

STRENGTHENING ANALYTICAL THINKING FOR OBSERVATIONAL STUDIES (STRATOS): Update on 2020-2023 Research Activities of Topic Group 8: “Survival Analysis”

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Topic Group 8 “Survival Analysis” (TG8) aims at developing a systematic approach to time-to-event analyses of longitudinal observational studies. Many of our activities focus on addressing complex analytical issues that require *combining expertise concern-*

ing different aspects of survival analysis and/or a systematic, neutral and unbiased comparison of alternative statistical methods. This report presents a concise update on TG8 activities and accomplishments in 2020-2023, i.e. since the first TG8 report was published in *Biometric Bulletin* in 2019.

In the past four years, new experts in survival analysis have joined TG8, which currently involves 12 researchers from eight countries on three continents, including three co-chairs: Michal Abrahamowicz (Canada), Malka Gorfine (Israel) and Terry Therneau (USA); as well as nine members: Federico Ambrogi (Italy), Per Kragh Andersen (Denmark), Richard Cook (Canada), Maja Perme Pohar (Slovenia), Pierre Joly (France), Torben Martinussen (Denmark), Hein Putter (the Netherlands), Michael Schell (USA), and Jeremy Taylor (USA).

A major achievement for TG8 was the publishing of a comprehensive paper in *Statistics in Medicine* in 2021 [1]. This paper, jointly authored by all of the then nine members of the topic group, gives guidance to the use of intensity-based (i.e. hazard-based) models, for the analysis of time-to-event data from observational studies. In any general multi-state model, the transition intensities are the fundamental parameters in the sense that a specification of all intensities allows for a likelihood-based inference in the model as well as for simulations from the model. We argue that also for models for a single event, as studied in the paper, the intensity provides a natural, dynamic description of the process of event occurrence. Important features of intensity-based models include the ease with which both right-censoring and delayed entry may be accounted for, the close connection with the proper choice of a time origin for the analysis, and the natural incorporation of time-dependent covariates. Such models are useful in spite of the fact that specification of a single event intensity may not suffice for the purpose of estimating absolute

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risks of event occurrence and that contrasts between intensities do not necessarily allow for a causal interpretation.

In the paper, a review of the Cox proportional hazards model (and some alternatives) is provided as well as checklists, both for the purpose of investigating covariates and censoring before fitting any model, and for subsequent evaluation of the fit of a model [1]. Much attention is paid to a discussion of problems with immortal time bias and the way in which time-dependent covariates may be used for mitigating its impact. The above-mentioned shortcomings when estimating absolute risks and when aiming at causal interpretations are discussed and, finally, three examples are worked through in detail, thus providing illustrations of the use of intensity-based models, their interpretation, and the application of the check lists. Data and R code for the examples are given as part of the Supplementary Materials and the reference list includes 68 papers, most of which explore more in-depth specific analytical issues frequently encountered in survival analysis and/or propose new methods to address them, thus providing inspiration for further reading.

More recently, some TG8 members started inter-group collaborations with selected other STRATOS TGs. These projects focus on complex analytical challenges that require combining expertise in different areas of statistical research, and possibly smoothing some differences between their respective research paradigms and approaches. Specifically, Terry Therneau, one of TG8 co-chairs, collaborated with the members of TG6, which focuses on predictive and diagnostic models, to propose a unified framework for the validation of prediction models built using time-to-event analyses of right-censored outcomes. This collaboration resulted in a recent publication in *Annals of Internal Medicine* [2]. The work started out with a large collection of work to summarize; publications in this area have been voluminous. The paper chose to focus on Cox model prediction since that forms the bulk of survival modeling in medical research. In summary, there are a small number of fundamental principles. Of primary importance is to first think through what successful validation would be, for a particular study, e.g., if our target is to use the results to manage a patient's care for the next two years, then one should focus on predictions over a 2-year window. As well, discrimination and calibration represent different targets, one of which may be more relevant to the question at hand. There is no 'gold standard' target. The second principle is that calibration must be based on predictions with a causal interpretation such as the probability of remaining alive at some chosen time or the mean time in state; the hazard ratio itself is not a valid target. The third principle is to recognize that the fundamental issue in validation of a survival model is that the validation data set will itself be censored, the valid methods for doing so all reprise approaches that have stood the test of time for primary analysis of censored outcomes.

In July 2022, most TG8 members met in-person at the 31th International Biometric Conference (IBC), in Riga, Latvia, and discussed the ideas for new TG8 projects, including the main objectives and general approaches to address the resulting new challenges. These discussions identified three 'internal' projects, each of which will involve several TG8 members, often with complementary expertise and/or slightly diverging views concerning specific analytical issues and/or preferred modeling strategies. The first project aims at developing guidance for multi-state modeling. This project will expand the approaches of the aforementioned TG8 guidance paper for classic single-endpoint survival analysis by Andersen et al [1] to more complex analyses involving transitions between different, consecutive or mutually exclusive states. In this ongoing project, we offer a comprehensive introduction to multistate models, focusing particularly on the general construction of the likelihood function. We subsequently delve

into advanced methodologies tailored for multistate settings, including intermittent observations, pseudo values, and the frailty approach to accommodate within- or between-subject dependence. Additionally, we provide an updated list of pertinent R and Python packages.

The second project will focus on analytical challenges regarding the choice of the multivariable regression model in time-to-event analyses. Whereas the first TG8 guidance paper [1] has briefly outlined the alternatives to the immensely popular Cox proportional hazards model, the latter dominates real-world applications of survival analysis, especially in clinical and epidemiological research. The proposed project will aim at developing and validating objective empirical criteria for choosing between proportional hazards, additive hazards, accelerated failure time and hybrid models. Flexible modeling of the possibly non-linear effects of continuous predictors will be also explored, within each modeling framework. Diagnostic tools to identify violations of the underlying assumptions, and modeling strategies to account for such violations, and to represent time-varying and/or non-linear effects, will be also systematically evaluated. The initial phase will focus on time-fixed (baseline) covariates, but later we will attempt to tackle additional complexities raised by time-varying covariates. The third project will delve into the specific challenges and issues associated with employing machine learning methods for censored survival outcomes. This encompasses recent advancements in deep learning and random forest techniques tailored for survival data. While much of the current research in this burgeoning field focuses primarily on metrics such as ROC-AUC and specific loss functions, bias and calibration are frequently overlooked. Therefore, our objective is to conduct a comprehensive comparison and validation of existing machine learning methods.

Furthermore, we intend to initiate two interdisciplinary projects that will entail close collaborations with other STRATOS TGs. These projects will center on the multifaceted challenges increasingly encountered in complex longitudinal observational studies with repeated measurements of time-varying covariates (TVCs), such as risk/prognostic factors or exposures. One project will address specific challenges related to both measurement and modeling of TVCs, including (i) sparse, irregular measures over time, (ii) measurement errors, as well as possibly their (iii) non-linear effects and/or (iv) cumulative effects on the outcome. This will require combining TG8 expertise in survival analysis with expertise in: (i) Missing Data (TG1), (ii) Measurement Errors (TG4), (iii) Functional Forms (TG2) and (iv) Causal Inference (TG7). Another project will focus on the choice of causal estimands for time-to-event analyses involving time-varying exposures, and will combine expertise of TG8 with Causal Inference (TG7) and Prediction (TG6). The goal will be to develop estimands that could predict changes in both relative and absolute risks that will follow different dynamic interventions or treatment regimes.

In the past three years, TG8 members have also contributed to invited sessions and symposia organized by the STRATOS Initiative. Terry Therneau has presented invited talks at both: (i) Symposium on "Statistical challenges in observational research and guidance recommendations from the STRATOS initiative" at the virtual annual conference of the Society for Epidemiological Research (SER) in June 2021 (talk entitled "A multi-state model for dementia"), and (ii) invited session "Prediction with observational data: STRATOS perspective" at the 31th International Biometric Conference (IBC), in Riga, Latvia, in July 2022 (talk entitled "Assessing performance of survival predictions models"). Michal Abrahamowicz was a co-organizer of both the SER Symposium and IBC session, and gave, on behalf of TG8, a talk on "Selected challenges in multivariable time-to-event analyses" at the invited session "Various issues in multivariable model building" during the Royal Statistical Society (RSS) International Conference in

Manchester, UK, in September 2021. Malka Gorfine presented the talk “The STRATOS initiative - TG8 Report” that summarized recent TG8 accomplishments and activities, as well as plans for future projects, at the (virtual) general STRATOS conference in March 2023.

[1] Andersen PK, Perme MP, van Houwelingen HC, Cook RJ, Joly P, Martinussen T, Taylor JMG, Abrahamowicz M, Therneau TM, for the Topic Group 8 of the STRATOS initiative. Analysis of time-to-event for observational studies: Guidance to the use of intensity models. *Statistics in Medicine* 2021; 40(1):185-211. doi.org/10.1002/sim.8757.

[2] McLernon DJ, Giardello N, van Calster B, Wynants L, van Geloven N, van Schmeden M, Therneau TM, Steyerberg E, for Topic Groups 6 and 8 of the STRATOS initiative. Assessing performance and clinical usefulness in prediction models with survival outcomes: practical guidance for Cox proportional hazards models. *Annals of Internal Medicine* 2023; 176(1):105-114. doi.org/10.7326/M22-0844.

Region News

Argentinian Region (RArg)

Argentine Region Academic Activities

Between 9-12 October 2023, the Argentine Group of Biostatistics (GAB), the Argentine Region of the IBS, held the XXVII Scientific Meeting of the GAB and the Biostatistics Teaching Conference. The events took place at the Faculty of Natural Sciences of the National University of Salta, with the collaboration of this institution. The Biostatistics Teaching Conference, the first specific event focused on the teaching of biostatistics held in the country, had the participation of 90 attendees, both in-person and virtually. The conferences and workshops were led by local and foreign specialists and focused on higher education teaching.

The GAB Annual Scientific Meeting featured renowned speakers from the Argentinean Region as well as from Chilean and Central America & Caribbean Regions. Specialists in areas such as agronomy, chemometrics, medicine, and the environment were also present. Additionally, courses and workshops on current topics of interest were offered during the event, and numerous works were presented in poster format. This event brought together researchers, educators, and students interested in the practical applications of statistics in biological sciences, including biologists, agronomists, computer scientists, chemists, veterinarians, and statisticians. It was an excellent opportunity to promote knowledge exchange among colleagues, receive constructive feedback, and facilitate professional networking.

Young Biometricians Contest

During the XXVII Scientific Meeting of the GAB 2023, the “Susana Fillippini Young Biometricians Contest” took place. Preselected finalists, both undergraduate and graduate students, presented their analytical solutions for the same dataset, and the winners were determined by a five-member jury. The jury commended the participants for their participative attitude and their contribution to biometrics and announced the winners:

- **Undergraduate Level:** First place for Magdalena Damiani and Valentín Rozenblit with a score of 96/100, and Second place for Rubén Mendoza with 90/100.

- **Graduate Level:** First place for Juan Manuel Fiore and Martín Rodríguez Núñez with a score of 98/100.

This contest is held each year to promote the development of skills in statistical consulting among young students directly or indirectly involved in Biometrics.

Silvia Suhring
Biometric Bulletin Correspondent

Australasian Region (AR)

Conference

November 27 to December 1 finally saw a resumption of our biannual conference after a four-year hiatus. It was very good to see old friends and reunite with colleagues, especially our Australian colleagues. The conference was held in the Copthorne Hotel and Resort Bay of Islands, Waitangi, NZ—a venue which turned out to be very pleasant indeed. And, unusually so for New Zealand, the weather cooperated all week with only one bout of rain which happened whilst most were asleep. The conference was a joint event with the Statistical Ecology and Environment Monitoring conference which bought a few extra delegates. Keynote speakers were (in order of appearance): Hans-Pieter Piepho (U. Hohenheim, DE), Lisa Warbrick (Indigenous Genomics Institute, NZ), Adrian Baddeley (Curtin U., AU), David Warton (UNSW, AU), and Joanne Potts (The Analytical Edge, AU).



Caption: IBS-AR conference delegates at the Waitangi Treaty Grounds

E. A. (Alf) Cornish Awards

The conference also allowed the resumption of the Cornish Awards which recognise members in the Australasian Region who have given ‘long-time’ service to the Biometric Society and for the advancement of biometry. The worthy recipients were Past President, Mario D’Antuono (Perth, WA), and IBS Council Representative Chris Triggs (Auckland, NZ).

Annual General Meeting

The AGM saw a variety of issues discussed, the most important of these being the election of office holders and the selection of the next conference location. Alison Kelly (QLD) was nominated and elected as incoming president! With Alison’s election, Vanessa Cave steps down