STRengthening Analytical Thinking for Observational Studies (STRATOS): Introducing the Survival Analysis Topic Group (TG8)

Per Kragh Andersen[1], Michal Abrahamowicz[2], Terry M. Therneau[3] on behalf of STRATOS TG8.

[1]Biostatistics, University of Copenhagen, Denmark.

[2]Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada.

[3]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA.

This article continues the series describing the STRATOS initiative and its topic groups. In previous issues the topic groups: Missing Data (TG1), Measurement Error (TG4), Initial Data Analysis (TG3), Selection of Variables and Functional Forms in Multivariable Analysis (TG2), Causal inference (TG7), High-dimensional Data (TG9), and Study Design (TG5) were presented. In this issue, we introduce the STRATOS Topic Group 8 (TG8): Survival Analysis, and we report on current activities and future plans. In the initial paper describing the STRATOS initiative (Sauerbrei et al., 2014), TGs 1-7 were presented, however, it soon became apparent that survival analysis poses a number of challenges for which guidance on several levels are warranted. This led to the formation of TG8 later in 2014 with Michal Abrahamowicz (McGill University, Canada) Terry Therneau (Mayo Clinic, USA), and Per Kragh Andersen (University of Copenhagen, Denmark) as co-chairs. Further members of TG8 are: Richard Cook (University of Waterloo, Canada), Hans van Houwelingen (Leiden University, The Netherlands), Pierre Joly (University of Bordeaux, France), Torben Martinussen (University of Copenhagen, Denmark), Maja Pohar Perme (University of Ljubljana, Slovenia), and Jeremy Taylor (University of Michigan, USA).

The aim of TG8 is to provide guidance for the way in which time-to-event data arising from observational studies are analyzed and on how results are interpreted. This is needed because survival analysis is one of the methodologies most frequently used in modern epidemiological studies of human health. Indeed, numerous health outcomes, such as disease occurrence, progression, relapse, cure, or death, are the end results of longitudinal evolution in the relevant biological parameters, or the effects of exposures and treatments that accumulate over time; hence a time-to-event paradigm provides a natural framework for their analyses. As a consequence, all statisticians working in a medical research environment are very likely to be involved in the applications of time-to-event analyses, even if their training and interests have focused on deferent areas of statistical research. On the other hand, the specific nature of time-to-event data requires addressing particular challenges, first of all related to censored observations but also to changes over time in the risk of the outcome and in the values of the predictors. Reviews (e.g., by Altman et al., 1995) have shown that many applications of survival analysis suffer from a number of shortcomings and this is in spite of the fact that several non-technical books and journal articles have described principles of analysis.

So far, most of our attention has been focused on a paper for statisticians giving guidance about the use of intensity models in observational studies with a time-to-event outcome. Since, in general multistate models, the intensity is the basic parameter this seems an obvious parameter to target. Focus in the paper is on a single occurrence of a single type of event, such as (cause-specific) death, onset/diagnosis of a disease, or first hospital re-admission. Recurrent themes are that hazard models known from survival analysis are applicable in such situations and that studies of this kind have a number of common features. These include, e.g., specification of the time axis for analysis, how to deal with incomplete observation in the form of right-censoring and delayed entry, and how to use and interpret models including time-dependent covariates. Also, the concept of immortal time bias is relevant in all such studies. We provide some check lists that we find useful to consider, however, it is important to emphasize that these check lists cannot be taken as `cookbooks' on how to conduct time to event analysis in observational studies. Rather, they are meant as guidelines and we emphasize that the most important item to consider when planning such an analysis is to clearly specify the research question and think about to what extent the available data allow an answer to that question. We also identify research questions for which an intensity model only provides one step towards an answer and where further analyses are needed. These include risk prediction for non-fatal events and causal inference.

Finally, we present some worked examples using the methods summarized and going through the check lists provided. Further details concerning these examples are collected as Supplementary Material that also includes information on how the methods are conducted in R.

Even though the paper is not short, it fails to discuss a number of aspects that are also of importance. These include most mathematical details about properties of the methods, as well as analysis of data with competing risks, recurrent events, and more general multi-state models. We focus on the Cox regression model throughout (and to a lesser extent the piecewise exponential/`Poisson' model) and discussion of AFT models, additive hazards models as well as random effects (`frailty') models, e.g. joint models for the event intensity and an internal time-dependent covariate, is not included. Some of these may be topics for forthcoming papers from TG8.

Members of TG8 have had a number of telephone conference calls and (subgroups) have met in person at the ISCB conference in Utrecht (2015), at IBC meetings in Copenhagen (2017) and Barcelona (2018), and at the Lifetime Data Science Conference in Pittsburgh (2019). Finally, two meetings (2016 and 2019) at Banff International Research Station in Canada have been instrumental for our work.

Members of TG8 have given presentations on behalf of the topic group. Terry Therneau talked about "The STRATOS survival task group" at ISCB in Utrecht in 2015 and about "Survival models for observational studies: issues and recommendations" at ISCB in Melbourne 2018. Maja Pohar Perme talked about "On some practical issues in the analysis of survival data" at ISCB in Birmingham 2016. Michal Abrahamowicz talked about "Flexible modeling of non-linear and time-dependent effects of predictors in survival analysis" at IBC in Victoria 2016, about "Time-related complexities in the

analyses of observational time-to-event studies of health: why do we need more refined statistical methods?" at HEC in Munich 2017, about "STRATOS and flexible modelling of time-dependent covariates in time-to-event analyses" at a reginal IBS meeting in Thessaloniki 2017, and (with Y. Wang) about "Assessing non-linear and time-dependent effects of a sparsely measured time-varying covariate" at ISCB in Melbourne 2018.

References

Altman, D.G., De Stavola, B.L., Love, S.B., Stepniewska, K.A. (1995). Review of survival analyses published in cancer journals. Br. J. Cancer 72, 511-18.

Sauerbrei, W., Abrahamowicz, M., Altman, D.G., le Cessie, S., Carpenter, J. on behalf of the STRATOS initiative. (2014). STRengthening Analytical Thinking for Observational Studies: the STRATOS initiative. Statist. in Med. 33, 5413-5432.3

Region News

Australasian Region (AR)

http://www.biometricsociety.org.au/about.html

Biometrics by the Botanic Gardens
Regional Conference, Adelaide, 1-6 December 2019

Make a note in your diary and book the first week in December for coming to Adelaide, South Australia. Short courses and workshops on a range of topics will be given on Sunday 1st Dec and Monday 2nd Dec, with the main conference running from Tuesday 3rd - Friday 6th Dec. Attuned to the interests of the regional membership, the conference will look at statistics research and applications in medicine and public health, agriculture and environment, genetics, natural sciences and education. Invited speakers include international and Australasian statisticians at various stages of their careers: Marti Anderson, Daniela Bustos-Korts, James Carpenter, Claudia Czado, Joanne De Faveri, Max Moldovan, Blair Robertson and Christopher Wikle.

Early bird registration closes: 19th September 2019.

More information is available on the conference website, www.ausbiometric2019.org.

Save the Dates...

26-28 Nov 2019: New Zealand Statistical Association Conference, Dunedin, New Zealand, www.otago.ac.nz/nzsa

1-6 Dec 2019: IBS-AR Regional Conference, Adelaide, Australia, www.ausbiometric2019.org

30 Nov-4 Dec 2020: Australasian Applied Statistics Conference 2020, Victoria, Australia

IBS-AR Student Scholarships

To help attract enthusiastic and talented students to career paths in biometrics, the Australasian Region offers scholarships for suitably qualified students who intend to undertake a fourth or honours year of study, or a coursework Masters, in statistics, mathematical statistics, biostatistics, bioinformatics or biometrics. We are delighted to announce the winners of this year's highly contested award: Anna Greenwood (masters in biostatistics at the University of Melbourne) and Harriet Plant (honours student at the University of Auckland). Congratulations!

Biography – Anna Greenwood

I was born in Poland and from a young age I have always had a passion for problem solving and mathematics. When choosing my university degree, I was torn between studying medicine or mathematics and the mathematics won. I completed my undergraduate degree with honours in mathematics at the University of Melbourne focusing on statistics and stochastic processes. Since graduating I have worked for the last 10 years in the finance industry applying problem solving, statistical and computing skills to manage risks and produce analysis to improve the way the business operates and build my management and business skills. Whilst the finance industry offers challenging problems in itself, going forward, I would like to use my skills in the field of medical research where I see many opportunities to be able to enhance people's quality of life, if only even in a small way, through the use of the enormous amounts of health data we are accumulating. I feel particularly passionate about researching food related intolerance and links between gut health and overall health and well-being, having been exposed to some of these impacts with my children. This year I have embarked on the start of my masters in biostatistics at the University of Melbourne, which I hope will be just the beginning of my future in this field. I also look forward to meeting many of the wonderful people making a difference in this field already.

Anna Greenwood, IBS-AR Student Scholarship recipient.