IRISH STATISTICAL ASSOCIATION

28TH CONFERENCE ON APPLIED STATISTICS IN IRELAND

UCD BELFIELD

16TH JULY 2008

CASI 2008

28th Conference on Applied Statistics in Ireland

UCD Belfield, Wednesday 16th July 2008 **Theatre O/P**

ISA organised Special IBC Session on Gosset Centenary		
08.45 – 10.45	James Hanley McGill University	Student's z, t and s: What if Gosset had R
	Stephen Senn University of Glasgow	The Trial at Kalamazoo
	Steve Ziliak Roosevelt University	Guinnessometrics: William Sealy Gosset and the economic foundation of Student's t
	David Cox Nuffield College	Student and statistical inference
Keynote 1		
11.15 – 12.00	Finbarr O'Sullivan University College Cork	Statistical Aspects of Quantitative Imaging with PET for Cancer Applications
Contributed Session 1		
12.00 – 12.45	Kevin Hayes University of Limerick	A test of discordancy for Bland-Altman method comparison plots using single replicates
	Sally McClean University of Ulster	Costing medical interventions using non-homogeneous Markov models
	Harry Khamis Wright State University	A Comparison of Graphical Procedures for Testing the Proportional Hazards Assumption in the Cox Model
Lunch (Own Arrangments)		
Contributed Session 2		
14.00 – 14.45	Susana Conde University of Limerick	Simulation study: Search Algorithms in Contingency Tables
	Paul Wilson NUI Galway	The Dragnet test: A New Approach to Choosing Between Models
	Patrick Murphy UCD Dublin	Non response in the quarterly national household survey
Keynote 2		
14.45 – 15.30	Brian Ripley University of Oxford	Fitting Models by Simulation
Coffee		
Contributed Session 3		
16.00 – 17.00	Norma Coffey University of Limerick	Estimating Functional Principal Components using the Linear Mixed Effects Model.
	Lalit Garg University of Ulster	Healthcare resource planning using a discrete time Markov model
	Vijay Sarode Mulund College of Commerce	Logistic Modeling to determine delivery complications among women in slum in greater Mumbai
	Jing Xu University of Limerick	Linear Constrained Two-stage Estimate of Marginal Linear Models with Longitudinal Data
17.00 – 17.30	ISA Meeting	
17.30 – 19.00	Poster Session and Reception	
19.30 for 8pm	Dinner (Montrose Hotel)	

ABSTRACTS FOR CONTRIBUTED ORAL PRESENTATIONS

Conference on Applied Statistics in Ireland, 28th Meeting,
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A TEST OF DISCORDANCY FOR BLAND-ALTMAN METHOD COMPARISON PLOTS USING SINGLE REPLICATES

Kevin Hayes*[1], Kevin O'Brien[1] and Anthony Kinsella[2]

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Altman and Bland [1] criticise the use of correlation, regression and differences between means when analysing data which arises from the experimental comparison of two techniques or methods of measurement. They propose a simple graphical technique based on a plot of case-wise differences between methods against case-wise means of the methods, hereafter referred to as the Bland-Altman method comparison plot. All case-wise differences between two methods showing good agreement are expected to fall within the limits of agreement set at plus or minus 2 standard deviations of the average difference. Ryan and Woodall [5] report that the subsequent Lancet paper by Bland and Altman [2] is the **sixth** most highly cited statistical paper ever. The Bland-Altman method has become the expected (often obligatory) approach for presenting determinations of method reliability in many scientific journals [4, for example]. The successful impact of this paper is perhaps, in part, due to the fact that only an informal inspection of the graphical method is required supplemented by the correlation coefficient of the plotted quantities.

Altman and Bland [1] argue that their method comparison plot makes "it easier to assess the magnitude of disagreement (both error and bias), spot outliers, and see whether there is any trend." However, no guidance is provided about how the method comparison plot should be used for outlier identification. Bland and Altman [3] recommend the labour intensive approach of calculating the limits of agreement with and then without outlying values, in order to evaluate their impact on results, but are clear that they "do not recommend excluding outliers from analyses."

The aim of this work is to introduce a test of discordancy (outlier test) for agreement studies between two techniques or methods. Our approach, based on the Mahalanobis distance considers outlying observations in the both the case-wise differences and the case-wise means simultaneously.

[1] Altman, D. G. and J. M. Bland (1983), "Measurement in Medicine: The Analysis of Method Comparison Studies," The Statistician: Journal of the Institute of Statisticians, 32, 307–317.

[2] Bland, J. M. and D. G. Altman (1986), "Statistical Methods for Assessing Agreement Between Two Methods of Clinical Measurement," The Lancet, i .

[3] Bland, J. M. and D. G. Altman (1999), "Measuring Agreement in Method Comparison Studies," Statistical Methods in Medical Research, 8, 135–160.

[4] Hollis, S. (1996), "Analysis of Method Comparison Studies," Annals of Clinical Biochemistry, 33, 1–4.

[5] Ryan, T. and W. Woodall (2005), "The Most-Cited Statistical Papers," Journal of Applied Statistics, 32, 461–474.

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COSTING MEDICAL INTERVENTIONS USING NON-HOMOGENEOUS MARKOV MODELS

Sally McClean[1*], Lalit Garg[1], Maria Barton[1] and Peter Millard[2]

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We have previously used non-homogeneous Markov models to describe movements of patients between hospital and community care states; these may be actual, or virtual and described by a phase-type distribution. Typically the states might be "acute", "diagnosis", "treatment", or "long-stay" in hospital and "dependent", "recovered" in community care. This basic approach, which provides distributions for patient numbers in each state throughout time, can be extended to include costs for a healthcare system with Poisson admissions and an absorbing state, typically death. The distribution of costs were previously evaluated for any time and expressions derived for the mean and variances of costs.

In this paper we extend the previous approach to a healthcare system where we include costs of making a transition form one state to another as well as costs of residing in a state. Thus we may evaluate the overall costs of therapy or a clinical intervention by adding additional costs and new states. This model can be used to determine costs for the entire system for different treatment strategies. Such models can also help us to assess the complex relationship between hospital and community care where there may be possible trade-offs between hospital treatment costs and community care costs.

Stroke disease is a particularly relevant application for our approach as patients that do not receive appropriate therapy or rehabilitation in a timely manner may subsequently build up huge costs over time within community services. Modelling can assess where and how stroke patients should be treated. In particular, thrombolysis (clot busting drugs), if administered at the right time can produce substantial improvements. We illustrate our approach by assessing thrombolysis compared with alternative rehabilitative care within the hospital In future work we plan to obtain more accurate cost estimates for stroke patients and carry out a thorough evaluation.

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A COMPARISON OF GRAPHICAL PROCEDURES FOR TESTING THE PROPORTIONAL HAZARDS ASSUMPTION IN THE COX MODEL

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Six graphical procedures to check the assumption of proportional hazards for the Cox model are described and compared. A new way of comparing the graphical procedures using a Kolmogorov-Smirnov like maximum deviation criterion for rejection is derived for each procedure.

The procedures are evaluated in a simulation study under proportional hazards and five different forms of nonproportional hazards: (1) increasing hazards, (2) decreasing hazards, (3) crossing hazards, (4) diverging hazards, and (5) nonmonotonic hazards.

The procedures are compared in the two-sample case corresponding to two groups with different hazard functions. Only Type I censoring is considered. None of the procedures under consideration require partitioning of the survival time axis.

Results indicate that the Arjas plot, a plot of estimated cumulative hazard versus number of failures, is superior to the other procedures under almost every form of nonproportional hazards, especially crossing and nonmonotonic hazards. For increasing hazards, the smoothed plot of the ratio of log cumulative baseline hazard rates versus time or the smoothed plot of scaled Schoenfeld residuals versus time perform the best. The Andersen plot performs very poorly for increasing, decreasing, and diverging hazards.

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SIMULATION STUDY: SEARCH ALGORITHMS IN CONTINGENCY TABLES

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In statistical software packages, automatic algorithms for finding optimal hierarchical log-linear models (HLLMs) in (multi-dimensional) contingency tables are dated, having been developed in a model-fitting paradigm, in which, typically, the dimension of the table p is small, rather than in today's data-mining framework.

Accordingly, we have developed automatic search algorithms in R for finding optimal HLLMs in multi-dimensional contingency tables. The algorithms have been designated: BE, BE2, FS and FS2. These algorithms work backwards, forwards, or stagewise until an optimal HLLM is found. The "short horizon" searches are conducted using the likelihood ratio criterion.

In order to evaluate the performance of the algorithms a comprehensive simulation study is underway. The simulation involves two strategies A and B (Conde and MacKenzie, 2008). In strategy A random contingency tables are drawn as random compositions (Nijenhuis, 1971). This means that the structure of the tables generated are not "formulated" in advance. In strategy B random contingency tables are drawn assuming an initial model structure is true. In both cases, we wish to determine whether the algorithm being tested can identify the true model structure. We also conducted tests using real datasets based on comorbidities (Conde and MacKenzie, 2007a).

A core scenario using strategy A involved generating m = 1000 random compositions. In relation to strategy B, preliminary results in relation to formulated models are encouraging. In almost all the cases the final model found by the algorithms (BE, BE2 and FS) identified the correct model or one in the neighbourhood of the correct model. More details will be presented at the conference and in Conde & MacKenzie (2007b) forthcoming. To date the new algorithms have performed well.

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THE DRAGNET TEST: A NEW APPROACH TO CHOOSING BETWEEN MODELS

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In statistical analysis the substitution of a maximum likelihood estimator of a parameter $\hat{\tau}$ for the true, but unknown, parameter τ of a model for given data, is so commonplace that possible consequences of the fact that the values of τ and $\hat{\tau}$ may differ considerably are often overlooked.

For example, say we wish to choose between a Poisson model M_f and a geometric model M_g ,for count data with a mean, and hence a parameter maximum likelihood estimate of  . If the log-likelihood, $l_{M_f}(2) > l_{M_g}(2)$ we conclude that M_f is to be preferred over M_g. If however the true parameter value differs from 2, (which it certainly will), then our selection of M_f as the more suitable model may have been erroneous.

We propose a new test, the *dragnet test* whose origins lie in the Cox test for non-nested models. Unlike the Cox test the dragnet evaluates S pairs of p-values at S *fixed* parameter values determined by sampling from the parameter spaces of both models, thus obtaining a weighted cross section of possible model classifications. Also the hypotheses of the dragnet test are simple, i.e. they specify the parameters of M_f and M_g, and hence problems with biased estimation of p-values are avoided.

This fixing of parameters also enables the dragnet test to be extended to nested or overlapping models.

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NON RESPONSE IN THE QUARTERLY NATIONAL HOUSEHOLD SURVEY

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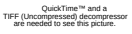
The widely reported phenomenon of socio-economic status (SES) bias in response rates to surveys remains one of the major problems which researchers face when dealing with survey data.

The purpose of this paper is to present the results of a study, conducted in Ireland, which provided an unprecedented opportunity to examine the characteristics of both the non-respondents and respondents to a survey and to compare characteristics of both with the target population.

Anonymised records on 41,280 participants in the Irish Quarterly National Household Survey (a nationwide survey of households conducted by the Irish Central Statistics Office) provided data for this study into SES bias. Our findings appear to contradict the perceived position on SES bias in surveys.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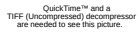
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HEALTHCARE RESOURCE PLANNING USING A DISCRETE TIME MARKOV MODEL

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Optimum utilization of scarce healthcare resources is important to ensure quality of care with available budget and resources. A good understanding of process dynamics of the health care system can help care planners and policy makers in future resource requirement forecasting. This knowledge can be used in designing policies to allocate required budget to ensure resource availability according to the current admission policy. Also, if availability of resources or budget is a constraint then the future admission policy can be adapted to meet future availability of resources. This paper presents a non-homogeneous discrete time Markov model to estimate the future resource requirements based on current admission policy. We also demonstrate how this model can also be used to decide the present rate of admission based on the number of beds and other resources (such as care professionals, nurses, instruments etc) available in a given time in the future or based on a given limit on healthcare costs (budget) at a time in future. We can also use this model to estimate the long term effect of change in an admission policy.

We model the periods of patients' stay in the hospital and community (after first admission in the hospital) as phases in a discrete time Markov chain having absorption phase death. Time dependent covariates like patient's age are updated daily to have a more realistic model. We can model a fixed number of admissions daily as well as a variable admission rate with a fixed rate of change in the admission rate. An application of the model is presented for the 7-phase healthcare system having 4 hospital and 3 community phases. Our model also estimates the total cost for providing care over a given time period, total daily cost and average cost per patient. We evaluated our model by fitting it to historical patient dataset from a London hospital. This model can serve as a valuable decision support tool in healthcare, making information readily available to care professionals and policy makers.

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LOGISTIC MODELING TO DETERMINE DELIVERY COMPLICATIONS AMONG WOMEN IN A SLUM IN GREATER MUMBAI

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This study uses primary data, collected using cluster sampling of sample size of 346 reproductive women who have given at least one live birth prior to survey on antenatal care indicators, antenatal check-ups, and reproductive health problems during the pregnancy and the complications while delivering a child from Ramabai Nagar slum.

This paper examines utilization of health services available to these women in slums in Mumbai and also checks whether non utilization of ANC and having reproductive health problems during pregnancy creates complications during child delivery on the basis of standard of living index constructed from household amenities, housing quality and sources of drinking water, electricity and toilet facilities.

The findings using logistic regression reveals unimaginable low level of utilization of health services for illiterate women in the study area. Besides these there is evidence that those respondents did no go for ANC and had reproductive health problems during the pregnancy creates problems during child delivery, particularly to illiterate mothers.

This paper suggests that awareness is required at every stage of ANC particular to illiterate women with low SLI category women in a slum.

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LINEAR CONSTRAINED TWO-STAGE ESTIMATE OF MARGINAL LINEAR MODELS WITH LONGITUDINAL DATA

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Longitudinal studies are common in biomedicine, epidemiology, and other fields of natural and social sciences. One of its defining features is that each independent subjects is measured repeatedly over a time period. In recent years, statisticians have found it necessary to impose restrictions on regression parameters in practical cases of longitudinal studies, such as the human tumour xenograft experiments, the comparative study among diabetic groups, the prospective randomized trial of early childhood educational intervention and so on (see, for examples, Edwards et al. (2001), Cysneiros and Paula (2004), Tan et al.(2005), Fang et al. (2006)).

Some authors were devoted to hypothesis testing and estimation problems. Because of constraints, an analytical formula for the estimators cannot be derived from the iteration algorithms of constrained optimal procedure. For this reason, statistical properties (including the asymptotic distributions of the estimators, which are essential to statistical inference) were not obtained. In fact, theoretical studies on asymptotic behavior of constrained parameter estimates in longitudinal analysis are seldom seen in the literature.

In this paper, we give estimate methods of the marginal linear models with inequality constraints and derive asymptotic behavior of constrained problems. In order to improve the efficiency of estimate, we propose a constrained two-stage estimation by taking within-subject correlation and constraints into consideration simultaneously. We introduce a 'working covariance matrix' and choose its inverse matrix as weighting matrix. After the estimate of working covariance matrix is given, the numerical solution of the estimators of the regression parameters can be obtained from a quadratic programming problem.

We derive the asymptotic properties of constrained estimators by appealing to the method used in Wang (1996). Because of within-sub ject correlation and the unknown covariance matrix, some other tools are used, such as the Cramer-Wold theorem and the central limit theorem of Lindeberg-Feller.

Using the Kuhn-Tucker condition, we show that the asymptotic distribution of constrained estimators is the piecewise Gaussian distribution. When the covariance structure is specified correctly, simulations demonstrate that the constrained two-stage (TS) estimators are consistent and the most efficient among the three estimators: the constrained TS, the constrained OLS and the TS.

ABSTRACTS FOR POSTER PRESENTATIONS

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EFFECTS OF ASTROGLIA AND NEUROTROPHINS ON MORPHOLOGY OF DOPAMINERGIC NEURONS

Pearl Deacon and Kingshuk Roy Choudhury

University College Cork

One treatment for Parkinson's Disease is the transplantation of neurons from the ventral mesencephalon into the striatum, where the death of DA neurons occurs. Two experiments were performed, prior to transplantation, to examine how different culture conditions affected the morphology of DA neurons. The morphology is quantified here by the number of neurites, or branches, which a neuron possesses. Neurites are classified as Primary, Secondary, Tertiary and Quaternary, as per level of branching. The first data set comprises numbers of neurites in cells co-cultured with astroglia from different regions of the brain (STR, CTX, VM, HY) and Control; the second comprises numbers in cells cultured with neurotrophins (GF), with HY-astroglial-conditioned medium (HACM), and with the combination HACM+GF.

Each neuron yields a hierarchical structure, which is modelled by estimating the rates (i.e., the mean number of Primary neurites, the mean number of Secondary neurites per Primary, and so on for each level). The joint likelihood of observing X_l neurites at the l^{th} level in the i^{th} cell may be factored as follows, and each of the likelihoods maximized separately:

$$L\left(X_p{}^i, X_s{}^i, X_t{}^i, X_q{}^i\right) = L_{\theta_p}\left(X_p{}^i\right) L_{\theta_s}\left(X_s{}^i \mid X_p{}^i\right) L_{\theta_t}\left(X_t{}^i \mid X_s{}^i\right) L_{\theta_q}\left(X_q{}^i \mid X_t{}^i\right).$$

GLMs with Gamma errors are shown to be suitable for this purpose, given under-dispersion in the data. The weighted GLM used to model the Secondary rates in the first study, for example, is:

$$\frac{1}{E\left[Y_{ijkl}\right]} = b_o + b_1\left(STR\right)_i + b_2\left(CTX\right)_j + b_3\left(VM\right)_k + b_4\left(HY\right)_l,$$

$$V\left[Y_{ijkl}\right] = \sigma^2\mu_{ijkl}^2 \Big/ w_{ijkl}, \text{ where } Y = \frac{X_s}{X_p} \mid X_p \text{ and weights } w = X_p.$$

In Study One, groups with significantly higher rates than Control are VM (at Primary level), HY, STR and CTX (at Secondary level), HY and VM (at Quaternary level). In Study Two, all groups have significantly higher rates than Control at Primary and Secondary levels, but the increase gained at Primary level by GF alone is diminished when combined with HACM, and vice versa. At Secondary level, the mean rate of GF is increased when combined with HACM, but the mean rate of HACM is lessened when combined with GF. At Quaternary level, HACM has a higher mean than GF. In both studies, permutation tests for differences between groups in their combined rates across all levels of branching were also performed.

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NON RESPONSE IN THE QUARTERLY NATIONAL HOUSEHOLD SURVEY

Denise Earle and Catherine Hurley

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Graphics are an integral part of statistical analysis. Unfortunately, it is often the case that not enough effort is spent on producing these graphics. Generally they are constructed with the ordering of variables and/or observations corresponding to the order in which they are listed in the data. However, as shown in the literature, the quality of graphics is often greatly improved when the data is ordered (Friendly & Kwan 2003, Hurley 2004).

In this presentation we investigate the quality of several recently developed seriation algorithms, including a simulated annealing algorithm described in Brusco et al (2007), an optimal leaf ordering algorithm described in Bar-Joesph et al (2001) and an algorithm described in Chen (2002), which is based on iteratively generated correlation matrices. We assess the quality of the algorithms in two ways:

(i) graphically using displays such as parallel coordinate plots, heatmaps and scatterplot matrices and (ii) numerically using various merit and loss functions. All of the algorithms listed above are implemented in the R package seriation (Hahsler et al 2007).

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ADJUSTING FOR UNMEASURED COVARIATES - AN EXAMPLE FROM PATIENT SATISFACTION SURVEYS

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In practice, the situation often arises where covariates are not measured, even though they may be suspected, on the basis of evidence from other studies, to influence the outcome of interest. We describe a Bayesian approach whereby we incorporate the prior knowledge of other studies to estimate the effect of an unmeasured covariate in the current study.

We apply this approach to three groups of simulated data on weight, height and gender, with gender missing for one group, and show that by synthesising the three groups we can identify the true relationship between height and weight for males and females separately.

Finally we apply this method to data from Insight 2007, a study of patients satisfaction with health services in Ireland, in which outpatients were asked about their waiting time for treatment but General Practice and Emergency Department patients were not.

We find a relationship between waiting time and satisfaction for the groups of patients where this was not measured, and modification of some covariates that were measured for each group.

This approach is easily implemented using BUGs, with implications for practical application.

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DETECTING HIGH-RISK AREAS IN DISEASE MAPPING USING EMPIRICAL BAYES CONFIDENCE INTERVALS AND FULLY BAYES DECISION RULES

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There are two main approaches to disease mapping within the general Bayesian framework, the Empirical and the Fully Bayes approach, and both of them are very good for smoothing purposes. However, although smoothing is a desirable property of the model, an excess of smoothing may hinder the detection of high risk areas, being these two goals of disease mapping somewhat contradictory, i.e, the larger amount of smoothing, the more difficult is to detect a high-risk area.

Identifying extreme regions minimizing the misclassification of background or normal areas, and then, avoiding false alarms is very important in epidemiology. Bayesian decision rules, based on the posterior distribution of the relative risks, have been investigated, but any similar study has been conducted under the EB approach.

Within this framework, second order correct estimators of the MSE of the log-relative risk predictor can be used to build appropriate confidence intervals for the relative risks. Their ability to detect raised-risk areas is investigated through a simulation study using the geographical structure of the well-known Scottish lip cancer data.

Bayesian credibility intervals and decision rules, based on the posterior distribution of the relative risks, are also investigated to check if any of the approaches is better than the others at classifying the regions. The conclusion is that both approaches lead to the same amount of smoothing, but Bayesian decision rules, exploiting the posterior distribution of the relative risks, are more powerful to detect raised-risk areas than EB confidence intervals. On the other hand, it is very difficult to define a decision rule that can be routinely applied in every real setting.

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PAIRWISE COMPARISONS OF TREATMENT GROUPS VIA EULERIAN TOURS AND HAMILTONIAN DECOMPOSITIONS

Catherine B. Hurley[1] and R.W. Oldford[2]

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We present improved graphical displays for two classical data analysis problems. Conventionally in one-way anova, treatment differences are visualized by drawing confidence intervals for all pairs of treatments. Hsu and Peruggia and more recently Heiberger and Holland devised a rather visually complicated display which also presents the group means along with the pairwise comparisons. Our display consists of horizontal boxplots for each treatment where boxplots are repeated as necessary so that each pair of treatments appear adjacently for ease of comparison. To enhance the comparison, a (Tukey HSD) confidence interval is drawn between every pair of treatments, so that significantly different treatments are easily identified. Furthermore, the confidence intervals may be ordered to give prominence to important comparisons.

In two-factor anova, treatment interactions are visualized by constructing an interaction plot, where near-parallelism of line segments suggests non-significant treatment interactions. We present examples where assessment of parallelism is affected by the order of factor levels. As a remedy, we reduce the dependence on order by repeating treatments so the interaction plots show line segments connecting all pairs of treatment levels for one factor while holding the second factor fixed.

In both of the above problems, the improved graphical displays make use of sequences of treatment groups where groups are repeated so that all groups appear adjacently. These sequences amount to finding eulerian paths on the complete graph where each vertex represents a treatment group. We present a variety of algorithms for constructing eulerian paths, for the situations where the graph edges are weighted, and where a hamiltonian decomposition is required. Other applications of eulerian tours and hamiltonians in statistical graphics include star glyphs and parallel coordinates

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SEROLOGICAL AND MOLECULAR EPIDEMIOLOGY OF HEPATITIS B VIRUS IN HSE-SA

Grainne Murray[1], Cathal Doherty[1], Colin McCarthy[1], Cillian McNamara[1], Kathleen O'Sullivan[2]*, Mary Horgan[3], John Levis[3], Bernie Crowley[3], Liam J. Fanning[3]

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Aims
The aim of this study was to determine if HBV viral load differed between hepatitis B e-antigen (HBeAg) positive and hepatitis B e-antigen (HBeAg) negative patients. A further aim was to explore the associations with genotype.

Methods
Measurements recorded at first sampling from 373 untreated patients infected were statistically analysed using SPSS employing descriptive statistics, Mann-Whitney U, Kruskal-Wallis and Chi-square tests.

Results
HBV viral load was higher for HBeAg positive patents ($P<0.001$). HBeAg status was associated with genotype ($P<0.01$), and for genotypes A ($P<0.05$), D ($P<0.05$), and C ($P<0.05$) HBV viral load was higher for HBeAg positive patents. Age did not differ between HBeAg-postive and-negative patients ($P>0.2$) and the difference between genotypes on HBV viral load achieved a borderline significance ($P=0.05$).

Conclusions
These results suggest that HBeAg status at first sampling is a useful indicator of HBV viral load; HBeAg positive patents have higher viral loads. The predominant genotype was A. HBeAg status was associated with genotype and for genotypes A, C, and D, HBeAg positive patients had higher viral loads. HBeAg status was not related to age. Genotype shows some indication of an association with magnitude of viral load.

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SHOULD SPATIAL EFFECTS BE ALLOWED FOR IN CLUSTER RCTS IN PRIMARY CARE?

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Typical advice on the design and analysis of cluster randomized trials (C-RCTs) in Primary Care focuses on allowance for the clustering at the level of the unit of allocation. However in Primary Care, Practices are also organized spatially, with possibly overlapping populations.

One way to allow for spatial effects on the error variance is through a multiple membership model. These are a form of hierarchical model in which each lower level unit is a member of more than one higher level unit. Membership may be determined through adjacency or through Euclidean distance of centroids or in other ways such as the proportion of overlapping population. Such models may be estimated for Normal, binary and Poisson responses in the current version of Stata (v10) as well as in WinBUGS or MLWin.

We analysed a dummy trial and two real cluster-allocated studies (one allocating general practices within one City and the other allocating general practices within one County) to investigate the extent to which ignoring spatial effects affected the estimate of treatment effect, using different methods for defining membership with Akaike's Information Criterion to determine the "best" model.

The results can only of course be illustrative and not necessarily apply to all C-RCTs, however, we believe that the possibility of spatial effects should be considered when designing any C-RCT in a Primary Care setting.

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PRINCIPLED PROOF OF PRINCIPLE STUDIES

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Sometimes a feasibility study is undertaken before a full-scale study to (i) determine whether to proceed with a project and (ii) decide the best approach to adopt. A key point is that the outcome variables for a feasibility study are NOT in general the same as for the main study, but reflect factors that affect successful trial conduct, such as recruitment.

Proof of principle studies may be regarded as a particular kind of feasibility study that employs either the actual outcome variable of interest or a valid surrogate for it. Just because a study is badged as "proof of principle" however, is no excuse for it to be small or lack proper objectives. Principled planning of such studies requires justification of sample size with definition of: a) the exact principle is that is being tested b) the criterion that will be used to test support for the principle c) the actions that will then follow.

In terms of sample size, a proof of principle study needs either to detect a clinically relevant (and statistically significant) effect or to rule it out, as these are clear guides for further action.

Use of surrogate response variables can reduce study size but the principle at stake is then, strictly speaking, not that for the actual response. Study sizes may also be reduced by single arm trials (limited through not using concurrent controls) or by using strict eligibility criteria to ensure homogeneity of participants (but at the price of external validity).

Other things being equal, a proof of principle study needs to be about the same size as the superiority study required to demonstrate a clinically relevant difference (CRD), but it is then the per protocol analysis – as for equivalence – that is the conservative analysis, with implications for trial conduct.