[C19] - Survival data analysis 6

[C19.1] Using dynamic prediction to inform the optimal intervention time for individuals in an abdominal aortic aneurysm screening programme

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Aim
To demonstrate how a joint longitudinal and survival model can be used to predict the optimal time of intervention for individuals under surveillance with an abdominal aortic aneurysm (AAA).

Background
The UK National AAA Screening Programme has recently been set up to screen men aged 65 for AAA with the ultimate aim of preventing serious health outcomes such as ruptured AAA. Men diagnosed with small AAA are monitored at regular intervals until their aneurysm diameter reaches 5.5cm, at which point individuals are considered for surgical intervention. However, the choice of intervention threshold is debated and not universally agreed.

Methods
We develop a joint model for AAA diameter growth and risk of rupture and consider whether the current recommended diameter threshold for intervention is optimal in terms of maximising expected life-years. This requires a trade-off between the joint and competing considerations of 1) preventing deaths from rupture, 2) postoperative deaths from elective surgery and 3) non-AAA mortality. Using data on AAA growth and rupture from repeat ultrasound scans in the Multicentre Aneurysm Screening Study we illustrate how a joint longitudinal and survival model can obtain dynamic predictions of rupture events for individuals with different AAA diameter trajectories, and use the predictions to calculate the optimal time of intervention. Variability in the optimal intervention time is accounted for using Monte Carlo simulations of the conditional survival probabilities.

Results
Results indicate that both underlying AAA diameter and rate of growth are important predictors of rupture and impact on decisions regarding when to surgically intervene. The optimal intervention threshold for an individual is not a constant quantity and can dynamically change throughout follow-up.

Conclusions
Individualised predictions of when to intervene are obtainable and can inform whether major surgery should be brought forward or delayed based on the prognosis of the patient.

[C19.2] Multiple imputation of time-dependent covariates in survival analysis: Two-stage joint model with multiple continuous markers

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A central component of modern epidemiological research is the establishment of large-scale cohort studies collecting data from individuals over time, often including a wide range of time-varying characteristics such as body mass index, blood pressure and blood glucose levels. Incorporation of such time-dependent covariates in the study of the incidence of health events (death, diabetes onset, etc.) is of great interest, but raises some challenges. Specifically, it is well-known that the last observation carried forward (LOCF) approach often used to deal with time-dependent covariates in survival analysis leads to bias in regression coefficients. The problem arises due to measurement error and the discrete-time observation of a continuous-time stochastic process, particularly with non-synchronous updating of covariates as occurs, for instance, when participants skip follow-up visits. Joint models of longitudinal and time-to-event outcomes, developed recently, are based on maximising the likelihood derived from the joint distribution of both processes and address these issues. However, the computational complexity of the corresponding likelihood functions limits the flexibility of available joint modelling software packages, for example they often deal with only one time-dependent covariate and are constrained to parametric hazard functions or proportional hazards models.

We propose a two-stage approach to fitting joint models when dealing with multiple time-dependent continuous covariates that is applicable to both the Cox and additive hazards semiparametric models. The approach is based on multiple imputation by-chained equations (MICE), using a procedure readily implementable within MICE packages available in mainstream statistical software. As such, the method is intuitive to the practical researcher already familiar with multiple imputation routines. Results from a simulation study showed that the method provides gains in terms of bias and precision compared with the LOCF approach across a wide range of scenarios. A large cohort study is used to illustrate the practical value of the approach.

[C19.3] Extension of the association structure in joint models to include weighted cumulative effects

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Accurate modelling of the effect of endogeneous time-varying covariates on the relative risk of events involves the use of Joint modelling techniques. In the standard formulation of joint models, the current underlying value of the subject-specific marker is assumed to be associated with the risk of an event occurring at the same time t, through an association parameter alpha. This parameterization fails to address instances wherein the longitudinal outcome has a cumulative effect on the hazard of the event. We postulate a model that allows the risk of an event at time t to be dependent on the integrated longitudinal profile, and further specify the inclusion of a weight function which allows us to incorporate differences in the development of the longitudinal profile over time in the calculation of hazard ratios between subjects.

Motivated by a study measuring diabetes related risk factors and complications, we focus on the relationship between the biomarker HbA1c and the development of sight threatening retinopathy (STR), since the impact of the HbA1c marker on the risk of STR is expected to be cumulative, with the evolution of the HbA1c marker over time contributing to progressively greater damage to the vascular structure of the retina. Opting for a parametric approach, we propose the use of the Normal and Skewed Normal probability density functions as weight functions, which display the oft exhibited form seen in many longitudinal biomarkers, similar to an exponential decay curve, with more recent biomarker levels being more relevant than early follow-up values. These weight functions provide parameters with clinically relevant interpretations whilst retaining a degree of flexibility. In addition, they also allow answering of important clinical questions regarding the relative importance of various segments of the biomarkers history in the estimation of the risk of the event.

[C19.4] A novel approach for jointly modeling survival times and recurrent episodes of disease progression

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Accurate modelling of the effect of endogeneous time-varying covariates on the relative Recurrent episodes of disease progression (tumors, seizures etc) have an impact on their survival times, which requires analysis of recurrent events and survival in practice. Such analysis is mainly done either fitting models separately for recurrent events and survival or by fitting standard survival models where recurrent events are included as covariates in the survival model. However, literature gives evidences that treating both of these outcomes as responses in a joint model is more efficient[1]. Multivariate survival models could have been used for this purpose if the timings of the recurring events are available. In contrast, this study proposes a model which only requires the cumulative count of the recurring event treating the count variable as a Poisson or Negative Binomial and survival data can assume any parametric distribution or semi-parametric Cox model. The only constraint viable is the assumption of proportional hazards in survival times, which facilitates estimating the survival model through a Poisson regression model. Hence, the survival model is represented by a Poisson model and another Poisson model is assumed for the count variable enabling joint modeling of survival and count to be accomplished by joint modeling of two Poissons.The method is applied to a clinical trial dataset with survival time and event counts. Being able to assume any parametric or non-parametric model for survival data and not imposing any restrictions between the distributions of count and survival data in contrast to [1] formulates the main significance. The method can be applied for any data scenario which requires joint modeling of count and survival and extending the model for hierarchical/clustered data constitutes future work.

References

Cowling, B. J., Hutton, J. L., & Shaw, J. E. H. (2006).Joint modelling of event counts and survival times.Journal of the Royal Statistical Society: Series C (Applied Statistics), 55(1), 31-39.

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