



# 9th Survival Analysis for Junior Researchers

**13. - 15. September 2023**

Castle Reisensburg | Ulm

**Information and Abstracts**

**abbvie**

The Roche logo consists of the word "Roche" in a bold, blue, sans-serif font, enclosed within a thin blue hexagonal border.



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# Welcome

Welcome to the Survival Analysis for Junior Researchers (SAfJR) conference. We are elated to host this year's conference and hope for three nice days in southern Germany.

This year's conference is the ninth time SAfJR has continued its triumph in a different European city. The conference brings together career-young statisticians working with time-to-event data and offers them interesting days full of scientific discussions, interesting applications and a unique opportunity to present and connect with other junior researchers.

We would like to thank you for all the interesting contributions. They allowed us to assemble an exciting program with topics from Causality, Clinical trials, multi-state models or recurrent events.

This year SAfJR will be accompanied by three experts in the field of survival analysis. Torsten Hothorn outlines the connection between transformation models and time-to-event questions. Torben Martinussen will share his thoughts on the interpretation of the hazard ratio within a causal inference framework. Jan Feifel discusses the use of multistate models to analyze treatment sequences in electronic health records.

The scientific program will be supplemented with plenty of opportunities to interact. The regular breaks, mutual lunches, a Poster and Fingerfood Session, Conference dinner and the original Bavarian Bar will invite you to do so. We hope that the conference will bring you new inspiration, new contacts and an awesome time. We are looking forward to meeting you.

With best wishes from the SAfJR 2023 Organizing Committee,

Alexander, Jan, Jasmin, Judith and Sandra

Don't hesitate to contact us via [safjr2023@uni-ulm.de](mailto:safjr2023@uni-ulm.de)



# Program

Wednesday 13th September 2023

08:30 - 08:55		Registration
08:55 - 09:10		Welcome
09:10 - 10:25	<b>Torsten Hothorn</b> Zurich, Switzerland	A Transformation Perspective on Survival Analysis-Part 1
10:25 - 10:50		Coffee Break
10:50 - 12:05	<b>Torsten Hothorn</b> Zurich, Switzerland	A Transformation Perspective on Survival Analysis-Part 2
12:05 - 12:15		Short Break
12:15 - 12:45	<b>Dominic Edelmann</b> Heidelberg, Germany	Efficient Sampling Strategies for Non-Rare Events: A Journey Through Nested Case-Control in Cancer Biomarker Research
12:45 - 14:00		Lunch
14:00 - 15:00		<b>Session 1</b> Chair: Damjan Manevski
	<b>Alina Schenk</b> Bonn, Germany	Pseudo-Value Regression Trees
	<b>Léa Orsini</b> Paris, France	Frequentist and Bayesian generalized method of moments for pseudo-observations in survival analysis
	<b>Yael Travis-Lumer</b> Jerusalem, Israel	Pseudo-observations for bi-variate survival data
15:00 - 15:15		Short Break
15:15 - 16:35		<b>Session 2</b> Chair: Denis Rustand
	<b>Jost Viebrock</b> Bremen, Germany	Addressing confounding of primary and competing events
	<b>Ilaria Prosepe</b> Leiden, The Netherlands	Combining sequential stratification and inverse probability of treatment weighting to estimate the survival benefit of liver transplantation
	<b>Marta Spreafico</b> Leiden, The Netherlands	Investigating positivity violations in marginal structural survival models: a simulation study
	<b>Matthew Smith</b> London, England	On Causal Inference for the Relative Survival Setting
16:35 - 17:00		Coffee Break
17:00 - 18:20		<b>Session 3</b> Chair: Alice Richardson
	<b>Daniel Gomon</b> Leiden, The Netherlands	Dynamic prediction of survival using multivariate Functional Principal Component Analysis: a strict landmarking approach
	<b>Juliette Murris</b> Paris, France	Random survival forests for analysing survival data with recurrent events
	<b>Sophie Langbein</b> Bremen, Germany	Interpretable Machine Learning for Survival Analysis
	<b>Alonso Silva Allende</b> Paris, France	Exploring Survival Analysis Methods: A Comparison of Classical, Deep Learning, and Tabular Approaches
18:20 - 19:00		Evening Break
19:00 - 21:00		<b>Poster &amp; Fingerfood</b>

## Thursday 14th September 2023

08:45 - 9:45	<b>Session 4</b> Chair: Alina Schenk <b>Simon Mack</b> Magdeburg, Germany <b>Merle Munko</b> Magdeburg, Germany <b>Ariane Cwiling</b> Paris, France	How to correctly infer the progression-free-survival ratio under right-censoring, and an RMST-based alternative Multiple Contrast Tests for the RMST in General Factorial Designs Prediction of the restricted mean survival time
09:45 - 10:10	Coffee Break	
10:10 - 11:10	<b>Session 5</b> Chair: Alexander Stemke <b>Denis Rustand</b> Thuwal, Saudi Arabia <b>Hortense Doms</b> Louvain-la-Neuve, Belgium <b>Tiphaine Saulnier</b> Bordeaux, France	INLAjoint: Bayesian Inference for Joint Models of Longitudinal and Survival Data with Dynamic Risk Prediction Flexible joint model for time-to-event and non-Gaussian longitudinal outcomes Joint analysis of disease progression markers and death using individual temporal recalibration
11:10 - 11:25	Short Break	
11:25 - 12:45	<b>Session 6</b> Chair: Edouard Bonneville <b>Andrea Toloba</b> Barcelona, Spain <b>Angela Carollo</b> Rostock, Germany <b>Marina Zamsheva</b> Halle-Wittenberg, Germany <b>Myrthe D'Haen</b> Hasselt, Belgium	Interval-censored regression covariates Modelling smooth hazards with two time scales Modelling chronic disease mortality by methods from reliability theory Copula based quantile modelling under dependent censoring
12:45 - 14:00	Lunch	

14:00 - 15:00	<b>Torben Martinussen</b> Copenhagen, Denmark	Subtleties in the interpretation of hazard ratios
15:00 - 15:15		Short Break
15:15 - 16:35		<b>Session 7</b>
		Chair: Dominic Edelmann
	<b>Damjan Manevski</b> Ljubljana, Slovenia	Expected life years lost or saved compared to the general population
	<b>Edouard Bonneville</b> Leiden, The Netherlands	Imputing missing covariates for competing risks analyses when using the Fine–Gray model
	<b>Jonathan Broomfield</b> Leicester, United Kingdom	Combining multi-state survival individual patient data and aggregate data in rare disease natural history models
	<b>Leonie Courcoult</b> Bordeaux, France	A joint model for competing risks and longitudinal marker with a time-dependent subject-specific variance
16:35 - 17:00		Coffee Break
17:00 - 18:00		<b>Session 8</b>
		Chair: Marta Spreafico
	<b>Chengyuan Lu</b> Leiden, The Netherlands	Maximum likelihood estimation in the additive hazards model
	<b>Balint Tamasi</b> Zürich, Switzerland	Flexible regression for correlated survival data with mixed-effects additive transformation models
	<b>Maximilian Bardo</b> Göttingen, Germany	The shape of the relative frailty variance induced by discrete random effect distributions in univariate and multivariate survival models
18:00 - 19:00		Evening Break
19:00 - 21:00		<b>Conference Dinner</b>

## Friday 15 September 2023

08:45 - 10:05

**Bor Vratnar**  
Ljubljana, Slovenia

**Jonas Brugger**  
Vienna, Austria

**Vera Arntzen**  
Leiden, The Netherlands

**Yunwei Zhang**  
Sydney, Australia

10:05 - 10:30

### Session 9

Chair: Alice Richardson

Evaluating cancer screening programmes using survival analysis

A two-step approach for analysing time-to-event data under non-proportional hazards

When exactly? Two overlooked biases in SARS-CoV-2 incubation time estimation related to information regarding exposure

Evaluation of the impact of left-censoring on the validity of time-dependent propensity score matching method

Coffee Break

10:30 - 11:30

**Jan Feifel**  
Darmstadt, Germany

Real world evidence supporting clinical development in Oncology - Using multistate models to analyze treatment sequences in electronic health records

11:30 - 12:00

Awards and closing remarks

# Conference Information

## Transportation

Günzburg can be reached with ICE, EC and RE train connections. The train to Ulm lasts 20 minutes, the train to Augsburg 30-60 minutes. More details on German trains can be obtained at [www.bahn.de](http://www.bahn.de). Public transport from Günzburg train station or Günzburg center to Castle Reisensburg is rather unfortunate. From the train station, you need 20 minutes to walk, and from the center, you need 35 minutes to walk to Reisensburg Castle.

Alternatively, you can call a cab using one of these phone numbers.

Taxi Essenwanger, Tel. +498221 5584

Taxi Günzburg, Tel. +498221 1313

+498221 1414

+498221 1515

Taxi Pascha, Tel. +498221 1717

Taxi Schwabenkutsche, Tel. +498221 4434

Taxi Tepe, Tel. +498221 1616

All events at Reisensburg castle are reachable by foot within minutes.

## Conference Venue

The ninth Survival Analysis for Junior Researchers Conference will take place at the Castle Reisensburg in Günzburg.

Reisensburg Castle dates back to a first settlement 4000 years ago. In the sixth century, the area was named with a castle. Until the nineteenth century the castle was owned by several aristocrats. From 1966 the castle was restored and since 1997 it belongs to the corporate assets of the University of Ulm.

The main part of the conference will take place at the Red room. The room is located at the connection of the South Wing and the main castle. The location is also marked on the map on page 9.



Coffee and cookies will be served at each break intersecting two sessions. The breaks will take place at the entrance hall and Colonnade.

The Poster & Fingerfood session will take place at the Colonnade.

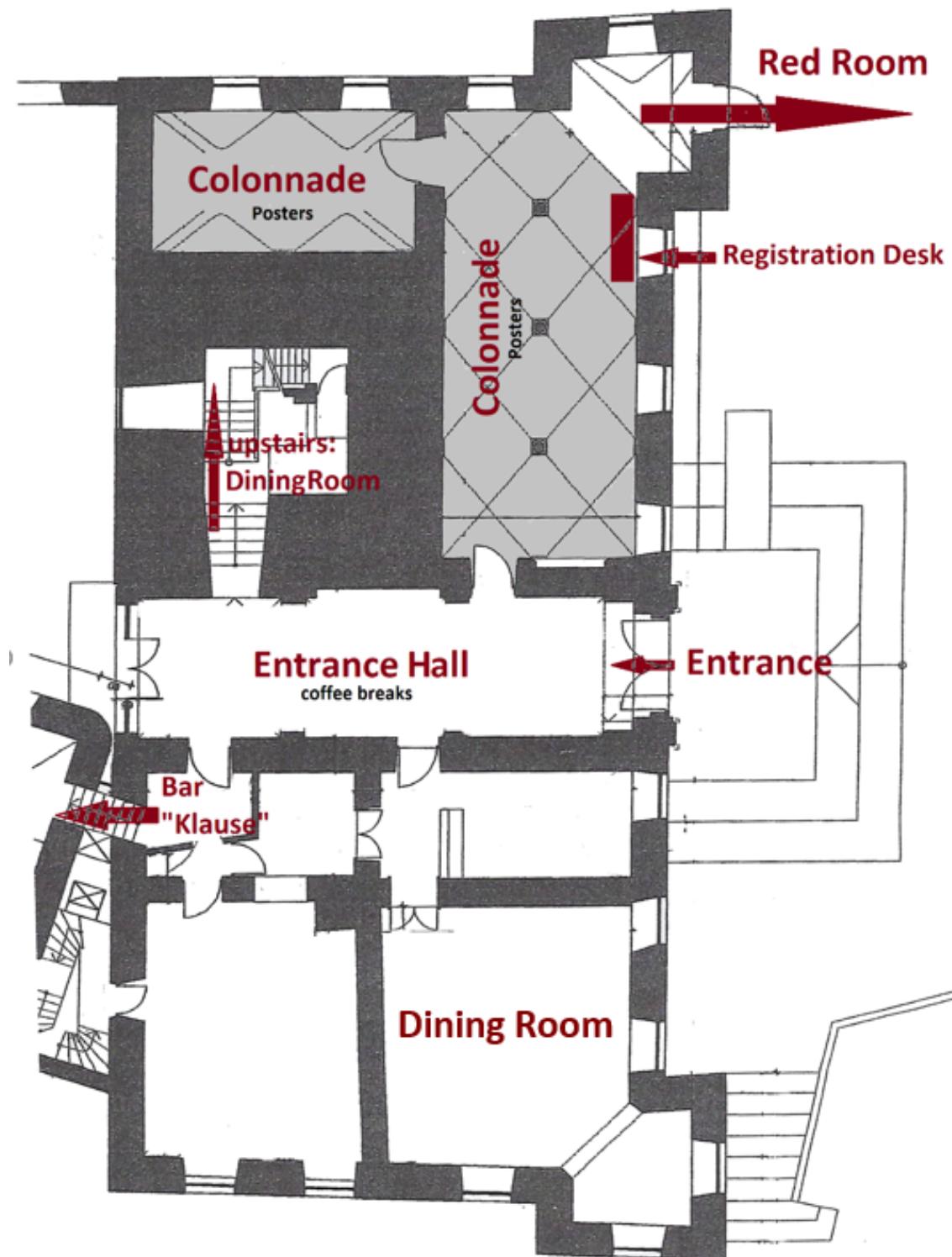
The conference fee includes lunch and dinner on Wednesday and Thursday. Water will be served as well on these occasions. Additionally, there will be cake and pretzels during some breaks. Coffee and tea will also be served during the breaks.

Every participant can order beverages at all times during the day from the waitresses. These beverages are not included in the conference fee and have to be paid on Friday or during check-out. If you order additional drinks, please state your full name to the waitress. This is required for the payment process.

Lunch will be served in the dining rooms located on the ground floor of the main building. The conference dinner will take place at the dining rooms on the first floor.

Throughout the castle, you will find several meeting points with tables and chairs/sofas. There will be also filled refrigerators with beverages. If you take a beverage please mark the taken beverage at the provided list on the site. Please note, those beverages are not included in the conference fee and have to be paid on Friday or during check-out.

This map depicted the ground floor of main building of the Reisensburg castle and highlight several points of interest.



## Accommodation at Reisensburg Castle

Not only will the castle be the conference venue, but the participants can also be accommodated there, hopefully providing an extraordinary ambiance.

Check-in and reception will be open from Tuesday 17:00 until 20:00. Check-in after the reception hours is possible, however, we recommend you to contact the organization team. They will open the main gate and allocate your room.

The participants staying at Reisensburg Castle are either staying in the North or in the South Wing of the castle. There are double and single rooms, which have been allocated regarding your booking preferences. Please note, that no change in rooms is possible. All rooms are booked.



The South Wing (left picture) or the North Wing (right picture) of Reisensburg Castle

At check-out you will be provided with an official invoice for the accommodation. Additionally, the beverages consumed during the conference will be paid. Note, credit card payment is only possible for bills larger than 10 Euro.

## Prizes for best oral and poster presentations

Springer has generously provided the prizes for the best poster and best oral presentations. All winners will be awarded a free Textbook to be selected from the Springer Series in Statistics or Springer Texts in Statistics. Further details will be provided to the winners after the Award session.



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Website: <https://www.springer.com>

## Organizing committee



Dr. Jan Feifel is a statistician and data scientist at Merck KGaA. He focuses on machine/statistical learning and time-to-event methods for real-world data across therapeutic areas. Also, he is contributing to the COMBACTE consortium developing non-standard sampling designs and is curious about causal inference.



Jasmin Rühl is a doctoral candidate in Biostatistics at Augsburg University. Her research addresses inference for causal effect estimates in survival data based on different resampling methods.



Sandra Schmeller is a doctoral candidate in Biostatistics at Ulm University. Her current research interests involve multistate models, especially in the field of stem cell transplanted patients data.



Alexander Stemke is a doctoral candidate in Statistics at Ulm University and employee at Boehringer Ingelheim. His research interests involve Bayesian survival analysis, especially with regards to safety analysis and causal inference. Currently dealing with meta-analytic predictive priors to enhance clinical trials.



Judith Vilsmeier is a doctoral candidate in Biostatistics at Ulm University. Her current research interests involve nonstandard event histories and estimation of complex outcomes in non-Markov multi-state models.



# Information on the short course

## A Transformation Perspective on Survival Analysis (Tutorial)

**Instructor:** Torsten Hothorn<sup>1</sup>

<sup>1</sup> University of Zurich; Zurich (Switzerland)

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### **Summary:**

It is well known that many prominent models in survival analysis can be understood as transformation models. Cox' proportional hazards model is maybe the most prominent case, but also other models, such as the Weibull or the reverse time proportional hazards model, belong to this class.

Survival analysts have always been forced to work with models for conditional distributions (usually looking at conditional survivor functions) because a simple mean regression is neither interesting nor appropriate for describing the impact of patient characteristics on some time-to-event outcome. Thus, the field has much to offer in the recent development of distributional regression models, ie models for a conditional distribution and not just a conditional mean. For this discussion to be fruitful in practice, however, one has to address some old-fashioned habits, such as application of the partial likelihood for semiparametric inference in Cox models.

We will discuss connections between many well-known and some less well-known and even some novel members in the family of transformation models. Once we understood the conceptual simplicity of this model family, we'll introduce a generic estimation approach based on simple maximum likelihood estimators for fully parameterised transformation models. These estimators are also the key ingredient to machine-learning-flavoured approaches, such as transformation trees, transformation forests, and transformation boosting machines.

[ctm.R-forge.R-project.org](http://ctm.R-forge.R-project.org)

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**Course preparation:** Please bring your laptop, with R installed, as well as the latest version of the R-packages `tram`, `TH.data`, `tramME` and `trtf`.



**Torsten Hothorn** is Professor of Biostatistics ad personam at the Epidemiology, Biostatistics and Prevention Institute of the University of Zurich. His research interests lie at the intersection between medical statistics, statistical modelling, machine learning, and statistical software. Over the last two decades, he contributed ensemble methods for regression and survival analysis, model-based recursive partitioning for stratified medicine, and transformation models in general. He has written several textbooks about the application of statistical models in R. Additional, he is the author of the R packages `tram`, `trft`, `mvnorm` and many more. During a tutorial, he will share his insides into the field of transformation models and their application to survival data with us.

# Keynote Sessions

## Subtleties in the interpretation of hazard ratios

Torben Martinussen<sup>1</sup>

<sup>1</sup> University of Copenhagen; Copenhagen (Denmark)

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**Abstract:**

The hazard ratio is one of the most commonly reported measures of treatment effect in randomised trials, yet the source of much misinterpretation. This point was made clear by Hernán (2010) in a commentary, which emphasised that the hazard ratio contrasts populations of treated and untreated individuals who survived a given period of time, populations that will typically fail to be comparable - even in a randomised trial - as a result of different pressures or intensities acting on both populations. The commentary has been very influential, but also a source of surprise and confusion. In this talk, I aim to provide more insight into the subtle interpretation of hazard ratios and differences, by investigating in particular what can be learned about a treatment effect from the hazard ratio becoming 1 after a certain period of time. We further define a hazard ratio that has a causal interpretation and study its relationship to the Cox hazard ratio. I will first give a brief introduction to causal inference.

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**Torben Martinussen** is a professor in the Section of Biostatistics at Copenhagen University. Most of his research focuses on time-to-event endpoints. He is especially interested in regression models, instrumental variables and causal inference for survival data. Additionally to more than 100 published research papers he is referee in several high-ranked statistics journals. Together with Thomas Scheike he wrote the well-known textbook "Dynamic regression models for survival data". He also contributed to the timereg-package in R focusing on regression models for survival data.

# Real world evidence supporting clinical development in Oncology – Using multistate models to analyze treatment sequences in electronic health records

Caroline Foch<sup>1</sup>, Jan Feifel<sup>1</sup>, Chris P. Pescott<sup>1</sup>

<sup>1</sup> Merck Healthcare KGaA, Darmstadt Germany

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## Abstract:

Modern drug development is often associated with the term personalized medicine, tailoring disease treatment to smaller patient groups. In Oncology, patients receive many lines of therapy, and the effect of the complete sequence of treatments on the outcomes is of interest. This differs from the individual effect of therapy A or therapy B on the outcome. A clinical trial would include patients newly diagnosed with malignancies and randomized them to first-line (1L) with therapy A until progression then second-line (2L) with therapy B, or to 1L therapy B until progression then therapy A. Then it would estimate the time from 1L initiation to death for both treatment strategy A then B, or B then A. The analysis could be carried out via a conventional Cox Proportional Hazard model. Nowadays, real-world data (RWD) such as electronic health records in Oncology have also the potential to fill gaps in knowledge about the performance of approved treatments used in routine care settings (Lasiter 2022). When emulating the targeted clinical trial in RWD (Hernán 2022), patients that have already been treated with A, B, and likely further therapies thereafter or in addition, pose an additional challenge. To account for the dynamic nature of the treatment change from one line to the next line, multistate model might be useful to model such time-to-event data (Andersen 1993). Although these models are not new, applying them to RWD raises some specific methodological challenges. Within the context of an Oncology non-interventional study, we will present the methodological challenges related to both the treatment sequencing and the real-world data, and how to account for them in time-to-event analyses.

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**Jan Feifel** is a statistician and senior real-world data scientist within the Research and Development Department of Merck Healthcare KGaA. He is interested in research connecting Epidemiology, Statistics, and clinical drug development, therein, he focuses on machine/statistical learning and time-to-event methods for real-world data across therapeutic areas. Also, he is contributing to the COMBACTE consortium developing non-standard sampling designs and is curious about causal inference. He is a member of the IBS-DR and co-lead of the statistics of stochastic processes working group. He is looking forward to interesting discussions at Castle Reisensburg about time-to-event research and beyond.

# Oral Contributions

## Efficient Sampling Strategies for Non-Rare Events: A Journey Through Nested Case-Control in Cancer Biomarker Research

D. Edelmann<sup>1</sup>, K. Ohneberg<sup>2</sup>, N. Becker<sup>1</sup>, A. Benner<sup>2</sup> and M. Schumacher<sup>3</sup>

<sup>1</sup> German Cancer Research Center; Heidelberg (Germany)

<sup>2</sup> Max Rubner-Institut; Karlsruhe (Germany)

<sup>3</sup> Institute for Medical Biometry and Statistics, Freiburg im Breisgau (Germany)

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### Abstract:

In clinical and epidemiological cancer research, biological samples collected during studies are routinely stored in biobanks. After assessing the main endpoints, researchers may use these samples to measure additional biomarkers and investigate their associations with patient survival outcomes. However, given the considerable costs and time involved in biomarker analysis, it is often infeasible to perform measurements on every patient. Consequently, the development of efficient sampling strategies for patients is crucial to enable accurate estimation of the biomarker's association with survival. While established methods exist for situations where the number of feasible samples exceeds the number of events (e.g. nested case-control sampling), there is limited guidance on addressing non-rare event scenarios.

In 2015, a young and naïve mathematician joined forces with four biostatisticians on a research project focused on this challenge. Together, they embarked on a tedious journey involving countless meetings, in-depth scientific dialogues, a letter to the editor and occasional disputes with fellow researchers, including the notorious Reviewer 2. During this arduous journey, the fellowship gained valuable insights by learning from their own missteps as well as the errors of others.

In this talk, we give an introduction to nested case-control (NCC) sampling and the associated weighting techniques for estimation in the proportional hazards model. We pay special attention to the adaptations of NCC for non-rare events, comparing and contrasting our approaches with innovative methods proposed by other researchers. Moreover we share anecdotes about the development of the research project, aiming to impart valuable insights gained along the way. We reflect on failures, successes and misunderstandings with fellow researchers and discuss how these experiences can be helpful for future research.

### Keywords:

nested case-control; non-rare events; inverse probability weighting.

### References:

D. Edelmann, K. Ohneberg, N. Becker, A. Benner and M. Schumacher (2020): Which patients to sample in clinical cohort studies when the number of events is high and measurement of additional markers is constrained by limited resources. *Cancer Medicine*, 9(20), 7398-7406.

D. Edelmann, K. Ohneberg, N. Becker, A. Benner and M. Schumacher (2023): Letter to the editor regarding the paper "New weighting methods when cases are only a subset of events in a nested case-control study" by Qian M. Zhou, Xuan Wang, Yingye Zheng, and Tianxi Cai. *Biometrical journal* 65(4): e2200360.

Q. M. Zhou, X. Wang, Y. Zheng and T. Cai (2022): New weighting methods when cases are only a subset of events in a nested case-control study. *Biometrical Journal*, 64(7), 1240-1259.

# Pseudo-Value Regression Trees

A. Schenk<sup>1</sup>, M. Berger<sup>1</sup>, M. Schmid<sup>1</sup>

<sup>1</sup> Department of Medical Biometry, Informatics and Epidemiology, Medical Faculty, University of Bonn, Bonn, Germany

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### **Abstract:**

In this work, we present a semi-parametric modeling technique for estimating the survival function from a set of left-truncated and right-censored time-to-event data. Our method, named pseudo-value regression trees (PRT), is based on the pseudo-value regression framework, modeling individual-specific survival probabilities by computing pseudo-values and relating them to a set of covariates. The standard approach to pseudo-value regression is to fit a main-effects model using generalized estimating equations (GEE) (Andersen and Pohar Perme, 2010). PRT extend this approach by building a multivariate regression tree (Hothorn et al., 2006) with pseudo-value outcome and by successively fitting a set of regularized additive models to the data in the nodes of the tree. Due to the combination of tree learning and additive modeling, PRT are able to perform variable selection and to identify relevant interactions between the covariates, thereby addressing several limitations of the standard GEE approach. In addition, PRT includes time-dependent covariate effects in the node-wise models. Interpretability of the PRT fits is ensured by controlling the tree depth. Based on the results of two simulation studies, we investigate the properties of the PRT method and compare it to several alternative modeling techniques. Furthermore, we illustrate PRT by analyzing survival in 3,652 patients enrolled for SUCCESS-A (de Gregorio et al., 2020), a randomized study on primary invasive breast cancer.

### **Keywords:**

Gradient boosting; Interactions; Model trees; Pseudo-values; Survival probabilities

### **References:**

- P. K. Andersen and M. Pohar Perme (2010): Pseudo-observations in survival analysis. *Statistical Methods in Medical Research*, 19(1):71-99.
- A. de Gregorio, L. Häberle, P. A. Fasching, V. Müller, I. Schrader, R. Lorenz, H. Forstbauer, T. W. P. Friedl, E. Bauer, N. de Gregorio, M. Deniz, V. Fink, I. Bekes, U. Andergassen, A. Schneeweiss, H. Tesch, S. Mahner, S. Y. Brucker, J. U. Blohmer, T. N. Fehm, G. Heinrich, K. Lato, M. W. Beckmann, B. Rack and W. Janni (2020): Gemcitabine as adjuvant chemotherapy in patients with high-risk early breast cancer – results from the randomized phase III SUCCESS-A trial. *Breast Cancer Research*, 22(1):111.
- T. Hothorn, K. Hornik and A. Zeileis (2006): Unbiased recursive partitioning: A conditional inference framework. *Journal of Computational and Graphical Statistics*, 15(1):651-674.

# Frequentist and Bayesian generalized method of moments for pseudo-observations in survival analysis

L. Orsini<sup>1</sup>, C. Brard<sup>1</sup>, E. Lesaffre<sup>2</sup>, D. Dejardin<sup>3</sup> and G. Le Teuff<sup>1</sup>

<sup>1</sup> CESP, INSERM U1018, Université Paris-Saclay, UVSQ; Villejuif (France)

<sup>2</sup> I-Biostat, KU-Leuven; Leuven (Belgium)

<sup>3</sup> Product Development, Data Sciences, F. Hoffmann-La Roche AG; Basel (Switzerland)

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## Abstract:

The analysis of pseudo-observations offers an alternative to the Cox model and is particularly interesting for complex survival modeling (Andersen et al., 2003). Its advantage lies in overcoming the complexity of censored data modeling. Pseudo-observations can be analyzed using Generalized Estimating Equations (GEE). We propose a new approach, the generalized method of moments (GMM) developed by Hansen (1982), for analyzing Kaplan-Meier-based pseudo-observations. In the frequentist framework, this approach based on minimizing quadratic inference functions has better theoretical efficiency than GEE when the working correlation matrix is misspecified (Qu et al., 2000). Yin (2009) proposed a Bayesian version based on a pseudo-likelihood function. In the Bayesian framework, the analysis of pseudo-observations may offer an attractive alternative to the Bayesian survival analysis, avoiding the baseline hazard function specification. Therefore, we extended the frequentist and Bayesian GMM to the pseudo-observations analysis specificities (with a cloglog link function and under different working correlation matrices). We compared the performances of these approaches to the Cox, GEE, and Bayesian piecewise exponential models through a simulation study of two-arm randomized clinical trials. The frequentist GMM gave similar performances compared to GEE. The Bayesian GMM slightly overestimates the treatment effect for small sample sizes. Higher variances were observed with pseudo-observations-based models. For illustration, we used three randomized clinical trials involving Ewing-Sarcoma patients with different sample sizes and prognostics regarding overall survival. GMM approaches gave valid estimates compared to the benchmark approaches. The Bayesian GMM analysis of pseudo-observations also opens new perspectives on analyzing complex survival models.

## Keywords:

Generalized method of moments; Pseudo-observations; Survival analysis; Bayesian analysis

## References:

- A. Qu, B. G. Lindsay, and B. Li (2000). Improving generalised estimating equations using quadratic inference functions. *Biometrika*, 87(4):823–836.
- G. Yin (2009). Bayesian generalized method of moments. *Bayesian Analysis*, 4(2):191–208.
- L. P. Hansen (1982). Large Sample Properties of Generalized Method of Moments Estimators. *Econometrica*, 50(4): 1029.
- P. K. Andersen, J. P. Klein, and S. Rosthøj (2003): Generalised linear models for correlated pseudo-observations, with applications to multi-state models. *Biometrika*, 90(1):15–27.

# Pseudo-observations for bi-variate survival data

Y. Travis-Lumer<sup>1</sup>, M. Mandel<sup>1</sup> and R. Betensky <sup>2</sup>

<sup>1</sup> Hebrew University of Jerusalem; Jerusalem (Israel)

<sup>2</sup> New York University; New York (New York)

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## **Abstract:**

Pseudo-observations are frequently used in survival analysis to estimate model parameters in a generalized linear model. This method is used regularly to estimate quantities such as survival probabilities, restricted mean life, competing risks cumulative incidence, and other quantities that depend on a univariate failure-time variable. In this work, we propose to generalize the pseudo-observations approach to situations when a bi-variate failure-time variable is observed, subject to right censoring. Our method is based on the idea of first estimating the joint survival function of both failure times and then using it to define the relevant pseudo-observations. Once the pseudo-observations are calculated, we can then estimate the associated regression coefficients, where the pseudo-observations are used as the response in a generalized linear model. We consider several estimators for the joint survival function, including non-parametric and semi-parametric estimators, and different censoring mechanisms. Our proposed method enables estimation of quantities such as joint survival probabilities, conditional survival probabilities, and conditional expectations. In fact, our method can also be used to estimate marginal survival probabilities and can be seen as a general framework that includes estimation of univariate quantities as special cases. Nevertheless, the proposed method is especially useful in situations where standard survival analysis methods do not apply. Finally, we demonstrate the method using simulations.

## **Keywords:**

pseudo-observations; multi-variate survival analysis; censoring; generalized linear models; generalized estimating equations.

## Session 2

# Addressing confounding of primary and competing events

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### **Abstract:**

Epidemiological research includes the exploration of the effect of an exposure, e.g. smoking, on a health outcome. This outcome is often the time to an event of primary interest, e.g. time to dementia. In time-to-event-settings, competing events may occur. A competing event is such that it prevents the primary event to occur or renders it meaningless. The way how competing events are handled is relevant to the interpretation of results. For example, in smokers, the total mortality increases while the overall risk of a dementia diagnosis, perhaps surprisingly, decreases (Rojas-Saunero et al., 2021). Whether or not such findings can be viewed as biased depends on the exact research question. Young et al. (2020) introduce "total effect" and "controlled direct effect": While the total effect describes the overall effect of an exposure regardless of the competing event, the direct effect is the effect in a hypothetical world where the competing event is eliminated. The latter may be implausible: for example, evaluating colonoscopy as a way to decrease the colorectal cancer incidence rate in an elderly population, we cannot prevent the patients from dying. In settings where elimination is sensible, "censoring"(=eliminating) of the competing event must take confounding with the primary event into account. In this work, we study the role of confounding between the competing and primary events. We show how to correct for time-varying and baseline confounding by inverse probability weighting. This is illustrated with a simulation study reinforcing the conclusions of Rojas-Saunero et al. (2021); and we assess the potential bias when the analysis does not reflect the causal question. As an outlook, we provide a perspective on separable effects (Stensrud et al., 2022).

### **Keywords:**

causal inference; direct / total causal effects; simulation study; baseline / time-varying confounding; inverse probability weighting.

### **References:**

Rojas-Saunero, L Paloma and Young, Jessica G. and Didelez, Vanessa and Ikram, M. Arfan and Swanson, Sonja A. (2021): Some very nice title. medRxiv, 2021-06.

Young, Jessica G and Stensrud, Mats J and Tchetgen Tchetgen, Eric J and Hernán, Miguel A (2020): A causal framework for classical statistical estimands in failure-time settings with competing events Statistics in medicine, 39(8):1199–1236.

Stensrud, Mats J and Young, Jessica G and Didelez, Vanessa and Robins, James M and Hernán, Miguel A (2020): Separable effects for causal inference in the presence of competing events Journal of the American Statistical Association, 117(537):175–183.

# Combining sequential stratification and inverse probability of treatment weighting to estimate the survival benefit of liver transplantation

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## Abstract:

For patients with end-stage liver disease, liver transplant represents a life-saving treatment. However, due to a limited supply of donor organs, many patients are placed on a wait-list. Organ allocation organizations have recently shown interest in using survival benefit, defined as the difference in expected survival with and without transplant, as a criterion for donor allocation.

Estimating survival benefit from observational registry data presents two main challenges: time-dependent confounding, generated by biomarkers which are highly predictive of both wait-list survival as well as transplantation chances, and multiple time scales.

The aim of this study is to propose a method for estimating individualized survival benefit in such a way that it would be possible to then predict survival benefit on a dynamic population of patients, at any time a donor becomes available. Previous work has proposed sequential stratification to account for the two time axes (Q. Gong and D.E Schaubel, 2013). In the proposed method, sequential stratification is combined with adjustments for time-dependent confounding using inverse probability of treatment weighting (IPTW). Differently from previous work (Q. Gong and D.E Schaubel, 2013, 2017), the proposed approach estimates survival benefit via only one marginal structural model, where treatment is a time-dependent covariate.

We present simulation results showing that our method can estimate survival benefit on the dynamic population unbiasedly, as opposed to simpler methods. We also apply the proposed method to liver transplant data from the Eurotransplant region and show the potential effect of allocating donors based on survival benefit.

The proposed methodology allows for the dynamic estimation of survival benefit for currently wait-listed patients and can help support decisions on which wait-list patients should be prioritized.

## Keywords:

sequential stratification; inverse probability of treatment weighting; survival analysis; causal inference; survival benefit.

## References:

- Q. Gong and D.E Schaubel (2013): Partly Conditional Estimation of the Effect of a Time-Dependent Factor in the Presence of Dependent Censoring. *Biometrics*, 69(2):338-347.
- Q. Gong and D.E Schaubel (2017): Estimating the average treatment effect on survival based on observational data and using partly conditional modeling: Treatment Effect on Survival via Partly Conditional Regression. *Biometrics*, 73(1):134-144.

# Investigating positivity violations in marginal structural survival models: a simulation study

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## Abstract:

Marginal Structural Models (MSM) with Inverse Probability of Treatment Weighting (IPTW) are used to estimate the causal effect of an exposure on survival outcomes, accounting for the presence of time-dependent confounders. Longitudinal observational data are increasingly used in this context, as IPTW creates a new pseudo-population where exposure is no longer affected by confounders. The accuracy of the estimates relies on four key causal assumptions: no interference, positivity, consistency, and conditional exchangeability. However, these assumptions are difficult to test and often rely on expert knowledge. The impact of violations of these assumptions is not widely understood, making it a statistical challenge.

In this work, a simulation study is performed to investigate the effect of violations of the positivity assumption on the performance MSM-IPTW estimators in a survival context with time-dependent confounders. Building on the algorithms by Havercroft and Havercroft and Didelez (2012) and Keogh et al. (2021), two simulation settings with binary exposure are investigated. Both algorithms are extended to incorporate strict violations of positivity by varying confounder thresholds, follow-up length, and sample size. Non-strict cases where some exposure levels are rare within certain confounder levels are also considered. Results show that even modest violations of positivity can lead to estimators that are very unstable and/or may exhibit high variability.

Assessing positivity is a delicate process, as even modest violations can yield to poor estimator. This study is the first to analyse violations of the positivity assumption in a survival framework with time-dependent confounders. The findings highlight the importance of carefully assessing causal assumptions and the impact of positivity violations in a survival context in presence of time-dependent confounders.

## Keywords:

Marginal structural models; Survival outcomes; Positivity assumption; Simulation studies

## References:

- W.G. Havercroft, V. Didelez (2012): Simulating from marginal structural models with time-dependent confounding. *Statistics in medicine*, 31(30):4190–4206.
- R.H. Keogh, S.R. Seaman, J.M. Gran, S. Vansteelandt (2021): Simulating longitudinal data from marginal structural models using the additive hazard model. *Biometrical Journal*, 63:1526–1541.

# On Causal Inference for the Relative Survival Setting

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## Abstract:

In public health research, the causal effect of a treatment (or exposure/intervention/policy) on cause-specific death after a disease diagnosis is often of interest. Other causes of death prevent the event of interest from happening, thus defining a competing risk setting. In such settings, the total (or direct) causal effect can be estimated when the cause of death is known because the overall hazard of death can be decomposed into the sum of cause-specific hazards (due to the disease and due to other-cause) (Young *et al*, 2020). However, this relies on a strong assumption of knowing the exact cause of death, which, if violated, could lead to biased estimates of the causal effect: in population-based settings, records for the cause of death are often unreliable or poorly recorded.

Alternatively, one could estimate the causal effect of the treatment in a relative survival setting by using external information obtained from population life tables (stratified by sociodemographic characteristics) to estimate the other-cause hazard and then estimate the disease-specific hazard (Pohar Perme *et al*, 2016). The relationship between these hazards can be arranged to give a probability that an observed death is due to the event of interest or other causes (Maringe *et al*, 2018). In a sample of a population of patients with a disease of interest, we propose to weight the overall mortality (regardless the cause of death) by the probability of event-type. After applying weights, the total causal effect is estimated using the g-formula in a conventional competing risk analysis, thereby providing marginal causal interpretations for the estimand of interest (Young *et al*, 2020).

We will illustrate the performance of our proposed methodological framework using a simulation study and highlight its benefits and interpretation in a practical application using data from a sample of patients with cancer.

## Keywords:

Causal Inference; Competing Risks; Relative Survival; Epidemiology; Cancer.

## References:

- C. Maringe, M. Pohar Perme, J. Stare, B. Rachet (2018): Explained variation of excess hazard models. *Statistics in Medicine*, 37(14):2284-2300. <https://doi.org/10.1002/sim.7645>
- M. Pohar Perme, J. Estève, B. Rachet (2016): Analysing population-based cancer survival – settling the controversies. *BMC Cancer*, 16(933). <https://doi.org/10.1186/s12885-016-2967-9>
- J.G. Young, M.J. Stensrud, E.J. Tchetgen Tchetgen, M.A. Hernán. (2020): A causal framework for classical statistical estimands in failure-time settings with competing events. *Statistics in Medicine*, 39(8):1199–1236. doi:10.1002/sim.8471

## Session 3

# Dynamic prediction of survival using multivariate Functional Principal Component Analysis: a strict landmarking approach

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### **Abstract:**

Dynamically updating the prediction of patient survival probabilities using longitudinal measurements has become of great importance with routine data collection becoming more common. Landmark analysis is a very popular approach for this problem due to its simplicity and computational feasibility. Recently, multi-step landmarking procedures have been developed where the longitudinal trajectories are first summarised using an appropriate method, such as Functional Principal Component Analysis (FPCA). The benefit of using FPCA is that no underlying structure needs to be specified for the longitudinal trajectories. Afterwards, these summaries are used in a survival model (e.g. Cox regression) to make predictions. Many of these approaches however fail to landmark the training data, an approach we call “relaxed” landmarking.

Longitudinal outcomes are often compared between subjects on a study time scale, even though the time of entry into the study might not be clinically relevant. Especially in an observational study this might not be the case, as participants will differ significantly in age at baseline. We would therefore like to eliminate the natural variation in the longitudinal trajectories caused by the age disparity between subjects before performing further analyses.

We develop an Age-based Centered multivariate Functional Principal Component Analysis (ABC mF-PCA) technique to describe subjects using their age-at-observation and extend the multi-step landmarking approach proposed by Li and Luo (2019). We show in a simulation study that erroneously modelling covariates using time-on-study instead of using age-at-observation drastically reduces prediction accuracy. We formalise the difference between a “relaxed” landmarking approach where only validation data is landmarked and a “strict” landmarking approach where all data is landmarked. An application of our method to an observational study on Alzheimer’s disease (ADNI) shows that strict landmarking approaches significantly improve prediction accuracy.

Relaxed landmarking approaches introduce bias in the survival model, thereby failing to effectively use the information contained in the longitudinal outcomes and do not significantly improve prediction accuracy, whereas a strict landmarking approach can substantially improve prediction accuracy. Modelling longitudinal covariates on an appropriate and meaningful time scale is vital to extract relevant information for prediction purposes.

### **Keywords:**

Dynamic prediction; Functional Principal Component Analysis; Landmark Analysis

### **References:**

K. Li and S. Luo (2019): Dynamic prediction of Alzheimer’s disease progression using features of multiple longitudinal outcomes and time-to-event data. *Statistics in Medicine*, 38(24):4804-4818.

# Random survival forests for analysing survival data with recurrent events

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## Abstract:

Random survival forests (RSF) are commonly used in medical research. Such approaches have shown their utility in modelling complex relationships between predictors and survival outcomes, overcoming for instance linearity or low dimensionality assumptions (number of individuals greater than the number of predictors). Nevertheless, such RSF have not been adapted to survival data with recurrent events. This work presents an extension of the RSF for this type of data by exploiting concepts from non-parametric survival analysis and statistical learning.

Based on the survival tree methodology introduced by Ishwaran, *et al.* (2008), the key construction steps were adapted to the pattern of recurrent events and using a non-parametric approach. The splitting rule at each node for data partitioning is the pseudo-score test and the estimation at each terminal node is carried out by the Nelson-Aalen estimator of the mean cumulative function. As an ensemble method, the random forest is then obtained by combining several of such trees to produce one optimal model, ensuring estimates stability and addressing overfitting issues. The score is an adjustment of the Harrell's concordance index to recurrent event data and considers the event occurrence rates across individuals. Variable importance through permutation is also computed. Several trees were already built on bladder dataset from the survival package in R. Results were very promising with C-index values greater than 0.5 and up to 0.89. Further results are yet to be available based on both simulated data and readily accessible samples for the application of the proposed approach.

The proposed approach for survival analysis with recurrent events represents a novel and promising method for analysing time-to-recurrence data. It namely embodies new basics for further development and applications in statistical learning. Therefore, this work is deemed of great interest for survival analysis with recurrent events in medical research.

## Keywords:

survival analysis; recurrent events; ensemble methods.

## References:

Ishwaran, H., Kogalur, U. B., Blackstone, E. H., & Lauer, M. S. (2008). Random survival forests.

# Interpretable Machine Learning for Survival Analysis

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## Abstract:

With the spread and rapid advancement of black box machine learning models, the field of interpretable machine learning (IML) has become increasingly important over the last decade. This is particularly relevant for survival analysis, where explainability can uncover a model's potential biases and limitations and provide more mathematically sound ways to understand how and which features are influential for prediction or constitute risk factors. Thus, transparency and accountability are promoted in sensitive areas, such as clinical decision making processes, the development of targeted therapies, interventions or in other healthcare related contexts. However, the lack of readily available IML methods may have deterred researchers from leveraging the full potential of machine learning for analyzing time-to-event data (P. Wang et al., 2019).

A few local, model-agnostic IML methods have been extended to survival outcomes, such as counterfactual explanations, local interpretable model-agnostic explanations (LIME) or Shapley additive explanations (SHAP) (M. S. Kovalev et al., 2020, 2021; M. Krzyziński et al., 2023). M. Krzyziński et al. (2023) have developed survex to implement three of those methods for survival analysis in R. However, the vast majority of IML methods, including partial dependence plots (PDP), individual conditional expectation (ICE), and accumulated local effects (ALE) plots, have yet to be tailored for survival analysis and implemented in software. Further, none of the proposed extensions is capable of explaining survival models with competing risks.

We present a comprehensive review of IML methods for survival analysis. In addition, we formally detail how commonly used IML methods can be adapted to survival outcomes and competing risks and implement methods such as PDP, ICE and ALE in an open-source R package. The software design is focusing on compatibility with existing packages for machine learning survival models, thereby enhancing accessibility for researchers and practitioners in the field of survival analysis. Lastly, the potential of future research for improving model-agnostic as well as developing model-specific IML methods is explored.

## Keywords:

machine learning; interpretable machine learning; explainable AI; R; model-agnostic IML.

## References:

P. Wang, Y. Li and C. Reddy (2019): Machine Learning for Survival Analysis: A Survey. ACM Computing Surveys (CSUR) 51:6:1-36.

M. Krzyziński, M. Spytek, H. Baniecki and P. Biecek (2023): SurvSHAP(t): Time-dependent explanations of machine learning survival models. Knowledge-Based Systems 262:110234.

M. S. Kovalev, L. V. Utkin and E. M. Kasimov (2020): SurvLIME: A method for explaining machine learning survival models. Knowledge-Based Systems 203:106164.

M. S. Kovalev, L. V. Utkin and E. M. Kasimov (2021): Counterfactual explanation of machine learning survival models. Informatica 32.4:817-847.

# Exploring Survival Analysis Methods: A Comparison of Classical, Deep Learning, and Tabular Approaches

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## **Abstract:**

Survival analysis has several applications in fields such as medicine, engineering, and economics. With the recent progress of complex deep learning models, there has been an increasing interest in exploring their potential in several fields including natural language processing, image processing, and survival analysis. Deep learning models handle complex data structures like images and natural language. On the other hand, survival analysis handle data that consists of time-to-event outcomes, and traditional statistical approaches includes Cox-regression model and random survival forests. Despite the recent progress in deep learning, their performance on survival analysis tasks shows only a marginal improvement compared with traditional methods (Lee et al., 2018).

This work proposes a modification of the NODE (Popov et al., 2019) and TabNet (Arik and Pfister, 2020) models to survival analysis tasks. This is based on the fact that tabular models can effectively handle structured data, which is very common in survival analysis tasks. In this way, this work explores the potential of tabular methods in survival analysis, an idea that has been relatively unexplored in recent years. Also, this work compares classical survival methods based on random forest trees (Random Survival Forest, XGBoost Survival Embeddings), deep learning methods based on transformers (DeepHit, DeepSurv), and the tabular architectures, using a strict benchmarking on several open datasets like METABRIC, GBSG, SUPPORT, among others.

Furthermore, regarding evaluation methods, one problem in evaluating the performance of survival analysis models is the use of the concordance index as a metric (Harrell et al., 1982). While the concordance index is commonly used to measure the effectiveness of models, it only provides a comparison based on rank and does not measure the accuracy of exact match predictions. This can be problematic in some contexts, so for this reason this work proposes alternative metrics (in addition to concordance index and Brier score) for a more accurate evaluation of survival models.

## **Keywords:**

tabular models; deep learning; random survival forest; pytorch; open datasets.

## **References:**

- C. Lee, W. Zame, J. Yoon, and M. van der Schaar (2018): DeepHit: A Deep Learning Approach to Survival Analysis With Competing Risks. Proceedings of the AAAI Conference on Artificial Intelligence, 32(1).
- F. E. Harrell, R. M. Califf, D. B. Pryor, K. L. Lee and R. A. Rosati. Evaluating the Yield of Medical Tests. JAMA. 1982;247(18):2543–2546.
- S. O. Arik and T. Pfister (2020): TabNet: Attentive Interpretable Tabular Learning. arXiv preprint arXiv:1908.07442, cs.LG.
- S. Popov, S. Morozov and A. Babenko (2019): Neural Oblivious Decision Ensembles for Deep Learning on Tabular Data. arXiv preprint arXiv:1909.06312, cs.LG.

# How to correctly infer the progression-free-survival ratio under right-censoring, and an RMST-based alternative

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### **Abstract:**

The progression-free-survival ratio (PFSr) is a popular endpoint in oncology trials, where the patients serve as their own control. However, the current, popular methodology by Hoff is rather based on heuristics and intuitions, and ignores potentially right-censoring leading to biased results. In this talk, we point out the close connection between this popular endpoint and the relative treatment effect, also known as the concordance measure. We apply recent results about the latter for multivariate survival data borrowing techniques from competing risks. In this way, we develop a mathematically correct inference strategy for the PFSr under right-censoring. Moreover, we propose the ratio of restricted mean survival times as an alternative measure in this context. For both endpoints, valid resampling procedures are presented to improve the performance for small sample sizes. The novel methods are exemplified by an extensive simulation study and a real data analysis.

### **Keywords:**

Paired survival data; Progression-free-survival ratio; Resampling; Restricted mean survival time; Techniques for competing risks.

# Multiple Contrast Tests for the RMST in General Factorial Designs

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## Abstract:

Several methods in survival analysis rely on the proportional hazards assumption, such as the famous Cox proportional hazards model (Cox, 1972). However, this assumption is neither always satisfied nor easy to check. Therefore, effect estimands that do not rely on this assumption, such as the restricted mean survival time (RMST), are highly desirable in practical applications. The RMST is defined as the area under the survival curve up to a prespecified time point and, thus, summarizes the survival curve into a meaningful estimand.

For two-sample comparisons based on the RMST, Horiguchi and Uno (2020) detected an inflation of type-I error of the asymptotic test for small samples and, therefore, proposed a permutation test under exchangeability. Ditzhaus et al. (2021) extended this approach such that different censoring distributions in the two groups are allowed. The first aim is to further extend the permutation test of Ditzhaus et al. (2021) for general factorial designs and general linear hypotheses by considering a Wald-type test statistic and its asymptotic behavior. Additionally, a groupwise bootstrap approach is considered.

Moreover, when a global test detects a significant difference by comparing the RMSTs of more than two groups, it is of interest which specific RMST differences cause the result. However, global tests do not provide this information. Therefore, the next step is to develop multiple linear hypothesis tests for the RMST. Hereby, we incorporate the asymptotic exact dependency structure between the local test statistics to gain more power. Finally, the small sample performance of the proposed global and multiple testing procedures are analyzed in simulations.

## Keywords:

factorial design; multiple testing; nonproportional hazards; resampling; RMST.

## References:

- D. R. Cox (1972): Regression models and life-tables. *Journal of the Royal Statistical Society. Series B (Methodological)*, 34(2):187–220.
- M. Ditzhaus, M. Yu and J. Xu (2021): Studentized permutation method for comparing restricted mean survival times with small sample from randomized trials. *arXiv preprint arXiv:2102.10186*.
- M. Horiguchi and H. Uno (2020): On permutation tests for comparing restricted mean survival time with small sample from randomized trials. *Statistics in Medicine*, 39(20):2655–2670.

# Prediction of the restricted mean survival time

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## Abstract:

Survival analysis provides robust methods adapted to censored data. The majority of these methods aim to estimate outcomes such as the survival function and to make inferences about the impact of covariates on the hazard rate, using models like the well-established Cox model. However, few methods are used in practice for prediction purposes. The focus of our work centers on the prediction of the restricted mean survival time (RMST), defined as the expected duration until the occurrence of an event of interest or a predefined time horizon. The RMST is a clinically meaningful quantity, whose prediction has gained considerable attention in recent years due to its interpretability (Andersen et al., 2004; Tian et al., 2014; Wang and Schaubel, 2018). Thus, there is a need for exploring methods to evaluate the performance of prediction models in this context. The C-index (Heagerty and Zheng, 2005) has become a widely used metric, however it has been shown not to be a proper scoring function (Blanche et al., 2018). In this talk, we propose a new measure designed to approximate the mean squared error of a RMST prediction model, relying on inverse probability censoring weighting (IPCW). This measure is derived from the Brier score estimator in Gerds and Schumacher (2006). In addition, we introduce a new algorithm for the construction of prediction intervals for the RMST. This model-agnostic algorithm combines conformal prediction and censoring weighting. We extend this approach to study local and global variable importance within a prediction model. These methods are derived from the leave-one-covariate-out procedure in Lei et al. (2018) which we combine with IPCW. We prove that the new tools developed for this analysis framework are asymptotically valid. We present experiments on simulations and real data as an illustration of our theoretical results.

## Keywords:

RMST prediction; Brier score; conformal; prediction intervals; variable importance.

## References:

- P. K. Andersen, M. G. Hansen and J. P. Klein (2004): Regression analysis of restricted mean survival time based on pseudo-observations. *Lifetime Data Analysis*, 10(4):335-350.
- P. Blanche, M. W. Kattan and T. A. Gerds (2018): The c-index is not proper for the evaluation of t-year predicted risks. *Biostatistics*, 20(2):347-357.
- T. A. Gerds and M. Schumacher (2006): Consistent estimation of the expected brier score in general survival models with right-censored event times. *Biometrical Journal*, 48(6):1029-1040.
- P. J. Heagerty and Y. Zheng (2005): Survival Model Predictive Accuracy and ROC Curves. *Biometrics*, 61(1):92-105.
- J. Lei, M. G'Sell, A. Rinaldo, R. J. Tibshirani and L. Wasserman (2018): Distribution-free predictive inference for regression. *Journal of the American Statistical Association*, 113(523):1094-1111.
- L. Tian, L. Zhao and L. J. Wei (2014): Predicting the restricted mean event time with the subject's baseline covariates in survival analysis. *Biostatistics*, 15(2):222-233.
- X. Wang and D. E. Schaubel (2018): Modeling restricted mean survival time under general censoring mechanisms. *Lifetime Data Analysis*, 24(1):176-199.

## Session 5

# INLAjoint: Bayesian Inference for Joint Models of Longitudinal and Survival Data with Dynamic Risk Prediction

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### **Abstract:**

The R package INLAjoint is designed to handle a variety of longitudinal models, including mixed effects, proportional odds and zero-inflated models, as well as survival models such as frailty, mixture cure, competing risks, and multi-state models. These models can be assembled to form complex joint models with shared or correlated random effects, providing a flexible and efficient method for analyzing multivariate longitudinal and survival data.

The INLA algorithm performs Bayesian inference through deterministic approximation, it avoids the long computation times and convergence issues encountered when fitting the most complex joint models with standard iterative algorithms. Indeed, simulation studies demonstrate that INLAjoint substantially reduces computation time and the variability of parameter estimates compared to alternative strategies such as Markov chain Monte Carlo, Monte Carlo expectation maximization or Newton-like algorithms (Rustand et al., 2023 a,b).

A key application of joint models is the dynamic prediction of the risk of an event, such as death or disease progression, based on changes in the longitudinal outcome(s) over time. INLAjoint allows for the estimation of dynamic risk predictions and can incorporate changes in the longitudinal outcome to update future risk predictions.

Overall, INLAjoint offers a flexible and efficient method for modeling joint longitudinal and survival outcomes, handling a range of models, and enabling dynamic risk predictions. These features make it a valuable tool for analyzing complex health data and may help towards personalized decision in medicine.

### **Keywords:**

Bayesian inference; Joint modeling; Dynamic Prediction.

### **References:**

- Rustand, D., van Niekerk, J., Rue, H., Tournigand, C., Rondeau, V., & Briollais, L. (2023 a): Bayesian estimation of two-part joint models for a longitudinal semicontinuous biomarker and a terminal event with INLA: Interests for cancer clinical trial evaluation. *Biometrical Journal*, 2100322.
- Rustand, D., van Niekerk, J., Krainski, E. T., Rue, H., & Proust-Lima, C. (2023 b): Fast and flexible inference approach for joint models of multivariate longitudinal and survival data using Integrated Nested Laplace Approximations. *arXiv:2203.06256*.

# Flexible joint model for time-to-event and non-Gaussian longitudinal outcomes

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## Abstract:

In medical studies, while the primary interest is often to record the time at which a particular event occurs, information on multiple biomarkers is also collected longitudinally throughout the follow-up period. This provides a combination of survival and longitudinal information on each individual under study. To measure the association between repeated measurements and the risk of an event, joint models for longitudinal and time-to-event data are frequently used. In the most common joint model approach, repeated measurements of a biomarker are modelled using a linear mixed model and the risk of event is modelled using a proportional hazard model. The latter assumes a linear relationship between the survival covariates and the log hazard. In this work, we propose an extension that allows for possible non-linear effects of some survival covariates by using Bayesian penalised B-splines (Lang and Brezger, 2004). Our model is valid for Gaussian and non-Gaussian longitudinal responses since we use a generalized linear mixed model for the longitudinal process. The parameters are estimated under a Bayesian approach using Markov chain Monte Carlo algorithms. A simulation study is conducted to evaluate the accuracy of our methodology. Finally, the study that motivated our research concerns patients with a first progression of glioblastoma. Glioblastoma is the most common brain cancer in adults, but its survival prognosis is very poor. It is therefore essential to be able to identify prognostic factors for this cancer in order to guide treatment strategies. We use our methodology on these data to assess the effects of potential prognostic factors more accurately.

## Keywords:

Joint models; Survival analysis; Bayesian P-splines.

## References:

S. Lang and A. Brezger (2004): Bayesian P-splines. *Journal of Computational and Graphical Statistics*, 13:183-212.

# Joint analysis of disease progression markers and death using individual temporal recalibration

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## Abstract:

Establishing the natural history of a disease permits to better understand its progression over time. However, in complex diseases, its study often faces multiple challenges. When the disease is difficult to diagnose, uncertainty remains around the time of disease onset. Patients are potentially recruited in cohorts at different disease stages, making time in study no longer meaningful. Occurrence of clinical events, such as death, also interrupts follow-ups, inducing missing data potentially not at random. (Saulnier et al., 2022)

The present work introduces a joint model combining a disease progression model (Li et al., 2019) based on an individual temporal recalibration to describe markers progression according to the latent disease time and a survival model to assess the association with death. The methodology is motivated by the study of Multiple system atrophy (MSA), a rare neurodegenerative disease. (Foubert-Samier et al., 2020)

The markers' progressions are described according to disease time using nonlinear mixed-effect models. Disease time is defined according to disease severity at inclusion and an individual random shift. The risk of death is jointly modeled according to the markers' dynamics and the individual temporal shift. Estimation, implemented in the R-package LTSM, is carried out in the Maximum Likelihood Framework using Quasi-Monte-Carlo approximations and Marquardt-Levenberg optimizer. (Philipps et al., 2020)

Annual data of 663 patients from the French MSA cohort were analyzed over 10.8 years. MSA progression was described by the Unified MSA Rating Scale sumscores I (functional sphere) and II (motor sphere). Once time recalibrated, their progressions spanned over 12 years. Compared to non-dependent patients at inclusion, mean time gaps between moderately-dependent and helpless patients at inclusion were 2.56 (95%CI=2.36,2.76) and 5.84 (95%CI=4.92,6.77) years, respectively. Risk of death highly depended on markers' dynamics and individual shift (with higher risk for more advanced patients).

This latent disease time approach has potential to describe complex disease progression while accounting for heterogeneity of patients' profiles and informative dropout.

## Keywords:

longitudinal data; individual time recalibration; disease progression; informative dropout; joint model.

## References:

- A. Foubert-Samier, A. Pavy-Le Traon, F. Guillet et al. (2020): Disease progression and prognostic factors in multiple system atrophy: A prospective cohort study. *Neurobiology of Disease*, 139:104813.
- D. Li, S. Iddi, W.K. Thompson et al. (2019): Alzheimer's Disease Neuroimaging Initiative. Bayesian latent time joint mixed effect models for multicohort longitudinal data. *Statistical Methods in Medical Research*, 28: 835–45.
- V. Philipps, B.P. Hejblum, M. Prague et al. (2020): Robust and efficient optimization using a Marquardt-Levenberg algorithm with R package marqLevAlg. *R Journal*.
- T. Saulnier, V. Philipps, W.G. Meissner et al. (2022): Joint models for the longitudinal analysis of measurement scales in the presence of informative dropout. *Methods Elsevier*, 203:142–51.

## Session 6

### Interval-censored regression covariates

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#### **Abstract:**

Concentrations of metabolites in blood plasma are usually measured with laboratory techniques that have limits of detection and quantification, resulting in some measurements being interval-censored. Research in nutritional epidemiology often combines metabolites from the same family; these combined measurements result in overlapping intervals that may provide enough information to draw inferences about the variable of interest. Nutrition data provides hence a source of censoring different from the standard time-to-event data and, in contrast to the latter, the censoring is mostly encountered in covariates.

Scientific literature on regression models with interval-censored covariates is rather scarce. The GEL algorithm (Gómez et al., 2003) was developed to fit a linear regression model with an interval-censored covariate. The approach has been recently employed for HIV data (Morrison et al., 2022), and has been extended to generalized linear models (Gómez et al., 2022). Our work currently focuses on residual analysis and goodness-of-fit statistics for generalized linear models with interval-censored covariates. The censoring nature of the data is transferred to residuals, so existing procedures for model checking must be adapted. Further research is planned to accommodate other response schemes, such as non-exponential family distributions and censored responses. This work is nourished by methods of survival analysis for interval-censored data.

#### **Keywords:**

interval censoring; generalized linear models; residual analysis.

#### **References:**

- G. Gómez Melis, A. Espinal and S. W. Lagakos (2003): Inference for a linear regression model with an interval-censored covariate. *Statistics in Medicine*, 22(3):409-425.
- G. Gómez Melis, M. Marhuenda-Muñoz and K. Langohr (2022): Regression analysis with interval-censored covariates. Application to liquid chromatography. In Sun J., Chen DG. (eds) *Emerging topics in modeling interval-censored survival data*. ICSA Book Series in Statistics. Springer, Cham.
- D. Morrison, O. Laeyendecker and R. Brookmeyer (2022): Regression with interval-censored covariates: Application to cross-sectional incidence estimation. *Biometrics*, 78(3):908-921.

# Modelling smooth hazards with two time scales

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## Abstract:

Time to event data can involve more than one time scale. For example, in medical and epidemiological studies, time since disease onset and age of the patient (which is time since birth) may jointly determine the occurrence of an event, such as death or severe complication. The hazard over two time scales,  $t$  and  $s$ , can be modelled by two-dimensional  $P$ -splines. The Lexis plane is first divided in a grid of small bins, and the data are binned in two arrays of exposure times and events counts. Then, a model for the log-hazard is estimated using Poisson regression and a linear combination of the tensor-product of two  $B$ -splines bases, built over the two time axes, whose coefficients are restricted by difference penalties. In case there are covariates available, the approach can be extended to a proportional hazards (PH) model with a baseline hazard varying over two time scales. To efficiently estimate this model array algorithms are employed (see Currie et al. (2006)). The results of the estimation can be visualized as an image plot of the (log-)hazard over the two time scales. Finally, this bivariate hazard can be compared with a simpler hazard, where the effect of the two time scales is additive on the log-scale, rather than non-additive. To make statistical models accessible for data analyses and to promote their usage statistical software is essential. Therefore we developed the R-package TwoTimeScales which implements the model presented in Carollo et al. (2020). Here we use the proposed model, and the companion software, to study time to the first cardiovascular (CVD) complication after diabetes onset for patients diagnosed with Type 1 Diabetes Mellitus (T1D). The data come from the DCCT/EDIC study (Nathan, 2013), and the two relevant time scales are age and duration of diabetes.

## Keywords:

Time to event; Time scales; P-splines; Diabetes.

## References:

- Carollo, A., H. Putter, P. Eilers, and J. Gampe (2020): Hazard smoothing along two time scales. In: *Proceeding of the 35<sup>th</sup> International Workshop on Statistical Modelling*, 31-34.
- Currie, I. D., M. Durban, and P. H. C. Eilers (2006): Generalized linear array models with applications to multidimensional smoothing. *Journal of the Royal Statistical Society: Series B*, 68(2):259-280.
- Nathan, D. M. (2013): The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. *Diabetes Care*, 37:9-16.

# Modelling chronic disease mortality by methods from reliability theory

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## Abstract:

Methods of accelerated life testing (ALT) are widely used in reliability theory for estimating lifetime of technical items (Nelson, 1980). To this task, items are exposed systematically to higher stress levels of, e.g. temperature, voltage or pressure. By exposing the items to these higher stress levels, failures happen more quickly, providing more information and statistical power for analysis in a shorter period of time. With respect to chronic diseases in humans we conceptualize the diagnosis of a chronic disease here as inducing stress which is expected to shorten its residual lifetime, or, equivalently, accelerating its time to death.

We use the tampered random variable (TRV) model of Degroot and Goel (1979) and Gompertz distributions to model impact of type 2 diabetes on lifetime using data from the population-based CARLA cohort (Greiser et al., 2009). The TRV model correctly accounts for the semi-competing risk structure in the data, uses information from prevalent as well as incident cases of disease and takes truncation property in the cohort data into account. In addition, using parametric distributions offers reporting model results on the original time scale. In an extension of the estimation procedure, we also allow the age at diabetes diagnosis to be observed not exactly, but only in an interval. Model parameters can be estimated by maximum likelihood method, and we give some preliminary results of a simulation study showing our approach works well.

The  $\gamma$  parameter of the TRV model describes the impact of a diabetes diagnosis and can be interpreted conveniently as an acceleration factor of time. We present the first results for the analysis of the CARLA cohort data. The remaining lifetime after diagnosis would be divide by  $\gamma$ , that is in average 1.17 [95%CI : 1.09, 1.25] for men and 1.25 [95%CI : 1.15, 1.35] for women.

## Keywords:

accelerated life testing; Gompertz distribution; survival time; chronic disease; maximum likelihood.

## References:

- M.H. Degroot and P.K. Goel (1979): Bayesian estimation and optimal designs in partially accelerated life testing. Naval Research Logistics Quarterly, 26(2):223-235.
- K.H. Greiser, A. Kluttig, B. Schumann, C.A. Swenne, J.A. Kors, O. Kuss, J. Haerting, H. Schmidt, J. Thiery and K. Werdan (2009): Cardiovascular Diseases, Risk Factors and Short-Term Heart Rate Variability in an Elderly General Population: The Carla Study 2002–2006. European Journal of Epidemiology, 24(3):123-142.
- W. Nelson (1980): Accelerated Life Testing - Step-Stress Models and Data Analyses. IEEE Transactions on Reliability, R-29(2):103-108.

# Copula based quantile modelling under dependent censoring

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## Abstract:

In the context of survival analysis under random right censoring, one may observe a censoring time  $C$  for some values rather than the survival time  $T$ . Often such censoring is dealt with under an independence assumption on  $T$  and  $C$  given the covariate  $X$ . However, in some cases this may not be a very realistic assumption; by taking care of the possible dependency, inference on the survival time could be handled more accurately. In our research, this inference for  $T$  is done with a focus on quantile regression, but some broader regression results are obtained as a by-product as well. In order to capture any dependence, the quantile model for  $T$  is derived from a bivariate copula model for  $(T, C)$ . For this copula model, we follow the approach proposed in Czado and Van Keilegom (2022), that allows taking a flexible copula parameter to deal with the in practice often unknown association. It comes at the cost of marginals that are necessarily fully parametric, but this can be overcome by considering the family of so-called *enriched asymmetric Laplace* (EAL) distributions for  $T$ : while preserving the parametric character, they enable introducing sufficient modelling flexibility by means of Laguerre orthogonal polynomials. By modifying the reasoning in Czado and Van Keilegom (2022), we show identifiability of the bivariate model, comprising *all* parameters for  $T$  rather than only its quantiles. In this sense, the work also falls within the scope of distributional regression.

## Keywords:

Survival analysis; dependent censoring; quantile regression; copulas; parametric modelling.

## References:

- C. Czado and I. Van Keilegom (2022): Dependent censoring based on parametric copulas. *Biometrika*, <https://doi.org/10.1093/biomet/asac067>.

## Session 7

# Expected life years lost or saved compared to the general population

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### Abstract:

For cohorts with long-term follow-up, the number of years lost due to a certain disease yields a measure with a simple and appealing interpretation. A recent overview of this methodology has been published and two measures have been proposed (Andersen, 2013, 2017). In this work, a third option is introduced (Manevski et al., 2023), which may be useful in the settings in which the other two measures are inappropriate. In all three measures, the survival of the given data set is compared to the expected survival in the general population which is calculated using external mortality tables. The first measure is defined in the competing risks setting and assumes an excess hazard compared to the general population, while the other two measures also allow estimation for groups that live better than the general population. In this case, the observed survival of the patients is compared to that in the general population, the starting point of this comparison depends on the study entry (e.g. disease diagnosis or simply the age at which the inclusion criteria were known to be met). We illustrate the differences between the three measures, their assumptions, interpretation and the corresponding estimators, as well as the possible challenges (e.g. extrapolation) that could occur in practice. The developed methodology will be illustrated using real-life data based on the recently developed R implementation in the package `relsurv`.

### Keywords:

life years lost, competing risks, mortality tables, relative survival.

### References:

- D. Manevski, N. Ružić Gorenjec, P. K. Andersen, M. Pohar Perme (2023): Expected life years compared to the general population. *Biometrical Journal*, 65, 2200070.
- P. K. Andersen (2013): Decomposition of number of life years lost according to causes of death. *Statistics in Medicine*, 32:5278–5285.
- P. K. Andersen (2017): Life years lost among patients with a given disease. *Statistics in Medicine*, 36(22):3573–3582.

# Imputing missing covariates for competing risks analyses when using the Fine–Gray model

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## Abstract:

The Fine–Gray (FG) model for the subdistribution hazard is widely used for the development of prognostic models in the presence of competing events. At model development, when missing values occur in covariates, researchers may choose to multiply impute them. While previous work has investigated the use of multiple imputation (MI) for cause-specific (CS) Cox proportional hazards models (Bartlett and Taylor, 2016), no such guidance exists in the FG context. Notably, whether a substantive-model-compatible approach (known as SMC-FCS, see Bartlett et al. (2015)) can be extended to the FG model is an open question.

Assuming interest lies in estimating the risk of only one of the competing events (henceforth referred to as ‘cause 1’), we propose a MI approach that makes use of the parallels between the FG model and the standard (single-event) Cox model. Namely, in the presence of random right censoring, the potential censoring times for those failing from competing events can be multiply imputed, after which standard software for fitting Cox models can be used to fit a FG model.

Our approach therefore involves multiply imputing the potential censoring times in a first step, and then imputing the missing covariates analogously to the single-event setting in a second step. Compatibility between the imputation model and the FG model is ensured when the second step is done using existing SMC-FCS software. In a simulation study, we compared the performance our approach with an approximately compatible alternative, as well as with imputing compatibly with a CS model. This demonstrated that our approach is to be preferred when the FG model for cause 1 is correctly specified.

The proposed two-step approach therefore provides a way to impute missing covariates compatibly with a FG model, making efficient use of existing software.

## Keywords:

multiple imputation; missing covariates; Fine–Gray model.

## References:

- J. W. Bartlett and J. M. Taylor (2016): Missing covariates in competing risks analysis. *Biostatistics*, 17(4), 751-763.
- J. W. Bartlett, S. R. Seaman, I. R. White, J. R. Carpenter, and Alzheimer’s Disease Neuroimaging Initiative\* (2015): Multiple imputation of covariates by fully conditional specification: accommodating the substantive model. *Statistical methods in medical research*, 24(4), 462-487.

# Combining multi-state survival individual patient data and aggregate data in rare disease natural history models

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## Abstract:

Multi-state survival analysis considers several potential events of interest along a disease pathway. In the era of personalised medicine, such analyses are becoming crucial to model complex patient trajectories and are increasingly being used in health technology assessments to represent the natural history of a disease. In rare diseases, multi-state natural history modelling is often limited by data paucity and heterogeneity. Previous work investigated scenarios when individual patient data (IPD) is available from all data sources (Broomfield et al., 2023), and found that one-stage approaches can struggle to converge or be subject to bias in relevant predictions, whereas a two-stage approach may be more robust and less subject to bias. We extend this to scenarios where some data sources only provide aggregate data (AD) and compare two methods for combining this AD with any available IPD. A two-stage method collapsing the IPD into AD and performing an AD multi-state survival meta-analysis is compared to a one-stage method based on simulating multiple sets of IPD from AD (Yamaguchi et al., 2014). The number of simulated sets of IPD in the one-stage approach was also investigated, since this method has not previously been considered in a survival setting. The ratio of studies providing AD only to studies providing full IPD was varied, as was the form of the AD (from full model output to a single transition rate). While the two-stage method is straightforward to implement, it cannot handle covariate patterns as readily and so struggles to produce generalisable predictions. The one-stage method is able to capture covariate distributions and standardise over relevant (e.g. study-specific) populations, which is of particular use in natural history modelling as this allows a meaningful baseline comparison to be constructed for a new trial or study. We demonstrate model implementations in Stata.

## Keywords:

multi-state; individual patient data; aggregate data; meta-analysis; rare diseases

## References:

- J. Broomfield, K. Abrams, S. Freeman, N. Latimer, M. Rutherford, M. Crowther, on behalf of Project HERCULES, the CINRG investigators and D-RSC members (2023): Modelling the multi-state natural history of rare diseases with heterogeneous individual patient data: a simulation study. [Manuscript submitted for publication].
- Y. Yamaguchi, W. Sakamoto, M. Goto, J. Staessen, J. Wang, F. Gueyffier and R. Riley (2014): Meta-analysis of a continuous outcome combining individual patient data and aggregate data: a method based on simulated individual patient data. *Research Synthesis Methods*, 5: 322-351.

# A joint model for competing risks and longitudinal marker with a time-dependent subject-specific variance

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## **Abstract:**

A high level of blood pressure is a well-known risk factor for several major cardio- and cerebrovascular diseases but an increasing number of studies suggests that individual blood pressure variability may also be an independent risk factor for these events. However, these studies suffer from significant methodological weaknesses and often consider a time-independent variability (de Courson et al, 2021). The objective of this work was to develop and apply a location-scale joint model with a time-dependent subject-specific variance for the longitudinal marker and competing events to study the association between blood pressure variability and health events.

The proposed joint model combines a mixed model for longitudinal data and a cause-specific model for competing events with proportional intensities. The residual variance of the marker is modelled according to subject-specific random intercept and random slope and possibly covariates. The risk of events may depend simultaneously on the current value of the residual variance, as well as, the current value and the current slope of the marker. The estimation procedure maximizes the likelihood function and is implemented in an R-package. The estimation procedure was validated through a simulation study. The model was applied to the data of the PROGRESS clinical trial for the prevention of the recurrence of stroke that includes 6105 subjects followed over 5 years with 12 measurement times for blood pressure (Mac Mahon et al, 2001).

We demonstrated that the risk of major cardio- or cerebrovascular events and the risk of competing death increased with the variability of blood pressure. It may be relevant for investigating the association between the variability of markers and the risk of health events in various fields of medical research (e.g., emotional instability and psychiatric events).

## **Keywords:**

Location-scale model, Heterogeneous variance, Blood Pressure, Cardio- and Cerebrovascular diseases

## **References:**

- H. de Courson, L. Ferrer, A. Barbieri, P. J. Tully, M. Woodward, J. Chalmers, C. Tzourio and K. Leffondré (2021): Impact of model choice when studying the relationship between blood pressure variability and risk of stroke recurrence. *Hypertension*, 78(5):1520–1526.
- S. Mac Mahon, S. Neal, C. Tzourio, A. Rodgers, M. Woodward, J. Cutler, C. Anderson, and J. Chalmers (2001): Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *The Lancet*, 358(9287):1033–1041.

## Session 8

# Maximum likelihood estimation in the additive hazards model

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### **Abstract:**

The additive hazards model specifies the effect of covariates on the hazard in an additive way, in contrast to the popular Cox model, in which it is multiplicative. As non-parametric model, additive hazards offer a very flexible way of modeling time-varying covariate effects. It is most commonly estimated by ordinary least squares. In this paper we consider the case where covariates are bounded, and derive the maximum likelihood estimator under the constraint that the hazard is non-negative for all covariate values in their domain. We show that the maximum likelihood estimator may be obtained by separately maximizing the log-likelihood contribution of each event time point, and we show that the maximizing problem is equivalent to fitting a series of Poisson regression models with an identity link under non-negativity constraints. We derive an analytic solution to the maximum likelihood estimator. We contrast the maximum likelihood estimator with the ordinary least squares estimator in a simulation study and show that the maximum likelihood estimator has smaller mean squared error than the ordinary least squares estimator. An illustration with data on patients with carcinoma of the oropharynx is provided.

### **Keywords:**

Additive hazards; Constrained optimization; Maximum likelihood.

# Flexible regression for correlated survival data with mixed-effects additive transformation models

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## Abstract:

Mixed-effects additive transformation models provide a powerful and flexible framework for regression analysis of correlated time-to-event outcomes. Building on the likelihood-based transformation model framework by Hothorn et al. (2018), this approach extends the model to include random effects and penalized additive terms. The direct parameterization of the conditional outcome distribution allows for efficient accommodation of any form of random censoring and truncation.

The resulting mixed-effects additive transformation model is particularly useful in complex survival settings with correlated data, nonlinear predictor-outcome relationships, and non-proportional effects. The fully parametric likelihood-based estimation and inference of the model is discussed, and a fast and efficient R implementation, called `tramME` (Tamási and Hothorn, 2021), is presented.

In addition, the model's versatility is demonstrated with example applications, including complex grouped data structures and spatially dependent data, where the outcome is interval-censored due to rounded event times. This type of data is difficult to handle with alternative approaches, making mixed-effects additive transformation models and the accompanying software a valuable tool for addressing common issues encountered in survival analysis.

Overall, this approach offers a viable complement to traditional methods and provides a robust and distribution-free framework for regression analysis of correlated time-to-event outcomes.

## Keywords:

additive models; correlated data; mixed-effects models; regression; transformation models.

## References:

- T. Hothorn, L. Möst and P. Bühlmann (2018): Most likely transformations. *Scandinavian Journal of Statistics*, 45(1):110–134.
- B. Tamási and T. Hothorn (2021): `tramME`: Mixed-effects transformation models using Template Model Builder. *The R Journal*, 13(2):398–418.

# The shape of the relative frailty variance induced by discrete random effect distributions in univariate and multivariate survival models

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## **Abstract:**

In statistical models for the analysis of time-to-event data, individual heterogeneity is usually accounted for by means of one or more random effects, also known as frailties. In the vast majority of the literature, the random effect is assumed to follow a continuous probability distribution. However, in some areas of application, a discrete frailty distribution may be more appropriate. We investigate and compare various existing families of discrete univariate and shared frailty models by taking as our focus the variance of the relative frailty distribution in survivors. The relative frailty variance (RFV) among survivors provides a readily interpretable measure of how the heterogeneity of a population, as represented by a frailty model, evolves over time. We explore the shape of the RFV for the purpose of model selection and review available discrete random effect distributions in this context. We find non-monotone trajectories of the RFV for discrete univariate and shared frailty models, which is a rare property. Furthermore, we proof that for discrete time-invariant univariate and shared frailty models with (without) an atom at zero, the limit of the RFV approaches infinity (zero), if the support of the discrete distribution can be arranged in ascending order. Through the one-to-one relationship of the RFV with the cross-ratio function in shared frailty models, which we generalize to the higher-variate case, our results also apply to patterns of association within a cluster. Extensions and contrasts to discrete time-varying frailty models and contrasts to correlated discrete frailty models are discussed.

## **Keywords:**

Association; Discrete distributions; Frailty; Heterogeneity; Time-to-event models.

## Session 9

# Evaluating cancer screening programmes using survival analysis

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### **Abstract:**

Cancer screening is a programme for medical screening of asymptomatic people who are at risk of developing cancer. Typically, participants are regularly screened every few years using blood tests, urine tests, medical imaging, or other methods. Among cases who are screened regularly some are diagnosed with cancer based on screening tests (screen-detected cases) and some based on symptoms appearing in the interval between two consecutive screening tests (interval cases). The hypothesis is that the screening programmes improve chances of survival for screen-detected cases as these cases are diagnosed and treated at an earlier stage of the disease compared to counterfactual scenario where their cancer would have been detected based on symptoms. We would like to test this hypothesis empirically. So far, the problem has been tackled by comparing the survival functions of screen-detected cases and interval cases. Realizing that the direct comparison between these two groups would result in biased results, previous research focused on parametric solutions to remove the bias. We argue that the problem lies elsewhere – that this comparison, in fact, does not reflect the question of interest. Therefore, in this study, we precisely define the contrast corresponding to the hypothesis defined above. Since the contrast of interest refers to hypothetical quantities, we discuss which data and under what assumptions can be used for estimation. We also propose a non-parametric framework for evaluating the effectiveness of cancer screening programmes under certain assumptions. The proposed ideas are illustrated using simulated data. The problem is motivated by the need to evaluate breast cancer screening programme in Slovenia.

### **Keywords:**

cancer screening programmes; lead time; length time bias; survival analysis.

# A two-step approach for analysing time-to-event data under non-proportional hazards

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## **Abstract:**

Survival analysis is a statistical method for evaluating time-to-event data, such as death or disease progression, in oncology trials. Usually, in such oncology trials, a new treatment regimen is compared to a control group, normally the standard of care. Traditional survival analysis methods like the Cox-proportional hazards model or the log-rank test assume the hazard ratio of two groups to be constant over time. However, this assumption is often violated in real-world applications. An example of that are immuno-oncology drugs, which often exhibit a delayed onset of their effects. To address this, more robust methods for survival analysis under non-proportional hazards have been developed. We propose a two-step procedure for comparing hazard functions of two groups in the presence of non-proportional hazards. The procedure starts with a pre-test to assess the proportional hazards assumption, followed by a method for comparing hazard functions that is conditioned on the pre-test result. In a simple framework, depending on the pre-test results, either a standard log-rank test or a weighted log-rank test will be performed. We show for which scenarios such a two-step procedure might yield a type 1 error rate inflation and discuss how strict control can be achieved. The efficacy of the two-step approach will be evaluated through comparison with established methods such as weighted log-rank tests or max-combo test in broad simulation study.

## **Keywords:**

survival analysis; oncology trials; non-proportional hazards; log-rank test.

# When exactly? Two overlooked biases in SARS-CoV-2 incubation time estimation related to information regarding exposure

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## Abstract:

Exposure information is essential for estimating the incubation time of an infectious disease, i.e. from infection to symptom onset, but is almost always interval censored. Interval censored time origins complicate analysis (Arntzen et al., 2023). For SARS-CoV-2 data on exposure has been collected retrospectively, mostly by interviewing detected cases. However, our memory is imperfect, with recent exposures being more precisely recalled than older ones (differential recall). Remembering when exactly we visited a particular café is straightforward if it was yesterday, but becomes more difficult when it was longer ago. Interval-censored observations with less precise exposures, i.e. wider intervals, are often excluded from analysis. This creates bias in the presence of differential recall, because longer incubation times are more likely to be excluded.

Another bias occurred in the initial estimates of SARS-CoV-2 incubation time. These estimates were based on data concerning travellers from Wuhan. Only those that developed symptoms after departure were included. Therefore, short incubation times were underrepresented (left truncation). This aspect was not taken into account in the analyses. In fact, there is no standard method to correct for left truncation with interval censored time origins.

For each of the two scenarios, we performed a simulation study to investigate the bias in estimated percentiles of the SARS-CoV-2 incubation time. Incubation times were generated from a Weibull distribution (median 5.4 days, 95<sup>th</sup> percentile 9.8 days). Our findings indicate that in presence of differential recall, restricting analysis to a subset of narrow exposure windows leads to underestimation up to 5 days in the median and even more in the 95<sup>th</sup> percentile, depending on the rate of differential recall. Neglecting left truncation in the data leads to considerable overestimation, up to multiple days in the median and 95<sup>th</sup> percentile.

## Keywords:

differential recall; left truncation; incubation time; SARS-CoV-2; interval-censoring.

## References:

Vera H. Arntzen, Marta Fiocco, Nils Leitzinger and Ronald B. Geskus (2023): Towards robust and accurate estimates of the incubation time distribution, with focus on upper tail probabilities and SARS-CoV-2 infection. Statistics in Medicine, 2023;1-20.

# Evaluation of the impact of left-censoring on the validity of time-dependent propensity score matching method

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## Abstract:

The propensity score (PS) matching approach forms pairs of treated and non-treated subjects with similar score values to study the average treatment effect of the treated individuals (Austin, P. C., 2011). One variation of PS matching, the time-dependent PS matching approach, has been developed to effectively handle time-dependent treatment. In this case, the PS is estimated using survival models such as the Cox model, as opposed to standard logistic regression.

In registry-based studies, the disease onset time is often left-censored because subjects joined the registry after diagnosis. When interest lies in quantifying the effect of this disease on another disease, we could consider the use of PS matching (Xie et al., 2017). But, the validity of PS matching with left-censored time-dependent treatment variables has not been thoroughly explored.

Motivated by the presence of left-censored diabetes onset time among National Diabetes Services Scheme subjects used to investigate the effect of diabetes on aging-related diseases such as dementia, our study aims to comprehensively examine the impact of left censoring on the validity of the time-dependent PS using the developed Evaluation of left censoring on Time-dependent propensity score (Eleft-Tips) approach.

In this talk, we will first introduce our Eleft-Tips approach, where we consider 17 different scenarios where left censoring is not random but instead depends on variables that may be associated with both treatment and outcome variables. Within each scenario, three different time-dependent PS calculation approaches based on different time-dependent Cox models are examined.

Our results show the validity of the time-dependent PS matching approach depends on both the factors used in the calculation of PS and the amount of left censoring present. This highlights the need to carefully apply the time-dependent PS when left censoring is present in the data.

## Keywords:

propensity score matching; left censoring; time-dependent covariates; time-dependent propensity score; diabetes.

## References:

Austin, P. C. (2011): An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate behavioral research*, 46(3), 399-424.

Xie, Y., Bowe, B., Li, T., Xian, H., Yan, Y., & Al-Aly, Z. (2017): Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ open*, 7(6), e015735.

National Diabetes Service Scheme. <https://www.ndss.com.au/>



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# Evaluation of event rate differences using stratified Kaplan-Meier estimates with Mantel-Haenszel weights and adjusted hybrid variance estimators

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## **Abstract:**

The assessment of differences in event rates is a common endeavor in the evaluation of the efficacy and safety of new treatments in clinical trials and in particular in oncology. We investigate the performance of different hypothesis tests for overall survival to reliably determine the efficacy of a novel treatment. The evaluation focuses on the comparison of event rates obtained via Kaplan-Meier estimates for a pre-specified point in time. We investigate stratified analyses with different stratum weights for a Z-test for differences in event probabilities. Borkowf's adjusted hybrid variance estimator instead of the Greenwood or Peto estimator assures non-zero variances at all time points and, thus, the suggested weighted test statistics are well-defined. Data were simulated to reflect realistic scenarios occurring in clinical trials with multiple strata, including one experimental and one control arm. Our particular interest is in the performance in scenarios with underlying hazard rates satisfying Cox' proportional hazards model and when the assumptions of the stratified Z-test for differences in event probabilities are satisfied but not the Cox model. Treatment effects are specified by a hazard ratio or a difference in survival probabilities at time of interest, respectively. Our simulation study compares the performance of Mantel-Haenszel-type weights with inverse variance weights, in particular for very low event rates in some strata. The necessity of non-zero variance estimates – especially in the presence of strong prognostic stratification effects – is illustrated. Finally, the results are compared with those of an unstratified Z-test and a Cox model.

## **Keywords:**

Overall survival; Stratified Z-test; Kaplan-Meier; Mantel-Haenszel weights; Borkowf's non-zero variance estimator.

## **References:**

- Borkowf, C.B. (2005): A simple hybrid variance estimator for the Kaplan-Meier survival function. *Statist. Med.*, 24, pp. 827-851..
- Greenland, S. and Robins, J.M. (1985)): Estimation of a common effect parameter from sparse follow-up data. *Biometrics*, 41, pp. 55-68..

# Finite-sample bias of the linear excess relative risk in cohort studies of computed tomography-related radiation exposure and cancer

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## Abstract:

The linear excess relative risk (ERR) is the most commonly reported measure of association in radiation epidemiological studies when individual dose estimates are available. The ERR model is preferred to Cox regression in this framework, since it allows to analyse linear dose-response trends, which are more suitable in radiation epidemiology. While the asymptotic properties of the ERR estimator are well understood, there is evidence of small sample bias in case-control studies of treatment-related radiation exposure and second cancer risk (Roberti et al., 2021). Cohort studies of cancer risk after exposure to low doses of radiation from diagnostic procedures, e.g., computed tomography examinations, typically have small numbers of cases and risks are small (Meulepas et al., 2019; Berrington de Gonzalez et al., 2016). Therefore, understanding the properties of the estimated ERR is essential for interpretation and analysis of such studies. We present results of a simulation study that evaluates the finite-sample bias of the ERR estimator and its confidence interval using simulated data, resembling a retrospective cohort study of radiation-related leukaemia risk following computed tomography examinations in childhood and adolescence. We show that the ERR is overestimated by about 30%. As the number of cases increases, the ERR is approximately unbiased estimate. The Firth correction yields a bias of generally around or under 5% in studies of typical size. The results indicate the importance of conducting large studies and pooling those for unbiased risk estimates and, if this is not possible, to use methods which adjust for small-sample bias, using the Firth correction.

## Keywords:

Linear excess relative risk; simulation study; epidemiology; cohort study; cumulative exposure dose

## References:

- S. Roberti, F. van Leeuwen, M. Hauptmann and R.M. Pfeiffer (2021): Bias correction for estimates from linear excess relative risk models in small case-control studies. *Stat Med*, 40(26):5831-5852.
- A. Berrington de Gonzalez, J.A. Salotti, K. McHugh, M.P. Little, R.W. Harbron, C. Lee, E. Ntowe, M.Z. Braganza, L. Parker, P. Rajaraman, C. Stiller, D.R. Stewart, A.W. Craft and M.S. Pearce (2016): Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. *Br J Cancer*, 114(4):388-394.
- J.M. Meulepas, C.M. Ronckers, A.M.J.B. Smets, R.A.J. Nievelstein, P. Gradowska, C. Lee, A. Jahnen, M. van Straten, M.Y. de Wit, B. Zonnenberg, W.M. Klein, J.H. Merks, O. Visser, F.E. van Leeuwen and M. Hauptmann (2019): Radiation Exposure From Pediatric CT Scans and Subsequent Cancer Risk in the Netherlands. *J Natl Cancer Inst*, 111(3):256-263.

# Signal detection of adverse drug reactions: The Bayesian Power generalized Weibull Shape Parameter test

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## Abstract:

After the release of a drug on the market, pharmacovigilance monitors the occurrence and changes in known adverse drug reactions (ADRs) as well as detects new ADRs in the population. This is done to keep a drug's harm profile updated and can potentially result in adjustments of the prescription labeling or – in the extreme case – a recall of the product from the market. In recent years the interest in the use of longitudinal electronic health records for pharmacovigilance increased. Sauzet and Cornelius (2022) provided a test based on the power generalized Weibull (PgW) distribution shape parameters (PgWSP). If both shape parameters of the PgW distribution are equal to one, the distribution reduces to an exponential distribution with constant hazard over time. This is interpreted as no temporal association between a drug and an adverse event.

Signal detection can be improved by incorporating existing knowledge about the ADR profile of drugs from the same family or based on expert knowledge about the drug mechanism. Therefore, we propose the development of a Bayesian PgWSP test. The test compares a region of practical equivalence (ROPE) around one reflecting the null hypothesis with the estimated credibility intervals (Kruschke, 2015). If the intersection between ROPE and credibility interval is empty for at least one shape parameter, a signal is raised.

We performed a simulation study to tune the optimal ROPE and credibility interval for signal detection using a Bayesian PgWSP approach. Samples are generated under varying conditions regarding sample size, prevalence, and proportion of adverse events. Prior assumptions considered are no ADR, ADR at the beginning, middle, or end of the observation period. A range of ROPE and credibility interval types are considered. The optimal ROPE and credibility interval tuning parameters are determined based on the area under the curve.

## Keywords:

pharmacology, signal detection, time-to-event models, Bayesian test, generalized Weibull distribution.

## References:

- J. Kruschke (2015): Doing Bayesian data analysis: A tutorial with R, JAGS, and Stan. Deutschland: Elsevier Science..
- O. Sauzet and V. Cornelius(2022): Generalised weibull model-based approaches to detect non-constant hazard to signal adverse drug reactions in longitudinal data. Frontiers in Pharmacology, DOI: 10.3389/fphar.2022.889088.

# Non-proportional hazards and time-dependent covariates: An application with COVID-19 hospitalized patients

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## **Abstract:**

Invasive ventilation is widely considered as a risk factor for acute renal failure in critically ill patients. Given the high prevalence of invasive ventilation in COVID-19 hospitalized patients, the focus of the study was to evaluate the additional effect of COVID-19 on the need for renal replacement therapy (RRT).

In the context of this analysis, the following statistical challenges arose: The primary endpoint was time to RRT with ICU death as competing risk. The time-to-event model should evaluate the effect of COVID-19 additionally to the time-dependent co-variable invasive ventilation (documented on a daily basis), as well as other potential confounding factors, e.g. age and gender. The evaluation of this effect revealed a non-proportional hazards behavior, i.e. showing a reversing trend over time. Furthermore, the influence of invasive ventilation on the need of RRT was assumed to be time-delayed. In consequence to the non-proportional hazards behavior, the group factor COVID-19 was divided into time-varying categories to allow the use of a Cox-proportional hazards model. In the first model, patients dying in an ICU before the start of RRT were censored at the day of death. As sensitivity analysis, the model was repeated for the combined endpoint time to RRT or death.

These models were applied in a study using data of adult patients of 154 intensive care units (ICU) participating in the benchmarking project of the Austrian Centre for Documentation and Quality Assurance in Intensive Care (ASDI). The cohort included 5457 patients with and 58565 patients without COVID-19, all with ICU discharge or death on ICU documented in 2020 or 2021 and a length of stay of more than 2 days.

Overall, this study highlights the importance of accounting for time-dependent covariates and non-proportional hazards in time-to-event analysis, particularly in the context of COVID-19 research.

## **Keywords:**

non-proportional hazards; time-dependent covariates; COVID-19; renal replacement therapy; invasive ventilation.

# A simulation-based comparison of statistical methods for time-to-event data analysis under non-proportional hazards

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## Abstract:

We present the results of a comprehensive simulation study that evaluates the performance of statistical methods for time-to-event analysis under non-proportional hazards (NPH). The study covers a wide range of plausible distributional assumptions and typical design options. It compares the operating characteristics of selected statistical methods for testing and estimation in clinical trials with time-to-event endpoints under NPH. The selection of methods is based on a systematic review of the scientific literature (CONFIRMS, 2022a) to identify available options for methods for testing and estimation under NPH. The selection of simulation scenarios is based on a review of past marketing authorization procedures (CONFIRMS, 2022b) reporting results from 18 distinct trials. The study covers four broad scenario classes - crossing hazards, delayed onset of treatment effect, progression, and differential treatment effects in subgroups, in addition data was generated from pharmacokinetic models and by sampling from data reconstructed from Kaplan-Meier plots of three trials identified in (CONFIRMS, 2022b).

The findings have important regulatory implications for clinical trials that are pivotal for drug development and benefit-risk assessment under NPH. Additionally, the open-source software package SimNPH (Fellinger, Klinglmüller, 2023) was developed to facilitate simulation of time-to-event data.

## Keywords:

Clinical Trials; Pharmaceutical Statistics; Simulation Study; Non-Proportional Hazards, Time-To-Event Analysis

## References:

CONFIRMS Consortium (2022a): Report on the systematic literature review: Statistical analysis of trials where nonproportional hazards are expected. Deliverable 2 , Submitted

CONFIRMS Consortium (2022b): Review of EMA EPARS where nonproportional hazards were identified. Deliverable 2 , Report, Submitted

T.Fellinger, F.Klinglmüller (2023): SimNPH: an R-package to Simulate Non-Proportional Hazards  
<https://github.com/SimNPH/SimNPH>

# Mortality analysis of a 5-year follow-up study of COPD patients with survival trees

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## Abstract:

Tree-based models are increasingly popular due to their ability to identify complex relationships. In survival analysis, survival tree methods adapt these models to allow for the study of censored outcomes. They are among the most popular nonparametric alternatives to usual parametric or semi-parametric models, such as the Cox model.

This work analyzes a data set from a 5-year follow-up study of 543 COPD patients from Galdakao-Usansolo Hospital in Biscay, Spain. The COPD study considers patients' death as the event of interest to identify the variables associated with patients' death risk. One to four assessments per individual were collected during the follow-up period, and several variables were considered. The patients' examinations include physical evaluations (e.g., the 6-minute walk test), pulmonary function tests such as the forced expiratory volume in the first second (FEV1%) or the dyspnea level, and sociodemographic variables such as age or smoking. In addition, patients completed Health-Related Quality of Life tests such as the George's Respiratory Questionnaire (SGRQ).

To deal with the wide variety of variables considered for survival and the study's longitudinal nature, we explored the LTRCtrees R package for survival trees (W. Fu and J.S. Simonoff, 2017). This methodology allows the use of time-varying covariates to build survival trees. We analyzed these survival trees for the COPD data and selected the adequate tree model. The proper model was chosen according to the optimal hyperparameter combination, which was selected based on the model's prediction performance. For that purpose, a k-fold cross-validation method was conducted regarding the popular Integrated Brier Score (IBS). We also provide graphical results that facilitate the interpretability of the variables' impact on the patient's survival. For instance, we determined the 6-minute walking test or the Charlson Comorbidity Index as significant risk factors.

## Keywords:

Survival Trees; Time-To-Event; Longitudinal Study; COPD.

## References:

W. Fu and J.S. Simonoff (2017). Survival trees for left-truncated and right-censored data, with application to time-varying covariate data. *Biostatistics* (Oxford, England), 18(2), 352–369.

# **Added value of multistate models in randomized controlled trials: A Demonstration Analysis**

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## **Abstract:**

Multistate models are a useful tool to examine underlying mechanisms in complex data structures [L. Meira-Machado et al. (2009), P. Hougaard (1999), J. G. et al. (2022), D. Hazard et al. (2020)]. Similar to the work of K. Bakunina et al. (2022), we will investigate the added value of using a subclass of these models in randomized controlled trials (RCTs) alongside commonly used methods like composite endpoint analyses and Kaplan-Meier-estimation. In particular, we will take a closer look at illness-death- and extended illness-death-models and their use in RCTs. Therefore we will give a motivating example and utilize data from two randomized, controlled safety and efficacy trials. The goal of these trials was to study the safety and efficacy of two drugs that were planned to reduce the incidence of ventilation-associated pneumonia in adult ICU patients.

We will apply illness-death- and extended illness-death-models on the data from these projects to give further insights into the underlying mechanisms. In the end, we have found that using illness-death and extended illness-death-models provide deeper insight into the relations of different probabilities of interest often investigated in RCTs. These models also differentiate the relations of mechanisms that are not observable when using less complex models. In conclusion, the illness-death and extended illness-death-models are a class of models that are a great addition to widely used methods.

## **Keywords:**

Multistate model; Mechanical Ventilation; Randomized controlled Trial; Length of Stay; Illness-Death-Model.

## **References:**

- L. Meira-Machado, J. de Uña-Álvarez, C. Cadarso-Suárez and P. K. Andersen (2009): Multi-State Models for the Analysis of Time-to-Event Data. *Statistical Methods in Medical Research*, 18(2): 195–222.
- P. Hougaard (1999): Multi-State Models: A Review. *Lifetime Data Analysis*, 5(3): 239–64.
- J. G. Le-Rademacher, T. M. Therneau, and Fang-Shu Ou (2022): The Utility of Multistate Models: A Flexible Framework for Time-to-Event Data. *Current Epidemiology Reports*, 9(3): 183–89.
- D. Hazard, K. Kaier, M. von Cube, M. Grodd, L. Bugiera, L. Lambert and M. Wolkewitz (2020): Joint Analysis of Duration of Ventilation, Length of Intensive Care, and Mortality of COVID-19 Patients: A Multistate Approach. *BMC Medical Research Methodology*, 20(1): 206.
- K. Bakunina, H. Putter, J. Versluis, E. A. S. Koster, B. van der Holt, M. G. Manz, D. A. Breems, B. T. Gjertsen, J. Cloos, P. J. M. Valk, J. Passweg, T. Pabst, G. J. Ossenkoppele, B. Löwenberg, J. J. Cornelissen, L. C. de Wreede (2021): The added value of multi-state modelling in a randomized controlled trial: The HOVON 102 study re-analyzed. *Clinical Infectious Diseases*, 11(3): 630–640.

# **Propensity score matching method for time-dependent exposure in survival data**

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## **Abstract:**

Propensity score matching analysis (PSM) is commonly used by medical researchers to account for confounders. The propensity score, defined by Rosenbaum and Rubin, is the probability that an individual be assigned to the treatment group based on the baseline covariates observed (Rosenbaum and Rubin,1983). Typically, a binary logistic regression model estimates the propensity score (PS) using time-fixed covariates. In the case of time-varying treatment or exposure in the dataset, the logistic regression method can cause bias. Since subjects with early and late exposure are treated the same. However, propensity score matching analysis is created for each person at study entry without considering its time-dependent feature. Therefore, conventional propensity score matching analysis may be insufficient to correct this bias. This study aims to illustrate how to perform propensity score analysis in the presence of time-dependent exposure. We used to Kawasaki data set in the study (Shi et al.,2019). R 4.1.3 program was used in all statistical analyses. According to the results, the propensity score matching method, which directly adjusts the propensity score predicted by a binary logistic regression model or a Cox regression model without considering time-dependent exposure, still includes significant bias. As a result, the time-dependent PS matching method can help to achieve a result approaching the unbiased effect. In conclusion, this method is recommended to be used in case of time dependent exposure. This method can be compared in different size data sets.

## **Keywords:**

propensity score; covariate; case-control; matching; time-dependent.

## **References:**

- PR. Rosenbaum and DB. Rubin (1983): The central role of the propensity score in observational studies for causal effects. *Biometrika*,70:41-55.
- H. Shi, H. Qui, Z. Jin (2019): Coronary artery lesion risk and mediating mechanism in children with complete and incomplete Kawasaki disease. *J Investig Med*, 67:950-6.

# **Performance of multi-state prediction models for the clinical course of hospitalized COVID-19 patients: temporal and geographic comparisons of external validations**

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## **Abstract:**

Multi-state methodology (Andersen and Keiding, 2002) enables the prediction of hospitalized COVID-19 patients' clinical courses while avoiding some of the most severe biases (competing risks, immortal time, selection) in hospital epidemiology. We developed a prediction model based on data collected from COVID-19 admissions to the University Medical Center in Freiburg, Germany from January 27, 2020 to December 31, 2021. The model incorporates two transitory states (regular ward, intensive care unit (ICU)) and two absorbing states (discharge alive, in-hospital death) as described in Hazard et al. (2020). The transitions among the states are adjusted for several covariates at admission: age, sex, body mass index, oxygen saturation, and lymphopenia. In addition, techniques to model changing circumstances of the pandemic (new treatments, variants, vaccinations, etc.) via surrogate covariates (e.g. time since pandemic outset) were explored. As a temporal validation, an initial model was developed on admissions in Freiburg until May 21st, 2021 and validated on admissions occurring thereafter. To incorporate geographic aspects of an external validation, the model was then applied to data from the Bellvitge University Hospital in Barcelona, Spain. Lastly, to investigate the challenges of prediction at the outset of a pandemic, a model was developed based on publicly available hospital data (Roimi et al., 2021) on every hospitalized COVID-19 patient in Israel from March 1 to May 2, 2020. The model was then validated on the two aforementioned European data sets.

The performance of the models was evaluated with regard to predicted state occupation and transition probabilities by calculating prediction errors using Brier and Kullback–Leibler scores as outlined in Spitoni et al. (2021). Furthermore, dynamic prediction was demonstrated as a contrast to multi-state prediction. Non-parametric Aalen Johansen estimators were calculated to determine the improvement of covariate inclusion in all models. The development of summary measures for the prediction model was also explored.

## **Keywords:**

multi-state models; COVID-19; competing risks; prediction; validation.

## **References:**

- P.K. Andersen and N. Keiding(2002): Multi-state models for event history analysis. Statistical methods in medical research , 11(2):91-115.
- D. Hazard et al. (2020): Joint analysis of duration of ventilation, length of intensive care, and mortality of COVID-19 patients: a multistate approach. BMC medical research methodology, 20:1-9.
- Roimi et al. (2021): Development and validation of a machine learning model predicting illness trajectory and hospital utilization of COVID-19 patients: a nationwide study. Journal of the American Medical Informatics Association, 28(6):1188-1196.
- C. Spitoni and V. Lammens and H. Putter(2018): Prediction errors for state occupation and transition probabilities in multi-state models. Biometrical Journal, 60(1):34-48.

# Comparison of variable selection strategies in transplant data

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## Abstract:

Selecting variables for the development of a statistical model in prognostic research is a critical and mostly necessary step. Despite its importance in empirical science and medicine, there is no consensus on how to best select variables Heinze G, Wallisch C, Dunkler D. (2018); Sauerbrei W, Perperoglou A, Schmid M, et al. (2020). We assess variable selection methods on kidney transplant patient data by comparing classical variable selection methods (univariate p-value selection, AIC, BIC, backward or augmented backward selection) and variable selection methods based on machine learning (penalisation, high dimensional methods, garrote) by empirically evaluating statistical measures (i.e. model performance, bias, selection stability) based on resampling techniques. We consider the following settings:

- prediction of bacterial infections for up to 2 years post transplant.
- prediction of kidney function through estimated glomerular filtration rate (eGFR).

As a side goal, we further investigate important prognostic factors for bacterial infection after 2 years and eGFR.

## Keywords:

variable selection; simulation study; prediction model; kidney transplant.

## References:

Heinze G, Wallisch C, Dunkler D. (2018): Variable selection - A review and recommendations for the practicing statistician Biom J Biom Z., 60(3):431-449.

Sauerbrei W, Perperoglou A, Schmid M, et al. (2020): State of the art in selection of variables and functional forms in multivariable analysis?outstanding issues. Diagn Progn Res., 4(1):3.

# Bayesian analysis of McDonald exponentiated gamma model based on LINEX and quadratic loss functions

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## Abstract:

We propose a Bayesian analysis of McDonald exponentiated gamma (McEG) distribution. The McEG distribution provides greater flexibility in fitting lifetime data compared to other popular extensions of the gamma distribution such as the exponentiated gamma, beta exponentiated gamma, and Kumaraswamy exponentiated gamma distributions. However, a Bayesian framework for the McEG model has not been implemented in the literature. To address this gap, we investigate and develop a Bayesian approach for estimating the parameters of the McEG distribution using independent gamma priors. We evaluate the performance of the McEG model using two loss functions: squared error loss function (SELF) and linear-exponential (LINEX) loss function. We employ Monte Carlo Markov Chain (MCMC) methods, specifically the Metropolis-Hastings algorithm, to obtain summaries of interest relating to the posterior distribution. To demonstrate the significance of the McEG distribution, we apply it to a real-life dataset on blood cancer and compare its performance with competitor models.

## Keywords:

Bayesian analysis; gamma priors; McDonald exponentiated gamma distribution; Metropolis Hasting algorithm; Monte Carlo Markov chain .

## References:

- Al-Babtain, A., Merovci, F. and Elbatal, I. (2015): The McDonald exponentiated gamma distribution and its statistical properties. Springer Plus, doi:10.1186/2193-1801-4-2.
- Al-Saiary, Z.A. and Bakoban, R.A. (2020): The Topp-Leone Generalized Inverted Exponential Distribution with Real Data Applications. Entropy (Basel),doi: 10.3390/e22101144. .
- Cordeiro, G.M., Lemonte, A.J. and Ortega, E.M.M. (2013c): An extended fatigue life distribution. Statistics, 47(3):626-653.
- Cordeiro,G.M., Hashimoto,E. M., Ortega,E. M. M. and Pascoa, M.A. R. (2012c): The McDonald extended exponential distribution: properties and applications. AStA Advances in Statistical Analysis, 96(3):409-433.
- Cordeiro, G.M., Cintra, R. J., Rego, L. C. and Ortega, E.M.M. (2012b): The McDonald normal distribution. Pakistan Journal of Statistics and Operation Research,8(3):301-329.
- Cordeiro, G.M. and Lemonte, A.J. (2012): The McDonald inverted beta distribution. Journal of the Franklin Institute, 349(3):1174-1197.
- Gupta, R. C., Gupta, R. D. and Gupta, P. L. (1998):Modeling failure time data by Lehman alternatives.Communications in Statistics—Theory and Methods, 27:887–904.
- Hashimoto, E. M., Ortega, E. M. M., Cordeiro, G. M. and Pascoa, M. A. R. (2015): The McDonald Extended Weibull Distribution.Journal of Statistical Theory and Practice, 9(3):608-632.
- Tahir, M.H. , Mansoor, M., Zubair, M. and Hamedani,G.G.(2014): McDonald log-logistic distribution with an application to breast cancer data.Journal of Statistical Theory and Applications, 13(1):65-82.

# **Applications of flexible parametric relative survival approaches for the extrapolation of all-cause survival.**

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## **Abstract:**

In Health Technology Assessment (HTA), survival extrapolation is an essential component for the economic evaluation of novel interventions. There are various modelling approaches which have been developed to extrapolate survival functions to provide long-term treatment effect estimates for the target population (Gray J et al., 2021). However, it is difficult to predict the unknown long-term mortality from the data contained within the short follow-up of a typical RCT, as the long-term marginal hazard function can change beyond follow-up depending on the characteristics of chronic diseases. Providing long-term survival estimates for recent cohorts of cancer patients is also useful in observational studies when characterising the loss in life expectancy due to a diagnosis of cancer. As an alternative to extrapolating from standard parametric survival models, we could consider an approach to constrain the long-term excess mortality by imposing a specific assumption such as a cure or constant excess hazard for the disease-specific mortality. This is then combined with external life-table data in a relative survival modelling framework to account for the influence on the long-term all-cause mortality of age or other demographic factors. In the constrained models, the flexible parametric survival model is a useful tool given the added flexibility through restricted cubic spline functions over standard parametric survival models (Andersson et al., 2014).

We analyse US SEER data (SEER Program, 2020) using the flexible parametric survival models for 4 different cancer types to extrapolate survival beyond follow-up. We impose constraints to assume a constant excess hazard after follow-up in the relative survival model. Standard and constant excess hazard models are fitted comparing different lengths of follow-up and placement of boundary knots. We compare the prediction results among the models. Longer follow-up and later placement of boundary knots for the spline function provide better agreement for the constrained models compared to the empirical survival.

## **Keywords:**

Extrapolation; Flexible parametric survival model; Relative survival modelling; Marginal survival functions.

## **References:**

Gray, J., Sullivan, T., Latimer, N.R., Salter, A., Sorich, M.J., Ward, R.L. and Karnon, J. (2021): Extrapolation of survival curves using standard parametric models and flexible parametric spline models. *Medical Decision Making*, 41(2), pp.179-193.

Andersson, T.M.L., Dickman, P.W., Eloranta, S., Lambe, M. and Lambert, P.C. (2013): Estimating the loss in expectation of life due to cancer using flexible parametric survival models. *Statistics in medicine*, 32(30), pp.5286-5300.

Surveillance, Epidemiology, and End Results (SEER) Program. SEER\*Stat Database: incidence - SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.

# Target trial emulation with multi-state model analysis

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## Abstract:

Observational studies on the effectiveness of treatments for hospitalised patients with Coronavirus Disease 2019 (COVID-19) are prone to immortal-time bias, confounding bias, and competing risks (Martinuka et al., 2021). Failure to account for these methodological challenges can lead to inaccurate results (Wolkewitz and Schumacher, 2017). We aimed to emulate a target trial with multi-state model analysis to evaluate the effectiveness of a point treatment using exemplary single centre observational data from COVID-19 patients ( $n = 501$ ) hospitalised from March 2020 to February 2021. Emulation was done via the clone-censor-weight technique (Maringe et al., 2020). We modelled a multi-state model with three absorbing states: in-hospital death, discharge alive, and transfer to other healthcare facilities. Admission to the intensive care unit was defined as an intermediate state. As a result, target trial emulation analysis with cloning and censoring allowed us to account for immortal-time bias by considering early fatal and non-fatal outcomes in both treatment groups. By cloning patients, baseline confounding bias was avoided. Additionally, the inverse probability of censoring weights was applied to address the selection bias introduced by artificial censoring. Our results show that target trial emulation analysis with the clone-censor-weight technique avoids common methodological biases. Extending to the multi-state model allowed us to avoid competing risk bias, an issue often ignored in both randomised and observational studies. The multi-state model analysis enables insights into treatment effects on all clinically important and heterogeneous endpoints. However, comparing outcomes between two treatment arms in the multi-state model with the intermediate event could be potentially biased due to different patient's disease severity levels and unbalanced prognostic covariates, which should be considered in the analysis.

## Keywords:

Methodological bias; Multi-state models; Observational data; Target trial emulation; Treatment evaluation.

## References:

- C. Maringe, S.B. Majano, A. Exarchakou (2020): Reflection on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *International Journal of Epidemiology*, 49(5):1719–1729.
- O. Martinuka, M. von Cube and M. Wolkewitz (2021): Methodological evaluation of bias in observational coronavirus disease 2019 studies on drug effectiveness. *Clinical Microbiology and Infection*, 27(7):949–957.
- M. Wolkewitz and M. Schumacher (2017): Survival biases lead to flawed conclusions in observational treatment studies of influenza patients. *Journal of Clinical Epidemiology*, 84:121–129.

# Analysis of time-dependent centre-specific frailty through compensator decomposition in a recurrent events framework

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## Abstract:

In clinical studies, predictive models developed for the quantification of a given outcome in a follow-up period often need to integrate information related to the prior clinical history of the patient, such as recurrent events. Furthermore, it is often the case that data come from a multi-centric study and the net effect generated by the centre in this time frame (i.e., the "frailty" of the centre) is worth being studied and included in the model.

As proposed by Baraldo et al. (2013) and Spreafico and Ieva (2021), the recurrent events and their characterization in the patient's clinical history can be modelled through a marked point process formulation for recurrent events (Andersen and Gill (1982)). The Doob-Meyer decomposition theorem allows us to focus on the modelization of the compensator of the process, for which a Cox-type model is adopted. The baseline hazard is estimated through the Breslow estimator (Breslow (1975)) and smoothed. The realizations of the process compensator, for each patient along the observation period, can be expressed as a function of estimated parameters and thus computed.

Under the assumption that patients are fidelized to a given centre, we propose employing functional data analysis and functional principal component analysis (Ramsay and Silverman (2005)) to decompose the patient's compensator into the time-dependent population mean function, a time-dependent centre-specific term and a time-dependent patient-specific term composed by a finite sum of orthonormal bases multiplied by their scores. The element of novelty lies in the isolation and exploration of the time-dependent centre-specific term, which is computed by taking into account information on all the patients cured in that centre. This term plays the role of time-dependent shared frailty in a recurrent events framework.

## Keywords:

marked point processes; recurrent events; Cox model; time-dependent shared frailties; functional data analysis.

## References:

- P. K. Andersen and R. D. Gill (1982): Cox's regression model for counting processes: A large sample study. *The Annals of Statistics*, 10:1100–1120.
- S. Baraldo, F. Ieva, A. M. Paganoni and V. Vitelli (2013): Outcome prediction for heart failure telemonitoring via generalized linear models with functional covariates. *Scandinavian Journal of Statistics*, 40(3):403–416.
- N. E. Breslow (1975): Analysis of survival data under the proportional hazards model. *International Statistical Review/Revue Internationale de Statistique*, 43(1):45–57.
- J. Ramsay and B. W. Silverman (2005): *Functional Data Analysis*. Springer Series in Statistics. Springer.
- M. Spreafico and F. Ieva (2021): Functional modeling of recurrent events on time-to-event processes. *Biometrical Journal*, 63(5):948–967.

# **Impact of prior time on dialysis on the treatment effect of kidney transplant on survival - the Stockholm CREATinine Measurements Project**

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## **Abstract:**

End Stage Renal Disease is the last phase of Chronic Kidney Disease, where the patients' kidneys no longer work sufficiently. In this stage, renal replacement therapy (RRT) is needed, either dialysis or kidney transplant. With only a limited supply of donor kidneys, assessing their impact on survival is important and challenging. Numerous studies have advocated for preemptive kidney transplant - transplant without initiating dialysis first - but clear evidence is hard to find. In a setting unsuitable for RCTs, the usual observational suspects including confounding, selection bias, lead time bias and immortal time bias lurk behind the corner.

Trial emulation (Danaei et al., 2013; Gran et al., 2010) offers an approach to designing analyses of observational studies that helps avoid these biases. To assess the impact of time spent on dialysis post ESRD and before kidney transplant, we set up emulated trials which start at different times since RRT initiation using data from SCREAM (Stockholm CREATinine Measurements project - (Runesson et al., 2016)).

We focus on an ITT-analysis (comparing transplant now with still on dialysis but potentially transplanted later) and allowed the treatment effect to smoothly change over the different trials to allow for an impact of prior time on dialysis on the transplant effect on residual. With the estimated covariate specific HR of transplant on subsequent overall survival heavily depending on prior time on dialysis - but a surprisingly constant effect on the survival difference-scale, this is an interesting case study to explore the complexities of causal time-to-event analyses using observational data.

## **Keywords:**

Trial Emulation; Kidney Transplant; Sequential Cox.

## **References:**

Danaei, Goodarz and Rodríguez, Luis A. García and Cantero, Oscar Fernández and Logan, Roger and Hernán, Miguel A. (2013):Observational Data for Comparative Effectiveness Research: An Emulation of Randomised Trials of Statins and Primary Prevention of Coronary Heart Disease Statistical Methods in Medical Research 22 (1): 70–96

Gran, Jon Michael and Røysland, Kjetil and Wolbers, Marcel and Didelez, Vanessa and Sterne, Jonathan A. C. and Ledegerber, Bruno and Furrer, Hansjakob and von Wyl, Viktor and Aalen, Odd O.(2010): A Sequential Cox Approach for Estimating the Causal Effect of Treatment in the Presence of Time-Dependent Confounding Applied to Data from the Swiss HIV Cohort Study. (2010) Statistics in Medicine 29 (26): 2757–68

Runesson, Björn and Gasparini, Alessandro and Qureshi, Abdul Rashid and Norin, Olof and Evans, Marie and Barany, Peter and Wettermark, Björn and Elinder, Carl Gustaf and Carrero, Juan Jesús (2016): The Stockholm CREATinine Measurements (SCREAM) Project: Protocol Overview and Regional Representativeness Clinical Kidney Journal 9 (1): 119–27

# On the Generalized Gamma Marginalized Two-Part Joint Model: An Improvement to Analyse Semi-Continuous Medical Cost and Survival Data

Mohadeseh Shojaei Shahrokhbadi<sup>1</sup>, Sayed Jamal Mirkamali<sup>2</sup> and Ding-Geng (Din) Chen<sup>3</sup>

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## **Abstract:**

Marginalized Two-part Joint Models (MTJMs) were initially developed to address some challenges associated with medical costs, including right skewness, clumping at zero, and censoring due to death or incomplete follow-up. (Smith et al. , 2017) & (Smith et al. , 2019) The MTJMs are perhaps one the most considered approaches when the primary interest is to gain insight into the complex relationships between the average medical costs amongst the entire population of both users and non-users as one outcome and the occurrence of death as another outcome. The initial MTJM was constructed upon the log-normal (LN) distribution with a constant variance parameter for analyzing positive values (i.e., non-zero) costs. However, practical studies show that the log-normality assumption could be violated. ( Shojaei Shahrokhbadi, et al. , 2021) This paper extends the classical MTJM by considering a generalized gamma (GG) distribution which contains LN distribution as a limiting case. A series of simulation studies are conducted to examine the finite-sample properties of the proposed MTJM model with respect to the bias of the parameter estimates, coverage of probability coverage, and estimation efficiency. The simulation results show that when the response distribution is unknown or misspecified, the GG-based MTJM provides a potentially more robust estimator than the classical LN-based MTJM. The advantage of the new MTJM is also demonstrated by analyzing electronic health records (EHRs) data collected in Iran.

## **Keywords:**

Zero-inflated; Generalized Gamma distribution; Log-Normal distribution; Weibull distribution; Gamma distribution.

## **References:**

- Smith, Valerie A., et al. (2017): A marginalized two-part model for longitudinal semicontinuous data. Statistical methods in medical research 26.4 (2017): 1949-1968.
- Smith, Valerie A., et al (2019): A marginalized two-part model with heterogeneous variance for semicontinuous data. Statistical Methods in Medical Research 28.5 (2019): 1412-1426.
- Shojaei Shahrokhbadi, M., et al. (2021): Marginalized Two-Part Joint Modeling of Longitudinal Semi-Continuous Responses and Survival Data: With Application to Medical Costs. Mathematics, 9.20 (2021): 2603.

# Dynamic prediction of survival with many longitudinal covariates: a review and empirical comparison

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## Abstract:

Collecting longitudinal information on the health of patients has become more and more common. Such information can be used to monitor disease progression, and it can thus play a crucial role for the (dynamic) prediction of survival outcomes. However, until recently there was a lack of methods that could handle many longitudinal covariates as predictors of survival.

Over the last 5 years, several methods that make it possible to incorporate information from many longitudinal covariates into dynamic prediction models have been proposed, including MFPCox (Li et al., 2019), Penalized Regression Calibration (Signorelli et al., 2021), functional survival forests (Lin et al., 2021) and DynForest (Devaux et al., 2023). These approaches differ in terms of how they model the longitudinal covariates' evolution over time, and how they model the relationship between the longitudinal covariates and the survival outcome. Because these methods are fairly new, to date little is known about their advantages and limitations, as well as about their performance with real-world data.

In this talk we will first provide an overview of the aforementioned methods, focusing in particular on the different strategies that they use to model and summarize disease progression. We will also discuss the consequences that such strategies can have for observational / clinical studies where repeated measurements follow an unbalanced (potentially sparse) design, and where age at baseline can be a very important confounder. Finally, we will present the results of a systematic comparison of the predictive performance of these methods using three real-world datasets that differ in terms of disease type, sample size, number of longitudinal covariates, and length of the follow-up.

## Keywords:

dynamic prediction; longitudinal data; risk prediction models; survival analysis.

## References:

- Devaux, A., Helmer, C., Genuer, R., and Proust-Lima, C. (2023): Random survival forests with multivariate longitudinal endogenous covariates. arXiv preprint arXiv:2208.05801.
- Li, K., and Luo, S. (2019): Dynamic prediction of Alzheimer's disease progression using features of multiple longitudinal outcomes and time-to-event data. *Statistics in Medicine*, 38(24), 4804-4818.
- Lin, J., Li, K. and Luo, S. (2021): Functional survival forests for multivariate longitudinal outcomes: Dynamic prediction of Alzheimer's disease progression. *Statistical Methods in Medical Research*, 30(1), 99-111.
- Signorelli, M., Spitali, P., Szigyarto, C. A. K., MARK-MD Consortium and Tsonaka, R. (2021): Penalized regression calibration: A method for the prediction of survival outcomes using complex longitudinal and high-dimensional data. *Statistics in Medicine*, 40(27), 6178-6196.

# A reduced rank proportional hazards model for age-related multimorbidity event data

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## **Abstract:**

The identification of biomarkers of aging is an important biomedical research theme. Most current statistical methods that aim to capture the aging process either use chronological age or time-to-mortality as the outcome of interest. There is however a shift in the field towards the study of health span and patterns of age-related multi-morbidity, as aging entails more than lifespan duration alone. Several large epidemiological studies, such as the UK Biobank and the Leiden Longevity Study, have recently incorporated detailed age-at-disease-onset profiles, obtained from electronic health records. The availability of these data opens new analytical possibilities. Nevertheless, analyses conducted thus far oversimplify the complexity of multi-morbidity patterns, for instance by ignoring information on age-at-disease-onset or by failing to acknowledge that age-related diseases are likely driven by a shared set of underlying factors.

We propose a new methodological framework for the analysis of age-related multi-morbidity data, based on multiple-outcome survival modeling. Specifically, we propose to use a reduced rank proportional hazards model. This model can be fitted on the (possibly right-censored and left-truncated) age-at-disease-onset of several age-related diseases simultaneously. It assumes that there is a set of shared latent factors that drives all age-related diseases considered, thereby reducing the dimensionality of the problem and providing insight into different facets of the aging process. As there is a strong interest in the use of high-dimensional omics data as biomarkers of aging, we illustrate how to include penalization in the reduced rank proportional hazards framework.

The use and intuitive interpretation of the reduced rank proportional hazards model is illustrated by applying it to age-related multimorbidity and mortality data from the UK Biobank, using high-dimensional metabolomics data as predictor variables. A comparison of the reduced rank model to simpler alternative models is made to highlight its added value.

## **Keywords:**

multiple-outcome survival modeling; electronic health records; omics.

# Estimating Quality-Adjusted Life Expectancy in Cancer Populations in a Relative Survival-Style Framework

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## **Abstract:**

Quality of life (QoL) refers to an individuals perception of their own health and welfare, including physical, mental and environmental factors. Cancer patients frequently experience physical symptoms such as pain and fatigue, and mental health conditions such as depression and anxiety as a result of either the disease itself or their treatment. While survival is often the primary outcome measure for assessing cancer, incorporating QoL information allows for a more comprehensive understanding of the patient-level impact of cancer diagnoses.

Previous studies have primarily compared QoL between groups with cancer or between cancer patients and healthy controls. There has been little investigation into the full impact on QoL across a patients lifetime post-diagnosis. Previous methods for quality-adjusted life expectancy (QALE) have used Kaplan-Meier survival estimates alongside a QoL function, as well as utilising other parametric and semi-parametric survival models.

We propose new methods to estimate QALE using Royston-Parmar flexible parametric survival models and QoL information relative to a matched general population cancer-free cohort. We make assumptions regarding the non-linearity of QoL impact at different time-points post-diagnosis, given larger impact is likely in the short-term. We generate QoL functions for both the cancer and cancer-free cohorts to estimate the additional QoL burden a cancer diagnosis is responsible for. By accounting for QoL in the cancer-free cohort, we avoid the scenario of "perfect health" in the general population, which would significantly impact the accuracy of the QALE estimation.

By assessing the impact of QoL in cancer patients, we identify scenarios where variation in QoL is a preventable inequality. The proposed methods provide a more comprehensive understanding of the impact of cancer diagnoses and treatment on patient QoL across their post-diagnosis pathway. Future work will better estimate the relative impact stratified by stage and treatment, but here we focus on the fundamental methodology.

## **Keywords:**

Quality of Life; Cancer Epidemiology; Flexible Parametric Models; Relative Survival.

# Obtaining UK cancer stage-specific life expectancy estimates in the presence of incomplete historical stage information

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## Abstract:

Measures of life expectancy, including changes in life expectancy, provide tangible metrics to measure both the overall burden of cancer on society and the lifetime of an individual. Other measures merely present a snapshot at one time. Life expectancy metrics can be quality-adjusted and are compatible with cost-effectiveness analyses.

Completeness of recording for cancer stage at diagnosis is often historically poor in cancer registries, making it challenging to provide the long-term stage-specific survival estimates required for obtaining stage-specific life expectancy estimates. In previous work we have illustrated that the differences in stage-specific survival are driven by differences in short-term prognosis, and hence combining the period analysis approach used to obtain up-to-date survival metrics with multiple imputation techniques analysis provides long-term stage-specific survival estimates that are not likely to be sensitive to imputed historical stage data(Stannard et al., 2023).

In the UK, long-term stage-specific survival estimates have not been produced using whole population data due to poor completeness of historical stage information. Here we offer stage-specific life expectancy estimates for a range of cancer sites using data from the UK National Cancer Registration and Analysis Service (NCRAS). Period analysis was applied and missing stage at diagnosis information was imputed using the MI-TVE-Approx approach developed by Keogh and Morris(Keogh and Morris, 2018). We fit a flexible parametric excess hazard model for each cancer stage on the excess hazard scale and the differences in stage-specific marginal life expectancy were assessed.

We estimate life expectancy metrics using the relative survival approach(Andersson et al., 2013), which relies on population mortality rates given in national lifetables. The Covid-19 pandemic has disproportionately affected cancer patients and hence it is important to assess the suitability of existing lifetables. Disruption to the healthcare system has led to changes in reported cancer incidence and survival. We consider sensitivity analyses under several scenarios to assess the impact of mis-specified lifetables.

## Keywords:

Life expectancy; Missing data; Relative survival; Flexible parametric models; COVID-19.

## References:

- R. Stannard, P. C. Lambert, T. M. L. Andersson and M. Rutherford (2022): Obtaining long-term stage-specific relative survival estimates in the presence of incomplete historical stage information. *British Journal of Cancer*, 127(6):1061-1068.
- R. H. Keogh and T. P. Morris (2018): Multiple imputation in Cox regression when there are time-varying effects of covariates. *Statistics in Medicine*, 37(25):3661-3678.
- T. M. L. Andersson, P. W. Dickman, S. Eloranta, M. Lambe and P. C. Lambert (2013): Estimating the loss in expectation of life due to cancer using flexible parametric survival models. *Statistics in Medicine*, 32(30):5286-5300.

# Kaplan-Meier estimate adjusted for events of interest of a rare or single updating: Prediction of a decrease of COVID-19 antibodies below laboratory cut-off in time

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## Abstract:

In a non-parametric fashion, survival function, i.e., a probability of non-experiencing an event of interest by an individual until a given time point, is commonly estimated using the Kaplan-Meier estimator. The Kaplan-Meier estimator assumes the event of interest experience is irreversible – once an individual has experienced the event, they could no longer be considered as non-experiencing ones (Kaplan and Meier, 1958). However, there are situations when an event of interest could be spontaneously reversible in time, with no option for on-the-fly updating the event's change.

In this work, we address the described problem and adjust the Kaplan-Meier estimator to consider that not all individuals who experienced the event of interest necessarily have to stay in the state determined by the event; they could transit back to the state before the event experience. So, the event is reversible in time, but its change is hard to measure in real-time. Thus, we cannot use multistate models; we instead derive exact formulas for the adjusted Kaplan-Meier estimator and its variance using the delta method.

Finally, we apply the proposed estimation to 663 individuals' decrease of COVID-19 blood antibodies below the laboratory cut-off. The antibodies below the laboratory cut-off may mean not only that the individual antibodies have exceeded the cut-off but decreased below it but also that the antibodies have been growing but have reached the cut-off yet. So, an individual whose COVID-19 antibodies are evinced below the laboratory cut-off could still reach the cut-off afterward, having sufficient COVID-19 antibody level (Štěpánek et al., 2023).

Applying the traditional Kaplan-Meier estimator to data collected as a time snapshot could underestimate true COVID-19 antibodies in time. The proposed adjustment enables handling such data and explains why other studies may indicate a level of COVID-19 antibody in time higher than the actual data.

## Keywords:

survival function estimation; adjusted Kaplan-Meier estimator; event of interest not updated in real time; a decrease of COVID-19 antibodies below laboratory cut-off; delta method.

## References:

- E. L. Kaplan, P. Meier (1958): Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*, 53:457–481.
- L. Štěpánek, F. Habarta, I. Malá, L. Štěpánek, M. Nakládalová, A. Boriková, L. Marek (2023): Machine Learning at the Service of Survival Analysis: Predictions Using Time-to-Event Decomposition and Classification Applied to a Decrease of Blood Antibodies against COVID-19. *Mathematics*, 11:819–845.

# Dynamic Landmarking for propensity score matched data - A methodological approach to visualize biased treatment estimates

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## **Abstract:**

Propensity score matching has become a popular method for estimating causal treatment effects in non-randomized studies. However, for time-to-event outcomes, the estimation of hazard ratios based on propensity scores can be challenging if omitted or unobserved covariates are present, but disregarded. Not accounting for such covariates could lead to heavily biased treatment estimates (Stürmer et al. (2010)). Researchers often do not know whether or which covariates will induce this bias. To address this issue, we extended a previously described method, "Dynamic Landmarking", which was originally developed for randomized trials (Strobel et al. (2023)). The method is based on successively deletion of sorted observations and gradually fitting Cox models until no sufficient number of events is contained in the data. In addition, the balance of observed, but omitted covariates can be measured by the z-differences (Kuss (2013)). By simulation we show, that "Dynamic Landmarking" provides a good visual tool for detecting biased treatment estimates also in propensity score matched data. We illustrate the approach with a data set from cardiac surgery and provide some recommendations on how to use and interpret "Dynamic Landmarking" in propensity score matched studies.

## **Keywords:**

Propensity Score; Treatment estimates; Bias.

## **References:**

T. Stürmer, KJ. Rothman, J. Avorn, RJ. Glynn (2010): Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution-a simulation study. Am J Epidemiol. 2010;172(7):843-854

A. Strobel, A. Wienke, O. Kuss (2023): How hazardous are hazard ratios? An empirical investigation in individual patient data from 27 large randomized clinical trials. European Journal of Epidemiology. Under Review.

O. Kuss (2013): The z-difference can be used to measure covariate balance in matched propensity score analyses. Journal of Clinical Epidemiology. 2013;66(11): 1302-1307.

# Robust joint models to restrict feedback

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## **Abstract:**

Since the advent of joint models for correlated survival and longitudinal data, an explosion of applications and methodologies followed. From the current biomedical literature, joint models are one of the most widely used frameworks to analyze survival and longitudinal datasets. Before the joint models era, two stage models were proposed where usually the longitudinal biomarker model would be estimated and then the smoothed predictor or random effects were used in the survival model. Although more complex, joint models were shown to decrease bias in the estimates and lead to smaller standard errors. Two-stage models are still considered for various complex models due to the computational burden of inference of joint models. Various works on correcting these two-stage models for bias have been proposed such as reweighing with importance sampling by Mauff et al. (2020) or a multiplicative correction factor with an informative prior by Leiva-Yamaguchi and Alvares (2020). These and other approaches aim to infer the results of the joint model without the computational cost thereof.

The literature provides boundless arguments in favor of joint models and their use in applications. What we seldom find in the literature, are discussions on the inherent feedback between the sub-models in a joint model and the potential impact of this feedback mechanism under model misspecification. This concern is exacerbated when we consider further complications such as multiple events i.e. competing risks, multi-state models and/or multiple biomarkers. Due to the complexity of joint models it is clear that no one solution can exist to safeguard against this misspecification and its feedback, but we endeavor to present a more robust alternative to a joint model that also propagates the uncertainty from one component to the others using a proposed *scenario-based model*.

## **Keywords:**

Feedback, Joint models, Misspecification, Robustness

## **References:**

- V. Leiva-Yamaguchi and D. Alvares (2020): A two-stage approach for Bayesian joint models of longitudinal and survival data: Correcting bias with informative prior. *Entropy*, 23(1).
- K. Mauff, E. Steyerberg, I. Kardys, E. Boersma and D. Rizopoulos, (2020): Joint models with multiple longitudinal outcomes and a time-to-event outcome: a corrected two-stage approach. *Statistics and Computing*, 30(4):999–1014.

# **Protection from previous natural infection compared with vaccination against SARS-CoV-2 – discussion of statistical issues.**

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## **Abstract:**

The fight against SARS-CoV-2 has been a major task during the past months and years. In order to get the pandemic under control one important tool is the availability of vaccines. Furthermore researchers are investigating the protective effect of a previous SARS-CoV-2 infection for a further infection (natural protection rate). One interest lies in the comparison of protection rates after infection or vaccine, eg. Chemaitlely et al. (2022) and Powell et al. (2022). When evaluating protection rates after vaccination or infection, researchers consider different effect measures like 1-hazard ratio, 1-odds ratio, or 1-risk ratio. Although these measures differ when facing competing risks, they are used interchangeably.

Comparison of protection rate via vaccine and natural infection induces several challenges: Per epidemiological definition a reinfection after a SARS-CoV-2 infection is only possible after 90 days (Chemaitlely et al., 2022; Powell et al., 2022), whereas there is no such constraint after vaccination. Furthermore, death plays a more prominent role as competing event during the first 90 days after infection compared to vaccine.

In order to discuss the arising statistical issues when investigating protection rates, we have access to real world data from several databases of the Stockholm region (information of over two million people, 2020-2022). Information about SARS-CoV-2 infections and vaccinations is given, as well as several patients characteristics. Thus, we can examine imbalances between groups at baseline and during follow-up and discuss solutions to address them.

For a comparison between immunization via infection or vaccination, we emphasize to consider several investigations in order to draw comprehensive conclusions. We highlight different aspects of effect measures and insights drawn from different analyses. The aim is to promote an awareness of the differences between the immunization reasons in order to create a fair comparison and to prevent comparisons of apples and oranges.

## **Keywords:**

protection rate; vaccination; conditional survival; competing risks; survival of the fittest.

## **References:**

H. Chemaitlely, H. Ayoub, S. AlMukdad et al. (2022): Protection from previous natural infection compared with mRNA vaccination against SARS-CoV-2 infection and severe COVID-19 in Qatar: a retrospective cohort study. *The Lancet Microbe*, 3(12):e944-e955.

A. Powell, F. Kirseborn, J. Stowe, et al. (2022): Protection against symptomatic infection with delta (B.1.617.2) and omicron (B.1.1.529) BA.1 and BA.2 SARS-CoV-2 variants after previous infection and vaccination in adolescents in England, August, 2021–March, 2022: a national, observational, test-negative, case-control study. *The Lancet Infectious Diseases*, 23(4):435-444.

# **Use of pseudo-observations in multi-state models: development and application of user-defined link function in GLM.**

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## **Abstract:**

Pseudo-observations (PSO) have increased in popularity in survival analysis due to the ability to analyse survival data using standard regression techniques. Pseudo-observations are calculated for each individual based on jackknifing and can then be used as an outcome variable. Using PSO, we can estimate a mean value of a parameter at a fixed point in time and use generalised linear models (GLM) to model the effect of covariates on the outcome. (Anderssen and Pohar Perme, 2010)

To obtain PSO, we need to specify a well-behaved estimator of the outcome of interest. If the outcome of interest is the survival function at a specific time,  $t$ , the Kaplan Meier estimator can be used. Similarly, if investigating competing risks or multistate models, the outcome would be the cumulative incidence function (CIF) at time  $t$ , and the Aalen-Johansen estimator would be used.

We explored the use of PSO in the competing risk setting. For any individual in the dataset, we estimate PSO for each of the cause-specific CIFs for competing events. We generated stacked data in order to directly estimate the overall risk for each individual into constituent parts reflecting the risk of experiencing either competing event. Using the property that the sum of the predicted probabilities of being in a state should sum to 1 for each individual, we defined a link function which allows the user to fit a generalised linear regression model that has a similar interpretation to a multinomial logistic regression model. This allows the user to fit one model estimating the probability of being in any of the states, rather than fitting separate models for each state. The approach extends easily to more general multistate models with multiple disease states. A further extension is to obtain marginal estimates using regression standardization.

## **Keywords:**

Pseudo-observations; Competing risks; Multistate models; User-defined link function; Multinomial logistic regression.

## **References:**

Per K Anderssen and Maja Pohar Perme (2010): Pseudo-observations in survival analysis. SAGE Publications, 19(1):71-99.

# Testing for sufficient follow-up in censored survival data by using extremes

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## **Abstract:**

In survival analysis, one often encounters that some individuals, referred to as cured individuals, never experience the event of interest. When analyzing time-to-event data with a cure fraction, it is crucial to check the assumption of 'sufficient follow-up', which means that the right extreme of the censoring time distribution is larger than the right extreme of the survival time distribution for the non-cured individuals. However, the available methods to test this assumption are limited in the literature. In this article, we study the problem of testing whether follow-up is sufficient for light-tailed distributions and develop a simple novel test. The proposed test statistic compares an estimator of the non-cure proportion under sufficient follow-up to one without the assumption of sufficient follow-up. For large values of the test statistic, we will reject the null hypothesis. A bootstrap procedure is employed to approximate the critical values of the test. We also carry out extensive simulations to evaluate its finite sample performance and illustrate the practical use with applications to lung and breast cancers datasets.

## **Keywords:**

Bootstrap; Cure models; Extreme value theory; Hypothesis test; Kaplan-Meier estimator; Survival analysis.

# Single-index mixture cure model under monotonicity constraints

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## Abstract:

With advances in medical research, certain cancer patients can be cured. The cured patients will never experience cancer relapse but it is impossible to differentiate them from the uncured patients. Mixture cure models have been developed to account for the heterogeneity of the population, which is assumed to be a mixture of cured and susceptible subjects. Mixture cure models consist of two sub-models: one for the uncured probability (incidence) and another for the conditional survival function of the susceptible subjects (latency). Various methods have been proposed to model the relationship between the incidence and covariates (Sy and Taylor, 2000; Xu and Peng, 2014). Amico et al. (2019) introduced a single-index model for the incidence, which links a linear predictor to the incidence by a nonparametric link function estimate. Under some circumstances, a monotone link is expected and a monotone link estimate is more appropriate, while the approach of Amico et al. (2019) may result in a non-monotone estimate. Our goal is to develop a novel method for estimating a single-index model for the incidence under monotonicity constraints.

We propose a monotone single-index model for the incidence and assume a Cox proportional hazard model for the latency. We introduce a new estimation technique that combines the profile maximum likelihood approach with methods from isotonic regression and kernel smoothing. The monotone single-index structure relaxes the parametric assumption while maintaining monotonicity of the link estimate. We study the consistency of the proposed estimator and investigate the behaviour of the estimator through a simulation study. The simulation showed the introduced method improves the behavior of the estimator and makes it more stable with respect to the choice of bandwidth compared to the smooth non-monotone estimator. To illustrate its practical use, the proposed method is applied to melanoma cancer survival data.

## Keywords:

mixture cure model; single-index model; isotonic estimation; kernel smoothing.

## References:

- J. P. Sy and J. M. G. Taylor (2000): Estimation in a Cox proportional hazards cure model. *Biometrics*, 56(1):227-236.
- J. Xu and Y. Peng (2014): Nonparametric cure rate estimation with covariates. *Canadian Journal of Statistics*, 42(1):1-17.
- M. Amico, I. Van Keilegom and C. Legrand (2019): The single-index/Cox mixture cure model. *Biometrics*, 75(2):452-462.



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