max}$	ED_{50}	α	prior prob. π_j
Optimistic	16.8	70	1	0.35
Pessimistic	11.2	200	1	0.35
Good-high-doses	11.2	70	4	0.30

3 Description of the considered designs

Once we have described the assumed model and the objective of the trial, we can describe the four considered designs in more detail. In the simulations in the next sections, we consider a total sample size of $n = 300$ patients.

3.1 Balanced design

Since we have $n = 300$ patients and $k = 6$ treatment arms, we have $n/k = 50$ patients per treatment arm.

Table 2: Optimal non-adaptive design

Dose x_d	0	20	40	60	80	100
Weight w_d	0.385	0.038	0.062	0.096	0.119	0.300
n_d	115	11	19	29	36	90

3.2 Optimal non-adaptive design

As mentioned before, a non-adaptive design is characterised by the allocation ratios $w_0, w_1, \ldots, w_{k-1}$ for the treatment arms 0 (placebo) and $1, 2, \ldots, k-1$ (active doses). In common notation for experimental design, a design characterised by the observational points (here doses) and their allocation ratios (weights) is often called ξ and can be written as

$$\xi = \begin{pmatrix} x_0 & x_1 & \ldots & x_{k-1} \\ w_0 & w_1 & \ldots & w_{k-1} \end{pmatrix}.$$

Our prior knowledge consists of three different scenarios which we can call ϑ_j with $j = 1$ for the optimistic, $j = 2$ for the pessimistic and $j = 3$ for the good-high-doses scenario. We are interested in the design ξ (i.e. the weights w_d) which maximises the average efficiencies for the scenarios,

$$\sum_{j=1}^{3} \pi_j \mathrm{Eff}(\xi, \vartheta_j), \tag{2}$$

using the prior probabilities $\pi_1 = \pi_2 = 0.35, \pi_3 = 0.30$ (see Table 1). We call this design optimal non-adaptive design. We have calculated this optimal design by a numerical method using a first order exchange algorithm, see e.g. Atkinson et al. (2007), see Table 2. The patient numbers n_d are obtained by rounding $300w_d$ (while ensuring a total sum of 300).

The approach to maximize average efficiencies (2) is called "optimal-on-average approach" in contrast to a "maximin approach" where the minimal efficiency over the scenarios is maximised, see Fackle-Fornius et al. (2015).

3.3 Adaptive two-stage design

For this design, we start as above with the optimal non-adaptive design but only for the first part of the study with 100 patients. Given the weights in Table 2, the patient numbers are 38, 4, 6, 10, 12, 30 for doses $0, 20, \ldots, 100$,

respectively (rounding $100w_d$ and ensuring a total sum of 100). Based on the results Y_{di} of 100 patients, we calculate posterior probabilities for the three scenarios according to the Bayes formula. With these posterior probabilities, we calculate a new optimal non-adaptive design for the whole 300 patients. We do this in the same way as we did before with the only exception that we optimise restricted to the fact that we have already a certain number of patients treated with each dose. In practice, it takes some time to collect and analyse the data from the first part of the study while recruitment of new patients is ongoing. Therefore we assume that even patient number 101 to 140 are included according to the starting design. Then, for patient number 141 to 300, the new optimal non-adaptive design is applied.

3.4 Fully sequential adaptive design

As before we assume that we include 140 patients according to the optimal non-adaptive design. When patient 141 enters the study, the results of the first 100 patients are analysed, posterior probabilities calculated and the treatment of this patient is chosen in order to maximise our optimality criterion. We continue in this way, updating the posterior probabilities on an ongoing basis for determining the treatment of the next patient. We assume throughout the study that we have a lag of 40 patients, i.e. when including patient number $i+1$, the results of $i-40$ patients are available.

4 Efficiency for designs

For each scenario and each design, we performed 5000 simulations. Based on these simulations, we calculated relative efficiencies between the designs.

We need simulations as available asymptotic formulae for the efficiency is to crude for finite sample sizes when adaptive designs are considered. Therefore, we compute mean squared errors (MSE) of the estimates in the simulations. More precisely, for a certain design and a certain simulation scenario, we obtain the MSE at dose x for estimation of $f(x) - f(0)$ by

$$\mathrm{MSE}(x, \xi, \vartheta) = \frac{1}{s} \sum_{l=1}^{s} \left[\{\hat{f}_l(x) - \hat{f}_l(0)\} - \{f(x) - f(0)\} \right]^2,$$

where s is the total number of simulations and $\hat{f}_l$ denotes the estimated function in the lth run of the simulation. We replace then in equation (1) the function $d(x, \xi, \vartheta)$ by $\mathrm{MSE}(x, \xi, \vartheta)$ and calculate Φ; if the scenario is such

Table 3: Efficiency gain (Example 1)

Scenario	Efficiency gain		
	from balanced to optimal non-adaptive	from optimal non-adaptive to adaptive two-stage	from adaptive two-stage to fully sequential
Optimistic	+12%	+10%	+3%
Pessimistic	+62%	+1%	±0%
Good-high-doses	-4%	+7%	+8%
Overall	+24%	+6%	+3%

that the first part of the Φ-formula applies we use numerical integration over $[x_\delta, x_{\max}]$ where $\delta = 5$ and x_δ depends on the scenario. Then $\Phi(\xi_b, \vartheta)/\Phi(\xi_a, \vartheta)$ gives us the relative efficiency of Design ξ_b relative to Design ξ_a.

We went step by step and calculated the efficiency gain from the balanced design to the optimal non-adaptive design, from the optimal non-adaptive design to the adaptive two-stage design and finally from the adaptive two-stage to the fully sequential design. Results are summarized in Table 3.

We see a quite large efficiency gain of +24% from the balanced design to the optimal design, which is mainly due to an efficiency gain if the underlying scenario is the pessimistic one (+62% efficiency gain; note that the increased allocation to the highest dose is especially important in this scenario). Surprisingly, we cannot improve it much further with the considered adaptive designs: if we use the adaptive two-stage design, we gain additionally +6%, and if we go even further and adapt after each patient, we can gain +3% more efficiency. With these moderate efficiency gains for the adaptive design it is in most situations hard to justify the additional complexity of an adaptive trial.

Why is there not more gain from adaptive dosing? Let us consider for example the optimistic scenario and the comparison between the optimal non-adaptive design and the adaptive two-stage design with average efficiency gain of 10% (see Table 3). The cumulative distribution function for the MSE from the simulations of the optimal non-adaptive design and the adaptive two-stage design are shown in Figure 3 (a). We can see that the cumulative distribution function for the adaptive design is mostly above the function for the non-adaptive optimal design which reflects smaller MSE. However, if we look closer into the tail region of the distribution (Figure 3 (b)), we see that this is reversed in the part above 0.97 (i.e. for the largest 3% of the MSE). In the part with large MSE, the adaptive design is even worse than the

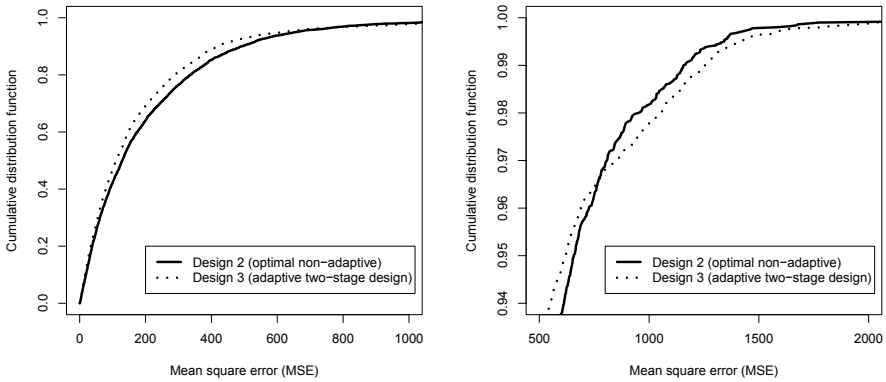

Figure 3: Cumulative distribution function of the MSE for the optimal non-adaptive design and the adaptive two-stage design (optimistic scenario). (a) Left figure: whole cumulative distribution, (b) Right figure: tail of the cumulative distribution

non-adaptive. Since the large MSE have also a high impact on the average efficiency of a design, these approximately 3% of the simulations contribute that the efficiency of the adaptive two-stage design becomes not too good compared to the optimal non-adaptive design. How can the high MSEs be interpreted? Due to the assumed variability, some of the simulations have interim data suggesting a totally different dose-response-shape compared to the true scenario. In these cases, the problem for the adaptive design is that an inferior design is chosen for the part after the interim analysis based on the wrong interim estimate. This has then an additional negative impact on the precision of the final estimate.

5 When is an adaptive design useful?

We modify now the prior assumptions in order to investigate in which cases adaptive designs are useful compared to the non-adaptive optimal design. In our first modification (Example 2), we change the optimistic scenario to a "realistic" ($E_{\max} = 11.2, ED_{50} = 70, \alpha = 1$) which is closer to the other two scenarios, see Figure 4. Otherwise, we change nothing: we keep the other two

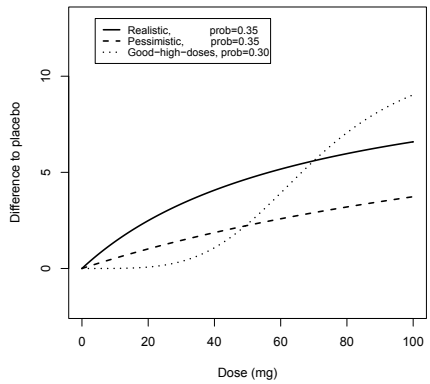

Figure 4: Prior knowledge about dose-efficacy scenarios (Example 2)

scenarios and prior probabilities.

The efficiency gains based on 5000 simulations per scenario and design are summarised in Table 4. We have an even larger gain from the balanced to the optimal non-adaptive design. We explain this as follows: The scenarios are more similar compared to the example before. Therefore, a non-adaptive design can be better optimised for all scenarios simultaneously. But when we go further to adaptive designs we have even an efficiency loss. When there is a good understanding prior to the trial with a few possible scenarios which are not too different, then there is no need to introduce interim analyses for design modification. In these cases, interim analyses could rather lead to an inferior design due to the variability in the data used for interim decisions.

In our second modification (Example 3), we use exactly the same scenarios and prior probabilities as in the main example (Example 1, see Figure 2). We change only the underlying variability. Instead of the assumption $\sigma = 10$ in Example 1 and 2, we use $\sigma = 6$. Again, we performed 5000 simulations per scenario and design with results shown in Table 5. As before, we have a good gain with the optimal non-adaptive design. In contrast to the examples before, we see also a good gain with the adaptive two-stage design (+16%) which is similar for all three scenarios (+18, +13, +16%, respectively). An additional gain of 5% is made when using the fully sequential design. In this example, we have seen that the adaptive dosing has value which could justify the more

complicated logistics of an adaptive trial. Here, the possible scenarios are sufficiently different in relation to the underlying variability. This makes it possible to obtain good information from the interim analysis to improve the prior probabilities to reliable posterior probabilities for the scenarios.

6 Discussion

We have seen that there is a large gain in efficiency when optimal design theory is applied and an optimal non-adaptive design is chosen instead of a traditional balanced design. Using interim data to change allocation ratios (adaptive dosing) is an attractive concept but it depends on the situation whether it can lead to a further gain in efficiency or not. This is in line with the observation from a recent simulation study, McCallum and Bornkamp (2015), concluding that "the benefit of including an interim analysis has not been shown to universally to improve the performance of a dose-finding study".

If the possible scenarios are similar or the variance is large, decisions based on interim data could lead into the wrong direction. In these cases, an optimal non-adaptive design might be the better choice. If differences between the possible scenarios are large (in relation to the variability of data in interim analysis), there is a clear gain from adaptive dosing.

Most investigations in this context are forced to build on simulation studies as available asymptotic formulae for the efficiency of adaptive designs are to crude for finite sample sizes. However, in the context of a simplified dose-response model (one-parameter model), Dette et al. (2013) successfully derived explicit expressions for the asymptotic efficiency of the adaptive design which are precise and suited for comparison. Based on these expressions, they

Table 4: Efficiency gain (Example 2)

Scenario	Efficiency gain		
	from balanced to optimal non-adaptive	from optimal non-adaptive to adaptive two-stage	from adaptive two-stage to fully sequential
Realistic	+48%	-4%	-1%
Pessimistic	+64%	+2%	-6%
Good-high-doses	+8%	-1%	+2%
Overall	+42%	-1%	-2%

Table 5: Efficiency gain in case of small variance $\sigma^2 = 6^2$ (Example 3)

Scenario	Efficiency gain		
	from balanced to optimal non-adaptive	from optimal non-adaptive to adaptive two-stage	from adaptive two-stage to fully sequential
Optimistic	+13%	+18%	+5%
Pessimistic	+79%	+13%	+4%
Good-high-doses	-3%	+16%	+6%
Overall	+31%	+16%	+5%

were able to compare the efficiency of non-adaptive and adaptive design in this setting. The combined evidence from simulation studies and algebraic investigations for simplified models gives a good picture about when adaptive designs are useful.

Once it is concluded that an adaptive design is useful, it remains the question whether it is feasible for the study to be planned. Logistical issues need to be resolved before such a design can be applied. Miller et al. (2014) discuss an example where a simplified adaptive dose-finding design was conducted. The use of an interim analysis offers the important benefit that the study can be stopped early (so called futility stopping) when results in the interim suggest that no dose of the drug will be useful.

A further important point for adaptive designs is that the statistical inference at the end of the trial need to take the adaptivity into account. Note that in the context of clinical studies significance tests and their frequentist properties (type I error and power) are of importance. For example Miller (2010) has derived a trend-test which controls the type I error for an adaptive two stage dose-finding trial.

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Optimum Experiments for Logistic Models with Sets of Treatment Combinations

Anthony C. Atkinson[1]

Abstract

The motivation is an experiment in deep-brain therapy in which each patient receives a set of eight distinct treatment combinations and provides a response to each. The experimental region contains sixteen different sets of eight treatments. With only six parameters in the linear model, it is unlikely that all sixteen points in the design region need to be included in the experiment. The structure of such experiments is elucidated in a response surface setting for a binomial model with the logistic link in which each choice of an experimental setting provides a response at each of s distinct settings of the explanatory variables. An extension of the "General Equivalence Theorem" for D-optimum designs is provided for experiments with sets of treatment combinations. Links are made to the work of Hans Nyquist.

Key words: Equivalence theorem; induced design region; local optimality;minimax design; treatment sets

1 Introduction

It is a privilege to have been asked to contribute to this Festschrift to celebrate the 65th birthday of Professor Hans Nyquist (so young!) and it has been a pleasure to read some of his papers in preparation for writing this contribution. In this reading I have been struck several times by the extent of our common interests, for example Hadi and Nyquist (1994) on sensitivity analysis in statistics and my own book (Atkinson, 1985) on regression diagnostics.

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This paper, however, is about the application of the methods of optimum experimental design to the linear logistic model.

The scientific motivation is an experiment in deep-brain therapy in which each patient receives a set of eight treatment combinations and provides a response to each. The structure of such experiments is most easily seen in a response surface setting where each choice of an experimental setting provides a response at each of s distinct settings of the explanatory variables. Atkinson (2016) explores this structure for designs when the errors of observation are independent with constant variance and provides a generalization of the equivalence theorem of Kiefer and Wolfowitz (1960). The extension in this paper is to the more interesting case of designs for generalized linear models, illustrated here for binomial data with the logistic link. Throughout the focus is on D-optimum designs.

The paper starts in §2 with a brief review of the linear logistic model and the theory of optimum experimental design. The main numerical results are in §3. In the first part, §3.1, D-optimum designs are found for a two-variable first-order model. The structure of the designs is illustrated both in the design region of the experimental variables and in the induced design region that depends upon the model. Section 3.2 provides numerical results for the optimum design when now the design region contains six sets of two observations. The numerical results suggest an extended equivalence theorem which is presented in §4. Other design criteria and extensions of the model are briefly considered in §5. Section 6 provides some discussion of numerical algorithms for finding optimum designs. The paper closes with comments on aspects of design for the motivating medical experiment.

2 The Logistic Model

The linear logistic model for a binomial random variable y_i with mean μ_i and linear predictor η_i is

$$\log\{\mu_i/(1-\mu_i)\} = \eta_i = \theta^T f(x_i). \tag{1}$$

The parameter vector θ is $p\times 1$, with $f(x_i)$ a known function of the explanatory variables x_i. The purpose of the experiment is to obtain good estimates of θ. For binomial observations $y_i = R_i/n_i$, where R_i is the number of successes in n_i trials.

Maximum likelihood estimation for generalized linear models reduces to weighted least squares. For the binomial distribution and the logistic link the weights are $q_i = \mu_i(1-\mu_i)$.

As is standard in the theory of optimum experimental design, an experimental design ξ places a fraction w_i of the experimental trials at the conditions x_i. A design with n points of support is written as

$$\xi = \left\{ \begin{array}{cc} x_1 & x_2 \dots x_n \\ w_1 & w_2 \dots w_n \end{array} \right\}, \tag{2}$$

where $w_i > 0$ and $\sum_{i=1}^{n} w_i = 1$. There are thus two sets of weights: the w_i, which determine the proportion of experimentation at x_i, and the GLM weights q_i. Any realisable experimental design for a total of N trials will require that the weights w_i are ratios of integers, that is $w_i = r_i/N$, where r_i is the number of replicates at condition x_i. The mathematics of finding optimal experimental designs and demonstrating their properties is greatly simplified, as in this paper, by the consideration of continuous designs in which the integer restriction is ignored.

The information matrix for the design ξ with n support points is written

$$M(\xi;\theta) = \sum_{i=1}^{n} w_i q_i f(x_i) f(x_i)^T = F^T W Q F, \tag{3}$$

where F is the $n \times p$ extended design matrix, with ith row $f^T(x_i)$ and W and Q are diagonal matrices of weights. For generalized *linear* models, the parameter values enter only through the GLM weights q_i.

3 Optimum Designs

3.1 Single Observations

D-optimum designs, minimizing the generalized variance of the estimate of θ, maximize the determinant $|F^T W Q F|$ over the design region $\mathcal{X}$ through choice of the optimum design ξ^*. Examples for the two variable logistic model

$$\log\{\mu/(1-\mu)\} = \eta = \theta_0 + \theta_1 x_1 + \theta_2 x_2 \,, \tag{4}$$

are given in Atkinson et al. (2007, §22.4.4) for a series of parameter values in which $\theta_1 = \theta_2$. For the design of this section the parameter values are instead $(0, 1.5, 2)$.

Table 1 shows the D-optimum design when the design region is $\mathcal{X} = [-1, 1]^2$. This and the design of §3.2 were found numerically using the R function `optim`, discussed in §6.

Table 1: D-optimum design for first-order linear predictor in two variables with the logistic link; $\theta = (0, 1.5, 2)^T$. The design region is $\mathcal{X} = [-1, 1]^2$

Obs.	x_1	x_2	w_i	μ_i	$d(x_i)$
1	1	-1	0.324	0.378	3.00
2	-1	1	0.225	0.622	3.00
3	-1	-0.068	0.260	0.163	3.00
4	0.050	1	0.192	0.889	3.00

The table shows that, for these parameter values, the design has support close to four points of the 3^2 factorial; the design weights are not quite equal, ranging from 0.192 to 0.324. For the first two design points, those at the corners of the design region, the values of μ_i are 0.378 and 0.622, summing to one. The values at the other two design points are 0.163 and 0.889, close to the values of 0.176 and 0.824 that are optimum for the model with a single variable. See, for example, Atkinson et al. (2007, p. 400).

The support points of the design are shown in Figure 1, together with shading showing extreme values of the response. In the lightly shaded area $\mu \leq 0.15$, whereas, in the darker region, $\mu \geq 0.85$. The figure illustrates how the design avoids extreme values of the response where the variance of the response is high and the weights q_i small.

The "general equivalence theorem" for D-optimality (Kiefer and Wolfowitz, 1960) provides conditions for the optimality of a design ξ which depend on the sensitivity function

$$d(x, \xi; \theta) = f^T(x) M^{-1}(\xi; \theta) f(x) q_i, \tag{5}$$

although, in their case, $q_i = 1$. For the optimum design $\bar{d}(x, \xi^*; \theta)$, the maximum value of the sensitivity function over $\mathcal{X}$, equals p, the number of parameters in the linear predictor. These values occur at the points of support of the design. The last column of Table 1 shows that the values are indeed three at the four support points. However, checking the optimality of the design requires a search over $\mathcal{X}$ to verify that these are the maximum values.

As the information matrix (3) is of a weighted form, design for the additive linear predictor

$$\eta(\boldsymbol{x}) = \theta_0 + \sum_{j=1}^{p-1} \theta_j x_j \,, \tag{6}$$

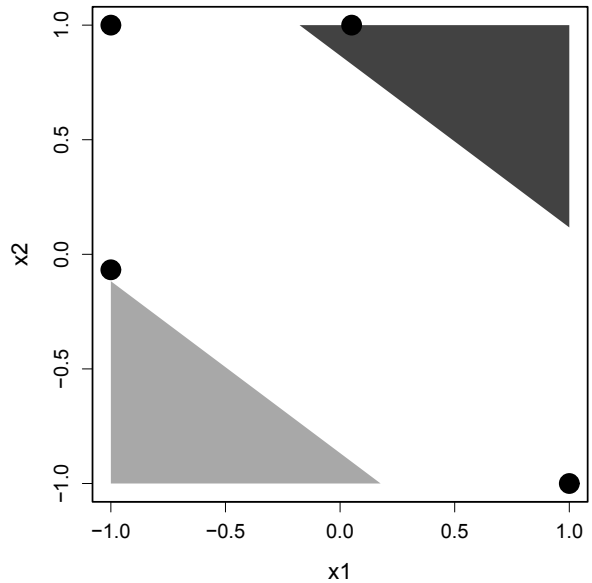

Figure 1: Support points of the D-optimum design for first-order linear predictors in two variables with the logistic link; $\theta = (0, 1.5, 2)^T$. In the lightly shaded area $\mu \leq 0.15$, whereas, in the darker region, $\mu \geq 0.85$.

is equivalent to (unweighted) design for the linear model

$$E(y_i) = \theta_0\sqrt{q_i} + \sum_{j=1}^{p-1} \theta_j \sqrt{q_i} x_{ij}, = \theta_0 z_0 + \sum_{j=1}^{p-1} \theta_j z_{ij}\,, \tag{7}$$

Hence the original design region $\mathcal{X}$ can be transformed to the induced design region $\mathcal{Z}$ for the induced variables $z_0, \ldots, z_k$. Clearly, $\mathcal{Z}$ depends on both $\mathcal{X}$ and θ. Since the design is unweighted in (7), D-optimum designs for first-order models are at extreme values in $\mathcal{Z}$. Ford et al. (1992) used the relationship with linear model design to provide geometric insight into the structure of designs for single variable generalized linear models, as did Fackle-Fornius and Nyquist (2010) for the c-optimum designs mentioned in §5.

Figure 2 shows the induced design region for $\theta = (0, 1.5, 2)^T$. Since the dimension of θ is three, this is also the dimension of $\mathcal{Z}$. The region in the figure is projected onto z_1 and z_2, so ignoring $z_0 = \sqrt{q}$. As Figure 1 shows, some extreme values of x do not provide informative experiments; as a result,

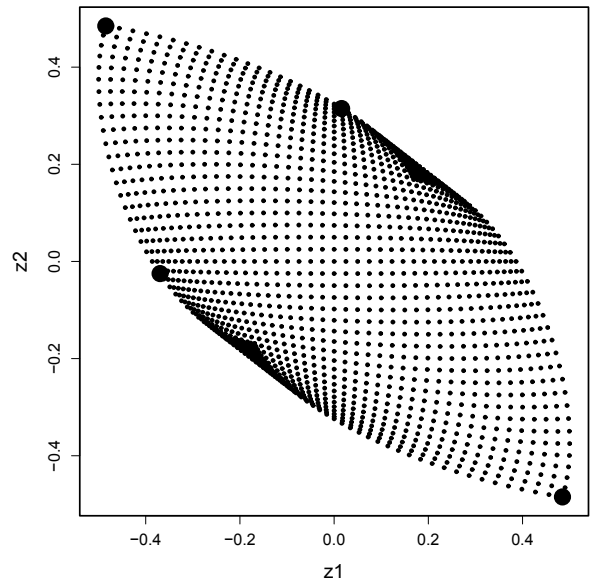

Figure 2: Support points of the D-optimum design for first-order linear predictors in two variables with the logistic link in the induced design region $\mathcal{Z}$.

the corners of $\mathcal{Z}$ appear folded over. As expected, the design points are at extreme points in $\mathcal{Z}$.

3.2 Sets of Observations

Instead of single observations, now suppose that the experimental design consists of the choice of pairs of experimental conditions. An example is in Table 2. There are twelve individual conditions, grouped into the six sets in column 2. The design problem is to find the six weights for these sets that give the D-optimum design.

The structure of the design region is exhibited in Figure 3. The black dots are close to the four optimum design points for single observations presented in Table 1. The four crosses combined with the conditions at their nearest dot, form the first four sets in the table. One of the remaining two sets of points, both represented by open circles, has been chosen to be at conditions that are important for second-order response surface designs for unweighted

Table 2: D-optimum design for first-order linear predictor in two variables with the logistic link; $\theta = (0, 1.5, 2)^T$. The design region contains six sets of two observations.

Obs.	Set	x_1	x_2	w_i	w_i^{SET}	μ_i	$d(x_i)$	$d_{\text{AVE}}(x_i)$
1	1	1.0	-1.0	0.164	0.327	0.378	3.17	3.00
2	1	0.9	-0.9	0.164	0.327	0.389	2.83	3.00
3	2	-0.9	0.9	0.084	0.169	0.611	3.35	3.00
4	2	-0.7	0.7	0.084	0.169	0.587	2.65	3.00
5	3	-1.0	0.0	0.138	0.276	0.182	3.10	3.00
6	3	-0.9	-0.1	0.138	0.276	0.175	2.90	3.00
7	4	0.0	1.0	0.114	0.228	0.881	3.05	3.00
8	4	0.0	0.8	0.114	0.228	0.832	2.95	3.00
9	5	-1.0	-1.0	0.0	0.0	0.029	1.86	1.99
10	5	-0.9	-0.9	0.0	0.0	0.041	2.11	1.99
11	6	0.0	0.0	0.0	0.0	0.500	1.38	1.51
12	6	0.1	0.1	0.0	0.0	0.587	1.64	1.51

regression models. The other set is chosen to have low values of μ.

The optimum weights at the 12 points of observation are given in the fifth column of the table, with the weights for the sets in column six. The design, like the design for individual observations, has four points of support, the last two sets having zero weight. The weights are similar to those in Table 1, the largest difference being for set 2, for which observation 3 has been taken, for purposes of illustration, at conditions that are not quite those of the optimum design of Table 1. The values of μ_i in column 7 show that both observations for set 5 have a value of μ less than 5%, and so will be uninformative.

The most interesting results are the values of the sensitivity functions in the last two columns of the table. There are three parameters in the model, and the D-optimum design for individual observations had a value of three for the sensitivity function at the points of the optimum design. Here, for the first four sets, the near optimum point had a value slightly greater than three, with the related point represented by a cross, having a value slightly less than 3. The implication is, if it were possible, that the "crosses" should be moved closer to the "dots". The values of the sensitivity functions for the other two sets are mostly below 2, an indication that readings at the points are not informative.

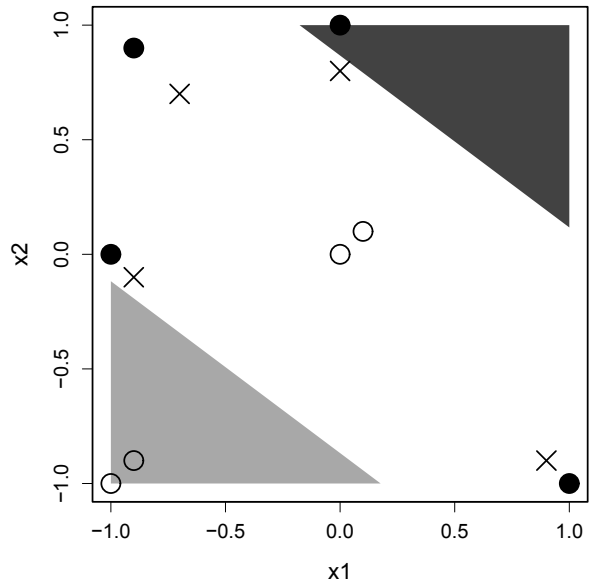

Figure 3: Sets of points: the black circles are close to the D-optimum design shown in Figure 2, with the nearby X the second in each set of observations. The unfilled circles denote two further pairs of points.

The last column gives the average values of the sensitivity functions for each set. These are exactly three for the four sets which are included in the optimum design. The implications for a generalization of the equivalence theorem are considered in the next section.

Figure 4 shows the sets of points in the induced design region, providing geometric insight into the structure of the design. The black dots for the near optimum design lie on the boundary of $\mathcal{Z}$, except for the slightly sub-optimal point 3 with co-ordinates (-0.9, 0.9) which is a little inside. All the related points in these sets lie, as the crosses show, slightly further inside the region. The points for set 5 lie in the centre of the region and the points for set 6 in a highly folded region of the projection, again away from the boundary.

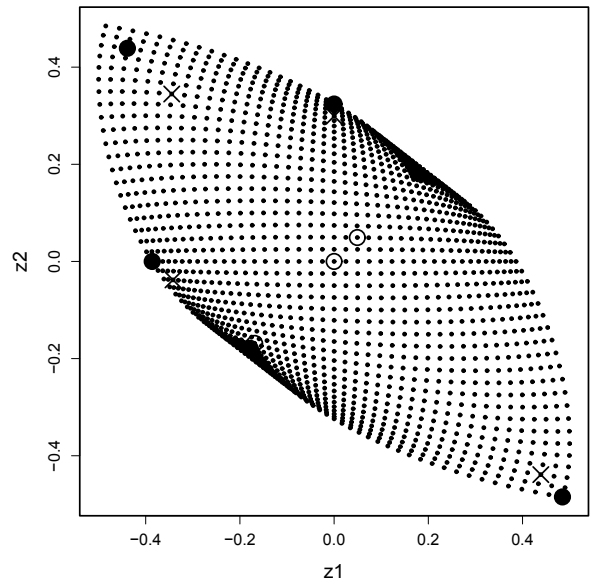

Figure 4: Sets of points in the induced design region $\mathcal{Z}$: the black circles are close to the D-optimum design shown in Figure 2, with the nearby X the second in each set of observations. The unfilled circles denote two further pairs of points.

4 Equivalence Theorem

The numerical results for designs with sets of points suggest that an equivalence theorem applies that is an extension of that for individual observations.

Some notation is needed. Let S_i denote the ith set of observations, taken at points $x_{i1}, x_{i2}, \ldots, x_{is}$, $(i = 1, \ldots, m)$ and let

$$d_{\text{AVE}}(i, \xi; \theta) = \sum_{j \in S_i} d(x_{ij}, \xi; \theta)/s. \tag{8}$$

Further, let $\bar{d}_{\text{AVE}}(\xi; \theta)$ be the maximum over the m sets S_i, that is over $\mathcal{X}$, of $d_{\text{AVE}}(i, \xi; \theta)$.

Then the **Equivalence Theorem** states the equivalence of the following three conditions on ξ^*:

1. The design ξ^* maximizes $|M(\xi; \theta)|$.

2. The design ξ^* minimizes $\bar{d}_{\text{AVE}}(\xi;\theta)$.

3. The value of $\bar{d}_{\text{AVE}}(\xi^*;\theta) = p$, this maximum occurring at the points of support of the design.

As a consequence of 3, we obtain the further condition:

4. For any non-optimum design the value of $\bar{d}_{\text{AVE}}(\xi;\theta) > p$.

The proof of this theorem follows from the additive nature of the information matrix. Standard proofs of the equivalence theorem for individual observations, such as those in Pronzato and Pázman (2013, §5.2) and Fedorov and Leonov (2014, §2.4.2) depend on the directional derivative at a point in $\mathcal{X}$. Here, with the extension to a set of observations, the directional derivative is the sum of the derivatives for the individual observations. The theorem applies equally when $\mathcal{X}$ is a continuous region, as in Figure 1 for single observations. However, the definition of the sets of points in the continuous region may not be straightforward.

The assumption in this paper is that all sets contain the same number, s, of design points. With sets containing different numbers of observations, costs need to be included in the design criterion. Elfving (1952) formulated optimum design criteria when costs are included in experiments with individual observations. Fedorov and Leonov (2014, Chapter 7) present many applications in pharmacokinetic experiments.

5 Other Design Criteria

The designs found in this paper depend on the value of θ and so are only locally optimum. Chaloner and Larntz (1989) incorporate prior information on θ in their Bayesian design criterion for individual observations, leading to maximization of the expectation of $M(\xi;\theta)$ over the parameter space Θ. Sitter (1992) overcomes dependence on θ by finding minimax designs or, since the design criterion has been written in this paper as a maximization problem, maximin designs, in which the design is found by maximizing the design criterion for the worst performance over Θ. Such designs can, however, be sensitive to the boundaries of Θ and sometimes have particularly good properties for values of θ that are unlikely. Another way of avoiding dependence of the design on the value of θ follows from Cox (1988). As the effects of the explanatory variables decrease, that is, for example, as θ_1 and θ_2 in (4) decrease, but with θ_0 non-zero, designs tend to those for homoskedastic regression models.

These designs can be surprisingly efficient for some generalized linear models, but not usually, for binomial responses. Atkinson and Woods (2015) provide a survey of results on optimum designs for individual observations from generalized linear models.

These approaches all use D-optimality. However, the properties of designs for other criteria, such as A-, c-, E or T-optimality could also be explored for sets of points. There is some work, for individual observations, on the use of other criteria for generalized linear models. One criterion is D_A-optimality, in which a set A of linear combinations of the parameters is of interest. Petterson and Nyquist (2003) combine D_A-optimality with Bayesian design, using a uniform prior to produce "Laplace designs". Fackle-Fornius and Nyquist (2010) use c-optimality, that is D_A-optimality when A is a vector, to explore designs for finding the maximum response in a single-variable quadratic model with the logistic link.

In §3 the induced design region $\mathcal{Z}$ is a continuous region. It was used to illustrate the optimality, or otherwise, of given design points. For the single variable logistic model of Fackle-Fornius and Nyquist (2010), $\mathcal{Z}$ becomes a curve. Geometric results of Elfving (1952) help in trying to find the structure of the optimum design in $\mathcal{Z}$ independently of θ. The procedure has a similar geometry to that of the "design locus" introduced by Box and Lucas (1959) for D-optimality in nonlinear regression models.

It is assumed in this paper and the references that the observations are independent. However, it is likely that there will be correlation between the observations within a set, since these come from a single unit; in the medical experiment, that is from a single patient. A mixed model would then be appropriate for design and analysis. Fedorov and Leonov (2014, p.92) give references on design for linear mixed-effects models; Nyquist (1997) provides a test for the presence of such correlations.

6 Algorithms

Numerical algorithms are essential for the construction of any but the simplest optimum designs. Much of the discussion in the literature, for example Fedorov and Leonov (2014, Chapter 3), stresses the desirability of using algorithms that take account of the specific structure of optimum designs. An example is Nyquist (2013) for the numerically tricky problem of finding minimax designs. However, the designs for this paper were found using a general purpose numerical algorithm.

There are two sets of constraints in the maximization problem providing

the design of §3.1. The first is on the design weights which must be non-negative and sum to one. The other is on the design points, which must be within $\mathcal{X}$. Atkinson et al. (2007, §9.5) suggest search over an unconstrained space Ψ, using transformation to polar co-ordinates to calculate weights w_i that satisfy the required constraints. Here use was made of a simpler approach taking advantage of the upper and lower constraints on variables in the R function `optim`.

The search variables are ψ_i. Taking

$$w_i = \psi_i / \sum_{j=1}^{n} \psi_j \tag{9}$$

with $0 \leq \psi_j \leq 1$ provides weights that satisfy the required constraints. Similarly, for each explanatory variable $\mathcal{X}$ is such that $-1 \leq x_{ij} \leq 1$, which is a straightforward constraint. Of course, the w_i are in $n-1$ dimensions, so that (9) is not unique; the same weights are obtained when all ψ_i are replaced by $a\psi_i, (a \neq 0)$. However the Quasi-Newton BGFS algorithm did not show any difficulty in converging.

With four design points and with each x_i lying in two dimensions, the proposed method requires an optimization in 12 dimensions. However, as in many cases, it is possible to guess the form of the optimum design. In this case the results of Atkinson et al. (2007) suggest that only two co-ordinates of the x_{ij} are unknown, thus reducing the search to six dimensions. The equivalence theorem is then used to confirm that the found design is indeed optimum in the class of all designs.

7 Further Design Aspects of the Medical Problem

In the experiment in deep-brain therapy there are two factors, stimulation at three levels and conditions at four levels. There are thus twelve treatment combinations. However, for safety reasons, it is not possible to expose each patient to all twelve. Instead, it was proposed to take measurements at only eight combinations; sixteen such sets were chosen. The design region this contained 16 distinct points, each of which would give a set of eight measurements from one patient.

A design question is, which of the sixteen sets should be used and in what proportions? Since the linear model for the factors contains only 1 + 2 + 3 = 6 parameters, it is unlikely that all sixteen points in the design region need

to be included in the experiment. Even if an optimum design satisfying the equivalence theorem does include all sixteen, it may not be unique; there may be optimum designs requiring fewer distinct design points. An example of such an optimum design for a two-factor logistic model is shown by Atkinson et al. (2007, p. 404). There are two distinct four-point D-optimum designs. Six-point designs that are a convex linear combination of these two designs are also D-optimum.

The equivalence theorem also provides a method of treatment allocation in clinical trials in which patients arrive sequentially. In the experiment in deep-brain therapy there is a prognostic factor, initial severity of the disease. The effect of this variable is not the focus of the trial, so that it would be considered a nuisance factor. Sequential construction of the D_S-optimum design for the treatment effects would aim for balance over the prognostic factor and lead to the most efficient inference about the treatments. However, such deterministic allocation rules are unacceptable in clinical trials, where they may lead to selection bias. A randomized rule based on D-optimality, such as those described by Atkinson (2015), should instead be used.

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Exact D-Optimal Designs for Michaelis-Menten Model with Correlated Observations by Particle Swarm Optimization

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Abstract

We apply the Particle Swarm Optimization (PSO) algorithm to find locally exact D-optimal designs for the widely used Michaelis-Menten model when errors are correlated. We show that our PSO-generated designs agree with the theoretical designs provided by Dette and Kunert (2014), when each subject has up 2 repeated observations. We further demonstrate that PSO can also easily generate such exact D-optimal designs with 3, 4, 5 and 6 repeated observations efficiently when theoretical results are no longer available. For comparison purposes, our work assumes the same correlation structure as in Dette and Kunert (2014) but we expect PSO can also directly and efficiently generate exact D-optimal designs for other models with various correlation structures and multiple repeated measurements.

Key words: locally optimal designs, nature-inspired metaheuristic algorithms, nonlinear models, repeated observations.

1 Introduction

The Michaelis-Menten model is a nonlinear model widely used to approximate and study complicated enzyme kinetic biological systems. Because of the

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simplicity and effectiveness of this model, it enjoys wide applications in several fields, such as biochemistry (Maloney and Heidel, 2003), biology (Butler and Wolkowicz, 1985) or environmental study (Yu and Rappaport, 1996; Yu and Gu, 2007). The biochemical reaction rate expressed by the Michaelis-Menten model in its simplest form is

$$E(\upsilon) = \eta(\theta, s) = \frac{as}{b+s},\ s \in S,\ \theta = (a, b)^\top,$$

where υ is the observed velocity of the chemical reaction when the substrate concentration applied is s. The set S is user-selected, compact and represents the range of concentrations available to observe υ. The mean response is a nonlinear function $\eta(\theta, s)$ with two parameters a and b. The parameter b is called Michaelis-Menten constant, which controls the rate of the reaction and so between the two parameters, it is the more biologically meaningful parameter. The maximum velocity attainable is a, which is reached when the substrate concentration is increased without bound.

This model can also be used to study growth curves of subjects or different species of animals by taking repeated measurements on the animal (Lopez et al., 2000). Suppose that there are n subjects to be investigated, and for each subject, m repeated observations are allowed over a period of time. Dette and Kunert (2014) used the following Michaelis-Menten model and addressed some design issues when the responses are correlated:

$$\upsilon = \eta(\theta, s_{i,j}) + \epsilon_{i,j} = \frac{as_{i,j}}{b+s_{i,j}} + \epsilon_{i,j},\ j = 1, ..., m,\ i = 1, ..., n. \tag{1}$$

Here the error terms $\epsilon_{i,j}$ are normally distributed with mean 0 and constant variance and we assume $\epsilon_{i,j}$ and $\epsilon_{i',j'}$ are independent if $i \neq i'$, and each pair of $\epsilon_{i,j}$ and $\epsilon_{i,j'}$ has the correlation coefficient $\lambda^{|s_{i,j}-s_{i,j'}|}$, $j, j' = 1, ..., m$ where $\lambda \in (0, 1)$ and $s_{i,j}, s_{i,j'} \in S$.

Optimal design problems for Michaelis-Menten model have been studied quite extensively in the literature; see for example, Dunn (1988), Rasch (1990), Dette and Wong (1999) and Boer et al. (2000), who all addressed somewhat different aspects of the design problems. A commonality is that they assumed independent observations and worked with approximate designs, which are probability measures defined on a user-selected compact interval S. We denote a generic approximate design ξ with k points by

$$\left\{ \begin{array}{ccc} s_1 & \dots & s_k \\ p_1 & \dots & p_k \end{array} \right\}, \tag{2}$$

where $s_1, \ldots, s_k$ are the design points in the pre-specified experimental region, S, and p_i's are the corresponding weights with $p_1 + \cdots + p_k = 1$. If the total number of observations for the study is predetermined and equal to N, the implemented design from ξ takes roughly Np_i observations at $x_i, i = 1, \ldots, k$ subject to the constraint that each Np_i is a positive integer and they sum to N. Because of the rounding, the implemented design may not be unique even though the approximate design is. In contrast, exact optimal designs optimize the criterion by directly finding k, the number of design points, the locations of the points $x_i, i = 1, \ldots, k$ and the number of observations n_i at $x_i, i = 1, \ldots, k$ subject to $n_1 + \ldots + n_k = N$. Finding exact optimal designs for any problem is much more difficult than finding optimal approximate designs because unlike the latter, there is no unified approach to solving them and the mathematics required is usually very involved and specific for each problem. There is also no easy way to confirm if the exact optimal design found is optimal among all exact designs.

Following convention, we measure the worth of a design by its Fisher information matrix obtained by taking the negative of the expectation of the second derivatives of the log likelihood function. For a nonlinear model, such as the Michaelis-Menten model, this matrix depends on the model parameters, $\theta = (a, b)^\top$. Using the approximate design ξ, a direct calculation shows the Fisher information matrix is

$$\begin{aligned} M(\theta, \xi) &= \int \frac{\partial \eta(s,\theta)}{\partial \theta} \frac{\partial \eta(s,\theta)}{\partial \theta^T} \, \xi(ds) \\ &= \int (\frac{as}{b+s})^2 \begin{pmatrix} \frac{1}{a^2} & -\frac{1}{a(b+s)} \\ -\frac{1}{a(b+s)} & \frac{1}{(b+s)^2} \end{pmatrix} \xi(ds) \\ &= \sum_{i=1}^{k} p_i (\frac{as_i}{b+s_i})^2 \begin{pmatrix} \frac{1}{a^2} & -\frac{1}{a(b+s_i)} \\ -\frac{1}{a(b+s_i)} & \frac{1}{(b+s_i)^2} \end{pmatrix}. \end{aligned}$$

For approximate designs, it is typical that we formulate the design criterion as a convex function of the information matrix, $M(\theta, \xi)$ and the design sought is the one that minimizes the criterion over all possible approximate designs on S. For example, if we want to estimate the parameters accurately, a common criterion is the D-optimality criterion $\log |M(\theta, \xi)^{-1}|$, which is a convex function of the information matrix. The resulting optimal design depends on the nominal parameters θ and is called the locally D-optimal approximate design. Because the set S is compact, and the criterion is convex, an equivalence theorem is available to verify the optimality of any design. Equivalence theorems are widely discussed in design monographs, such as Fedorov (1972),

Silvey (1980), Atkinson and Donev (1992) and Berger and Wong (2009). This is one reason why it is appealing to work with approximate designs.

A popular algorithm for finding an optimal approximate design is the Fedorov algorithm which exchanges design points sequentially to improve the design criterion values (Fedorov, 1972). Several modifications to the algorithms have been proposed and widely used over the years. They are generally referred to as the exchange type algorithms and some details can be found in Atkinson and Donev (1992). In addition to the exchange type methods, other optimization approaches have been used to search for optimal designs. More recent algorithms that seem effective for finding optimal designs are nature-inspired metaheuristic algorithms, such as particle swarm optimization (PSO).

In this paper, we investigate the effectiveness of PSO for finding optimal exact designs for the Michaelis-Menten model with correlated errors. Our work differs from the above work in that we search for an exact optimal design and the model has correlated outcomes. Our goal is to apply PSO to generate locally exact D-optimal designs for the model and show our results agree with the theoretical designs reported in Dette and Kunert (2014). PSO is then employed to tackle a more complicated setup where more measurements are required from each subject.

The rest of the article is organized as follows. We introduce and review particle swarm optimization in Section 2. Then we apply PSO to search for locally exact D-optimal designs for the Michaelis-Menten model with correlated responses and compare them with the theoretical designs when possible in Section 3. Section 4 contains a conclusion.

2 Particle Swarm Optimization for Searching Optimal Designs

Recently a class of algorithms called nature-inspired metaheuristic algorithms has proved very popular in the optimization literature. Whitacre (2011a,b) provided reasons for the rapid rise and interest in these algorithms. Early users of such algorithms to find exact optimal designs include Haines (1987), who used an annealing algorithm to search for optimal designs for linear regression models, and Montepiedra et al. (1998), who used a genetic algorithm to construct exact D-optimal designs for low order polynomial models. Of particular note is the particle swarm optimization (PSO) introduced by Eberhart and Kennedy (1995) for tackling optimization problems. Nowadays, PSO appears to be very widely used across multiple disciplines to solve hard op-

timization problems. Qiu et al. (2014), Chen et al. (2015) and Wong et al. (2015) are among the early ones to apply PSO to find different types of optimal approximate designs for nonlinear models, including minimax optimal design problems where the criterion is not differentiable. This is possible because PSO does not require assumptions on the objective function, such as differentiability or convexity, and PSO conducts the search in a simple and effective way. For example, PSO does not require mutation or crossover operations as they are required in a genetic algorithm.

PSO is a metaheuristic optimization algorithm inspired from the way animals, such as birds and fishes, search for food. The birds fly continuously in the sky to look for food on the ground. Each has its own perception where the food is (local optimum) but it communicates with the rest and collectively decide as a flock where the food is (global optimum). Accordingly, each bird flies toward the global optimum in the direction of the local optimum (not giving up completely where it thinks the food is). Birds are referred as particles and each bird represents a candidate solution to the optimization problem. Velocities and locations of each bird are adjusted iteratively and if and when the flock converges, the perceived global optimum is found.

PSO requires that we have an initial flock of birds in the pre-defined search space. The size of the flock and the maximum number of iterations are user-selected, along with a stopping criterion. The latter can take on various forms; for example, one may terminate the search when the percentage change in the criterion value becomes extremely small over time. Let $X_i(t)$ be the location of the i-th particle at the t-th iteration, let $X_{L,i}(t-1)$ be the best location (local optimum) found by the i-th particle before the t-th iteration, and let $X_G(t-1)$ be best location (global optimum) determined collectively by the whole swarm before the t-th iteration. The two equations defining the movement of the flock in PSO are:

$$X_i(t) = X_i(t-1) + V_i(t) \tag{3}$$

and

$$\begin{aligned} V_i(t) &= wV_i(t-1) + c_1R_1 \otimes [X_{L,i}(t-1) - X_i(t-1)] \\ &\quad + c_2R_2 \otimes [X_G(t-1) - X_i(t-1)], \end{aligned} \tag{4}$$

where $V_i(t)$ is the velocity of the i-th particle at the t-iteration. There are several parameters in Eq. (4). The inertia weight represents how active the birds are and is denoted by w. This parameter may be chosen to be a constant

but more typically its value changes over time and eventually decreases to 0. The parameters c_1 and c_2 are two positive constants which are typically set by default to have the value 2, and R_1 and R_2 are two random vectors whose components are independently drawn from the uniform variate on $[0, 1]$. In practice, the number of iterations and the swarm size are the most influential parameters in PSO. A large swarm size generally allows the search area to be more thoroughly explored and so can help PSO finds the global optimum with a higher chance. Similarly, having more iterations tend to provide the particles more search experience from the random perturbation. However, having too large a flock and too many iterations can also be inefficient and the user should choose appropriate values pertinent to the problem at hand. More details on PSO and the related metaheuristic optimization algorithms are available in Yang (2010).

To apply PSO for solving our optimal design problems, we treat each particle as a design ξ in (2), and represent it as a vector, $(s_1, ..., s_n, p_1, ..., p_{n-1})^\top$. The objective function is the optimal design criterion $\Phi(\xi, \theta)$. Hence at the beginning of the PSO, we randomly generate initial particles (designs) on the design space. Then at each iteration, we update the particles (designs) based on the (3) and (4). We also watch out for those that flew outside the search boundaries and when this happens, we need to adjust those particles to make sure they are in the design space properly. The hope is that after a number of iterations, the particles will converge to a point and this point is supposedly the global best solution or the optimal design we are after. The details of PSO algorithm for optimal design search problem is shown in Algorithm 2.1.

3 Locally Exact D-optimal Designs

Assume model (1) holds and it has the autoregressive error structure. There are n subjects for the study and the research question is how to optimally select from S, m observations per subject to estimate the model parameters accurately. If we assume an exact design, ξ, is supported at s_{ij} with equal weight $1/N$ with $N = nm$, the information matrix is

$$M(\xi, \theta_0) = \frac{1}{N} \sum_{i=1}^{n} f_i^\top \Sigma_i^{-1} f_i,$$

Algorithm 2.1 PSO for optimal design search problem

1: Initialize particles

(1.1) Choose *initial particle (design)* ξ_i *and velocity* V_i, *for* $i = 1, ..., m$.

(1.2) Calculate *fitness values* $\Phi(\xi_i, \theta_0)$

(1.3) Determine *local and global best positions* $\xi_{L,i}$ *and* ξ_G

2: Repeat until stopping criteria are satisfied

(2.1) Calculate *particle moving velocity by (4)*

(2.2) Update *particle position by (3)*

(2.3) Calculate fitness values $\Phi(\xi_i, \theta_0)$

(2.4) Update *the best minimal (or best maximal) position* $\xi_{L,i}$ *and the corresponding best values* $\Phi(\xi_{L,i}, \theta_0)$ *and* $\Phi(\xi_G, \theta_0)$

3: Output ξ_G and $\Phi(\xi_G, \theta_0)$

where $\theta_0 = (a, b, \sigma^2, \lambda)$, and f_i is a $2 \times m$ matrix containing the first derivatives. The j-th row of f_i is

$$\left(\begin{array}{cc} \frac{s_{i,j}}{b+s_{i,j}} & -\frac{a s_{i,j}}{b+s_{i,j}^2} \end{array} \right), \ j = 1, ..., m.$$

The correlation matrix of the m responses from the i-th subject is represented by Σ_i with two parameters σ^2 and λ. It is an $m \times m$ matrix and the (j, k)-th element is

$$\sigma^2 \left(\lambda^{|s_{i,j} - s_{i,k}|} \right), \ j, k = 1, \ldots, m.$$

Thus, given the fixed parameters $\theta_0 = (a, b, \sigma^2, \lambda)$, the locally D-optimal design is to maximize

$$\Phi(\xi, \theta_0) = \log |M(\xi, \theta_0)|.$$

It is well known that D-optimal designs has an invariance property that allows us to assume, without loss of generality, that $S = [0, 1]$, which is the same as in Dette and Kunert (2014). It is also clear that the locally D-optimal design does not depend on a and σ^2 and following Dette and Kunert (2014),

we choose $a = \sigma^2 = 1$. For the design points, due to the balance assumption, we assume that the observations in each subject are taken at the same point, $s_{1j} = s_{2j} = \cdots = s_{nj}$, for $j = 1, \ldots, m$. As in Dette and Kunert (2014), we also assumed that the experimental conditions for each subject are the same. Accordingly, we set $n = 1$ and search for the locally exact D-optimal design for the individual subject.

We first consider the case when we have 2 observations from a single subject and the design questions are which two time points to take observations and how the spread out the observations between the two points. Dette and Kunert (2014) theoretically identified that the locally exact D-optimal design is supported at two points, u and 1, when $b \geq \frac{1}{3}$, and the design point u solves the equation

$$\frac{b - (2b+1)u}{u(1-u)(b+u)} = \frac{\log(\lambda)\lambda^{2(1-u)}}{1 - \lambda^{2(1-u)}}. \tag{5}$$

The solution has no closed form when $b < 1/3$. When there are 3 or 4 observations to be taken from each subject, locally exact D-optimal designs cannot be described analytically and only numerical results were provided. The numerical approach they used is to check all possible designs using a pre-specified grid.

Throughout, we systematically used Algorithm 2.1 to find the locally exact D-optimal designs. The number of particles we used was 256 and the maximum number of iterations allowed was 500. The PSO parameters c_1 and c_2 were set equal to 2 and the inertia weight, w started with a value of 0.95 and then linearly decreases to 0.4 in the first 350 iterations and then we set $w = 0.4$ for the remaining iterations. We chose $b = 0.2, 0.7, 1.2, 1.7, 2.2, 2.7$, $\lambda = 0.1, 0.5, 0.9$ and the number of observations per subject $m = 2, 3, 4$.

Table 1 displays locally exact D-optimal designs when $m = 2$ and shows that the PSO-generated designs, denoted by ξ_{PSO}, coincide with the analytical results, ξ^*, reported in Dette and Kunert (2014) when $b \geq 1/3$. For instance, when $b = 0.2$ and $\lambda = 0.9$, the design reported in Dette and Kunert (2014) is close to our design found by PSO, ξ_{PSO}. Table 2 and Table 3 display corresponding D-optimal exact designs when we have 3 or 4 observations from each subject, respectively. These tables show that Algorithm 2.1 was able to identify the exact D-optimal designs and agree to those found by Dette and Kunert (2014).

We next modify Algorithm 2.1 to search for exact D-optimal designs when we have resources to take more observations per subject. Table 4 displays the exact D-optimal designs found by the Algorithm 2.1 for 5 and 6 obser-

Table 1: Selected PSO-generated locally D-optimal exact designs with 2 observations per subject versus the theoretical designs ξ^*s found by Dette and Kunert (2014). All designs are equally weighted.

	ξ_{PSO}		ξ^*	
b	$\lambda = 0.1$			
0.2	0.14425	1	N/A	
0.7	0.30002	1	0.3000	1
1.2	0.36707	1	0.3670	1
1.7	0.40465	1	0.4046	1
2.2	0.42871	1	0.4287	1
2.7	0.44548	1	0.4455	1
	$\lambda = 0.5$			
0.2	0.15299	1	N/A	
0.7	0.33582	1	0.3358	1
1.2	0.41747	1	0.4175	1
1.7	0.46305	1	0.4630	1
2.2	0.49184	1	0.4918	1
2.7	0.51169	1	0.5117	1
	$\lambda = 0.9$			
0.2	0.16027	0.94453	0.1600	0.944
0.7	0.36832	1	0.3683	1
1.2	0.45849	1	0.4585	1
1.7	0.50706	1	0.5070	1
2.2	0.53691	1	0.537	1
2.7	0.55717	1	0.5571	1

vations per subject. Unlike the global numerical search approach in Dette and Kunert (2014), we are not constrained by the grid size imposed on S and PSO can still identify the best designs efficiently. The CPU time required by our Algorithm 2.1 to find the optimal design is short. On average, our MATLAB codes take around 4.11, 5.54, 6.72, 7.83 and 8.71 seconds to find the optimal designs when there are 2, 3, 4, 5 and 6 observations, respectively. The hardware we used was a PC with 3.50 GHz Intel(R) Core(TM) i7-4770K CPU. Our overall experience is that Algorithm 2.1 is efficient in identifying the locally exact D-optimal designs for the Michaelis-Menten model with the correlation structure considered here.

Table 2: PSO-generated locally D-optimal exact designs with 3 observations per subject versus the theoretical designs ξ^*s found by Dette and Kunert (2014). All designs are equally weighted.

	ξ_{PSO}			ξ^*		
b	$\lambda = 0.1$					
0.2	0	0.06730	1	0	0.067	1
0.7	0	0.20541	1	0	0.205	1
1.2	0	0.28554	1	0	0.286	1
1.7	0	0.33274	1	0	0.333	1
2.2	0	0.36320	1	0	0.363	1
2.7	0.35199	0.61652	1	0.352	0.617	1
	$\lambda = 0.5$					
0.2	0	0.061677	1	0	0.062	1
0.7	0	0.176060	1	0	0.176	1
1.2	0	0.249140	1	0	0.249	1
1.7	0	0.297390	1	0	0.297	1
2.2	0	0.330950	1	0	0.331	1
2.7	0	0.355240	1	0	0.355	1
	$\lambda = 0.9$					
0.2	0	0.059322	0.75632	0	0.059	0.755
0.7	0	0.172660	1	0	0.172	1
1.2	0	0.244440	1	0	0.244	1
1.7	0	0.292450	1	0	0.292	1
2.2	0	0.326100	1	0	0.326	1
2.7	0	0.350910	1	0	0.350	1

Table 3: PSO-generated locally D-optimal exact designs with 4 observations per subject versus the theoretical designs ξ^*s found by Dette and Kunert (2014). All designs are equally weighted.

	ξ_{PSO}				ξ^*			
b	$\lambda = 0.1$							
0.2	0	0.06168	0.46456	1	0	0.062	0.466	1
0.7	0	0.12791	0.36732	1	0	0.128	0.367	1
1.2	0	0.17921	0.45456	1	0	0.179	0.454	1
1.7	0	0.21202	0.50141	1	0	0.212	0.501	1
2.2	0	0.23434	0.53049	1	0	0.234	0.531	1
2.7	0	0.25049	0.55034	1	0	0.250	0.550	1
	$\lambda = 0.5$							
0.2	0	0.03898	0.12877	1	0	0.039	0.129	1
0.7	0	0.10119	0.28173	1	0	0.101	0.281	1
1.2	0	0.14643	0.38442	1	0	0.146	0.384	1
1.7	0	0.17849	0.44787	1	0	0.178	0.448	1
2.2	0	0.20155	0.48912	1	0	0.202	0.489	1
2.7	0	0.21898	0.51772	1	0	0.219	0.518	1
	$\lambda = 0.9$							
0.2	0	0.05228	0.28875	1	0	0.052	0.288	1
0.7	0	0.09848	0.27409	1	0	0.098	0.272	1
1.2	0	0.14276	0.37526	1	0	0.143	0.375	1
1.7	0	0.17441	0.43998	1	0	0.174	0.440	1
2.2	0	0.19743	0.48317	1	0	0.197	0.483	1
2.7	0	0.21476	0.51291	1	0	0.215	0.513	1

Table 4: PSO-generated locally exact D-optimal designs, ξ_{PSO}, with 5 and 6 observations per subject found by Algorithm 2.1, respectively. All designs are equally weighted.

	5 correlated observations					6 correlated observations					
b	$\lambda = 0.1$										
0.2	0	0.0361	0.1085	0.5361	1	0	0.0274	0.0724	0.1761	0.5813	1
0.7	0	0.0968	0.2493	0.5397	1	0	0.0764	0.1848	0.3546	0.6593	1
1.2	0	0.1322	0.3113	0.5761	1	0	0.1047	0.2375	0.4134	0.6649	1
1.7	0	0.1565	0.3506	0.6089	1	0	0.1242	0.2708	0.4499	0.6838	1
2.2	0	0.1738	0.3768	0.6316	1	0	0.1382	0.2937	0.4747	0.6996	1
2.7	0	0.1866	0.3955	0.6475	1	0	0.1488	0.3103	0.4924	0.7117	1
	$\lambda = 0.5$										
0.2	0	0.0323	0.0935	0.4020	1	0	0.0235	0.0595	0.1303	0.4399	1
0.7	0	0.0719	0.1774	0.3646	1	0	0.0563	0.1318	0.2424	0.4410	1
1.2	0	0.1042	0.2482	0.4752	1	0	0.0810	0.1843	0.3252	0.5423	1
1.7	0	0.1278	0.2965	0.5422	1	0	0.0996	0.2227	0.3824	0.6085	1
2.2	0	0.1452	0.3302	0.5845	1	0	0.1135	0.2500	0.4209	0.6493	1
2.7	0	0.1585	0.3549	0.6131	1	0	0.1242	0.2707	0.4487	0.6764	1
	$\lambda = 0.9$										
0.2	0	0.0317	0.0918	0.3778	1	0	0.0235	0.0598	0.1330	0.4156	1
0.7	0	0.0700	0.1720	0.3523	1	0	0.0547	0.1274	0.2332	0.4211	1
1.2	0	0.1010	0.2409	0.4624	1	0	0.0784	0.1784	0.3146	0.5260	1
1.7	0	0.1241	0.2893	0.5329	1	0	0.0968	0.2168	0.3733	0.5983	1
2.2	0	0.1418	0.3241	0.5781	1	0	0.1108	0.2447	0.4140	0.6426	1
2.7	0	0.1549	0.3492	0.6086	1	0	0.1216	0.2655	0.4429	0.6729	1

4 Conclusion

We investigated PSO capability to generate locally exact D-optimal designs for the Michaelis-Menten model with correlated outcomes. We implemented PSO using MATLAB codes to find the exact D-optimal designs as described in Algorithm 2.1. PSO was able to successfully and efficiently identify the best designs and they agreed with the theoretical exact D-optimal designs in Dette and Kunert (2014) when there were 2 observations per subject. Our PSO-generated designs also agree with other numerical results in their paper obtained using non-PSO methods. We further demonstrated that the PSO was also able to directly and efficiently generate exact D-optimal designs with more observations per subject. Because PSO is a general optimization technique and does not require assumptions on the function to be optimized for it to work well, we expect PSO should also perform well in finding exact D-optimal designs for other models with different correlation structure and multiple observations per subject. We close with an encouragement to others to explore and apply PSO in their search for optimal designs, and more generally, solve optimization problems in statistics.

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Another simplified Cox-model based on copulas and optimal designs for it

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Abstract

We propose a simplified version of the Cox binary model using copulas and provide corresponding D-optimal designs.

Key words: Binary data, coupled pairs, D-optimality

1 Introduction

I (WGM) have known Hans Nyquist for quite a while as a regular participant of the mODa conference series on optimal design. But it was in 2008 when we had our most memorable encounter. Hans had asked me to be the opponent for his PhD-student Daniel Bruce for the defense of the thesis Bruce (2008a) to which I gladly agreed. Little did I know that in Sweden the opponent was supposed to do the main work, particularly to provide a lecture about the candidates thesis. Well, to be fair, Stockholm university rewarded me quite generously for that task.

In the first chapter of his dissertation thesis Daniel Bruce enumerates a couple of real life situations where either a phenomenon with natural binary outcome is observed or an experiment with binary response is designed on coupled pairs (or multiples). For instance we may want to model the probablitiy for visual impairment (yes/no) on the left eye and on the right eye. We would assume that the probability for visual impairment is equal for both eyes and that it is more likely that both eyes are impared (or both are sound) rather than a single eye. Another example would be an experiment in which

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different batches of fish are fed different types of food in order to determine whether it affects some property of the fish. We would assume that each fish within a certain batch is affected with equal probability and also that the outcomes are dependent. More on the general setup can be found in Bruce and Nyquist (2007).

For these kind of questions one of the most frequently employed statistical models has been given in Cox (1972) and has found particular prominent use in twin studies (such as e.g. Zucknick et al. (2015)). I (WGM) remember well that I took the chance to start my opponents lecture off with a picture of my own twin boys, then 11 years old, which is displayed in Figure 1.

Figure 1: David (left) and Simon (right) Müller in 2008.

2 The model

Daniel Bruce built upon the general Cox model as given in Cox and Snell (1989) and imposed restrictions on the parameters to arrive at a simpler model. In the Cox model each possible outcome is treated as a seperate response category. For the bivariate case the probabilities are given in Table 1 with linear predictors η_{01}, η_{10} and η_{11} of a covariate vector $\boldsymbol{x}$.

		S_2 = 0	S_2 = 1
S_1	0	$\frac{1}{1+e^{\eta_{10}}+e^{\eta_{01}}+e^{\eta_{11}}}$	$\frac{e^{\eta_{01}}}{1+e^{\eta_{10}}+e^{\eta_{01}}+e^{\eta_{11}}}$
	1	$\frac{e^{\eta_{10}}}{1+e^{\eta_{10}}+e^{\eta_{01}}+e^{\eta_{11}}}$	$\frac{e^{\eta_{11}}}{1+e^{\eta_{10}}+e^{\eta_{01}}+e^{\eta_{11}}}$

Table 1: General bivariate Cox model.

If we had k entities $S_1, \ldots, S_k$ the model would consist of 2^k response categories with at least one parameter in each of the $2^k - 1$ linear predictors.

In contrast, in the simplified model proposed by Bruce each possible outcome of only the total $S = \sum_{i=1}^{k} S_i$ defines a response category. Furthermore, for a fixed $s = \sum_{i=1}^{k} s_i$ the probability of each realization $s_1, \ldots, s_k$ is assumed equal. Or in mathematical terms

$$\begin{aligned} P(S = s) &= \frac{e^{\eta_s}}{\sum_{i=0}^{k} e^{\eta_i}}, \\ P(S_1 = s_1, \ldots, S_k = s_k) &= \frac{P(S = s)}{\binom{k}{s}}. \end{aligned} \tag{1}$$

Again, for the bivariate case the probabilities are given in Table 2 with linear predictors η_1 and η_2 of a covariate vector $\boldsymbol{x}$.

		S_2 = 0	S_2 = 1
S_1	0	$\frac{1}{1+e^{\eta_1}+e^{\eta_2}}$	$\frac{e^{\eta_1}/2}{1+e^{\eta_1}+e^{\eta_2}}$
	1	$\frac{e^{\eta_1}/2}{1+e^{\eta_1}+e^{\eta_2}}$	$\frac{e^{\eta_2}}{1+e^{\eta_1}+e^{\eta_2}}$

Table 2: Simplified Cox model

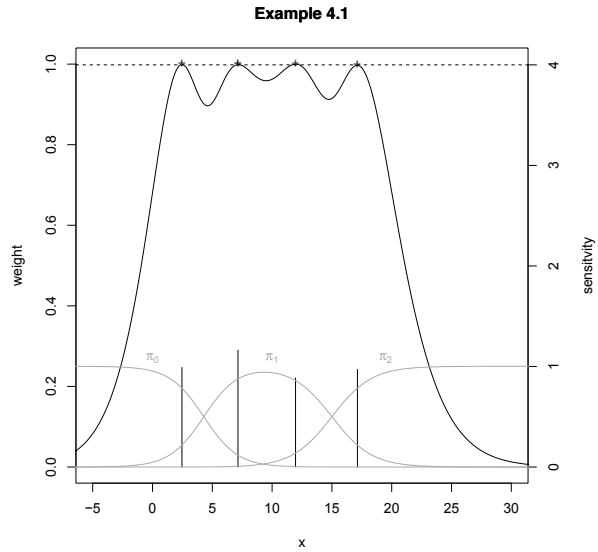

Figure 2: Design and probabilities as found in Bruce (2008a) on page 39.

As a consequence, the marginal probabilities $P(S_i = 0)$ are equal. Now if there were k entities we only have k response categories with at least one parameter in each linear predictor. Therefore the number of parameters is greatly reduced. One can show that this simplified model retains many properties of the general Cox model. For instance, in the bivariate case the conditional probablities of S_1 given S_2 and vice versa are logistic in η_1 and η_2 assuming the covariate $\boldsymbol{x}$ is held constant. Also the log-odds ratio is linear in the parameters and in $\boldsymbol{x}$. This allows for direct interpretation of the log-odds. Another nice property is that the likelihood and Fisher information matrix may be derived analytically even for a large number of entities. Details on these properties are given in Bruce (2008b).

An entire chapter of Bruces thesis (Bruce, 2008a) is devoted to optimal design of experiments. In example 4.1 on page 39 he illustrates a D-optimal design for a bivariate example with a single regressor x. We reproduced and confirmed the result which is displayed in Figure 2.

3 Another simplification

The simplified Cox model has certain advantages over the general Cox model, first and foremost the reduced number of parameters when dealing with multiple entities, but it still suffers from the lack of interpretability of the marginal probabilities from the parameters. In a new attempt to provide a simple model for binary response we now utilize some theoretical results as found in Perrone and Müller (2015) to build models based on copulas. Copulas in general allow us to define the margins and dependence structure of a multivariate random variable separately. We are also able to find D- and D_s-optimal designs for such models. The proof of a corresponding equivalence theorem is found in the appendix of Perrone and Müller (2015).

As we have seen earlier, all of the parameters of the simplified Cox model influence the margins and at the same time define the dependence structure and strength. While this allows for complex marginal behavior we would prefer to have a more direct and simpler structure instead. Therefore we decided to define the marginal probabilities as follows

$$P(S_1 = \cdots = S_k = 0) = \frac{1}{1 + e^{\eta_1}}, \tag{2}$$

where η_1 is a linear predictor of a covariate vector $\boldsymbol{x}$.

Now let us focus on the aforementioned example 4.1. There we assume a high level of negative association around $x = 9$ (see Figure 2). This means that if we observe S_1 then the probability of observing $S_2 = 1 - S_1$ (and $S = S_1 + S_2 = 1$) is high. Furthermore, from equation (2), it should be obvious that if x tends to large positive or negative values, the probability of observing $S_1 = S_2 = 1$ or $S_1 = S_2 = 0$ tends to 1. Quite naturally we can define

$$P(S_1 = S_2 = 1) = C_\alpha(\pi_1, \pi_1) \tag{3}$$

where $\pi_1 = P(S_i = 1)$ and C_α is some copula with parameter α. For the properties and choices of such copula functions see e.g. Nelsen (2007).

We need the copula parameter α to be a function of x in order to add flexibility. Let us therefore (rather arbitrarily) choose the rotated Gumbel copula (90 degrees) for which there is a simple relationship between the copula parameter $\alpha \in (-\infty, -1]$ and the corresponding Kendall's tau, a common measure of association: $\tau(\alpha) = -\frac{\alpha+1}{\alpha} \in [-1, 0]$. So we define

$$\begin{aligned} \tau(x) &= \frac{-1}{1 + e^{\eta_2}} \\ \Longrightarrow \alpha(x) &= -1 - e^{-\eta_2}, \end{aligned} \tag{4}$$

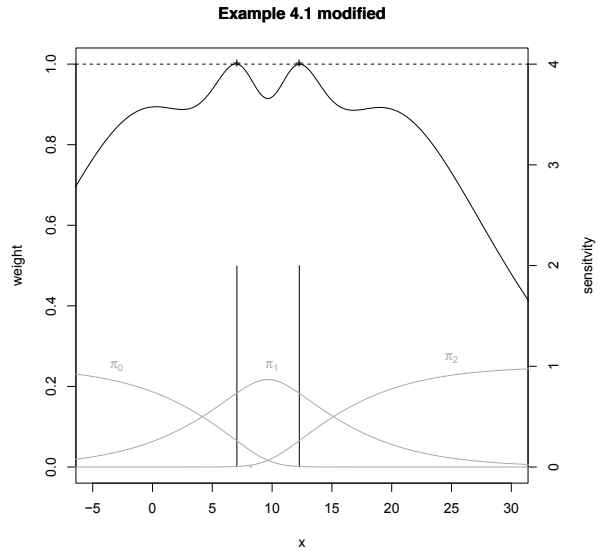

Figure 3: Design and probabilities for the new simplification.

which completes the model definition. By adjusting the initial values for η_1 and η_2 in this model we approximately fit the assumed progression of probabilities as found in Figure 2. Now the D-optimal design can be found and is presented in Figure 3. From it, it can be seen, that the probability curves correspond rather well to the ones from Bruce's simplified Cox model, but here now the optimal design is reduced to a two point design, which may be advantageous in practice. All computations were performed using the package DoCopulaE by A.Rappold available on CRAN, see Rappold (2015).

4 Conclusions

Copulas provide a flexible way of modelling dependence structures and allow better interpretation by separating the marginal behaviour. Here, we provided another simplification of the Cox model, which led to an optimal design with a reduced number of support points.

Allow me (WGM) to conclude with yet another personal remark. While

the defense of Daniels thesis went smoothly, a difficult moment in my career came only a few hours later. Daniel had invited Hans and me to a party in the evening to downtown Stockholm. As I had planned a touristic boat trip through the skerries for the afternoon, I asked Hans for the dressing requirements for the celebration afterwards. His answer "casual" put me quite at ease first, but let me freeze in horror later, when Daniels mother opened the doors dressed in an evening gown (as was the rest of the party). It was obvious that I was most seriously underdressed! (Hans beat me in wearing a suit and tie).

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Why are design in survey sampling and design of randomised experiments separate areas of statistical science?

Dan Hedlin[1]

1 Introduction

It is puzzling that design of randomised experiments and sampling design have diverged and become two separate areas of statistical science with weak interaction. As Kish (1965, p. 595) put it: "the separation of the sample surveys from experimental designs is an accident in the recent history of science...".

One reason may be lack of communication. Fienberg and Tanur (1987, p. 76) ask: "Why is it that modern researchers and students seem to be ignorant of these parallels across fields [surveys and experiments]?" Stephan (1948, p. 30): "... developments in agriculture and engineering had both direct and indirect effects on sampling survey practice. They provided principles of design and contributed to the growth of applied mathematical statistics. Still there were many practical problems and obstacles that delayed the immediate extension of the methods developed for field trials and manufacturing to large-scale surveys. One of the obstacles was the relative *lack of communication between statisticians engaged in different types of work*" (my emphasis).

Lack of communication is certainly a factor. However, the origins of randomised experiments and survey sampling are different.

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We identify two roots of survey sampling and we may call them 'mathematical' and 'arithmetical' (Bowley, 1906). One strand of survey sampling stems from population studies with one leg in arithmetical work limited to tabulation of population records (e.g. Swedish 18^{th} century population statistics) and another leg in more 'mathematical' work in which sources of uncertainty are accounted for. There were also researchers who very early began to use random sampling. For example, Laplace invented and constructed a survey sampling method to estimate the population in France in the beginning of the 19^{th} century. He used the central limit theorem to assess the accuracy of his estimates. His work on survey sampling was long buried in oblivion (Bethlehem, 2009). More impact did the work of Bowley (1913) have. He describes a sample survey of working-class households in Reading. Through a systematic sample (not clear if it is a random systematic sample or not) he estimates average household income and other population parameters. Other strands of early survey sampling have their roots in crop yield estimates and in opinion polls (Stephan, 1948).

To say that experiments also have two roots, one 'refined common sense' and one 'mathematical', may be to draw the parallel to surveys too far. However, experiments have a long and widely spread history. Sven Ove Hansson (2007, p.48) notes that "the Mende people in Sierra Leone have a special word, hungoo, for experiment. A hungoo can consist in planting two seeds in adjacent rows, and then measuring the output in order to determine which seed was best. This was probably an original habit, not one brought to the Mende by visiting Europeans. Similar experiments also occur in other parts of the world." Those experiments may well be denoted 'refined common sense', whereas Fisher (1935) certainly treated experiments 'mathematically'. But the tenuousness in the parallel to surveys may sit in the word 'roots': Fisher elaborated on existing practices of experiments.

In this article I attempt to cover large areas of statistical practice and history. Since I cannot possibly be deeply familiar with all aspects of the history of survey sampling and randomised experiments and the contemporary methodology, I will appreciate suggestions for correction and addition.

2 What is an experiment?

In Sven Ove Hansson's (2007) account an experiment, generally speaking, consists of four steps:

1. Make it happen, that is, make the phenomenon that you intend to study appear.
2. Separate. Disturbing factors needs to be removed.
3. Control. Factors that may influence the phenomenon must be controlled.
4. Observe. Obtain as exact observations as possible.

A fifth step would be to select the objects that will be included in the study. This fifth step could be subsumed into step 1:

1'. Make it happen. Select the objects that will be included in the study and make the phenomenon appear that you intend to study.

The separation step is crucial in a scientific experiment. There are two major ways to do this, elimination and effect separation (Hansson, 2007). R.A. Fisher stressed that in controlled experiments the purpose of introducing randomness into the design is to separate systematic variation from purely random error (Fienberg and Tanur, 1987, p. 77), that is, to conduct the separation step of the experiments. By 'control' Hansson refers to the control of external factors that may make the experiment inefficient. A standard procedure to control those is blocking.

3 What does an experimental statistician work with?

It is useful in research to distinguish between extraneous sources and what Kish (1987, pp. 3-5) calls explanatory variables, which comprise predictors

(independent variables) and predictands (dependent variables). The extraneous sources are largely undesirable in research. Kish classifies variables that come from extraneous sources into three groups, the two first being:

1. Controlled variables. "Control may be exercised either by design of the selection procedures or by estimation techniques in the statistical analysis, or perhaps by both" (Kish, 1987, p. 4).
2. Disturbing variables. These are confounding variables.

Kish (1965, p. 594) writes that the aim of efficient design, both in experiments and in surveys, is to move as many extraneous variables as is feasible into the class of controlled variables, and to control for them successfully. A common way to exercise control (i.e. move variables from being disturbing to the class controlled) through estimation is regression analysis. For example, if a researcher discovers that the incidence of cancer is higher in Bournemouth than in England in general, he can include age among the predictors and the otherwise disturbing variable age is 'controlled for' (and the higher incidence in Bournemouth will disappear). Various kinds of regression analyses are common also in survey sampling (Särndal et al., 1992).

Consider a field in an agricultural experiment. The soil will vary in all directions and hence potentially disturb the inference. How can we define blocks and find explanatory factors that accounts for all disturbing factors? Salsburg (2001, p. 47) paints the picture of how a discussion in Rothamsted may have gone:

R.A. Fisher sits back and smiles, letting the other researchers get more and more involved in complicated constructs. He has already considered these questions and has a simple answer. Those who knew him describe Fisher as sitting, quietly puffing on his pipe, while arguments raged about him, waiting for the moment when he could insert his answer. He removed the pipe from his mouth.

Randomise, he says.

Randomisation is an ingenious trick that helps to move variables from the class 'disturbing' to the class 'randomised'. So added to controlled variables and disturbing variables above, Kish has a third group:

3. Randomised variables. They are uncontrolled but treated as random errors.

Kish (1987) notes in his Figure 1.2.1 that in a successful and well-designed experiment all disturbing variables have been transformed to controlled or randomised variables.

Unlike the (successful) experimental statistician, the survey sampler will have to address remaining disturbing variables that for example nonresponse, measurement error and undercoverage have created.

4 What does a survey sampler work with?

The steps 1', 2, 3, 4 in the section 'What is an experiment?' are actually the same in a survey, with one exception. What does a survey practitioner do when conducting these steps?

1. Select the objects that will be included in the study and observe/measure the phenomenon/characteristic that you intend to study.
2. Separate. Disturbing factors needs to be removed.
3. Control. Factors that may influence the phenomenon must be controlled.
4. Observe. Obtain as exact observations as possible.

It is not usual in survey sampling to instigate a phenomenon; rather the survey practitioner strives to observe or measure without exerting influence on the phenomenon that is the object of the survey. Apart from this, steps 1 to 4 are at an abstract level similar in surveys and experiments. However, at a more practical level they are quite different:

1. The selection of units is a step that the survey practitioner devotes ample time to. The thinking about the best way to select units starts with a definition of the target population, which is usually a finite set. Routes to find units in the target population and observe their study variables are identified or devised.

2. Disturbing factors in surveys are removed or ameliorated. To give an example, interviewer effects are undesirable but unavoidable in telephone or face-to-face interviews (Biemer and Lyberg, 2003, Ch. 5). They are mitigated through training and clear procedures.

3. Control is exercised through sampling design (e.g. stratification) or estimation (e.g. generalised regression estimation, Särndal et al. (1992)).

4. The observations are made through a *mode* (any medium that is used to measure or collect information from observed units). Biemer and Lyberg (2003, Ch. 6) give an excellent account on modes and their (disturbing) errors.

As noted above, disturbing factors in surveys abound. As early as in the beginning of the 20$^{\text{th}}$ century, Bowley addressed the measurement problem in his survey on daily household income among working-class families in Reading (Bowley, 1913). He used a model to compute weekly household income.

5 How is randomness created?

The statistician has to pinpoint the source of randomness she or he is going to take into account. This is actually an intersubjective procedure. In some areas of statistics randomness is trust upon the objects of study. Design-based survey sampling and randomised experiments are two of those areas. Consider a target population of N objects, $\mathbf{U} = \{u_1, u_2, \ldots, u_N\}$, and an indicator $\mathbf{I} = \{I_1, , I_2, \ldots, I_N\}$. In a survey,

$$I_k = \begin{cases} 0 & \text{if unit } k \text{ is not included in the sample} \\ 1 & \text{it is included in the sample} \end{cases}$$

In an experiment with two treatments,

$$I_k = \begin{cases} 0 & \text{if unit } k \text{ is given treatment A} \\ 1 & \text{treatment B} \end{cases}$$

The purpose is to observe a variable $\mathbf{y} = \{y_1, y_2, \ldots, y_n\}$ in the sample of size n. The variable $\mathbf{y}$ is referred to as study variable in survey sampling and response variable in experiments. It can be multivariate.

In both surveys and experiments there is a set S of all vectors $\mathbf{I}$. In both cases, S is the set that defines the randomness which helps the statistician to place the actual result of the survey or experiment in a certain position of the stochastic distribution and make inference.

In surveys, a sample is one realisation of the stochastic vector $\mathbf{I}$. In design-based survey sampling, a sampling design is a function $p(\cdot)$ such that $p(I_s)$ is the probability of selecting the sample I_s. For example, simple random sampling is defined as the function $p(\cdot)$ where all $p(s)$ are the same and all samples have the same predetermined size, n. The probability $p(s)$ in simple random sampling is the inverse of $\binom{n}{N}$. The probability of selecting one particular unit is referred to as inclusion probability. Unfortunately, simple random sampling is often referred to as 'random sampling'. The term 'random sampling' for simple random sampling is cursory, or even sloppy, as there are many other random sampling designs. In fact, research into different random sampling designs was intense in the middle of the 20$^{\text{th}}$ century. Around 1980 the focus changed to estimation.

The design-based framework was founded by Bowley (1913) and Neyman (1934).

Random sampling plays a less critical role in model-based survey sampling. To the contrary, it has been argued that random sampling is not only unneeded, it may even be counter-productive (Valliant et al., 2000, p. 19). In model-based survey sampling a large number of tentative samples are drawn and the sample that is most 'balanced' is selected for data collection. The most basic form of balance is $\bar{x}_s = \bar{X}_U$, where $\mathbf{x} = \{x_1, x_2, \ldots, x_N\}$ is a variable known for all units in the target population and $\bar{x}_s$ and $\bar{X}_U$ are the sample and population averages. Randomness is not devised by the statistician, it is rather assumed to be inherent in the study variable that is assumed to have some stochastic distribution. Model-based survey sampling is of a more recent date than the design-based framework, despite the fact that it is in some respects closer to mainstream statistics than is design-based survey sampling. The two articles introducing model-based survey sampling are Brewer (1963) and Royall (1970).

The main difference between experiments and model-based survey sampling in terms of the role of randomness is that in experiments treatment is randomised to separate factors (see the section 'What is an experiment?') whereas in model-based survey sampling there is no active randomisation. In

both cases, however, randomness constitutes 'left-overs' when everything that is feasible to control has been addressed. This randomness stems from the perceived or real stochastic nature of $\mathbf{y} = \{y_1, y_2, \ldots, y_N\}$. In design-based survey sampling the study variable is believed to be, or taken as, non-stochastic.

6 What drove the separation?

One clue to the root of the separation of surveys and experiments can be sensed in the very first sentence in Stephan's paper on the history of survey sampling (1948, p. 12): 'Modern sampling practice is the result of combining statistical theory with scientific *knowledge about the material* that is being sampled' (my emphasis).

In conversation (Fienberg and Tanur, 1987, p. 86) William Madow noted three factors driving the separation of experiments and surveys:

1. the complexity of the populations sampled in large scale surveys (heterogeneity, skewness, and mixture properties)
2. the large sizes of samples selected in large scale surveys made it possible to draw inferences that did depend on a probability structure imposed by the survey designer and did not depend on assumed probability densities (see design-based and model-based survey sampling above)
3. from the early work of Fisher the simplest analysis of variance model did not permit a negative intraclass correlation coefficient, while cluster sampling as defined for finite sampling would yield a negative intraclass correlation

The survey samplers around the 1940s, William Madow included, addressed the issue of population complexity by introducing sampling designs with unequal inclusion probabilities. Knowledge about the population was essential to devise a cost-efficient sampling design. There was an enormous growth of complex sampling designs. For example, Brewer and Hanif (1983) list more than 40 sampling designs of the πps type (probability proportional to size without replacement) that they had found in the literature. Some modern textbooks, for example Chambers and Clark (2012), are organised around

types of population, with chapter headings such as 'homogenous population', 'clustered population', etc.

The textbook by Hansen et al. (1953) played an instrumental role in shaping the survey sampling practices. They include fairly little material on randomised experiments. That is in fact true for the vast majority of textbooks in surveys sampling with one notable exception: Yates (1981). Frank Yates was early in his career employed by R.A. Fisher in Rothamsted.

Another driver of the separation was the growth of the literature in both fields. It just became very hard for newcomers to statistics to master both survey sampling and randomised experiments (Fienberg and Tanur, 1987).

7 Different desiderata

You cannot have it all in research. It is sometimes useful to map the aim of research onto three dimensions: representation, control and realism (Kish, 1987; O'Muircheartaigh, 1999). These can be called desiderata (Weisberg, 2006). By representation we mean whether it is possible to generalise to a wider population, by control we mean whether confounders are in control and finally by realism we have the validity of the research in mind.

Kish (1987, p. 9) notes that only rarely all three desiderata can be satisfied adequately in any research, and often you can have only one of the three. Kish goes on to say that experiments are strong on control, weak on representation and often also on realism. Perhaps Kish had in mind the type of experiments where subjects are chosen out of convenience. For example, Godden and Baddeley (1975, 1980) test the effect of changing the physical context on how well subjects recall a list of words. The subjects were divers from the university diving club and the physical contexts were under-water and above water. In Phase III clinical trials the sampling design is certainly not a convenience sample but still it may fall considerably short of what in official statistics would be considered as a good, random sample that provides reliable grounds for representation. So there is more than a grain of truth in the claim that experiments are weak on representation.

Surveys, Kish (1987) claims, are strong on representation and realism. They are strong on realism because "measurements can often be made in the

'natural settings' of actual populations" (Kish, 1987, p. 9). I disagree with the last point. I believe that collecting data through a survey is very different from making real-life observations. An exception may be surveys on crop yields and similar topics.

A fourth desideratum may be precision. Surveys often sacrifice precision in study variables to be measured in the survey. One common sacrifice is the use of Lickert scales or similar where something that is more or less continuous is mapped onto a, say, five-point scale. Another sacrifice is when the survey designer deliberately simplifies questions (for example, by asking how often respondents eat vegetables instead of asking about the amount of vegetables). In sum, I believe surveys are strong on representation only, although in terms of control there have been substantial recent advances in estimation where 'auxiliary' variables (controlled variables) remove disturbing variables, not only to reduce bias but also to improve precision in estimates.

8 Exploring the rationale behind the separation

Different origins and lack of communication aside, are there rational reasons for the fact that design in survey sampling and design of randomised experiments are separate areas of statistical science?

Our notes above suggest four possible reasons:

1. Experimental research and survey sampling may have different aims.
2. Survey sampling faces substantial challenges with disturbing variables.
3. Knowledge about the population structure is paramount in surveys, which has led to an interest in complex sampling designs.
4. In the survey sampling area there is a choice between design-based inference, where moments are taken over $p(\cdot)$, and model-based inference where moments are taken over the non-sampled part of $\mathbf{y} = \{y_1, y_2, \ldots, y_N\}$ conditional on I_s.

To the discussion above on different aims (realism, precision, control and representation) the dimension analytical and descriptive aim should be added (Thompson, 1997). You have a descriptive aim when you strive at estimating a function of $\mathbf{y} = \{y_1, y_2, \ldots, y_N\}$ (uni- or multivariate), and an analytical aim when the goal is to estimate parameters in a model that captures the relationship between predictors and predictands. Surveys have usually descriptive aims and experiments analytical aims.

A further intriguing issue, which we have not touched upon so far, is whether survey samplers and experimental statisticians have different ways of thinking about optimality in terms of inferential precision. This issue can be organised at least under the three headings: 'interest', 'what kind of critical points' and 'what objective function (loss function)'.

To start with 'interest', the mere existence of a book like Atkinson et al. (2007) suggests a stronger emphasis on optimality in experiments. However, in practice, experimental designs are often chosen in a traditional fashion, even in expensive clinical trials (Fackle-Fornius et al., 2015). Optimality plays a backstage role in surveys. Results on optimal choices like Neyman allocation (Neyman, 1934) appeared rather early in the development of survey theory, but now cost-efficiency, rather than optimality, attracts greater interest. The main reason may be the fact that most surveys have several purposes: there are many study variables and subpopulations. In model-based sampling the focus shifted early from optimality to robustness, the reason being fear of bias (Valliant et al., 2000, Ch. 3).

Turning to 'what loss function', mean squared error is the by far most often used loss function in surveys. I would argue that at least in official statistics the most relevant function is the 'survey error', that is, the difference between the true finite population parameter and the estimate. The central position of the MSE appears to be due to its mathematical tractability.

Finally, as for the issue 'what kind of critical points' we note that experimental design with nonlinear models and surveys share one obstacle: the optimum depends on unknown parameters and hence the optimum is strictly speaking infeasible to identify ahead of the data collection. Practitioners use estimates ('guestimates') of those parameters to compute an optimal design in terms of minimum MSE. Instead of trying to locate a minimum of the objective function, a minimax type of criterion to find a good (minimum of the maximum variance over a reasonable range of values of the unknown pa-

rameters) optimum seems preferable (Scott and Smith, 1975; Cheng and Li, 1987; Fackle-Fornius et al., 2015). Hedlin (2002) suggests minimum risk of obtaining estimates with large error as a criterion. The downside is loss of mathematical tractability.

The interesting issue whether optimality is an area where survey sampling and randomised experiments can learn from each other is left for future research.

This article started with a quotation from Kish (1965): "The separation of the sample surveys from experimental designs is an accident in the recent history of science... ". It is intriguing to see what follows that quotation:

"... and it will diminish. With complete command over the research situation, we could introduce, with firm experimental controls, the desired effects and measurements into controlled and randomized portions of the entire target population".

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A note on equating test scores with covariates

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Key words: background information, covariates, future challenges

1 Equating test scores with covariates

Test score equating is the statistical process that is used to ensure that test scores from different versions of a test, for example achievement tests are comparable. There exist a number of data collection designs and test equating methods depending on if we have access to common items on the test versions or common test takers. One common data collection design is the equivalent group (EG) design which require the test taker group to be similar even if the test versions are administered at different places or at different time points. Another common data collection design is the non-equivalent groups with anchor test (NEAT) design which require the access to a number of common items (i.e. an anchor test) that has been given to a large number of test takers. The NEAT design is preferable in many test situations. A problem with the NEAT design is that although two groups might be nonequivalent we may not always have access to an anchor test. Recently, a number of ways to circumvent this has been proposed which not only uses test scores but also covariates. The aim of this note is to highlight some future challenges when equating test scores when we have nonequivalent groups and no anchor test.

During 2015 three independent studies were published which all used covariates in test score equating in different ways. In the first study, by Wiberg and Bränberg (2015), covariates were actively used to improve the test equating through a new design called the non-equivalent groups with covariates (NEC) design. In the NEC design, the test takers are categorized through a

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number of covariates that correlate highly with the test scores and these categories are used in a similar way as anchor test scores are used in the NEAT design.

In the second study, by Haberman (2015), pseudo-equivalent groups were constructed by using background information of the test takers. From this information Haberman created weighted samples of test takers which resembled samples from equivalent groups. Linking, which is similar to equating but less restricted, was performed on the weighted samples. In the third study, by Longford (2015), a test score equating method was proposed which was built on causal inference. Especially the ideas of matching with inverse proportional weighting and matched-pairs based on coarsened propensity scored derived from covariates. In all these methods the key ingredient is the use of covariates. It is interesting that all these three studies were published within a few months in the beginning of 2015, without any reference to each other. As equating test scores is an important part of ensuring fairness in standardized achievement tests I expect more research in test score equating with covariates the next following years as there are many equating methods where one could incorporate covariates, including for example item response theory (IRT) equating.

In Sweden, test score equating are used in the Swedish Scholastic Assessment Test (SweSAT) college admissions test. The SweSAT is a paper and pencil test with 160 multiple-choice binary-scored items which consists a quantitative and a verbal section that are equated separately. The test is given twice a year and since 2011 an anchor test is given to a smaller number of test takers. Before the anchor test was introduced, different test taker groups were used with specific values on their covariates to ensure equivalence between test groups when performing equating with an EG design. Some covariates are regularly collected at each test occasion, and it has been shown that education level and age correlate with the test scores and that gender influence the test scores (Bränberg et al., 1990). Although there is now an anchor test for the SweSAT, covariates are still important to facilitate backward comparison of the test results over the years.

2 Future challenges

There are many future challenges which are connected to test equating and the use of covariates. It must however be emphasized that without good covariates we cannot perform a well working equating with covariates. A huge challenge is thus to examine which covariates could be used and how to regularly collect

them. Possible covariates which one could include are for example the test takers response times to the items or the results from other tests. A guideline when choosing covariates could be to examine the correlation between the covariates and the test scores, as covariates which correlate highly with the test scores tend to work well in the equating situation.

There are many equating methods around and some people may argue that we do not need more equating methods. However there might be situations when one need a new equating method. One such possibility could be to examine the possibility to equate a multidimensional test multidimensionally. It is however unclear if we would gain anything compared with equating the different dimensions separately, as a study comparing the use of multidimensional IRT and unidimensional IRT showed only small differences (Wiberg, 2012). It is also possible that for computerized multistage tests one might need a special equating method in the future.

Another huge challenge when equating large scale assessments, is if one actively use covariates as in the NEC design, is how to reach out to the public and explain the use of covariates in the equating of test scores. It is important that a large scale assessment is perceived as fair for all test takers. In Sweden we have a tradition of explaining how everything works, including the equating method of a standardized test, to the public. Thus, in order to use new equating methods in Sweden one has to be prepared to explain its advantages over traditional equating methods. This is interestingly of less importance in for example the USA, where the equating process is typically secret in many large scale assessments as the tests are developed and administered by private companies and not from a governmental institution as in Sweden.

Finally, during the past few years equating packages has been developed for the freeware R (R Development Core Team, 2015). Equating specific packages include for example *equate* (Albano, 2014), *kequate* (Andersson et al., 2013) and *SNSequate* (González, 2014). Although many equating methods are incorporated in these packages there are still many equating methods which one could incorporate into R packages in order to make them more accessible for the users. This is something I hope will happen within a near future. A final reflection is that there are excellent theoretical test equating books around, and thus the focus should be on implementing recent well working equating methods. Initiatives as new equating R packages and the new applied test equating book by González and Wiberg (in preparation) is thus of great importance.

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Assessing dependence, independence, and conditional independence

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Abstract

Independence between several variables implies mutual independence between all pairs of variables. But when do we have dependence and still mutual independence? To answer such kind of questions we need to understand how dependence and independence can be specified and compared. This essay presents convenient tools for assessing dependence, independence and conditional independence and demonstrates that a central balance between independence and mutual independence based on entropies has a corresponding set of balances between conditional and unconditional independencies.

Key words: Stochastic and functional dependence, independence, mutual independence, conditional independence, likelihood ratio, divergence, entropy, test statistics.

1 Introduction

1.1 Stochastic and functional dependence

In explorative data analysis and statistical modelling, a fundamental problem is to assess which variables might be treated as independent. More specifically, dependence between variables can be stochastic dependence or functional dependence. Stochastic dependence means that there is covariation between the

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outcomes of different variables but says nothing about whether this is a consequence of direct or indirect causes of other variables. Functional dependence of a variable Y on some other variable X can be considered as stochastic dependence between X and Y degenerated into deterministic dependence so that for each possible outcome of X there is a unique outcome of Y, and the variation in Y is entirely determined by the variation in X. Similarly, stochastic independence between variables means no covariation between their outcomes, so that their simultaneous outcome frequencies are proportional to the marginal outcome frequencies of each variable.

1.2 Independence and conditional independence

Even if two variables are stochastically dependent, it might be possible to find a third variable such that the two variables are stochastically independent conditional on each fixed outcome of the third variable. Such conditional independence can be difficult to assess, particularly in multivariate settings where the conditioning might involve two or more variables.

1.3 Multivariate data

The typical setup of multivariate data needed for the investigation of dependence and independence comprise m variables (attributes, properties, measurements) defined on n objects (units, individuals, cases). Data can be presented in a matrix with m columns and n rows such that the entries in row i are the ith m-variate observation, and the entries in column j are the n observations on the jth variable for $i = 1, \ldots, n$ and $j = 1, \ldots, m$.

Categorical variables often have a small number of categories occurring with frequencies summing to the total n. Continuous variables might be measured and rounded to convenient accuracy so that they appear as categorical. Generally, neither numerical nor ordinal but only nominal scales are needed for all variables in the present context. In some cases, it might be convenient to use quartiles or deciles or some other categorization for ordinal or numerical variables. Thus we consider the data matrix as a collection of n observations on m categorical variables.

1.4 Marginal distributions

The m-variate distribution has usually a number of different possible outcomes that is much larger than the number of rows n, but only a fraction of the distinct possible outcomes occurs among the rows. Usually, however, n is much larger than the number of distinct possible outcomes of any univariate marginal distribution, or even much larger than the number of distinct possible outcomes of any bivariate or trivariate marginal distribution among the m variables. This implies that data suffice to estimate at least the lower dimensional marginal distributions. Marginal distributions are sometimes required to have an average of at least 5 or 10 observations per outcome in order to yield reasonably reliable frequency distributions.

If we allow X, Y and Z to be variables or sequences of variables chosen from the m variables in the data matrix, and if their numbers of distinct possible outcomes r, s and t are sufficiently small compared to n to allow reliable frequency distributions, then n is large enough for the investigation of various kinds of dependence, independence and conditional independence in the (X, Y, Z)-distribution. In the following we first consider bivariate distributions in detail, and then extend the results to trivariate distributions.

2 Bivariate categorical distributions

2.1 Likelihood ratio for independence

Let X and Y be two categorical variables with simultaneous probability distribution $P(X = x, Y = y) = p(x, y)$ and empirical relative frequency distribution $n(x, y)/n$ for r distinct possible outcomes of X labelled $x = 1, \ldots, r$ and s distinct possible outcomes of Y labelled $y = 1, \ldots, s$. The bivariate probability distribution of (X, Y) and its empirical estimate both have at most rs distinct possible outcomes. Stochastic independence between X and Y implies that the bivariate probability distribution of (X, Y) is given by the product of the univariate marginal probabilities $P(X = x)P(Y = y) = q(x, y)$ and estimated by the product of the empirical marginal relative frequencies. Such independence is denoted

$$X \perp Y$$

and the log likelihood ratio

$$\log[p(x,y)/q(x,y)]$$

can be used for testing it. For different outcomes, the ratios can be both smaller than and larger than 1, so the log likelihood ratio can be both negative and positive. However, it is possible to use the convexity of the logarithm function in order to prove that the expected log likelihood ratio is always non-negative. Therefore, large values of the expected log likelihood ratio indicate deviation from independence.

2.2 Divergence as test statistic

The expected log likelihood ratio is called the divergence between the distributions p and q, and it is denoted and given by

$$D(p,q) = \sum_{x=1}^{r}\sum_{y=1}^{s} p\,(x,\,y)\log\frac{p\,(x,\,y)}{q\,(x,\,y)} \geq 0.$$

When p is the general distribution of (X,Y) and q specifies independence $X\perp Y$ it is convenient to denote the divergence

$$D(p,q) = D(X\perp Y).$$

It measures the fit of independence to the bivariate distribution. When p and q are estimated by empirical distributions it can be shown by approximation of the logarithm function that the divergence is closely related to the Pearson goodness-of-fit statistic, and

$$2nD/\log(e)$$

is asymptotically chi-square distributed with d degrees of freedom as n tends to infinity. Here d is obtained as the difference between the degrees of freedom for p and q. The degrees of freedom for p is $rs-1$ and for q is $r-1+s-1$ so that $d=(r-1)(s-1)$. It is convenient to use D/d as test statistic and reject independence when it is, say, more than 2 standard deviations above its expected value, which is

$$D/d > \left(1+\sqrt{8/d}\right)\log(e)/2n.$$

2.3 Divergence and entropies

The divergence $D(p,q) = D(X \perp Y)$ is not only related to statistical likelihood theory but has also an interpretation in terms of information theoretic entropy measures. This is important since it makes it possible to systematically extend model testing to more complicated multivariate cases.

The entropy of X, sometimes called the information in X, is defined as the expected uncertainty of X, and the uncertainty of the event $X = x$ is defined as the order of magnitude of the probability $P(X = x) = p(x)$. For instance, a probability $p = 0.001$ has order of magnitude $\log(1/p) = 3$ in decimal information units (called dits) obtained with log base 10, and a probability $p = 1/8$ has order of magnitude $\log(1/p) = 3$ in binary information units (called bits) obtained with log base 2. Thus, the entropy of X is equal to

$$H(X) = E \log[1/p(X)] = \sum_{x=1}^{r} p(x) \log[1/p(x)],$$

where the sum is extended over all distinct outcomes x of X with $p(x) > 0$. In information theory it is common to use log to base 2. Here log is used without specifying the base, and when a specific base b is intended this is obtained by dividing the entropy by $\log(b)$. For instance, we used natural logarithms with base e above giving uncertainty in natural information units (called nits).

The definition of entropy for categorical variables extends immediately to multivariate cases and

$$H(X,Y) = E \log[1/p(X,Y)]$$

where $p(x,y) = P(X = x, Y = y)$. It is therefore possible to express the divergence

$$D(X \perp Y) = H(X) + H(Y) - H(X,Y)$$

as a combination of univariate and bivariate entropies. In information theory this combination is called the joint entropy of X and Y, and denoted

$$J(X,Y) = H(X) + H(Y) - H(X,Y).$$

It can be interpreted as the approximate number of information units that are common to the two variables. Joint entropy is always non-negative, and it is 0 if and only if there is independence $X \perp Y$. Its upper bound is the bivariate

entropy $H(X,Y)$. This upper bound might be equal to $H(X)$ if X explains Y in the sense that there is a single outcome of Y for each outcome of X, that is, there is a function f so that $Y = f(X)$, which is denoted as $X \to Y$. When $H(X,Y) = H(X)$ it follows that $H(Y) \leq H(X)$ with equality if and only if X and Y are equivalent in the sense that they explain each other, which is denoted by $X \longleftrightarrow Y$.

2.4 A partition of bivariate entropy into three divergences

The bivariate entropy $H(X,Y)$ can be represented as a sum of three non-negative entropies according to

$$H(X,Y) = EH(X\,|Y) + J(X,Y) + EH(Y\,|X),$$

where

$$EH(Y\,|X\,) = \sum_{x=1}^{r} P(X=x)H(Y\,|X=x)$$

$$= \sum_{x=1}^{r}\sum_{y=1}^{s} P(X=x)P(Y=y\,|X=x)\log[1/P(Y=y\,|X=x)]$$

$$= H(X,Y) - H(X)$$

$$= H(Y) - J(X,Y),$$

and analogously for the other expected conditional entropy. Thus the bivariate entropy counts information units in three disjoint sets (some may be empty) corresponding to units that are informative for only one of the variables or for both. If $J(X,Y) = 0$ we have $X \perp Y$, if $EH(Y\,|X) = 0$ we have $X \to Y$, and if $EH(X\,|Y) = 0$ we have $Y \to X$. If we denote

$$EH(Y\,|X) = D(X \to Y) \quad \text{and} \quad EH(X\,|Y) = D(Y \to X),$$

we have got the bivariate entropy expressed as a sum of three divergences

$$H(X,Y) = D(Y \to X) + D(X \perp Y) + D(X \to Y).$$

If the interval from 0 to $H(X,Y)$ is divided into a first subinterval of length $D(Y \to X)$, a middle subinterval of length $D(X \perp Y)$, and a last subinterval

of length $D(X \to Y)$, then the first subinterval is not smaller than the last if and only if the variables satisfy the general inequalities

$$0 \leq H(Y) \leq H(X) \leq H(X,Y) \leq H(X) + H(Y).$$

3 Trivariate categorical distributions

3.1 Likelihood ratios for independence and conditional independence

With three categorical variables X, Y, Z of r, s, t possible distinct outcomes for each, there are at most rst possible outcomes for the trivariate (X,Y,Z)-distribution. Various kinds of independence and conditional independence can be specified, and some of them imply some of the others.

An important equivalence is that $(X,Y) \perp Z$ if and only if $X \perp Z$ and $Y \perp Z \,|X$. Since X and Y are exchangeable here, it also holds true that $(X,Y) \perp Z$ if and only if $Y \perp Z$ and $X \perp Z \,|Y$. Thus, the independence between the bivariate (X,Y)-distribution and the univariate Z-distribution is equivalent to a combination of independence and conditional independence for pairs of variables.

Another important fact is that $(X,Y) \perp Z$ together with $X \perp Y$ is equivalent to trivariate independence, which means that every pair of variables is independent as well as conditionally independent. It is not sufficient for trivariate independence that every pair of variables is independent. Neither is it sufficient that every pair is conditionally independent. Not even two of each of the two kinds of independence is sufficient for trivariate independence. The crucial thing is that a combination of mutual independence with any conditional independence or a combination of mutual conditional independence with any unconditional independence is required to guarantee trivariate independence.

The likelihood ratios for the independencies $(X,Y) \perp Z$ and $X \perp Y$ are

$$P(X=x, Y=y, Z=z)/P(X=x, Y=y)P(Z=z)$$

and

$$P(X=x, Y=y)/P(X=x)P(Y=y),$$

so by multiplication of these two ratios we get the likelihood ratio for trivariate independence

$$P(X = x, Y = y, Z = z)/P(X = x)P(Y = y)P(Z = z).$$

The likelihood ratio for conditional independence $X \perp Y \,|Z$ is given by

$$P(X = x, Y = y, Z = z)P(Z = z)/P(X = x, Z = z)P(Y = y, Z = z).$$

3.2 Divergences and tests

The divergence for trivariate independence is the expected value of its log likelihood ratio, which is the sum of the log likelihood ratios of $(X, Y) \perp Z$ and $X \perp Y$ so we have

$$D((X, Y) \perp Z \text{ and } X \perp Y) = D((X, Y) \perp Z) + D(X \perp Y).$$

The degrees of freedom d for trivariate independence can be obtained as the difference between the degrees of freedom for the general trivariate distribution and for the distribution with trivariate independence, which is $d = rst - 1 - (r - 1 + s - 1 + t - 1)$. It can also be obtained as the sum of the degrees of freedom for the divergences of each independence assumption, which is $d = d' + d''$ where $d' = (rs - 1)(t - 1)$ and $d'' = (r - 1)(s - 1)$. Hence, $d = rst - r - s - t + 2$.

The divergence of conditional independence is

$$D(X \perp Y \,|Z),$$

and its degrees of freedom d is given by the difference between the degrees of freedom for the general trivariate distribution and for the distribution with conditional independence, which is $d = rst - 1 - [t - 1 + t(r - 1 + s - 1)] = (r - 1)(s - 1)t$.

Testing can be performed by using that for large values of n, the empirical divergences are distributed so that $2nD/\log(e)$ is approximately chi square distributed with d degrees of freedom.

3.3 Divergences and entropies

We can express divergences by joint entropies according to

$$D((X,Y)\perp Z) = J((X,Y),Z)$$

and

$$D(X\perp Y) = J(X,Y),$$

and the divergence of trivariate independence is the sum

$$\begin{gathered} D((X,Y)\perp Z \text{ and } X\perp Y) = J((X,Y),Z) + J(X,Y) \\ = H(X,Y) + H(Z) - H(X,Y,Z) + H(X) + H(Y) - H(X,Y) \\ = H(X) + H(Y) + H(Z) - H(X,Y,Z), \end{gathered}$$

which is also denoted by $J(X,Y,Z)$ not to be confused with $J((X,Y),Z)$.

The divergence of conditional independence is given by

$$\begin{gathered} D(X\perp Y\,|Z) = EJ(X,Y\,|Z) \\ = H(X,Z) + H(Y,Z) - H(Z) - H(X,Y,Z). \end{gathered}$$

Functional dependence $(X,Y)\to Z$ can be identified by

$$EH(Z\,|X,Y) = H(X,Y,Z) - H(X,Y) = 0.$$

We define the divergence from such dependence by this expected entropy

$$D((X,Y)\to Z) = EH(Z\,|X,Y).$$

3.4 Partitions of trivariate entropy into divergences

It is possible to partition trivariate entropy $H(X,Y,Z)$ into six non-negative entropies according to

$$\begin{gathered} H(X,Y,Z) = \\ EH(X\,|Y,Z) + EH(Y\,|X,Z) + EH(Z\,|X,Y) + \\ J(X,Y) + EJ(X,Z\,|Y) + EJ(Y,Z\,|X). \end{gathered}$$

Here the three expected entropies are divergences for functional dependencies, the joint entropy is divergence for independence $D(X \perp Y)$, and the two expected joint entropies are divergences for conditional independencies. By interchanging the variables there are three similar partitions into six non-negative divergences, where the three expected entropies are the same but the joint entropy and one of the expected joint entropies differ between any two partitions. It is possible to combine the three partitions in a partition into seven parts of which six are non-negative divergences and one is a balancing central part $C(X, Y, Z)$ that can be positive, negative or zero. The central part together with any expected joint entropy is equal to the corresponding joint entropy. Thus

$$\begin{gathered} H(X, Y, Z) = \\ EH(X \,|Y, Z) + EH(Y \,|X, Z) + EH(Z \,|X, Y) + \\ EJ(X, Y \,|Z) + EJ(X, Z \,|Y) + EJ(Y, Z \,|X) + C(X, Y, Z), \end{gathered}$$

where

$$\begin{gathered} C(X, Y, Z) = \\ J(X, Y) - EJ(X, Y \,|Z) = J(X, Z) - EJ(X, Z \,|Y) = J(Y, Z) - EJ(Y, Z \,|X). \end{gathered}$$

The central part represents a certain balance in the three dimensional distribution. For instance, if there is mutual independence, the central part is negative or zero and the three expected joint entropies are all equal. Generally, the three joint entropies as well as the three expected joint entropies can all have different values but they are always restricted to yield the same difference between joint entropy and expected joint entropy for each pair of variables.

The value of the central part can be symmetrically given as a linear combination of all univariate, bivariate and trivariate entropies according to

$$C(X, Y, Z) = S_1 - S_2 + S_3,$$

where

$$\begin{aligned} S_1 &= H(X) + H(Y) + H(Z), \\ S_2 &= H(X, Y) + H(X, Z) + H(Y, Z), \\ S_3 &= H(X, Y, Z). \end{aligned}$$

Now trivariate independence has a divergence that can be given as $J(X,Y,Z) = S_1 - S_3$ and mutual independence has divergence

$$J(X,Y) + J(X,Z) + J(Y,Z) = 2S_1 - S_2 = (S_1 - S_2 + S_3) + (S_1 - S_3).$$

Therefore

$$C(X,Y,Z) = J(X,Y) + J(X,Z) + J(Y,Z) - J(X,Y,Z)$$

can be given as the difference between the divergences for mutual independence and for trivariate independence. As a consequence, the balance between independence and conditional independence can also be interpreted as a balance between mutual independence and trivariate independence. In particular, if there is mutual independence, the three expected joint entropies $EJ(X,Y\,|Z)$, $EJ(X,Z\,|Y)$, and $EJ(Y,Z\,|X)$ are all equal to $J(X,Y,Z)$. Generally, we can say that the difference between the measures of dependence and conditional dependence is equal to the difference between the measures of mutual and trivariate dependence, and this is equal to half the difference between the measures of trivariate and mutual conditional dependence in accordance with the formula

$$\begin{gathered} C(X,Y,Z) = J(X,Y) - EJ(X,Y\,|Z) = \\ J(X,Z) - EJ(X,Z\,|Y) = \\ J(Y,Z) - EJ(Y,Z\,|X) = \\ J(X,Y) + J(X,Z) + J(Y,Z) - J(X,Y,Z) = \\ (1/2)[J(X,Y,Z) - EJ(X,Y\,|Z) - EJ(X,Z\,|Y) - EJ(Y,Z\,|X)]. \end{gathered}$$

Mutual conditional dependence is measured by the sum of three deviations from conditional dependence, and this sum is larger than the measure of trivariate dependence if and only if C is negative. As a consequence, we have that

$$\begin{gathered} 3J(X,Y,Z) = \\ 2[J(X,Y) + J(X,Z) + J(Y,Z)] + [EJ(X,Y\,|Z) + EJ(X,Z\,|Y) + EJ(Y,Z\,|X] \end{gathered}$$

so that trivariate dependence can be said to weight mutual dependence twice as much as mutual conditional dependence.

4 Some examples

Multivariate independence implies independence in all bivariate marginal distributions, but mutual independence does not imply multivariate independence. A simple example of dependence in a trivariate distribution with mutual independence between any two variables is given by a uniform probability distribution of (X, Y, Z) over the four outcomes $(0, 0, 1)$, $(0, 1, 0)$, $(1, 0, 0)$, and $(1, 1, 1)$. All univariate and bivariate marginal distributions are uniform. Therefore, there is mutual independence but the eight trivariate outcomes do not have the uniform distribution that would be required by trivariate independence.

Using entropies in this example, we see that $H(X) = H(Y) = H(Z) = 1$, $H(X, Y) = H(X, Z) = H(Y, Z) = 2$, and $H(X, Y, Z) = 2$ so that $J(X, Y) = J(X, Z) = J(Y, Z) = 0$ and $J(X, Y, Z) = H(X)+H(Y)+H(Z)-H(X, Y, Z) = 1$ implying mutual independence but not trivariate independence. The balancing central part $C(X, Y, Z) = -1$, and any two variables are dependent conditionally on the third according to $EJ(X, Y\,|Z) = EJ(X, Z\,|Y) = EJ(Y, Z\,|X) = 1$. We also find $EH(X\,|Y, Z) = EH(Y\,|X, Z) = EH(Z\,|X, Y) = 0$, which implies that any pair of variables determines the third variable. In fact, any variable is an indicator variable of equality between the values of the other two variables. For instance, $Z = 1$ if $(X, Y) = (0, 0)$ or $(1, 1)$, and $Z = 0$ if $(X, Y) = (0, 1)$ or $(1, 0)$. Thus, Z can be considered as a redundant variable that interferes with the bivariate distribution of (X, Y) and creates explainable dependence. However, not all trivariate dependence occurring together with mutual independence can be demystified in this way. This can be seen and understood by looking further at the multivariate entropies. Let us consider the following extended example.

Assume that (X, Y, Z) has a uniform distribution over 32 of the 64 outcomes (x, y, z) with x, y and z being integers chosen from 1,2,3,4. The integers should be chosen so that (x, y, z) has an odd number of odd integers. It is convenient to think of a cube of side length 4 divided into 64 small cubes of side length 1 and assign equal probabilities to 32 small cubes that have no common side areas. Due to the symmetry it follows that all univariate and bivariate marginal distributions are uniform. Now $H(X) = H(Y) = H(Z) = 2$, $H(X, Y) = H(X, Z) = H(Y, Z) = 4$, and $H(X, Y, Z) = 5$ so that $J(X, Y) = J(X, Z) = J(Y, Z) = 0$ and $J(X, Y, Z) = H(X)+H(Y)+H(Z)-H(X, Y, Z) = 1$ implying mutual independence but not

trivariate independence. As in the previous example we have $C(X,Y,Z) = -1$ and find $EJ(X,Y\,|Z) = EJ(X,Z\,|Y) = EJ(Y,Z\,|X) = 1$, which means that any two variables are dependent conditionally on the third. However, now $EH(X\,|Y,Z) = EH(Y\,|X,Z) = EH(Z\,|X,Y) = 1$, which implies that no pair of variables determines the third variable. The trivariate dependence in this example is therefore not a consequence of some functional relationships between the variables, which it was in the previous example. But still we have mutual independence and know that it can occur together with trivariate dependence even without redundancy between the variables.

Both the examples considered above are very symmetric and based on uniform distributions that do not give the full flavour of how entropies can be useful for comparing variables and judging the strengths of functional relationships, of stochastic dependence, and of conditional dependence. For such examples the reader is referred to some of my students' bachelor theses, which apply multivariate entropy methods to real survey data of different kinds: Drea-Persson and Karjalainen (2012), Langemar and Eriksson (2012), Harki and Klaesson (2013), Nikoforova and Marcus (2013), Jonsson and Ygge (2014). There are also illustrations with network data in Frank and Shafie (2015).

5 Comments on literature

Even if entropy is a concept used in statistics, both in general theoretical texts like Ellis (2012) and Kallenberg (2002), and in attempts to combine statistics and information theory as in Kullback (1959) and Gokhale and Kullback (1978), the potential of multivariate entropies is not yet widely recognized. Bivariate joint entropy measures can be considered as natural alternatives to some of the statistical measures of association. A good old source is Goodman and Kruskal (1979), and some early attempts to find useful entropy measures are Theil (1967) in economic applications and Krippendorff (1986) in social science applications. Systematic use of multivariate entropies is described in Frank (2000). Elaborations of multivariate entropies as exploratory tools are given in Frank (2011), and applications to network data are illustrated in Shafie and Frank (2015) and Frank and Shafie (2015).

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A Short Note on Matrices Used in Statistics

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Abstract

Matrices find many applications in various research areas and real-life problems. In spite of the availability of many innovative tools in statistics, the main tool of the applied statistician remains the linear model. Patterned matrices are often used to model dependence structure of longitudinal or repeated measures data. In this paper, some properties of symmetric circular Toeplitz matrices will be outlined which are useful for inference in linear models. Special focus is on block matrices having Kronecker structure since they arise in many applications for modelling spatio-temporal data.

Key words: Block matrix; Toeplitz matrix; eigenvalues; inverse of the matrix.

1 Introduction

Matrices play an important role in statistics and in many other disciplines (e.g. data mining, bioinformatics, engineering). In statistical applications, the first step is to represent available data in a matrix form, which substantially simplifies data manipulations and use of statistical software for the data analysis. In many areas of statistics, it has become a routine to use matrix algebra in the presentation and the derivation of results. In particular, in linear statistical models and multivariate analysis, a knowledge of matrix algebra is of utmost importance for exploring complex interrelations among variables.

There is a number of special matrices, such as symmetric, banded and orthogonal matrices, which are routinely used in statistics (Harville, 1997; Bradley and Meek, 1986). Patterned matrices are of special interest in statistics (Olkin and Press, 1969; Reinsel, 1982; Kim and Zimmerman, 2012) and

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statistical applications (Viana and Olkin, 2000), since they yield parsimonious modelling of dependence structures arising in various applications (e.g. medicine, economy, signal processing). For example,

$$CS = \begin{pmatrix} \tau_1 & \tau_2 & \tau_2 & \tau_2 \\ \tau_2 & \tau_1 & \tau_2 & \tau_2 \\ \tau_2 & \tau_2 & \tau_1 & \tau_2 \\ \tau_2 & \tau_2 & \tau_2 & \tau_1 \end{pmatrix}, \qquad T = \begin{pmatrix} \tau_1 & \tau_2 & \tau_3 & \tau_2 \\ \tau_2 & \tau_1 & \tau_2 & \tau_3 \\ \tau_3 & \tau_2 & \tau_1 & \tau_2 \\ \tau_2 & \tau_3 & \tau_2 & \tau_1 \end{pmatrix},$$

compound symmetry matrix — symmetric circular Toeplitz matrix

The block-matrices are of utmost importance when complex real-life phenomena should be modelled. Nowadays, the structures involving the Kronecker product of patterned matrices have become a standard option for data analysts. For example, $\mathbf{I} \otimes \mathbf{I}$, $\mathbf{I} \otimes \mathbf{\Sigma}$, and $\mathbf{\Psi} \otimes \mathbf{\Sigma}$.

In the next sections, we focus on two specific patterns, compound and circular symmetry which are described by compound symmetry and symmetric circular Toeplitz matrices, respectively.

2 Block CS-Matrix

The compound symmetry matrices (CS-matrices) are widely used in statistics and various applications (e.g. for split-plot designs). Hence, its properties including spectrum and the inverse are well-studied (Searle, 1982). We consider a block CS-matrix which can be used for example for modelling equicorrelated hierarchical data (Roy et al., 2015). Let us define the following matrix

$$\mathbf{J}_{n_i}^{\nu_i} = \begin{cases} \mathbf{I}_{n_i}, \text{ if } \nu_i = 0, \\ \mathbf{J}_{n_i}, \text{ if } \nu_i = 1, \end{cases}$$

where $\mathbf{I}_{n_i}$ is the identity matrix of order n_i, $\mathbf{J}_{n_i}$ is an $n_i \times n_i$ matrix with all elements equal to 1, $i = 1, \ldots, s$.

The covariance matrix $\mathbf{\Sigma}_s$, also called s-exchangeable, has the following structure (Searle and Henderson, 1979):

$$\mathbf{\Sigma}_s = \sum_{\nu_s=0}^{1} \cdots \sum_{\nu_1=0}^{1} c_{\nu_s \ldots \nu_2 \nu_1} \mathbf{J}_{n_s}^{\nu_s} \otimes \cdots \otimes \mathbf{J}_{n_2}^{\nu_2} \otimes \mathbf{J}_{n_1}^{\nu_1}, \tag{1}$$

where $c_{\nu_s \ldots \nu_2 \nu_1}$ are constants. Note that $\mathbf{\Sigma}_s$ completely defined by 2^s elements.

The covariance matrix $\mathbf{\Sigma}_s$ given by (1) can be also written in a recursive form (Nahtman, 2006) which highlights its block structure:

$$\mathbf{\Sigma}_s = \mathbf{I}_{n_s} \otimes \mathbf{\Sigma}_{s-1}^{(1)} + (\mathbf{J}_{n_s} - \mathbf{I}_{n_s}) \otimes \mathbf{\Sigma}_{s-1}^{(2)},$$

where, for $h = 1, \ldots, 2^s$,

$$\begin{aligned} \mathbf{\Sigma}_0^{(i_h)} &= \tau_h, \\ \mathbf{\Sigma}_k^{(i_k)} &= \mathbf{I}_{n_k} \otimes \mathbf{\Sigma}_{k-1}^{(2i_k-1)} + (\mathbf{J}_{n_k} - \mathbf{I}_{n_k}) \otimes \mathbf{\Sigma}_{k-1}^{(2i_k)}, \\ i_k &= 1, \ldots, 2^{s-k},\ k = 1, \ldots, s-1, \end{aligned}$$

and the constants τ_h are covariances between the components of the corresponding random vector.

As an example, we can consider the covariance matrices of random factors with exchangeable levels representing main and interaction effects, respectively:

$$\begin{aligned} \mathbf{\Sigma}_1 &= \mathbf{I}_{n_1}\tau_1 + (\mathbf{J}_{n_1} - \mathbf{I}_{n_1})\tau_2, \\ \mathbf{\Sigma}_2 &= \mathbf{I}_{n_2} \otimes (\mathbf{I}_{n_1}\tau_1 + (\mathbf{J}_{n_1} - \mathbf{I}_{n_1})\tau_2) + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes (\mathbf{I}_{n_1}\tau_3 + (\mathbf{J}_{n_1} - \mathbf{I}_{n_1})\tau_3). \end{aligned}$$

3 Block SC-Toeplitz Matrix

Symmetric circular Toeplitz matrices (SC-Toeplitz matrices) often arise in various research fields as statistics, econometrics, engineering, seismology, biology, and it is of interest to explore their special structure and properties. For example, image restoration applications often yield least squares problems with large, structured matrices. These matrices are usually banded block Toeplitz matrices with Toeplitz blocks. Moreover, they also can be expressed as the sum of the Kronecker products of such matrices (see e.g. Kamm and Nagy, 2000; Wirfält and Jansson, 2014).

Recall that an $n \times n$ matrix $\mathbf{T}$ of the form

$$\mathbf{T} = \begin{pmatrix} t_1 & t_2 & t_3 & \cdots & t_n \\ t_n & t_1 & t_2 & \cdots & t_{n-1} \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ t_2 & t_3 & t_4 & \cdots & t_1 \end{pmatrix} \equiv \mathrm{Toep}(t_1, t_2, t_3, \ldots, t_n)$$

with $t_j = t_{n-j+2}$, $j = 2, \ldots, n$, is called a SC-Toeplitz matrix. The matrix $\mathbf{T}$ depends on $[n/2] + 1$ parameters, here $[\bullet]$ stands for the integer part.

Let us define a SC-matrix, $\mathbf{SC}(n,k)$, of size n as follows:

$$(\mathbf{SC}(n,k))_{ij} = \begin{cases} 1, & \text{if } |i-j| = k \text{ or } |i-j| = n-k, \\ 0, & \text{otherwise,} \end{cases},$$

where $k = 1, \ldots, [n/2]$. Furthermore,

$$\mathbf{SC}(n,k) = \text{Toep}(\overbrace{\underbrace{0,\ldots,0}_{k},1,0,\ldots,0,1,\underbrace{0,\ldots,0}_{k-1}}^{n}).$$

For notational convenience denote $\mathbf{SC}(n,0) = I_n$.

Notice that matrices $\mathbf{SC}(n,0), \mathbf{SC}(n,1), \ldots, \mathbf{SC}(n,[n/2])$ are linearly independent and they commute. Furthermore, it is easy to see that

$$\text{Toep}(t_1, t_2, t_3, \ldots, t_2) = \sum_{i=0}^{[n/2]} t_{i+1}\mathbf{SC}(n,i)$$

.

Block SC-Toeplitz matrix is defined in a similar way:

$$\mathbf{\Sigma}_T = \begin{pmatrix} \mathbf{T}_1 & \mathbf{T}_2 & \mathbf{T}_3 & \cdots & \mathbf{T}_{n_1} \\ \mathbf{T}_{n_1} & \mathbf{T}_1 & \mathbf{T}_2 & \cdots & \mathbf{T}_{n_1-1} \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ \mathbf{T}_2 & \mathbf{T}_3 & \mathbf{T}_4 & \cdots & \mathbf{T}_1 \end{pmatrix} \equiv \text{Toep}(\mathbf{T}_1, \mathbf{T}_2, \mathbf{T}_3, \ldots, \mathbf{T}_{n_1}), \quad (2)$$

where $\mathbf{T}_i$ is a SC-Toeplitz matrix with $[n_2/2]+1$ parameters, $i = 1, \ldots, n_1$, and $\mathbf{T}_j = \mathbf{T}_{n_1-j+2}$, $j = 2, \ldots, n_1$. Hence, the matrix $\mathbf{\Sigma}_T$ is defined by $([n_1/2]+1)([n_2/2]+1)$ parameters.

Any block SC-Toeplitz matrix can be represented using SC-matrices.

Theorem. The covariance matrix $\mathbf{\Sigma}_T$ with the structure defined in (2) can be represented as

$$\mathbf{\Sigma}_T = \sum_{k_s=0}^{[n_s/2]} \cdots \sum_{k_1=0}^{[n_1/2]} \tau_k \mathbf{SC}(n_s,k_s) \otimes \cdots \otimes \mathbf{SC}(n_1,k_1),$$

where τ_k are constants, $k = 1$ for $s = 1$, and otherwise,

$$k = \sum_{h=2}^{s} \prod_{i=1}^{h-1} ([\frac{n_i}{2}]+1)k_h + k_1.$$

The following recursive structure of $\mathbf{\Sigma}_T$ can be used for obtaining its eigenvalues using the information about its blocks (Nahtman and von Rosen, 2008):

$$\mathbf{\Sigma}_T = \sum_{i=0}^{[n_s/2]} \mathbf{SC}(n_s, i) \otimes \mathbf{T}_{i,s-1}, \tag{3}$$

where

$$\begin{aligned} \mathbf{T}_{k,j} &= \sum_{i=0}^{[n_j/2]} \mathbf{SC}(n_j, i) \otimes \mathbf{T}_{k([n_j/2]+1)+i,j-1}, \\ \mathbf{T}_{l,0} &= \tau_l, \end{aligned}$$

$k = 0, \ldots, [n_{j+1}/2]$, $j = 1, \ldots, s-1$, $l = 0, \ldots, \prod_{i=1}^{s}([n_i/2]+1) - 1$.

4 Spectral Properties of Block CS-Matrix and Block SC-Toeplitz Matrix

Since patterned covariance matrices occur frequently in statistical modelling, it is useful to review some of their spectral properties which are used, for example, in estimation and hypotheses testing.

We start with the block CS-matrix $\mathbf{\Sigma}_s = \mathbf{I}_{n_s} \otimes \mathbf{\Sigma}_{s-1}^{(1)} + (\mathbf{J}_{n_s} - \mathbf{I}_{n_s}) \otimes \mathbf{\Sigma}_{s-1}^{(2)}$. Let $\lambda_i^{(1)}$ and $\lambda_i^{(2)}$ be eigenvalues of CS-matrices $\mathbf{\Sigma}_{s-1}^{(1)}$ and $\mathbf{\Sigma}_{s-1}^{(2)}$, respectively, $i = 1, \ldots, r$, and $r = n_1 \cdot \ldots \cdot n_{s-1}$.

Theorem (Nahtman, 2006). The spectrum of $\mathbf{\Sigma}_s$ comprises eigenvalues of the form (i) $\lambda_i^{(1)} + (n_s - 1)\lambda_i^{(2)}$, each of multiplicity 1, and (ii) $\lambda_i^{(1)} - \lambda_i^{(2)}$, each of multiplicity $n_s - 1$.

In order to describe the spectrum of a block SC-Toeplitz matrix, we recall that the eigenvalues of $\mathbf{T} = \mathrm{Toep}(t_1, t_2, \ldots, t_n)$ are given by

$$\lambda_k = \sum_{j=1}^{n} t_j \cos\left(\frac{2\pi}{n}(k-1)(n-j+1)\right),$$

where $\lambda_i = \lambda_{n-i+2}$, $k = 1, \ldots, n$.

The corresponding eigenvectors $\boldsymbol{w}^1, \ldots, \boldsymbol{w}^n$ are the following

$$w_j^k = \frac{1}{n}[\cos(2\pi(j-1)(k-1)/n) + \sin(2\pi(j-1)(k-1)/n)].$$

It is worth noting that the eigenvectors $\boldsymbol{w}^1, \ldots, \boldsymbol{w}^n$ are independent of $\mathbf{T}$ elements. Moreover, let $\mathbf{W} = (\boldsymbol{w}^1, \ldots, \boldsymbol{w}^n)$, with $\boldsymbol{w}^k = (w_1^k, \ldots, w_n^k)^{\mathrm{T}}$, $k = 1, \ldots, n$. Then $\mathbf{W}\mathbf{W}^{\mathrm{T}} = \mathbf{I}_n$ and $\mathbf{1}_n^{\mathrm{T}}\mathbf{W} = (\sqrt{n}, 0, \ldots, 0)$.

Next, we consider a special case of $\boldsymbol{\Sigma}_T$ defined in (3), namely,

$$\boldsymbol{\Sigma}_{T,2} = \sum_{k_2=0}^{[n_2/2]} \mathbf{SC}(n_2, k_2) \otimes \boldsymbol{\Sigma}_{k_1}, \tag{4}$$

where $\boldsymbol{\Sigma}_{k_1} = \sum_{k_1=0}^{[n_1/2]} \tau_k \mathbf{SC}(n_1, k_1)$, $k = k_2([n_1/2]+1) + k_1 + 1$. Observe, that it is straightforward to get the eigenvalues for a general case when treating $\boldsymbol{\Sigma}_{k_1}$ as a block SC-Toeplitz matrix.

Theorem. Let $\lambda_i^{(k_1)}$ be the distinct eigenvalues of block $\boldsymbol{\Sigma}_{k_1}$ in (4) of multiplicities m_i, $i = 1, \ldots, [n_2/2]+1$, $k_1 = 0, \ldots, [n_1/2]$. The eigenvalues of $\boldsymbol{\Sigma}_2$ are as follows.
If n_1 is odd,

$$\lambda_{h,i} = \lambda_i^{(0)} + 2\sum_{k_1=1}^{[n_1/2]} \lambda_i^{(k_1)} \cos(2\pi h k_1/n_1), h = 1, \ldots, n_1.$$

The multiplicity of $\lambda_{n_1,i}$ is m_i, all other eigenvalues are of multiplicity $2m_i$.

If n_1 is even,

$$\lambda_{h,i} = \lambda_i^{(0)} + 2\sum_{k_1=1}^{n_1/2-1} \lambda_i^{(k_1)} \cos(2\pi h k_1/n_1) + \lambda_i^{(n_1/2)} \cos(\pi h), h = 1, \ldots, n_1.$$

The eigenvalues $\lambda_{n_1,i}$ and $\lambda_{n_1/2,i}$ are of multiplicity m_i, all other eigenvalues are of multiplicity $2m_i$.

In general case, we can state the following result (Nahtman and von Rosen, 2008).

Theorem. Let $\boldsymbol{\Lambda}(n_h, k_h)$ be a diagonal matrix with the eigenvalues of $\mathbf{SC}(n_h, k_h)$, $h = 0, \ldots, [n_h/2]$, on the main diagonal. Let $\boldsymbol{\Lambda}_s$ be a diagonal matrix with the eigenvalues of $\boldsymbol{\Sigma}_s$ on the main diagonal. Then

$$\boldsymbol{\Lambda}_s = \sum_{k_s=0}^{[n_s/2]} \cdots \sum_{k_1=0}^{[n_1/2]} \tau_k \boldsymbol{\Lambda}(n_s, k_s) \otimes \cdots \otimes \boldsymbol{\Lambda}(n_1, k_1),$$

where τ_k are constants with k defined above.

5 Patterned Matrices in Linear Models

The statistical interest towards using patterned covariance structures in normal linear models has been large over the years due to demand for better modelling and hence understanding the dependence structure of the data, often large and complex, arising in different applications including medicine, biology, psychology and education.

Let $\boldsymbol{y}_1, \ldots, \boldsymbol{y}_n$ be a random sample from $N_p(\mathbf{1}_{n_2} \otimes \boldsymbol{\mu}, \boldsymbol{\Sigma})$, where $\boldsymbol{\mu} : n_1 \times 1$ is an unknown mean vector, $p = n_2 n_1$, and $\mathbf{Y} = (\boldsymbol{y}_1, \ldots, \boldsymbol{y}_n)$. Hence,

$$\mathbf{Y} \sim N_{p,n}((\mathbf{1}_{n_2} \otimes \boldsymbol{\mu})\mathbf{1}_n^{\mathrm{T}}, \boldsymbol{\Sigma}, \mathbf{I}_n),$$

where $N_{p,n}((\mathbf{1}_{n_2} \otimes \boldsymbol{\mu})\mathbf{1}_n^{\mathrm{T}}, \boldsymbol{\Sigma}, \mathbf{I}_n)$ denotes the $p \times n$ matrix normal distribution with mean matrix $(\mathbf{1}_{n_2} \otimes \boldsymbol{\mu})\mathbf{1}_n'$ and $\boldsymbol{\Sigma} : p \times p$ the covariance matrix between rows of $\mathbf{Y}$.
For the following linear model, which could be used for modelling hierarchical data structures,

$$\boldsymbol{y}_i = \mu \mathbf{1}_p + \mathbf{Z}_1 \boldsymbol{\gamma}_1 + \mathbf{Z}_2 \boldsymbol{\gamma}_2 + \boldsymbol{\epsilon},$$

where $\boldsymbol{y}_i \sim N_p(\mu \mathbf{1}_p, \boldsymbol{\Sigma})$, $\boldsymbol{\Sigma} = \mathbf{Z}_1 \mathbf{V}_1 \mathbf{Z}_1^{\mathrm{T}} + \mathbf{V}_2 + \sigma^2 \mathbf{I}_p$, $\mathbf{Z}_1 = \mathbf{I}_{n_2} \otimes \mathbf{1}_{n_1}$ and $\mathbf{Z}_2 = \mathbf{I}_{n_2} \otimes \mathbf{I}_{n_1}$, the following three specific covariance matrices, denoted by $\boldsymbol{\Sigma}_1$, $\boldsymbol{\Sigma}_2$ and $\boldsymbol{\Sigma}_3$, are of interest:

- $\boldsymbol{\Sigma}_1 = \mathbf{I}_{n_2} \otimes \boldsymbol{\Sigma}^{(1)} + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes \boldsymbol{\Sigma}^{(2)}$,
  $\boldsymbol{\Sigma}^{(i)} : n_1 \times n_1$ is an unstructured matrix, $i = 1, 2$.
- $\boldsymbol{\Sigma}_2 = \mathbf{I}_{n_2} \otimes \boldsymbol{\Sigma}^{(1)} + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes \boldsymbol{\Sigma}^{(2)}$,
  $\boldsymbol{\Sigma}^{(i)} : n_1 \times n_1$ is a SC-Toeplitz matrix, $i = 1, 2$.
- $\boldsymbol{\Sigma}_3 = \mathbf{I}_{n_2} \otimes \boldsymbol{\Sigma}^{(1)} + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes \boldsymbol{\Sigma}^{(2)}$,
  $\boldsymbol{\Sigma}^{(i)} : n_1 \times n_1$ is a CS-matrix, $i = 1, 2$.

The number of unknown variance-covariance parameters in $\boldsymbol{\Sigma}_1$, $\boldsymbol{\Sigma}_2$ and $\boldsymbol{\Sigma}_3$ are $n_1(n_1+1)$, $2([n_1/2]+1)$ and 4, respectively. We shall focus on the covariance matrix (see e.g. Olkin, 1973; Liang et al., 2012, 2015)

$$\boldsymbol{\Sigma}_2 = \mathbf{I}_{n_2} \otimes \boldsymbol{\Sigma}^{(1)} + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes \boldsymbol{\Sigma}^{(2)},$$

where $\boldsymbol{\Sigma}^{(1)}$ and $\boldsymbol{\Sigma}^{(2)}$ are SC-Toeplitz matrices.

The spectral properties of the matrix Σ_2 are stated in the following theorem.

Theorem. Let $\lambda_1^{(i)}, \ldots, \lambda_{n_1}^{(i)}$ be the eigenvalues of a SC-Toepliz matrix $\mathbf{\Sigma}^{(i)}$ of order n_1, $i = 1, 2$. Then $\mathbf{\Sigma}_2$ has the eigenvalues of the following form

$$\begin{aligned} \lambda_{1h} &= \lambda_h^{(1)} + (n_2 - 1)\lambda_h^{(2)}, \\ \lambda_{2h} &= \lambda_h^{(1)} - \lambda_h^{(2)}, \end{aligned}$$

where $h = 1, \ldots, n_1$.

Furthermore, if n_1 is odd, the multiplicity of λ_{i1} is $(n_2 - 1)^{i-1}$, the eigenvalues $\lambda_{i2}, \ldots, \lambda_{in_1}$ are of the multiplicity $2(n_2 - 1)^{i-1}$, $i = 1, 2$. If n_1 is even, the multiplicities of both λ_{i1} and $\lambda_{i\frac{n_1}{2}}$ are $(n_2 - 1)^{i-1}$ and other eigenvalues $\lambda_{i2}, \ldots, \lambda_{in_1}$ are of the multiplicity $2(n_2 - 1)^{i-1}$, $i = 1, 2$. The number of distinct eigenvalues for $\mathbf{\Sigma}_2$ is $2([n_1/2] + 1)$.
The eigenvectors $\boldsymbol{v}_1^1 \ldots, \boldsymbol{v}_1^{n_1}, \boldsymbol{v}_2^1, \ldots, \boldsymbol{v}_2^{n_1(n_2-1)}$ corresponding to λ_{kh}, are of the following form

$$\boldsymbol{v}_k^i = \boldsymbol{w}_2^{h_2} \otimes \boldsymbol{w}_1^{h_1},$$

where the vectors $\boldsymbol{w}_2^{h_2}$ and $\boldsymbol{w}_1^{h_1}$ are the eigenvectors of CS-matrix and SC-Toeplitz matrix, correspondingly, $k = 1, 2$.

6 On the Inverse of Block Patterned Matrices

There are many statistical problems where the inverse of a matrix is needed. Moreover, in other disciplines the inverse matrices can be of interest in their own right.

It is worth noting that the structure of CS and SC-Toeplitz matrices carries over to their inverses. Foe example, the inverse of CS-matrix

$$\mathbf{\Sigma}_s = \sum_{\nu_s=0}^{1} \cdots \sum_{\nu_1=0}^{1} c_{\nu_s \ldots \nu_2 \nu_1} \mathbf{J}_{n_s}^{\nu_s} \otimes \cdots \otimes \mathbf{J}_{n_2}^{\nu_2} \otimes \mathbf{J}_{n_1}^{\nu_1}$$

can be presented in the following form (Searle and Henderson, 1979):

$$\mathbf{\Sigma}_s^{-1} = \sum_{\nu_s=0}^{1} \cdots \sum_{\nu_1=0}^{1} d_{\nu_s \ldots \nu_2 \nu_1} \mathbf{J}_{n_s}^{\nu_s} \otimes \cdots \otimes \mathbf{J}_{n_2}^{\nu_2} \otimes \mathbf{J}_{n_1}^{\nu_1},$$

where

$$\begin{pmatrix} d_{00\ldots0} \\ \vdots \\ d_{11\ldots1} \end{pmatrix} = \bigotimes_{i=s}^{1} \begin{pmatrix} 1 & 0 \\ -\frac{1}{n_i} & \frac{1}{n_i} \end{pmatrix} \begin{pmatrix} \lambda_{00\ldots0}^{-1} \\ \vdots \\ \lambda_{ss-1\ldots1}^{-1} \end{pmatrix},$$

and $\lambda_{\alpha_s \ldots \alpha_2 \alpha_1}$'s are the distinct eigenvalues of $\mathbf{\Sigma}_s$ (for details, see Nahtman, 2006). Furthermore,

$$\begin{pmatrix} \lambda_{00\ldots0} \\ \vdots \\ \lambda_{11\ldots1} \end{pmatrix} = \bigotimes_{i=s}^{1} \begin{pmatrix} 1 & 0 \\ 1 & n_i \end{pmatrix} \begin{pmatrix} c_{00\ldots0} \\ \vdots \\ c_{ss-1\ldots1} \end{pmatrix}.$$

In general, one can use the block structure of $\mathbf{\Sigma}_h = \mathbf{I}_{n_2} \otimes \mathbf{\Sigma}^{(1)} + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes \mathbf{\Sigma}^{(2)}$, $h = 1, 2, 3$, as defined in Section 5 in order to invert it.

Then, noting that the structure of $\mathbf{\Sigma}_h$ is carried over to its inverse, we have (assuming that the corresponding inverses exist):

$$\mathbf{\Sigma}_2^{-1} = \mathbf{I}_{n_2} \otimes \mathbf{\Sigma}_{1,1}^{-1} + (\mathbf{J}_{n_2} - \mathbf{I}_{n_2}) \otimes \mathbf{\Sigma}_{1,2}^{-1},$$

where

$$\begin{aligned} \mathbf{\Sigma}_{1,1}^{-1} &= \mathbf{\Sigma}_{1,2}^{-1} + (\mathbf{\Sigma}_1^{(1)} - \mathbf{\Sigma}_1^{(2)})^{-1}, \\ \mathbf{\Sigma}_{1,2}^{-1} &= -(\mathbf{\Sigma}_1^{(1)} + 2\mathbf{\Sigma}_1^{(2)})^{-1} \mathbf{\Sigma}_1^{(2)} (\mathbf{\Sigma}_1^{(1)} - \mathbf{\Sigma}_1^{(2)})^{-1}. \end{aligned}$$

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Central limit theorems from a teaching perspective

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Abstract

Central limit theorems and their applications constitute highlights in probability theory and statistical inference. However, as a teacher, especially in undergraduate courses, you are faced with the challenges of how to introduce the results. These challenges especially concern ways of presentation and discussion of under which conditions asymptotic (approximate) results hold. This paper attempts to present some relevant examples for possible use in the classroom.

Key words: Asymptotic theory, Cauchy distribution, Lindeberg-Lévy central limit theorem

1 Introduction

Introducing the error term in a linear regression model during a course in statistics occasionally gives rise to comments from students such as "How can we motivate the assumption of normality?". A common reply is that the error is supposed to be the aggregate of many "disturbances", i.e. a sum of many random variables and therefore we can assume that, at least, normality holds approximately. The teacher might then (rightfully) receive the follow-up question: "We have been taught that the terms should be iid in order to assume approximate normality for the sum and is it realistic to assume that here?" The teacher must then shamefully admit that the students previously have been somewhat misled to believe that there is something called THE central limit theorem, whereas in reality, there are many versions of central limit theorems. In some of them, the assumption that the terms have the same distribution is dropped, and there are also examples of limit normality results,

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where the assumption of independence is relaxed. On the other hand, there are cases where the observations are indeed iid (independent and identically distributed), but the limit distribution is not normal. Students who have taken a few courses in statistics are usually more worried about how many observations they sum than anything else. This is mostly due to rules of thumb like "the sample size 30 is usually enough".

2 Presenting a central limit theorem

Textbooks used for a first course in probability theory usually (without a proof) include the following result, known in the literature as the Lindeberg-Lévy central limit theorem:
Let $X_1, \ldots, X_n$ be iid random variables with mean μ and finite variance σ^2 and further let $S_n = \sum_{i=1}^{n} X_i$. Then

$$P\Big(\frac{S_n - n\mu}{\sqrt{n}\sigma} \leq a\Big) \to \Phi(a), \text{ as } n \to \infty, \text{for all } a \in R$$

(Note that it is understood here that μ is finite, which follows from the assumption that the variance σ^2 is finite.)
The presentation is sometimes as an approximate result rather than as an asymptotic:

$$\text{If } n \text{ is large, then } S_n \text{ is approximately } N(n\mu, n\sigma^2)$$

or equivalently

$$\text{If } n \text{ is large, then } \bar{X} = S_n/n \text{ is approximately } N(\mu, \sigma^2/n)$$

These latter ways of presenting the theorem are probably preferable if the students have poor mathematical background.
In a second course in probability theory, the Lindeberg-Lévy theorem is often presented including a proof using some type of generating function. Usually the moment generating function is the chosen tool as in e.g. Casella and Berger (2002). The authors include two versions of central limit results, where in the first it is assumed that the moment generating function exists in a neighbourhood of 0. In that case the proof is rather straightforward. Then, a "stronger form of the Central Limit Theorem" (Lindeberg-Lévy) is stated without a proof, since in that case you need the use of characteristic functions instead. It is argued that dealing with complex variables is beyond the scope of the

book. In a teaching situation you do not have much of a choice if the students are not familiar with complex numbers. However, to really appreciate the meaning of the statement about a moment generating function existing in a neighbourhood of 0 is probably rather difficult for most students. The good thing though with this assumption is that you do not need to specify that σ^2 is finite.

Inlow (2010) presents a moment generating proof involving use of Slutsky's theorem without actually requiring the existence of the moment generating function of the constituent random variables, which are assumed (absolutely) continuous. As the author comments the proof is unfortunately accessible for graduate students only.

The superior property of a characteristic function compared with a moment generating function is of course that the former always exists and the proof of this is so elegant that we should include it here!

Suppose the random variable X is continuous. (The proof is similar in the discrete case.) Its characteristic function is given by $\rho(t) = E(e^{itX})$ and $|\rho(t)| = |\int_{-\infty}^{\infty} e^{itx} f(x)\mathrm{dx}| \leq \int_{-\infty}^{\infty} |e^{itx} f(x)|\mathrm{dx}$

Now, since $|f(x)| = f(x)$ and $|e^{itX}| = |\cos tx + i\sin tx| = \sqrt{\cos^2 tx + \sin^2 tx} = 1$, we finally get that $|\rho(t)| \leq \int_{-\infty}^{\infty} f(x)\mathrm{dx} = 1$ and we are done.

3 Relaxing the iid assumption

When we deviate from iid cases, the situation naturally becomes more complicated. If we first consider a sequence of random variables which are independent, but not necessarily identically distributed, we can rely on results such as the Lindeberg-Feller central limit theorem. This theorem includes what is called the Lindeberg condition and this might be too technical for an undergraduate course, but one could mention that this condition implies that

$$\max_{i=1,\ldots,n} \frac{\sigma_i^2}{s_n^2} \to 0, \quad \text{as } n \to \infty, \tag{1}$$

where $\sigma_i^2 = \mathrm{Var}(X_i)$, $i = 1, \ldots n$ and $s_n^2 = \sum_{i=1}^n \sigma_i^2$. The interpretation is that the contribution of any individual random variable is arbitrarily small for (sufficiently) large n.

An example of where we may have use for this result is when we consider a sequence of independent Bernoulli variables $X_1, \ldots, X_n$, where $P(X_i = 1) = p_i$, $i = 1, \ldots, n$. When $p_i = p$, $i = 1, \ldots, n$, the students know that we get a binomial distribution from S_n and that we can approximate this

distribution with a normal for large n. Now, a sufficient condition for (1) is that $s_n^2 = \sum_{i=1}^n p_i(1-p_i) \to \infty$, which will be obtained if p_i is kept away from values too close to either 0 or 1.
Let us now have a look at the independence part of the iid assumption. If the students are familiar with time series modelling the following simple moving average type of situation may illustrate the case of nonindependent random variables: Let

$$X_i = Z_i + Z_{i-1}, \quad i = 1, 2, \ldots,$$

where Z_0, Z_1, Z_2,... are iid with a common finite variance. Clearly X_1, X_2,... is not a sequence of independent variables, so what can we say about the distribution of S_n for large n? The simple trick is to rewrite S_n as

$$S_n = Z_0 + Z_n + 2\sum_{i=1}^{n-1} Z_i \tag{2}$$

The Lindeberg-Lévy theorem can be applied to the last sum of (2) and it can further be shown formally that Z_0 and Z_n are asymptotically negligible and we can therefore conclude that S_n is approximately normally distributed for large n.

4 Counter examples

Probably the most famous counter example of an iid situation where a central limit theorem does not apply is when X_i is Cauchy(θ_1, θ_2), $i = 1, \ldots, n$ (also named the Lorentz distribution by physicists). The pdf is

$$f(x) = \frac{\theta_2}{\pi(\theta_2^2 + (x-\theta_1)^2)} \quad -\infty < x < \infty,\ \theta_2 > 0$$

This density function looks innocent enough, being symmetric around θ_1, but as is well-known, the mean μ and the variance σ^2 do not exist. A natural and interesting case is when we put $\theta_1 = 0$ and $\theta_2 = 1$. A student might then be tempted to draw the conclusion that the mean really is 0 using the following (wrong) argument: $E(X) = \lim_{a\to\infty} \frac{1}{\pi}\int_{-a}^{a} \frac{x}{1+x^2}\mathrm{dx} = \lim_{a\to\infty} \frac{1}{2\pi}[\ln(1+x^2)]_{-a}^{a} = 0$, thereby not following the rules of generalized integrals. As pointed out by e.g. Casella and Berger (2002), we should first check if $E(|X|) < \infty$, which does not hold here.
So can we instead determine the distribution of some function of S_n in the general case of $X \sim$ Cauchy(θ_1, θ_2)? As it turns out, S_n/n has also a Cauchy

distribution. To prove this we cannot use the moment generating function for X, since it does not exist, but instead the characteristic function $\rho(t)$ is of help. If X is Cauchy(θ_1, θ_2), then $\rho(t) = e^{\theta_1 it - \theta_2|t|}$ and the characteristic function for S_n/n is $(\rho(t/n))^n = (e^{\theta_1 \frac{it}{n} - \theta_2|\frac{t}{n}|})^n = \rho(t)$! So, in a trivial sense S_n/n converges to a Cauchy(θ_1, θ_2).
A student may at this stage comment that this distribution seems extreme and therefore not realistic. Thus it is good to be able to point out a few situations where the Cauchy distribution turns up. The most well-known is probably where we look at the ratio $Y = Z_1/Z_2$, where Z_1 and Z_2 are $N(0,1)$ and independent. Y is then Cauchy(0,1) and if we first confront a student with the ratio, he/she will probably sense that there might be a problem with the denominator, since there is a substantial probability that it will attain a value close to 0. A second example is related to physics. If we have a ray at an angle γ which has a uniform distribution, then $\tan(\gamma)$ has a Cauchy distribution. A third example is related to statistical inference, since a Cauchy$(0,1)$ distribution is the same as a t-distribution with one degree of freedom.
Before leaving the Cauchy distribution it is worth telling the students that besides the obvious observation that θ_1 is the median, the scale parameter θ_2 is $(q_3 - q_1)/2$ (half the interquartile range).
If a student finds the Cauchy distribution somewhat extreme, then probably the following member of the inverse-gamma family of densities will be regarded as ballistic. Suppose that X has density

$$f(x) = \frac{1}{\sqrt{2\pi x^3}} e^{-\frac{1}{2x}}, \quad x > 0 \tag{3}$$

The mean and variance do not exist, so we cannot apply a central limit theorem to an iid sequence $X_1, \ldots, X_n$. However, it holds that $\bar{X}$ has the same distribution as nX_1. This has the quite amazing effect that $\bar{X}$ has more variability (we have to be careful about not using the word variance here!) than one single variable X_1.
Also it is worth pointing out that the distribution given by the density (3) is not pathologic, since it can be used for e.g. modelling first passsage times in a one-dimensional Brownian motion.
These two examples (and more) of situations where a central limit theorem cannot be applied, are to be found in Bagui et al. (2013).

5 Summary

When teaching central limit theorem results, it is desirable to discuss other issues than mere sample sizes to make students aware of at least something of the involved complexity. Having done that hopefully facilitates understanding of when and how to apply central limit theorems in real world situations.

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The Analysis of Covariance using R and SAS : A Few Surprises

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Abstract

The analysis of covariance (ANCOVA) using R (Crawley, 2013) may give different values than that of SAS (Littell et al., 2002) for certain important components of the outcomes. Their similarities and differences are investigated and explained with the anorexia data (Tamhane, 2009).

Key words: ANCOVA, Model Comparisons, R, SAS

1 Prelude

With great pleasure, pride, and admiration, I dedicate this article in honor of Professor Hans Nyquist on his 65th birthday. His friendship, kindness, and scientific collaboration are valuable treasures in my life. During this celebration of his fundamental contributions in the general area of Statistics, wishing Hans and his family members all the happiness, health, prosperity and peace now as well as years to come.

2 ANCOVA using R and SAS

A completely randomized experiment was performed to compare three treatment therapies: control, behavioral, and family, for treating anorexia patients to recover from their loosing weights (Tamhane (2009)). The patients were randomly assigned to three treatment therapies. The response variable y was the weight gain (lb) after therapies and an observed covariate x was baseline weight prior to starting therapies. The data are given in Table 1 for 51 patients: 17 patients for each of three treatment therapies. Denote the

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Table 1: Data on $(x_{ij},\ y_{ij})$, $i = 1, 2, 3,\ j = 1, ..., 17$

Patient	Control	Behavioral	Family
	$i = 1$	$i = 2$	$i = 3$
j	$(x,\ y)$	$(x,\ y)$	$(x,\ y)$
1	(80.7, -0.5)	(80.5, 1.7)	(83.8, 11.4)
2	(89.4, -9.3)	(84.9, 0.7)	(83.3, 11.0)
3	(91.8, -5.4)	(81.5, -0.1)	(86.0, 5.5)
4	(74.0, 12.3)	(82.6, -0.7)	(82.5, 9.4)
5	(78.1, -2.0)	(79.9, -3.5)	(86.7, 13.6)
6	(88.3,-10.2)	(88.7, 14.9)	(79.6, -2.9)
7	(87.3,-12.2)	(94.9, 3.5)	(76.9, -0.1)
8	(75.1, 11.6)	(76.3, 17.1)	(94.2, 7.4)
9	(80.6, -7.1)	(81.0, -7.6)	(73.4, 21.5)
10	(78.4, 6.2)	(80.5, 1.6)	(80.5, -5.3)
11	(77.6, -0.2)	(85.0, 11.7)	(81.6, -3.8)
12	(88.7, -9.2)	(89.2, 6.1)	(82.1, 13.4)
13	(81.3, 8.3)	(81.3, 1.1)	(77.6, 13.1)
14	(78.1, 3.3)	(76.5, -4.0)	(83.5, 9.0)
15	(70.5, 11.3)	(70.0, 20.9)	(89.9, 3.9)
16	(77.3, 0.0)	(80.4, -9.1)	(86.0, 5.7)
17	(85.2, -1.0)	(83.3, 2.1)	(87.3, 10.7)

data $(x,\ y)$ for the j^{th} patient under the i^{th} treatment therapy by $(x_{ij},\ y_{ij})$, $j = 1, ..., 17,\ i = 1, 2, 3$.

Consider the model M_1 for describing the data in Table 1 under the assumptions that y_{ij}, $i = 1, 2, 3,\ j = 1, ..., 17$, are independently normally distributed as

$$M_1 : y_{ij} \sim N(\beta_0 + \beta_1 x_{ij} + \beta_2 x_{ij}^2 + \gamma_{0i} + \gamma_{1i} x_{ij}, \sigma^2), \tag{1}$$

where the parameters β_0, β_1, β_2, γ_{0i}, γ_{1i} , and σ^2 are unknown.

Table 2: Type I − ANOVA for M_1

Source	DF	Sum Sq	Mean Sq	F value	P value
Treatment	2	479.30	239.65	5.45	0.0077
Covariate	1	391.65	391.65	8.91	0.0046
Sq. Covariate	1	451.15	451.15	10.27	0.0025
Treatment x Covariate	2	214.75	107.38	2.44	0.0985
Residual/Error	44	1933.10	43.93		
Total	50	3469.95			

Table 3: Type II and Type III Analyses for Models M_1 in R and SAS

Program	Source	DF	Type II		Type III	
			Sum Sq	P value	Sum Sq	P value
SAS	Treatment	2	**174.02**	0.1501	174.02	0.1501
R			**728.17**	0.0009	174.02	0.1501
SAS	Covariate	1	488.63	0.0017	**366.13**	0.0060
R			488.63	0.0017	**346.71**	0.0074
SAS, R	Sq. Covariate	1	338.36	0.0081	338.36	0.0081
SAS, R	Treatment x Covariate	2	214.75	0.0985	214.75	0.0985

Type I, Type II, and Type III analyses are now performed for the data in Table 1. Type I analysis in Table 2 gives the same output for SAS and R. However, a few components in Type II and Type III analyses are different in their output. Table 3 summarizes their similarities and differences.

3 Figuring out the Differences and Similarities in R and SAS

The Sums of Squares Residual/Error are identical for Types I, II, and III analyses under a model M_w and their common value is denoted by SSE_w.

Define $z_{1ij} = 1$ for i = 1 and $z_{1ij} = 0$ for i = 2 and 3, $z_{3ij} = 1$ for i = 3 and $z_{3ij} = 0$ for i = 1 and 2. Introducing now the models below so that y_{ij}, $i = 1, 2, 3$, $j = 1, ..., 17$, are independently

$$\begin{cases} M_{1.1} : N(\beta_0 + \beta_1 x_{ij} + \beta_2 x_{ij}^2 + \gamma_{1i} x_{ij}, \sigma^2), \\ M_{1.2} : N(\beta_0 + \beta_2 x_{ij}^2 + \gamma_{0i} + \gamma_{1i} x_{ij}, \sigma^2), \\ M_{1.2}^* : N(\beta_0 + \beta_2 x_{ij}^2 + \gamma_{01} z_{1ij} + \gamma_{03} z_{3ij} + \gamma_{01} z_{1ij} x_{ij} + \gamma_{03} z_{3ij} x_{ij}, \sigma^2), \\ M_{1.3} : N(\beta_0 + \beta_1 x_{ij} + \gamma_{0i} + \gamma_{1i} x_{ij}, \sigma^2), \\ M_{1.4} : N(\beta_0 + \beta_1 x_{ij} + \beta_2 x_{ij}^2 + \gamma_{0i}, \sigma^2), \\ M_2 : N(\beta_0 + \beta_1 x_{ij} + \beta_2 x_{ij}^2 + \gamma_{0i}, \sigma^2), \\ M_{2.1} : N(\beta_0 + \beta_1 x_{ij} + \beta_2 x_{ij}^2, \sigma^2), \\ M_{2.2} : N(\beta_0 + \beta_2 x_{ij}^2 + \gamma_{0i}, \sigma^2), \\ M_{2.3} : N(\beta_0 + \beta_1 x_{ij} + \gamma_{0i}, \sigma^2), \\ M_{2.3.2} : N(\beta_0 + \gamma_{0i}, \sigma^2), \\ M_{2.3.2.1} : N(\beta_0, \sigma^2), \end{cases} \tag{2}$$

As reflected in the numbering systems of the models, $M_{1.1}$, $M_{1.2}$, $M_{1.3}$ and M_2 are nested within M_1, $M_{2.2}$ and $M_{2.3}$ are nested within M_2, $M_{2.3.2}$ is nested within $M_{2.3}$, and $M_{2.3.2.1}$ is nested within $M_{2.3.2}$. The Sums of Squares Residual/Error for these models are given in Table 4. In Table 5, the Sums of Squares in Tables 2 and 3 are expressed in terms of SSE_w values. Table 5 explains why the Type II Treatment Sums of Squares in SAS and R are different for M_1 as well as why the Type III Covariate Sums of Squares in SAS and R are different for M_1.

4 Model Comparisons: M_1 Versus M_2

The least squares fitted values for the model Mw are denoted by $\widehat{y}_{ij}^{(w)}, w = 1, 2, i = 1, 2, 3, j = 1, ..., 17$. The residuals or estimated errors are $(y_{ij} - \widehat{y}_{ij}^{(w)})$ and the sums of squares of residuals (SSE_w) with degrees of freedom $(DF(E)_w)$, the mean squares of residuals (MSE_w) and the residual standard errors (RSE_w) are

Table 4: The values of $SSE(M_w)$, $w = 1, 1.1, 1.2, 1.3, 2, 2.1, 2.2, 2.3, 2.3.2, 2.3.2.1$

w	M_w	$SSE(M_w)$	DF
1	M_1	1933.10	44
1.1	$M_{1.1}$	2107.12	46
1.2	$M_{1.2}$	2299.23	45
1.2*	$M^*_{1.2}$	2279.81	45
1.3	$M_{1.3}$	2271.46	45
2	M_2	2147.82	46
2.1	$M_{2.1}$	2876.02	48
2.2	$M_{2.2}$	2636.48	47
2.3	$M_{2.3}$	2599.00	47
2.3.2	$M_{2.3.2}$	2990.65	48
2.3.2.1	$M_{2.3.2.1}$	3469.95	50

$$\begin{cases} SSE_w = \sum_{i=1}^{3} \sum_{j=1}^{17} (y_{ij} - \widehat{y}_{ij}^{(w)})^2, \\ MSE_w = SSE_w / DF(E)_w, \\ RSE_w = (MSE_w)^{1/2}. \end{cases} \tag{3}$$

Note that SSE is also notationally represented by RSS. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the model M_w are defined as

$$\begin{cases} AIC_w = n + n\ log(2\pi) + n\ log(SSE_w/n) + 2\,p_w, \\ BIC_w = n + n\ log(2\pi) + n\ log(SSE_w/n) + p_w\ log(n), \end{cases} \tag{4}$$

where n = the sample size = 51 and p_w = the number of estimated parameters in the model M_w = (51 - $DF(E)_w$) + 1. (Note that the last term 1 in p_w is represented by the parameter σ^2.) The computations in Table 6 are done by using the R program which includes the first two terms in AIC_w and BIC_w although they can be ignored without making any difference to the model comparisons. The coefficients of determination (R^2) and adjusted coefficient of determination (R^2_a) are defined for the model M_w as

Table 5: Types I, II, and III Sums of Squares under M_1
in terms of $SSE(M_w)$ values in Table 4

	Sum of Squares under M_1			
Source	Program	Type I	Type II	Type III
Treatment	SAS	479.30 $= SSE(M_{2.3.2.1})$ $-SSE(M_{2.3.2})$	**174.02** $= \mathbf{SSE}(\mathbf{M_{1.1}})$ $-\mathbf{SSE}(\mathbf{M_1})$	174.02 $= SSE(M_{1.1})$ $-SSE(M_1)$
Treatment	R	479.30 $= SSE(M_{2.3.2.1})$ $-SSE(M_{2.3.2})$	**728.17** $= \mathbf{SSE}(\mathbf{M_{2.1}})$ $-\mathbf{SSE}(\mathbf{M_2})$	174.02 $= SSE(M_{1.1})$ $-SSE(M_1)$
Covariate	SAS	391.65 $= SSE(M_{2.3.2})$ $-SSE(M_{2.3})$	488.63 $= SSE(M_{2.2})$ $-SSE(M_2)$	**366.13** $= \mathbf{SSE}(\mathbf{M_{1.2}})$ $-\mathbf{SSE}(\mathbf{M_1})$
Covariate	R	391.65 $= SSE(M_{2.3.2})$ $-SSE(M_{2.3})$	488.63 $= SSE(M_{2.2})$ $-SSE(M_2)$	**346.71** $= \mathbf{SSE}(\mathbf{M^*_{1.2}})$ $-\mathbf{SSE}(\mathbf{M_1})$
Sq. Covariate	SAS and R	451.15 $= SSE(M_{2.3})$ $-SSE(M_2)$	338.36 $= SSE(M_{1.3})$ $-SSE(M_1)$	338.36 $= SSE(M_{1.3})$ $-SSE(M_1)$
Treatment x Covariate	SAS and R	214.75 $= SSE(M_2)$ $-SSE(M_1)$	214.75 $= SSE(M_{1.4})$ $-SSE(M_1)$	214.75 $= SSE(M_{1.4})$ $-SSE(M_1)$

Table 6: SSE_w, AIC_w, BIC_w, R^2_w, R^2_{aw}, and RSE_w for $w = 1, 2$

w	p_w	SSE_w	f_w	AIC_w	BIC_w	R^2_w	R^2_{aw}	RSE_w
1	8	**1933.10**	185.39	**346.12**	361.57	**0.44**	**0.37**	**6.63**
2	6	2147.85	190.76	347.49	**359.08**	0.38	0.33	6.83

$$\begin{cases} n\bar{y} = \sum_{i=1}^{3}\sum_{j=1}^{17} y_{ij}, \\ SST = \sum_{i=1}^{3}\sum_{j=1}^{17} (y_{ij} - \bar{y})^2, \\ R^2_w = 1 - (SSE_w/SST), \\ R^2_{aw} = 1 - [(SSE_w/DF(E)_w)/(SST/(n-1))]. \end{cases} \tag{5}$$

Define $f_w = 51\, log(SSE_w/51)$, $w = 1, 2$. Table 6 presents the numerical values of SSE_w, f_w, AIC_w, BIC_w, R^2_w, R^2_{aw}, and RSE_w for $w = 1, 2$. The model M_1 is performing better than M_2 with respect to (w.r.t.) the criterion functions AIC and RSE having the smaller values indicated in bold and w.r.t. the criterion functions R^2 and R^2_a having the larger values indicated also in bold. The model M_2 is performing better over M_1 w.r.t. the criterion function BIC. Since $3.93 = log(51) > 2$, the penalty for a bigger model having a higher p value is much more under BIC than AIC. So, it is not surprising to have the AIC conclusions being different from that of BIC.

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A Structural Equation Model of Job Satisfaction, Burnout, Vigor and Depression: A Study from Turkey[1]

Nuran Bayram[2]

Abstract

Aim: The aim of the study was to investigate the relationships among job satisfaction, burnout, vigor and depression among academic staff in Turkey.

Method: The study participants ranged in age from 23 years to 67 years, approximately 53 % were female, 69 % were married. The Minnesota job satisfaction scale, the Shirom-Melamed burnout and vigor measure, and Lovibond's depression scales were used. Printed questionnaires were sent to the entire academic staff of a single academic institution and were filled out anonymously.

Results: The results were χ^2/df=2.684; GFI=0.94; CFI=0.95; RMSEA=0.07; SRMR=0.04. The goodness of fit provided evidence that the hypothesized model was stable. All estimated path coefficients were significant. 47 % of the variance in depression was explained by the direct effect of burnout, 23 % of the variance in vigor was explained by the direct effect of burnout and depression. 24 % percent of the variance in job satisfaction was explained by the direct effect of burnout, depression and vigor.

[1]The first version of this study was presented at the 5th International Academic Conference in 2013, Buenos Aires, Argentina.

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Conclusion: Structural equation model showed that burnout and depression are negatively affected by job satisfaction, that vigor are positively affected by job satisfaction, and that vigor and depression play a mediating role for burnout.

Key words: Structural Equation Model, Job Satisfaction, Burnout, Vigor, Depression

Introduction

Job satisfaction is simply how people feel about their jobs and different aspects of their jobs. Job satisfaction is a pleasurable or positive emotional state resulting from the appraisal of one's job or job experiences (Wright and Cropanzano, 2004) and it is an important issue in every work environment. Job satisfaction has emotional, cognitive and behavioral components (Bernstein and Nash, 2008). The emotional component refers to feelings regarding the job, such as boredom, anxiety, or excitement. The cognitive component of job satisfaction refers to beliefs regarding one's job, for example, feeling that one's job is mentally demanding and challenging. Finally, the behavioral component includes people's actions in relation to their work. These actions may include being tardy, staying late, or pretending to be ill in order to avoid work (Bernstein and Nash, 2008).

Emotional exhaustion, depersonalization and low personal accomplishment are the three main components of burnout syndrome (Maslach et al., 2001). Burnout has been mentioned as an effective response to ongoing work-related stress (Shirom, 2003a). The three facets of burnout are: physical fatigue, emotional exhaustion, and cognitive weariness. Physical fatigue refers to one's feelings of tiredness and low levels of energy in carrying out daily tasks at work. Emotional exhaustion refers to one's feeling too weak to display empathy to clients or coworkers. Cognitive weariness refers to one's feelings of slow thinking processes and reduced mental agility (Shirom, 2003a).

Vigor has been defined as having a high level of energy, motivation to invest effort at work, and resilience and has been accepted as a part of work engagement (Bakker and Demerouti, 2008). Vigor comprises one's feelings of possessing physical strength, emotional energy, and cognitive liveliness (Shirom, 2003b). These facets are physical strength that refers to one's physical

and empathy to significant others and cognitive liveliness that refers to one's flow of thought processes and mental agility.

The depression assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest or involvement, anhedonia and inertia (Lovibond and Lovibond, 1995). In other words, depression is characterized by low positive affect, loss of self-esteem and incentive, and a sense of hopelessness (absence of positive affect) (Brown et al., 1997).

The aim of the study was to investigate the relationships among job satisfaction, burnout, vigor and depression among academic staff in Turkey.

Method

Study participants

368 academic staff participated in the study. The study participants ranged in age from 23 years to 67 years. Printed questionnaires were sent to the entire academic staff of a single academic institution and were filled out anonymously.

Instruments

In this study four different instruments have been used to measure job satisfaction, burnout, vigor and depression.

Job satisfaction: To determine job satisfaction we used the Turkish version of the Minnesota Job Satisfaction Scale (MJSS). These 20 items evaluate two dimensions: intrinsic (Cronbach's Alpha=0.89) and extrinsic (Cronbach's Alpha=0.82). Responses are rated on a 5-point Likert scale ranging from 1 for not satisfied to 5 for very satisfied. The highest point of this scale is 100 and the lowest 20. High scores mean greater job satisfaction.

Burnout: To measure burnout we used the Turkish version of the Shirom-Melamed Burnout Measure (SMBM). This 12-item questionnaire evaluates three burnout dimensions: physical fatigue (4 items, Cronbach's Alpha=0.95),

emotional exhaustion (4 items, Cronbach's Alpha=0.91) and cognitive weariness (4 items, Cronbach's Alpha=0.91). Responses are rated on a 7-point Likert scale ranging from 1 for never to 7 for always (Melamed et al., 1999; Shirom, 2003a). High scores mean greater burnout.

Vigor: To measure vigor we used the Turkish version of the Shirom-Melamed Vigor Measure (SMVM). This 14-item questionnaire evaluates three vigor dimensions: physical strength (5 items, Cronbach's Alpha=0.91), emotional energy (4 items, Cronbach's Alpha=0.94) and cognitive liveliness (5 items, Cronbach's Alpha=0.91). All items are scored on a 7-point Likert scale ranging from 1 for never to 7 for always (Melamed et al., 1999). High scores mean greater vigor.

Depression: To measure depression we used the Turkish version of DASS-42. This 42-item instrument evaluates symptoms of depression, anxiety and stress. Each of the three scales consists of 14 items that are answered using a 0–3 scale where 0 = did not apply to me at all and 3 = applied to me very much or most of the time. In this study, we used only depression dimension (Cronbach's Alpha=0.93). High scores mean greater depression.

Data Analyses

Descriptive statistics, reliability analysis (Cronbach's alpha), and Structural equation modeling (SEM) were performed. SEM was used to show the effects of burnout, vigor and depression on job satisfaction. SEM specifies the direct and indirect effects among latent variables and is used to describe the amount of explained variance for each variable. The adequacy of the model was assessed by (1) Goodness-of-Fit Index (GFI), which shows the amount of variances and covariance explained by the model and should be greater than 0.90 for an adequate fit of the model; (2) Comparative Fit Index (CFI), which should be also greater than 0.90 for an adequate fitness; (3) Root Mean Square Error of Approximation (RMSEA), which should be below 0.05 for a good fit; and (4) Standardized Root Mean Square Residual (SRMR) which should be below 0.05 for a good fit model (Steiger, 1990; Byrne, 2001; Hoyle, 1995; Bayram, 2010).

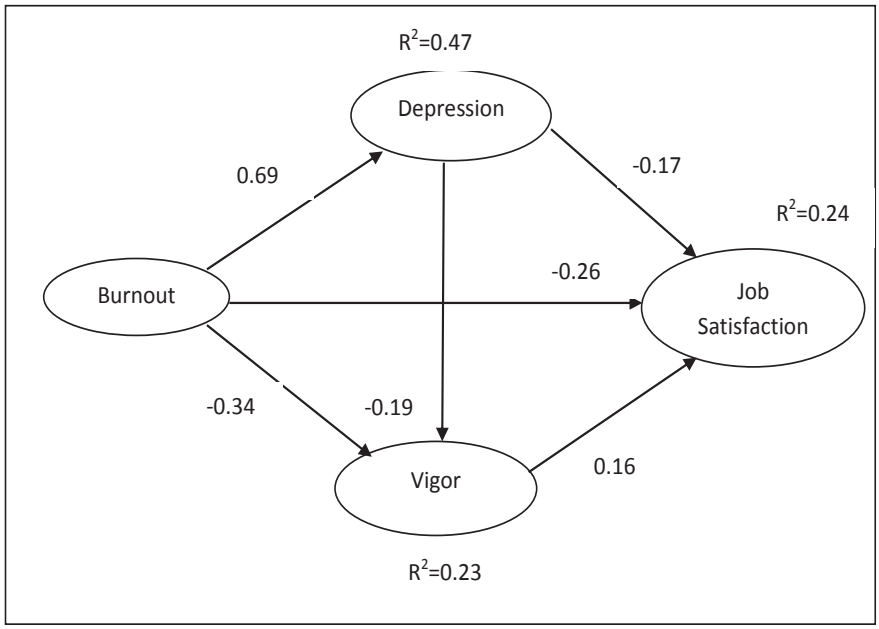

Figure 1. Structural equation model for job satisfaction

Results

Of the 368 respondents, 195 (53 %) were females and 173 (47 %) males. 42 % of the participants were professors (including associate and assistant professors), and 58 % were research fellows or residents. The mean ages of the professors and research fellows were 43.23± 0.70 (std) and 31.67± 0.32 (std) years respectively. In terms of their marital status, 31 % of the participants were single and 69 % were married.

Covariations between the error terms were allowed in this model, but these are not shown in the figure (Figure 1). The arrows in Figure 1 indicate hypothesized paths. The results were χ^2/df=2.684; GFI=0.94; CFI=0.95; RMSEA=0.07; SRMR=0.04. The goodness of fit provided evidence that the

hypothesized model was stable. To estimate the direction and magnitude of the effects among latent variables identified, a recursive SEM was fitted using the maximum likelihood estimation method. The best fitting solution is illustrated in Figure 1. The path coefficients are the standardized estimates of direct effects which are interpreted as standardized regression coefficients. All estimated path coefficients were significant. 47 % of the variance in depression was explained by the direct effect of burnout, 23 % of the variance in vigor was explained by the direct effect of burnout and depression. 24 % of the variance in job satisfaction was explained by the direct effect of burnout, depression and vigor.

Discussion and Conclusion

The objective of this study was to analyze the relationship between Turkish academics' job satisfaction, burnout, vigor and depression. The study used the structural equation model to determine these variables' relations, and found that burnout and depression negatively affects job satisfaction. Shirom et al. (2006) and Schaufeli et al. (2008) also found a negative relation between depression and job satisfaction. Moreover, many studies in the relevant literature have found that burnout and job satisfaction are negatively correlated (Maslach and Jackson, 1981; Shahab and Ali, 2013; Koustelios and Tsigilis, 2005; Özyurt et al., 2006; Kılıç et al., 2011; Kalliath and Morris, 2002). The model also determined that vigor has a positive influence on job satisfaction. There are many relevant studies that have also found a positive correlation between vigor and job satisfaction (Shirom et al., 2006; Schaufeli et al., 2008; Rothmann, 2008; Hakanen and Schaufeli, 2012; Aydogan et al., 2009). According to the model, vigor and depression play a mediating role for burnout.

Burnout is a developmental stage of depression (Ahola et al., 2006; Iacovides et al., 2003). Previous studies have shown that symptoms of burnout and depression are widely known (Bakker et al., 2000; Glass and McKnight, 1996; Leiter and Durup, 1994; Shirom and Ezrachi, 2003). The findings of this study indicate that the effect of burnout on depression is positive and strong (0.69). There are many relevant studies that have also found a positive correlation between burnout and depression (Toker et al., 2005; Shirom and Ezrachi, 2003).

As stated above, burnout influences job satisfaction negatively (-0.26). This finding is consistent with many other studies in the relevant literature (Maslach and Jackson, 1981; Shahab and Ali, 2013; Koustelios and Tsigilis, 2005; Özyurt et al., 2006; Kılıç et al., 2011; Kalliath and Morris, 2002). Burnout also has a negative effect on vigor (-0.34). The negative correlation between vigor and burnout is also supported by the findings of many relevant studies (Schaufeli and Bakker, 2003; Oerlemans and Bakker, 2014; Shimazu et al., 2008; Brand-Labuschagne et al., 2013; Demerouti et al., 2010).

The model also shows that depression has a negative effect on vigor (-0.19). The negative correlation between depression and vigor is also supported by the relevant studies (Shirom et al., 2006; Schaufeli et al., 2008). Similarly, depression has a negative effect on job satisfaction (-0.17). Hagan and Kay (2007) found the same result in their study to determine the effect of depression on job satisfaction.

According to the model, vigor has positive effect on job satisfaction (0.16), and many studies in the relevant literature have determined that there is a positive correlation between vigor and job satisfaction (Rothmann, 2008; Narainsamy and Van Der Westhuizen, 2013; Cheng et al., 2014).

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A new index describing the degree of virginity of forest structure

Mats Hagner[1]

In forest research there is often a need to express the structure of a forest. In a natural forest small and big trees are locally mixed, while plantation forests contain trees of more similar size. Species are also mixed, but aggregated. It is of great interest to describe this structure.

In forest mapping a traditionally used method is to divide the forest into "stands". The area of a stand can vary from one to several hectares and it is used for description of a forest with a specific feature. In the past it was necessary to describe forests in this simplified way, as all details could not be included in a drawn map. Today this has been changed as laser scanning gives data and coordinates for single trees and computers are capable of giving a lot of data for each tree.

When the "stand" was the smallest unit, a suitable description of structure was the "diameter distribution" for the stand. To form this distribution a huge number of diameters had to be registered and sampled within all parts of the stand. Variation within the stand, i.e. aggregation, could not be described.

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To find a better way I proposed to Hans Nyqvist a description based on the un-equality between neighboring trees. Our discussions ended up in the "Dissimilarity coefficient", shortened to "Disco", see Hagner and Nyquist (1998). This index is described in the following way.

A random tree is found and its diameter is measured ($d1$). The closest standing tree is found and its diameter is registered ($d2$). The dissimilarity is defined as

$$\frac{|d1 - d2|}{d1 + d2}$$

Its range is from 0 to 1. Among trees of equal size Disco is 0, and when one tree in the pair is close to zero Disco is close to 1. Disco of the stand is the average of all pairs.

In a natural stand of trees the distribution of diameters forms a Gamma Distribution which has a Disco = 0.500. When I tested this in a virgin rain forest in Borneo, I obtained an average of 0.501 (Hagner (2001)) which shows Disco seems to function very well. In forests in Sweden that have been thinned from below in accordance with conventional ideas, Disco has been ca 0.2. In stands left to develop naturally for more than 40 years, I have found Disco 0.35-0.48.

It is convenient for a forester to measure only larger trees, i.e. diameter from 8 cm and up. In such a case the diameter distribution can be truncated at 7.999. If this figure is withdrawn from each value the remaining distribution is still equal to a Gamma distribution, and Disco can be estimated from the transformed values.

Aggregation can be studied by a running line formed by the Disco-values for single pairs, if the pairs are taken along a straight line through the forest. Another method is to form new pairs by randomly redistribute all the original values of $d2$, by permutation, see Hagner and Nyqvist (1996). If Disco in the new pairs is bigger, then the values were aggregated.

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Paranormal Activity: An Essay in Honor of Hans Nyquist in Celebration of His Sixty-Fifth Birthday

Don Coursey[1]

1 Getting Started: A Normal Beginning

Combine knowledge of tastes, technology, and resources. Mix them following the rules of an interactive institution. And you will yield economic models of behavior.

In the late 1970's, understanding this process was my full-time job as a graduate student in economics at the University of Arizona. My goal was to become a scientist of economics. I had started my academic life in the physical sciences but, due to the serendipity of required electives in my course of studies, had fallen deeply in love with microeconomics and fascinated in how science might be better applied to social behavior.

But I was anxious. And insecure. I had chosen a science for my career that was based upon theory. But a science that, unlike physical sciences, was deficient in providing either suggestions of functional form or the promise of absolute constants of nature.

My anxiety spanned many dimensions and generated much self-questioning. What forms of utility and welfare functions actually describe human satisfaction? Where do discontinuities come from? How should Type I and Type II errors be weighted in the process of understanding personal and policy choices? How and why are people hard-wired to function in a world of choice under

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uncertainty? What can go wrong when models of behavior are divorced from systems of which they are only a part? In short, was the world of economics a "Normal" or even a "normal" place to investigate?

I shared these thoughts and worries with my advisors assuming that they knew the answers to my questions. In an experimental manner, Vernon Smith was wrestling with his answers to these questions through the development of laboratory experimental systems. In a statistical manner, Lester Taylor was wrestling with his answers to these questions through the development of econometric models of consumer behavior.

Taylor, in the fall of 1980, alerted me to the fact that Hans Nyquist would be visiting the economics department at Arizona. Nyquist was a few years past completion of his doctor thesis concerning non-normality in regression analysis and was interested in interacting with economists concerning applications of his work.

Thus began our five-year collaboration. Which, to me, was the spice of my late-graduate and early-professorial intellectual life, and laid the foundational platform for all of my later research and teaching career.

Our work resulted in two econometric papers (Coursey and Nyquist, 1983, 1986). In a time of IBM punch-cards, no personal computers, nor internet or e-mail, and separated by two continents, we managed to explore the nature of errors in consumer budget allocations. What was important about this work is that we showed that the world of consumer choice generates error processes where normality is the exception; rather than the rule. A world where, relative to the normal distribution, errors are generated that most often are consistent with "thinner" or "fatter" factors at work; that is, distribution tails either too thin or fat to be consistent with normal assumptions.

This work is what it is. More importantly for me was learning from Nyquist the processes associated with the art of statistical insight. Our papers were our science. What went on outside the written pages of this work was my insight into Nyquist's eye as a researcher: his ability to begin an investigation with absolutely no prior statistical assumptions, his ability to balance the intricate details of an investigation with the broader whole, and his ability to apply the gleaned wisdom of prior investigation to the present. This was my introduction to the art of statistical analysis. My interactions with Nyquist provided a perfect complement to my graduate studies and set the stage for

my future activities as an economist. Without this underpinning, my work would be less rich, have missed critical insight, and even wondered off on paths that would have resulted in incorrect inference.

I will illustrate these points in what follows. I have chosen examples from my research only because only in one's own body of work can a person delineate the important self-reflections related to my interactions with Nyquist.

2 Paranormal Tastes

Let me begin with economic tastes. A fundamental question about the policy is why and when states decide to invest resources to improve environmental quality. Suggested answers to this question involve income, politics, geography, education, behavioral tipping-points, demographics, and a variety of other factors. A standard approach involves conducting multiple-regressions to sort-out the individual and collective factors that influence demand for environmental quality. Quite often inflection points or threshold levels are incorporated into stories that purport to explain environmental demand.

In a series of papers with Christopher Hartwell (Coursey and Hartwell, 2000, 2015), he and I have shown that while these explanations shed some evidence on environmental demand, they miss the larger picture. And that research that ignores this larger picture is ignoring regression information that in turn affects assumptions about models' underlying error structures. Much work in this arena has been built from the bottom-up and has missed two important factors that Hartwell and I have identified.

The first is that the demand for environmental quality is best described by a holistic, cultural set of variables. Increased demand for environmental investment is not merely the sum of the effects of a list of independent variable changing. Rather it is the agglomeration effect of these variables (especially income and political freedom) that drive environmental demand. The second is that geographical closeness to other states produces lattice externalities that must be captured (in a manner similar to time-series autocorrelation) to fully explain different state outcomes with respect to the environment.

At the end of the day, these factors can be corrected by careful thinking about the error structure of models. But the art of this problem involves care-

ful thinking about how policy decisions are affected. Perhaps this work and associated work on environmental demand would have turned out the same if I had never met Nyquist and had merely kept beating upon the problem until it yielded. I doubt it. And, more importantly, the results would have been stale; offering little guidance to me or those who have followed regarding how to improve the research.

3 Paranormal Technology

The most surprising project that I have conducted involves technology and economic behavior (Rabinovici et al., 2004). In the United States, many recreational beaches can become afflicted with harmful bacteria. If people swim in such waters, they may in turn experience negative health outcomes. Therefore, significant resources are devoted in determining the day-to-day safety of these areas.

The problem is that tests for bacterial contamination operate with a technological lag. Samples of water (at significant economic costs) taken in the morning at a particular location take twenty-four hours to be evaluated. A beach manager must make decisions to open or close a beach based upon the known condition of the beach one day earlier. Four outcomes of this process are forthcoming. Two are most readily understood: a safe beach is open for swimming and consumers reap the welfare benefits of swimming or an unsafe beach is closed and swimmers avoid the negative health consequences of becoming sick. But two other outcomes are possible and seem to be less thought of by both beach managers and the public: a safe beach is closed and consumers forego swimming benefits or an unsafe beach is open and consumers become sick.

In the United States a "safe/unsafe" beach is defined by the United States Environmental Protection Agency as whether the bacteria context is below/above a threshold level. My charge in this project was to determine, in a cost/benefit analysis, whether this threshold level was optimal; that is, did it balance the joint desires of people to swim and to not become sick.

Two lessons from my time with Nyquist made this project so much more that it might have been. The first was discovering that beach managers were ignoring statistical information about how bacteria levels are auto-correlated

through time. It is hard to gather the talent and make the choices that result in the production of a stellar ice hockey team. But usually, once such a team is constructed, it remains competitive for some time. Similarly, it might take time to contaminate a beach with bacteria. But once contaminated, it may remain so until forces of nature have time to run their course.

The second insight was to remember that there must always be a null hypothesis in a scientific effort. This may seem trivial and I am not attempting to be cynical or condescending to my reader. Rather, it is amazing to me how much social science often pretends to have a null when it really is just shopping among alternatives. My alternatives were different bacterial threshold levels. At the last minute, I declared that the null ought to be, both logically and statistically, to do nothing. That is, to not spend the resources to do any testing and just let people swim if they desire.

Years later I am still stunned by the results. We found that the null hypothesis, no testing, to generate the largest net benefits. How can this be so? Ex post, most beaches are safe most of the time. Second, the Markov-chain cleansing process of the beaches happens quickly. And most importantly, the benefits enjoyed by thousands of swimmers at beaches massively outweigh the occasional, and relatively small health effects when a few swimmers become sick. The results of this study, while counterintuitive to many, are now applied in many beach management protocols around the country.

Again, the readers of this essay will recognize that I am really only talking about structures of error terms and weights on Type I/II errors. But in the bigger picture, I am talking about a system that need a holistic understanding before any estimation take place.

4 Paranormal Resources

My third example relates to economic resources. In particular, a resource called life. I have been interested for many years how we, as a civilization, treat endangered animal species from the perspective of economics. Simply put, I have attempted to measure how much these animals are worth.

To a non-economist, such an effort may sound immoral. Or, if forced to place a value on an animal, they might express an immeasurable or “infinite”

value on its life. Such feelings and expressions might be fine in coffee houses or over cocktails, but the reality of making policy trade-offs under limited resource constraints leads us to an alternative reality: difficult and often painful choices must be made when conserving natural resources including protecting endangered animals.

My research question was to examine how much, based upon quantifiable measures, we spend or do not spend to save animals and to determine the implicit, revealed value of each animal. To do this, I spent years collecting information about over 250 animal species in the United States; the type of animal, its location, its date of listing, its program for conservation, and the monetary resources amortized to save it.

As this data-collection was slowly proceeding, I had the leisure to think about endangered species as a public good and what that might mean to my statistical analysis. Usually when economists think of functional forms for public goods they are thinking from their textbooks; the public good is defined by either the summation or the product of its components. Think here of collections to fund a new museum or the combined efforts of a football team to produce a score on the playing field. But in the area of endangered species, two other, non-classical functional forms, often diametrically opposed, are relevant. One functional form might indicate that society ought to consider most aggressively saving those species that are in most critical condition; in the limit those with only a few representative male and female individuals extant. A second functional form more Nietzschean in form might argue that saving the most valuable, the most "uber-species," ought to hold sway. How society might choose to apply, or not to apply these standards became a critical part of my preparations for the econometric analysis that followed. And again, at a technical level, this involved being aware of functional form and the nature of errors in a regression. But at a higher level, the question of who wants to save what and how and what that means to the statistics presents a metaphysical challenge. Nyquist was, again, there to help me; to a-priori drive my regression strategy.

The results are perhaps most easily described colloquially (Coursey, 1998, 2000, 2002). Americans want to save endangered species. But not in the biblical sense of Noah's Ark. People may care about all of the animals, but they do not want an Ark large enough for all to board. Among those that do get aboard, Americans further want to discriminate among different animal types. Birds and mammals are expected to travel first-class. Others such as

reptiles and amphibians will ride in second class. Still others will find room only in the lower steerage compartments. And, to a fantastically robust extent, that is what the machinations of the public-policy and political processes do for American citizens. Americans get what they want whether it be at odds with what they need in the eyes of biological and ecological experts. To my satisfaction, these results continue to generate debate concerning what ought to be the role of economics as it brushes against its ken; that limit where efficiency meets higher-level criteria.

5 Paranormal Institutions

My final example of Nyquist's influence comes from a project that I have spent the last ten years exploring – whether it is possible to build and operate real-time trading markets for water. A question of economic institutions.

Especially in the arid west, demand for water often exceeds seasonal supply of water in the United States. Historically, command and control institutions have been utilized to find ways of ameliorating this imbalance. And, as populations and climates have evolved, efforts to find a balance have been unsuccessful. Often times, spectacularly unsuccessful.

To an economist, a solution to this problem of imbalance is a market. The intuition is that water markets ought to be as simple to create as lemonade markets in the summer. Like markets where children organically appear on the streets during the warm months and who offer to voluntarily sell cold drinks to thirsty customers, larger-scale water markets ought not be overly complex to implement. It is just a matter of bringing together water owners with those who desire the water.

But then reality begins to intrude. Physics states that water will run downhill towards the sea. Human desires turn this truism on its head; water is seen to run uphill towards money. Animals that use river and lake systems need minimal flows in order to survive. Moving water from one point to another in an exchange may produce externalities that affect third-party type users not involved in the original exchange. Building hydrological models of water systems involves complexity and a lot of resources. Historical experiences with water allocation and with property right legislation regarding water cause people to be threatened by a change in water allocation methods.

My ten years working on this problem have produced the highest highs and the lowest lows of my intellectual career (Broadbent et al., 2010, 2014). At heart, the reason for this is that the project has involved integrating three systems: hydrology, economics, and culture. The work is not done. But progress has been made. Le Chatelier has helped me to understand the philosophy of my lows. Nyquist has helped me to understand how to address these lows and to address them in a rational framework.

6 Not a Normal Person

I have been reading a lot lately about intellectual magic (Wulf, 2015). In particular, how much Alexander von Humboldt's polymath life was affected by his interaction with Goethe and Gauss; and theirs with his. It is a beautiful story that even they and the best historians of the last two hundred years cannot fully explain in words. A story of the best of art meeting the best of science. A story that is not discussed or thought about much these days in the academy.

In preparing these remarks, I have had to reflect upon what has been special, rewarding, or magical about the last thirty years. Learning to think about statistical economics through the eyes of a man who is both a mathematician and an artist is at the top of my list. Sharing this with thousands of my own students is second.

From all of us to you Hans Nyquist, skål.

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