Joint models of longitudinal and time-to-event data: extensions and recent developments

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WHAT IS JOINT MODELLING?

- In clinical trials or cohort studies, measurements are repeatedly measured over time (e.g. cardiac ejection fraction), which we call longitudinal data.
- In addition, the time to one or more clinical endpoints (e.g. death) is recorded, which we call time-to-event data.
- Historically, these data have been analysed separately.

Problems with standard models?

- Sicker patients more likely to drop out of study → informative missingness
- Repeated outcomes measured with error → estimator attenuation
- Time-varying covariates treated as constant between follow-up time in event-time model → unrealistic

EXTENSION TO MULTIVARIATE DATA

In practice, multiple (k ≥ 1) repeated measures will be recorded for each patient.

In addition, multiple (G ≥ 1), recurrent, or competing events might be of clinical importance.

Harnessing all available data in a single model is advantageous, leading to improved predictions and reduced bias, making it an attractive tool in an era of personalized medicine.

RECENT METHODOLOGICAL DEVELOPMENTS

- Research has predominantly focused on univariate data, but a review identified a growing methodological literature on multivariate data.
- Majority of articles only considered either multivariate longitudinal or time-to-event data, not both.
- Numerous innovations in models, distributional assumptions, estimation methodologies.
- Diverse range of association structures (red box in model graph above) linking sub-models.
- Limited clinical applications, with methodological papers concentrating mostly on cardiovascular, neurodegenerative, lung, cancer, and HIV/AIDS diseases.

SOFTWARE

- Currently no statistical software available to fit joint models to multivariate longitudinal data.
- A number of software options for fitting joint models to competing risks data, each incorporating different sub-models and association structures.
- Multivariate data increases number of random effects in model, leading to exponential increase in computational time.
- joinerR package freely available for installation in R software for fitting joint models to univariate data.
- Development of joinerR to incorporate multivariate outcomes is on-going.

META-ANALYSIS (MA) OF JOINT OUTCOMES

- Investigation to examine the benefits of joint models in a multi study case.
- Consider two stage MA where models are fitted to each study then study coefficients pooled using standard MA methods.

Findings**

Separate (orange) and joint models gave similar results in longitudinal MA and joint models increasingly underestimated as association increased.

Within joint modelling methods, worse coverage where profile likelihood (red, blue, green) estimated standard errors rather than bootstraping (purple).

Conclusion: Benefit of pooling joint modelling results in MA over separate results for time-to-event coefficients where association exists between longitudinal and time-to-event outcomes.

*All results available from author

JOINT OUTCOME MA – SIMULATION STUDY

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