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CONTROL ID: 3344490
PRESENTER: Emma Gerard
PRESENTER (INSTITUTION ONLY): Inserm, Sanofi R&D
TITLE: Bayesian dose-finding design for schedules using pharmacokinetic and pharmacodynamic (PK/PD) information
ABSTRACT BODY:
Abstract Body: Context: Phase I dose-finding trials in oncology seek to find the Maximum Tolerated Dose of a drug under a specific schedule. Evaluating drug-schedules aims at improving treatment safety while maintaining efficacy. However, while we can reasonably assume that toxicity increases with dose, the relationship between toxicity and multiple schedules remains elusive.

Objective: The aim of this work was to develop a Bayesian dose-finding design for multiple schedules using PK/PD information to estimate the Maximal Tolerated Dose-Sequence (MTDS) at the end of the trial. We propose to model the binary toxicity via a summary of the profile of a toxicity-related biomarker, viewed as a continuous PD endpoint.

Methods: Firstly, the relationship between the PD biomarker profile and the dose-sequence is modelled using non-linear mixed models.
Secondly, we propose 2 Bayesian approaches to model the relationship between a summary of the biomarker profile and toxicity. For the first approach, we consider a Bayesian 2-parameters logistic model using a value of interest of the biomarker profile. For the second approach, we propose a Bayesian hierarchical model using a latent variable considering longitudinal values of the biomarker profile.
Finally, we integrated both models via simulations to analyse the entire relationship between the dose-sequence and toxicity in order to recommend the MTDS.

Results: We evaluated the operating characteristics of our methods through simulation studies under various scenarios. The results showed that our methods perform better than usual model-based designs in terms of percentage of MTDS correct selection. Moreover, due to the additional PK/PD information, our methods estimate more precisely the entire dose-sequence-toxicity curve and can propose untested sequences for expansion studies. Our methods will be applied to an ongoing dose-escalation trial for patients with relapsed or refractory acute myeloid leukemia (NCT03594955).

Conclusion: Our proposed dose-finding design for multiple schedules provides a reliable way to identify the MTDS when toxicity can be related to a PD biomarker. However, as the methods are applied at the end of the trial (once all data has been collected), they can be sensitive to the dose-escalation design. We are therefore extending our design to a sequential dose-allocation approach.
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CONTROL ID: 3356158

PRESENTER: Thomas Neyens

PRESENTER (INSTITUTION ONLY): Hasselt University, Catholic University of Leuven

TITLE: Mapping Species Richness Using Opportunistic Samples: a Case Study on Ground-floor Bryophyte Species Richness in the Belgian Province of Limburg

ABSTRACT BODY:

Abstract Body: In species richness studies, citizen-science surveys where participants make individual decisions regarding sampling strategies provide a cost-effective approach to collect a large amount of data. However, it is unclear to what extent the bias inherent to opportunistically collected samples may invalidate our inferences. Here, we compare spatial predictions of forest ground-floor bryophyte species richness in Limburg (Belgium), based on crowd- and expert-sourced data, where the latter are collected by adhering to a rigorous geographical randomisation and data collection protocol. We develop a log-Gaussian Cox process model to analyse the opportunistic sampling process of the crowd-sourced data and assess its sampling bias. We then fit two geostatistical Poisson models to both data-sets and compare the parameter estimates and species richness predictions. We find that the citizens had a higher propensity for locations that were close to their homes and environmentally more valuable. The estimated effects of ecological predictors and spatial species richness predictions differ strongly between the two geostatistical models. Unknown inconsistencies in the sampling process, such as unreported observer's effort, and the lack of a hypothesis-driven study protocol can lead to the occurrence of multiple sources of sampling bias, making it difficult, if not impossible, to provide reliable inferences.

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CONTROL ID: 3360456

PRESENTER: Girault GNANGUENON GUESSE

PRESENTER (INSTITUTION ONLY): INRAE, Montpellier University

TITLE:

An exploratory penalized regression to identify combined effects of functional agri-environmental variables

ABSTRACT BODY:

Abstract Body:

The development of new sensors allows observation at high frequency of the dynamics of agri-environmental variables affecting production. New challenge arises to model and predict fruit quality from these agri-environmental data. Modelling in agriculture had previously focused on plant growth and yield, whereas knowledge and models are not well established for fruit quality. There is a need for information extraction and statistical exploration in the case where the links between the quality variables and the functional environmental data are potentially non-linear. Usual functional data analysis (Ramsay and Silverman, 2005) are not adapted to extract information in the case of multivariate explanatory functional data. We propose a new approach using joint distributions of agri-environmental variables to explain a real (scalar) quality variable. Our exploratory approach is similar to boosting techniques that identifies various joint distributions associated to the explanatory environmental data. It associates penalized and structured regressions (Tibshirani and Taylor 2011, 2012) to select an optimal joint distribution that best explains the variable to be predicted. This approach has the additional advantage of being able to integrate, if necessary, so-called "expert knowledge" from the literature or other sources into the modelling process in order to improve the reliability of the results. Developed initially for agriculture, it is generic and can be used to solve scalar-on-function problems with the main hypothesis of identifying combined effects of functional explanatory variables. One limitation of this approach is the risk of overestimation, but various criteria are available to overcome it. The approach is validated on simulations and on real data.

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CONTROL ID: 3367418
PRESENTER: Paul Lambert
PRESENTER (INSTITUTION ONLY): University of Leicester, Karolinska Institutet
TITLE: A marginal model for relative survival
ABSTRACT BODY:
Abstract Body: In quantifying the probability of survival in cancer patients using cancer registry data, it is common to estimate marginal relative survival, which under assumptions can be interpreted as marginal net survival. Net survival is a hypothetical construct giving the probability of being alive if it was only possible to die of the cancer under study and enables comparisons between populations with differential mortality rates due to other causes. Cause of death information is either unavailable or, more commonly, deemed unreliable and so expected mortality rates are used so that mortality in excess of that expected can be estimated.

Marginal relative survival can be estimated non-parametrically (Pohar Perme estimator) or in a modelling framework. In the modelling framework, even when just interested in the marginal survival in a population it is necessary to model covariates that affect the expected mortality rates (e.g. age, sex and calendar year). The marginal relative survival function is then obtained through regression standardization. Given that these covariates will generally have non-proportional effects, the model can become complex even before other exposure variables are considered.

We propose a flexible parametric model incorporating restricted cubic splines that directly estimates marginal relative survival and thus removes the need to model covariates that affect the expected mortality rates. In order to do this the likelihood needs to incorporate the marginal expected mortality rates at each event time taking account of informative censoring. In addition time-dependent weights need to be incorporated into the likelihood. An approximation is proposed using data expansion which enables the marginal model to be fitted using standard software to fit relative survival models.

The advantage of this approach is that when there is interest in marginal effects there is no need to model the effect of covariates for which the expected mortality rates vary and thus simplifies the modelling process. Additional weights can be incorporated when needing to standardize to an external reference population, which is common in these studies.

The methods are illustrated using English cancer registration data. In addition a simulation study has been performed comparing estimation using a non-parametric approach, regression-standardization and the new marginal model showing that the method has good statistical properties.

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CONTROL ID: 3367738

PRESENTER: Maren Vranckx

PRESENTER (INSTITUTION ONLY): Hasselt University, Data Science Institute (DSI), Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat)

TITLE: Do’s and don’ts of model comparison techniques

ABSTRACT BODY:

Abstract Body: Several model comparison techniques exist to select a best model from a set of candidate models. This study explores the performance of model comparison statistics among several Bayesian software packages that are often used for spatially discrete disease modelling: the deviance information criterion (DIC), the Watanabe-Akaike information criterion (WAIC) and the log marginal predictive likelihood (LMPL). We focus on the software packages CARBayes, OpenBUGS, NIMBLE and Stan, in which we fit Poisson models to disease incidence outcomes with intrinsic conditional autoregressive, convolution conditional autoregressive and log-normal error terms. From three data analyses, that differ in the number of areal units and disease prevalence, we learn important disparities in model selection. Based on these conclusions, we provide recommendations on the optimal use of model comparison statistics for all kind of applications.

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CONTROL ID: 3368004
PRESENTER: Sarah Booth
PRESENTER (INSTITUTION ONLY): University of Leicester
TITLE: Accounting for Calibration Drift due to Improvements in Baseline Survival during Prognostic Model Development

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ABSTRACT BODY:

Abstract Body: Introduction
Prognostic models which are used to produce long-term survival predictions are often developed using datasets which cover a long diagnosis period. If survival is continually improving during this time, it can lead to predictions which under-estimate the survival of recently diagnosed patients. The developments here focus on models which produce survival predictions following a cancer diagnosis, however these methods can be generalised to other outcomes.

Methods
An extensive comparison of approaches for accounting for improvements in survival was performed. This included modelling calendar time directly by including the year of diagnosis as a predictor, and if required, allowing for non-proportional hazards and interaction terms. Alternative period analysis based methods involved using delayed-entry techniques to analyse the most recent subset of data and temporal recalibration which uses this subset to re-estimate the baseline hazard of standard prognostic models. We compare approaches in a simulation setting under a range of plausible assumptions and further show examples of models for colon cancer developed using US population-based registry data from the SEER database.

Results
Accounting for changes in baseline survival often improved the calibration of the predictions for new patients compared to the standard model. However, when time-dependent effects for the year of diagnosis were included, this sometimes resulted in inaccurate survival predictions. This is likely due to the most recently diagnosed patients having a limited amount of follow-up which leads to the inappropriate extrapolation of a non-linear interaction effect based on the long-term information from patients who were diagnosed earlier.

Conclusion
Care should be taken when modelling complex trends in calendar time; particularly when allowing the effect of calendar time to be time-dependent. A more conservative approach to produce up-to-date survival predictions can be achieved using period analysis based methods as less extrapolation is required.

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CONTROL ID: 3386667

PRESENTER: Olivier Bouaziz

PRESENTER (INSTITUTION ONLY): Université de Paris

TITLE: Regression modelling for interval-censored data with application to a dental dataset

ABSTRACT BODY:

Abstract Body: A new method for the analysis of time to ankylosis complication on a dataset of replanted teeth is proposed. In order to deal with these left-censored, interval-censored and right-censored data a Cox model with piecewise constant baseline hazard is introduced. Estimation is carried out with the EM algorithm by treating the true event times as unobserved variables. This estimation procedure is shown to produce a block diagonal Hessian matrix of the baseline parameters. Taking advantage of this interesting feature of the estimation method a L0 penalised likelihood method is implemented in order to automatically determine the number and locations of the cuts of the baseline hazard. This procedure allows to detect specific areas of time where patients are at greater risks for ankylosis. The method can be directly extended to the inclusion of exact observations and to a cure fraction. Theoretical results are obtained which allow to derive statistical inference of the model parameters from asymptotic likelihood theory. Through simulation studies, the penalisation technique is shown to provide a good fit of the baseline hazard and precise estimations of the resulting regression parameters.

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