

# *Machine Learning in Survival Analysis*



## **Getting Started**



# *Main Title*

Standard blurb goes here

%%Placeholder for Half title

**Series page goes here (if applicable); otherwise blank**

Machine Learning in Survival Analysis

Raphael Sonabend, Andreas Bender

**Imprint page here; PE will provide text**





---

# *Table of contents*

---

|   |           |
|---|-----------|
| <b>Getting Started</b>  | <b>3</b>  |
| <b>Preface</b>  | <b>xi</b> |
| <b>Authors</b>  | <b>xv</b> |
| <b>Symbols and Notation</b>                                       | <b>1</b>  |
| <b>Symbols and Notation</b>                                       | <b>1</b>  |
| <b>1 Introduction</b>   | <b>3</b>  |
| 1.1 Why is this book needed? . . . . .                            | 4         |
| 1.2 Reproducibility . . . . .                                     | 5         |
| <b>I Survival Analysis and Machine Learning</b>                   | <b>7</b>  |
| <b>2 MLSA From Start to Finish</b>                                | <b>9</b>  |
| <b>3 Statistical Learning</b>                                     | <b>11</b> |
| 3.1 Machine Learning . . . . .                                    | 11        |
| 3.1.1 Terminology and Methods . . . . .                           | 12        |
| 3.1.2 Machine Learning in Classification and Regression . . . . . | 15        |
| 3.1.2.1 Classification . . . . .                                  | 15        |
| 3.1.2.2 Regression . . . . .                                      | 15        |
| <b>4 Survival Analysis</b>  | <b>17</b> |
| 4.1 Survival Data and Definitions . . . . .                       | 18        |
| 4.1.1 Quantifying the Distribution of Event Times . . . . .       | 18        |
| 4.1.2 Single-event, right-censored data . . . . .                 | 19        |
| 4.1.3 Types of Censoring . . . . .                                | 20        |
| 4.1.4 Censoring vs. Truncation . . . . .                          | 23        |
| 4.1.5 Objective functions . . . . .                               | 24        |
| <b>5 Event-history Analysis</b>                                   | <b>25</b> |
| 5.1 Competing Risks . . . . .                                     | 26        |
| 5.2 Multi-state Models . . . . .                                  | 27        |
| 5.3 Recurrent Events . . . . .                                    | 28        |
| <b>6 Survival Task</b>  | <b>29</b> |
| 6.1 Survival Prediction Problems . . . . .                        | 29        |
| 6.2 Survival Analysis Task . . . . .                              | 31        |

|            |  |           |
|------------|--|-----------|
| <b>II</b>  | <b>Evaluation</b>  | <b>33</b> |
| <b>7</b>   | <b>What are Survival Measures?</b>                                       | <b>35</b> |
| 7.1        | Survival Measures . . . . .  | 35        |
| 7.2        | How are Models Evaluated? . . . . .                                      | 36        |
| <b>8</b>   | <b>Discrimination Measures</b>   | <b>39</b> |
| 8.1        | Time-Independent Measures . . . . .                                      | 39        |
| 8.1.1      | Concordance Indices . . . . .  | 40        |
| 8.1.2      | Choosing a C-index . . . . .   | 42        |
| 8.2        | Time-Dependent Measures . . . . .  | 43        |
| 8.2.1      | Concordance Indices . . . . .  | 43        |
| 8.2.2      | Area Under the Curve . . . . .   | 43        |
| <b>9</b>   | <b>Calibration Measures</b>  | <b>49</b> |
| 9.1        | Point Calibration . . . . .  | 49        |
| 9.1.1      | Calibration by Reduction . . . . .                                       | 50        |
| 9.1.2      | Houwelingen's $\alpha$ . . . . .   | 50        |
| 9.2        | Probabilistic Calibration . . . . .                                      | 51        |
| 9.2.1      | Kaplan-Meier Comparison . . . . .  | 51        |
| 9.2.2      | D-Calibration . . . . .  | 51        |
| <b>10</b>  | <b>Evaluating Distributions by Scoring Rules</b>                         | <b>55</b> |
| 10.1       | Classification Losses . . . . .  | 55        |
| 10.2       | Survival Losses . . . . .  | 56        |
| 10.2.1     | Integrated Graf Score . . . . .  | 57        |
| 10.2.2     | Integrated Survival Log Loss . . . . .                                   | 59        |
| 10.2.3     | Survival density log loss . . . . .                                      | 59        |
| 10.2.4     | Right-censored log loss . . . . .  | 60        |
| 10.2.5     | Absolute Survival Loss . . . . .   | 60        |
| 10.3       | Prediction Error Curves . . . . .  | 60        |
| 10.4       | Baselines and ERV . . . . .  | 61        |
| <b>11</b>  | <b>Evaluating Survival Time</b>  | <b>63</b> |
| 11.1       | Distance measures . . . . .  | 64        |
| 11.2       | Over- and under-predictions . . . . .                                    | 64        |
| <b>12</b>  | <b>Choosing Measures</b>   | <b>67</b> |
| 12.1       | Defining the experiment . . . . .  | 67        |
| 12.1.1     | Predictive experiments . . . . .   | 67        |
| 12.1.2     | Benchmark experiments . . . . .  | 68        |
| 12.1.3     | Investigation . . . . .  | 69        |
| 12.2       | Conclusions . . . . .  | 69        |
| <b>III</b> | <b>Models</b>  | <b>71</b> |
| <b>13</b>  | <b>Classical Models</b>  | <b>73</b> |
| 13.1       | A Review of Classical Survival Models . . . . .                          | 73        |
| 13.1.1     | Non-Parametric Distribution Estimators . . . . .                         | 74        |
| 13.1.2     | Continuous Ranking and Semi-Parametric Models: Cox PH . . . . .          | 76        |
| 13.1.3     | Conditional Distribution Predictions: Parametric Linear Models . . . . . | 77        |

|  |            |
|--|------------|
| <b>14 Machine Learning Survival Models</b>                               | <b>83</b>  |
| 14.1 A Survey of Machine Learning Models for Survival Analysis . . . . . | 83         |
| <b>15 Tree-Based Methods</b>   | <b>87</b>  |
| 15.1 Random Forests . . . . .  | 87         |
| 15.1.1 Random Forests for Regression . . . . .                           | 87         |
| 15.1.2 Random Forests for Survival Analysis . . . . .                    | 90         |
| 15.1.2.1 Splitting Rules . . . . .                                       | 90         |
| 15.1.2.2 Terminal Node Prediction . . . . .                              | 92         |
| 15.1.3 Conclusions . . . . .   | 95         |
| <b>16 Support Vector Machines</b>  | <b>97</b>  |
| 16.1 SVMs for Regression . . . . .                                       | 97         |
| 16.2 SVMs for Survival Analysis . . . . .                                | 101        |
| 16.2.1 Survival time SSVMs . . . . .                                     | 101        |
| 16.2.2 Ranking SSVMs . . . . .   | 102        |
| 16.2.3 Hybrid SSVMs . . . . .  | 104        |
| 16.3 Conclusion . . . . .  | 105        |
| <b>17 Boosting Methods</b>   | <b>107</b> |
| 17.1 GBMs for Regression . . . . .                                       | 107        |
| 17.2 GBMs for Survival Analysis . . . . .                                | 110        |
| 17.2.1 PH and AFT GBMs . . . . .   | 110        |
| 17.2.2 Discrimination Boosting . . . . .                                 | 111        |
| 17.2.3 CoxBoost . . . . .  | 112        |
| 17.3 Conclusion . . . . .  | 113        |
| <b>18 Neural Networks</b>  | <b>115</b> |
| 18.1 Neural Networks . . . . .   | 115        |
| 18.1.1 Neural Networks for Regression . . . . .                          | 115        |
| 18.1.2 Neural Networks for Survival Analysis . . . . .                   | 118        |
| 18.1.2.1 Probabilistic Survival Models . . . . .                         | 119        |
| 18.1.2.2 Deterministic Survival Models . . . . .                         | 126        |
| 18.1.3 Conclusions . . . . .   | 126        |
| <b>19 Alternative Methods</b>  | <b>129</b> |
| <b>20 Choosing Models</b>  | <b>131</b> |
| <b>IV Reduction Techniques</b>   | <b>133</b> |
| <b>21 Reductions</b>   | <b>135</b> |
| 21.1 Representing Pipelines . . . . .                                    | 136        |
| 21.2 Introduction to Composition . . . . .                               | 136        |
| 21.2.1 Taxonomy of Compositors . . . . .                                 | 137        |
| 21.2.2 Motivation for Composition . . . . .                              | 138        |
| 21.3 Introduction to Reduction . . . . .                                 | 138        |
| 21.3.1 Reduction Motivation . . . . .                                    | 140        |
| 21.3.2 Task, Loss, and Data Reduction . . . . .                          | 140        |
| 21.3.3 Common Mistakes in Implementation of Reduction . . . . .          | 141        |
| 21.4 Composition Strategies for Survival Analysis . . . . .              | 142        |

|           |   |            |
|-----------|---|------------|
| 21.4.1    | C1) Linear Predictor $\rightarrow$ Distribution . . . . .                       | 143        |
| 21.4.2    | C2) Survival Time $\rightarrow$ Distribution . . . . .                          | 143        |
| 21.4.3    | C3) Distribution $\rightarrow$ Survival Time Composition . . . . .              | 144        |
| 21.4.4    | C4) Survival Model Averaging . . . . .  | 144        |
| 21.5      | Novel Survival Reductions . . . . .   | 144        |
| 21.5.1    | R7-R8) Survival $\rightarrow$ Probabilistic Classification . . . . .            | 145        |
| 21.5.1.1  | Composition: Binning Survival Times . . . . .                                   | 145        |
| 21.5.1.2  | Composition: Survival to Classification Outcome . . . . .                       | 146        |
| 21.5.1.3  | Reduction to Classification Bias . . . . .                                      | 148        |
| 21.5.1.4  | Multi-Label Classification Algorithms . . . . .                                 | 148        |
| 21.5.1.5  | Censoring in Classification . . . . .   | 149        |
| 21.5.1.6  | R7) Probabilistic Survival $\rightarrow$ Probabilistic Classification . . . . . | 149        |
| 21.5.1.7  | R8) Deterministic Survival $\rightarrow$ Probabilistic Classification . . . . . | 150        |
| 21.6      | Conclusions . . . . .   | 152        |
| <b>22</b> | <b>Competing Risks Pipelines</b>  | <b>153</b> |
| <b>23</b> | <b>Discrete Time Survival Analysis</b>  | <b>155</b> |
| <b>24</b> | <b>Connections to Poisson Regression and Processes</b>                          | <b>157</b> |
| <b>25</b> | <b>Connections to Regression and Imputation</b>                                 | <b>159</b> |
| 25.0.0.1  | Deletion $\#\{\text{sec-redux-regr-del}\}$ . . . . .                            | 160        |
| 25.0.0.2  | Imputation . . . . .  | 161        |
| 25.0.0.3  | The Decision to Impute or Delete . . . . .                                      | 162        |
| <b>26</b> | <b>Advanced Methods</b>   | <b>163</b> |
| <b>V</b>  | <b>Extensions and Outlook</b>   | <b>165</b> |
| <b>27</b> | <b>Common problems in survival analysis</b>                                     | <b>167</b> |
| 27.1      | Evaluation and prediction . . . . .   | 167        |
| <b>28</b> | <b>Survival Software</b>  | <b>169</b> |
| <b>29</b> | <b>What's next for MLSA?</b>  | <b>171</b> |
|           | <b>Exercises</b>  | <b>173</b> |
|           | <b>Exercises</b>  | <b>173</b> |
|           | <b>References</b>   | <b>175</b> |
|           | <b>References</b>   | <b>175</b> |

---

# Preface

---

“Everything happens to everybody sooner or later if there is time enough” - George Bernard Shaw

“...but in this world nothing can be said to be certain, except death and taxes.” - Benjamin Franklin

A logical consequence of Bernard Shaw’s quote is that if there is time enough, then everybody will have experienced a given event at some point. This is one of the central assumptions to survival analysis (specifically to single-event analysis, but we’ll get to that later). As nothing can be certain (except death and taxes), machine learning can be used to predict the probability people will experience the event and *when*. This is exactly the problem that this book tackles.

With immortality only being a theoretical concept, there is never ‘time enough’, hence survival analysis assumes that the event of interest is guaranteed to occur within an object’s lifetime. This event could be a patient entering remission after a cancer diagnosis, the lifetime of a lightbulb after manufacturing, the time taken to finish a race, or any other event that is observed over time. Survival analysis differs from other fields of Statistics in that uncertainty is explicit encoded in the survival problem; this uncertainty is known as ‘censoring’. For example, say a model is being built to predict when a marathon runner will finish a race and to learn this information the model is fed data from every marathon over the past five years. Across this period, there will be many runners who never finish their race. Instead, these runners are said to be ‘censored’ and the model uses all information up until the point of censoring (dropping out the race), and learns that they ran for at least as long as their censoring time (the time they dropped out). Censoring is unique to survival analysis and without the presence of censoring, survival analysis is mathematically equivalent to regression.

This book covers survival analysis in the most common right-censoring setting for independent censoring, as well as discussing competing risk frameworks for dependent censoring - these terms will all be covered in the introduction of the book.

**A note from Raphael:** I wrote my PhD thesis about machine learning applications to survival analysis as I was interested in understanding why more researchers were not using machine learning models for survival analysis. Since then I’ve had the pleasure to work with, and advise, researchers across different sectors, including pharmaceutical companies, governmental agencies, funding organisations, and research institutions. I hope that this book continues to help researchers discover machine learning survival analysis and to navigate the nuances and complexities it presents.

**A note from Andreas:** FIXME.

## Overview

This textbook is intended to fill a gap in the literature by providing a comprehensive introduction to machine learning in the survival setting. If you are interested in machine learning or survival analysis separately then you might consider James et al. (2013), Hastie, Tibshirani, and Friedman (2001), Bishop (2006) for machine learning and Collett (2014), J. D. Kalbfleisch and Prentice (1973) for survival analysis. This book serves as a complement to the above examples and introduces common machine learning terminology from simpler settings such as regression and classification, but without diving into the detail found in other sources, instead focusing on extension to the survival analysis setting.

This book may be useful for Masters or PhD students who are specialising in machine learning in survival analysis, machine learning practitioners looking to work in the survival setting, or statisticians who are familiar with survival analysis but less so with machine learning. The book could be read cover-to-cover, but this is not advised. Instead it may be preferable to dip into sections of the book as required and use the ‘signposts’ that direct the reader to sections of the book that are relevant to each other.

The book is split into five parts:

**Part I: Survival Analysis and Machine Learning** The book begins by introducing the basics of survival analysis and machine learning and unifying terminology between the two to enable meaningful description of ‘machine learning in survival analysis’ (MLSA). In particular, the survival analysis ‘task’ and survival ‘prediction types’ are defined.

**Part II: Evaluation** The second part of the book discusses measures for evaluating survival models. These are presented in different classes that reflect the prediction types identified in Part I. In each chapter, the measure class is introduced, particular metrics are listed, and commentary is provided on how and when to use the measures. The final chapter of Part II briefly discusses when to use a given measure class and provides recommendations for model comparison.

**Part III: Models** Part III is a deep dive into machine learning models for solving survival analysis problems. This begins with ‘classical’ models that may not be considered ‘machine learning’ and then continues by exploring different classes of machine learning models including random forests, support vector machines, gradient boosting machines, neural networks, and other less common classes. Each model class is introduced in the simpler regression setting and then extensions to survival analysis are discussed. Differences between model implementations are not discussed, instead the focus is on understanding how these models are built for survival analysis - in this way readers are well-equipped to independently follow individual papers introducing specific implementations.

**Part IV: Reduction Techniques** The next part of the book introduces reduction techniques in survival analysis, which is the process of solving the survival analysis task by using methods from other fields. In particular, chapters focus on demonstrating how any survival model can be used in the competing risks setting, discrete time modelling, Poisson methods, pseudovalues (reduction to regression), and other advanced modelling methods.

**Part V: Extensions and Outlook** The final part of the book provides some miscellaneous chapters that may be of use to readers. The first chapter lists common practical problems that occur when running survival analysis experiments and solutions that we have found useful. The next lists open-source software at the time of writing for running machine learning survival analysis experiments. The final chapter is our outlook on survival analysis and where the field may be heading.

Exercises are provided at the end of the book so you can test yourself as you go along.

## **Citing this book**

Whilst this book remains a work in progress you can cite it as

Sonabend. R, Bender. A. (2024). Machine Learning in Survival Analysis.  
<https://www.mlsabook.com>.

```
@book{MLSA2024
  title = {Machine Learning in Survival Analysis},
  editor = {Raphael Sonabend, Andreas Bender},
  url = {https://www.mlsabook.com},
  year = {2024}
}
```

Please see the front page of the book website (<https://www.mlsabook.com>) for full licensing details.

We hope you enjoy reading this book.

Raphael and Andreas





---

## ***Authors***

---

Raphael Sonabend is the CEO and Co-Founder of OSPO Now, a company providing virtual open-source program offices as a service. They are also a Visiting Researcher at Imperial College London. Raphael holds a PhD in statistics, specializing in machine learning applications for survival analysis. They created the R packages `mlr3proba`, `survivalmodels`, and the Julia package `SurvivalAnalysis.jl`. Raphael co-edited and co-authored *Applied Machine Learning Using mlr3 in R* (Bischl et al. 2024).

Andreas Bender is...



# Symbols and Notation

⚠ Minor changes expected!

This page is a work in progress and minor changes will be made over time.

The most common symbols and notation used throughout this book are presented below; in rare cases where different meanings are intended within the book, this will be made clear.

A lower-case letter in normal font,  $x$ , refers to a single, fixed observation. When in bold font, a lower-case letter,  $\mathbf{x}$ , refers to a vector of fixed observations, and an upper-case letter,  $\mathbf{X}$ , represents a matrix. A letter in normal font with a single subscript, refers to a single element from a vector, for example  $x_i$  would be the  $i$ th element in vector  $\mathbf{x}$ , whereas two subscripts refer to a single element from a matrix, for example  $x_{ij}$  would be the element in the  $i$ th row and  $j$ th column of matrix  $\mathbf{X}$ . When referring to a row of a matrix,  $\mathbf{X}$ , then a subscript is used with a bold-face lower-case letter, for example the  $i$ th row would be  $\mathbf{x}_i$ , in contrast the  $j$ th column would be written as  $\mathbf{x}_{\cdot j}$ . Calligraphic letters,  $\mathcal{X}$ , are used to denote sets.

A matrix will always be defined with its dimensions using the notation,  $\mathbf{X} \in \mathcal{X}^{n \times p}$ , or if  $\mathcal{X}$  is the set of Reals, it may be written as “ $\mathbf{X}$  is a  $n \times p$  Real-valued matrix”. By default, a ‘vector’ will refer to a column vector, which may be thought of as a matrix with  $n$  rows and one column, and may be represented as:

$$\mathbf{x} = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix}$$

Vectors are usually defined using transpose notation, for example the vector above may instead be written as  $\mathbf{x}^\top = (x_1 \ x_2 \ \cdots \ x_n)$  or  $\mathbf{x} = (x_1 \ x_2 \ \cdots \ x_n)^\top$ . Vectors may also be defined in a shortened format as,  $\mathbf{x} \in \mathcal{X}^n$ , which implies a vector of length  $n$  with elements as represented above.

Typically, a ‘hat’,  $\hat{x}$ , will refer to the prediction or estimation of a variable,  $x$ , with bold-face used again to represent vectors. A ‘bar’,  $\bar{x}$ , refers to the sample mean of  $\mathbf{x}$ . Capital letters in normal font,  $X$ , refer to scalar or vector random variables, which will be made clear from context.  $\mathbb{E}(X)$  and  $\text{Var}(X)$  are the expectation and variance of the random variable  $X$  respectively. We write  $A \perp\!\!\!\perp B$ , to denote that  $A$  and  $B$  are independent, i.e., that  $P(A \cap B) = P(A)P(B)$ .

A function  $f$ , will either be written as a formal map of domain to codomain,  $f : \mathcal{X} \rightarrow \mathcal{Y}; (x, y) \mapsto f(x, y)$  (which is most useful for understanding inputs and outputs), or more simply and commonly as  $f(x, y)$ . Given a random variable,  $X$ , following distribution  $\zeta$  (mathematically written  $X \sim \zeta$ ), then  $f_X$  denotes the probability density function, and

analogously for other distribution defining functions. In the survival analysis context (Chapter 4), a subscript “0” refers to a “baseline” function, for example,  $S_0$  is the baseline survival function.

Common variables and acronyms used in the book are given in Table 0.1 and Table 0.2 respectively.

Table 0.1: Common variables used throughout the book.

| Variable   | Definition   |
|--|--|
| $\mathbb{R}, \mathbb{R}_{>0}, \mathbb{R}_{\geq 0}, \bar{\mathbb{R}}$ | Set of Reals, positive Reals (excl. zero), non-negative Reals (incl. zero), and Reals including $\pm\infty$ .  |
| $\mathbb{N}_{>0}$  | Set of Naturals excluding zero.  |
| $(\mathbf{X}, \mathbf{t}, \delta)$                                   | Survival data where $\mathbf{X}$ is an $n \times p$ matrix of features, $\mathbf{t}$ is a vector of observed outcome times, and $\delta$ is a vector of observed outcome indicators. |
| $\beta$  | Vector of model coefficients/weights.  |
| $\eta$   | Linear predictor, $X\beta$ .   |
| $\mathcal{D}, \mathcal{D}_{train}, \mathcal{D}_{test}$               | Dataset, training data, and testing data.  |

Table 0.2: Common acronyms used throughout the book.

| Acronym | Definition                                  |
|---------|---|
| AFT     | Accelerated Failure Time                    |
| cdf     | Cumulative Distribution Function            |
| chf     | Cumulative Hazard Function                  |
| CPH     | Cox Proportional Hazards                    |
| GBM     | Gradient Boosting Machine                   |
| GLM     | Generalised Linear Model                    |
| IPC(W)  | Inverse Probability of Censoring (Weighted) |
| ML      | Machine Learning                            |
| pdf     | Probability Density Function                |
| PH      | Proportional Hazards                        |
| (S)SVM  | (Survival) Support Vector Machine           |
| t.v.i.  | Taking Values In                            |

# Introduction

---

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

---

## TODO

- Mention somewhere that SA can be used to solve T-year prediction problems (i.e., see if we can get classif users over to SA).
  - Also SA can be used for censoring/truncation
- 

Writing after a global pandemic, applications of survival analysis are more relevant than ever. Predicting the time from onset of COVID-19 symptoms to hospitalisation, or the time from hospitalisation to intubation, or intubation to death, are all time-to-event predictions that are at the centre of survival analysis. As well as morbid applications, survival analysis predictions may be concerned with predicting the time until a customer cancels their gym membership, or the lifetime of a lightbulb; any event that is guaranteed (or at least very likely) to occur can be modelled by a survival analysis prediction. As these predictions can be so sensitive, for example a model predicting when a child should be taken off breathing support (Data Study Group Team 2020), the best possible predictions, evaluated to the highest standard, are a necessity. In other fields of predictive modelling, machine learning has made incredible breakthroughs (such as AlphaFold), therefore applying machine learning to survival analysis is a natural step in the evolution of an important field.

Survival analysis is the field of Statistics focusing on modelling the distribution of an event, which may mean the time until the event takes place, the risk of the event happening, the probability of the event occurring at a single time, or the event's underlying probability distribution. Survival analysis ('survival') is a unique field of study in Statistics as it includes the added difficulty of 'censoring'. Censoring is best described through example: a study is conducted to determine the mortality rate of a group of patients after diagnoses with a particular disease. If a patient dies during this study then their outcome is 'death' and their time of death can be recorded. However if a patient drops-out of the study before they die, then their time of death (though guaranteed to occur) is unknown and the only available information is the time at which they left the study. This patient is now said to be *censored* at the time they drop out. The censoring mechanism allows as much outcome information (time and event) to be captured as possible for all patients (observations).

Machine learning (ML) is the field of Statistics primarily concerned with building models to either predict outputs from inputs or to learn relationships from data (Hastie, Tibshirani, and Friedman 2001; James et al. 2013). This book is limited to the former case, or

more specifically supervised learning, as this is the field in which the vast majority of survival problems live. Relative to other areas of supervised learning, development in survival analysis has been slow – the majority of developments in machine learning for survival analysis have only been in the past decade (see chapters (?@sec-review)-(Chapter 7)). This appears to have resulted in less interest in the development of machine learning survival models (?@sec-review), less rigour in the evaluation of such models (Chapter 7), and fewer off-shelf/open-source implementations (R. Sonabend et al. 2021). This book seeks to set the foundations for clear workflows, good practice, and precise results for ‘machine learning survival analysis’.

---

## 1.1 Why is this book needed?

Firstly, whilst there are many books dedicated to regression and classification as machine learning problems (the ‘bibles’ of machine learning focus entirely on regression and classification only (Bishop 2006; Hastie, Tibshirani, and Friedman 2001; James et al. 2013)), there is a deficit of books covering the survival analysis setting. By writing this book we hope to fill this gap and enable more practitioners to use cutting-edge methods in survival analysis. Survival analysis has important applications in healthcare, finance, engineering and more, all fields that directly impact upon individual lives on a day-to-day basis, and should perhaps be considered as important as classification and regression. The result of this gap in interest, is the erroneous assumption that one field can be directly applied to another. For example there is evidence of researchers treating censoring as a nuisance to be ignored and using regression models instead (Schwarzer, Vach, and Schumacher 2010). Censoring is indeed a challenge and may contribute to making survival analysis less accessible than other fields, but this need not be the case; a clear unification of terminology and presentation of methods may help make ‘machine learning survival analysis’ more accessible. Added accessibility could lead to more academics (and non-academics) engaging with the field and promoting good standards of practice, as well as developing more novel models and measures.

Where survival models have been developed, these have skewed towards ‘ranking models’, which predict the relative risk of an event occurring (Section 6.1). In many applications these predictions are sufficient, for example in randomised control trials if assessing the increased/decreased risk of an event after treatment. However, there are many use-cases where predicting an individual’s survival probability distribution is required. Take, for example, an engineer calculating the lifetime of a plane’s engine.<sup>1</sup> There are three important reasons to replace a jet engine at the optimal time:

- financial: jet engines are very expensive and replacing one sooner than required is a waste of money;
- environmental: an engine being replaced too early is a waste of potential usage;
- safety: if the engine is replaced too late then there is a risk to passengers.

Now consider examples for the three possible ‘prediction types’ the engineer can make:

- i. A ‘relative risk prediction’: This engine is twice as likely to fail as another.
- ii. A ‘survival time prediction’: The engine is expected to fail in 30 days.

---

<sup>1</sup>In this engineering context, survival analysis is usually referred to as reliability analysis.

- iii. A ‘survival distribution prediction’: The lifetime of the engine is distributed according to the probability distribution  $\zeta$ .

The first prediction type is not useful as the underlying relative risk may be unknown and the engineer is concerned with the individual lifetime. The second prediction type provides a useful quantity for the engineer to work with however there is no uncertainty captured in this prediction. The third prediction type can capture the uncertainty of failure over the entirety of the positive Reals (though usually only a small subset is possible and useful). With this final prediction type, the engineer can create safe decisions: ‘replace the engine at time  $\tau$ , where  $\tau$  is the time when the predicted probability of survival drops below 60%,  $S(\tau) = 0.6$ ’. There are ethical, economic, and environmental reasons for a good survival distribution prediction and this book considers a distribution prediction to be the most important prediction type.

Evaluating predictions from survival models is of the utmost importance. This is especially important as survival models are often deployed in the public domain, particularly in healthcare. Physical products in healthcare, such as new vaccines, undergo rigorous testing and research in randomised control trials before being publically deployed; the same level of rigour should be expected for the evaluation of survival models that are used in life-and-death situations. Evaluation measures for regression and classification are well-understood with important properties, however survival measures have not undergone the same treatment. For example many survival models are still being evaluated solely with concordance indices that have been repeatedly criticised (Gönen and Heller 2005; Rahman et al. 2017; Schmid and Potapov 2012).

---

## 1.2 Reproducibility

This book includes simulations and figures generated in R, the code for any figures or experiments in this book are freely available at <https://github.com/mlsa-book/MLSA> under an MIT licence and all content on this website is available under CC BY 4.0. We use [renv](#) to manage package versions, you can find our lockfile at <https://github.com/mlsa-book/MLSA/blob/main/book/renv.lock>.





## Part I

# Survival Analysis and Machine Learning



## 2

---

### *MLSA From Start to Finish*

---

TODO (150-200 WORDS)

**!** Page coming soon!

**We are working on this page and it will be available soon!**



# 3

## Statistical Learning

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

TODO

- $\mathcal{D}$  - labeled data set with  $n$  observation
- Observations:  $(\mathbf{x}^{(i)}, y^{(i)})$  where  $\mathbf{x}^{(i)} \in \mathcal{X}$  is a  $p$ -dimensional feature vector and  $y^{(i)} \in \mathcal{Y}$  is a label
- Data set:  $\mathcal{D} = ((\mathbf{x}^{(1)}, y^{(1)}), \dots, (\mathbf{x}^{(n)}, y^{(n)}))$
- Assume  $\mathcal{D} \stackrel{i.i.d.}{\sim} (\mathbb{P}_{xy})^n$  (unknown distribution)
- ML model:  $f : \mathcal{X} \rightarrow \mathbb{R}^g$  assigning a prediction in  $\mathbb{R}^g$
- ML learners,  $\mathcal{J}$ , configured by hyperparameters  $\lambda \in \Lambda$ , are  $\mathcal{J} : \mathbb{D} \times \Lambda \rightarrow \mathcal{H}, (\mathcal{D}, \lambda) \mapsto \hat{f}$  where  $\mathcal{H}$  is the function space to which a model belongs and  $\hat{f}$  is a trained model with learned hyperparameters  $\hat{\theta} \in \mathcal{H}$ .
- Models are evaluated with loss functions which measure the discrepancy between predictions and true values  $L : \mathcal{Y} \times \mathbb{R}^g \rightarrow \mathbb{R}, (\hat{f}(\mathbf{x}), \mathbf{y}) \mapsto l(\hat{f}(\mathbf{x}), \mathbf{y})$
- To prevent overfitting, models are evaluated on unseen test data to ensure unbiased performance estimation and the generalization error  $GE(\mathcal{J}, \lambda, n_{train}, l) := \lim_{n_{test} \rightarrow \infty} \mathbb{E}_{\mathcal{D}_{train}, \mathcal{D}_{test} \sim \mathbb{P}_{xy}} [l(\mathbf{y}_{test}, \mathbf{F}_{\mathcal{D}_{test}, \mathcal{J}(\mathcal{D}_{train}, \lambda)})]$  where  $\mathbf{F}_{\mathcal{D}_{test}, \mathcal{J}(\mathcal{D}_{train}, \lambda)}$  is the matrix of predictions from a model trained on  $\mathcal{D}_{train}$  and making predictions on  $\mathcal{D}_{test}$ .

### 3.1 Machine Learning

This section begins with a very brief introduction to machine learning and a focus on regression and classification; the survival machine learning task is then introduced (Section 6.2). Of the many fields within machine learning (ML), the scope of this book is narrowed to supervised learning. Supervised learning is the sub-field of ML in which predictions are made for outcomes based on data with observed dependent and independent variables. For example predicting someone's height is a supervised learning problem as data can be collected

for features (independent variables) such as age and sex, and outcome (dependent variable), which is height. Predictive survival analysis problems fall naturally in the supervised learning framework as there are identifiable features and (multiple types of) outcomes.

### 3.1.1 Terminology and Methods

Common supervised learning methods are discussed in a simplified setting with features  $X$  *t.v.i.*  $\mathcal{X}$  and outcomes  $Y$  *t.v.i.*  $\mathcal{Y}$ ; usually outcomes are referred to as ‘targets’ (a ‘target for prediction’). Let  $\mathcal{D}_0 = \{(X_1, Y_1), \dots, (X_n, Y_n)\}$  be a (training) dataset where  $(X_i, Y_i) \stackrel{i.i.d.}{\sim} (X, Y)$ . The methods below extend naturally to the survival setting.

#### Strategies and Models

In order to clearly separate between similar objects, several terms for machine learning are now introduced and clearly distinguished.

Let  $g : \mathcal{X} \rightarrow \mathcal{Y}$  be the true (but unknown) mapping from the features to outcomes, referred to as the *true prediction functional*. Let  $\mathcal{G}$  be the set of *prediction functionals* such that  $\forall \Upsilon \in \mathcal{G}, \Upsilon : \mathcal{X} \rightarrow \mathcal{Y}$ . A *learning* or *fitting algorithm* is defined to be any function of the form  $\mathcal{A} : \mathcal{X}^n \times \mathcal{Y}^n \rightarrow \mathcal{G}$ . The goal of supervised learning is to *learn*  $g$  with a learning algorithm *fit* on (i.e. the input to the algorithm is) training data,  $\hat{g} := \mathcal{A}(\mathcal{D}_{train}) \in \mathcal{G}$ . Note that  $\hat{g}$  may take hyper-parameters that can be set or tuned (see below). The learning algorithm is ‘good’ if  $\hat{g}(X) \approx g(X)$  (see ‘Evaluation’ below).

The learning algorithm is determined by the chosen *learning strategy* and *model*, where a model is a complete specification of a learning strategy including hyper-parameters. These terms are more clearly illustrated by example:

- i. Learning strategy – simple linear regression
- ii. Model –  $y = \beta_0 + \beta_1 x$  where  $x \in \mathbb{R}$  is a single covariate,  $y \in \mathbb{R}$  is the target, and  $\beta_0, \beta_1 \in \mathbb{R}$  are model coefficients.
- iii. Learning algorithm (model fitting) – Minimise the residual sum of squares:  
 $(\hat{\beta}_0, \hat{\beta}_1) := \operatorname{argmin}_{\beta_0, \beta_1} \left\{ \sum_{i=1}^n (y_i - \beta_0 - \beta_1 x_i)^2 \right\}$  for  $(x_i, y_i) \in \mathcal{D}_{train}, i = 1, \dots, n$ .
- iv. Prediction functional –  $\hat{g}(x) = \hat{\beta}_0 + \hat{\beta}_1 x$

To further illustrate the difference between learning strategy and model, note that the same learning strategy ‘simple linear regression’ could either utilise the model above or instead a model without intercept,  $y = \beta x$ , in which case the learning algorithm and prediction functional would also be modified.

The model in (ii) is called *unfitted* as the model coefficients are unknown and the model cannot be used for prediction. After step (iii) the model is said to be fit to the training data and therefore the model is *fitted*.<sup>1</sup> It is common to refer to the learning algorithm (and associated hyper-parameters) as the unfitted model and to refer to the prediction functional (and associated hyper-parameters) as the fitted model.

<sup>1</sup>The terms ‘fitted’ and ‘unfitted’ are used instead of ‘fit’ and ‘unfit’ to prevent confusion with words such as ‘suitable’ and ‘unsuitable’.

## Evaluation

Models are *evaluated* by evaluation measures called *losses* or *scores*,<sup>2</sup>  $L : \mathcal{Y} \times \mathcal{Y} \rightarrow \bar{\mathbb{R}}$ . Let  $(X^*, Y^*) \sim (X, Y)$  be test data (i.e. independent of  $\mathcal{D}_{train}$ ) and let  $\hat{g} : \mathcal{X} \rightarrow \mathcal{Y}$  be a prediction functional fit on  $\mathcal{D}_{train}$ , then these evaluation measures determine how closely predictions,  $\hat{g}(X^*)$ , relate to the truth,  $Y^*$ , thereby providing a method for determining if a model is ‘good’.<sup>3</sup>

## Task

A machine learning *task* is a simple mechanism to outline the problem of interest by providing: i) the data specification; ii) the definition of learning; iii) the definition of success (when is a prediction ‘good’?) (Franz J. Király et al. 2021). All tasks in this paper have the same definitions of learning and success. For (ii), the aim is to learn the true prediction functional,  $g$ , by fitting the learning algorithm on training data,  $\hat{g} := \mathcal{A}(\mathcal{D}_0)$ . For (iii), a predicted functional is considered ‘good’ if the *expected generalization error*,  $\mathbb{E}[L(Y^*, \hat{g}(X^*))]$ , is low, where  $(X^*, Y^*) \sim (X, Y)$  is independent of the training data  $\mathcal{D}_0$ , and  $L$  is some loss that is chosen according to the domain of interest (regression, classification, survival).

## Resampling

Models are *tested* on their ability to make predictions. In order to avoid ‘optimism of training error’ (James et al. 2013) – overconfidence caused by testing the model on training data – models are tested on previously unseen or ‘held-out’ data. *Resampling* is the procedure of splitting one dataset into two or more for separated training and testing. In this paper only two resampling methods are utilised: *holdout* and *cross-validation*. Holdout is the process of splitting a primary dataset into training data for model fitting and testing data for model predicting. This is an efficient method but may not accurately estimate the expected generalisation error for future model performance, instead this is well-estimated by  $K$ -fold cross-validation (KCV) (Hastie, Tibshirani, and Friedman 2001). In KCV, data is split into  $K \in \mathbb{N}_{>0}$  ‘folds’ such that  $K - 1$  of the folds are used for model training and the final  $K$ th fold for testing. The testing fold is iterated over all  $K$  folds, so that each at some point is used for testing and then training (though never at the same time). In each iteration the model is fit on the training folds, and predictions are made and evaluated on the testing fold, giving a loss  $L_k := L(\hat{g}(X^k), Y^k)$ , where  $(X^k, Y^k)$  are data from the  $k$ th fold. A final loss is defined by,  $L^* := \frac{1}{K} \sum_{k=1}^K L_k$ . Commonly  $K = 5$  or  $K = 10$  (Breiman and Spector 1992; Kohavi 1995).

## Model Performance Benchmarking

Whilst *benchmarking* often refers to speed tests, i.e. the time taken to complete an operation, it can also refer to any experiment in which objects (mathematical or computational) are compared. In this report, a benchmark experiment will either refer to the comparison of multiple models’ predictive abilities, or comparison of computational speeds and object sizes for model fitting; which of these will be clear from context.

<sup>2</sup>The term ‘loss’ is usually utilised to refer to evaluation measures to be minimised, whereas ‘scores’ should be maximised, this is returned to in (@sec-eval).

<sup>3</sup>Here evaluation refers specifically to predictive ability; other forms of evaluation and further discussion of the area are provided in (@sec-eval).

## Model Comparison

Models can be analytically compared on how well they make predictions for new data. Model comparison is a complex topic with many open questions (Demšar 2006; Dietterich 1998; Nadeau and Bengio 2003) and as such discussion is limited here. When models are compared on multiple datasets, there is more of a consensus in how to evaluate models (Demšar 2006) and this is expanded on further in (R. E. B. Sonabend 2021). Throughout this book there are small simulation experiments for model comparison on single datasets however as these are primarily intended to aid exposition and not to generalise results, it suffices to compare models with the conservative method of constructing confidence intervals around the sample mean and standard error of the loss when available (Nadeau and Bengio 2003).

## Hyper-Parameters and Tuning

A *hyper-parameter* is a model parameter that can be set by the user, as opposed to coefficients that are estimated as part of model fitting. A hyper-parameter can be set before training, or it can be tuned. *Tuning* is the process of choosing the optimal hyper-parameter value via automation. In the simplest setting, tuning is performed by selecting a range of values for the hyper-parameter(s) and treating each choice (combination) as a different model. For example if tuning the number of trees in a random forest (Section 15.1),  $m_r$ , then a range of values, say 100, 200, 500 are chosen, and three models  $m_{r100}, m_{r200}, m_{r500}$  are benchmarked. The optimal hyper-parameter is given by whichever model is the best performing. *Nested resampling* is a common method to prevent overfitting that could occur from using overlapping data for tuning, training, or testing. Nested resampling is the process of resampling the training set again for tuning.



### 3.1.2 Machine Learning in Classification and Regression

Before introducing machine learning for survival analysis, which is considered ‘non-classical’, the more standard classification and regression set-ups are provided; these are referenced throughout this book.

#### 3.1.2.1 Classification

Classification problems make predictions about categorical (or discrete) events, these may be *deterministic* or *probabilistic*. Deterministic classification predicts which category an observation falls into, whereas probabilistic classification predicts the probability of an observation falling into each category. In this brief introduction only binary single-label classification is discussed, though the multi-label case is considered in ?? In binary classification, there are two possible categories an observation can fall into, usually referred to as the ‘positive’ and ‘negative’ class. For example predicting the probability of death due to a virus is a probabilistic classification task where the ‘positive’ event is death.

A probabilistic prediction is more informative than a deterministic one as it encodes uncertainty about the prediction. For example it is clearly more informative to predict a 70 chance of rain tomorrow instead of simply ‘rain’. Moreover the latter prediction implicitly contains an erroneous assumption of certainty, e.g. ‘it will rain tomorrow’.

##### Classification Task

**Box 3.1.** Let  $(X, Y)$  be random variables t.v.i.  $\mathcal{X} \times \mathcal{Y}$  where  $\mathcal{X} \subseteq \mathbb{R}^p$  and  $\mathcal{Y} = \{0, 1\}$ . Then,

- The probabilistic classification task is the problem of predicting the probability of a single event taking place and is specified by  $g : \mathcal{X} \rightarrow [0, 1]$ .
- The deterministic classification task is the problem of predicting if a single event takes place and is specified by  $g : \mathcal{X} \rightarrow \mathcal{Y}$ .

The estimated prediction functional  $\hat{g}$  is fit on training data  $\setminus (X_1, Y_1), \dots, (X_n, Y_n) \stackrel{i.i.d.}{\sim} (X, Y)$  and is considered ‘good’ if  $\mathbb{E}[L(Y^*, \hat{g}(X^*))]$  is low, where  $(X^*, Y^*) \sim (X, Y)$  is independent of  $(X_1, Y_1), \dots, (X_n, Y_n)$  and  $\hat{g}$ .

In the probabilistic case, the prediction  $\hat{g}$  maps to the estimated probability mass function  $\hat{p}_Y$  such that  $\hat{p}_Y(1) = 1 - \hat{p}_Y(0)$ .

#### 3.1.2.2 Regression

A regression prediction is one in which the goal is to predict a continuous outcome from a set of features. For example predicting the time until an event (without censoring) occurs, is a regression problem.

##### Regression Task

**Box 3.2.** Let  $(X, Y)$  be random variables t.v.i.  $\mathcal{X} \times \mathcal{Y}$  where  $\mathcal{X} \subseteq \mathbb{R}^p$  and  $\mathcal{Y} \subseteq \mathbb{R}$ . Let  $\mathcal{S} \subset \text{Distr}(\mathcal{Y})$  be a convex set of distributions on  $\mathcal{Y}$ . Then,

- The probabilistic regression task is the problem of predicting a conditional distribution over the Reals and is specified by  $g : \mathcal{X} \rightarrow \mathcal{S}$ .
- The deterministic regression task is the problem of predicting a single continuous value in the Reals and is specified by  $g : \mathcal{X} \rightarrow \mathcal{Y}$ .

The estimated prediction functional  $\hat{g}$  is fit on training data  $\setminus (X_1, Y_1), \dots, (X_n, Y_n) \stackrel{i.i.d.}{\sim} (X, Y)$

$(X, Y)$  and is considered ‘good’ if  $\mathbb{E}[L(Y^*, \hat{g}(X^*))]$  is low, where  $(X^*, Y^*) \sim (X, Y)$  is independent of  $(X_1, Y_1), \dots, (X_n, Y_n)$  and  $\hat{g}$ .

Whilst regression can be either probabilistic or deterministic, the latter is much more common and therefore in this book ‘regression’ refers to the deterministic case unless otherwise stated.

# 4

---

## *Survival Analysis*

---

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

---

TODO

---

As discussed in the introduction, *Survival Analysis* is concerned with data where the outcome is a time-to-event. Because the collection of such data takes place in the temporal domain (it takes time to observe a duration), the event of interest is often unobservable. For example, because the event did not occur by the end of the data collection period or because of the occurrence of another event that prevents the event of interest from being observed. In survival analysis terminology these are referred to as *censoring* and *competing risks*.

This chapter defines these and related terms and introduces basic terminology and mathematical definitions. Section 4.1 starts with the common single-event, right-censored data setting and then extends to further types of censoring as well as truncation. Chapter 5 introduces event-history analysis, which is a generalisation to settings with multiple, potentially competing or recurrent events. Section 6.1 defines common prediction types of survival models, which is particularly important for machine learning based survival analysis. Finally, in order to cleanly discuss *machine learning survival analysis*, the *survival task* is introduced in Section 6.2.

While these definitions and concepts are not new to survival analysis, we feel that it is of utmost importance for machine learning practitioners to be able identify and specify the survival problem present in their data correctly, as misspecification cannot be detected by comparing the predictive performance of alternate models. The predictive performance can only detect if one model is better suited to minimize a given objective function, but not whether or not the objective function is specified correctly. The latter depends on the (assumptions about the) data generating process and has to be also reflected in the definition of the evaluation measure.

## 4.1 Survival Data and Definitions

This section describes the basic template for a survival analysis problem and introduces key definitions that will be used throughout this book.

### 4.1.1 Quantifying the Distribution of Event Times

This section introduces functions that can be used to fully characterise a probability distribution, termed here as *distribution defining functions*. Particular focus is given to distribution defining functions that are important in survival analysis.

For now, assume a continuous, positive, random variable  $Y$  taking values in (t.v.i.)  $\mathbb{R}_{\geq 0}$ . A standard representation of the distribution of  $Y$  is given by the probability density function (pdf),  $f_Y : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$ , and cumulative distribution function (cdf),  $F_Y : \mathbb{R}_{\geq 0} \rightarrow [0, 1]; (\tau) \mapsto P(Y \leq \tau)$ .

As discussed in Chapter 1, it is more common to describe the distribution of event times  $Y$  via the *survival function* and *hazard function* (often also referred to as *hazard rate*) than the pdf or cdf.

The survival function is defined as

$$S_Y(\tau) = P(Y > \tau) = \int_{\tau}^{\infty} f_Y(u) du,$$

is the probability of not observing an event until some point  $\tau \geq 0$  and thus simply the compliment of the cdf:  $S_Y(\tau) = 1 - F_Y(\tau)$ .

The hazard function is given by

$$h_Y(\tau) = \frac{f_Y(\tau)}{S_Y(\tau)}.$$

The hazard function is interpreted as the instantaneous risk to observe an event given that the event has not been observed up until that point. This is not a probability and  $h_Y$  can be greater than one.

The cumulative hazard function (chf) can be derived from the hazard function by

$$H_Y(\tau) = \int_0^{\tau} h_Y(u) du$$

The cumulative hazard function relates to the survival function by

$$H_Y(\tau) = \int_0^{\tau} h_Y(u) du = \int_0^{\tau} \frac{f_Y(u)}{S_Y(u)} du = \int_0^{\tau} -\frac{S_Y'(u)}{S_Y(u)} du = -\log(S_Y(\tau))$$

These last relationships are particularly important, as many methods estimate the hazard rate, which is then used to calculate the cumulative hazard and survival probability

$$S_Y(\tau) = \exp(-H_Y(\tau)) = \exp\left(-\int_0^{\tau} h_Y(u) du\right). \quad (4.1)$$

Unless necessary to avoid confusion, subscripts are dropped from  $S_Y, h_Y$  etc. going forward and instead these functions are referred to as  $S$  and  $h$  (and so on).

Normally, these quantities could be estimated using standard techniques like regression modeling (estimation of parameters of an assumed distribution). However, in contrast to standard settings,  $Y$  is only observed partially, due to different types of censoring and truncation described below.

#### 4.1.2 Single-event, right-censored data

Survival analysis has a more complicated data setting than other fields as the ‘true’ data generating process is not directly observable but instead engineered variables are defined to capture observed information. Let,

- $X$  t.v.i.  $\mathcal{X} \subseteq \mathbb{R}^p, p \in \mathbb{N}_{>0}$  be the generative random variable representing the data *features/covariates/independent variables*.
- $Y$  t.v.i.  $\mathcal{Y} \subseteq \mathbb{R}_{\geq 0}$  be the (partially unobservable) *true survival time*.
- $C$  t.v.i.  $\mathcal{C} \subseteq \mathbb{R}_{\geq 0}$  be the (partially unobservable) *true censoring time*.

The object of interest in survival analysis is  $Y$ . However, in the presence of censoring  $C$ , it is impossible to fully observe  $Y$ . Instead, the observable variables are given by

- $T := \min\{Y, C\}$ , the *outcome time* (realisations of this random variable will be referred to as *observed outcome time*).
- $\Delta := \mathbb{I}(Y = T) = \mathbb{I}(Y \leq C)$ , the *event indicator* (also known as the *censoring* or *status indicator*).

Together  $(T, \Delta)$  is referred to as the *survival outcome* or *survival tuple* and they form the dependent variables. The survival outcome provides a concise mechanism for representing the outcome time and indicating which outcome (event or censoring) took place.

A *survival dataset* is a  $n \times p$  Real-valued matrix defined by  $\mathcal{D} = ((\mathbf{x}_1, t_1, \delta_1) \cdots (\mathbf{x}_n, t_n, \delta_n))^\top$ , where  $(t_i, \delta_i)$  are realisations of the respective random variables  $(T_i, \Delta_i)$  and  $\mathbf{x}_i$  is a  $p$ -dimensional row-vector,  $\mathbf{x}_i = (x_{i1} \ x_{i2} \cdots x_{ip})$ .

Finally the following terms are used frequently throughout this book. Let  $(t_i, \delta_i) \stackrel{i.i.d.}{\sim} (T, \Delta), i = 1, \dots, n$ , be observed survival outcomes. Then,

- The *set of unique* or *distinct time-points* refers to the set of time-points in which at least one observation experiences the event or is censored,  $\mathcal{U}_O \subseteq \{t_i\}_{i \in \{1, \dots, n\}}$ .
- The *set of unique observed event times* refers to the set of unique time-points in which an event (and not censoring) occurred,  $\mathcal{U}_D := \{t_i : \delta_i = 1\}_{i \in \{1, \dots, n\}}$ . Sometimes the ordered, unique events times are also denoted by  $t_{(i)}, i = 1, \dots, m \leq n, t_{(1)} < t_{(2)} < \cdots < t_{(m)}$ .
- The *risk set* at a given time-point,  $\tau$ , is the index-set of observation units at risk for the event just before  $\tau$ ,  $\mathcal{R}_\tau := \{i : t_i \geq \tau\}$  where  $i$  is a unique row/subject in the data. Consequently, for right-censored data, we have  $\mathcal{R}_0 = \{1, \dots, n\}$  and  $\mathcal{R}_\tau \supseteq \mathcal{R}_{\tau'}, \forall \tau < \tau'$ . Note that in a continuous setting, ‘just before’ refers to an infinitesimally smaller time than  $\tau$ , in practice as this is unobservable the risk set is defined at  $\tau$ .
- The *number of observations at risk* at  $\tau$  is the cardinality of the risk set,  $|\mathcal{R}_\tau|$ , and is denoted by  $n_\tau := \sum_i \mathbb{I}(t_i \geq \tau)$ .
- The *number of events* at  $\tau$  is denoted by  $d_\tau := \sum_i \mathbb{I}(t_i = \tau, \Delta_i = 1)$ . Note: For truly continuous variables  $T_i$  we would expect  $d_{t_i} = 1, \forall i = 1 \dots, n$ , however, in practice we often observe ties due to finite measurement precision, such that  $d_\tau > 1$  occurs quite frequently in real-world datasets.

The quantities  $\mathcal{R}_\tau$ ,  $n_\tau$ , and  $d_\tau$  underlie many models and measures in survival analysis. Particularly non-parametric methods (Chapter 13) like the Kaplan-Meier estimator (Kaplan and Meier 1958) are based on the ratio  $d_\tau / n_\tau$ .

Table 4.1 exemplifies an observed survival dataset with a modified version of the `rats` data (Therneau 2015), which contains the time until occurrence of a tumor ( $\delta_i = 1$  if a tumor occurred at the outcome time  $t_i$  and  $\delta_i = 0$  otherwise). In this example, the above quantities would be:

- $\mathcal{U}_0 = \{49, 91, 101, 102, 104\}$ : with 104 included only once
- $\mathcal{U}_D = \{49, 102, 104\}$ : with the inclusion of 104 due to the event at  $t_5$ , not censoring at  $t_3$
- $\mathcal{R}_{\tau=102} = \{3, 5, 6\}$  (these rats' outcome times are greater or equal to  $\tau = 102$  so they are at risk for the event at this time)
- $n_{\tau=102} = |\mathcal{R}_{102}| = 3$
- $d_{\tau=102} = 1$ : As only  $i = 5$  experienced the event (and not censoring) at this time.

Table 4.1: Subset of the `rats` (Therneau 2015) time-to-event dataset. Rows are individual observations ( $ID$ ),  $\mathbf{x}; j$  columns are features,  $t$  is observed time-to-event,  $\delta$  is the event indicator.

| ID ( $i$ ) | litter ( $\mathbf{x}_{;1}$ ) | rx ( $\mathbf{x}_{;2}$ ) | sexF ( $\mathbf{x}_{;3}$ ) | time ( $t$ ) | status ( $\delta$ ) |
|------------|------------------------------|--------------------------|----------------------------|--------------|---------------------|
| 1          | 1                            | 1                        | 1                          | 101          | 0                   |
| 2          | 1                            | 0                        | 1                          | 49           | 1                   |
| 3          | 1                            | 0                        | 1                          | 104          | 0                   |
| 4          | 2                            | 1                        | 0                          | 91           | 0                   |
| 5          | 2                            | 0                        | 0                          | 104          | 1                   |
| 6          | 2                            | 0                        | 0                          | 102          | 1                   |

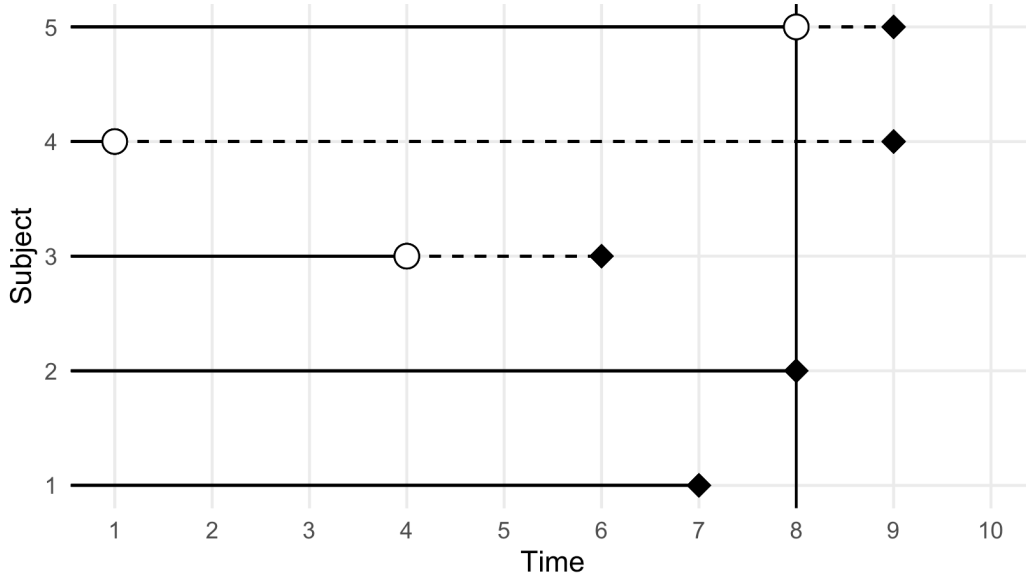
- The Kaplan-Meier estimate of the average survival function of the training data *survival distribution* is the Kaplan-Meier estimator (Section 13.1.1) fit (Section 3.1.1) on training data  $(T_i, \Delta_i)$  and is denoted by  $\hat{S}_{KM}$ .
- The Kaplan-Meier estimate of the average survival function of the training data *censoring distribution* is the Kaplan-Meier estimator fit on training data  $(T_i, 1 - \Delta_i)$  and is denoted by  $\hat{G}_{KM}$ .

### 4.1.3 Types of Censoring

In *Survival Analysis* three types of censoring are commonly defined, right-censoring, left-censoring, and interval-censoring. The latter can be viewed as the most general case with the other types being special cases. Multiple types of censoring and/or truncation (Section 4.1.4) can occur in any given data set and it is vital to identify which types are present in order to correctly select models and measures for the data. Note that below we always assume one type of censoring at a time, while in real data sets different types of censoring (and truncation) can co-occur.

#### Right-censoring Types

Right-censoring is the most common form of censoring in survival data and it occurs either when an observation is removed from the study before the end and before experiencing the event (for reasons unrelated to the event of interest), or when they experience the event after the observation period. In either case, their true outcome time is unknown, but we do know that it is to the right of the observed censoring time, hence *right-censoring*.



<- FIXME: ADD REF TO THESIS IF WE KEEP THIS FIGURE ->

Sometimes, right-censoring is also subdivided into Type-I, Type-II and Type-III censoring. In Type-I, or *administrative*, censoring occurs at the fixed, pre-defined end of the study  $\tau_u$ , in which case the outcome is given by  $(T_i = \min(Y_i, \tau_u), \mathbb{I}(Y_i \leq \tau_u))$ . Type-II censoring also occurs when the study ends, however, in this case the study ends when a pre-defined number of subjects experienced the event of interest and so  $\tau_u$  is random. Type-III censoring occurs when censoring times *randomly* follow an unknown distribution and we observe  $(T_i = \min(Y_i, C_i), \mathbb{I}(Y_i \leq C_i))$ . Different types of right-censoring can, and often do, co-occur in any given data set.

In practice, these different types of right-censoring are usually handled the same during modeling and evaluation and so this book refers to ‘right-censoring’ generally, which could occur from any combination of the above types.

### Left-censoring

Left-censoring occurs when the event happens at some unknown time before the study start. While quiet rare in medical settings, this type of data often occurs in sociology studies when retrospective interviews are conducted.

Consider a survey about phone use where smartphone users are all asked the question “How old were you when you used a smartphone for the first time?”. Let  $A_i$  denote the age of the participants during the interview, let  $T_i$  be the time at which they first used a smartphone, and let  $\Delta_i$  be the usual censoring indicator with 1 indicating the event of interest and 0 otherwise. If the participant remembers the age they first used a phone then  $(T_i, \Delta_i) = (Y_i, 1)$  where  $Y_i \leq A_i$ . However, if the individual does not remember when the event occurred, then they are left-censored at  $A_i$  and  $(T_i, \Delta_i) = (A_i, 0)$ , where  $A_i < Y_i$ .

### Interval-censoring

Interval-censoring occurs when the event takes place in some interval within the study period, but the exact time of event is unknown. This often occurs in data resulting from regular or irregular check-ups, as often occurs in electronic health record data. For example,

say one patient is checked for skin cancer every year and another every two years. This data would be collected on a yearly scale and over three years may look something like:

| Patient | Year | Status |
|---------|------|--------|
| 1       | 1    | 0      |
| 1       | 2    | 1      |
| 1       | 3    | 1      |
| 2       | 1    | 0      |
| 2       | 2    | ?      |
| 2       | 3    | 1      |

As data is collected annually for patient 1, it is *known* that they had skin cancer in year 2. On the other hand, patient 2's data is only collected every other year, so whilst it is known they had cancer in year 3, it is unknown if they already had cancer the year before (assuming for now there's no method to test how 'old' the cancer is). In this case, the second patient is interval censored between years one and three.

Formally, consider  $L_i$  and  $R_i$  two consecutive check-up times for subject  $i$ . If the event is observed at  $R_i$  then it must have occurred sometime before then, hence  $Y_i \in (L_i, R_i]$ . If no event occurred then  $Y_i > R_i$  and  $R_i$  is the right-censoring time.

### Censoring Notation

The survival outcome notation defined above,  $(T, \Delta)$ , can lead to ambiguity when multiple censoring types are present. For example, the survival outcome  $(T, 0)$  might indicate right-censoring at time  $T$  or left-censoring at time  $T$ . One could resolve this by re-defining the survival tuple such that  $(T, -1)$  indicates left-censoring,  $(T, 0)$  indicates right-censoring, and  $(T, 1)$  indicates no censoring, but this quickly clashes with notation when multiple events of interest may occur (discussed below). Instead the survival outcome may instead be presented as a tuple of times between  $(0, \infty)$  which indicate the range at which the event could take place, then if an observation is left-censored at  $\tau$  their outcome is  $(0, t)$ , as it is known their outcome occurred before  $t$ . Alternatively  $(t, \infty)$  would indicate right-censoring, and  $(t_1, t_2)$  would indicate interval-censoring. If the event is observed, the range is just the observed time  $(t, t)$ .

### Censoring 'Dependence'

Censoring may be defined as *uninformative* if  $Y \perp\!\!\!\perp C$  and *informative* otherwise. However, these definitions can be misleading as the term 'uninformative' could imply that  $C$  is independent of both  $X$  and  $Y$ , and not just  $Y$ . To avoid misinterpretation, the following definitions are used in this book.

**Definition 4.1** (Independent Censoring). Let  $(X, T, \Delta, Y, C)$  be defined as above, then

- If  $C \perp\!\!\!\perp X$ , censoring is *feature-independent*, otherwise censoring is *feature-dependent*.
- If  $C \perp\!\!\!\perp Y$ , then censoring is *event-independent*, otherwise censoring is *event-dependent*.
- If  $(C \perp\!\!\!\perp Y) | X$ , censoring is conditionally independent of the event given covariates, or *conditionally event-independent*.
- If  $C \perp\!\!\!\perp (X, Y)$ , censoring is *uninformative*, otherwise censoring is *informative*.

Non-informative censoring can generally be well-handled by models as true underlying patterns can still be detected and the reason for censoring does not affect model inference



or predictions. However, in the real-world, censoring is rarely non-informative as reasons for drop-out or missingness in outcomes tend to be related to the study of interest. Event-dependent censoring is a tricky case that, if not handled appropriately (by a competing-risks framework), can easily lead to poor model development; the reason for this can be made clear by example. Say a study is interested in predicting the time between relapses of stroke but a patient suffers a brain aneurysm due to some separate neurological condition, then there is a high possibility that a stroke may have occurred if the aneurysm had not. A survival model is unlikely to distinguish the censoring event (aneurysm) from the event of interest (stroke) and will confuse predictions. In practice, the majority of models and measures assume that censoring is conditionally event-independent and hence censoring can be predicted by the covariates whilst not directly depending on the event. For example, if studying the survival time of ill pregnant patients in hospital, then dropping out of the study due to pregnancy is clearly dependent on how many weeks pregnant the patient is when the study starts (for the sake of argument assume no early/late pregnancy due to illness).

#### 4.1.4 Censoring vs. Truncation

While sometimes confused or misnamed, it is very important to differentiate between censoring and truncation, as the methods for handling them differ substantially. Truncation can occur in non time-to-event settings, however this usually refers to truncating (or removing) an entire subject from a dataset. As discussed in Chapter 1, truncation in survival analysis refers to partially truncating a period of time and is quite relevant in survival analysis (for example in multi-state settings, Section 5.2).

In general, while censored observations have incomplete information about the time-to-event, they are still part of the data set. Truncation on the other hand often leads to observations not entering the data set (at least not at time 0). This will usually introduce bias that needs to be accounted for.

##### Left-truncation

Left-truncation often occurs when study participation is conditional on the occurrence of another event. This is best explained through examples:

In a study from the 18th century (**brostrom.influence.1987?**), when childhood and maternal mortality were relatively high, data was collected on infant survival during the first year after birth based on whether the mother was alive. Data was collected by adding an infant to the study when their mother died, then two other infants, whose mothers were alive, were matched into the study based on their age and features. The age of the infant at entrance into the study therefore signifies a *left-truncation event*, as infants who die before their mothers never enter the data and the *left-truncation time* is given by the infants' age at which the mother died.

More formally, let  $T_i^l$  the subject-specific left truncation time. Then we only observe subjects with  $Y_i > T_i^l$  or  $C_i > T_i^l$ . Subjects with  $Y_i < T_i^l$  never enter the data.

Notably, left-truncation also plays an important role when modeling recurrent events or multi-state data, as the data generating process induces left-truncation (Chapter 5).

##### Right-truncation

Right-truncation often occurs in retrospective sampling based on registry data, that is the registry is queried for cases reported by a certain cut-off time (see for example Vakulenko-

Lagun, Mandel, and Betensky (2020)). A common example is the estimation of the incubation period of an infectious disease, that is time from infection to the disease onset. Known cases are entered into a data base. However, at anytime when we query the data base, we only observe the subset of the infected population that already experienced the disease onset and not the subset with a longer incubation periods.

Formally, let  $T_i^r$  the right-truncation time (here time from infection until the time at which the registry is queried), then subjects only enter the data set when  $T_i < T_i^r$ . This is illustrated in Figure 4.1 using 3 subjects. All 3 subjects were infected during the observation period, however, the right-truncation time  $T_2^r$  of subject 2 is shorter than the incubation period  $T_2$  for this subject, thus at the time of querying the data base, this subject will not be included in the sample, as  $T_2 > T_2^r$ . Note the difference to right-censoring. If subject 2 was right-censored, the subject would be in our sample and we would know time of infection, but not the time of disease onset. In case of right-truncation on the other hand, the subject is not included in the sample at time of data extraction, as subject are only included in the registry after disease onset. Overall this leads to a bias towards shorter incubation times and potentially feature values that lead to shorter incubation times.

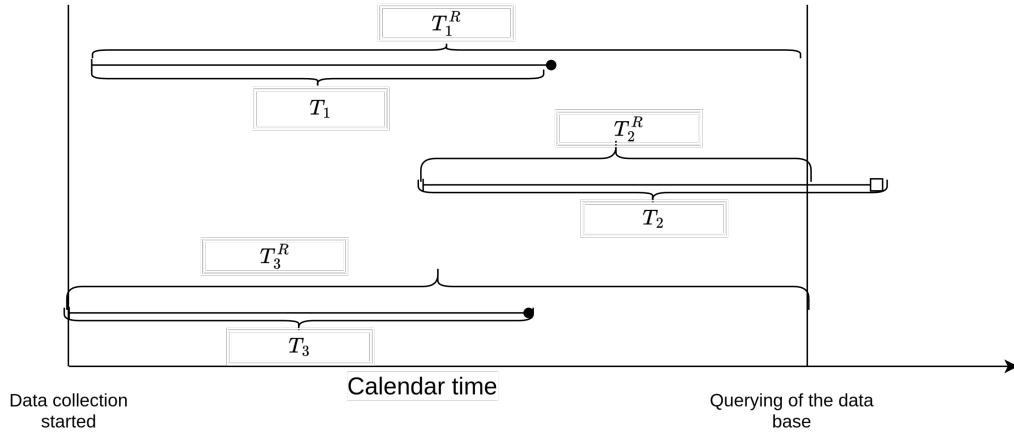


Figure 4.1: Illustration of right-truncation based on registry data. For subjects 1 and 3 the right-truncation time is longer than the incubation period, therefore they are included in the sample when the registry is queried. For subject 2 on the other hand the right-truncation time is shorter, therefore it's excluded from the sample.

#### 4.1.5 Objective functions

This section describes how the likelihood is constructed for observations subject to different types of censoring and truncation. For machine learning survival analysis this can be used to construct the objective (or loss) function for any survival task.

! Major changes expected!

This page is a work in progress and major changes will be made over time.

# 5

## Event-history Analysis

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

In this section we will go beyond single-event data or at least view time-to-event data more generally as data in which one could observe multiple, potentially mutually exclusive events. From this more general point of view such data is sometimes referred to *event-history data* and its analysis as *event-history analysis* (EHA). The table below gives one way to classify the different types of data that could occur in EHA, where we differentiate between the number of occurrences of the same event type (rows) and whether we consider the occurrence of the same event or different events (columns).

|                 | single outcome   | many outcomes   |
|-----------------|------------------|-----------------|
| one/first event | single event     | competing risks |
| multiple events | recurrent events | multi state     |

Another way to think about event history is in terms of transitions between different states, as illustrated in Figure 5.1. Usually, a subject starts out in state 0 (for example, healthy) and transitions to different states from there. States from which further transitions are possible are called *transient*, otherwise a state is called *terminal*. If no transition happens within the follow-up time, the subject remains in the initial state, in event history terms the observation is censored for this transition.

In the *single-event setting* (Figure 5.1, left panel), a subject can only transition to one state (the event of interest). In the *competing risks setting* (Figure 5.1, middle panel, see Section 5.1), a subject could transition to any of the  $K$  mutually exclusive states, thus the subject is *at risk* for a transition to multiple states. However, once one of them occurs, it is impossible to transition to another (for example, death from different causes). In both cases, the event needs not be terminal, we just end the observation after the first occurrence of an event.

In the most general case, the *multi-state setting* (Figure 5.1 right panel, see Section 5.2), there are multiple transient and terminal states with potential back transitions (for example, moving between different stages of an illness with the possibility of (partial) recovery and

death as terminal event). The *recurrent events setting* is as a special case of the multi-state setting but could also be treated as a more general case of the single event setting with correlated observations (Section 5.3 and Figure 5.2) .

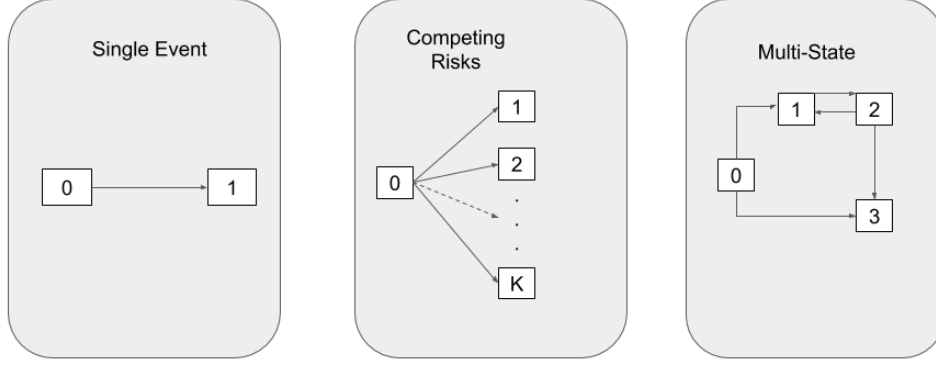


Figure 5.1: Illustration of different types of time-to-event outcomes. Left: Standard single-event setting with transition from initial state (0) to state (1); Middle: Competing risks setting with  $k$  competing events. Once one of the  $\{1, \dots, k\}$  events is observed, the others cannot be observed; Right: Multi-state setting where subjects can transition between multiple transient and terminal states with possible back-transitions.

## 5.1 Competing Risks

In contrast to single-event survival analysis, competing risks are concerned with the time to the first of many, mutually exclusive events. Mutually exclusive here means that once one of the events occurs, we can not observe the others. As in the single event case, the events may not necessarily be terminal (such as death), instead they just signify the end of the period of interest for a given observation.

Formally, let  $Y$  be the time-to-event as before. In the competing risks setting, there is now an additional random variable  $E_Y \in \{1, \dots, k\}$ , which denotes one of  $k$  competing events that can occur at event time  $Y$ . The survival outcome notation,  $(T, \Delta)$  has to be extended to accommodate for the possible competing risks. Previously,  $\Delta = 1$  if right-censoring is observed, this can be modified by multiplying  $\Delta$  by the index of the event that occurs. Now,  $\Delta \in \{0, 1, \dots, k\}$  where  $\Delta = 0$  still indicates censoring and  $\Delta = j$  means the  $j$ th event occurred.

The predominate approach to competing-risks analysis is known as *cause-specific hazards*, where  $h_{0e}$  is defined as the hazard for the transition from initial state 0 to state  $e = 1, \dots, k$ :

$$h_{0e}(\tau) = \lim_{\Delta\tau \rightarrow 0} \frac{P(\tau \leq Y \leq \tau + \Delta\tau, E = e \mid Y \geq \tau)}{\Delta\tau}, \quad e = 1, \dots, k.$$

As competing events are mutually exclusive at any time  $\tau$ , it is useful to further define the:

- *all-cause hazard*,  $h(\tau) = \sum_{e=1}^k h_{0e}(\tau)$ : which is the...
- *all-cause cumulative hazard*:  $H(\tau) = \int_0^\tau h(u) du = \sum_{e=1}^k \int_0^\tau h_{0e}(u) du = \sum_{e=1}^k H_{0e}(\tau)$ , and
- *all-cause survival probability*:  $S(\tau) = P(Y \geq \tau) = \exp(-H(\tau))$

Note that whilst the all-cause survival probability is defined in the same way as the standard survival probability, the interpretation is that *none* of the events occurred before  $\tau$ . The all-cause survival probability is also not directly estimated but instead calculated from the cause specific hazards.

Another important distribution function in competing risks analysis is the *Cumulative Incidence Function* (CIF), which denotes the probability of experiencing an event  $E$  before time  $\tau$

$$F_e(\tau) = P(Y \leq \tau, E = e) = \int_0^\tau h_{0e}(u) S(u) du.$$

Intuitively the CIF is the probability of not experiencing any event,  $S(u)$ , multiplied with the hazard of experiencing an event of type  $e$ ,  $h_{0e}(u)$ .

Calculating the CIF (in addition to the cause-specific hazards) is particularly important when making statements about the absolute risk (probability) for an event of type  $e$ , as it depends on all cause-specific hazards via  $S(\tau)$ .

This will be particularly relevant when assessing how features affect the probability for observing a specific event. While some features might strongly affect some of the cause-specific hazards, if an event has overall low prevalence, then the absolute probability of observing the event will still be low. Hence the CIF is useful for incorporating this information into an interpretable quantity.

Following Beyersmann, Allignol, and Schumacher (2012), this book assumes that the cause-specific hazards model fully describes the data generating processes and doesn't require an independence assumption for the competing events.

---

## 5.2 Multi-state Models

! Major changes expected!

This page is a work in progress and major changes will be made over time.

### 5.3 Recurrent Events

! Major changes expected!

This page is a work in progress and major changes will be made over time.

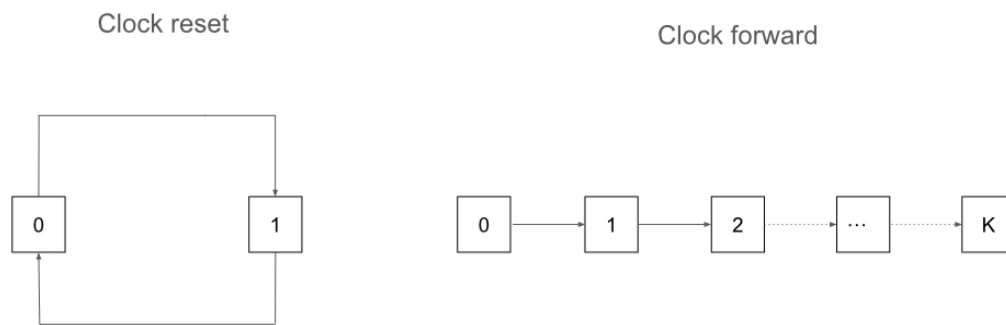


Figure 5.2: Illustration of transitions in the recurrent events setting. Left: “Clock reset” representation of recurrent events. Each time an event occurs, the clock is reset to 0 and we once again wait for occurrence of an event (of the same type); Right: “Clock forward” representation. A subject transitions from 1-st, to 2-nd, etc. to K-th event occurrence

# 6

## Survival Task

TODO (150-200 WORDS)

! Major changes expected!

This page is a work in progress and major changes will be made over time.

TODO

### 6.1 Survival Prediction Problems

This section continues by defining the survival problem. Defining a single ‘survival prediction problem’ (or ‘task’) is important mathematically as conflating survival problems could lead to confused interpretation and evaluation of models. Let  $(\mathbf{X}, \mathbf{t}, \delta)$  and  $\mathcal{D}$  be as defined in Section 4.1. A general survival prediction problem is one in which:

- a survival dataset,  $\mathcal{D}$ , is split (Section 3.1.1) for training,  $\mathcal{D}_{train}$ , and testing,  $\mathcal{D}_{test}$ ;
- a survival model is fit on  $\mathcal{D}_{train}$ ; and
- the model predicts some representation of the unknown true survival time,  $Y$ , given  $\mathcal{D}_{test}$ .

The process of fitting is model-dependent, and can range from simple maximum likelihood estimation of model coefficients, to complex algorithms. The model fitting process is discussed in more abstract detail in (Section 3.1) and then concrete algorithms are discussed in (?@sec-review). The different survival problems are separated by *prediction types* or *prediction problems*, which can also be thought of as predictions of different representations of  $Y$ . Four prediction types are possible:

1. The *relative risk* of an individual for experiencing an event: A single continuous ranking.
2. The *time until an event* occurs: A single continuous value.
3. The *prognostic index* for a model: A single continuous value.
4. The *survival distribution*: A probability distribution.

The first three of these are referred to as *deterministic* problems as they predict a single value whereas the fourth is *probabilistic* and returns a full survival distribution. Definitions

of these are expanded on below but first note that survival predictions differ from other fields in two respects:

- The outcome of interest is  $Y$ , which is different to the outcome used for model training, ( $T = \min(Y, C), \Delta = \mathbb{I}(Y \leq C)$ ). This differs from, say, regression in which the same object (a single continuous variable) is used for fitting and predicting.
- With the exception of the time-to-event prediction, all other prediction types do not predict  $\mathbb{E}(Y)$  but some other related quantity.

Survival prediction problems must be clearly separated as they are inherently incompatible. For example, it is not meaningful to compare a relative risk prediction from one observation to a survival distribution of another. Whilst these prediction types are separated above, they can be viewed as special cases of each other. Both (1.) and (2.) may be viewed as variants of (3.); and (1.), (2.), and (3.) can all be derived from (4.); this is elaborated on below and discussed fully in Chapter 21.

### Relative Risk/Ranking

This is a common survival problem and is defined as predicting a continuous rank for an individual's relative risk of experiencing the event. For example, given three subjects,  $\{i, j, k\}$ , a relative risk prediction may predict the risk of event as  $\{0.1, 0.5, 10\}$  respectively. From these predictions, the following types of conclusions can be drawn:

- Conclusions comparing subjects. For example,  $i$  is at the least risk; the risk of  $j$  is only slightly higher than that of  $i$  but the risk of  $k$  is considerably higher than  $j$ ; the corresponding ranks for  $i, j, k$ , are 1, 2, 3;
- Conclusions comparing risk groups. For example, thresholding the risks at 1.0 means that  $i$  and  $j$  are in a low-risk group whilst  $k$  is in a high-risk group.

So whilst many important conclusions can be drawn from these predictions, the values themselves have no meaning when not compared to other individuals. Interpretation of these rankings has historically been conflicting, with some using the interpretation “higher ranking implies higher risk” whereas others may assume “higher ranking implies lower risk”. The difference is often due to model types (for example, PH and AFT models have opposite interpretation, Chapter 13) but can also be due to software implementation differences. In this book, a higher ranking will always imply a higher risk of event (as in the example above).

### Time to Event

Predicting a time to event is the problem of predicting the expectation  $\hat{y} = \mathbb{E}(y|\mathbf{x})$ . A time-to-event prediction is a special case of a ranking prediction as an individual with a longer survival time will have a lower overall risk: if  $\hat{y}_i, \hat{y}_j$  and  $\hat{r}_i, \hat{r}_j$  are survival time and ranking predictions for subjects  $i$  and  $j$  respectively, then  $\hat{y}_i > \hat{y}_j \rightarrow \hat{r}_i < \hat{r}_j$ .

For practical purposes, time-to-event would be the ideal prediction type as it is easy to interpret and communicate. However, this type of prediction is rare because only a subset of the domain of  $Y$  is observed due to censoring. For non-parametric methods, the estimated cdf is improper and thus integration requires extrapolation of the cdf. For parametric models, the distribution of event times is fully specified once the parameters of the assumed distribution have been estimated, however, if the parameters were estimated based on only a small subset of the possible domain of  $Y$ , this essentially still constitutes extrapolation and will in most cases yield implausible predictions. A popular alternative is therefore to estimate the *restricted mean survival time* (RMST) (K. Han and Jung 2022; Andersen, Hansen, and



Klein 2004).

### Prognostic Index

Given covariates,  $\mathbf{X} \in \mathbb{R}^{n \times p}$ , and a vector of model coefficients,  $\beta \in \mathbb{R}^p$ , the linear predictor is defined by  $\eta := \mathbf{X}^\top \beta \in \mathbb{R}^n$ . The prognostic index is a term often used to refer to some transformation,  $\phi$ , on the linear predictor,  $\phi(\eta)$ , (which could simply be the identity function ( $f(x) = x$ )). Assuming a predictive function (for survival time, risk, or distribution defining function) of the form  $g(\varphi)\phi(\eta)$ , for some function  $g$  and variables  $\varphi$  where  $g(\varphi)$  is constant for all observations (for example Cox PH (Section 13.1.2)), then predictions of  $\eta$  are a special case of predicting a relative risk, as predictions of  $\phi(\eta)$  if  $\phi$  is rank preserving – this assumption is sometimes written as “if there is a one-to-one mapping between the prediction and the expected survival times”. A higher prognostic index may imply a higher or lower risk of event, dependent on the model structure. As stated above, if the prognostic index is used for a rank prediction, then this book always assumes “higher value higher risk”.

### Survival Distribution

Predicting a survival distribution refers specifically to predicting the distribution of an individual subject’s survival time, i.e., modelling the distribution of the event occurring over  $\mathbb{R}_{\geq 0}$ . Therefore, this is seen as the probabilistic analogue to the deterministic time-to-event prediction, these definitions are motivated by similar terminology in machine learning regression problems (Section 3.1).

Distributional prediction can in theory target any of the quantities introduced in Section 4.1.1 but predicting  $S(t)$  and/or  $h(t)$  is most common. Hazard based approaches are particularly relevant for non- and semi-parametric estimation of the distribution, where no assumptions are made about the underlying distribution of event times.

---

## 6.2 Survival Analysis Task

The survival prediction problems identified in Section 6.1 are now formalised as machine learning tasks.

### Survival Task

**Box 6.1.** Let  $(X, T, \Delta)$  be random variables t.v.i.  $\mathcal{X} \times \mathcal{T} \times \{0, 1\}$  where  $\mathcal{X} \subseteq \mathbb{R}^p$  and  $\mathcal{T} \subseteq \mathbb{R}_{\geq 0}$ . Let  $\mathcal{S} \subseteq \text{Distr}(\mathcal{T})$  be a convex set of distributions on  $\mathcal{T}$  and let  $\mathcal{R} \subseteq \mathbb{R}$ . Then,

- The probabilistic survival task is the problem of predicting a conditional distribution over the positive Reals and is specified by  $g : \mathcal{X} \rightarrow \mathcal{S}$ .
- The deterministic survival task is the problem of predicting a continuous value in the positive Reals and is specified by  $g : \mathcal{X} \rightarrow \mathcal{T}$ .
- The survival ranking task is specified by predicting a continuous ranking in the Reals and is specified by  $g : \mathcal{X} \rightarrow \mathcal{R}$ .

Any other survival prediction type falls within one of the tasks in Box 6.1, for example predicting log-survival time is the deterministic task and predicting prognostic index or linear predictor is the ranking task. Removing the separation between the prognostic index

and ranking prediction types is due to them both making predictions over  $\mathbb{R}$  and hence their difference lies in interpretation only.

In this book, unless otherwise specified, the term *survival task*, will be used to refer to the probabilistic survival task. As a final note, these definitions are given in the most general case where the time variable is over  $\mathbb{R}_{\geq 0}$ . In practice, all models instead assume time is over  $\mathbb{R}_{> 0}$  and so a subject  $i$  that experiences an outcome at 0 is either deleted or their outcome time is set to  $T_i = \epsilon$  for some very small  $\epsilon \in \mathbb{R}_{> 0}$ .

Part II

**Evaluation**



## *What are Survival Measures?*

---

TODO (150-200 WORDS)

 Minor changes expected!

**This page is a work in progress and minor changes will be made over time.**

In this part of the book we discuss one of the most important parts of the machine learning workflow, model evaluation (Foss and Kotthoff 2024). In the next few chapters we will discuss different metrics that can be used to measure a model’s performance but before that we will just briefly discuss why model evaluation is so important.

In the simplest case, without evaluation there is no way to know if predictions from a trained machine learning model are any good. Whether one uses a simple Kaplan-Meier estimator, a complex neural network, or anything in between, there is no guarantee any of these methods will actually make useful predictions for a given dataset. This could be because the dataset is inherently difficult for any model to be trained on, perhaps because it is very ‘noisy’, or because a model is simply ill-suited to the task, for example using a Cox Proportional Hazards model when its key assumptions are violated. Evaluation is therefore crucial to trusting any predictions made from a model.

---

### 7.1 Survival Measures

Evaluation can be used to assess in-sample and out-of-sample performance.

In-sample evaluation measures the quality of a model’s ‘fit’ to data, i.e., whether the model has accurately captured relationships in the training data. However, in-sample measures often cannot be applied to complex machine learning models so this part of the book omits these measures. Readers who are interested in this are directed to Collett (2014) and Hosmer Jr, Lemeshow, and May (2011) for discussion on residuals; Choodari-Oskooei, Royston, and Parmar (2012), Kent and O’Quigley (1988) and Patrick Royston and Sauerbrei (2004) for  $R^2$  type measures; and finally Volinsky and Raftery (2000), Hurvich and Tsai (1979), and Liang and Zou (2008) for information criterion measures.

Out-of-sample measures evaluate the quality of model predictions on new and previously unseen (by the model) data. By following established statistical methods for evaluation, and ensuring that robust resampling methods are used (James et al. 2013), evaluation provides a method for estimating the ‘generalisation error’, which is the expected model performance

on new datasets. This is an important concept as it provides confidence about future model performance without limiting results to the current data. Survival measures are classified into measures of:

- Discrimination (aka ‘separation’) – A model’s discriminatory power refers to how well it separates observations that are at a higher or lower risk of event. For example, a model with good discrimination will predict that (at a given time) a dead patient has a higher probability of being dead than an alive patient.
- Calibration – Calibration is a roughly defined concept (Collins et al. 2014; F. E. Harrell, Lee, and Mark 1996; Rahman et al. 2017; Van Houwelingen 2000) that generally refers to how well a model captures average relationships between predicted and observed values.
- Predictive Performance – A model is said to have good predictive performance (or sometimes ‘predictive accuracy’) if its predictions for new data are ‘close to’ the truth.

These measures could also be categorised into how they evaluate predictions. Discrimination measures compare predictions pairwise where pairs of observations are created and then the predictions for these pairs are compared within and across each other in some way. Calibration measures evaluate predictions holistically by looking at some ‘average’ performance across them to provide an idea of how well suited the model is to the data. Measures of predictive performance evaluate individual predictions and usually take the sample mean of these to estimate the generalisation error.

In the next few chapters we categorise measures by the type of survival prediction they evaluate, which is a more natural taxonomy for selecting measures, but we use the above categories when introducing each measure.

---

## 7.2 How are Models Evaluated?

As well as using measures to evaluate a model’s performance on a given dataset, evaluation can also be used to measure future performance, to compare and select models, and to tune internal processes. In most cases, models should not be trained/predicted/evaluated on their own, instead a number of simpler reference models should be simultaneously trained and evaluated on the same data, which is known as a ‘benchmark experiment’. This is especially important for survival models, as *all* survival measures depend on the censoring distribution and therefore cannot be interpreted out of context and without comparison to other models. Benchmark experiments are used to empirically compare models across the same data and measures, meaning that if one model outperforms another then that model can be selected for future experiments (though simpler models are preferred if the performance difference is marginal). A model is usually said to ‘outperform’ another if it has a lower generalisation error.

The process of model evaluation is dependent on the measure itself. Measures that are ‘decomposable’ (predictive performance measures) calculate scores for individual predictions and take the sample mean over all scores, on the other hand ‘aggregate’ measures (discrimination and calibration) return a single score over all predictions. The simplest method to estimate the generalisation error is ‘holdout’ resampling, where a dataset  $\mathcal{D}$  is split into non-overlapping subsets for training  $\mathcal{D}_{train}$  and testing  $\mathcal{D}_{test}$ . The model is trained on  $\mathcal{D}_{train}$  and predictions,  $\hat{\mathbf{y}}$  are made based on the features in  $\mathcal{D}_{test}$ . The model is evaluated by using a measure,  $L$ , to compare the predictions to the observed data in the test set,  $L(\mathbf{y}_{test}, \hat{\mathbf{y}})$ .

Where possible, (repeated)  $k$ -fold cross-validation (kCV) should be used for more robust estimation of the generalisation error and for model comparison. In kCV, the data is partitioned into  $k$  folds (often  $k$  is 5 or 10), which are non-overlapping subsets. A model is trained on  $k - 1$  folds and evaluated on the  $k$ th fold, this process is repeated until each of the  $k$  folds has acted as the test set exactly once, the computed loss from each iteration is averaged into the final loss, which provides a good estimate of the generalisation error.

For the rest of this part of the book we will introduce different survival measures, discuss their advantages and disadvantages, and in Chapter 12 we will provide some recommendations for choosing measures. We will not discuss the general process of model resampling or evaluation further but recommend Casalicchio and Burk (2024) to readers interested in this topic.





## Discrimination Measures

TODO (150-200 WORDS)

 Minor changes expected!

**This page is a work in progress and minor changes will be made over time.**

The next measures discussed are ‘discrimination measures’, which evaluate how well models separate observations into different risk groups. A model is said to have good discrimination if it correctly predicts that one observation is at higher risk of the event of interest than another, where the prediction is ‘correct’ if the observation predicted to be at higher risk does indeed experience the event sooner.

In the survival setting, the ‘risk’ is taken to be the continuous ranking prediction. All discrimination measures are ranking measures, which means that the exact predicted value is irrelevant, only its relative ordering is required. For example given predictions  $\{100, 2, 299.3\}$ , only their rankings,  $\{2, 1, 3\}$ , are used by measures of discrimination.

This chapter begins with time-independent measures (Section 8.1), which measure concordance between pairs of observations at a single observed time point. The next section focuses on time-dependent measures (Section 8.2), which are primarily AUC-type measures that evaluate discrimination over all possible unique time-points and integrate the results for a single metric.

### 8.1 Time-Independent Measures

The simplest form of discrimination measures are concordance indices, which, in general, measure the proportion of cases in which the model correctly ranks a pair of observations according to their risk. These measures may be best understood in terms of two key definitions: ‘comparable’, and ‘concordant’.

**Definition 8.1** (Concordance). Let  $(i, j)$  be a pair of observations with outcomes  $\{(t_i, \delta_i), (t_j, \delta_j)\}$  and let  $r_i, r_j \in \mathbb{R}$  be their respective risk predictions. Then  $(i, j)$  are called (F. E. J. Harrell et al. 1984; F. E. Harrell, Califf, and Pryor 1982):

- *Comparable* if  $t_i < t_j$  and  $\delta_i = 1$ ;
- *Concordant* if  $r_i > r_j$ .

Note that this book defines risk rankings such that a higher value implies higher risk of event and thus lower expected survival time (Section 6.1), hence a pair is concordant if  $\mathbb{I}(t_i < t_j, r_i > r_j)$ . Other sources may instead assume that higher values imply lower risk of event and hence a pair would be concordant if  $\mathbb{I}(t_i < t_j, r_i < r_j)$ .

Concordance measures then estimate the probability of a pair being concordant, given that they are comparable:

$$P(r_i > r_j | t_i < t_j \cap \delta_i)$$

These measures are referred to as time *independent* when  $r_i, r_j$  is not a function of time as once the observations are organised into comparable pairs, the observed survival times can be ignored. The time-dependent case is covered in Section 8.2.1.

While various definitions of a ‘Concordance index’ (C-index) exist (discussed in the next section), they all represent a weighted proportion of the number of concordant pairs over the number of comparable pairs. As such, a C-index value will always be between  $[0, 1]$  with 1 indicating perfect separation, 0.5 indicating no separation, and 0 being separation in the ‘wrong direction’, i.e. all high risk observations being ranked lower than all low risk observations.

Concordance measures may either be reported as a value in  $[0, 1]$ , a percentage, or as ‘discriminatory power’, which refers to the percentage improvement of a model’s discrimination above the baseline value of 0.5. For example, if a model has a concordance of 0.8 then its discriminatory power is  $(0.8 - 0.5)/0.5 = 60\%$ . This representation of discrimination provides more information by encoding the model’s improvement over some baseline although is often confused with reporting concordance as a percentage (e.g. reporting a concordance of 0.8 as 80%). In theory this representation could result in a negative value, however this would indicate that  $C < 0.5$ , which would indicate serious problems with the model that should be addressed before proceeding with further analysis. Representing measures as a percentage over a baseline is a common method to improve measure interpretability and closely relates to the ERV representation of scoring rules.

Learn more about baseline comparison

See Section 10.4 to learn more about calculating measures with respect to an arbitrary baseline.

### 8.1.1 Concordance Indices

Common concordance indices in survival analysis can be expressed as a general measure:

Let  $\hat{\mathbf{r}} = (\hat{r}_1 \hat{r}_2 \dots \hat{r}_m)^\top$  be predicted risks,  $(\mathbf{t}, \delta) = ((t_1, \delta_1) (t_2, \delta_2) \dots (t_m, \delta_m))^\top$  be observed outcomes, let  $W$  be some weighting function, and let  $\tau$  be a cut-off time. Then, the time-independent (‘ind’) *survival concordance index* is defined by,

$$C_{ind}(\hat{\mathbf{r}}, \mathbf{t}, \delta | \tau) = \frac{\sum_{i \neq j} W(t_i) \mathbb{I}(t_i < t_j, \hat{r}_i > \hat{r}_j, t_i < \tau) \delta_i}{\sum_{i \neq j} W(t_i) \mathbb{I}(t_i < t_j, t_i < \tau) \delta_i}$$

The choice of  $W$  specifies a particular variation of the c-index (see below). The use of the cut-off  $\tau$  mitigates against decreased sample size (and therefore high variance) over time

due to the removal of censored observations (see Figure 8.1)). For  $\tau$  to be comparable across datasets, a common choice would be to set  $\tau$  as the time at which 80%, or perhaps 90% of the data have been censored or experienced the event.

There are multiple methods for dealing with tied predictions and times. Strictly, tied times are incomparable given the definition of ‘comparable’ given above and hence are usually ignored in the numerator. On the other hand, ties in the prediction are more problematic but a common method is to set a value of 0.5 for observations when  $r_i = r_j$  (Therneau and Atkinson 2020). Specific concordance indices can be constructed by assigning a weighting scheme for  $W$  which generally depends on the Kaplan-Meier estimate of the censoring distribution fit on training data,  $\hat{G}_{KM}$ , or the Kaplan-Meier estimate for the survival function of the survival distribution fit on training data,  $\hat{S}_{KM}$ , or both. Measures that use  $\hat{G}_{KM}$  are referred to as Inverse Probability of Censoring Weighted (IPCW) measures as the estimated censoring distribution is utilised to weight the measure in order to compensate for removed censored observations. This is visualised in Figure 8.1 where  $\hat{G}_{KM}$ ,  $\hat{G}_{KM}^{-2}$ , and  $\hat{S}_{KM}$  are computed based on the **whas** dataset (Hosmer Jr, Lemeshow, and May 2011).

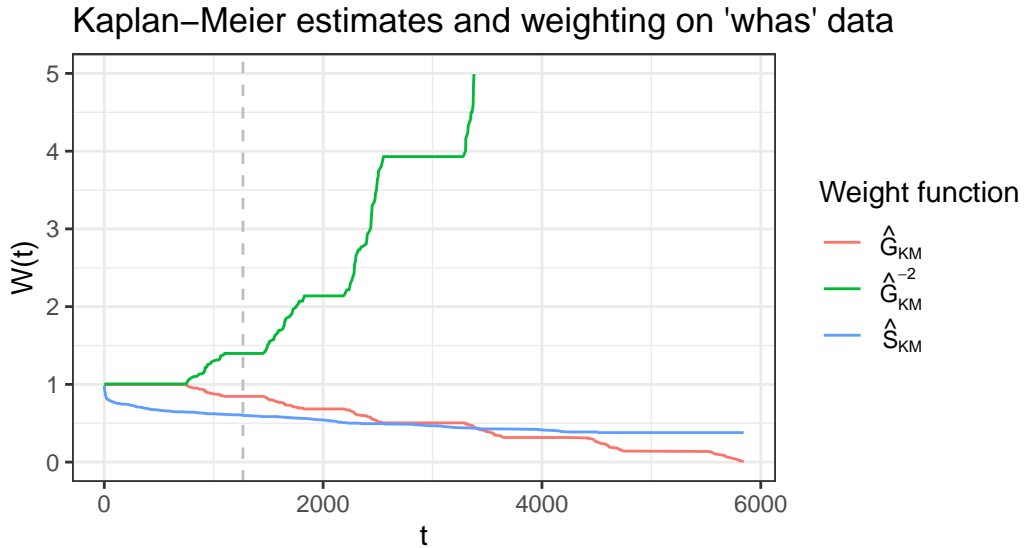


Figure 8.1: Weighting functions obtained on the **whas** dataset. x-axis is follow-up time. y-axis is outputs from one of three weighting functions:  $\hat{G}_{KM}$ , survival function based on the censoring distribution of the **whas** dataset (red), and  $\hat{G}_{KM}^{-2}$  (green),  $\hat{S}_{KM}$ , marginal survival function based on original **whas** dataset (blue), . The vertical gray line at  $t = \tau = 1267$  represents the point at which  $\hat{G}(t) < 0.6$ .

The following weights have been proposed for the concordance index:

- $W(t_i) = 1$ : Harrell’s concordance index,  $C_H$  (F. E. J. Harrell et al. 1984; F. E. Harrell, Califf, and Pryor 1982), which is widely accepted to be the most common survival measure and imposes no weighting on the definition of concordance. The original measure given by Harrell has no cut-off,  $\tau = \infty$ , however applying a cut-off is now more widely accepted in practice.
- $W(t_i) = [\hat{G}_{KM}(t_i)]^{-2}$ : Uno’s C,  $C_U$  (Uno et al. 2011).
- $W(t_i) = [\hat{G}_{KM}(t_i)]^{-1}$

- $W(t_i) = \hat{S}_{KM}(t_i)$
- $W(t_i) = \hat{S}_{KM}(t_i)/\hat{G}_{KM}(t_i)$

All methods assume that censoring is conditionally-independent of the event given the features (`?@sec-surv-set-cens`), otherwise weighting by  $\hat{S}_{KM}$  or  $\hat{G}_{KM}$  would not be applicable. It is assumed here that  $\hat{S}_{KM}$  and  $\hat{G}_{KM}$  are estimated on the training data and not the testing data (though the latter may be seen in some implementations, e.g. Therneau (2015)).

### 8.1.2 Choosing a C-index

With multiple choices of weighting available, choosing a specific measure might seem daunting. Matters are only made worse by debate in the literature, reflecting uncertainty in measure choice and interpretation. In practice, when a suitable cut-off  $\tau$  is chosen, all these weightings perform very similarly (Rahman et al. 2017; Schmid and Potapov 2012). For example, Table 8.1 uses the `whas` data again to compare Harrell’s C with measures that include IPCW weighting, when no cutoff is applied (top row) and when a cutoff is applied when  $\hat{G}(t) = 0.6$  (grey line in Figure 8.1). The results are almost identical when the cutoff is applied but still not massively different without the cutoff.

Table 8.1: Comparing C-index measures (calculated on the `whas` dataset using a Cox model with three-fold cross-validation) with no cut-off (top) and a cut-off when  $\hat{G}(t) = 0.6$  (bottom). First column is Harrell’s C, second is the weighting  $1/\hat{G}(t)$ , third is Uno’s C.

|          | W=1  | W=G <sup>-1</sup> | W=G <sup>-2</sup> |
|----------|------|-------------------|-------------------|
| tau=Inf  | 0.74 | 0.73              | 0.71              |
| tau=1267 | 0.76 | 0.75              | 0.75              |

On the other hand, if a poor choice is selected for  $\tau$  (cutting off too late) then IPCW measures can be highly unstable (Rahman et al. 2017), for example the variance of Uno’s C drastically increases with increased censoring (Schmid and Potapov 2012).

In practice, all C-index metrics provide an intuitive measure of discrimination and as such the choice of C-index is less important than the transparency in reporting. ‘C-hacking’ (R. Sonabend, Bender, and Vollmer 2022) is the deliberate, unethical procedure of calculating multiple C-indices and to selectively report one or more results to promote a particular model or result, whilst ignoring any negative findings. For example, calculating Harrell’s C and Uno’s C but only reporting the measure that shows a particular model of interest is better than another (even if the other metric shows the reverse effect). To avoid ‘C-hacking’:

- i) the choice of C-index should be made before experiments have begun and the choice of C-index should be clearly reported;
- ii) when ranking predictions are composed from distribution predictions, the composition method should be chosen and clearly described before experiments have begun.

As the C-index is highly dependent on censoring within a dataset, C-index values between experiments are not directly comparable, instead comparisons are limited to comparing model rankings, for example conclusions such as “model A outperformed model B with respect to Harrell’s C in this experiment”.

Learn about distribution to ranking compositions.

See Section 21.4 to learn more about creating ranking predictions from distribution predictions using composition.

## 8.2 Time-Dependent Measures

In the time-dependent case, where the metrics are computed based on specific survival times, the majority of measures are based on the Area Under the Curve, with one exception which is a simpler concordance index.

### 8.2.1 Concordance Indices

In contrast to the measures described above, Antolini's C (Antolini, Boracchi, and Biganzoli 2005) provides a time-dependent ('dep') formula for the concordance index. The definition of 'comparable' is the same for Antolini's C, however, concordance is now determined using the individual predicted survival probabilities calculated at the smaller event time in the pair:

$$P(\hat{S}_i(t_i) < \hat{S}_j(t_i) | t_i < t_j \cap \delta_i)$$

Note that observations are concordant when  $\hat{S}_i(t_i) < \hat{S}_j(t_i)$  as at the time  $t_i$ , observation  $i$  has experienced the event and observation  $j$  has not, hence the expected survival probability for  $\hat{S}_i(t_i)$  should be as close to 0 as possible (noting inherent randomness may prevent the perfect  $\hat{S}_i(t_i) = 0$  prediction) but otherwise should be less than  $\hat{S}_j(t_i)$  as  $j$  is still 'alive'. Once again this probability is estimated with a metric that could include a cut-off and different weighting schemes (though this is not included in Antolini's original definition):

$$C_{dep}(\hat{\mathbf{S}}, \mathbf{t}, \delta | \tau) = \frac{\sum_{i \neq j} W(t_i) \mathbb{I}(t_i < t_j, \hat{S}_i(t_i) < \hat{S}_j(t_i), t_i < \tau) \delta_i}{\sum_{i \neq j} W(t_i) \mathbb{I}(t_i < t_j, t_i < \tau) \delta_i}$$

where  $\hat{S} = (\hat{S}_1 \ \hat{S}_2 \ \dots \ \hat{S}_m)^\top$ .

Antolini's C provides an intuitive method to evaluate the discrimination of a model based on distribution predictions without depending on compositions to ranking predictions.

### 8.2.2 Area Under the Curve

#### Warning

We are still discussing how to structure and write this section so the contents are all subject to change. The text below is 'correct' but we want to add more detail about estimation of AUC so the book can be more practical, otherwise we may remove the section completely, let us know your thoughts about what you'd like to see here!

AUC, or AUROC, measures calculate the Area Under the Receiver Operating Characteristic (ROC) Curve, which is a plot of the *sensitivity* (or true positive rate (TPR)) against  $1 - \textit{specificity}$  (or true negative rate (TNR)) at varying thresholds (described below) for the predicted probability (or risk) of event. Figure 8.2 visualises ROC curves for two classification models. The blue line is a featureless baseline that has no discrimination. The red line is a decision tree with better discrimination as it comes closer to the top-left corner.

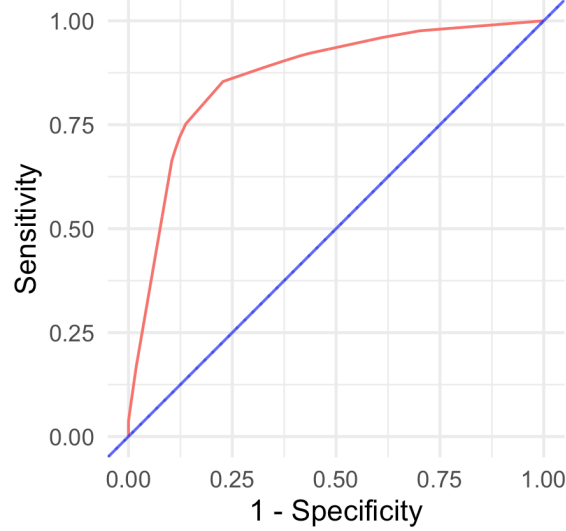


Figure 8.2: ROC Curves for a classification example. Red is a decision tree with good discrimination as it ‘hugs’ the top-left corner. Blue is a featureless baseline with no discrimination as it sits on  $y = x$ .

In a classification setting with no censoring, the AUC has the same interpretation as Harrell’s C (Uno et al. 2011). AUC measures for survival analysis were developed to provide a time-dependent measure of discriminatory ability (Patrick J. Heagerty, Lumley, and Pepe 2000). In a survival setting it can reasonably be expected for a model to perform differently over time and therefore time-dependent measures are advantageous. Computation of AUC estimators is complex and as such there are limited accessible metrics available off-shelf. There is limited evidence of these estimators used in the literature, hence discussion of these measures is kept brief.

The AUC, TPR, and TNR are derived from the *confusion matrix* in a binary classification setting. Let  $b_i, \hat{b}_i \in \{0, 1\}$  be the true and predicted binary outcomes respectively for some observation  $i$ . The confusion matrix is then given by:

|                 | $b_i = 1$ | $b_i = 0$ |
|-----------------|-----------|-----------|
| $\hat{b}_i = 1$ | TP        | FP        |
| $\hat{b}_i = 0$ | FN        | TN        |

where  $TN := \sum_i \mathbb{I}(b_i = 0, \hat{b}_i = 0)$  is the number of true negatives,  $TP := \sum_i \mathbb{I}(b_i = 1, \hat{b}_i = 1)$  is the number true positives,  $FP := \sum_i \mathbb{I}(b_i = 0, \hat{b}_i = 1)$  is the number of false positives, and  $FN := \sum_i \mathbb{I}(b_i = 1, \hat{b}_i = 0)$  is the number of false negatives. From these are derived

$$TPR := \frac{TP}{TP + FN} \quad (8.1)$$

$$TNR := \frac{TN}{TN + FP} \quad (8.2)$$

In classification, a probabilistic prediction of an event can be *thresholded* to obtain a deterministic prediction. For a predicted  $\hat{p} := \hat{P}(b = 1)$ , and threshold  $\alpha$ , the thresholded binary prediction is  $\hat{b} := \mathbb{I}(\hat{p} > \alpha)$ . This is achieved in survival analysis by thresholding the linear predictor at a given time for different values of the threshold and different values of the time. All measures of TPR, TNR and AUC are in the range  $[0, 1]$  with larger values preferred.

Weighting the linear predictor was proposed by Uno *et al.* (2007) (Uno et al. 2007) and provides a method for estimating TPR and TNR via

$$TPR_U(\hat{\eta}, \mathbf{t}, \delta | \tau, \alpha) = \frac{\sum_{i=1}^m \delta_i \mathbb{I}(k(\hat{\eta}_i) > \alpha, t_i \leq \tau) [\hat{G}_{KM}(t_i)]^{-1}}{\sum_{i=1}^m \delta_i \mathbb{I}(t_i \leq \tau) [\hat{G}_{KM}(t_i)]^{-1}}$$

and

$$TNR_U(\hat{\eta}, \mathbf{t} | \tau, \alpha) \mapsto \frac{\sum_{i=1}^m \mathbb{I}(k(\hat{\eta}_i) \leq \alpha, t_i > \tau)}{\sum_{i=1}^m \mathbb{I}(t_i > \tau)}$$

where  $\hat{\eta} = (\hat{\eta}_1 \hat{\eta}_2 \dots \hat{\eta}_m)^\top$  is a vector of predicted linear predictors,  $\tau$  is the time at which to evaluate the measure,  $\alpha$  is a cut-off for the linear predictor, and  $k$  is a known, strictly increasing, differentiable function.  $k$  is chosen depending on the model choice, for example if the fitted model is PH then  $k(x) = 1 - \exp(-\exp(x))$  (Uno et al. 2007). Similarities can be drawn between these equations and Uno's concordance index, in particular the use of IPCW. Censoring is again assumed to be at least random once conditioned on features. Plotting  $TPR_U$  against  $1 - TNR_U$  for varying values of  $\alpha$  provides the ROC.

The second method, which appears to be more prominent in the literature, is derived from Heagerty and Zheng (2005) (Patrick J. Heagerty and Zheng 2005). They define four distinct classes, in which observations are split into controls and cases.

An observation is a *case* at a given time-point if they are dead, otherwise they are a *control*. These definitions imply that all observations begin as controls and (hypothetically) become cases over time. Cases are then split into *incident* or *cumulative* and controls are split into *static* or *dynamic*. The choice between modelling static or dynamic controls is dependent on the question of interest. Modelling static controls implies that a 'subject does not change disease status' (Patrick J. Heagerty and Zheng 2005), and few methods have been developed for this setting (Kamarudin, Cox, and Kolamunnage-Dona 2017), as such the focus here is on *dynamic* controls. The incident/cumulative cases choice is discussed in more detail below.<sup>1</sup>

The TNR for dynamic cases is defined as

---

<sup>1</sup>All measures discussed in this section evaluate model discrimination from 'markers', which may be a *predictive* marker (model predictions) or a *prognostic* marker (a single covariate). This section always defines a marker as a ranking prediction, which is valid for all measures discussed here with the exception of one given at the end.

$$TNR_D(\hat{\mathbf{r}}, N|\alpha, \tau) = P(\hat{r}_i \leq \alpha | N_i(\tau) = 0)$$

where  $\hat{\mathbf{r}} = (\hat{r}_1 \hat{r}_2 \dots \hat{r}_n)^\top$  is some deterministic prediction and  $N(\tau)$  is a count of the number of events in  $[0, \tau)$ . Heagerty and Zheng further specify  $y$  to be the predicted linear predictor  $\hat{\eta}$ . Cumulative/dynamic and incident/dynamic measures are available in software packages ‘off-shelf’, these are respectively defined by

$$TPR_C(\hat{\mathbf{r}}, N|\alpha, \tau) = P(\hat{r}_i > \alpha | N_i(\tau) = 1)$$

and

$$TPR_I(\hat{\mathbf{r}}, N|\alpha, \tau) = P(\hat{r}_i > \alpha | dN_i(\tau) = 1)$$

where  $dN_i(\tau) = N_i(\tau) - N_i(\tau-)$ . Practical estimation of these quantities is not discussed here.

The choice between the incident/dynamic (I/D) and cumulative/dynamic (C/D) measures primarily relates to the use-case. The C/D measures are preferred if a specific time-point is of interest (Patrick J. Heagerty and Zheng 2005) and is implemented in several applications for this purpose (Kamarudin, Cox, and Kolamunnage-Dona 2017). The I/D measures are preferred when the true survival time is known and discrimination is desired at the given event time (Patrick J. Heagerty and Zheng 2005).

Defining a time-specific AUC is now possible with

$$AUC(\hat{\mathbf{r}}, N|\tau) = \int_0^1 TPR(\hat{\mathbf{r}}, N|1 - TNR^{-1}(p|\tau), \tau) dp$$

Finally, integrating over all time-points produces a time-dependent AUC and as usual a cut-off is applied for the upper limit,

$$AUC^*(\hat{\mathbf{r}}, N|\tau^*) = \int_0^{\tau^*} AUC(\hat{\mathbf{r}}, N|\tau) \frac{2\hat{p}_{KM}(\tau)\hat{S}_{KM}(\tau)}{1 - \hat{S}_{KM}^2(\tau^*)} d\tau$$

where  $\hat{S}_{KM}, \hat{p}_{KM}$  are survival and mass functions estimated with a Kaplan-Meier model on training data.

Since Heagerty and Zheng’s paper, other methods for calculating the time-dependent AUC have been devised, including by Chambless and Diao (Chambless and Diao 2006), Song and Zhou (Song and Zhou 2008), and Hung and Chiang (Hung and Chiang 2010). These either stem from the Heagerty and Zheng paper or ignore the case/control distinction and derive the AUC via different estimation methods of TPR and TNR. Blanche *et al.* (2012) (Blanche, Latouche, and Viallon 2012) surveyed these and concluded ‘regarding the choice of the retained definition for cases and controls, no clear guidance has really emerged in the literature’, but agree with Heagerty and Zeng on the use of C/D for clinical trials and I/D for ‘pure’ evaluation of the marker. Blanche *et al.* (2013) (Blanche, Dartigues, and Jacqmin-Gadda 2013) published a survey of C/D AUC measures with an emphasis on non-parametric estimators with marker-dependent censoring, including their own Conditional IPCW (CIPCW) AUC, which is not discussed further here as it cannot be used for evaluating predictions (R. E. B. Sonabend 2021).



Reviews of AUC measures have produced (sometimes markedly) different results (Blanche, Latouche, and Viallon 2012; Li, Greene, and Hu 2018; Kamarudin, Cox, and Kolamunnage-Dona 2017) with no clear consensus on how and when these measures should be used. The primary advantage of these measures is to extend discrimination metrics to be time-dependent. However, it is unclear how to interpret a threshold of a linear predictor and moreover if this is even the ‘correct’ quantity to threshold, especially when survival distribution predictions are the more natural object to evaluate over time.



# 9

## *Calibration Measures*

TODO (150-200 WORDS)

 Minor changes expected!

**This page is a work in progress and minor changes will be made over time.**

Calibration measures evaluate the ‘average’ quality of survival distribution predictions. This chapter is kept relatively short as the literature in this area is scarce (Rahman et al. 2017), this is likely due to the meaning of calibration being unclear in a survival context (Van Houwelingen 2000). However the meaning of calibration is better specified once specific metrics are introduced. As with other measure classes, only measures that can generalise beyond Cox PH models are included here but note that several calibration measures for re-calibrating PH models have been discussed in the literature (Demler, Paynter, and Cook 2015; Van Houwelingen 2000).

Calibration measures can be grouped (Andres et al. 2018) into those that evaluate distributions at a single time-point, ‘1-Calibration’ or ‘Point Calibration’ measures, and those that evaluate distributions at all time-points ‘distributional-calibration’ or ‘probabilistic calibration’ measures. A point-calibration measure will evaluate a function of the predicted distribution at a single time-point whereas a probabilistic measure evaluates the distribution over a range of time-points; in both cases the evaluated quantity is compared to the observed outcome,  $(t, \delta)$ .

### 9.1 Point Calibration

Point calibration measures can be further divided into metrics that evaluate calibration at a single time-point (by reduction) and measures that evaluate an entire distribution by only considering the event time. The difference may sound subtle but it affects conclusions that can be drawn. In the first case, a calibration measure can only draw conclusions at that one time-point, whereas the second case can draw conclusions about the calibration of the entire distribution. This is the same caveat as using prediction error curves for scoring rules.

Learn more about prediction error curves

See Section 10.3 to learn more about prediction error curves.

### 9.1.1 Calibration by Reduction

Point calibration measures are implicitly reduction methods as they use classification methods to evaluate a full distribution based on a single point only. For example, given a predicted survival function  $\hat{S}$ , one could calculate the survival function at a single time point,  $\hat{S}\tau$  and then use probabilistic classification calibration measures. Using this approach one may employ common calibration methods such as the Hosmer–Lemeshow test (Hosmer and Lemeshow 1980). Measuring calibration in this way can have significant drawbacks as a model may be well-calibrated at one time-point but poorly calibrated at all others (Haider et al. 2020). To mitigate this, one could perform the Hosmer–Lemeshow test (or other applicable tests) multiple times with multiple testing correction at many (or all possible) time points, however this would be less efficient and more difficult to interpret than other measures discussed in this chapter.

Learn more about reduction

See Chapter 21 to learn more about reduction.

### 9.1.2 Houwelingen’s $\alpha$

As opposed to evaluating distributions at one or more arbitrary time points, one could instead evaluate distribution predictions at meaningful times. van Houwelingen proposed several measures (Van Houwelingen 2000) for calibration but only one generalises to all probabilistic survival models, termed here ‘Houwelingen’s  $\alpha$ ’. The measure assesses if the model correctly estimates the theoretical ‘true’ cumulative hazard function of the underlying data generating process,  $H = \hat{H}$ .

The statistic is derived by noting the closely related nature of survival analysis and counting processes, and exploiting the fact that the sum of the cumulative hazard function is an estimate for the number of events in a given time-period (Hosmer Jr, Lemeshow, and May 2011). As this result is often surprising result to readers, below is a short experiment using R that demonstrates how the sum of the cumulative hazard estimated by a Kaplan-Meier estimator is identical to the number of randomly simulated deaths in a dataset:

```
set.seed(42)
library(survival)

event = rbinom(100, 1, 0.7)
times = runif(100)
H = survfit(Surv(times, event) ~ 1)$cumhaz
sum(event) / sum(H)
#> [1] 1
```

Houwelingen’s  $\alpha$  is then defined by substituting  $H$  for the observed total number of deaths and summing over all predictions:

$$H_{\alpha}(\delta, \hat{\mathbf{H}}, \mathbf{t}) = \frac{\sum_i \delta_i}{\sum_i \hat{\mathbf{H}}_i(t_i)}$$

with standard error  $SE(H_{\alpha}) = \exp(1/\sqrt{\sum_i \delta_i})$ . A model is well-calibrated with respect to

$H_\alpha$  if  $H_\alpha = 1$ .

The next metrics we look at evaluate models across a spectrum of points to assess calibration over time.

## 9.2 Probabilistic Calibration

Calibration over a range of time points may be assessed quantitatively or qualitatively, with graphical methods often favoured. Graphical methods compare the average predicted distribution to the expected distribution, which can be estimated with the Kaplan-Meier curve, discussed next.

### 9.2.1 Kaplan-Meier Comparison

The simplest graphical comparison compares the average predicted survival curve to the Kaplan-Meier curve estimated on the testing data. Let  $\hat{S}_1, \dots, \hat{S}_m$  be predicted survival functions, then the average predicted survival function is the mixture:  $\hat{\bar{S}} = \frac{1}{m} \sum_{i=1}^m \hat{S}_i(\tau)$ . This estimate can be plotted next to the Kaplan-Meier estimate of the survival distribution in a test dataset (i.e., the true data for model evaluation), allowing for visual comparison of how closely these curves align. An example is given in Figure 9.1, a Cox model (CPH), random survival forest, and relative risk tree with distribution composition, are all compared to the Kaplan-Meier estimator. This figure highlights the advantages and disadvantages of this method. The relative risk tree is clearly poorly calibrated as it increasingly diverges from the Kaplan-Meier. In contrast, the Cox model and random forest cannot be directly compared to one another, as both models frequently overlap with each other and the Kaplan-Meier estimator. Hence it is possible to say that the Cox and forests models are better calibrated than the risk tree, however it is not possible to say which of those two is better calibrated and whether their distance from the Kaplan-Meier is significant or not at a given time (when not clearly overlapping).

This method is useful for making broad statements such as “model X is clearly better calibrated than model Y” or “model X appears to make average predictions close to the Kaplan-Meier estimate”, but that is the limit in terms of useful conclusions. One could refine this method for more fine-grained information by instead using relative risk predictions to create ‘risk groups’ that can be plotted against a stratified Kaplan-Meier, however this method is harder to interpret and adds even more subjectivity around how many risk groups to create and how to create them (Patrick Royston and Altman 2013). The next measure we consider includes a graphical method as well as a quantitative interpretation.

### 9.2.2 D-Calibration

D-Calibration (Andres et al. 2018; Haider et al. 2020) evaluates a model’s calibration by assessing if the predicted survival distributions follow the Uniform distribution as expected, which is motivated by the result that for any random variable  $X$  it follows  $S_X(x) \sim \mathcal{U}(0, 1)$ . This can be tested using a  $\chi^2$  test-statistic:

$$\chi^2 := \sum_{i=1}^n \frac{(O_i - E_i)^2}{E_i}$$

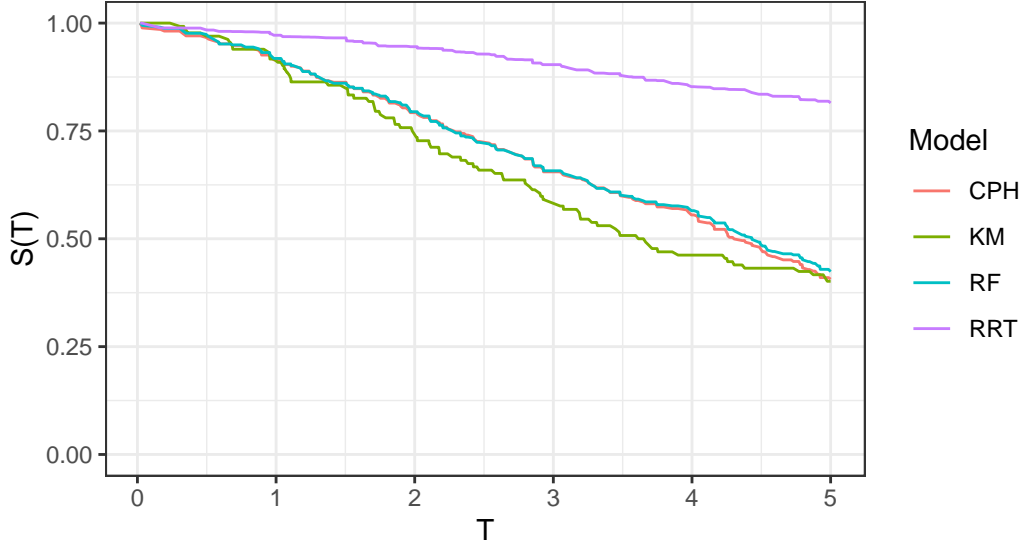


Figure 9.1: Comparing the calibration of a Cox PH (CPH), random forest (RF), and relative risk tree (RRT) to the Kaplan-Meier estimate of the survival function calculated on a test set. The calibration of RRT notably decreases over time whereas RF and CPH are closer to the Kaplan-Meier curve.

where  $O_1, \dots, O_n$  is the observed number of events in  $n$  groups and  $E_1, \dots, E_n$  is the expected number of events.

To utilise this test, the  $[0, 1]$  codomain of  $S_i$  is cut into  $B$  disjoint contiguous intervals ('bins') over the full range  $[0, 1]$ . Let  $m$  be the total number of observations, then assuming a discrete uniform distribution as the theoretical distribution, the expected number of events in each bin is  $E_i = m/B$  (as the probability of an observation falling into each bin is equal).

The observations in the  $i$ th bin,  $b_i$ , are defined by the set:

$$b_i := \{j = 1, \dots, m : \lceil \hat{S}_i(t_j)B \rceil = i\}$$

where  $j = 1, \dots, m$  are the indices of the observations,  $\hat{S}_i$  are observed (i.e., predicted) survival functions,  $t_i$  are observed (i.e., the ground truth) outcome times, and  $\lceil \cdot \rceil$  is the ceiling function. The observed number of events in  $b_i$  is then the number of observations in that set:  $O_i = |b_i|$ .

The D-Calibration measure, or  $\chi^2$  statistic, is now defined by,

$$D_{\chi^2}(\hat{\mathbf{S}}, \mathbf{t}) := \frac{\sum_{i=1}^B (O_i - \frac{m}{B})^2}{m/B}$$

where  $\hat{\mathbf{S}} = (\hat{S}_1 \hat{S}_2 \dots \hat{S}_m)^\top$  and  $\mathbf{t} = (t_1 t_2 \dots t_m)^\top$ .

This measure has several useful properties. Firstly, one can test the null hypothesis that a model is 'D-calibrated' by deriving a  $p$ -value from comparison to  $\chi^2_{B-1}$ . Secondly,  $D_{\chi^2}$  tends to zero as a model is increasingly well-calibrated, hence the measure can be used for model

comparison. Finally, the theory lends itself to an intuitive graphical calibration method as a D-calibrated model implies:

$$p = \frac{\sum_i \mathbb{I}(T_i \leq \hat{F}_i^{-1}(p))}{m}$$

where  $p$  is some value in  $[0, 1]$ ,  $\hat{F}_i^{-1}$  is the  $i$ th predicted inverse cumulative distribution function, and  $m$  is again the number of observations. In words, the number of events occurring at or before each quantile should be equal to the quantile itself, for example 50% of events should occur before their predicted median survival time. Therefore, one can plot  $p$  on the x-axis and the right hand side of the above equation on the y-axis. A D-calibrated model should result in a straight line on  $x = y$ . This is visualised in Figure 9.2 for the same models as in Figure 9.1. This figure supports the previous findings that the relative risk tree is poorly calibrated in contrast to the Cox model and random forest but again no direct comparison between the latter models is possible.

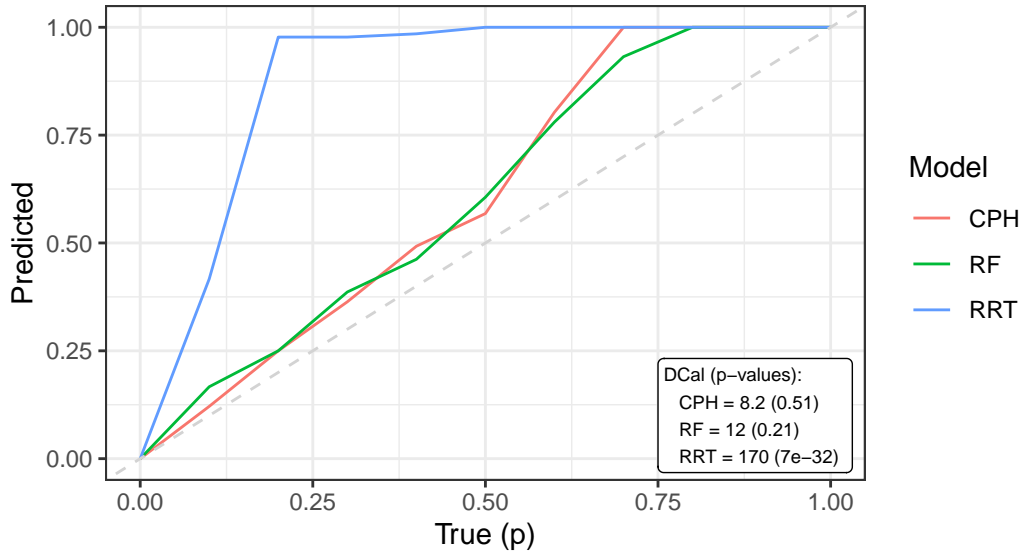


Figure 9.2: Comparing the D-calibration of a Cox PH (CPH), random forest (RF), and relative risk tree (RRT) to the expected distribution on  $y=x$ . As with Figure 9.1, the relative risk tree is clearly not D-calibrated (as supported by the figures in the bottom-right). The CPH and RF are closer to the  $y=x$  however neither follow it perfectly.

Whilst D-calibration has the same problems as the Kaplan-Meier method with respect to visual comparison, at least in this case there are quantities to help draw more concrete solutions. For the models in Figure 9.2, it is clear that the relative risk tree is not D-calibrated with  $p < 0.01$  indicating the null hypothesis of D-calibration, i.e., the predicted quantiles not following a Discrete Uniform distribution, can be comfortably rejected. Whilst the D-calibration for the Cox model is smaller than that of the random forest, the difference is unlikely to be significant, as is seen in the overlapping curves in the figure.

The next chapter will look at scoring rules, which provides a more concrete method to analytically compare the predicted distributions from survival models.





# Evaluating Distributions by Scoring Rules

TODO (150-200 WORDS)

⚠ Minor changes expected!

**This page is a work in progress and minor changes will be made over time.**

Scoring rules evaluate probabilistic predictions and (attempt to) measure the overall predictive ability of a model in terms of both calibration and discrimination (Gneiting and Raftery 2007; Murphy 1973). In contrast to calibration measures, which assess the average performance across all observations on a population level, scoring rules evaluate the sample mean of individual predictions across all observations in a test set. As well as being able to provide information at an individual level, scoring rules are also popular as probabilistic forecasts are widely recognised to be superior to deterministic predictions for capturing uncertainty in predictions (A. P. Dawid 1984; A. Philip Dawid 1986). Formalisation and development of scoring rules has primarily been due to Dawid (A. P. Dawid 1984; A. Philip Dawid 1986; A. Philip Dawid and Musio 2014) and Gneiting and Raftery (Gneiting and Raftery 2007); though the earliest measures promoting “rational” and “honest” decision making date back to the 1950s (Brier 1950; Good 1952). Few scoring rules have been proposed in survival analysis, although the past few years have seen an increase in popularity in these measures. Before delving into these measures, we will first describe scoring rules in the simpler classification setting.

Scoring rules are pointwise losses, which means a loss is calculated for all observations and the sample mean is taken as the final score. To simplify notation, we only discuss scoring rules in the context of a single observation where  $L_i(\hat{S}_i, t_i, \delta_i)$  would be the loss calculated for some observation  $i$  where  $\hat{S}_i$  is the predicted survival function (from which other distribution functions can be derived), and  $(t_i, \delta_i)$  is the observed survival outcome.

## 10.1 Classification Losses

In the simplest terms, a scoring rule compares two values and assigns them a score (hence ‘scoring rule’), formally we’d write  $L : \mathbb{R} \times \mathbb{R} \mapsto \bar{\mathbb{R}}$ . In machine learning, this usually means comparing a prediction for an observation to the ground truth, so  $L : \mathbb{R} \times \mathcal{P} \mapsto \bar{\mathbb{R}}$  where

$\mathcal{P}$  is a set of distributions. Crucially, scoring rules usually refer to comparisons of true and predicted *distributions*. As an example, take the Brier score (Brier 1950) defined by:

$$L_{\text{Brier}}(\hat{p}_i, y_i) = (y_i - \hat{p}_i(y_i))^2$$

This scoring rule compares the ground truth to the predicted probability distribution by testing if the difference between the observed event and the truth is minimized. This is intuitive as if the event occurs and  $y_i = 1$ , then  $\hat{p}_i(y_i)$  should be as close to one as possible to minimize the loss. On the other hand, if  $y_i = 0$  then the better prediction would be  $\hat{p}_i(y_i) = 0$ .

This demonstrates an important property of the scoring rule, *properness*. A loss is *proper*, if it is minimized by the correct prediction. In contrast, the loss  $L_{\text{improper}}(\hat{p}_i, y_i) = 1 - L_{\text{Brier}}(\hat{p}_i, y_i)$  is still a scoring rule as it compares the ground truth to the prediction probability distribution, but it is clearly improper as the perfect prediction ( $\hat{p}_i(y_i) = y_i$ ) would result in a score of 1 whereas the worst prediction would result in a score of 0. Proper losses provide a method of model comparison as, by definition, predictions closest to the true distribution will result in lower expected losses.

Another important property is *strict properness*. A loss is *strictly proper* if the loss is uniquely minimized by the ‘correct’ prediction. Consider now the loss  $L_0(\hat{p}_i, y_i) = 0$ . Not only is this a strictly proper scoring rule but it is also proper. The loss can only take the value 0 and is therefore guaranteed to be minimized by the correct prediction. It is clear however that this loss is useless. In contrast, the Brier score is minimized by only one value, which is the optimal prediction (Figure 10.1). Strictly proper losses are particularly important for automated model optimisation, as minimization of the loss will result in the ‘optimum score estimator based on the scoring rule’ (Gneiting and Raftery 2007).

Mathematically, a classification loss  $L : \mathcal{P} \times \mathcal{Y} \rightarrow \bar{\mathbb{R}}$  is *proper* if for any distributions  $p_Y, p$  in  $\mathcal{P}$  and for any random variables  $Y \sim p_Y$ , it holds that  $\mathbb{E}[L(p_Y, Y)] \leq \mathbb{E}[L(p, Y)]$ . The loss is *strictly proper* if, in addition,  $p = p_Y$  uniquely minimizes the loss.

As well as the Brier score, which was defined above, another widely used loss is the log loss (Good 1952), defined by

$$L_{\text{logloss}}(\hat{p}_i, y_i) = -\log \hat{p}_i(y_i)$$

These losses are visualised in Figure 10.1, which highlights that both losses are strictly proper (A. Philip Dawid and Musio 2014) as they are minimized when the true prediction is made, and converge to the minimum as predictions are increasingly improved.

---

## 10.2 Survival Losses

Analogously to classification losses, a survival loss  $L : \mathcal{P} \times \mathbb{R}_{>0} \times \{0, 1\} \rightarrow \bar{\mathbb{R}}$  is *proper* if for any distributions  $p_Y, p$  in  $\mathcal{P}$ , and for any random variables  $Y \sim p_Y$ , and  $C$  t.v.i.  $\mathbb{R}_{>0}$ ; with  $T := \min(Y, C)$  and  $\Delta := \mathbb{I}(T = Y)$ ; it holds that,  $\mathbb{E}[L(p_Y, T, \Delta)] \leq \mathbb{E}[L(p, T, \Delta)]$ . The loss is *strictly proper* if, in addition,  $p = p_Y$  uniquely minimizes the loss. A survival loss is referred to as outcome-independent (strictly) proper if it is only (strictly) proper when  $C$  and  $Y$  are independent.

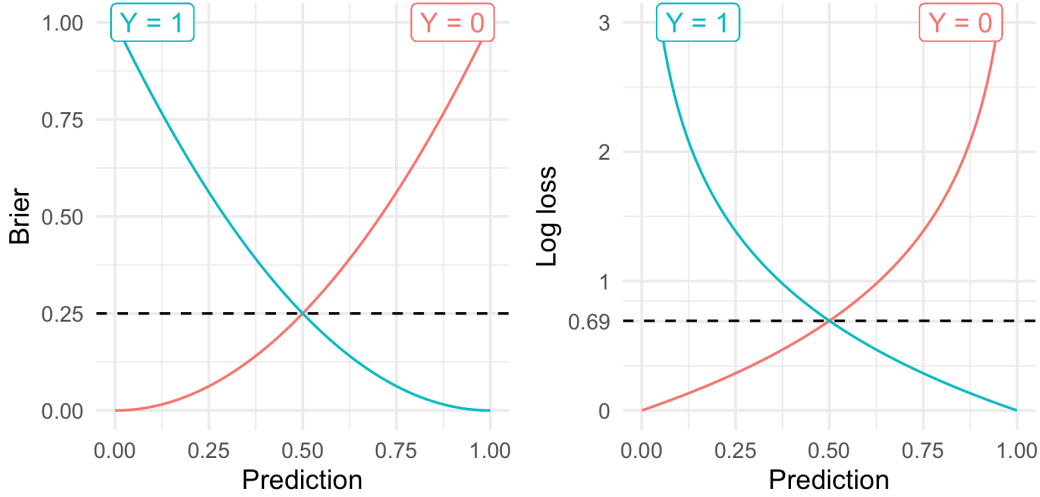


Figure 10.1: Brier and log loss scoring rules for a binary outcome and varying probabilistic predictions. x-axis is a probabilistic prediction in  $[0, 1]$ , y-axis is Brier score (left) and log loss (right). Blue lines are varying Brier score/log loss over different predicted probabilities when the true outcome is 1. Red lines are varying Brier score/log loss over different predicted probabilities when the true outcome is 0. Both losses are minimized when  $\hat{p}_i(y_i) = y_i$ .

With these definitions, the rest of this chapter lists common scoring rules in survival analysis and discusses some of their properties. As with other chapters, this list is likely not exhaustive but will cover commonly used losses.

### 10.2.1 Integrated Graf Score

The Integrated Graf Score (IGS) was introduced by Graf (Graf and Schumacher 1995; Graf et al. 1999) as an analogue to the integrated brier score (IBS) in regression. It is likely the commonly used scoring rule in survival analysis, possibly due to its intuitive interpretation.

The loss is defined by

$$L_{IGS}(\hat{S}_i, t_i, \delta_i | \hat{G}_{KM}) = \int_0^{\tau^*} \frac{\hat{S}_i^2(\tau) \mathbb{I}(t_i \leq \tau, \delta_i = 1)}{\hat{G}_{KM}(t_i)} + \frac{\hat{F}_i^2(\tau) \mathbb{I}(t_i > \tau)}{\hat{G}_{KM}(\tau)} d\tau \quad (10.1)$$

where  $\hat{S}_i^2(\tau) = (\hat{S}_i(\tau))^2$  and  $\hat{F}_i^2(\tau) = (1 - \hat{S}_i(\tau))^2$ , and  $\tau^* \in \mathbb{R}_{\geq 0}$  is an upper threshold to compute the loss up to, and  $\hat{G}_{KM}$  is the Kaplan-Meier trained on the censoring distribution for IPCW (Section 8.1).

At first glance this might seem intimidating but it is worth taking the time to understand the intuition behind the loss. Recall the classification Brier score,  $L(\hat{p}_i, y_i) = (y_i - \hat{p}_i(y))^2$ , this provides a method to compare and evaluate a probability mass function at one time-point. The *integrated Brier score* (IBS), also known as the *CRPS*, is the integral of the Brier score for all real-valued thresholds (Gneiting and Raftery 2007) and hence allows predictions to be evaluated over multiple points as  $L(\hat{F}_i, y_i) = \int (\hat{F}_i(y_i) - \mathbb{I}(y_i \geq x))^2 dy$  where  $\hat{F}_i$  is the predicted cumulative distribution function and  $x$  is some meaningful threshold. In survival

analysis,  $\hat{F}_i(\tau)$  represents the probability of an observation having experienced the event at or before  $\tau$ , and the ground truth to compare to is therefore whether the observation has actually experienced the event at  $\tau$ , which is the case when  $t_i \leq \tau$ . Hence the IBS becomes  $L(\hat{F}_i, t_i) = \int (\hat{F}_i(\tau) - \mathbb{I}(t_i \leq \tau))^2 d\tau$ . Now for a given time  $\tau$ :

$$L(\hat{F}_i, t) = \begin{cases} (\hat{F}_i(\tau) - 1)^2 = (1 - \hat{F}_i(\tau))^2 = \hat{S}_i^2(\tau), & \text{if } t_i \leq \tau \\ (\hat{F}_i(\tau) - 0)^2 = \hat{F}_i^2(\tau), & \text{if } t_i > \tau \end{cases} \quad (10.2)$$

In words, if an observation has not yet experienced an outcome ( $t_i > \tau$ ) then the loss is minimized when the cumulative distribution function (the probability of having already died) is 0, which is intuitive as the optimal prediction is correctly identifying the observation has yet to experience the event. In contrast, if the observation has experienced the outcome ( $t_i \leq \tau$ ) then the loss is minimized when the survival function (the probability of surviving until  $\tau$ ) is 0, which follows from similar logic.

The final component of the Graf score is accommodating for censoring. At  $\tau$  an observation will either have

1. Not experienced the event:  $I(t_i > \tau)$ ;
2. Experienced the event:  $I(t_i \leq \tau, \delta_i = 1)$ ; or
3. Been censored:  $I(t_i \leq \tau, \delta_i = 0)$

In the Graf score, censored observations are discarded. If they were not then Equation 10.2 would imply their contribution would be treated the same as those who had experienced the event. However this assumption would be entirely wrong as a censored observation is guaranteed not to have experienced the event, hence an ideal prediction for a censored observation is a high survival probability up until the point of censoring, at which time comparison to ground truth is unknown as this is no longer observed.

The act of discarding censored observations means that the sample size decreases over time. To compensate for this, IPCW is used to increasingly weight predictions as  $\tau$  increases. Hence, IPCW weights,  $W_i$  are defined such that

$$W_i = \begin{cases} \hat{G}_{KM}^{-1}(t_i), & \text{if } \mathbb{I}(t_i \leq \tau, \delta_i = 1) \\ \hat{G}_{KM}^{-1}(\tau), & \text{if } \mathbb{I}(t_i > \tau) \end{cases}$$

The weights total 1 when divided over all samples and summed (Graf et al. 1999). They are also intuitive as observations are either weighted by  $G(\tau)$  when they are still alive and therefore still part of the sample, or by  $G(t_i)$  otherwise.

As well as being intuitive, when censoring is uninformative, the Graf score consistently estimates the mean square error  $L(t, S|\tau^*) = \int_0^{\tau^*} [\mathbb{I}(t > \tau) - S(\tau)]^2 d\tau$ , where  $S$  is the correctly specified survival function (Gerds and Schumacher 2006). However, despite these promising properties, the IGS is improper and must therefore be used with care (Rindt et al. 2022; R. Sonabend 2022). In practice, experiments have shown that the effect of impropersness is minimal and therefore this loss should be avoided for automated routines such as model tuning, however it can still be used for model evaluation. In addition, a small adaptation of the loss results in a strictly proper scoring rule simply by altering the weights such that  $W_i = \hat{G}_{KM}^{-1}(t_i)$  for all uncensored observations and 0 otherwise (R. Sonabend 2022), resulting in the reweighted Graf score:

$$L_{RGS}(\hat{S}_i, t_i, \delta_i | \hat{G}_{KM}) = \delta_i \mathbb{I}(t_i \leq \tau^*) \int_0^{\tau^*} \frac{(\mathbb{I}(t_i \leq \tau) - \hat{F}_i(\tau))^2}{\hat{G}_{KM}(t_i)} d\tau$$

The addition of  $\mathbb{I}(t_i \leq \tau^*)$  completely removes observations that experience the event after the cutoff time,  $\tau^*$ , this ensures there are no cases where the  $G(t_i)$  weighting is calculated on time after the cutoff. Including an upper threshold (i.e.,  $\tau^* < \infty$ ) effects properness and generalization statements. For example, by evaluating a model using the RGS with a  $\tau^*$  threshold, then the model may be said to only perform well up until  $\tau^*$  with its performance unknown after this time.

The change of weighting slightly alters the interpretation of the contributions at different time-points. By example, let  $(t_i = 4, t_j = 5)$  be two observed survival times, then at  $\tau = 3$ , the Graf score weighting would be  $\hat{G}_{KM}^{-1}(4)$  for both observations, whereas the RGS weights would be  $(KM\hat{G}^{-1}(4), KM\hat{G}^{-1}(5))$  respectively, hence there is always more ‘importance’ placed on observations that take longer to experience the event. In practice, the difference between these weights appears to be minimal (R. Sonabend 2022) but as RGS is strictly proper, it is more suitable for automated experiments.

### 10.2.2 Integrated Survival Log Loss

The integrated survival log loss (ISLL) was also proposed by Graf et al. (1999).

$$L_{ISLL}(\hat{S}_i, t_i, \delta_i | \hat{G}_{KM}) = - \int_0^{\tau^*} \frac{\log[\hat{F}_i(\tau)] \mathbb{I}(t_i \leq \tau, \delta_i = 1)}{\hat{G}_{KM}(t_i)} + \frac{\log[\hat{S}_i(\tau)] \mathbb{I}(t_i > \tau)}{\hat{G}_{KM}(\tau)} d\tau$$

where  $\tau^* \in \mathbb{R}_{>0}$  is an upper threshold to compute the loss up to.

Similarly to the IGS, there are three ways to contribute to the loss depending on whether an observation is censored, experienced the event, or alive, at  $\tau$ . Whilst the IGS is routinely used in practice, there is no evidence that ISLL is used, and moreover there are no proofs (or claims) that it is proper.

The reweighted ISLL (RISLL) follows similarly to the RIGS and is also outcome-independent strictly proper (R. Sonabend 2022).

$$L_{RISLL}(\hat{S}_i, t_i, \delta_i | \hat{G}_{KM}) = -\delta_i \mathbb{I}(t_i \leq \tau^*) \int_0^{\tau^*} \frac{\mathbb{I}(t_i \leq \tau) \log[\hat{F}_i(\tau)] + \mathbb{I}(t_i > \tau) \log[\hat{S}_i(\tau)]}{\hat{G}_{KM}(t_i)} d\tau$$

### 10.2.3 Survival density log loss

Another outcome-independent strictly proper scoring rule is the survival density log loss (SDLL) (R. Sonabend 2022), which is given by

$$L_{SDLL}(\hat{f}_i, t_i, \delta_i | \hat{G}_{KM}) = -\frac{\delta_i \log[\hat{f}_i(t_i)]}{\hat{G}_{KM}(t_i)}$$

where  $\hat{f}_i$  is the predicted probability density function. This loss is essentially the classification log loss  $(-\log(\hat{p}_i(t_i)))$  with added IPCW. Whilst the classification log loss has

beneficial properties such as being differentiable, this is more complex for the SDLL and it is not widely used in practice. A useful alternative to the SDLL which can be readily used in automated procedures is the right-censored log loss.

#### 10.2.4 Right-censored log loss

The right-censored log loss (RCLL) is an outcome-independent strictly proper scoring rule (Avati et al. 2020) that benefits from not depending on IPCW in its construction. The RCLL is defined by

$$L_{RCLL}(\hat{S}_i, t_i, \delta_i) = -\log[\delta_i \hat{f}_i(t_i) + (1 - \delta_i) \hat{S}_i(t_i)]$$

This loss is interpretable when we break it down into its two halves:

1. If an observation is censored at  $t_i$  then all the information we have is that they did not experience the event at the time, so they must be ‘alive’, hence the optimal value is  $\hat{S}_i(t_i) = 1$  (which becomes  $-\log(1) = 0$ ).
2. If an observation experiences the event then the ‘best’ prediction is for the probability of the event at that time to be maximised, as pdfs are not upper-bounded this means  $\hat{f}_i(t_i) = \infty$  (and  $-\log(t_i) \rightarrow \infty$  as  $t_i \rightarrow \infty$ ).

#### 10.2.5 Absolute Survival Loss

The absolute survival loss, developed over time by Schemper and Henderson (2000) and Schmid et al. (2011), is based on the mean absolute error is very similar to the IGS but removes the squared term:

$$L_{ASL}(\hat{S}_i, t_i, \delta_i | \hat{G}_{KM}) = \int_0^{\tau^*} \frac{\hat{S}_i(\tau) \mathbb{I}(t_i \leq \tau, \delta_i = 1)}{\hat{G}_{KM}(t_i)} + \frac{\hat{F}_i(\tau) \mathbb{I}(t_i > \tau)}{\hat{G}_{KM}(\tau)} d\tau$$

where  $\hat{G}_{KM}$  and  $\tau^*$  are as defined above. Analogously to the IGS, the ASL score consistently estimates the mean absolute error when censoring is uninformative (Schmid et al. 2011) but there are also no proofs or claims of properness. The ASL and IGS tend to yield similar results (Schmid et al. 2011) but in practice there is no evidence of the ASL being widely used.

---

### 10.3 Prediction Error Curves

As well as evaluating probabilistic outcomes with integrated scoring rules, non-integrated scoring rules can be utilised for evaluating distributions at a single point. For example, instead of evaluating a probabilistic prediction with the IGS over  $\mathbb{R}_{\geq 0}$ , instead one could compute the IGS at a single time-point,  $\tau \in \mathbb{R}_{\geq 0}$ , only. Plotting these for varying values of  $\tau$  results in ‘prediction error curves’ (PECs), which provide a simple visualisation for how predictions vary over the outcome. PECs are especially useful for survival predictions as they can visualise the prediction ‘over time’. PECs are mostly used as a graphical guide when comparing few models, rather than as a formal tool for model comparison. An example for

PECs is provided in Figure 10.2 for the IGS where the the Cox PH consistently outperforms the SVM.

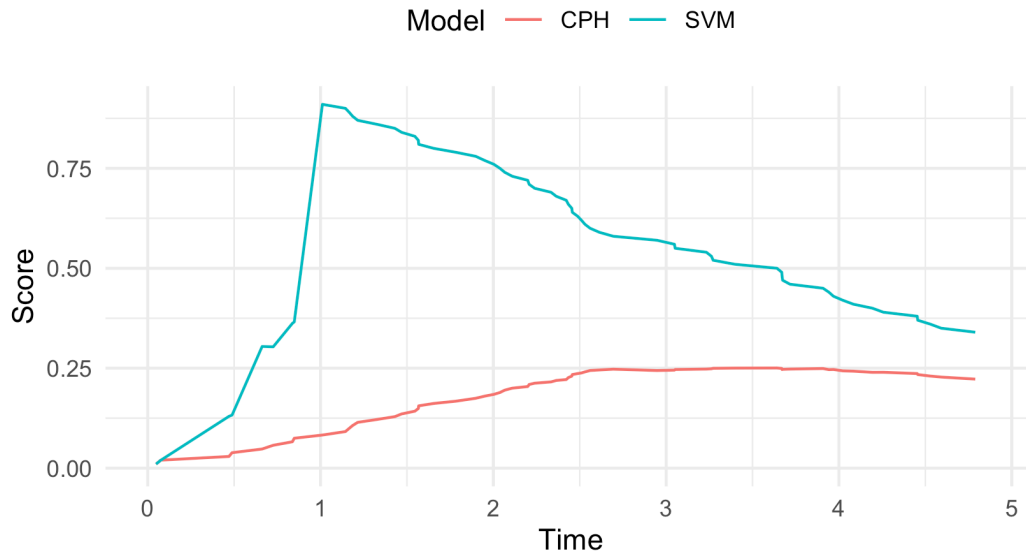


Figure 10.2: Prediction error curves for the CPH and SVM models from Chapter 9. x-axis is time and y-axis is the IGS computed at different time-points. The CPH (red) performs better than the SVM (blue) as it scores consistently lower. Trained and tested on randomly simulated data from **mlr3proba**.

## 10.4 Baselines and ERV

A common criticism of scoring rules is a lack of interpretability, for example, an IGS of 0.5 or 0.0005 has no meaning by itself, so below we present two methods to help overcome this problem.

The first method, is to make use of baselines for model comparison, which are models or values that can be utilised to provide a reference for a loss, they provide a universal method to judge all models of the same class by (Gressmann et al. 2018). In classification, it is possible to derive analytical baseline values, for example a Brier score is considered ‘good’ if it is below 0.25 or a log loss if it is below 0.693 (Figure 10.1), this is because these are the values obtained if you always predicted probabilities as 0.5, which is a reasonable baseline guess in a binary classification problem. In survival analysis, simple analytical expressions are not possible as losses are dependent on the unknown distributions of both the survival and censoring time. Therefore all experiments in survival analysis must include a baseline model that can produce a reference value in order to derive meaningful results. A suitable baseline model is the Kaplan-Meier estimator (Graf and Schumacher 1995; Lawless and Yuan 2010; Patrick Royston and Altman 2013), which is the simplest model that can consistently estimate the true survival function.

As well as directly comparing losses from a ‘sophisticated’ model to a baseline, one can

also compute the percentage increase in performance between the sophisticated and baseline models, which produces a measure of explained residual variation (ERV) (Edward L. Korn and Simon 1990; Edward L. Korn and Simon 1991). For any survival loss  $L$ , the ERV is,

$$R_L(S, B) = 1 - \frac{L|S}{L|B}$$


where  $L|S$  and  $L|B$  is the loss computed with respect to predictions from the sophisticated and baseline models respectively.

The ERV interpretation makes reporting of scoring rules easier within and between experiments. For example, say in experiment A we have  $L|S = 0.004$  and  $L|B = 0.006$ , and in experiment B we have  $L|S = 4$  and  $L|B = 6$ . The sophisticated model may appear worse at first glance in experiment A (as the losses are very close) but when considering the ERV we see that the performance increase is identical (both  $R_L = 33\%$ ), thus providing a clearer way to compare models.



## *Evaluating Survival Time*

TODO (150-200 WORDS)

 Minor changes expected!

**This page is a work in progress and minor changes will be made over time.**

When it comes to evaluating survival time predictions, there are few measures available at our disposal. As a result of survival time predictions being uncommon compared to other prediction types (Section 6.1), there are limited survival time evaluation measures in the literature. To our knowledge, there are no specialised ‘survival time measures’, instead regression measures are used by ignoring censored observations.

Before presenting these measures, consider what happens when censored observations are discarded. If censoring is truly independent, occurs randomly, and is *very* limited in the data, then there is little harm in discarding observations and treating this as a regression problem. However, if censoring is not independent, then discarding censored observations will lead to missing valuable insights about the model. For example, say the task of interest is to predict the probability of death due to kidney failure and patients are censored if they receive a transplant - this is clearly a competing risk as receiving a transplant greatly reduces the probability of death. If one were to predict the time to death for all patients and to not evaluate the quality of prediction for censored patients, then it would only be possible to conclude about the model’s performance for those who do not receive a transplant. On the surface this may appear to be of value, however, if at the time of prediction it is impossible to know who will receive a transplant (perhaps because the dataset omits relevant information such as time of hospital admission, wait on register, etc.), then for a given prediction for an observation, it would be impossible to know if the prediction is trustworthy - it would be if that patient does not receive a transplant, but would not be if they do not. In short, it is essential that predictions for individuals who end up being censored, are as good as those who are not, simply because there is no method to know which group observations will eventually fall into.

It is interesting to consider if IPCW strategies would compensate for this deficiency, however as we were unable to find research into this method, we have only included measures that we term ‘censoring-ignored regression measures’, which are presented in (P. Wang, Li, and Reddy 2019).

### 11.1 Distance measures

Survival time measures are often referred to as ‘distance’ measures as they measure the distance between the true,  $(t, \delta = 1)$ , and predicted,  $\hat{t}$ , values. These are presented in turn with brief descriptions of their interpretation.

#### Censoring-ignored mean absolute error, $MAE_C$

In regression, the mean absolute error (MAE) is a popular measure because it is intuitive to understand as it measures the absolute difference between true and predicted outcomes; hence intuitively one can understand that a model predicting a height of 175cm is clearly better than one predicting a height of 180cm, for a person with true height of 174cm.

$$MAE_C(\hat{\mathbf{t}}, \mathbf{t}, \delta) = \frac{1}{d} \sum_{i=1}^m \delta_i |t_i - \hat{t}_i|$$

Where  $d$  is the number of uncensored observations in the dataset,  $d = \sum_i \delta_i$ .

#### Censoring-ignored mean squared error

In comparison to MAE, the mean squared error (MSE), computes the squared differences between true and predicted values. While the MAE provides a smooth, linear, ‘penalty’ for increasingly poor predictions (i.e., the difference between an error of predicting 2 vs. 5 is still 3), but the square in the MSE means that larger errors are quickly magnified (so the difference in the above example is 9). By taking the mean over all predictions, the effect of this inflation is to increase the MSE value as larger mistakes are made.

$$MSE_C(\hat{\mathbf{t}}, \mathbf{t}, \delta) = \frac{1}{d} \sum_{i=1}^m \delta_i (t_i - \hat{t}_i)^2$$

Where  $d$  is again the number of uncensored observations in the dataset,  $d = \sum_i \delta_i$ .

#### Censoring-adjusted root mean squared error

Finally, the root mean squared error (RMSE), is simply the square root of the MSE. This allows interpretation on the original scale (as opposed to the squared scale produced by the MSE). Given the inflation effect for the MSE, the RMSE will be larger than the MAE as increasingly poor predictions are made; it is common practice for the MAE and RMSE to be reported together.

$$RMSE_C(\hat{\mathbf{t}}, \mathbf{t}, \delta) = \sqrt{MSE_C(\hat{\mathbf{t}}, \mathbf{t}, \delta)}$$

### 11.2 Over- and under-predictions

All of these distance measures assume that the error for an over-prediction ( $\hat{t} > t$ ) should be equal to an under-prediction ( $\hat{t} < t$ ), i.e., that it is ‘as bad’ if a model predicts an outcome time being 10 years longer than the truth compared to being 10 years shorter. In

the survival setting, this assumption is often invalid as it is generally preferred for models to be overly cautious, hence to predict negative events to happen sooner (e.g., predict a life-support machine fails after three years not five if the truth is actually four) and to predict positive events to happen later (e.g., predict a patient recovers after four years not two if the truth is actually three). A simple method to incorporate this imbalance between over- and under-predictions is to add a weighting factor to any of the above measures, for example the  $MAE_C$  might become

$$MAE_C(\hat{\mathbf{t}}, \mathbf{t}, \delta, \lambda, \mu, \phi) = \frac{1}{d} \sum_{i=1}^m \delta_i |(t_i - \hat{t}_i)[\lambda \mathbb{I}(t_i > \hat{t}_i) + \mu \mathbb{I}(t_i < \hat{t}_i) + \phi \mathbb{I}(t_i = \hat{t}_i)]|$$

where  $\lambda, \mu, \phi$  are any Real number to be used to weight over-, under-, and exact-predictions, and  $d$  is as above. The choice of these are highly context dependent and could even be tuned.




# 12

---

## *Choosing Measures*

---

TODO (150-200 WORDS)

 Minor changes expected!

**This page is a work in progress and minor changes will be made over time.**

After reading this part of the book, evaluating survival analysis models may appear more daunting than regression and classification settings, which, in contrast, have fewer (common) measures to choose from. In regression problems, the RMSE and MAE are common choices for evaluating how far predictions are from the truth. In classification, the Brier score or logloss may be used to evaluate probabilistic predictions and the accuracy score or TPR/TNR/FPR/FNR are common for deterministic predictions. In contrast, there are many more measures in survival analysis which are necessarily more complex, due to the need to handle censoring with many possible methods for doing so. Therefore, this final chapter aims to provide some simple to follow guidelines for selecting measures for different types of experiments.

---

### 12.1 Defining the experiment

Experiments may be performed to make predictions for new data, compare the performance of multiple models ('benchmark experiments'), investigate patterns in observed data, or some combination of these. Each experiment requires different choices of measures, with different levels of strictness applied to measure assumptions.

#### 12.1.1 Predictive experiments

In the real world, predictive experiments are most common. These are now daily occurrences as machine learning models are routinely deployed on servers to make ongoing predictions. In these cases, the exact task must be precisely stated before any model is deployed and evaluated. Common survival problems to solve include:

1. Identifying low and high risk groups in new data (for resource allocation);
2. Predicting the survival distribution for an individual over time; and
3. Predicting the survival probability for an individual at a specific time.

The first of these is a discrimination problem and it is therefore most important that the model optimises corresponding measures and that measure assumptions are justified. However, even this task may be more complex than it initially seems. For example, while some papers have shown flaws in Harrell's C (Gönen and Heller 2005; Rahman et al. 2017; Schmid and Potapov 2012; Uno et al. 2007), others have demonstrated that common alternatives yield very similar results (Rahman et al. 2017; Therneau and Atkinson 2020) and moreover some prominent alternatives may be harder to interpret due to high variance (Rahman et al. 2017; Schmid and Potapov 2012). In predictive experiment that may require more level of automation, it is important to be careful of C-hacking (Section 8.1.2) and to avoid overoptimistic results. Hence one should not compute a range of concordance indices and report the maximum but instead calculate a single discrimination measure and then establish a pre-defined threshold to determine if the deployed model is optimal, a natural threshold would be 0.5 as anything above this is better than a baseline model. Given Harrell's C to be increasingly over-optimistic with additional censoring (Rahman et al. 2017), it is advisable to use Uno's C instead.

If the task of interest is to predict survival distributions *over time*, then the choice of measure is more limited and only the RCLL and the proper Graf score are recommended. Both these measures can only be interpreted with respect to a baseline so use of the ERV representation is strongly recommended. As with the previous task, establishing a threshold for performance is essential prior to deployment and for ongoing evaluation. It is less clear in these cases what this threshold might be, but the simplest starting point would be to ensure that the model continues to outperform the baseline or a simpler gold-standard model (e.g., the Cox PH).

The final task of interest differs from the previous by only making predictions at a specific time. In this case, prediction error curves, and single-time point calibration measures can be used, as well as scoring rules with shorter cut-offs (i.e., the upper limit of the integral). It is imperative that model performance is never extrapolated outside of the pre-specified time.

### 12.1.2 Benchmark experiments

When conducting benchmark experiments, it is advisable to use a spread of measures so that results can be compared across various properties. In this case, models should be tested against discrimination, calibration, and overall predictive ability (i.e., with scoring rules). As models make different types of predictions, results from these experiments should be limited to metrics that are directly comparable, in other words, two models should only be compared based on the *same* metric. In benchmark experiments, models are compared across the same data and same resampling strategy, hence measure assumptions become less important as they are equally valid or flawed for all models. For example, if one dataset has particularly high amounts of censoring leading to an artificially higher concordance index, then this bias would affect all models equally and the overall experiment would not be affected. Hence, in these experiments it suffices to pick one or two measures for concordance, discrimination, and predictive ability, without having to be overly concerned with the individual metric.

This book recommends using Harrell's C and Uno's C for concordance as these are simplest to compute and including both enables more confidence in model comparison, i.e., if a model outperforms another with respect to both these measures then there can be higher confidence in drawing statements about the model's discriminatory power. For calibration, D-calibration is recommended as it can be meaningfully compared between models, and the RCLL is recommended for a scoring rule (which is proper for outcome-independent

censoring). No distance measure is recommended as these do not apply to the vast majority of models. All these measures can be used for automated tuning, in the case of discrimination tuning to Harrell's C alone should suffice (without also tuning to Uno's C).

### 12.1.3 Investigation

Investigating patterns in observed data is increasingly common as model interpretability methods have become more accessible (Molnar 2019). Before data can be investigated, any model that is trained on the data must first be demonstrated to be a good fit to the data. A model's fit to data can also be evaluated by resampling the data (Chapter 3) and evaluating the predictions. In this case, it is important to choose measures that are interpretable and have justified assumptions. Calibration measures are particularly useful for evaluating if a model is well fit to data, and any of the methods described in Chapter 9 are recommended for this purpose. Discrimination measures *may* be useful, however, given how susceptible they are to censoring, they can be difficult to interpret on their own, and the same is true for scoring rules. One method to resolve ambiguity is to perform a benchmark experiment of multiple models on the same data (ideally with some automated tuning) and then select the best model from this experiment and refit it on the full data (Becker, Schneider, and Fischer 2024) – this is a robust, empirical method that demonstrates a clear trail to selecting a model that outperforms other potential candidates. When investigating a dataset, one may also consider using different measures to assess algorithmic fairness (R. Sonabend et al. 2022), any measure that can be optimised (i.e., where the lowest or highest value is the best) may be used in this case. Finally, there are survival adaptations to the well-known AIC (Liang and Zou 2008) and BIC (Volinsky and Raftery 2000) however as these are generally only applicable to 'classical' models (Chapter 13), they are out of scope for this book and hence have not been discussed.

---

## 12.2 Conclusions

This part of the book focused on survival measures. Measures may be used to evaluate model predictions, to tune a model, or to train a model (e.g., in boosting or neural networks). Unlike other settings, there are many different choices of survival measures and it can be hard to determine which to use and when. In practice, like many areas of Statistics, the most important factor is to clearly define any experiment upfront and to be clear about which measures will be used and why. As a rule of thumb, good choices for measures are Harrell's C for evaluating discrimination, with Uno's C supporting findings, D-calibration for calibration, and the RCLL for evaluating overall predictive ability from distribution predictions. Finally, if you are restricted to a single measure choice (e.g., for automated tuning or continuous evaluation of deployed models), then we recommended selecting a scoring rule such as RCLL which captures information about calibration and discrimination simultaneously.





## Part III

# Models



# 13

## *Classical Models*

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

TODO

- change chapter name (don't use "classical")
- 

### 13.1 A Review of Classical Survival Models

This chapter provides a brief review of classical survival models before later chapters move on to machine learning models. 'Classical' models are defined with a very narrow scope in this book: low-complexity models that are either non-parametric or have parameters that can be fit with maximum likelihood estimation (or an equivalent method). In contrast, 'machine learning' (ML) models require more intensive model fitting procedures such as recursion or iteration. The classical models in this paper are fast to fit and highly interpretable, though can be inflexible and may make unreasonable assumptions. Whereas the ML models are more flexible with hyper-parameters however are computationally more intensive (both in terms of speed and storage), require tuning to produce 'good' results, and are often a 'black-box' with difficult interpretation.

As classical survival models have been studied extensively for decades, these are only discussed briefly here, primarily these are of interest as many of these models will be seen to influence machine learning extensions. The scope of the models discussed in this chapter is limited to the general book scope (**?@sec-surv-scope**), i.e. single event with right-censoring and no competing-risks, though in some cases these are discussed.

There are several possible taxonomies for categorising statistical models, these include:

- Parametrisation Type: One of non-, semi-, or fully-parametric. \ Non-parametric models assume that the data distribution cannot be specified with a finite set of parameters. In

contrast, fully-parametric models assume the distribution can be specified with a finite set of parameters. Semi-parametric models are a hybrid of the two and are formed of a finite set of parameters *and* an infinite-dimensional ‘nuisance’ parameter.

- **Conditionality Type:** One of unconditional or conditional. A conditional prediction is one that makes use of covariates in order to condition the prediction on each observation. Unconditional predictors, which are referred to below as ‘estimators’, ignore covariate data and make the same prediction for all individuals.
- **Prediction Type:** One of ranking, survival time, or distribution (Section 6.1).

Table 13.1 summarises the models discussed below into the taxonomies above for reference. Note that the Cox model is listed as predicting a continuous ranking, and not a survival distribution, which may appear inconsistent with other definitions. The reason for this is elaborated upon in Chapter 21. Though the predict-type taxonomy is favoured throughout this book, it is clearer to review classical models in increasing complexity, beginning with unconditional estimators before moving onto semi-parametric continuous ranking predictions, and finally conditional distribution predictors. The review is brief with mathematics limited to the model fundamentals but not including methods for parameter estimation. Also the review is limited to the ‘basic’ model specification and common extensions such as regularization are not discussed though they do exist for many of these models.

All classical models are highly transparent and accessible, with decades of research and many off-shelf implementations. Predictive performance of each model is briefly discussed as part of the review and then again in (R. E. B. Sonabend 2021).

Table 13.1: Table of models discussed in this literature review, classified by parametrisation, prediction type, and conditionality.

| Model <sup>1</sup>       | Parametrisation <sup>2</sup> | Prediction <sup>3</sup> | Conditionality |
|--------------------------|------------------------------|-------------------------|----------------|
| Kaplan-Meier             | Non                          | Distr.                  | Unconditional  |
| Nelson-Aalen             | Non                          | Distr.                  | Unconditional  |
| Akritas                  | Non                          | Distr.                  | Conditional    |
| Cox PH                   | Semi                         | Rank                    | Conditional    |
| Parametric PH            | Fully                        | Distr.                  | Conditional    |
| Accelerated Failure Time | Fully                        | Distr.                  | Conditional    |
| Proportional Odds        | Fully                        | Distr.                  | Conditional    |
| Flexible Spline          | Fully                        | Distr.                  | Conditional    |

\* 1. All models are implemented in the R package **survival** (Therneau 2015) with the exception of flexible splines, implemented in **flexsurv** (C. Jackson 2016), and the Akritas estimator in **survivalmodels** (R. Sonabend 2020). \* 2. Non = non-parametric, Semi = semi-parametric, Fully = fully-parametric. \* 3. Distr. = distribution, Rank = ranking.

### 13.1.1 Non-Parametric Distribution Estimators

#### Unconditional Estimators

Unconditional non-parametric survival models assume no distribution for survival times and estimate the survival function using simple algorithms based on observed outcomes and no covariate data. The two most common methods are the Kaplan-Meier estimator (**KaplanMeier1958?**), which estimates the average survival function of a training dataset,

and the Nelson-Aalen estimator (Aalen 1978; Nelson 1972), which estimates the average cumulative hazard function of a training dataset.

The Kaplan-Meier estimator of the survival function is given by

$$\hat{S}_{KM}(\tau|\mathcal{D}_{train}) = \prod_{t \in \mathcal{U}_O, t \leq \tau} \left(1 - \frac{d_t}{n_t}\right) \quad (13.1)$$

As this estimate is so important in survival models, this book will always use the symbol  $\hat{S}_{KM}$  to refer to the Kaplan-Meier estimate of the average survival function fit on training data  $(T_i, \Delta_i)$ . Another valuable function is the Kaplan-Meier estimate of the average survival function of the *censoring* distribution, which is the same as above but estimated on  $(T_i, 1 - \Delta_i)$ , this will be denoted by  $\hat{G}_{KM}$ .

The Nelson-Aalen estimator for the cumulative hazard function is given by

$$\hat{H}(\tau|\mathcal{D}_{train}) = \sum_{t \in \mathcal{U}_O, t \leq \tau} \frac{d_t}{n_t} \quad (13.2)$$

The primary advantage of these models is that they rely on heuristics from empirical outcomes only and don't require any assumptions about the form of the data. To train the models they only require  $(T_i, \Delta_i)$  and both return a prediction of  $\mathcal{S} \subseteq \text{Distr}(\mathcal{T})$  (**box-task-surv?**). In addition, both simply account for censoring and can be utilised in fitting other models or to estimate unknown censoring distributions. The Kaplan-Meier and Nelson-Aalen estimators are both consistent estimators for the survival and cumulative hazard functions respectively.

Utilising the relationships provided in (Section 6.1), one could write the Nelson-Aalen estimator in terms of the survival function as  $\hat{S}_{NA} = \exp(-\hat{H}(\tau|\mathcal{D}_{train}))$ . It has been demonstrated that  $\hat{S}_{NA}$  and  $\hat{S}_{KM}$  are asymptotically equivalent, but that  $\hat{S}_{NA}$  will provide larger estimates than  $\hat{S}_{KM}$  in smaller samples (Colosimo et al. 2002). In practice, the Kaplan-Meier is the most widely utilised non-parametric estimator in survival analysis and is the simplest estimator that yields consistent estimation of a survival distribution; it is therefore a natural, and commonly utilised, 'baseline' model (Harald Binder and Schumacher 2008; Herrmann et al. 2021; Huang et al. 2020a; P. Wang, Li, and Reddy 2019): estimators that other models should be 'judged' against to ascertain their overall performance (Chapter 7).

Not only can these estimators be used for analytical comparison, but they also provide intuitive methods for graphical calibration of models (Section 9.2). These models are never studied for prognosis directly but as baselines, components of complex models (Chapter 21), or graphical tools (Habibi et al. 2018; Jager et al. 2008; Moghimi-dehkordi et al. 2008). The reason for this is due to them having poor predictive performance as a result of omitting explanatory variables in fitting. Moreover, if the data follows a particular distribution, parametric methods will be more efficient (P. Wang, Li, and Reddy 2019).

### Conditional Estimators

The Kaplan-Meier and Nelson-Aalen estimators are simple to compute and provide good estimates for the survival time distribution but in many cases they may be overly-simplistic. Conditional non-parametric estimators include the advantages described above (no assumptions about underlying data distribution) but also allow for conditioning the estimation on the covariates. This is particularly useful when estimating a censoring distribution that

may depend on the data (Chapter 7). However predictive performance of conditional non-parametric estimators decreases as the number of covariates increases, and these models are especially poor when censoring is feature-dependent (Gerds and Schumacher 2006).

The most widely used conditional non-parametric estimator for survival analysis is the Akritas estimator (Akritas 1994) defined by<sup>1</sup>

$$\hat{S}(\tau|X^*, \mathcal{D}_{train}, \lambda) = \prod_{j: T_j \leq \tau, \Delta_j = 1} \left( 1 - \frac{K(X^*, X_j|\lambda)}{\sum_{l=1}^n K(X^*, X_l|\lambda) \mathbb{I}(T_l \geq T_j)} \right)$$

where  $K$  is a kernel function, usually  $K(x, y|\lambda) = \mathbb{I}(|\hat{F}_X(x) - \hat{F}_X(y)| < \lambda)$ ,  $\lambda \in (0, 1]$ ,  $\hat{F}_X$  is the empirical distribution function of the training data,  $X_1, \dots, X_n$ , and  $\lambda$  is a hyper-parameter. The estimator can be interpreted as a conditional Kaplan-Meier estimator which is computed on a neighbourhood of subjects closest to  $X^*$  (Blanche, Dartigues, and Jacqmin-Gadda 2013). To account for tied survival times, the following adaptation of the estimator is utilised (Blanche, Dartigues, and Jacqmin-Gadda 2013)

$$\hat{S}(\tau|X^*, \mathcal{D}_{train}, \lambda) = \prod_{t \in \mathcal{U}_O, t \leq \tau} \left( 1 - \frac{\sum_{j=1}^n K(X^*, X_j|\lambda) \mathbb{I}(T_j = t, \Delta_j = 1)}{\sum_{j=1}^n K(X^*, X_j|\lambda) \mathbb{I}(T_j \geq t)} \right) \quad (13.3)$$

If  $\lambda = 1$  then  $K(\cdot|\lambda) = 1$  and the estimator is identical to the Kaplan-Meier estimator.

The non-parametric nature of the model is highlighted in (Equation 13.3), in which both the fitting and predicting stages are combined into a single equation. A new observation,  $X^*$ , is compared to its nearest neighbours from a training dataset,  $\mathcal{D}_{train}$ , without a separated fitting procedure. One could consider splitting fitting and predicting in order to clearly separate between training and testing data. In this case, the fitting procedure is the estimation of  $\hat{F}_X$  on training data and the prediction is given by (Equation 13.3) with  $\hat{F}_X$  as an argument. This separated fit/predict method is implemented in **survivalmodels** (R. Sonabend 2020). As with other non-parametric estimators, the Akritas estimator can still be considered transparent and accessible. With respect to predictive performance, the Akritas estimator has more explanatory power than non-parametric estimators due to conditioning on covariates, however this is limited to a very small number of variables and therefore this estimator is still best placed as a conditional baseline.

### 13.1.2 Continuous Ranking and Semi-Parametric Models: Cox PH

The Cox Proportional Hazards (CPH) (Cox 1972), or Cox model, is likely the most widely known semi-parametric model and the most studied survival model (Habibi et al. 2018; Moghimi-dehkordi et al. 2008; Reid 1994; P. Wang, Li, and Reddy 2019). The Cox model assumes that the hazard for a subject is proportionally related to their explanatory variables,  $X_1, \dots, X_n$ , via some baseline hazard that all subjects in a given dataset share (‘the PH assumption’). The hazard function in the Cox PH model is defined by

$$h(\tau|X_i) = h_0(\tau) \exp(X_i\beta)$$

where  $h_0$  is the non-negative *baseline hazard function* and  $\beta = \beta_1, \dots, \beta_p$  where  $\beta_i \in \mathbb{R}$  are coefficients to be fit. Note the proportional hazards (PH) assumption can be seen as

<sup>1</sup>Arguments and parameters are separated in function signatures by a pipe, ‘|’, where variables to the left are parameters (free variables) and those to the right are arguments (fixed). In this equation,  $\tau$  is a parameter to be set by the user, and  $X^*, \mathcal{D}_{train}, \lambda$  are fixed arguments. This could therefore be simplified to  $\hat{S}(\tau)$  to only include free variables.

the estimated hazard,  $h(\tau|X_i)$ , is directly proportional to the model covariates  $\exp(X_i\beta)$ . Whilst a form is assumed for the ‘risk’ component of the model,  $\exp(X_i\beta)$ , no assumptions are made about the distribution of  $h_0$ , hence the model is semi-parametric.

The coefficients,  $\beta$ , are estimated by maximum likelihood estimation of the ‘partial likelihood’ (Cox 1975), which only makes use of ordered event times and does not utilise all data available (hence being ‘partial’). The partial likelihood allows study of the informative  $\beta$ -parameters whilst ignoring the nuisance  $h_0$ . The predicted linear predictor,  $\hat{\eta} := X^*\hat{\beta}$ , can be computed from the estimated  $\hat{\beta}$  to provide a ranking prediction.

Inspection of the model is also useful without specifying the full hazard by interpreting the coefficients as ‘hazard ratios’. Let  $p = 1$  and  $\hat{\beta} \in \mathbb{R}$  and let  $X_i, X_j \in \mathbb{R}$  be the covariates of two training observations, then the *hazard ratio* for these observations is the ratio of their hazard functions,

$$\frac{h(\tau|X_i)}{h(\tau|X_j)} = \frac{h_0(\tau) \exp(X_i\hat{\beta})}{h_0(\tau) \exp(X_j\hat{\beta})} = \exp(\hat{\beta})^{X_i - X_j}$$

If  $\exp(\hat{\beta}) = 1$  then  $h(\tau|X_i) = h(\tau|X_j)$  and thus the covariate has no effect on the hazard. If  $\exp(\hat{\beta}) > 1$  then  $X_i > X_j \rightarrow h(\tau|X_i) > h(\tau|X_j)$  and therefore the covariate is positively correlated with the hazard (increases risk of event). Finally if  $\exp(\hat{\beta}) < 1$  then  $X_i > X_j \rightarrow h(\tau|X_i) < h(\tau|X_j)$  and the covariate is negatively correlated with the hazard (decreases risk of event).

Interpreting hazard ratios is known to be a challenge, especially by clinicians who require simple statistics to communicate to patients (Sashegyi and Ferry 2017; Spruance et al. 2004). For example the full interpretation of a hazard ratio of ‘2’ for binary covariate  $X$  would be: ‘assuming that the risk of death is constant at all time-points then the instantaneous risk of death is twice as high in a patient with  $X$  than without’. Simple conclusions are limited to stating if patients are at more or less risk than others in their cohort. Further disadvantages of the model also lie in its lack of real-world interpretability, these include (Reid 1994):

- the PH assumption may not be realistic and the risk of event may not be constant over time;
- the estimated baseline hazard from a non-parametric estimator is a discrete step-function resulting in a discrete survival distribution prediction despite time being continuous; and
- the estimated baseline hazard will be constant after the last observed time-point in the training set (Gelfand et al. 2000).

Despite these disadvantages, the model has been demonstrated to have excellent predictive performance and routinely outperforms (or at least does not underperform) sophisticated ML models (Michael F. Gensheimer and Narasimhan 2018; Luxhoj and Shyur 1997; Van Belle et al. 2011) (and (R. E. B. Sonabend 2021)). Its simple form and wide popularity mean that it is also highly transparent and accessible.

The next class of models address some of the Cox model disadvantages by making assumptions about the baseline hazard.

### 13.1.3 Conditional Distribution Predictions: Parametric Linear Models

#### Parametric Proportional Hazards

The CPH model can be extended to a fully parametric PH model by substituting the unknown baseline hazard,  $h_0$ , for a particular parameterisation. Common choices for dis-

tributions are Exponential, Weibull and Gompertz (John D. Kalbfleisch and Prentice 2011; P. Wang, Li, and Reddy 2019); their hazard functions are summarised in ((**tab-survivaldists?**)) along with the respective parametric PH model. Whilst an Exponential assumption leads to the simplest hazard function, which is constant over time, this is often not realistic in real-world applications. As such the Weibull or Gompertz distributions are often preferred. Moreover, when the shape parameter,  $\gamma$ , is 1 in the Weibull distribution or 0 in the Gompertz distribution, their hazards reduce to a constant risk ((Figure 13.1)). As this model is fully parametric, the model parameters can be fit with maximum likelihood estimation, with the likelihood dependent on the chosen distribution.

Table 13.2: Exponential, Weibull, and Gompertz hazard functions and PH specification.

| Distribution <sup>1</sup>     | $h_0(\tau)^2$                  | $h(\tau X_i)^3$                               |
|-------------------------------|--------------------------------|---|
| Exp( $\lambda$ )              | $\lambda$                      | $\lambda \exp(X_i\beta)$                      |
| Weibull( $\gamma, \lambda$ )  | $\lambda\gamma\tau^{\gamma-1}$ | $\lambda\gamma\tau^{\gamma-1} \exp(X_i\beta)$ |
| Gompertz( $\gamma, \lambda$ ) | $\lambda \exp(\gamma\tau)$     | $\lambda \exp(\gamma\tau) \exp(X_i\beta)$     |

\* 1. Distribution choices for baseline hazard.  $\gamma, \lambda$  are shape and scale parameters respectively.

\* 2. Baseline hazard function, which is the (unconditional) hazard of the distribution. \* 3. PH hazard function,  $h(\tau|X_i) = h_0(\tau) \exp(X_i\beta)$ .

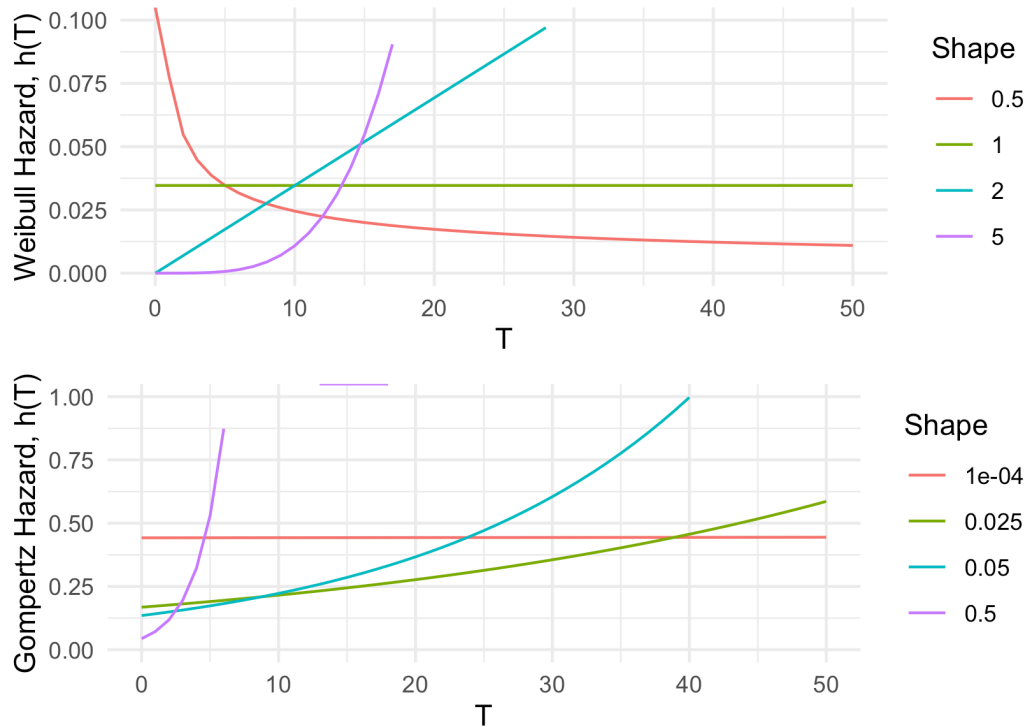


Figure 13.1: Comparing the hazard curves under Weibull and Gompertz distributions for varying values of the shape parameter; scale parameters are set so that each parametrisation has a median of 20. x-axes are time and y-axes are Weibull (top) and Gompertz (bottom) hazards as a function of time.



In the literature, the Weibull distribution tends to be favoured as the initial assumption for the survival distribution (Michael F. Gensheimer and Narasimhan 2018; Habibi et al. 2018; Hielscher et al. 2010; R. and J. 1968; Rahman et al. 2017), though Gompertz is often tested in death-outcome models for its foundations in modelling human mortality (Gompertz 1825). There exist many tests for checking the goodness-of-model-fit (**?@sec-eval-insample**) and the distribution choice can even be treated as a model hyper-parameter. Moreover it transpires that model inference and predictions are largely insensitive to the choice of distribution (Collett 2014; Reid 1994). In contrast to the Cox model, fully parametric PH models can predict absolutely continuous survival distributions, they do not treat the baseline hazard as a nuisance, and in general will result in more precise and interpretable predictions if the distribution is correctly specified (Reid 1994; Patrick Royston and Parmar 2002).

Whilst misspecification of the distribution tends not to affect predictions too greatly, PH models will generally perform worse when the PH assumption is not valid. PH models can be extended to include time-varying coefficients or model stratification (Cox 1972) but even with these adaptations the model may not reflect reality. For example, the predicted hazard in a PH model will be either monotonically increasing or decreasing but there are many scenarios where this is not realistic, such as when recovering from a major operation where risks tends to increase in the short-term before decreasing. Accelerated failure time models overcome this disadvantage and allow more flexible modelling, discussed next.

### Accelerated Failure Time

In contrast to the PH assumption, where a unit increase in a covariate is a multiplicative increase in the hazard rate, the Accelerated Failure Time (AFT) assumption means that a unit increase in a covariate results in an acceleration or deceleration towards death (expanded on below). The hazard representation of an AFT model demonstrates how the interpretation of covariates differs from PH models,

$$h(\tau|X_i) = h_0(\exp(-X_i\beta)\tau) \exp(-X_i\beta)$$

where  $\beta = (\beta_1, \dots, \beta_p)$  are model coefficients. In contrast to PH models, the ‘risk’ component,  $\exp(-X_i\beta)$ , is the exponential of the *negative* linear predictor and therefore an increase in a covariate value results in a decrease of the predicted hazard. This representation also highlights how AFT models are more flexible than PH as the predicted hazard can be non-monotonic. For example the hazard of the Log-logistic distribution ((Figure 13.2)) is highly flexible depending on chosen parameters. Not only can the AFT model offer a wider range of shapes for the hazard function but it is more interpretable. Whereas covariates in a PH model act on the hazard, in an AFT they act on time, which is most clearly seen in the log-linear representation,

$$\log Y_i = \mu + \alpha_1 X_{i1} + \alpha_2 X_{i2} + \dots + \alpha_p X_{ip} + \sigma \epsilon_i$$

where  $\mu$  and  $\sigma$  are location and scale parameters respectively,  $\alpha_1, \dots, \alpha_p$  are model coefficients, and  $\epsilon_i$  is a random error term. In this case a one unit increase in covariate  $X_{ij}$  means a  $\alpha_j$  increase in the logarithmic survival time. For example if  $\exp(X_i\alpha) = 0.5$  then  $i$  ‘ages’ at double the baseline ‘speed’. Or less abstractly if studying the time until death from cancer then  $\exp(X_i\alpha) = 0.5$  can be interpreted as ‘the entire process from developing tumours to metastasis and eventual death in subject  $i$  is twice as fast than the normal’, where ‘normal’ refers to the baseline when all covariates are 0.

Specifying a particular distribution for  $\epsilon_i$  yields a fully-parametric AFT model. Common distribution choices include Weibull, Exponential, Log-logistic, and Log-Normal (John D.

Kalbfleisch and Prentice 2011; P. Wang, Li, and Reddy 2019). The Buckley-James estimator (Buckley and James 1979) is a semi-parametric AFT model that non-parametrically estimates the distribution of the errors however this model has no theoretical justification and is rarely fit in practice (Wei 1992). The fully-parametric model has theoretical justifications, natural interpretability, and can often provide a better fit than a PH model, especially when the PH assumption is violated (Patel, Kay, and Rowell 2006; Qi 2009; Zare et al. 2015).

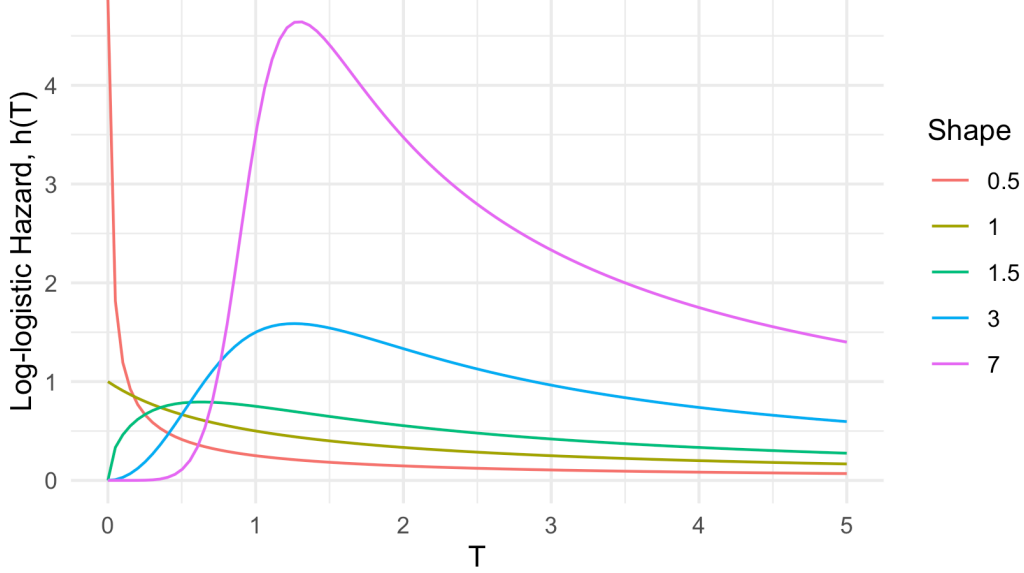


Figure 13.2: Log-logistic hazard curves with a fixed scale parameter of 1 and a changing shape parameter. x-axis is time and y-axis is the log-logistic hazard as a function of time.

### Proportional Odds

Proportional odds (PO) models (Bennett 1983) fit a proportional relationship between covariates and the odds of survival beyond a time  $\tau$ ,

$$O_i(\tau) = \frac{S_i(\tau)}{F_i(\tau)} = O_0(\tau) \exp(X_i\beta)$$

where  $O_0$  is the baseline odds.

In this model, a unit increase in a covariate is a multiplicative increase in the odds of survival after a given time and the model can be interpreted as estimating the log-odds ratio. There is no simple closed form expression for the partial likelihood of the PO model and hence in practice a Log-logistic distribution is usually assumed for the baseline odds and the model is fit by maximum likelihood estimation on the full likelihood (Bennett 1983).

Perhaps the most useful feature of the model is convergence of hazard functions (Kirmani and Gupta 2001), which states  $h_i(\tau)/h_0(\tau) \rightarrow 1$  as  $\tau \rightarrow \infty$ . This property accurately reflects real-world scenarios, for example if comparing chemotherapy treatment on advanced cancer survival rates, then it is expected that after a long period (say 10 years) the difference in risk between groups is likely to be negligible. This is in contrast to the PH model that assumes the hazard ratios are constant over time, which is rarely a reflection of reality.

In practice, the PO model is harder to fit and is less flexible than PH and AFT models, both of which can also produce odds ratios. This may be a reason for the lack of popularity of the PO model, in addition there is limited off-shelf implementations (Collett 2014). Despite PO models not being commonly utilised, they have formed useful components of neural networks (Section 18.1) and flexible parametric models (below).

### Flexible Parametric Models – Splines

Royston-Parmar flexible parametric models (Patrick Royston and Parmar 2002) extend PH and PO models by estimating the baseline hazard with natural cubic splines. The model was designed to keep the form of the PH or PO methods but without the semi-parametric problem of estimating a baseline hazard that does not reflect reality (see above), or the parametric problem of misspecifying the survival distribution.

To provide an interpretable, informative and smooth hazard, natural cubic splines are fit in place of the baseline hazard. The crux of the method is to use splines to model time on a log-scale and to either estimate the log cumulative Hazard for PH models,  $\log H(\tau|X_i) = \log H_0(\tau) + X_i\beta$ , or the log Odds for PO models,  $\log O(\tau|X_i) = \log O_0(\tau) + X_i\beta$ , where  $\beta$  are model coefficients to fit,  $H_0$  is the baseline cumulative hazard function and  $O_0$  is the baseline odds function. For the flexible PH model, a Weibull distribution is the basis for the baseline distribution and a Log-logistic distribution for the baseline odds in the flexible PO model.  $\log H_0(\tau)$  and  $\log O_0(\tau)$  are estimated by natural cubic splines with coefficients fit by maximum likelihood estimation. The standard full likelihood is optimised, full details are not provided here. Between one and three internal knots are recommended for the splines and the placement of knots does not greatly impact upon the fitted model (Patrick Royston and Parmar 2002).

Advantages of the model include being: interpretable, flexible, can be fit with time-dependent covariates, and it returns a continuous function. Moreover many of the parameters, including the number and position of knots, are tunable, although Royston and Parmar advised against tuning and suggest often only one internal knot is required (Patrick Royston and Parmar 2002). A recent simulation study demonstrated that even with an increased number of knots (up to seven degrees of freedom), there was little bias in estimation of the survival and hazard functions (Bower et al. 2019). Despite its advantages, a 2018 review (Ng et al. 2018) found only twelve instances of published flexible parametric models since Royston and Parmar’s 2002 paper, perhaps because it is more complex to train, has a less intuitive fitting procedure than alternatives, and has limited off-shelf implementations; i.e. is less transparent and accessible than parametric alternatives.

The PH and AFT models are both very transparent and accessible, though require slightly more expert knowledge than the CPH in order to specify the ‘correct’ underlying probability distribution. Interestingly whilst there are many papers comparing PH and AFT models to one another using in-sample metrics (`?@sec-eval-insample`) such as AIC (Georgousopoulou et al. 2015; Habibi et al. 2018; Moghimi-dehkordi et al. 2008; Zare et al. 2015), no benchmark experiments could be found for out-of-sample performance. PO and spline models are less transparent than PH and AFT models and are even less accessible, with very few implementations of either. No conclusions can be drawn about the predictive performance of PO or spline models due to a lack of suitable benchmark experiments.



TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

---

## 14.1 A Survey of Machine Learning Models for Survival Analysis

These next sections provide a technical, critical survey of machine learning models proposed for survival analysis with the focus on the ‘simpler’ setup of non-competing risks. Models are separated into their different ‘classes’ (1), which exists as a natural taxonomy in machine learning. Each class review is then further separated by first discussing the simpler and more standard regression setting, before expanding into their survival framework. The focus is once again on the different predict types of the model, which enables clear exposition and discussion around how some areas have successfully dealt with the survival predictive problem, whereas others have fallen short.

This is not the first survey of machine learning models for survival analysis. A recent 2017 survey (P. Wang, Li, and Reddy 2019) focused on covering the breadth of machine learning models for survival analysis and this survey is recommended to the reader as a strong starting point to understand which ML models are available for survival analysis. However whilst this provides a comprehensive review and a ‘big-picture’ view, there is no discussion about how successful the discussed models are in solving the survival task.

A comprehensive survey of neural networks was presented by Schwarzer *et al.* (2000) (Schwarzer, Vach, and Schumacher 2010) in which the authors collected the many ways in which neural networks have been ‘misused’ in the context of survival analysis. This level of criticism is vital in the context of survival analysis and healthcare data as transparency and understanding are often prioritised over predictive performance. Whilst the survey in this book will try not to be as critical as the Schwarzer review, it will aim to discuss models and how well they actually solve the survival problem.

Historically, surveys have focused primarily on predictive performance, which is generally preferred for complex classification and regression tasks. However in the context of survival analysis, transparency is of the utmost importance and any model that does not solve the task it claims to, despite strong predictive performance, can be considered sub-optimal.

The survey will also examine the accessibility of survival models. A model need not be open-source to be accessible, but it should be ‘user-friendly’ and not require expert cross-domain knowledge. For example, a neural network may require knowledge of complex model building, but if set-up correctly could be handled without medical or survival knowledge. Whereas a Gaussian Process requires knowledge of the model class, simulation, (usually) Bayesian modelling, and also survival analysis.

- (1) provides information about the models reviewed in this survey, including a model reference for use in the (R. E. B. Sonabend 2021) benchmark experiment, the predict types of the model, and in which R package it is implemented.

Table 14.1: Summarising the models discussed in (Section 14.1) by their model class and respective survival task.

| Class <sup>1</sup> | Name <sup>2</sup> | Authors (Year) <sup>3</sup>   | Task <sup>4</sup> | Implementation <sup>5</sup>   |
|--------------------|-------------------|---|-------------------|---|
| RF                 | RRT               | LeBlanc and Crowley (1992)<br>(LeBlanc and Crowley 1992)                      | Rank              | <b>rpart</b> (Therneau and Atkinson 2019)   |
| RF                 | RSDF-DEV          | Hothorn <i>et al.</i> (2004) (Hothorn et al. 2004)                            | Prob.             | <b>ipred</b> (Peters and Hothorn 2019)  |
| RF                 | RRF               | Ishwaran <i>et al.</i> (2004) (H. Ishwaran et al. 2004)                       | Rank              | -   |
| RF                 | RSCIFF            | Hothorn <i>et al.</i> (2006) (Hothorn et al. 2005)                            | Det., Prob.       | <b>party</b> (Hothorn, Hornik, and Zeileis 2006), <b>partykit</b> (Hothorn and Zeileis 2015)                  |
| RF                 | RSDF-STAT         | Ishwaran <i>et al.</i> (2008) (B. H. Ishwaran et al. 2008)                    | Prob.             | <b>randomForestSRC</b> (H. Ishwaran and Kogalur 2018), <b>ranger</b> (Wright and Ziegler 2017)                |
| GBM                | GBM-COX           | Ridgeway (1999) (Ridgeway 1999) & Buhlmann (2007) (Buhlmann and Hothorn 2007) | Prob.             | <b>mboost</b> (Hothorn et al. 2020), <b>xgboost</b> (T. Chen et al. 2020), <b>gbm</b> (Greenwell et al. 2019) |
| GBM                | CoxBoost          | Binder & Schumacher (2008) (Harald Binder and Schumacher 2008)                | Prob.             | <b>CoxBoost</b> (Harold Binder 2013)  |

| Class <sup>1</sup> | Name <sup>2</sup> | Authors (Year) <sup>3</sup>   | Task <sup>4</sup> | Implementation <sup>5</sup>             |
|--------------------|-------------------|---|-------------------|---|
| GBM                | GBM-AFT           | Schmid & Hothorn (2008) (Schmid and Hothorn 2008b)  | Det.              | <b>mboost</b> , <b>xgboost</b>          |
| GBM                | GBM-BUJAR         | Wang & Wang (2010) (Z. Wang and Wang 2010)  | Det.              | <b>bujar</b> (Z. Wang 2019)             |
| GBM                | GBM-GEH           | Johnson & Long (2011) (Johnson and Long 2011)   | Det.              | <b>mboost</b>                           |
| GBM                | GBM-UNO           | Mayr & Schmid (2014) (Mayr and Schmid 2014)   | Rank              | <b>mboost</b>                           |
| SVM                | SVCR              | Shivaswamy <i>et al.</i> (2007) (Shivaswamy, Chu, and Jansche 2007)   | Det.              | <b>survivalsvm</b> (Fouodo et al. 2018) |
| SVM                | SSVM-Rank         | Van Belle <i>et al.</i> (2007) (Van Belle et al. 2007)  | Rank              | <b>survivalsvm</b>                      |
| SVM                | SVRc              | Khan and Zubek (2008) (Khan and Bayer Zubek 2008)   | Det.              | -                                       |
| SVM                | SSVM-Hybrid       | Van Belle (2011) (Van Belle et al. 2011)  | Det.              | <b>survivalsvm</b>                      |
| SVM                | SSVR-MRL          | Goli <i>et al.</i> (2016) (Goli, Mahjub, Faradmal, and Soltanian 2016; Goli, Mahjub, Faradmal, Mashayekhi, et al. 2016) | Det.              | -                                       |
| ANN                | ANN-CDP           | Liestøl <i>et al.</i> (1994) (Liestøl, Andersen, and Andersen 1994)   | Prob.             | -                                       |
| ANN                | ANN-COX           | Faraggi and Simon (1995) (Faraggi and Simon 1995)   | Rank              | -                                       |
| ANN                | PLANN             | Biganzoli <i>et al.</i> (1998) (E. Biganzoli et al. 1998)   | Prob.             | -                                       |
| ANN                | COX-NNET          | Ching <i>et al.</i> (2018) (Ching, Zhu, and Garmire 2018)   | Prob.             | <b>cox-nnet*</b> (Ching 2015)           |

| Class <sup>1</sup> | Name <sup>2</sup> | Authors (Year) <sup>3</sup>  | Task <sup>4</sup> | Implementation <sup>5</sup>                           |
|--------------------|-------------------|--|-------------------|---|
| ANN                | DeepSurv          | Katzman <i>et al.</i> (2018) (J. L. Katzman et al. 2018)                   | Prob.             | <b>survivalmodels</b> (R. Sonabend 2020)              |
| ANN                | DeepHit           | Lee <i>et al.</i> (2018) (C. Lee et al. 2018)                              | Prob.             | <b>survivalmodels</b>                                 |
| ANN                | Nnet-survival     | Gensheimer & Narasimhan (2019) (Michael F. Gensheimer and Narasimhan 2019) | Prob.             | <b>survivalmodels</b>                                 |
| ANN                | Cox-Time          | Kvamme <i>et al.</i> (2019) (Kvamme, Borgan, and Scheel 2019)              | Prob.             | <b>survivalmodels</b>                                 |
| ANN                | PC-Hazard         | Kvamme & Borgan (2019) ( <b>Kvamme2019?</b> )                              | Prob.             | <b>survivalmodels</b>                                 |
| ANN                | RankDeepSurv      | Jing <i>et al.</i> (2019) (Jing et al. 2019)                               | Det.              | <b>RankDeepSurv</b> <sup>*,†</sup> (Jing et al. 2018) |
| ANN                | DNNSurv           | Zhao & Fend (2020) (Zhao and Feng 2020)                                    | Prob.             | <b>survivalmodels</b>                                 |

\* 1. Model Class. RSF – Random Survival Forest; GBM – Gradient Boosting Machine; SVM – Support Vector Machine; ANN – Artificial Neural Network. There is some abuse of notation here as some of the RSFs are actually decision trees and some GBMs do not use gradient boosting. \* 2. Model identifier used in this section and (R. E. B. Sonabend 2021). \* 3. Authors and year of publication, for RSFs this is the paper most attributed to the algorithm. \* 4. Survival task type: Deterministic (Det.), Probabilistic (Prob.), Ranking (Rank). \* 5. If available in R then the package in which the model is implemented, otherwise ‘\*’ signifies a model is only available in Python. With the exception of DNNSurv, all ANNs in **survivalmodels** are implemented from the Python package **pycox** (Kvamme 2018) with **reticulate** (Ushey, Allaire, and Tang 2020). \* † – Code available to create model but not implemented ‘off-shelf’.



# 15

## *Tree-Based Methods*

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

### 15.1 Random Forests

#### 15.1.1 Random Forests for Regression

Random forests are a composite algorithm built by fitting many simpler component models, decision trees, and then averaging the results of predictions from these trees. Decision trees are first briefly introduced before the key ‘bagging’ algorithm that composes these trees to a random forest. Woodland terminology is used throughout this subsection.

#### Decision Trees

Decision trees are a common model class in machine learning and have the advantage of being (relatively) simple to implement and highly interpretable. A decision tree takes a set of inputs and a given *splitting rule* in order to create a series of splits, or branches, in the tree that culminates in a final *leaf*, or *terminal node*. Each terminal node has a corresponding prediction, which for regression is usually the sample mean of the training outcome data. This is made clearer by example, (Figure 15.1) demonstrates a decision tree predicting the miles per gallon (`mpg`) of a car from the `mtcars` (Henderson and Velleman 1981) dataset. With this tree a new prediction is made by feeding the input variables from the top to the bottom, for example given new data,  $x = \{\text{wt} = 3, \text{disp} = 250\}$ , then in the first split the right branch is taken as  $\text{wt} = 3 > 2.32$  and in the second split the left branch is taken as  $\text{disp} = 250 \leq 258$ , therefore the new data point ‘lands’ in the final leaf and is predicted to have an `mpg` of 20.8. This value of 20.8 arises as the sample mean of `mpg` for the 11 (which can be seen in the box) observations in the training data who were sorted into this terminal node. Algorithmically, as splits are always binary, predictions are simply a series of conditional logical statements.

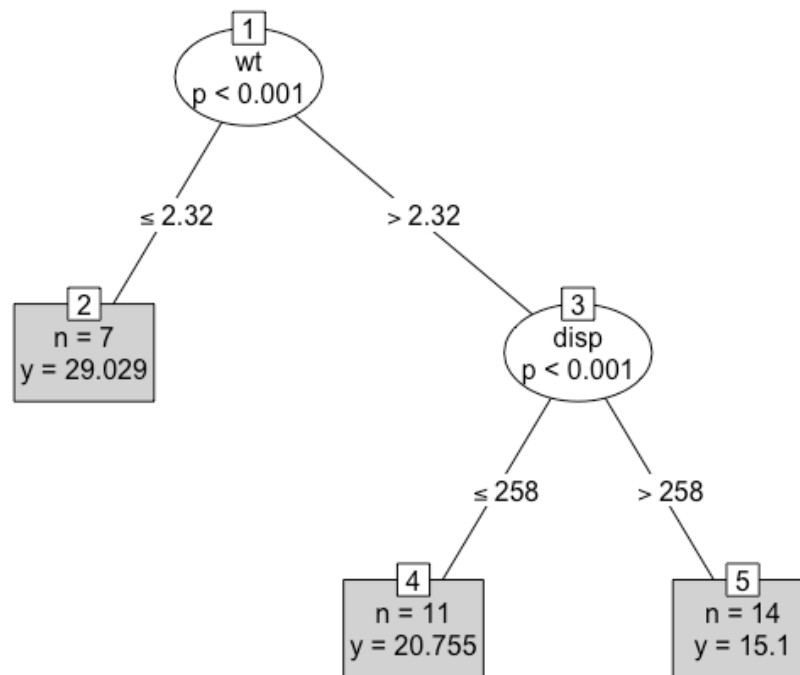


Figure 15.1: Demonstrating classification trees using the `mtcars` (Henderson and Velleman 1981) dataset and the `party` (Hothorn, Hornik, and Zeileis 2006) package. Ovals are leaves, which indicate the variable that is being split. Edges are branches, which indicate the cut-off at which the variable is split. Rectangles are terminal nodes and include information about the number of training observations in the node and the terminal node prediction.

### Splitting Rules

Precisely how the splits are derived and which variables are utilised is determined by the splitting rule.<sup>1</sup> In regression, the most common splitting rule is to select the cut-off for a given variable that minimises the mean squared error in each hypothetical resultant leaf. The goal is to find the variable and cutoff that leads to the greatest difference between the two resultant leaves and thus the maximal homogeneity within each leaf. For all decision tree and random forest algorithms going forward, let  $L$  denote some leaf, then let  $L_{xy}, L_x, L_y$  respectively be the set of observations, features, and outcomes in leaf  $L$ . Let  $L_{y,i}$  be the  $i$ th outcome in  $L_y$  and finally let  $L_{\bar{y}} = \frac{1}{n} \sum_{i=1}^n L_{y,i}$ . To simplify notation,  $i \in L$  is taken to be equivalent to  $i \in \{i : X_i \in L_X\}$ , i.e. the indices of the observations in leaf  $L$ .

Let  $c \in \mathbb{R}$  be some cutoff parameter and let  $L_{xy}^a(j, c) := \{(X_i, Y_i) | X_{ij} < c, i = 1, \dots, n\}$ ,  $L_{xy}^b(j, c) = \{(X_i, Y_i) | X_{ij} \geq c, i = 1, \dots, n\}$  be the two leaves containing the set of observations resulting from partitioning variable  $j$  at cutoff  $c$ . Then a split is determined by finding the arguments,  $(j^*, c^*)$  that minimise the sum of the mean squared errors (MSE) in both leaves (James et al. 2013),

$$(j^*, c^*) = \operatorname{argmin}_{j,c} \sum_{y \in L_y^a(j,c)} (y - L_{\bar{y}}^a(j,c))^2 + \sum_{y \in L_y^b(j,c)} (y - L_{\bar{y}}^b(j,c))^2 \quad (15.1)$$

This method is repeated from the first branch of the tree down to the very last such that observations are included in a given leaf  $L$  if they satisfy all conditions from all previous branches; features may be considered multiple times in the growing process. This is an intuitive method as minimising the above sum results in the set of observations within each individual leaf being as similar as possible, thus as an observation is passed down the tree, it becomes more similar to the subsequent leaves, eventually landing in a leaf containing homogeneous observations. Controlling how many variables to consider at each split and how many splits to make are determined by hyper-parameter tuning.

Decision trees are a powerful method for high-dimensional data as only a small sample of variables will be used for growing a tree, and therefore they are also useful for variable importance by identifying which variables were utilised in growth (other importance methods are also available). Decision trees are also highly interpretable, as demonstrated by (Figure 15.1). The recursive pseudo-algorithm in ((**alg-dt-fit?**)) demonstrates the simplicity in growing a decision tree (again methods such as pruning are omitted).

### Stopping Rules

The ‘stopping rule’ in ((**alg-dt-fit?**)) is usually a condition on the number of observations in each leaf such that leaves will continue to be split until some minimum number of observations has been reached in a leaf. Other conditions may be on the ‘depth’ of the tree, which corresponds to the number of levels of splitting, for example the tree in (Figure 15.1) has a depth of 2 (the first level is not counted).

### Random Forests

Despite being more interpretable than other machine learning methods, decision trees usually have poor predictive performance, high variance and are not robust to changes in the data. As such, *random forests* are preferred to improve prediction accuracy and decrease variance. Random forests utilise bootstrap aggregation, or *bagging* (Breiman 1996), to aggregate many decision trees. A pseudo fitting algorithm is given in ((**alg-rsf-fit?**)).

<sup>1</sup>Other methods for growing trees such as pruning are not discussed here as they are less relevant to random forests, which are primarily of interest. Instead see (e.g.) Breiman (1984) [Breiman1984].

Prediction from a random forest follows by making predictions from the individual trees and aggregating the results by some function  $\sigma$  (**alg-rsf-pred?**);  $\sigma$  is usually the sample mean for regression,

$$\hat{g}(X^*) = \sigma(\hat{g}_1(X^*), \dots, \hat{g}_B(X^*)) = \frac{1}{B} \sum_{b=1}^B \hat{g}_b(X^*)$$

where  $\hat{g}_b(X^*)$  is the terminal node prediction from the  $b$ th tree and  $B$  are the total number of grown trees (**B** is commonly used instead of  $N$  to note the relation to bootstrapped data).

Usually many (hundreds or thousands) trees are grown, which makes random forests robust to changes in data and ‘confident’ about individual predictions. Other advantages include having several tunable hyper-parameters, including: the number of trees to grow, the number of variables to include in a single tree, the splitting rule, and the minimum terminal node size. Machine learning models with many hyper-parameters, tend to perform better than other models as they can be fine-tuned to the data, which is why complex deep learning models are often the best performing. Although as a caveat: too many parameters can lead to over-fitting and tuning many parameters can take a long time and be highly intensive. Random forests lose the interpretability of decision trees and are considered ‘black-box’ models as individual predictions cannot be easily scrutinised.

### 15.1.2 Random Forests for Survival Analysis

Given time constraints and the scope of this book, this survey of random forests for survival analysis will primarily focus on ‘traditional’ decision trees and random forests and will not look at other sub-fields such as causal forests. A comprehensive review of random survival forests (RSFs) is provided in Bou-Hamad (2011) (Bou-Hamad, Larocque, and Ben-Ameur 2011), which includes extensions to time-varying covariates and different censoring types. In order to prevent overlap, this survey will focus primarily on methods that have off-shelf implementations, their prediction types, and how successfully these methods handle the problem of censoring. Random forests and decision trees for survival are termed from here as Random Survival Forests (RSFs) and Survival Decision Trees (SDTs) respectively.

Unlike other machine learning methods that may require complex changes to underlying algorithms, individual components of a random forest can be adapted without altering the fundamental algorithm. The principle random forest algorithm is unchanged for RSFs, the difference is in the choice of splitting rule and terminal node prediction, which both must be able to handle censoring. Therefore instead of discussing individual algorithms, the different choices of splitting rules and terminal node predictions are discussed, then combinations of these are summarised into five distinct algorithms.

#### 15.1.2.1 Splitting Rules

Survival trees and RSFs have been studied for the past four decades and whilst the amount of splitting rules to appear could be considered “numerous” (Bou-Hamad, Larocque, and Ben-Ameur 2011), only two broad classes are commonly utilised and implemented (H. Ishwaran and Kogalur 2018; Pölsterl 2020; Therneau and Atkinson 2019; Wright and Ziegler 2017). The first class rely on hypothesis tests, and primarily the log-rank test, to maximise dissimilarity between splits, the second class utilises likelihood-based measures. The first is discussed in more detail as this is common in practice and is relatively straightforward to implement and understand, moreover it has been demonstrated to outperform other splitting

rules (Bou-Hamad, Larocque, and Ben-Ameur 2011). Likelihood rules are more complex and require assumptions that may not be realistic, these are discussed briefly.

### Hypothesis Tests

The log-rank test statistic has been widely utilised as the ‘natural’ splitting-rule for survival analysis (Ciampi et al. 1986; B. H. Ishwaran et al. 2008; LeBlanc and Crowley 1993; Segal 1988). The log-rank test compares the survival distributions of two groups and has the null-hypothesis that both groups have the same underlying risk of (immediate) death, i.e. identical hazard functions.

Let  $L^A$  and  $L^B$  be two leaves then using the notation above let  $h^A, h^B$  be the (true) hazard functions derived from the observations in the two leaves respectively. The log-rank hypothesis test is given by  $H_0 : h^A = h^B$  with test statistic (Segal 1988),

$$LR(L^A) = \frac{\sum_{\tau \in \mathcal{U}_D} (d_\tau^A - e_\tau^A)}{\sqrt{\sum_{\tau \in \mathcal{U}_D} v_\tau^A}}$$

where  $d_\tau^A$  is the observed number of deaths in leaf  $A$  at  $\tau$ ,

$$d_\tau^A := \sum_{i \in L^A} \mathbb{I}(T_i = \tau, \Delta_i = 1)$$

$e_\tau^A$  is the expected number of deaths in leaf  $A$  at  $\tau$ ,

$$e_\tau^A := \frac{n_\tau^A d_\tau}{n_\tau}$$

and  $v_\tau^A$  is the variance of the number of deaths in leaf  $A$  at  $\tau$ ,

$$v_\tau^A := e_\tau^A \left( \frac{n_\tau - d_\tau}{n_\tau} \right) \left( \frac{n_\tau - n_\tau^A}{n_\tau - 1} \right)$$

where  $\mathcal{U}_D$  is the set of unique death times across the data (in both leaves),  $n_\tau = \sum_i \mathbb{I}(T_i \geq \tau)$  is the number of observations at risk at  $\tau$  in both leaves,  $n_\tau^A = \sum_{i \in L^A} \mathbb{I}(T_i \geq \tau)$  is the number of observations at risk at  $\tau$  in leaf  $A$ , and  $d_\tau = \sum_i \mathbb{I}(T_i = \tau, \Delta_i = 1)$  is the number of deaths at  $\tau$  in both leaves.

Intuitively these results follow as the number of deaths in a leaf is distributed according to  $\text{Hyper}(n_\tau^A, n_\tau, d_\tau)$ . The same statistic results if  $L^B$  is instead considered. ((**alg-dt-fit?**)) follows for fitting decision trees with the log-rank splitting rule,  $SR$ , to be maximised.

The higher the log-rank statistic, the greater the dissimilarity between the two groups, thereby making it a sensible splitting rule for survival, moreover it has been shown that it works well for splitting censored data (LeBlanc and Crowley 1993).<sup>2</sup> When censoring is highly dependent on the outcome, the log-rank statistic does not perform well and is biased (Bland and Altman 2004), which tends to be true of the majority of survival models. Additionally, the log-rank test requires no knowledge about the shape of the survival curves or distribution of the outcomes in either group (Bland and Altman 2004), making it ideal for an automated process that requires no user intervention.

---

<sup>2</sup>The results of this experiment are actually in LeBlanc’s unpublished 1989 PhD thesis and therefore it has to be assumed that LeBlanc is accurately conveying its results in this 1993 paper.

The log-rank *score* rule (Hothorn and Lausen 2003) is a standardized version of the log-rank rule that could be considered as a splitting rule, though simulation studies have demonstrated non-significant predictive performance when comparing the two (B. H. Ishwaran et al. 2008).

Alternative dissimilarity measures and tests have also been suggested as splitting rules, including modified Kolmogorov-Smirnov test and Gehan-Wilcoxon tests (Ciampi et al. 1988). Simulation studies have demonstrated that both of these may have higher power and produce ‘better’ results than the log-rank statistic (Fleming et al. 1980). Despite this, these do not appear to be in common usage and no implementation could be found that include these.

#### Likelihood Based Rules {.unnumbered .unlisted} Likelihood ratio statistics, or deviance based splitting rules, assume a certain model form and thereby an assumption about the data. This may be viewed as an advantageous strategy, as it could arguably increase interpretability, or a disadvantage as it places restrictions on the data. For survival models, a full-likelihood can be estimated with a Cox form by estimating the cumulative hazard function (LeBlanc and Crowley 1992). LeBlanc and Crowley (1992) (LeBlanc and Crowley 1992) advocate for selecting the optimal split by maximising the full PH likelihood, assuming the cumulative hazard function,  $H$ , is known,

$$\mathcal{L} := \prod_{m=1}^M \prod_{i \in L^m} h_m(T_i)^{\Delta_i} \exp(-H_m(T_i))$$

where  $M$  is the total number of terminal nodes,  $h_m$  and  $H_m$  are the (true) hazard and cumulative hazard functions in the  $m$ th node, and again  $L^m$  is the set of observations in terminal node  $m$ . Estimation of  $h_m$  and  $H_m$  are described with the associated terminal node prediction below.

The primary advantage of this method is that any off-shelf regression software with a likelihood splitting rule can be utilised without any further adaptation to model fitting by supplying this likelihood with required estimates. However the additional costs of computing these estimates may outweigh the benefits once the likelihood has been calculated, and this could be why only one implementation of this method has been found (Bou-Hamad, Larocque, and Ben-Ameur 2011; Therneau and Atkinson 2019).

### Other Splitting Rules

As well as likelihood and log-rank splitting rules, other papers have studied comparison of residuals (Therneau, Grambsch, and Fleming 1990), scoring rules (H. Ishwaran and Kogalur 2018), and distance metrics (Gordon and Olshen 1985). These splitting rules work similarly to the mean squared error in the regression setting, in which the score should be minimised across both leaves. The choice of splitting rule is usually data-dependent and can be treated as a hyper-parameter for tuning. However if there is a clear goal in prediction, then the choice of splitting rule can be informed by the prediction type. For example, if the goal is to maximise separation, then a log-rank splitting rule to maximise homogeneity in terminal nodes is a natural starting point. Whereas if the goal is to estimate the linear predictor of a Cox PH model, then a likelihood splitting rule with a Cox form may be more sensible.

#### 15.1.2.2 Terminal Node Prediction

Only two terminal node predictions appear in common usage.

### Predict: Ranking

Terminal node ranking predictions for survival trees and forests have been limited to those that use a likelihood-based splitting rule and assume a PH model form (H. Ishwaran et al. 2004; LeBlanc and Crowley 1992). In model fitting the likelihood splitting rule model attempts to fit the (theoretical) PH model  $h_m(\tau) = h_0(\tau)\theta_m$  for  $m \in 1, \dots, M$  where  $M$  is the total number of terminal nodes and  $\theta_m$  is a parameter to estimate. The model returns predictions for  $\exp(\hat{\theta}_m)$  where  $\hat{\theta}_m$  is the estimate of  $\theta_m$ . This is estimated via an iterative procedure in which in iteration  $j + 1$ ,  $\hat{\theta}_m^{j+1}$  is estimated by

$$\hat{\theta}_m^{j+1} = \frac{\sum_{i \in L^m} \Delta_i}{\sum_{i \in L^m} \hat{H}_0^j(T_i)}$$

where as before  $L^m$  is the set of observations in leaf  $m$  and

$$\hat{H}_0^j(\tau) = \frac{\sum_{i: T_i \leq \tau} \Delta_i}{\sum_{m=1}^M \sum_{\{i: i \in \mathcal{R}_\tau \cap L^m\}} \hat{\theta}_m^j}$$

which is repeated until some stopping criterion is reached. The same cumulative hazard is estimated for all nodes however  $\theta_m$  varies across nodes. This method lends itself naturally to a composition to a full distribution (Chapter 21) as it assumes a PH form and separately estimates the cumulative hazard and relative risk (`?@sec-surv-ml-models-ranfor-nov`), though no implementation of this composition could be found.

### Predict: Survival Distribution

The most common terminal node prediction appears to be predicting the survival distribution by estimating the survival function, using the Kaplan-Meier or Nelson-Aalen estimators, on the sample in the terminal node (Hothorn et al. 2004; B. H. Ishwaran et al. 2008; LeBlanc and Crowley 1993; Segal 1988). Estimating a survival function by a non-parametric estimator is a natural choice for terminal node prediction as these are natural ‘baselines’ in survival, similarly to taking the sample mean in regression. The prediction for SDTs is straightforward, the non-parametric estimator is fit on all observations in each of the terminal nodes. This is adapted to RSFs by bagging the estimator across all decision trees (Hothorn et al. 2004). Using the Nelson-Aalen estimator as an example, let  $m$  be a terminal node in an SDT, then the terminal node prediction is given by,

$$\hat{H}_m(\tau) = \sum_{\{i: i \in L^m \cap T_i \leq \tau\}} \frac{d_i}{n_i} \quad (15.2)$$

where  $d_i$  and  $n_i$  are the number of events and observations at risk at time  $T_i$  in terminal node  $m$ . Ishwaran (B. H. Ishwaran et al. 2008) defined the bootstrapped Nelson-Aalen estimator as

$$\hat{H}_{Boot}(\tau) = \frac{1}{B} \sum_{b=1}^B \hat{H}_{m,b}(\tau), \quad m \in 1, \dots, M \quad (15.3)$$

where  $B$  is the total number of bootstrapped estimators,  $M$  is the number of terminal nodes, and  $\hat{H}_{m,b}$  is the cumulative hazard for the  $m$ th terminal node in the  $b$ th tree. The bootstrapped Kaplan-Meier estimator is calculated analogously. More generally these can be considered as a uniform mixture of  $B$  distributions (Chapter 21).

All implemented RSFs can now be summarised into the following five algorithms:

**RRT** `{#mod-rrt}` \ LeBlanc and Crowley’s (1992) (LeBlanc and Crowley 1992) survival decision tree uses a deviance splitting rule with a terminal node ranking prediction, which assumes a PH model form. These ‘relative risk trees’ (RRTs) are implemented in the package **rpart** (Therneau and Atkinson 2019). This model is considered the least accessible and transparent of all discussed in this section as: few implementations exist, it requires assumptions that may not be realistic, and predictions are harder to interpret than other models. Predictive performance of the model is expected to be worse than RSFs as this is a decision tree; this is confirmed in (R. E. B. Sonabend 2021).

**RRF** `{#mod-rrf}` \ Ishwaran *et al.* (2004) (H. Ishwaran et al. 2004) proposed a random forest framework for the relative risk trees, which makes a slight adaptation and applies the iteration of the terminal node prediction after the tree is grown as opposed to during the growing process. No implementation for these ‘relative risk forests’ (RRFs) could be found or any usage in the literature.

**RSDF-DEV** `{#mod-rsdfdev}` \ Hothorn *et al.* (2004) (Hothorn et al. 2004) expanded upon the RRT by introducing a bagging composition thus creating a random forest with a deviance splitting rule, again assuming a PH form. However the ranking prediction is altered to be a bootstrapped Kaplan-Meier prediction in the terminal node. This is implemented in **ipred** (Peters and Hothorn 2019). This model improves upon the accessibility and transparency of the RRT by providing a more straightforward and interpretable terminal node prediction. However, as this is a decision tree, predictive performance is again expected to be worse than the RSFs.

**RSCIFF** `{#mod-rsciff}` \ Hothorn *et al.* (Hothorn et al. 2005) studied a conditional inference framework in order to predict log-survival time. In this case the splitting rule is based on an IPC weighted loss function, which allows implementation by off-shelf classical random forests. The terminal node predictions are a weighted average of the log-survival times in the node where weighting is determined by the Kaplan-Meier estimate of the censoring distribution. This ‘random survival conditional inference framework forest’ (RSCIFF) is implemented in **party** (Hothorn, Hornik, and Zeileis 2006) and **partykit** (Hothorn and Zeileis 2015), which additionally includes a distribution terminal node prediction via the bootstrapped Kaplan-Meier estimator. The survival tree analogue (SDCIFT) is implemented in the same packages. Implementation of the RSCIFF is complex, which is likely why all implementations (in the above packages) are by the same authors. The complexity of conditional inference forests may also be the reason why several reviews, including this one, mention (or completely omit) RSCIFFs but do not include any comprehensive details that explain the fitting procedure (Bou-Hamad, Larocque, and Ben-Ameur 2011; H. Wang and Li 2017). In this regard, it is hard to claim that RSCIFFs are transparent or accessible. Moreover the authors of the model state that random conditional inference forests are for “expert user[s] only and [their] current state is rather experimental” (Hothorn and Zeileis 2015). Finally with respect to model performance, there is evidence that they can outperform RSDFs (below) dependent on the data type (Nasejje et al. 2017) however no benchmark experiment could be found that compared them to other models.

**RSDF-STAT** `{#mod-rsdfstat}` \ Finally Ishwaran *et al.* (2008) (B. H. Ishwaran et al. 2008) proposed the most general form of RSFs with a choice of hypothesis tests (log-rank and log-rank score) and survival measure (Brier, concordance) splitting rules, and a bootstrapped Nelson-Aalen terminal node prediction. These are implemented in **randomForestSRC** (H. Ishwaran and Kogalur 2018) and **ranger** (Wright and Ziegler 2017). There are several implementations of these models across programming languages, and extensive details for the fitting and predicting procedures, which makes them very accessible. The models utilise a standard random forest framework, which makes them transparent and familiar



to those without expert Survival knowledge. Moreover they have been proven to perform well in benchmark experiments, especially on high-dimensional data (Herrmann et al. 2021; Spooner et al. 2020).

### 15.1.3 Conclusions

Random forests are a highly flexible algorithm that allow the various components to be adapted and altered without major changes to the underlying algorithm. The result is that relatively few R implementations of RSFs cover almost half a century's worth of developments. The only algorithm that does not seem to be implemented is the relative risk forest.

A lack of accessibility, transparency, or proven performance makes RRT and RSDF-DEV a poor choice for model fitting. RSCIFF is potentially a powerful method with promising results in benchmark experiments, but even the authors recognise its complexity prevents it from being accessible. Ishwaran's RSFs on the other hand are more user-friendly and suitable for model fitting and deployment. Simulation studies have demonstrated that RSFs can perform well even with high levels of censoring and there is evidence that on some datasets these can outperform a Cox PH (B. H. Ishwaran et al. 2008). Ishwaran's model is highly flexible, and its implementation in software packages reflects this. Therefore one can still confidently conclude that random forests are a powerful algorithm in regression, classification, and survival analysis.



# Support Vector Machines

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

Support vector machines are a popular class of model in regression and classification settings due to their ability to make accurate predictions for complex high-dimensional, non-linear data. In survival analysis, survival support vector machines (SSVMs), are one of the few classes that can estimate survival times. However, experiments with SSVMs have demonstrated that they are best used for ranking predictions as their survival time predictions can be wildly out of range. As a consequence, SSVMs cannot easily be used to make distribution predictions. As usual this chapter starts with SVMs in the regression setting before moving to adaptations for survival analysis.

## 16.1 SVMs for Regression

In simple linear regression, the aim is to estimate the line  $y = b + x\beta_1$  by estimating the  $b, \beta_1$  coefficients. As the number of coefficients increases, the goal becomes to instead estimate the *hyperplane* that divides the higher-dimensional space into two separate parts. To visualize a hyperplane, imagine looking at a room from a birds eye view that has a dividing wall cutting the room into two halves (Figure 16.1). In this view, the room appears to have dimensions (x=left-right, y=top-bottom) and the divider is a simple line of the form  $y = b + x\beta_1$ . In reality, this room is actually three dimensional and has a third dimension (z=up-down) and the divider occupies these dimensions as a hyperplane of the form  $y = b + x\beta_1 + z\beta_2$ .

Continuing the linear regression example, consider a simple linear regression model where the objective is to find the  $\beta$  coefficients that minimize  $\sum_{i=1}^n (g(x) - y)^2$  where  $y = b + x\beta_1$ . In a higher-dimensional space, a penalty term can be added for variable selection to reduce model complexity, commonly of the form

$$\frac{1}{2} \sum_{i=1}^n (g(x) - y)^2 + \frac{\lambda}{2} \|\beta\|^2$$

for some penalty term  $\lambda$ . Minimizing this error function effectively minimizes the *average* dif-



Figure 16.1: Visualising a hyperplane by viewing a 3D room in two-dimensions with a wall that is now seen as a simple line. When standing in this room, the wall will clearly exist in three dimensional space.

ference between all predictions and true outcomes, resulting in a hyperplane that represents the best *linear* relationship between coefficients and outcomes.

Similarly to linear regression, support vector machines (SVMs) (Cortes and Vapnik 1995) also fit a hyperplane,  $g$ , on given training data,  $\mathbf{X}$ . However, in SVMs, the goal is to fit a *flexible* (non-linear) hyperplane that minimizes the difference between predictions and the truth for *individual* observations. A core feature of SVMs is that one does not try to fit a hyperplane that makes perfect predictions as this would overfit the training data and is unlikely to perform well on unseen data. Instead, SVMs use a regularized error function, which allows incorrect predictions (errors) for some observations, with the magnitude of error controlled by an  $\epsilon > 0$  parameter as well as slack parameters,  $\xi, \xi^*$ :

$$\begin{aligned} \min_{\beta, b, \xi, \xi^*} & \frac{1}{2} \|\beta\|^2 + \gamma \sum_{i=1}^n (\xi_i + \xi_i^*) \\ \text{subject to} & \begin{cases} g(\mathbf{x}_i) & \geq y_i - \epsilon - \xi_i \\ g(\mathbf{x}_i) & \leq y_i + \epsilon + \xi_i^* \\ \xi_i, \xi_i^* & \geq 0 \\ \forall i \in 1, \dots, n \end{cases} \end{aligned} \quad (16.1)$$

where  $g(\mathbf{x}_i) = \beta^T \mathbf{x}_i + b$  for model weights  $\beta, b \in \mathbb{R}$  and the usual training data  $(\mathbf{X}, \mathbf{t}, \delta)$ .

Figure 16.3 visualizes a support vector regression model in two dimensions. The red circles are values within the  $\epsilon$ -tube and are thus considered to have a negligible error. In fact, the red circles do not affect the fitting of the optimal line  $g$  and as long as they remain within the tube, the shape of  $g$  would not change. In contrast the blue diamonds have an unacceptable margin of error - as an example the top blue diamond will have  $\xi_i = 0$  but  $\xi_i^* > 0$ , thus influencing the estimation of  $g$ . Points on or outside the epsilon tube are referred to as *support vectors* as they affect the construction of the hyperplane. The  $\gamma \in \mathbb{R}_{>0}$  hyperparameter controls the slack parameters and thus as  $\gamma$  increases, the number of errors (and subsequently support vectors) is allowed to increase resulting in low variance but higher bias, in contrast a lower  $\gamma$  is more likely to introduce overfitting with low bias but high variance (Hastie, Tibshirani, and Friedman 2001).  $\gamma$  should be tuned to control this trade-off.

The other core feature of SVMs is exploiting the *kernel trick*, which uses functions known as *kernels* to allow the model to learn a non-linear hyperplane whilst keeping the computations limited to lower-dimensional settings. Once the model coefficients have been estimated using the optimization above, predictions for a new observation  $\mathbf{x}^*$  can be made using a function of the form

$$\hat{g}(\mathbf{x}^*) = \sum_{i=1}^n \alpha_i K(\mathbf{x}^*, \mathbf{x}_i) + b \quad (16.2)$$

Details (including estimation) of the  $\alpha_i$  Lagrange multipliers are beyond the scope of this book, references are given at the end of this chapter for the interested reader.  $K$  is a kernel function, with common functions including the linear kernel,  $K(x^*, x_i) = \sum_{j=1}^p x_{ij} x_j^*$ , radial kernel,  $K(x^*, x_i) = \exp(-\omega \sum_{j=1}^p (x_{ij} - x_j^*)^2)$  for some  $\omega \in \mathbb{R}_{>0}$ , and polynomial kernel,  $K(x^*, x_i) = (1 + \sum_{j=1}^p x_{ij} x_j^*)^d$  for some  $d \in \mathbb{N}_{>0}$ .

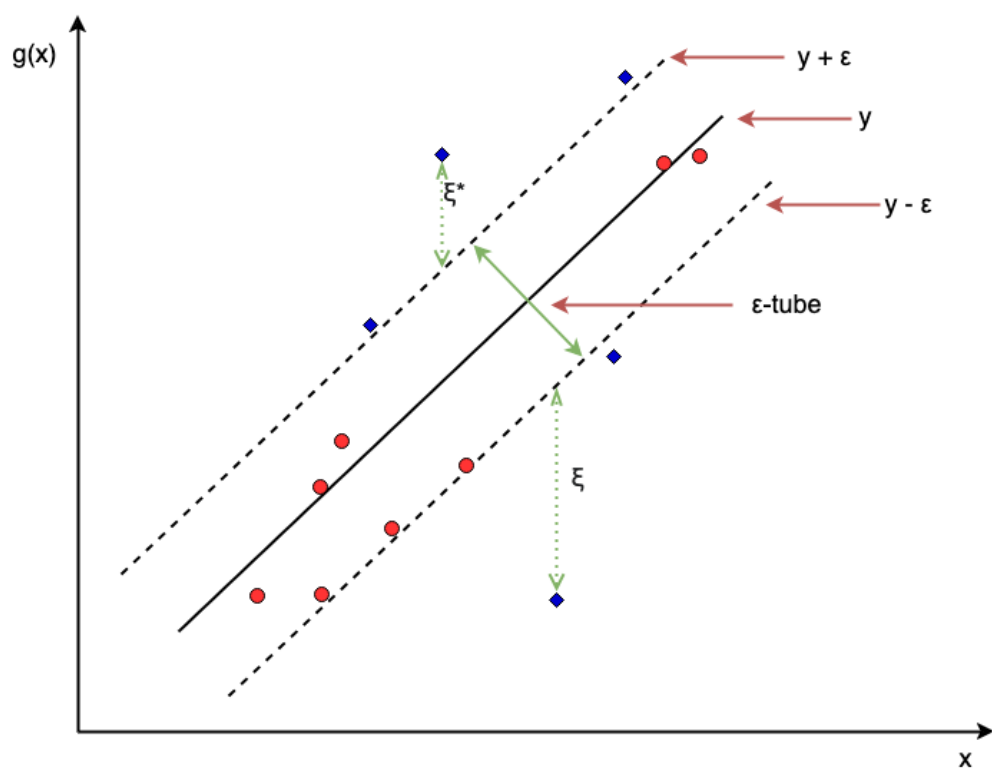


Figure 16.2: Visualising a support vector machine with an  $\epsilon$ -tube and slack parameters  $\xi$  and  $\xi^*$ . Red circles are values within the  $\epsilon$ -tube and blue diamonds are support vectors outside the tube.  $x$ -axis is single covariate,  $x$ , and  $y$ -axis is  $g(x) = x\beta_1 + b$ .

The choice of kernel and its parameters, the regularization parameter  $\gamma$ , and the acceptable error  $\epsilon$ , are all tunable hyper-parameters, which makes the support vector machine a highly adaptable and often well-performing machine learning method. The parameters  $\gamma$  and  $\epsilon$  often have no clear apriori meaning (especially true in the survival setting predicting abstract rankings) and thus require tuning over a great range of values; no tuning usually results in a poor model fit (Probst, Boulesteix, and Bischl 2019).

## 16.2 SVMs for Survival Analysis

Extending SVMs to the survival domain (SSVMs) is a case of: i) identifying the quantity to predict; and ii) updating the optimization problem (Equation 16.1) and prediction function (Equation 16.2) to accommodate for censoring. In the first case, SSVMs can be used to either make survival time or ranking predictions, which are discussed in turn. The notation above is reused below for SSVMs, with additional notation introduced when required.

### 16.2.1 Survival time SSVMs

To begin, consider the objective for support vector regression with the  $y$  variable replaced with the usual survival time outcome  $t$ :

$$\begin{aligned} \min_{\beta, b, \xi, \xi^*} \quad & \frac{1}{2} \|\beta\|^2 + \gamma \sum_{i=1}^n (\xi_i + \xi_i^*) \\ \text{subject to} \quad & \begin{cases} g(\mathbf{x}_i) & \geq t_i - \epsilon - \xi_i \\ g(\mathbf{x}_i) & \leq t_i + \epsilon + \xi_i^* \\ \xi_i, \xi_i^* & \geq 0 \\ \forall i \in 1, \dots, n \end{cases} \end{aligned}$$

In survival analysis, this translates to fitting a hyperplane in order to predict the true survival time. However, as with all adaptations from regression to survival analysis, there needs to be a method for incorporating censoring.

Recall the  $(t_l, t_u)$  notation to describe censoring as introduced in Chapter 4 where an observation is left-censored if the survival time is known to be less than some  $t \in \mathbb{R}_{>0}$ , hence  $(t_l, t_u) = (-\infty, t)$ , right-censored if  $(t_l, t_u) = (t, \infty)$ , or uncensored if  $(t_l, t_u) = (t, t)$ . Define  $L$  as the set of observations with a finite lower-bound time, which are those who are right-censored or uncensored, and define  $U$  as the analogous set of observations with a finite upper-bounded time.

Now consider these bounds in the context of the constraints above. The first constraint ensures the hyperplane is greater than some lower-bound created by subtracting the slack parameter from the true outcome – given the set definitions above this constraint only has meaning for observations with a finite lower-bound,  $i \in L$ , otherwise  $g(\mathbf{x}_i) \geq -\infty$ , which is not a particularly useful constraint. Similarly the second constraint ensures the hyperplane is less than some upper-bound, which again can only be meaningful for observations  $i \in R$ . Restricting the constraints in this way leads to the optimization problem (Shivaswamy, Chu, and Jansche 2007):

$$\min_{\beta, b, \xi, \xi^*} \frac{1}{2} \|\beta\|^2 + \gamma \left( \sum_{i \in R} \xi_i + \sum_{i \in L} \xi_i^* \right)$$

$$\text{subject to } \begin{cases} g(\mathbf{x}_i) & \geq t_i - \xi_i, i \in L \\ g(\mathbf{x}_i) & \leq t_i + \xi_i^*, i \in U \\ \xi_i \geq 0, i \in L; \xi_i^* \geq 0, i \in U \end{cases}$$

If no one is censored then the optimisation is identical to the regression optimisation in (Equation 16.1). Note that in SSVMs, the  $\epsilon$  parameters are typically removed to better accommodate censoring and to help prevent the same penalization of over- and under-predictions. In contrast, one could introduce more  $\epsilon$  and  $\gamma$  parameters to separate between under- and over-predictions and to separate right- and left-censoring, however this leads to eight tunable hyperparameters, which is inefficient and may actually increase overfitting (Fouodo et al. 2018; Land et al. 2011). The algorithm can be simplified to right-censoring only by removing the second constraint completely for anyone censored:

$$\min_{\beta, b, \xi, \xi^*} \frac{1}{2} \|\beta\|^2 + \gamma \sum_{i=1}^n (\xi_i + \xi_i^*)$$

$$\text{subject to } \begin{cases} g(\mathbf{x}_i) & \geq t_i - \xi_i^* \\ \delta_i g(\mathbf{x}_i) & \leq \delta_i t_i + \xi_i \\ \xi_i, \xi_i^* & \geq 0 \\ \forall i \in 1, \dots, n \end{cases}$$

With the prediction for a new observation  $\mathbf{x}^*$  calculated as,

$$\hat{g}(\mathbf{x}^*) = \sum_{i=1}^n \alpha_i^* K(\mathbf{x}_i, \mathbf{x}^*) - \delta_i \alpha_i' K(\mathbf{x}_i, \mathbf{x}^*) + b$$

Where again  $K$  is a kernel function and the calculation of the Lagrange multipliers is beyond the scope of this book.

### 16.2.2 Ranking SSVMs

As discussed in Chapter 11, survival time predictions are actually quite rare in survival analysis and more often than not survival times are used to infer rankings between observations. However, when ranking is the primary goal, SSVMs can be more effectively trained by updating the optimization function to penalize incorrect rankings as opposed to incorrect survival times.

A natural method to optimize with respect to ranking is to penalize predictions that result in disconcordant predictions. Recall the definition of concordance from Chapter 8: ranking predictions for a pair of comparable observations  $(i, j)$  where  $t_i < t_j \cap \delta_i = 1$ , is called concordant if  $r_i > r_j$ . Using the prognostic index as a ranking prediction (Section 6.2), a pair of observations is concordant if  $g(\mathbf{x}_i) > g(\mathbf{x}_j)$  when  $t_i < t_j$ , leading to:



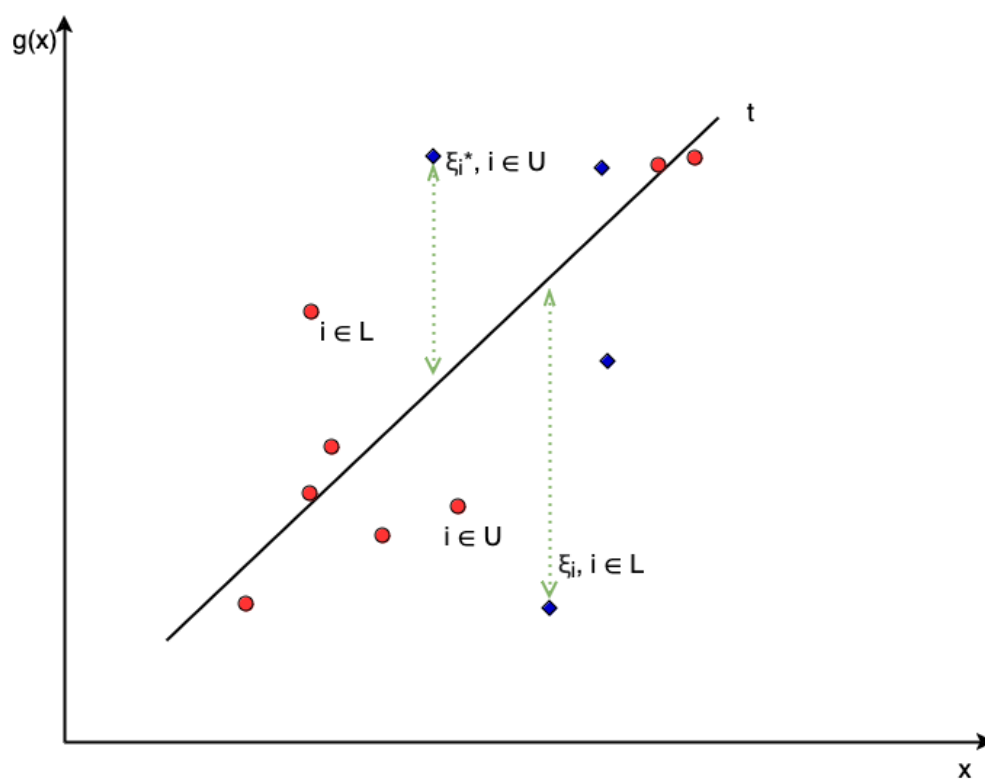


Figure 16.3: Visualising a survival time SVM. Blue diamonds are influential support vectors, which are uncensored or left-censored when  $g(\mathbf{x}) < t$  or uncensored or right-censored when  $g(\mathbf{x}) > t$ . Red circles are non-influential observations.

$$\begin{aligned} & \min_{\beta, b, \xi} \frac{1}{2} \|\beta\|^2 + \gamma \sum_{i=1}^n \xi_i \\ & \text{subject to } \begin{cases} g(\mathbf{x}_i) - g(\mathbf{x}_j) & \geq \xi_i, \forall i, j \in CP \\ \xi_i & \geq 0, i = 1, \dots, n \end{cases} \end{aligned}$$

where  $CP$  is the set of comparable pairs defined by  $CP = \{(i, j) : t_i < t_j \wedge \delta_i = 1\}$ . Given the number of pairs, the optimization problem quickly becomes difficult to solve with a very long runtime. To solve this problem Van Belle et al. (2011) found an efficient reduction that sorts observations in order of outcome time and then compares each data point  $i$  with the observation with the next smallest *survival* time, skipping over censored observations. For example, consider the observed outcomes  $\{(1, 1), (4, 0), (2, 1), (8, 0)\}$ , sorting by outcome time gives  $\{(1, 1), (2, 0), (4, 1), (8, 0)\}$ . The comparable pairs are then  $(i = 2, j = 1)$ ,  $(i = 3, j = 1)$ ,  $(i = 4, j = 3)$  where the censored second outcome is skipped over when finding a pair for observation 3. In this algorithm, the first observation is always assumed to be uncensored even if it was censored in reality. Using this reduction, the algorithm becomes

$$\begin{aligned} & \min_{\beta, b, \xi} \frac{1}{2} \|\beta\|^2 + \gamma \sum_{i=1}^n \xi_i \\ & \text{subject to } \begin{cases} g(\mathbf{x}_i) - g(\mathbf{x}_{j(i)}) & \geq t_i - t_{j(i)} - \xi_i \\ \xi_i & \geq 0 \\ \forall i = 1, \dots, n \end{cases} \end{aligned}$$

where  $j(i)$  is the observation with the next smallest survival time compared to  $i$ . Note the updated right hand side of the constraint, which plays a similar role to the  $\epsilon$  parameter by allowing ‘mistakes’ in predictions without penalty.

Prediction for a new observation  $\mathbf{x}^*$  are calculated as,

$$\hat{g}(\mathbf{x}^*) = \sum_{i=1}^n \alpha_i (K(\mathbf{x}_i, \mathbf{x}^*) - K(\mathbf{x}_{j(i)}, \mathbf{x}^*)) + b$$

Where  $\alpha_i$  are again Lagrange multipliers.

### 16.2.3 Hybrid SSVMs

Finally, Van Belle et al. (2011) noted that the ranking algorithm could be updated to add the constraints of the regression model, thus providing a model that simultaneously optimizes for ranking whilst providing continuous values that can be interpreted as survival time predictions. This results in the hybrid SSVM with constraints:

$$\begin{aligned}
& \min_{\beta, b, \xi, \xi', \xi^*} \frac{1}{2} \|\beta\|^2 + \gamma \sum_{i=1}^n \xi_i + \mu \sum_{i=1}^n (\xi'_i + \xi_i^*) \\
& \text{subject to } \begin{cases} g(\mathbf{x}_i) - g(\mathbf{x}_{j(i)}) & \geq t_i - t_{j(i)} + \xi_i \\ \delta_i g(\mathbf{x}_i) & \leq \delta_i t_i + \xi_i^* \\ g(\mathbf{x}_i) & \geq t_i - \xi'_i \\ \xi_i, \xi'_i, \xi_i^* & \geq 0 \\ \forall i = 1, \dots, n \end{cases}
\end{aligned}$$

The blue parts of the equation make up the ranking model and the red parts are the regression model.  $\gamma$  is the penalty associated with the regression method and  $\mu$  is the penalty associated with the ranking method setting  $\gamma = 0$  results in the regression SVM and  $\mu = 0$  results in the ranking SSVM. Hence, fitting the hybrid model and tuning these parameters is an efficient way to automatically detect which SSVM is best suited to a given task.

Once the model is fit, a prediction from given features  $\mathbf{x}^* \in \mathbb{R}^p$ , can be made using the equation below, again with the ranking and regression contributions highlighted in blue and red respectively.

$$\hat{g}(\mathbf{x}^*) = \sum_{i=1}^n \alpha_i (K(\mathbf{x}_i, \mathbf{x}^*) - K(\mathbf{x}_{j(i)}, \mathbf{x}^*)) + \alpha_i^* K(\mathbf{x}_i, \mathbf{x}^*) - \Delta_i \alpha'_i K(\mathbf{x}_i, \mathbf{x}^*) + b$$

where  $\alpha_i, \alpha_i^*, \alpha'_i$  are Lagrange multipliers and  $K$  is a chosen kernel function, which may have further hyper-parameters to select or tune.

### 16.3 Conclusion

#### Key takeaways

- Support vector machines (SVMs) are a highly flexible machine learning method that can use the ‘kernel trick’ to represent infinite dimensional spaces in finite domains;
- Survival SVMs (SSVMs) extend regression SVMs by either making survival time predictions, ranking predictions, or a combination of the two;
- The hybrid SSVM provides an efficient method that encapsulates all the elements of regression and ranking SSVMs and is therefore a good model to include in benchmark experiments to test the potential of SSVMs.

#### Limitations

- SSVMs can only perform well with extensive tuning of hyper-parameters over a wide domain. To-date, no papers have experimented with the tuning range for the  $\gamma$  and  $\mu$  parameters, we note (Fouodo et al. 2018) tune over  $(2^{-5}, 2^5)$ .
- Even using the regression or hybrid model, the authors’ experiments with the SSVM have consistently shown ‘survival time’ estimates tend to be unrealistically large.

- Due to the above limitation, regression estimates cannot be meaningful interpreted and as a consequence there is no sensible composition to create a distribution prediction from an SSVM. Hence, we are hesitant to suggest usage of SSVMs outside of ranking-based problems.

#### Further reading

- Shivaswamy, Chu, and Jansche (2007), Khan and Bayer Zubek (2008), Land et al. (2011), and Van Belle et al. (2011) to learn more about regression SSVMs.
- Evers and Messow (2008), Van Belle et al. (2007), Van Belle et al. (2008), and Van Belle et al. (2011) for more information about ranking SSVMs.
- Goli, Mahjub, Faradmal, and Soltanian (2016) and Goli, Mahjub, Faradmal, Mashayekhi, et al. (2016) introduce mean residual lifetime optimization SSVMs.
- Fouodo et al. (2018) surveys and benchmarks SSVMs.

## Boosting Methods

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

Boosting is a machine learning strategy that can be applied to any model class. Similarly to random forests, boosting is an ‘ensemble’ method that creates a model from a ‘committee’ of learners. The committee is formed of ‘weak’ learners that make poor predictions individually, which creates a ‘slow learning’ approach (as opposed to ‘greedy’) that requires many iterations for a model to be a good fit to the data. Boosting models are similar to random forests in that both make predictions from a large committee of learners. However the two differ in how this committee is correlated and in how it is combined to a prediction. In random forests, each decision tree is grown independently and their predictions are combined by a simple mean calculation. In contrast, weak learners in a boosting model are fit sequentially with errors from one learner used to train the next, predictions are then made by a linear combination of predictions from each learner (Figure 17.1).

### 17.1 GBMs for Regression

The best known boosting algorithm is likely AdaBoost (Freund and Schapire 1996), which is more generally a Forward Stagewise Additive Model (FSAM) with an exponential loss (Hastie, Tibshirani, and Friedman 2001). Today, the most widely used boosting model is the Gradient Boosting Machine (GBM) (J. H. Friedman 2001).

Figure 17.1 illustrates the process of training a GBM in a least-squares regression setting:

1. A weak learner,  $f_1$ , often a decision tree of shallow depth is fit on the training data  $(\mathbf{X}, \mathbf{y})$ .
2. Predictions from the learner,  $f_1(\mathbf{X})$ , are compared to the ground truth,  $\mathbf{y}$ , and the residuals are calculated as  $\mathbf{r}_1 = f_1(\mathbf{X}) - \mathbf{y}$ .
3. The next weak learner,  $f_2$ , uses the previous residuals for the target prediction,  $(\mathbf{X}, \mathbf{r}_1)$ .
4. This is repeated to train  $M$  learners,  $f_1, \dots, f_M$ .

Predictions are then made as  $\hat{\mathbf{y}} = f_1(\mathbf{X}) + f_2(\mathbf{X}) + \dots + f_M(\mathbf{X})$ .

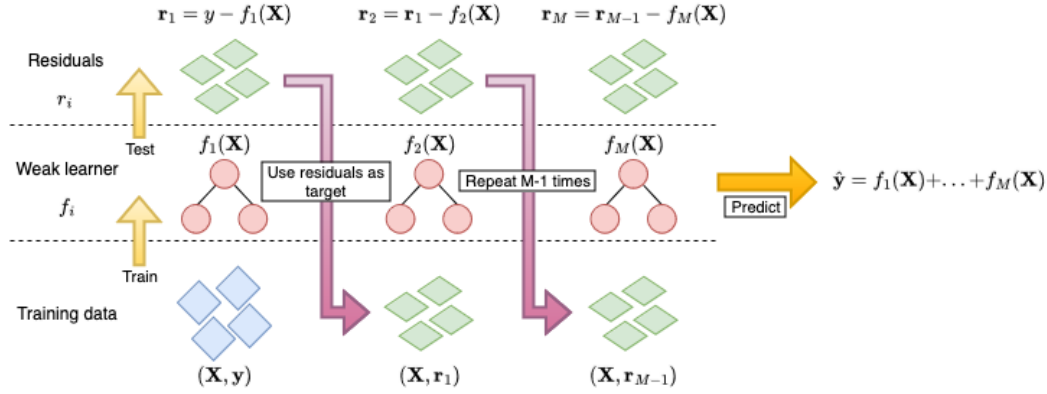


Figure 17.1: Least squares regression Boosting algorithm where the gradient is calculated as the difference between ground truth and predictions.

This is a simplification of the general gradient boosting algorithm, where the residuals are used to train the next model. More generally, a suitable, differentiable loss function relating to the problem of interest is chosen and the negative gradient is computed by comparing the predictions in each iteration with the ground truth. Residuals can be used in the regression case as these are proportional to the negative gradient of the mean squared error.

The algorithm above is also a simplification as no hyper-parameters other than  $M$  were included for controlling the algorithm. In order to reduce overfitting, three common hyper-parameters are utilised:

**Number of iterations,  $M$ :** The number of iterations is often claimed to be the most important hyper-parameter in GBMs and it has been demonstrated that as the number of iterations increases, so too does the model performance (with respect to a given loss on test data) up to a certain point of overfitting (Buhlmann 2006; Hastie, Tibshirani, and Friedman 2001; Schmid and Hothorn 2008a). This makes sense as the foundation of boosting rests on the idea that weak learners can slowly be combined to form a single powerful model. Finding the optimal value of  $M$  is critical as a value too small will result in poor predictions, whilst a value too large will result in model overfitting.

**Subsampling proportion,  $\phi$ :** Sampling a fraction,  $\phi$ , of the training data at each iteration can improve performance and reduce runtime (Hastie, Tibshirani, and Friedman 2001), with  $\phi = 0.5$  often used. Motivated by the success of bagging in random forests, stochastic gradient boosting (J. Friedman 1999) randomly samples the data in each iteration. It appears that subsampling performs best when also combined with shrinkage (Hastie, Tibshirani, and Friedman 2001) and as with the other hyper-parameters, selection of  $\phi$  is usually performed by nested cross-validation.

**Step-size,  $\nu$ :** The step-size parameter is a shrinkage parameter that controls the contribution of each weak learner at each iteration. Several studies have demonstrated that GBMs perform better when shrinkage is applied and a value of  $\nu = 0.1$  is often suggested (Buhlmann and Hothorn 2007; Hastie, Tibshirani, and Friedman 2001; J. H. Friedman 2001; D. K. K. Lee, Chen, and Ishwaran 2019; Schmid and Hothorn 2008a). The optimal values of  $\nu$  and  $M$  depend on each other, such that smaller values of  $\nu$  require larger values of  $M$ , and vice versa. This is intuitive as smaller  $\nu$  results in a slower learning algorithm and therefore more iterations are required to fit the model. Accurately selecting the  $M$  param-

eter is generally considered to be of more importance, and therefore a value of  $\nu$  is often chosen heuristically (e.g. the common value of 0.1) and then  $M$  is tuned by cross-validation and/or early-stopping, which is the process of monitoring the model's training performance and stopping when a set performance is reached or when performance stagnates (i.e., no improvement over a set number of rounds).

As well as these parameters, the underlying weak learner hyper-parameters are also commonly tuned. If using a decision tree, then it is usual to restrict the number of terminal nodes in the tree to be between 4 and 8, which corresponds to two or three splits in the tree. Including these hyper-parameters, the general gradient boosting machine algorithm is as follows:

1.  $g_0 \leftarrow$  Initial guess
2. **For**  $m = 1, \dots, M$ :
3.      $\mathcal{D}_{train}^* \leftarrow$  Randomly sample  $\mathcal{D}_{train}$  with probability  $\phi$
4.      $r_{im} \leftarrow -[\frac{\partial L(y_i, g_{m-1}(X_i))}{\partial g_{m-1}(X_i)}], \forall i \in \{i : X_i \in \mathcal{D}_{train}^*\}$
5.     Fit a weak learner,  $h_m$ , to  $(\mathbf{X}, \mathbf{r}_m)$
6.      $g_m \leftarrow g_{m-1} + \nu h_m$
7. **end For**
8. **return**  $\hat{g} = g_M$

Note:

1. The initial guess,  $g_0$ , is often the mean of  $y$  for regression problems but can also simply be 0.
2. Line 4 is the calculation of the negative gradient, which is equivalent to calculating the residuals in a regression problem with the mean squared error loss.
3. Lines 5-6 differ between implementations, with some fitting multiple weak learners and selecting the one that minimizes a simple optimization problem. The version above is simplest to implement and quickest to run, whilst still providing good model performance.

Once the model is trained, predictions are made for new data,  $\mathbf{X}_{test}$  with

$$\hat{Y} = \hat{g}(\mathbf{X}_{test}) = g_0(\mathbf{X}_{test}) + \nu \sum_{i=1}^M g_i(\mathbf{X}_{test})$$

GBMs provide a flexible, modular algorithm, primarily comprised of a differentiable loss to minimise,  $L$ , and the selection of weak learners. This chapter focuses on tree-based weak learners, though other weak learners are possible. Perhaps the most common alternatives are linear least squares (J. H. Friedman 2001) and smoothing splines (Bühlmann and Yu 2003), we will not discuss these further here as decision trees are primarily used for survival analysis, due the flexibility demonstrated in Section 15.1. See references at the end of the chapter for other weak learners. Extension to survival analysis therefore follows by considering alternative losses.

## 17.2 GBMs for Survival Analysis

Unlike other machine learning algorithms that historically ignored survival analysis, early GBM papers considered boosting in a survival context (Ridgeway 1999); though there appears to be a decade gap before further considerations were made in the survival setting. After that period, several developments by Binder, Schmid, and Hothorn, adapted GBMs to a framework suitable for survival analysis.

All survival GBMs make ranking predictions and none are able to directly predict survival distributions. However, depending on the underlying model, the predictions may be indirectly composed into a survival distribution, for example algorithms that assume a proportional hazards (PH) or accelerated failure time (AFT) form. This section starts with those models with simpler underlying forms, then explores more complex alternatives.

### 17.2.1 PH and AFT GBMs

The negative log-likelihood of the semi-parametric PH and fully-parametric AFT models can be derived from the (partial) likelihoods presented in Section 4.1.5. Given the likelihoods measure the goodness of fit of model parameters, algorithms that use these losses use boosting to train the model coefficients,  $\beta$ , hence at each iteration in the algorithm,  $g_m(\mathbf{x}_i) = \mathbf{x}_i \beta_m$ .

The Cox partial likelihood (Cox 1972, 1975) is given by

$$L^{PH}(\beta) = \prod_{i=1}^n \delta_i \frac{\exp(\eta_i)}{\sum_{j \in \mathcal{R}_{t_i}} \exp(\eta_j)}$$

with corresponding negative log-likelihood

$$-l^{PH}(\beta) = -\sum_{i=1}^n \delta_i \left[ \eta_i - \log \left( \sum_{j \in \mathcal{R}_{t_i}} \exp(\eta_j) \right) \right] \quad (17.1)$$

where  $\mathcal{R}_{t_i}$  is the set of patients at risk at time  $t_i$  and  $\eta_i = \mathbf{x}_i \beta$

The gradient of  $-l^{PH}$  at iteration  $m$  is then

$$r_{im} := \delta_i - \sum_{j=1}^n \delta_j \frac{\mathbb{I}(t_i \geq t_j) \exp(g_{m-1}(\mathbf{x}_i))}{\sum_{k \in \mathcal{R}_{t_j}} \exp(g_{m-1}(\mathbf{x}_k))} \quad (17.2)$$

where  $g_{m-1}(\mathbf{x}_i) = \mathbf{x}_i \beta_{m-1}$ .

For non-PH data, boosting an AFT model can outperform boosted PH models (Schmid and Hothorn 2008b). The AFT is defined by

$$\log \mathbf{y} = \eta + \sigma W$$

where  $W$  is a random noise variable independent of  $X$ , and  $\sigma$  is a scale parameter controlling the amount of noise; again  $\eta = \mathbf{X}\beta$ . By assuming a distribution on  $W$ , a distribution is assumed for the full parametric model. The model is boosted by simultaneously estimating  $\sigma$  and  $\beta$ . Assuming a location-scale distribution with parameters  $\mu$  and  $\sigma$ , one can set  $\mu :=$



$g(\mathbf{x}_i)$  and derive the negative log-likelihood in the  $m$ th iteration as (Klein and Moeschberger 2003)

$$-l_m^{AFT}(\beta) = -\sum_{i=1}^n \delta_i \left[ -\log \sigma + \log f_W \left( \frac{\log(t_i) - \hat{g}_{m-1}(\mathbf{x}_i)}{\hat{\sigma}_{m-1}} \right) \right] + \\ (1 - \delta_i) \left[ \log S_W \left( \frac{\log(t_i) - \hat{g}_{m-1}(\mathbf{x}_i)}{\hat{\sigma}_{m-1}} \right) \right]$$

where  $\hat{g}_{m-1}, \hat{\sigma}_{m-1}$  are the location-scale parameters estimated in the previous iteration. Note this key difference to other GBM methods in which two estimates are made in each iteration step. After updating  $\hat{g}_m$ , the scale parameter,  $\hat{\sigma}_m$ , is updated as

$$\hat{\sigma}_m := \operatorname{argmin}_{\sigma} -l_m^{AFT}(\beta)$$

$\sigma_0$  is commonly initialized as 1 (Schmid and Hothorn 2008b).

As well as boosting fully-parametric AFTs, one could also consider boosting semi-parametric AFTs, for example using the Gehan loss (Johnson and Long 2011) or using Buckley-James imputation (Z. Wang and Wang 2010). However, known problems with semi-parametric AFT models and the Buckley-James procedure (Wei 1992), as well as a lack of off-shelf implementation, mean that these methods are rarely used in practice.

### 17.2.2 Discrimination Boosting

Instead of optimising models based on a given model form, one could instead estimate  $\hat{\eta}$  by optimizing a concordance index, such as Uno's or Harrell's C Mayr and Schmid (2014). Consider Uno's C (Section 8.1):

$$C_U(\hat{g}, \mathcal{D}_{train}) = \frac{\sum_{i \neq j} \delta_i \{\hat{G}_{KM}(t_i)\}^{-2} \mathbb{I}(t_i < t_j) \mathbb{I}(\hat{g}(\mathbf{x}_i) > \hat{g}(\mathbf{x}_j))}{\sum_{i \neq j} \delta_i \{\hat{G}_{KM}(t_i)\}^{-2} \mathbb{I}(t_i < t_j)}$$

The GBM algorithm requires that the chosen loss, here  $C_U$ , be differentiable with respect to  $\hat{g}(X)$ , which is not the case here due to the indicator term,  $\mathbb{I}(\hat{g}(X_i) > \hat{g}(X_j))$ , however this term can be replaced with a sigmoid function to create a differentiable loss (Ma and Huang 2006)

$$K(u|\sigma) = \frac{1}{1 + \exp(-u/\sigma)}$$

where  $\sigma$  is a tunable hyper-parameter controlling the smoothness of the approximation. The measure to optimise is then,

$$C_{USmooth}(\beta|\sigma) = \sum_{i \neq j} \frac{k_{ij}}{1 + \exp[(\hat{g}(X_j) - \hat{g}(X_i))/\sigma]} \quad (17.3)$$

with

$$k_{ij} = \frac{\Delta_i(\hat{G}_{KM}(T_i))^{-2} \mathbb{I}(T_i < T_j)}{\sum_{i \neq j}^n \Delta_i(\hat{G}_{KM}(T_i))^{-2} \mathbb{I}(T_i < T_j)}$$

The negative gradient at iteration  $m$  for observation  $i$  is then calculated as,

$$r_{im} := - \sum_{j=1}^n k_{ij} \frac{-\exp(\frac{\hat{g}_{m-1}(\mathbf{x}_j) - \hat{g}_{m-1}(\mathbf{x}_i)}{\sigma})}{\sigma(1 + \exp(\frac{\hat{g}_{m-1}(\mathbf{x}_j) - \hat{g}_{m-1}(\mathbf{x}_i)}{\sigma}))} \quad (17.4)$$

The GBM algorithm is then followed as normal with the above loss and gradient. This algorithm may be more insensitive to overfitting than others (Mayr, Hofner, and Schmid 2016), however stability selection (Meinshausen and Bühlmann 2010), which is implemented in off-shelf software packages (Hothorn et al. 2020), can be considered for variable selection.

### 17.2.3 CoxBoost

Finally, ‘CoxBoost’ is an alternative method to boost Cox models and has been demonstrated to perform well in experiments. This algorithm boosts the Cox PH by optimising the penalized partial-log likelihood; additionally the algorithm allows for mandatory (or ‘forced’) covariates (Harald Binder and Schumacher 2008). In medical domains the inclusion of mandatory covariates may be essential, either for model interpretability, or due to prior expert knowledge. CoxBoost deviates from the algorithm presented above by instead using an offset-based approach for generalized linear models (Tutz and Binder 2007).

Let  $\mathcal{J}_{mand}$  be the indices of the mandatory covariates to be included in all iterations,  $m = 1, \dots, M$ , then for an iteration  $m$  the indices to consider for fitting are the set

$$I_m = \{\{1\} \cup \mathcal{J}_{mand}, \dots, \{p\} \cup \mathcal{J}_{mand}\} / \{\{j\} \cup \mathcal{J}_{mand} : j \in \mathcal{J}_{mand}\}$$

Therefore, in each iteration, the algorithm fits a weak learner on the mandatory covariates and *one* additional (non-mandatory) covariate.

In addition, a penalty matrix  $\mathbf{P} \in \mathbb{R}^{p \times p}$  is considered such that  $P_{ii} > 0$  implies that covariate  $i$  is penalized and  $P_{ii} = 0$  means no penalization. In practice, this is usually a diagonal matrix (Harald Binder and Schumacher 2008) and by setting  $P_{ii} = 0, i \in I_{mand}$  and  $P_{ii} > 0, i \notin I_{mand}$ , only optional (non-mandatory) covariates are penalized. The penalty matrix can be allowed to vary with each iteration, which allows for a highly flexible approach, however in implementation a simpler approach is to either select a single penalty to be applied in each iteration step or to have a single penalty matrix (Harold Binder 2013).

At the  $m$ th iteration and the  $k$ th set of indices to consider ( $k = 1, \dots, p$ ), the loss to optimize is the penalized partial-log likelihood given by

$$l_{pen}(\gamma_{mk}) = \sum_{i=1}^n \delta_i \left[ \eta_{i,m-1} + \mathbf{x}_{i,\mathcal{J}_{mk}} \gamma_{mk}^\top \right] - \delta_i \log \left( \sum_{j=1}^n \mathbb{I}(t_j \leq t_i) \exp(\eta_{i,m-1} + \mathbf{x}_{i,\mathcal{J}_{mk}} \gamma_{mk}^\top) \right) - \lambda \gamma_{mk}^\top \mathbf{P}_{mk} \gamma_{mk}$$

where  $\eta_{i,m} = \mathbf{x}_i \beta_m$ ,  $\gamma_{mk}$  are the coefficients corresponding to the covariates in  $\mathcal{J}_{mk}$  which is the possible set of candidates for a subset of total candidates  $k = 1, \dots, p$ ;  $\mathbf{P}_{mk}$  is the penalty matrix; and  $\lambda$  is a penalty hyper-parameter to be tuned or selected.<sup>1</sup>

<sup>1</sup>On notation, note that  $\mathbf{P}_{ij}$  refers to the penalty matrix in the  $i$ th iteration for the  $j$ th set of indices, whereas  $P_{ij}$  is the  $(i, j)$ th element in the matrix  $\mathbf{P}$ .

In each iteration, all potential candidate sets (the union of mandatory covariates and one other covariate) are updated by

$$\hat{\gamma}_{mk} = \mathbf{I}_{pen}^{-1}(0)U(0)$$

where  $U(\gamma) = \partial l / \partial \gamma(\gamma)$  and  $\mathbf{I}_{pen}^{-1} = \partial^2 l / \partial \gamma \partial \gamma^T(\gamma + \lambda \mathbf{P}_{mk})$  are the first and second derivatives of the unpenalized partial-log-likelihood. The optimal set is then found as

$$k^* := \operatorname{argmax}_k l_{pen}(\gamma_{mk})$$

and the estimated coefficients are updated with

$$\hat{\beta}_m = \hat{\beta}_{m-1} + \gamma_{mk^*}, \quad k^* \in \mathcal{J}_{mk}$$

This deviates from the standard GBM algorithm by directly optimizing  $l_{pen}$  and not its gradient, additionally model coefficients are iteratively updated instead of a more general model form.

## 17.3 Conclusion

### Key takeaways

- GBMs are a highly flexible and powerful machine learning tool. They have proven particularly useful in survival analysis as minimal adjustments are required to make use of off-shelf software.
- The flexibility of the algorithm allows all the models above to be implemented in relatively few open-source packages.
- There is evidence that boosting models can outperform the Cox PH even in low-dimensional settings (Schmid and Hothorn 2008b), which is not something all ML models can claim.

### Limitations

- Boosting, especially with tree learners, is viewed as a black-box model that is increasingly difficult to interpret as the number of iterations increase. However, there are several methods for increasing interpretability, such as variable importance and SHAPs (Lundberg and Lee 2017).
- Boosting often relies on intensive computing power, however, dedicated packages such as **xgboost** (T. Chen et al. 2020), exist to push CPU/GPUs to their limits in order to optimise predictive performance.

### Further reading

- Bühlmann and Yu (2003); Hothorn et al. (2020); Z. Wang and Wang (2010) for more general information and background on componentwise GBMs
- J. H. Friedman (2001); Z. Wang and Wang (2010) for linear least squares weak learners

- Bühlmann and Yu (2003); J. H. Friedman (2001) for decision tree weak learners
- Ridgeway (1999) for early research into GBMs for survival analysis
- Johnson and Long (2011) and Z. Wang and Wang (2010) for semi-parametric AFT boosting

TODO (150-200 WORDS)

! Major changes expected!

This page is a work in progress and major changes will be made over time.

## 18.1 Neural Networks

Before starting the survey on neural networks, first a comment about their transparency and accessibility. Neural networks are infamously difficult to interpret and train, with some calling building and training neural networks an ‘art’ (Hastie, Tibshirani, and Friedman 2001). As discussed in the introduction of this book, whilst neural networks are not transparent with respect to their predictions, they are transparent with respect to implementation. In fact the simplest form of neural network, as seen below, is no more complex than a simple linear model. With regard to accessibility, whilst it is true that defining a custom neural network architecture is complex and highly subjective, established models are implemented with a default architecture and are therefore accessible ‘off-shelf’.

### 18.1.1 Neural Networks for Regression

(Artificial) Neural networks (ANNs) are a class of model that fall within the greater paradigm of *deep learning*. The simplest form of ANN, a feed-forward single-hidden-layer network, is a relatively simple algorithm that relies on linear models, basic activation functions, and simple derivatives. A short introduction to feed-forward regression ANNs is provided to motivate the survival models. This focuses on single-hidden-layer models and increasing this to multiple hidden layers follows relatively simply.

The single hidden-layer network is defined through three equations

$$Z_m = \sigma(\alpha_{0m} + \alpha_m^T X_i), \quad m = 1, \dots, M \quad (18.1)$$

$$T = \beta_{0k} + \beta_k^T Z, \quad k = 1, \dots, K \quad (18.2)$$

$$g_k(X_i) = \phi_k(T) \quad (18.3)$$

where  $(X_1, \dots, X_n) \stackrel{i.i.d.}{\sim} X$  are the usual training data,  $\alpha_{0m}, \beta_0$  are bias parameters, and  $\theta = \{\alpha_m, \beta\}$  ( $m = 1, \dots, M$ ) are model weights where  $M$  is the number of hidden units.  $K$

is the number of classes in the output, which for regression is usually  $K = 1$ . The function  $\phi$  is a ‘link’ or ‘activation function’, which transforms the predictions in order to provide an outcome of the correct return type; usually in regression,  $\phi(x) = x$ .  $\sigma$  is the ‘activation function’, which transforms outputs from each layer. The  $\alpha_m$  parameters are often referred to as ‘activations’. Different activation functions may be used in each layer or the same used throughout, the choice is down to expert knowledge. Common activation functions seen in this section include the sigmoid function,

$$\sigma(v) = (1 + \exp(-v))^{-1}$$

tanh function,

$$\sigma(v) = \frac{\exp(v) - \exp(-v)}{\exp(v) + \exp(-v)} \quad (18.4)$$

and ReLU (Nair and Hinton 2010)

$$\sigma(v) = \max(0, v) \quad (18.5)$$

A single-hidden-layer model can also be expressed in a single equation, which highlights the relative simplicity of what may appear a complex algorithm.

$$g_k(X_i) = \sigma_0(\beta_{k0} + \sum_{h=1}^H (\beta_{kh} \sigma_h(\beta_{h0} + \sum_{m=1}^M \beta_{hm} X_{i;m})) \quad (18.6)$$

where  $H$  are the number of hidden units,  $\beta$  are the model weights,  $\sigma_h$  is the activation function in unit  $h$ , also  $\sigma_0$  is the output unit activation, and  $X_{i;m}$  is the  $i$ th observation features in the  $m$ th hidden unit.

An example feed-forward single-hidden-layer regression ANN is displayed in (Figure 18.1). This model has 10 input units, 13 hidden units, and one output unit; two bias parameters are fit. The model is described as ‘feed-forward’ as there are no cycles in the node and information is passed forward from the input nodes (left) to the output node (right).

### Back-Propagation

The model weights,  $\theta$ , in this section are commonly fit by ‘back-propagation’ although this method is often considered inefficient compared to more recent advances. A brief pseudo-algorithm for the process is provided below.

Let  $L$  be a chosen loss function for model fitting, let  $\theta = (\alpha, \beta)$  be model weights, and let  $J \in \mathbb{N}_{>0}$  be the number of iterations to train the model over. Then the back-propagation method is given by,

- **For**  $j = 1, \dots, J$ : *[i.]* Fix weights  $\theta^{(j-1)}$ . *[ii.]* Compute predictions  $\hat{Y} := \hat{g}_k^{(j)}(X_i | \theta^{(j-1)})$  with (Equation 18.6). *[iii.]* Calculate the gradients of the loss  $L(\hat{Y} | \mathcal{D}_{train})$ . *[iv.]* Update  $\alpha^{(r)}, \beta^{(r)}$  with gradient descent.
- **End For**

In regression, a common choice for  $L$  is the squared loss,

$$L(\hat{g}, \theta | \mathcal{D}_{train}) = \sum_{i=1}^n (Y_i - \hat{g}(X_i | \theta))^2$$

which may help illustrate how the training outcome,  $(Y_1, \dots, Y_n) \stackrel{i.i.d.}{\sim} Y$ , is utilised for model fitting.

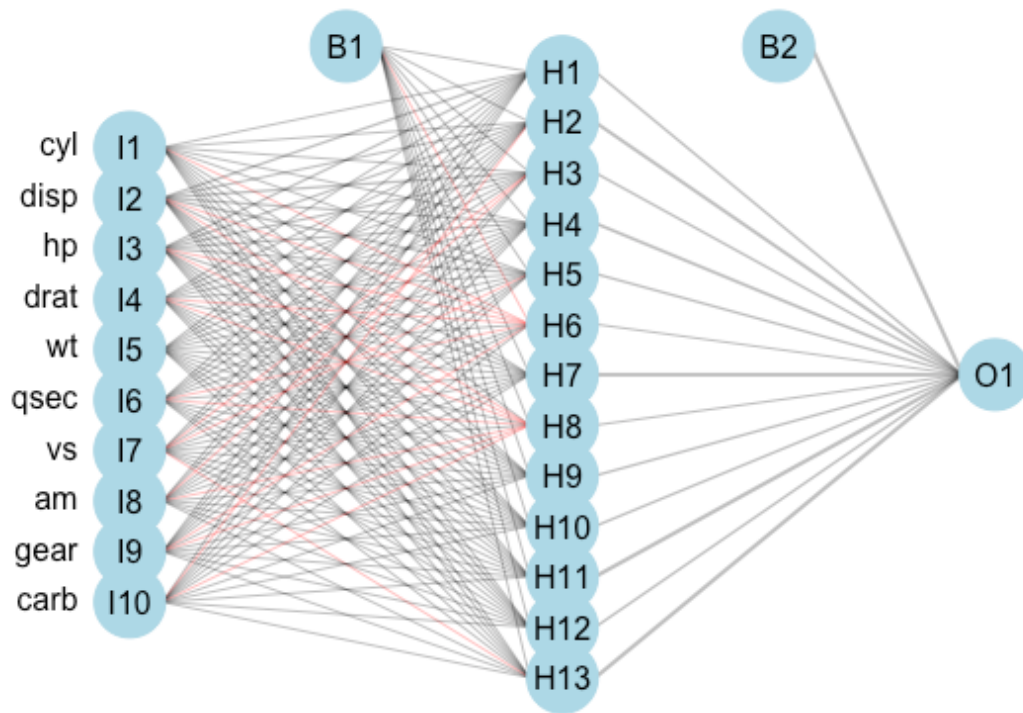


Figure 18.1: Single-hidden-layer artificial neural network with 13 hidden units fit on the `mtcars` (Henderson and Velleman 1981) dataset using the `nnet` (N. Venables and D. Ripley 2002) package, and `gamlss.add` (Stasinopoulos et al. 2020) for plotting. Left column are input variables, I1-I10, second column are 13 hidden units, H1-H13, right column is single output variable, O1. B1 and B2 are bias parameters.

### Making Predictions

Once the model is fitted, predictions for new data follow by passing the testing data as inputs to the model with fitted weights,

$$g_k(X^*) = \sigma_0(\hat{\beta}_{k0} + \sum_{h=1}^H (\hat{\beta}_{kh} \sigma_h(\hat{\beta}_{h0} + \sum_{m=1}^M \hat{\beta}_{hm} X_m^*))$$

### Hyper-Parameters

In practice, a regularization parameter,  $\lambda$ , is usually added to the loss function in order to help avoid overfitting. This parameter has the effect of shrinking model weights towards zero and hence in the context of ANNs regularization is usually referred to as ‘weight decay’. The value of  $\lambda$  is one of three important hyper-parameters in all ANNs, the other two are: the range of values to simulate initial weights from, and the number of hidden units,  $M$ .

The range of values for initial weights is usually not tuned but instead a consistent range is specified and the neural network is trained multiple times to account for randomness in initialization.

The regularization parameter and number of hidden units,  $M$ , depend on each other and have a similar relationship to the learning rate and number of iterations in the GBMs (`?@sec-surv-ml-models-boost`). Like the GBMs, it is simplest to set a high number of hidden units and then tune the regularization parameter (Bishop 2006; Hastie, Tibshirani, and Friedman 2001). Determining how many hidden layers to include, and how to connect them, is informed by expert knowledge and well beyond the scope of this book; decades of research has been required to derive sensible new configurations.

### Training Batches

ANNs can either be trained using complete data, in batches, or online. This decision is usually data-driven and will affect the maximum number of iterations used to train the algorithm; as such this will also often be chosen by expert-knowledge and not empirical methods such as cross-validation.

### Neural Terminology

Neural network terminology often reflects the structures of the brain. Therefore ANN units are referred to as nodes or neurons and sometimes the connections between neurons are referred to as synapses. Neurons are said to be ‘fired’ if they are ‘activated’. The simplest example of activating a neuron is with the Heaviside activation function with a threshold of 0:  $\sigma(v) = \mathbb{I}(v \geq 0)$ . Then a node is activated and passes its output to the next layer if its value is positive, otherwise it contributes no value to the next layer.

#### 18.1.2 Neural Networks for Survival Analysis

Surveying neural networks is a non-trivial task as there has been a long history in machine learning of publishing very specific data-driven neural networks with limited applications; this is also true in survival analysis. This does mean however that where limited developments for survival were made in other machine learning classes, ANN survival adaptations have been around for several decades. A review in 2000 by Schwarzer *et al.* surveyed 43 ANNs for diagnosis and prognosis published in the first half of the 90s, however only up to



ten of these are specifically for survival data.<sup>1</sup> Of those, Schwarzer *et al.* deemed three to be ‘na’ive applications to survival data’, and recommended for future research models developed by Liestøl *et al.* (1994) (Liestøl, Andersen, and Andersen 1994), Faraggi and Simon (1995) (Faraggi and Simon 1995), and Biganzoli *et al.* (1998) (E. Biganzoli *et al.* 1998).

This survey will not be as comprehensive as the 2000 survey, and nor has any survey since, although there have been several ANN reviews (B. D. Ripley and Ripley 2001; Huang *et al.* 2020b; Ohno-Machado 1996; Yang 2010; W. Zhu *et al.* 2020). ANNs are considered to be a black-box model, with interpretability decreasing steeply as the number of hidden layers and nodes increases. In terms of accessibility there have been relatively few open-source packages developed for survival ANNs; where these are available the focus has historically been in Python, with no R implementations. The new **survivalmodels** (R. Sonabend 2020) package,<sup>2</sup> implements these Python models via **reticulate** (Ushey, Allaire, and Tang 2020). No recurrent neural networks are included in this survey though the survival models SRN (Oh *et al.* 2018) and RNN-Surv (Giunchiglia, Nemchenko, and Schaar 2018) are acknowledged.

This survey is made slightly more difficult as neural networks are often proposed for many different tasks, which are not necessarily clearly advertised in a paper’s title or abstract. For example, many papers claim to use neural networks for survival analysis and make comparisons to Cox models, whereas the task tends to be death at a particular (usually 5-year) time-point (classification) (I. Han *et al.* 2018; Lundin *et al.* 1999; B. D. Ripley and Ripley 2001; R. M. Ripley, Harris, and Tarassenko 1998; Huseyin Seker *et al.* 2002), which is often not made clear until mid-way through the paper. Reviews and surveys have also conflated these different tasks, for example a very recent review concluded superior performance of ANNs over Cox models, when in fact this is only in classification (Huang *et al.* 2020a) (RM2) {sec:car\_reduxstrats\_mistakes}. To clarify, this form of classification task does fall into the general *field* of survival analysis, but not the survival *task* ((**box-task-surv?**)). Therefore this is not a comment on the classification task but a reason for omitting these models from this survey.

Using ANNs for feature selection (often in gene expression data) and computer vision is also very common in survival analysis, and indeed it is in this area that most success has been seen (Bello *et al.* 2019; Y.-C. Chen, Ke, and Chiu 2014; Cui *et al.* 2020; Lao *et al.* 2017; McKinney *et al.* 2020; Rietschel, Yoon, and Schaar 2018; H. Seker *et al.* 2002; Zhang *et al.* 2020; X. Zhu, Yao, and Huang 2016), but these are again beyond the scope of this survey.

The key difference between neural networks is in their output layer, required data transformations, the model prediction, and the loss function used to fit the model. Therefore the following are discussed for each of the surveyed models: the loss function for training,  $L$ , the model prediction type,  $\hat{g}$ , and any required data transformation. Notation is continued from the previous surveys with the addition of  $\theta$  denoting model weights (which will be different for each model).

### 18.1.2.1 Probabilistic Survival Models

Unlike other classes of machine learning models, the focus in ANNs has been on probabilistic models. The vast majority make these predictions via reduction to binary classification ???. Whilst almost all of these networks implicitly reduce the problem to classification, most are not transparent in exactly how they do so and none provide clear or detailed interface points in implementation allowing for control over this reduction. Most importantly, the

<sup>1</sup>Schwarzer conflates the prognosis and survival task, therefore it is not clear if all 10 of these are for time-to-event data (at least five definitely are).

<sup>2</sup>Created in order to run the experiments in [Sonabend2021b].

majority of these models do not detail how valid survival predictions are derived from the binary setting,<sup>3</sup> which is not just a theoretical problem as some implementations, such as the Logistic-Hazard model in **pycox** (Kvamme 2018), have been observed to make survival predictions outside the range  $[0, 1]$ . This is not a statement about the performance of models in this section but a remark about the lack of transparency across all probabilistic ANNs.

Many of these algorithms use an approach that formulate the Cox PH as a non-linear model and minimise the partial likelihood. These are referred to as ‘neural-Cox’ models and the earliest appears to have been developed by Faraggi and Simon (Faraggi and Simon 1995). All these models are technically composites that first predict a ranking, however they assume a PH form and in implementation they all appear to return a probabilistic prediction.

**ANN-COX** `{#mod-anncox}` Faraggi and Simon (Faraggi and Simon 1995) proposed a non-linear PH model

$$h(\tau|X_i, \theta) = h_0(\tau) \exp(\phi(X_i \beta)) \quad (18.7)$$

where  $\phi$  is the sigmoid function and  $\theta = \{\beta\}$  are model weights. This model, ‘ANN-COX’, estimates the prediction functional,  $\hat{g}(X^*) = \phi(X^* \hat{\beta})$ . The model is trained with the partial-likelihood function

$$L(\hat{g}, \theta | \mathcal{D}_{train}) = \prod_{i=1}^n \frac{\exp(\sum_{m=1}^M \alpha_m \hat{g}_m(X^*))}{\sum_{j \in \mathcal{R}_{t_i}} \exp(\sum_{m=1}^M \alpha_m \hat{g}_m(X^*))}$$

where  $\mathcal{R}_{t_i}$  is the risk group alive at  $t_i$ ;  $M$  is the number of hidden units;  $\hat{g}_m(X^*) = (1 + \exp(-X^* \hat{\beta}_m))^{-1}$ ; and  $\theta = \{\beta, \alpha\}$  are model weights.

The authors proposed a single hidden layer network, trained using back-propagation and weight optimisation with Newton-Raphson. This architecture did not outperform a Cox PH (Faraggi and Simon 1995). Further adjustments including (now standard) pre-processing and hyper-parameter tuning did not improve the model performance (Mariani et al. 1997). Further independent studies demonstrated worse performance than the Cox model (Faraggi and Simon 1995; Xiang et al. 2000).

**COX-NNET** `{#mod-coxnnnet}` COX-NNET (Ching, Zhu, and Garmire 2018) updates the ANN-COX by instead maximising the regularized partial log-likelihood

$$L(\hat{g}, \theta | \mathcal{D}_{train}, \lambda) = \sum_{i=1}^n \Delta_i \left[ \hat{g}(X_i) - \log \left( \sum_{j \in \mathcal{R}_{t_i}} \exp(\hat{g}(X_j)) \right) \right] + \lambda (\|\beta\|_2 + \|w\|_2)$$

with weights  $\theta = (\beta, w)$  and where  $\hat{g}(X_i) = \sigma(wX_i + b)^T \beta$  for bias term  $b$ , and activation function  $\sigma$ ;  $\sigma$  is chosen to be the tanh function ((Equation 18.4)). In addition to weight decay, dropout (Srivastava et al. 2014) is employed to prevent overfitting. Dropout can be thought of as a similar concept to the variable selection in random forests, as each node is randomly deactivated with probability  $p$ , where  $p$  is a hyper-parameter to be tuned.

Independent simulation studies suggest that COX-NNET does not outperform the Cox PH (Michael F. Gensheimer and Narasimhan 2019).

**DeepSurv** `{#mod-deepsurv}` DeepSurv (J. L. Katzman et al. 2018) extends these models to deep learning with multiple hidden layers. The chosen error function is the average

<sup>3</sup>One could assume they use procedures such as those described in Tutz and Schmid (2016) [Tutz2016] but there is rarely transparent writing to confirm this.

negative log-partial-likelihood with weight decay

$$L(\hat{g}, \theta | \mathcal{D}_{train}, \lambda) = -\frac{1}{n^*} \sum_{i=1}^n \Delta_i \left[ \left( \hat{g}(X_i) - \log \sum_{j \in \mathcal{R}_{t_i}} \exp(\hat{g}(X_j)) \right) \right] + \lambda \|\theta\|_2^2$$

where  $n^* := \sum_{i=1}^n \mathbb{I}(\Delta_i = 1)$  is the number of uncensored observations and  $\hat{g}(X_i) = \phi(X_i | \theta)$  is the same prediction object as the ANN-COX. State-of-the-art methods are used for data pre-processing and model training. The model architecture uses a combination of fully-connected and dropout layers. Benchmark experiments by the authors indicate that DeepSurv can outperform the Cox PH in ranking tasks (J. Katzman et al. 2016; J. L. Katzman et al. 2018) although independent experiments do not confirm this (Zhao and Feng 2020).

**\*\*Cox-Time\*\***  $\{\#mod-coxtime\}$  \ Kvamme *et al.* (Kvamme, Borgan, and Scheel 2019) build on these models by allowing time-varying effects. The loss function to minimise, with regularization, is given by

$$L(\hat{g}, \theta | \mathcal{D}_{train}, \lambda) = \frac{1}{n} \sum_{i: \Delta_i=1} \log \left( \sum_{j \in \mathcal{R}_{t_i}} \exp[\hat{g}(X_j, T_i) - \hat{g}(X_i, T_i)] \right) + \lambda \sum_{i: \Delta_i=1} \sum_{j \in \mathcal{R}_{t_i}} |\hat{g}(X_j, T_i)|$$

where  $\hat{g} = \hat{g}_1, \dots, \hat{g}_n$  is the same non-linear predictor but with a time interaction and  $\lambda$  is the regularization parameter. The model is trained with stochastic gradient descent and the risk set,  $\mathcal{R}_{t_i}$ , in the equation above is instead reduced to batches, as opposed to the complete dataset. ReLU activations (Nair and Hinton 2010) and dropout are employed in training. Benchmark experiments indicate good performance of Cox-Time, though no formal statistical comparisons are provided and hence no comment about general performance can be made.

**ANN-CDP**  $\{\#mod-anncdp\}$  \ One of the earliest ANNs that was noted by Schwarzer *et al.* (Schwarzer, Vach, and Schumacher 2010) was developed by Liestøl *et al.* (Liestøl, Andersen, and Andersen 1994) and predicts conditional death probabilities (hence ‘ANN-CDP’). The model first partitions the continuous survival times into disjoint intervals  $J_k, k = 1, \dots, m$  such that  $J_k$  is the interval  $(t_{k-1}, t_k]$ . The model then studies the logistic Cox model (proportional odds) (Cox 1972) given by

$$\frac{p_k(\mathbf{x})}{q_k(\mathbf{x})} = \exp(\eta + \theta_k)$$

where  $p_k = 1 - q_k$ ,  $\theta_k = \log(p_k(0)/q_k(0))$  for some baseline probability of survival,  $q_k(0)$ , to be estimated;  $\eta$  is the usual linear predictor, and  $q_k = P(T \geq T_k | T \geq T_{k-1})$  is the conditional survival probability at time  $T_k$  given survival at time  $T_{k-1}$  for  $k = 1, \dots, K$  total time intervals. A logistic activation function is used to predict  $\hat{g}(X^*) = \phi(\eta + \theta_k)$ , which provides an estimate for  $\hat{p}_k$ .

The model is trained on discrete censoring indicators  $D_{ki}$  such that  $D_{ki} = 1$  if individual  $i$  dies in interval  $J_k$  and 0 otherwise. Then with  $K$  output nodes and maximum likelihood estimation to find the model parameters,  $\hat{\eta}$ , the final prediction provides an estimate for the conditional death probabilities  $\hat{p}_k$ . The negative log-likelihood to optimise is given by

$$L(\hat{g}, \theta | \mathcal{D}_{train}) = \sum_{i=1}^n \sum_{k=1}^{m_i} [D_{ki} \log(\hat{p}_k(X_i)) + (1 - D_{ki}) \log(\hat{q}_k(X_i))]$$

where  $m_i$  is the number of intervals in which observation  $i$  is not censored.

Liestøl *et al.*  $\{\}$  discuss different weighting options and how they correspond to the PH assumption. In the most generalised case, a weight-decay type regularization is applied to the model weights given by

$$\alpha \sum_l \sum_k (w_{kl} - w_{k-1,l})^2$$

where  $w$  are weights, and  $\alpha$  is a hyper-parameter to be tuned, which can be used alongside standard weight decay. This corresponds to penalizing deviations from proportionality thus creating a model with approximate proportionality. The authors also suggest the possibility of fixing the weights to be equal in some nodes and different in others; equal weights strictly enforces the proportionality assumption. Their simulations found that removing the proportionality assumption completely, or strictly enforcing it, gave inferior results. Comparing their model to a standard Cox PH resulted in a ‘better’ negative log-likelihood, however

this is not a precise evaluation metric and an independent simulation would be preferred. Finally Listøl *et al.* included a warning “The flexibility is, however, obtained at unquestionable costs: many parameters, difficult interpretation of the parameters and a slow numerical procedure” (Liestøl, Andersen, and Andersen 1994).

**PLANN** {#mod-plann}\ Biganzoli *et al.* (1998) (E. Biganzoli *et al.* 1998) studied the same proportional-odds model as the ANN-CDP (Liestøl, Andersen, and Andersen 1994). Their model utilises partial logistic regression (Efron 1988) with added hidden nodes, hence ‘PLANN’. Unlike ANN-CDP, PLANN predicts a smoothed hazard function by using smoothing splines. The continuous time outcome is again discretised into disjoint intervals  $t_m, m = 1, \dots, M$ . At each time-interval,  $t_m$ , the number of events,  $d_m$ , and number of subjects at risk,  $n_m$ , can be used to calculate the discrete hazard function,<sup>4</sup>

$$\hat{h}_m = \frac{d_m}{n_m}, m = 1, \dots, M \quad (18.8)$$

This quantity is used as the target to train the neural network. The survival function is then estimated by the Kaplan-Meier type estimator,

$$\hat{S}(\tau) = \prod_{m:t_m \leq \tau} (1 - \hat{h}_m) \quad (18.9)$$

The model is fit by employing one of the more ‘usual’ survival reduction strategies in which an observation’s survival time is treated as a covariate in the model (Tutz and Schmid 2016). As this model uses discrete time, the survival time is discretised into one of the  $M$  intervals. This approach removes the proportional odds constraint as interaction effects between time and covariates can be modelled (as time-updated covariates). Again the model makes predictions at a given time  $m$ ,  $\phi(\theta_m + \eta)$ , where  $\eta$  is the usual linear predictor,  $\theta$  is the baseline proportional odds hazard  $\theta_m = \log(h_m(0)/(1 - h_m(0)))$ . The logistic activation provides estimates for the discrete hazard,

$$h_m(X_i) = \frac{\exp(\theta_m + \hat{\eta})}{1 + \exp(\theta_m + \hat{\eta})}$$

which is smoothed with cubic splines (Efron 1988) that require tuning.

A cross-entropy error function is used for training

$$L(\hat{h}, \theta | \mathcal{D}_{train}, a) = - \sum_{m=1}^M \left[ \hat{h}_m \log \left( \frac{h_l(X_i, a_l)}{\hat{h}_m} \right) + (1 - \hat{h}_m) \log \left( \frac{1 - h_l(X_i, a_l)}{1 - \hat{h}_m} \right) \right] n_m$$

where  $h_l(X_i, a_l)$  is the discrete hazard  $h_l$  with smoothing at mid-points  $a_l$ . Weight decay can be applied and the authors suggest  $\lambda \approx 0.01 - 0.1$  (E. Biganzoli *et al.* 1998), though they make use of an AIC type criterion instead of cross-validation.

This model makes smoothed hazard predictions at a given time-point,  $\tau$ , by including  $\tau$  in the input covariates  $X_i$ . Therefore the model first requires transformation of the input data by replicating all observations and replacing the single survival indicator  $\Delta_i$ , with a time-dependent indicator  $D_{ik}$ , the same approach as in ANN-CDP. Further developments have extended the PLANN to Bayesian modelling, and for competing risks (E. M. Biganzoli, Ambroggi, and Boracchi 2009).

<sup>4</sup>Derivation of this as a ‘hazard’ estimator follows trivially by comparison to the Nelson-Aalen estimator.

No formal comparison is made to simpler model classes. The authors recommend ANNs primarily for exploration, feature selection, and understanding underlying patterns in the data (E. M. Biganzoli, Ambrogi, and Boracchi 2009).

**Nnet-survival** {#mod-nnetsurvival}\ Aspects of the PLANN algorithm have been generalised into discrete-time survival algorithms in several papers (Michael F. Gensheimer and Narasimhan 2019; **Kvamme2019?**; Mani et al. 1999; Street 1998). Various estimates have been derived for transforming the input data to a discrete hazard or survival function. Though only one is considered here as it is the most modern and has a natural interpretation as the ‘usual’ Kaplan-Meier estimator for the survival function. Others by Street (1998) (Street 1998) and Mani (1999) (Mani et al. 1999) are acknowledged. The discrete hazard estimator (Equation 18.8),  $\hat{h}$ , is estimated and these values are used as the targets for the ANN. For the error function, the mean negative log-likelihood for discrete time (**Kvamme2019?**) is minimised to estimate  $\hat{h}$ ,

$$L(\hat{h}, \theta | \mathcal{D}_{train}) = -\frac{1}{n} \sum_{i=1}^n \sum_{j=1}^{k(T_i)} (\mathbb{I}(T_i = \tau_j, \Delta_i = 1) \log[\hat{h}_i(\tau_j)] + (1 - \mathbb{I}(T_i = \tau_j, \Delta_i = 1)) \log(1 - \hat{h}_i(\tau_j)))$$

where  $k(T_i)$  is the time-interval index in which observation  $i$  dies/is censored,  $\tau_j$  is the  $j$ th discrete time-interval, and the prediction of  $\hat{h}$  is obtained via

$$\hat{h}(\tau_j | \mathcal{D}_{train}) = [1 + \exp(-\hat{g}_j(\mathcal{D}_{train}))]^{-1}$$

where  $\hat{g}_j$  is the  $j$ th output for  $j = 1, \dots, m$  discrete time intervals. The number of units in the output layer for these models corresponds to the number of discrete-time intervals. Deciding the width of the time-intervals is an additional hyper-parameter to consider.

Gensheimer and Narasimhan’s ‘Nnet-survival’ (Michael F. Gensheimer and Narasimhan 2019) has two different implementations. The first assumes a PH form and predicts the linear predictor in the final layer, which can then be composed to a distribution. Their second ‘flexible’ approach instead predicts the log-odds of survival in each node, which are then converted to a conditional probability of survival,  $1 - h_j$ , in a given interval using the sigmoid activation function. The full survival function can be derived with (Equation 18.9). The model has been demonstrated not to outperform the Cox PH with respect to Harrell’s C or the Graf (Brier) score (Michael F. Gensheimer and Narasimhan 2019).

**PC-Hazard** {#mod-pchazard}\ Kvamme and Borgan deviate from nnet-survival in their ‘PC-Hazard’ (**Kvamme2019?**) by first considering a discrete-time approach with a softmax activation function influenced by multi-class classification. They expand upon this by studying a piecewise constant hazard function in continuous time and defining the mean negative log-likelihood as

$$L(\hat{g}, \theta | \mathcal{D}_{train}) = -\frac{1}{n} \sum_{i=1}^n \left( \Delta_i X_i \log \tilde{\eta}_{k(T_i)} - X_i \tilde{\eta}_{k(T_i)} \rho(T_i) - \sum_{j=1}^{k(T_i)-1} \tilde{\eta}_j X_i \right)$$

where  $k(T_i)$  and  $\tau_i$  is the same as defined above,  $\rho(t) = \frac{t - \tau_{k(t)-1}}{\Delta \tau_{k(t)}}$ ,  $\Delta \tau_j = \tau_j - \tau_{j-1}$ , and  $\tilde{\eta}_j := \log(1 + \exp(\hat{g}_j(X_i)))$  where again  $\hat{g}_j$  is the  $j$ th output for  $j = 1, \dots, m$  discrete time intervals. Once the weights have been estimated, the predicted survival function is given by

$$\hat{S}(\tau, X^* | \mathcal{D}_{train}) = \exp(-X^* \tilde{\eta}_{k(\tau)} \rho(\tau)) \prod_{j=1}^{k(\tau)-1} \exp(-\tilde{\eta}_j(X^*))$$

Benchmark experiments indicate similar performance to `nnet-survival` (Kvamme2019?), an unsurprising result given their implementations are identical with the exception of the loss function (Kvamme2019?), which is also similar for both models. A key result found that varying values for interval width lead to significant differences and therefore should be carefully tuned.

**DNNSurv** `{#mod-dnnsurv}` A very recent (pre-print) approach (Zhao and Feng 2020) instead first computes ‘pseudo-survival probabilities’ and uses these to train a regression ANN with sigmoid activation and squared error loss. These pseudo-probabilities are computed using a jackknife-style estimator given by

$$\tilde{S}_{ij}(T_{j+1}, \mathcal{R}_{t_j}) = n_j \hat{S}(T_{j+1} | \mathcal{R}_{t_j}) - (n_j - 1) \hat{S}^{-i}(T_{j+1} | \mathcal{R}_{t_j})$$

where  $\hat{S}$  is the IPCW weighted Kaplan-Meier estimator (defined below) for risk set  $\mathcal{R}_{t_j}$ ,  $\hat{S}^{-i}$  is the Kaplan-Meier estimator for all observations in  $\mathcal{R}_{t_j}$  excluding observation  $i$ , and  $n_j := |\mathcal{R}_{t_j}|$ . The IPCW weighted Kaplan-Meier estimate is found via the IPCW Nelson-Aalen estimator,

$$\hat{H}(\tau | \mathcal{D}_{train}) = \sum_{i=1}^n \int_0^\tau \frac{\mathbb{I}(T_i \leq u, \Delta_i = 1) \hat{W}_i(u)}{\sum_{j=1}^n \mathbb{I}(T_j \geq u) \hat{W}_j(u)} du$$

where  $\hat{W}_i, \hat{W}_j$  are subject specific IPC weights.

In their simulation studies, they found no improvement over other proposed neural networks. Arguably the most interesting outcome of their paper are comparisons of multiple survival ANNs at specific time-points, evaluated with C-index and Brier score. Their results indicate identical performance from all models. They also provide further evidence of neural networks not outperforming a Cox PH when the PH assumption is valid. However, in their non-PH dataset, DNNSurv appears to outperform the Cox model (no formal tests are provided). Data is replicated similarly to previous models except that no special indicator separates censoring and death, this is assumed to be handled by the IPCW pseudo probabilities.

**DeepHit** `{#mod-deephit}` DeepHit (C. Lee et al. 2018) was originally built to accommodate competing risks, but only the non-competing case is discussed here (Kvamme, Borgan, and Scheel 2019). The model builds on previous approaches by discretising the continuous time outcome, and makes use of a composite loss. It has the advantage of making no parametric assumptions and directly predicts the probability of failure in each time-interval (which again correspond to different terminal nodes), i.e.  $\hat{g}(\tau_k | \mathcal{D}_{test}) = \hat{P}(T^* = \tau_k | X^*)$  where again  $\tau_k, k = 1, \dots, K$  are the distinct time intervals. The estimated survival function is found with  $\hat{S}(\tau_K | X^*) = 1 - \sum_{k=1}^K \hat{g}_k(\tau_k | X^*)$ . ReLU activations were used in all fully connected layers and a softmax activation in the final layer. The losses in the composite error function are given by

$$L_1(\hat{g}, \theta | \mathcal{D}_{train}) = - \sum_{i=1}^N [\Delta_i \log(\hat{g}_i(T_i)) + (1 - \Delta_i) \log(\hat{S}_i(T_i))]$$

and

$$L_2(\hat{g}, \theta | \mathcal{D}_{train}, \sigma) = \sum_{i \neq j} \Delta_i \mathbb{I}(T_i < T_j) \sigma(\hat{S}_i(T_i), \hat{S}_j(T_i))$$

for some convex loss function  $\sigma$  and where  $\hat{g}_i(t) = \hat{g}(t | X_i)$ . Again these can be seen to be a cross-entropy loss and a ranking loss. Benchmark experiments demonstrate the model



outperforming the Cox PH and RSFs (C. Lee et al. 2018) with respect to separation, and an independent experiment supports these findings (Kvamme, Borgan, and Scheel 2019). However, the same independent study demonstrated worse performance than a Cox PH with respect to the integrated Brier score (Graf et al. 1999).

### 18.1.2.2 Deterministic Survival Models

Whilst the vast majority of survival ANNs have focused on probabilistic predictions (often via ranking), a few have also tackled the deterministic or ‘hybrid’ problem.

**RankDeepSurv** {#mod-rankdeepsurv}\ Jing *et al.* (Jing et al. 2019) observed the past two decades of research in survival ANNs and then published a completely novel solution, RankDeepSurv, which makes predictions for the survival time  $\hat{T} = (\hat{T}_1, \dots, \hat{T}_n)$ . They proposed a composite loss function

$$L(\hat{T}, \theta | \mathcal{D}_{train}, \alpha, \gamma, \lambda) = \alpha L_1(\hat{T}, T, \Delta) + \gamma L_2(\hat{T}, T, \Delta) + \lambda \|\theta\|_2^2$$

where  $\theta$  are the model weights,  $\alpha, \gamma \in \mathbb{R}_{>0}$ ,  $\lambda$  is the shrinkage parameter, by a slight abuse of notation  $T = (T_1, \dots, T_n)$  and  $\Delta = (\Delta_1, \dots, \Delta_n)$ , and

$$L_1(\hat{T}, \theta | \mathcal{D}_{train}) = \frac{1}{n} \sum_{\{i: I(i)=1\}} (\hat{T}_i - T_i)^2; \quad I(i) = \begin{cases} 1, & \Delta_i = 1 \cup (\Delta_i = 0 \cap \hat{T}_i \leq T_i) \\ 0, & \text{otherwise} \end{cases}$$

$$L_2(\hat{T}, \theta | \mathcal{D}_{train}) = \frac{1}{n} \sum_{\{i,j: I(i,j)=1\}} [(T_j - T_i) - (\hat{T}_j - \hat{T}_i)]^2; \quad I(i,j) = \begin{cases} 1, & T_j - T_i > \hat{T}_j - \hat{T}_i \\ 0, & \text{otherwise} \end{cases}$$

where  $\hat{T}_i$  is the predicted survival time for observation  $i$ . A clear contrast can be made between these loss functions and the constraints used in SSVM-Hybrid (Van Belle et al. 2011) (Section 16.2).  $L_1$  is the squared second constraint in 16.2.3 and  $L_2$  is the squared first constraint in 16.2.3. However  $L_1$  in RankDeepSurv discards the squared error difference for all censored observations when the prediction is lower than the observed survival time; which is problematic as if someone is censored at time  $T_i$  then it is guaranteed that their true survival time is greater than  $T_i$  (this constraint may be more sensible if the inequality were reversed). An advantage to this loss is, like the SSVM-Hybrid, it enables a survival time interpretation for a ranking optimised model; however these ‘survival times’ should be interpreted with care.

The authors propose a model architecture with several fully connected layers with the ELU (Clevert, Unterthiner, and Hochreiter 2015) activation function and a single dropout layer. Determining the success of this model is not straightforward. The authors claim superiority of RankDeepSurv over Cox PH, DeepSurv, and RSFs however this is an unclear comparison (RM2) {sec:car\_reduxstrats\_mistakes} that requires independent study.

### 18.1.3 Conclusions

There have been many advances in neural networks for survival analysis. It is not possible to review all proposed survival neural networks without diverting too far from the book scope. This survey of ANNs should demonstrate two points: firstly that the vast majority (if not all) of survival ANNs are reduction models that either find a way around censoring via imputation or discretisation of time-intervals, or by focusing on partial likelihoods only; secondly that no survival ANN is fully accessible or transparent.

Despite ANNs being highly performant in other areas of supervised learning, there is strong evidence that the survival ANNs above are inferior to a Cox PH when the data follows



the PH assumption or when variables are linearly related (Michael F. Gensheimer and Narasimhan 2018; Luxhoj and Shyur 1997; Ohno-Machado 1997; Puddu and Menotti 2012; Xiang et al. 2000; Yang 2010; Yasodhara, Bhat, and Goldenberg 2018; Zhao and Feng 2020). There are not enough experiments to make conclusions in the case when the data is non-PH. Experiments in (R. E. B. Sonabend 2021) support the finding that survival ANNs are not performant.

There is evidence that many papers introducing neural networks do not utilise proper methods of comparison or evaluation (Franz J. Király, Mateen, and Sonabend 2018) and in conducting this survey, these findings are further supported. Many papers made claims of being ‘superior’ to the Cox model based on unfair comparisons (RM2){sec:car\_reduxstrats\_mistakes} or miscommunicating (or misinterpreting) results (e.g. (Fotso 2018)). At this stage, it does not seem possible to make any conclusions about the effectiveness of neural networks in survival analysis. Moreover, even the authors of these models have pointed out problems with transparency (E. M. Biganzoli, Ambrogi, and Boracchi 2009; Liestol, Andersen, and Andersen 1994), which was further highlighted by Schwarzer *et al.* (Schwarzer, Vach, and Schumacher 2010).

Finally, accessibility of neural networks is also problematic. Many papers do not release their code and instead just state their networks architecture and available packages. In theory, this is enough to build the models however this does not guarantee the reproducibility that is usually expected. For users with a technical background and good coding ability, many of the models above could be implemented in one of the neural network packages in R, such as **nnet** (N. Venables and D. Ripley 2002) and **neuralnet** (Fritsch, Guenther, and N. Wright 2019); though in practice the only package that does contain these models, **survivalmodels**, does not directly implement the models in R (which is much slower than Python) but provides a method for interfacing the Python implementations in **pycox** (Kvamme 2018).



## *Alternative Methods*

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

This survey has not exhaustively covered all machine learning models and entire model classes have been omitted; this short section briefly discusses these classes.

### **Bayesian Models**

In terms of accessibility, many more off-shelf survival model implementations exist in the frequentist framework. Despite this, there is good evidence that Bayesian survival models, such as Bayesian neural networks (Bakker et al. 2004; Faraggi et al. 1997), can perform well (Bishop 2006) and a survey of these models may be explored in future work.

### **Gaussian Processes**

Gaussian Processes (GPs) are a class of model that naturally fit the survival paradigm as they model the joint distribution of random variables over some continuous domain, often time. The simplest extension from a standard Cox model to GP is given by the non-linear hazard

$$h(\tau|X_i) = h_0(\tau)\phi(g(\tau|X_i)); \quad g(\cdot) \sim \mathcal{GP}(0, k)$$

where  $\phi$  is a non-negative link function,  $\mathcal{GP}$  is a Gaussian process (Rasmussen and Williams 2004), and  $k$  is a kernel function with parameters to be estimated (Kim and Pavlovic 2018). Hyper-parameters are learnt by evaluating the likelihood function (Bishop 2006) and in the context of survival analysis this is commonly performed by assuming an inhomogeneous Poisson process (Fernández, Rivera, and Teh 2016; Saul 2016; Vehtari and Joensuu 2013). For a comprehensive survey of GPs for survival, see Saul (2016) (Saul 2016). There is evidence of GPs outperforming Cox and ML models (Fernández, Rivera, and Teh 2016). GPs are excluded from this survey due to lack of implementation (thus accessibility) and poorer transparency. Future research could look at increasing off-shelf accessibility of these models.

### **Non-Supervised Learning**

As well as pure supervised learning, there are also survival models that use active learning (Nezhad et al. 2019), transfer learning, or treat survival analysis as a Markov process. As with GPs, none of these are currently available off-shelf and all require expert knowledge to

be useful. These are not discussed in detail here but a very brief introduction to the Markov Process (MP) set-up is provided to motivate further consideration for the area.

- (2) visualises the survival set-up as a Markov chain. In each discrete time-point  $t_1, \dots, t_{K-1}$ , an individual can either move to the next time-point (and therefore be alive at that time-point), or move to one of the absorbing states ('Dead' and 'Censored'). The final time-point,  $t_K$ , is never visited as an individual must be dead or censored at the end of a study, and hence are last seen alive at  $t_{K-1}$ . In this set-up, data is assumed sequential and the time of death or censoring is determined by the last state at which the individual was seen to be alive, plus one, i.e. if an individual transitions from  $t_k$  to 'Death', then they died at  $t_{k+1}$ . This setting assumes the Markov property, so that the probability of moving to the 'next' state only depends on the current one. This method lends itself naturally to competing risks, which would extend the 'Dead' state to multiple absorbing states for each risk. Additionally, left-censoring can be naturally incorporated without further assumptions (Abner, Charnigo, and Kryscio 2013).

This set-up has been considered in survival both for Markov models and in the context of reinforcement learning (Data Study Group Team 2020), though the latter case is underdeveloped and future research could pursue this further.

## *Choosing Models*

TODO (150-200 WORDS)

**!** Page coming soon!

**We are working on this page and it will be available soon!**



## Part IV

# Reduction Techniques





TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

In this chapter, composition and reduction are formally introduced, defined and demonstrated within survival analysis. Neither of these are novel concepts in general or in survival, with several applications already seen earlier when reviewing models (particularly in neural networks), however a lack of formalisation has led to much repeated work and at times questionable applications (Section 18.1). The primary purpose of this chapter is to formalise composition and reduction for survival and to unify references and strategies for future use. These strategies are introduced in the context of minimal ‘workflows’ and graphical ‘pipelines’ in order to maximise their generalisability. The pipelines discussed in this chapter are implemented in [mlr3proba](#).

A *workflow* is a generic term given to a series of sequential operations. For example a standard ML workflow is fit/predict/evaluate, which means a model is fit, predictions are made, and these are evaluated. In this book, a *pipeline* is the name given to a concrete workflow. Section 21.1 demonstrates how pipelines are represented in this book.

Composition (Section 21.2) is a general process in which an object is built (or composed) from other objects and parameters. Reduction (Section 21.3) is a closely related concept that utilises composition in order to transform one problem into another. Concrete strategies for composition and reduction are detailed in sections Section 21.4 and Section 21.5.

## Notation and Terminology

The notation introduced in Chapter 4 is recapped for use in this chapter: the generative survival template for the survival setting is given by  $(X, T, \Delta, Y, C)$  t.v.i.  $\mathcal{X} \times \mathcal{T} \times \{0, 1\} \times \mathcal{T} \times \mathcal{T}$  where  $\mathcal{X} \subseteq \mathbb{R}^p$  and  $\mathcal{T} \subseteq \mathbb{R}_{\geq 0}$ , where  $C, Y$  are unobservable,  $T := \min\{Y, C\}$ , and  $\Delta = \mathbb{I}(Y = T)$ . Random survival data is given by  $(X_i, T_i, \Delta_i, Y_i, C_i) \stackrel{i.i.d.}{\sim} (X, T, \Delta, Y, C)$ . Usually data will instead be presented as a training dataset,  $\mathcal{D}_{train} = \{(X_1, T_1, \Delta_1), \dots, (X_n, T_n, \Delta_n)\}$  where  $(X_i, T_i, \Delta_i) \stackrel{i.i.d.}{\sim} (X, T, \Delta)$ , and some test data  $\mathcal{D}_{test} = (X^*, T^*, \Delta^*) \sim (X, T, \Delta)$ .

For regression models the generative template is given by  $(X, Y)$  t.v.i.  $\mathcal{X} \subseteq \mathbb{R}^p$  and  $Y \subseteq \mathbb{R}$ . As with the survival setting, a regression training set is given by  $\{(X_1, Y_1), \dots, (X_n, Y_n)\}$  where  $(X_i, Y_i) \stackrel{i.i.d.}{\sim} (X, Y)$  and some test data  $(X^*, Y^*) \sim (X, Y)$ .

## 21.1 Representing Pipelines

Before introducing concrete composition and reduction algorithms, this section briefly demonstrates how these pipelines will be represented in this book.

Pipelines are represented by graphs designed in the following way: all are drawn with operations progressing sequentially from left to right; graphs are comprised of nodes (or ‘vertices’) and arrows (or ‘directed edges’); a rounded rectangular node represents a process such as a function or model fitting/predicting; a (regular) rectangular node represents objects such as data or hyper-parameters. Output from rounded nodes are sometimes explicitly drawn but when omitted the output from the node is the input to the next.

These features are demonstrated in **?@fig-car-example**. Say  $y = 2$  and  $a = 2$ , then: data is provided ( $y = 2$ ) and passed to the shift function ( $f(x) = x + 2$ ), the output of this function ( $y = 4$ ) is passed directly to the next ( $h(x|a) = x^a$ ), this function requires a parameter which is also input ( $a = 2$ ), finally the resulting output is returned ( $y^* = 16$ ). Programmatically,  $a = 2$  would be a hyper-parameter that is stored and passed to the required function when the function is called.

This pipeline is represented as a pseudo-algorithm in (**alg-car-ex?**), though of course is overly complicated and in practice one would just code  $(y + 2)^a$ .

## 21.2 Introduction to Composition

This section introduces composition, defines a taxonomy for describing compositors (Section 21.2.1), and provides some motivating examples of composition in survival analysis (Section 21.2.2).

In the simplest definition, a model (be it mathematical, computational, machine learning, etc.) is called a *composite model* if it is built of two or more constituent parts. This can be simplest defined in terms of objects. Just as objects in the real-world can be combined in some way, so can mathematical objects. The exact ‘combining’ process (or ‘compositor’) depends on the specific composition, so too do the inputs and outputs. By example, a wooden table can be thought of as a composite object (Figure 21.1). The inputs are wood and nails, the combining process is hammering (assuming the wood is pre-chopped), and the output is a surface for eating. In mathematics, this process is mirrored. Take the example of a shifted linear regression model. This is defined by a linear regression model,  $f(x) = \beta_0 + x\beta_1$ , a shifting parameter,  $\alpha$ , and a compositor  $g(x|\alpha) = f(x) + \alpha$ . Mathematically this example is overly trivial as this could be directly modelled with  $f(x) = \alpha + \beta_0 + x\beta_1$ , but algorithmically there is a difference. The composite model  $g$ , is defined by first fitting the linear regression model,  $f$ , and then applying a shift,  $\alpha$ ; as opposed to fitting a directly shifted model.

### Why Composition?

Tables tend to be better surfaces for eating your dinner than bundles of wood. Or in modelling terms, it is well-known that ensemble methods (e.g. random forests) will generally outperform their components (e.g. decision trees). All ensemble methods are composite models and this demonstrates one of the key use-cases of composition: improved predictive

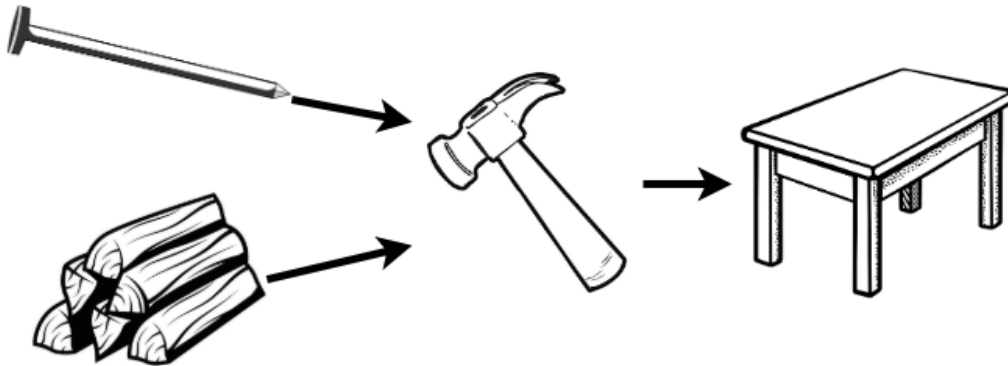


Figure 21.1: Visualising composition in the real-world. A table is a composite object built from nails and wood, which are combined with a hammer ‘compositor’. Figure not to scale.

performance. The second key use-case is reduction, which is fully discussed in Section 21.3. Section 21.2.2 motivates composition in survival analysis by demonstrating how it is already prevalent but requires formalisation to make compositions more transparent and accessible.

### Composite Model vs. Sub-models

A bundle of wood and nails is not a table and 1,000 decision trees are not a random forest, both require a compositor. The compositor in a composite model combines the components into a single model. Considering a composite model as a single model enables the hyper-parameters of the compositor and the component model(s) to be efficiently tuned whilst being evaluated as a single model. This further allows the composite to be compared to other models, including its own components, which is required to justify complexity instead of parsimony in model building (?@sec-eval-why-why).

#### 21.2.1 Taxonomy of Compositors

Just as there are an infinite number of ways to make a table, composition can come in infinite forms. However there are relatively few categories that these can be grouped into. Two primary taxonomies are identified here. The first is the ‘composition type’ and relates to the number of objects composed:

- [i)] i. Single-Object Composition (SOC) – This form of composition either makes use of parameters or a transformation to alter a single object. The shifted linear regression model above is one example of this, another is given in Section 21.4.3.
- i. Multi-Object Composition (MOC) – In contrast, this form of composition combines multiple objects into a single one. Both examples in Section 21.2.2 are multi-object compositions.

The second grouping is the ‘composition level’ and determines at what ‘level’ the composition takes place:

- [i)] i. Prediction Composition – This applies at the level of predictions; the component models could be forgotten at this point. Predictions may be combined from multiple models

(MOC) or transformed from a single model (SOC). Both examples in Section 21.2.2 are prediction compositions. i. Task Composition – This occurs when one task (e.g. regression) is transformed to one or more others (e.g. classification), therefore always SOC. This is seen mainly in the context of reduction (Section 21.3). i. Model Composition – This is commonly seen in the context of wrappers (Section 21.5.1.4), in which one model is contained within another. i. Data Composition – This is transformation of training/testing data types, which occurs at the first stage of every pipeline.

### 21.2.2 Motivation for Composition

Two examples are provided below to demonstrate common uses of composition in survival analysis and to motivate the compositions introduced in Section 21.4.

#### Example 1: Cox Proportional Hazards

Common implementations of well-known models can themselves be viewed as composite models, the Cox PH is the most prominent example in survival analysis. Recall the model defined by

$$h(\tau|X_i) = h_0(\tau) \exp(\beta X_i)$$

where  $h_0$  is the baseline hazard and  $\beta$  are the model coefficients.

This can be seen as a composite model as Cox defines the model in two stages (Cox 1972): first fitting the  $\beta$ -coefficients using the partial likelihood and then by suggesting an estimate for the baseline distribution. This first stage produces a linear predictor return type (Section 6.1) and the second stage returns a survival distribution prediction. Therefore the Cox model for linear predictions is a single (non-composite) model, however when used to make distribution predictions then it is a composite. Cox implicitly describes the model as a composite by writing “alternative simpler procedures would be worth having” (Cox 1972), which implies a decision in fitting (a key feature of composition). This composition is formalised in Section 21.4.1 as a general pipeline (C1). The Cox model utilises the (C1) pipeline with a PH form and Kaplan-Meier baseline.

#### Example 2: Random Survival Forests

Fully discussed in Section 15.1, random survival forests are composed from many individual decision trees via a prediction composition algorithm ((**alg-rsf-pred?**)). In general, random forests perform better than their component decision trees, which tends to be true of all ensemble methods. Aggregation of predictions in survival analysis requires slightly more care than other fields due to the multiple prediction types, however this is still possible and is formalised in Section 21.4.4.

---

## 21.3 Introduction to Reduction

This section introduces reduction, motivates its use in survival analysis (Section 21.3.1), details an abstract reduction pipeline and defines the difference between a complete/incomplete reduction (Section 21.3.2), and outlines some common mistakes that have been observed in the literature when applying reduction (Section 21.3.3).

Reduction is a concept found across disciplines with varying definitions. This report uses the Langford definition: reduction is “a complex problem decomposed into simpler subproblems so that a solution to the subproblems gives a solution to the complex problem” (Langford et al. 2016). Generalisation (or induction) is a common real-world use of reduction, for example sampling a subset of a population in order to estimate population-level results. The true answer (population-level values) may not always be found in this way but very good approximations can be made with simpler sub-problems (sub-sampling).

Reductions are workflows that utilise composition. By including hyper-parameters, even complex reduction strategies can remain relatively flexible. To illustrate reduction by example, recall the table-building example (Section 21.2) in which the task of interest is to acquire a table. The most direct but complex solution is to fell a tree and directly saw it into a table (Figure 21.2, top), clearly this is not a sensible process. Instead the problem can be reduced into simpler sub-problems: saw the tree into bundles of wood, acquire nails, and then use the ‘hammer compositor’ (Figure 21.1) to create a table (Figure 21.2, bottom).

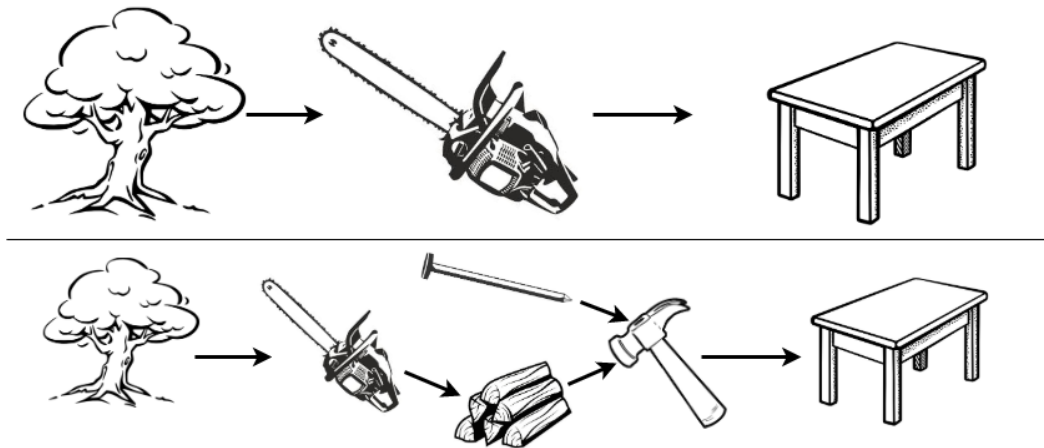


Figure 21.2: Visualising reduction in the real-world. The complex process (top) of directly sawing a tree into a table is inefficient and unnecessarily complex. The reduction (bottom) that involves first creating bundles of wood is simpler, more efficient, and yields the same result, though technically requiring more steps.

In a modelling example, predicting a survival distribution with the Cox model can be viewed as a reduction in which two sub-problems are solved and composed:

- i. predict continuous ranking;
- ii. estimate baseline hazard; and
- iii. compose with (C1) (Section 21.4.1).

This is visualised as a reduction strategy in **fig-car-cargraph**. The entire process from defining the original problem, to combining the simpler sub-solutions (in green), is the reduction (in red).

### 21.3.1 Reduction Motivation

Formalisation of reduction positively impacts upon accessibility, transparency, and predictive performance. Improvements to predictive performance have already been demonstrated when comparing random forests to decision trees. In addition, a reduction with multiple stages and many hyper-parameters allows for fine tuning for improved transparency and model performance (usual overfitting caveat applies, as does the trade-off described in [?@sec-car-pipelines-trade](#)).

The survey of ANNs (Section 18.1) demonstrated how reduction is currently utilised without transparency. Many of these ANNs are implicitly reductions to probabilistic classification (Section 21.5.1.6) however none include details about how the reduction is performed. Furthermore in implementation, none provide interface points to the reduction hyper-parameters. Formalisation encourages consistent terminology, methodology and transparent implementation, which can only improve model performance by exposing further hyper-parameters.

Accessibility is improved by formalising specific reduction workflows that previously demanded expert knowledge in deriving, building, and running these pipelines. All regression reductions in this chapter, are implemented in `\mlr3proba` (R. Sonabend et al. 2021) and can be utilised with any possible survival model.

Finally there is an economic and efficiency advantage to reduction. A reduction model is relatively ‘cheap’ to explore as they utilise pre-established models and components to solve a new problem. Therefore if a certain degree of predictive ability can be demonstrated from reduction models, it may not be worth the expense of pursuing more novel ideas and hence reduction can help direct future research.

### 21.3.2 Task, Loss, and Data Reduction

Reduction can be categorised into task, loss, and data reduction, often these must be used in conjunction with each other. The direction of the reductions may be one- or two-way; this is visualised in [?@fig-car-reduxdiag](#). This diagram should not be viewed as a strict fit/predict/evaluation workflow but instead as a guidance for which tasks,  $T$ , data,  $D$ , models,  $M$ , and losses,  $L$ , are required for each other. The subscript  $O$  refers to the original object ‘level’ before reduction, whereas the subscript  $R$  is in reference to the reduced object.

The individual task, model, and data compositions in the diagram are listed below, the reduction from survival to classification (Section 21.5.1) is utilised as a running example to help exposition.

- $T_O \rightarrow T_R$ : By definition of a machine learning reduction, task reduction will always be one way. A more complex task,  $T_O$ , is reduced to a simpler one,  $T_R$ , for solving.  $T_R$  could also be multiple simpler tasks. For example, solving a survival task,  $T_O$ , by classification,  $T_R$  (Section 21.5.1).
- $T_R \rightarrow M_R$ : All machine learning tasks have models that are designed to solve them. For example logistic regression,  $M_R$ , for classification tasks,  $T_R$ .
- $M_R \rightarrow M_O$ : The simpler models,  $M_R$ , are used for the express purpose to solve the original task,  $T_O$ , via solving the simpler ones. To solve  $T_O$ , a compositor must be applied, which may transform one (SOC) or multiple models (MOC) at a model- or prediction-level, thus creating  $M_O$ . For example predicting survival probabilities with logistic regression,  $M_R$ , at times  $1, \dots, \tau^*$  for some  $\tau^* \in \mathbb{N}_{>0}$  (Section 21.5.1.4).
- $M_O \rightarrow T_O$ : The original task should be solvable by the composite model. For example predicting a discrete survival distribution by concatenating probabilistic predictions at

the times  $1, \dots, \tau^*$  (Section 21.5.1.6).

- $D_O \rightarrow D_R$ : Just as the tasks and models are reduced, the data required to fit these must likewise be reduced. Similarly to task reduction, data reduction can usually only take place in one direction, to see why this is the case take an example of data reduction by summaries. If presented with 10 data-points  $\{1, 1, 1, 5, 7, 3, 5, 4, 3, 3\}$  then these could be reduced to a single point by calculating the sample mean, 3.3. Clearly given only the number 3.3 there is no strategy to recover the original data. There are very few (if any) data reduction strategies that allow recovery of the original data. Continuing the running example, survival data,  $D_O$ , can be binned (Section 21.5.1.1) to classification data,  $D_R$ .

There is no arrow between  $D_O$  and  $M_O$  as the composite model is never fit directly, only via composition from  $M_R \rightarrow M_O$ . However, the original data,  $D_O$ , is required when evaluating the composite model against the respective loss,  $L_O$ .<sup>1</sup> Reduction should be directly comparable to non-reduction models, hence this diagram does not include loss reduction and instead insists that all models are compared against the same loss  $L_O$ .

A reduction is said to be *complete* if there is a full pipeline from  $T_O \rightarrow M_O$  and the original task is solved, otherwise it is *incomplete*. The simplest complete reduction is comprised of the pipeline  $T_O \rightarrow T_R \rightarrow M_R \rightarrow M_O$ . Usually this is not sufficient on its own as the reduced models are fit on the reduced data,  $D_R \rightarrow M_R$ .

A complete reduction can be specified by detailing:

- i. the original task and the sub-task(s) to be solved,  $T_O \rightarrow T_R$ ;
- ii. the original dataset and the transformation to the reduced one,  $D_O \rightarrow D_R$  (if required); and
- iii. the composition from the simpler model to the complex one,  $M_R \rightarrow M_O$ .

### 21.3.3 Common Mistakes in Implementation of Reduction

In surveying models and measures, several common mistakes in the implementation of reduction and composition were found to be particularly prevalent and problematic throughout the literature. It is assumed that these are indeed mistakes (not deliberate) and result from a lack of prior formalisation. These mistakes were even identified 20 years ago (Schwarzer, Vach, and Schumacher 2010) but are provided in more detail in order to highlight their current prevalence and why they cannot be ignored.

RM1. Incomplete reduction. This occurs when a reduction workflow is presented as if it solves the original task but fails to do so and only the reduction strategy is solved. A common example is claiming to solve the survival task by using binary classification, e.g. erroneously claiming that a model predicts survival probabilities (which implies distribution) when it actually predicts a five year probability of death ((**box-task-classif?**)). This is a mistake as it misleads readers into believing that the model solves a survival task ((**box-task-surv?**)) when it does not. This is usually a semantic not mathematical error and results from misuse of terminology. It is important to be clear about model predict types (Section 6.1) and general terms such as ‘survival predictions’ should be avoided unless they refer to one of the three prediction tasks. RM2. Inappropriate comparisons. This is a direct consequence of (RM1) and the two are often seen together. (RM2) occurs when an incomplete reduction is directly compared to a survival model (or complete reduction model) using

<sup>1</sup>A complete diagram would indicate that  $D_O$  is split into training data, which is subsequently reduced, and test data, which is passed to  $L_O$ . All reductions in this section can be applied to any data splitting process.



a measure appropriate for the reduction. This may lead to a reduction model appearing erroneously superior. For example, comparing a logistic regression to a random survival forest (RSF) (Section 15.1) for predicting survival probabilities at a single time using the accuracy measure is an unfair comparison as the RSF is optimised for distribution predictions. This would be non-problematic if a suitable composition is clearly utilised. For example a regression SSVM predicting survival time cannot be directly compared to a Cox PH. However the SSVM can be compared to a CPH composed with the probabilistic to deterministic compositor (C3), then conclusions can be drawn about comparison to the composite survival time Cox model (and not simply a Cox PH). RM3. Naïve censoring deletion. This common mistake occurs when trying to reduce survival to regression or classification by simply deleting all censored observations, even if censoring is informative. This is a mistake as it creates bias in the dataset, which can be substantial if the proportion of censoring is high and informative. More robust deletion methods are described in Chapter 25. RM4. Oversampling uncensored observations. This is often seen when trying to reduce survival to regression or classification, and often alongside (RM3). Oversampling is the process of replicating observations to artificially inflate the sample size of the data. Whilst this process does not create any new information, it can help a model detect important features in the data. However, by only oversampling uncensored observations, this creates a source of bias in the data and ignores the potentially informative information provided by the proportion of censoring.

## 21.4 Composition Strategies for Survival Analysis

Though composition is common practice in survival analysis, with the Cox model being a prominent example, a lack of formalisation means a lack of consensus in simple operations. For example, it is often asked in survival analysis how a model predicting a survival distribution can be used to return a survival time prediction. A common strategy is to define the survival time prediction as the median of the predicted survival curve however there is no clear reason why this should be more sensible than returning the distribution mean, mode, or some random quantile. Formalisation allow these choices to be analytically compared both theoretically and practically as hyper-parameters in a workflow. Four prediction compositions are discussed in this section ((**tab-car-taxredcar?**)), three are utilised to convert prediction types between one another, the fourth is for aggregating multiple predictions. One data composition is discussed for converting survival to regression data. Each is first graphically represented and then the components are discussed in detail. As with losses in the previous chapter, compositions are discussed at an individual observation level but extend trivially to multiple observations.

Table 21.1: Compositions formalised in Section 21.4.

| ID <sup>1</sup> | Composition                      | Type <sup>2</sup> | Level <sup>3</sup> |
|-----------------|----------------------------------|-------------------|--------------------|
| C1)             | Linear predictor to distribution | MOC               | Prediction         |
| C2)             | Survival time to distribution    | MOC               | Prediction         |
| C3)             | Distribution to survival time    | SOC               | Prediction         |
| C4)             | Survival model averaging         | MOC               | Prediction         |
| C5)             | Survival to regression           | SOC               | Data               |



1. ID for reference throughout this book. 2. Composition type. Multi-object composition (MOC) or single-object composition (SOC). 3. Composition level.

### 21.4.1 C1) Linear Predictor $\rightarrow$ Distribution

This is a prediction-level MOC that composes a survival distribution from a predicted linear predictor and estimated baseline survival distribution. The composition (**?@fig-car-comp-distr**) requires:

- $\hat{\eta}$ : Predicted linear predictor.  $\hat{\eta}$  can be tuned by including this composition multiple times in a benchmark experiment with different models predicting  $\hat{\eta}$ . In theory any continuous ranking could be utilised instead of a linear predictor though results may be less sensible (**?@sec-car-pipelines-trade**).
- $\hat{S}_0$ : Estimated baseline survival function. This is usually estimated by the Kaplan-Meier estimator fit on training data,  $\hat{S}_{KM}$ . However any model that can predict a survival distribution can estimate the baseline distribution (caveat: see **?@sec-car-pipelines-trade**) by taking a uniform mixture of the predicted individual distributions: say  $\xi_1, \dots, \xi_m$  are  $m$  predicted distributions, then  $\hat{S}_0(\tau) = \frac{1}{m} \sum_{i=1}^m \xi_i.S(\tau)$ . The mixture is required as the baseline must be the same for all observations. Alternatively, parametric distributions can be assumed for the baseline, e.g.  $\xi = \text{Exp}(2)$  and  $\xi.S(t) = \exp(-2t)$ . As with  $\hat{\eta}$ , this parameter is also tunable.
- $M$ : Chosen model form, which theoretically can be any non-increasing right-continuous function but is usually one of:
  - Proportional Hazards (PH):  $S_{PH}(\tau|\eta, S_0) = S_0(\tau)^{\exp(\eta)}$
  - Accelerated Failure Time (AFT):  $S_{AFT}(\tau|\eta, S_0) = S_0(\frac{\tau}{\exp(\eta)})$
  - Proportional Odds (PO):  $S_{PO}(\tau|\eta, S_0) = \frac{S_0(\tau)}{\exp(-\eta) + (1 - \exp(-\eta))S_0(\tau)}$

Models that predict linear predictors will make assumptions about the model form and therefore dictate sensible choices of  $M$ , for example the Cox model assumes a PH form. This does not mean other choices of  $M$  cannot be specified but that interpretation may be more difficult (**?@sec-car-pipelines-trade**). The model form can be treated as a hyper-parameter to tune. \*  $C$ : Compositor returning the composed distribution,  $\zeta := C(M, \hat{\eta}, \hat{S}_0)$  where  $\zeta$  has survival function  $\zeta.S(\tau) = M(\tau|\hat{\eta}, \hat{S}_0)$ .

Pseudo-code for training (**(alg-car-comp-distr-fit?)**) and predicting (**(alg-car-comp-distr-pred?)**) this composition as a model ‘wrapper’ with sensible parameter choices (**?@sec-car-pipelines-trade**) is provided in appendix (**app-car?**).

### 21.4.2 C2) Survival Time $\rightarrow$ Distribution

This is a prediction-level MOC that composes a distribution from a predicted survival time and assumed location-scale distribution. The composition (**?@fig-car-comp-response**) requires:

- $\hat{T}$ : A predicted survival time. As with the previous composition, this is tunable. In theory any continuous ranking could replace  $\hat{T}$ , though the resulting distribution may not be sensible (**?@sec-car-pipelines-trade**).
- $\xi$ : A specified location-scale distribution,  $\xi(\mu, \sigma)$ , e.g. Normal distribution.

- $\hat{\sigma}$ : Estimated scale parameter for the distribution. This can be treated as a hyper-parameter or predicted by another model.
- $C$ : Compositor returning the composed distribution  $\zeta := C(\xi, \hat{T}, \hat{\sigma}) = \xi(\hat{T}, \hat{\sigma})$ .

Pseudo-code for training ((**alg-car-comp-response-fit?**)) and predicting ((**alg-car-comp-response-pred?**)) this composition as a model ‘wrapper’ with sensible parameter choices (**?@sec-car-pipelines-trade**) is provided in appendix (**app-car?**).

### 21.4.3 C3) Distribution $\rightarrow$ Survival Time Composition

This is a prediction-level SOC that composes a survival time from a predicted distribution. Any paper that evaluates a distribution on concordance is implicitly using this composition in some manner. Not acknowledging the composition leads to unfair model comparison (Section 21.3.3). The composition (**?@fig-car-comp-crank**) requires:

- $\zeta$ : A predicted survival distribution, which again is ‘tunable’.
- $\phi$ : A distribution summary method. Common examples include the mean, median and mode. Other alternatives include distribution quantiles,  $\zeta.F^{-1}(\alpha)$ ,  $\alpha \in [0, 1]$ ;  $\alpha$  could be tuned as a hyper-parameter.
- $C$ : Compositor returning composed survival time predictions,  $\hat{T} := C(\phi, \zeta) = \phi(\zeta)$ .

Pseudo-code for training ((**alg-car-comp-crank-fit?**)) and predicting ((**alg-car-comp-crank-pred?**)) this composition as a model ‘wrapper’ with sensible parameter choices (**?@sec-car-pipelines-trade**) is provided in appendix (**app-car?**).

### 21.4.4 C4) Survival Model Averaging

Ensembling is likely the most common composition in machine learning. In survival it is complicated slightly as multiple prediction types means one of two possible compositions is utilised to average predictions. The (**?@fig-car-comp-avg**) composition requires:

- $\rho = \rho_1, \dots, \rho_B$ :  $B$  predictions (not necessarily from the same model) of the same type: ranking, survival time or distribution; again ‘tunable’.
- $w = w_1, \dots, w_B$ : Weights that sum to one.
- $C$ : Compositor returning combined predictions,  $\hat{\rho} := C(\rho, w)$  where  $C(\rho, w) = \frac{1}{B} \sum_{i=1}^B w_i \rho_i$ , if  $\rho$  are ranking of survival time predictions; or  $C(\rho, w) = \zeta$  where  $\zeta$  is the distribution defined by the survival function  $\zeta.S(\tau) = \frac{1}{B} \sum_{i=1}^B w_i \rho_i.S(\tau)$ , if  $\rho$  are distribution predictions.

Pseudo-code for training ((**alg-car-comp-avg-fit?**)) and predicting ((**alg-car-comp-avg-pred?**)) this composition as a model ‘wrapper’ with sensible parameter choices (**?@sec-car-pipelines-trade**) is provided in appendix (**app-car?**).

---

## 21.5 Novel Survival Reductions

This section collects the various strategies and settings discussed previously into complete reduction workflows. (**tab-car-reduces?**) lists the reductions discussed in this section with IDs for future reference. All strategies are described by visualising a graphical pipeline and then listing the composition steps required in fitting and predicting.

This section only includes novel reduction strategies and does not provide a survey of pre-existing strategies. This limitation is primarily due to time (and page) constraints as every method has very distinct workflows that require complex exposition. Well-established strategies are briefly mentioned below and future research is planned to survey and compare all strategies with respect to empirical performance (i.e. in benchmark experiments).

Two prominent reductions are ‘landmarking’ (Van Houwelingen 2007) and piecewise exponential models (M. Friedman 1982). Both are reductions for time-varying covariates and hence outside the scope of this book. Relevant to this book scope is a large class of strategies that utilise ‘discrete time survival analysis’ (Tutz and Schmid 2016); these strategies include reductions (R7) and (R8). Methodology for discrete time survival analysis has been seen in the literature for the past three decades (Liestol, Andersen, and Andersen 1994). The primary reduction strategy for discrete time survival analysis is implemented in the R package `discSurv` (Welchowski and Schmid 2019); this is very similar to (R7) except that it enforces stricter constraints in the composition procedures and forces a ‘discrete-hazard’ instead of ‘discrete-survival’ representation (Section 21.5.1.2).

### 21.5.1 R7-R8) Survival $\rightarrow$ Probabilistic Classification

Two separate reductions are presented in `?@fig-car-R7R8` however as both are reductions to probabilistic classification and are only different in the very last step, both are presented in this section. Steps and compositions of the reduction (`?@fig-car-R7R8`):

**Fit F1)** A survival dataset,  $\mathcal{D}_{train}$ , is binned,  $B$ , with a continuous to discrete data composition (Section 21.5.1.1). **F2)** A multi-label classification model, with adaptations for censoring,  $g_L(D_B|\theta)$ , is fit on the transformed dataset,  $D_B$ . Optionally,  $g_L$  could be further reduced to binary,  $g_B$ , or multi-class classification,  $g_C$ , (Section 21.5.1.4). **Predict P1)** Testing survival data,  $\mathcal{D}_{test}$ , is passed to the trained classification model,  $\hat{g}$ , to predict pseudo-survival probabilities  $\tilde{S}$  (or optionally hazards (Section 21.5.1.2)). **P2a)** Predictions can be composed,  $T_1$ , into a survival distribution prediction,  $\zeta = \zeta_1, \dots, \zeta_m$  (Section 21.5.1.6); or, **P2b)** Predictions can be composed,  $T_2$ , to survival time predictions,  $\hat{T} = \hat{T}_1, \dots, \hat{T}_m$  (Section 21.5.1.7).

Further details for binning, multi-label classification, and transformation of pseudo-survival probabilities are now provided.

#### 21.5.1.1 Composition: Binning Survival Times

An essential part of the reduction is the transformation from a survival dataset to a classification dataset, which requires two separate compositions. The first (discussed here) is to discretise the survival times ( $B(\mathcal{D}_{train}|w)$  in `?@fig-car-R7R8`) and the second is to merge the survival time and censoring indicator into a single outcome (Section 21.5.1.2).

Discretising survival times is achieved by the common ‘binning’ composition, in which a continuous outcome is discretised into ‘bins’ according to specified thresholds. These thresholds are usually determined by specifying the width of the bins as a hyper-parameter  $w$ .<sup>2</sup> This is a common transformation and therefore further discussion is not provided here. An example is given below with the original survival data on the left and the binned data on the right ( $w = 1$ ).

<sup>2</sup>Binning is described here with equal widths but generalises to unequal widths trivially.

| X | Time (Cont.) | Died |
|---|--------------|------|
| 1 | 1.56         | 0    |
| 2 | 2            | 1    |
| 3 | 3.3          | 1    |
| 4 | 3.6          | 0    |
| 5 | 4            | 0    |

| X | Time (Disc.) | Died |
|---|--------------|------|
| 1 | [1, 2)       | 0    |
| 2 | [2, 3)       | 1    |
| 3 | [3, 4)       | 1    |
| 4 | [3, 4)       | 0    |
| 5 | [4, 5)       | 0    |

### 21.5.1.2 Composition: Survival to Classification Outcome

The binned dataset still has the unique survival data format of utilising two outcomes for training (time and status) but only making a prediction for one outcome (distribution). In order for this to be compatible with classification, the two outcome variables are composed into a single variable.<sup>3</sup> This is achieved by casting the survival times into a ‘wide’ format and creating a new outcome indicator.<sup>4</sup> Two outcome transformations are possible, the first represents a discrete survival function and the second represents a discrete hazard function.<sup>5</sup>

#### Discrete Survival Function Composition

In this composition, the data in the transformed dataset represents the discrete survival function. The new indicator is defined as follows,

$$Y_{i;\tau} := \begin{cases} 1, & T_i > \tau \\ 0, & T_i \leq \tau \cap \Delta_i = 1 \\ -1, & T_i \leq \tau \cap \Delta_i = 0 \end{cases}$$

At a given discrete time  $\tau$ , an observation,  $i$ , is either alive ( $Y_{i;\tau} = 1$ ), dead ( $Y_{i;\tau} = 0$ ), or censored ( $Y_{i;\tau} = -1$ ). Therefore  $\hat{P}(Y_{i;\tau} = 1) = \hat{S}_i(\tau)$ , motivating this particular choice of representation.

This composition is demonstrated below with the binned data (left) and the composed classification data (right).

| X | Time (Disc.) | Died |
|---|--------------|------|
| 1 | [1, 2)       | 0    |
| 2 | [2, 3)       | 1    |

<sup>3</sup>This is the first key divergence from other discrete-time classification strategies, which use the censoring indicator as the outcome and the time outcome as a feature.

<sup>4</sup>This is the second key divergence from other discrete-time classification strategies, which keep the data in a ‘long’ format.

<sup>5</sup>This is the final key divergence from other discrete-time classification strategies, which enforce the discrete hazard representation.

| X | Time (Disc.) | Died |
|---|--------------|------|
| 3 | [3, 4)       | 1    |
| 4 | [3, 4)       | 0    |
| 5 | [4, 5)       | 0    |

| X | [1,2) | [2,3) | [3,4) | [4,5) |
|---|-------|-------|-------|-------|
| 1 | -1    | -1    | -1    | -1    |
| 2 | 1     | 0     | 0     | 0     |
| 3 | 1     | 1     | 0     | 0     |
| 4 | 1     | 1     | -1    | -1    |
| 5 | 1     | 1     | -1    | -1    |

### Discrete Hazard Function Composition

In this composition, the data in the transformed dataset represents the discrete hazard function. The new indicator is defined as follows,

$$Y_{i;\tau}^* := \begin{cases} 1, & T_i = \tau \cap \Delta_i = 1 \\ -1, & T_i = \tau \cap \Delta_i = 0 \\ 0, & \text{otherwise} \end{cases}$$

At a given discrete time  $\tau$ , an observation,  $i$ , either experiences the event ( $Y_{i;\tau}^* = 1$ ), experiences censoring ( $Y_{i;\tau}^* = -1$ ), or neither ( $Y_{i;\tau}^* = 0$ ). Utilising sequential multi-label classification problem transformation methods (Section 21.5.1.4) results in  $\hat{P}(Y_{i;\tau}^* = 1) = \hat{h}_i(\tau)$ . If methods are utilised that do not ‘look back’ at predictions then  $\hat{P}(Y_{i;\tau}^* = 1) = \hat{p}_i(\tau)$  (Section 21.5.1.4).<sup>6</sup>

This composition is demonstrated below with the binned data (left) and the composed classification data (right).

| X | Time (Disc.) | Died |
|---|--------------|------|
| 1 | [1, 2)       | 0    |
| 2 | [2, 3)       | 1    |
| 3 | [3, 4)       | 1    |
| 4 | [3, 4)       | 0    |
| 5 | [4, 5)       | 0    |

| X | [1,2) | [2,3) | [3,4) | [4,5) |
|---|-------|-------|-------|-------|
| 1 | -1    | 0     | 0     | 0     |
| 2 | 0     | 1     | 0     | 0     |
| 3 | 0     | 0     | 1     | 0     |
| 4 | 0     | 0     | -1    | 0     |

<sup>6</sup>This important distinction is not required in other discrete-time reduction strategies that automatically condition the prediction by including time as a feature.

| X | [1,2) | [2,3) | [3,4) | [4,5) |
|---|-------|-------|-------|-------|
| 5 | 0     | 0     | 0     | -1    |

### Multi-Label Classification Data

In both compositions, survival data t.v.i.  $\mathbb{R}^p \times \mathbb{R}_{\geq 0} \times \{0, 1\}$  is transformed to multi-label classification data t.v.i.  $\mathbb{R}^p \times \{-1, 0, 1\}^K$  for  $K$  binned time-intervals. The multi-label classification task is defined in Section 21.5.1.4 with possible algorithms.

The discrete survival representation has a slightly more natural interpretation and is ‘easier’ for classifiers to use for training as there are more positive events (i.e. more observations alive) to train on, whereas the discrete hazard representation will have relatively few events in each time-point. However the hazard representation leads to more natural predictions (Section 21.5.1.6).

A particular bias that may easily result from the composition of survival to classification data is now discussed.

#### 21.5.1.3 Reduction to Classification Bias

The reduction to classification bias is commonly known (Zhou et al. 2005) but is reiterated briefly here as it must be accounted for in any automated reduction to classification workflow. This bias occurs when making classification predictions about survival at a given time and incorrectly censoring patients who have not been observed long enough, instead of removing them.

By example, say the prediction of interest is five-year survival probabilities after a particular diagnosis, clearly a patient who has only been diagnosed for three years cannot inform this prediction. The bias is introduced if this patient is censored at five-years instead of being removed from the dataset. The result of this bias is to artificially inflate the probability of survival at each time-point as an unknown outcome is treated as censored and therefore alive.

This bias is simply dealt with by removing patients who have not been alive ‘long enough’.<sup>7</sup> Paradoxically, even if a patient is observed to die before the time-point of interest, they should still be removed if they have not been in the dataset ‘long enough’ as failing to do so will result in a bias in the opposite direction, thus over-inflating the proportion of dead observations.

Accounting for this bias is particularly important in the multi-label reduction as the number of observable patients will decrease over time due to censoring.

#### 21.5.1.4 Multi-Label Classification Algorithms

As the work in this section is completely out of the book scope, the full text is in appendix (app-mlc?). The most important contributions from this section are:

- Reviewing problem transformation methods (Tsoumakas and Katakis 2007) for multi-label classification;
- Identifying that only binary relevance, nested stacking, and classifier chains are appropriate in this reduction; and

<sup>7</sup>Accounting for this bias is only possible if the study start and end dates are known, as well as the date the patient entered the study.

- Generalising these methods into a single wrapper for any binary classifier, the ‘LWrapper’.

### 21.5.1.5 Censoring in Classification

Classification algorithms cannot natively handle the censoring that is included in the survival reduction, but this can be incorporated using one of two approaches.

#### Multi-Class Classification

All multi-label datasets can also handle multi-class data, hence the simplest way in which to handle censoring is to make multi-class predictions in each label for the outcome  $Y_\tau$  *t.v.i.*  $\{-1, 0, 1\}$ . Many off-shelf classification learners can make multi-class predictions natively and simple reductions exist for those that cannot. As a disadvantage to this method, classifiers would then predict if an individual is dead or alive or censored (each mutually exclusive), and not simply alive or dead. Though this could be perceived as an advantage when censoring is informative as this will accurately reflect a real-world competing-risks set-up.

#### Subsetting/Hurdle Models

For this approach, the multi-class task is reduced to two binary class tasks: first predict if a subject is censored or not (dead or alive) and only if the prediction for censoring is below some threshold,  $\alpha \in [0, 1]$ , then predict if the subject is alive or not (dead or censored). If the probability of censoring is high in the first task then the probability of being alive is automatically set to zero in the final prediction, otherwise the prediction from the second task is used. Any classifier can utilise this approach and it has a meaningful interpretation, additionally  $\alpha$  is a tunable hyper-parameter. The main disadvantage is increases to storage and run-time requirements as double the number of models may be fit.

Once the datasets have been composed to classification datasets and censoring is suitably incorporated by either approach, then any probabilistic classification model can be fit on the data. Predictions from these models can either be composed to a distribution prediction (R7) or a survival time prediction (R8).

### 21.5.1.6 R7) Probabilistic Survival $\rightarrow$ Probabilistic Classification

This final part of the (R7) reduction is described separately for discrete hazard and survival representations of the data (Section 21.5.1.2).

#### Discrete Hazard Representation

In this representation recall that predictions of the positive class,  $P(Y_\tau = 1)$ , are estimating the quantity  $h(\tau)$ . These predictions provide a natural and efficient transformation from predicted hazards to survival probabilities. Let  $\hat{h}_i$  be a predicted hazard function for some observation  $i$ , then the survival function for that observation can be found with a Kaplan-Meier type estimator,

$$\tilde{S}_i(\tau^*) = \prod_{\tau} 1 - \hat{h}_i(\tau)$$

Now predictions are for a pseudo-survival function, which is ‘pseudo’ as it is not right-continuous. Resolving this is discussed below.

### Discrete Survival Representation

In this representation,  $P(Y_\tau = 1)$  is estimating  $S(\tau)$ , which means that predictions from a classification model result in discrete point predictions and not a right-continuous function. More importantly, there is no guarantee that a non-increasing function will be predicted, i.e. there is no guarantee that  $P(Y_j = 1) < P(Y_i = 1)$ , for time-points  $j > i$ .

Unfortunately there is no optimal way of dealing with predictions of this sort and ‘mistakes’ of this kind have been observed in some software implementation. One point to note is that in practice these are quite rare as the probability of survival will always decrease over time. Therefore the ‘usual’ approach is quite ‘hacky’ and involves imputing increasing predictions with the previous prediction, formally,

$$\tilde{S}(i+1) := \min\{P(Y_{i+1} = 1), P(Y_i = 1)\}, \forall i = \mathbb{R}_{\geq 0}$$

assuming  $\tilde{S}(0) = 1$ . Future research should seek more robust alternatives.

### Right-Continuous Survival Function

From either representation, a \ non-increasing but non-continuous pseudo-survival function,  $\tilde{S}$ , is now predicted. Creating a right-continuous function ( $T_1(\tilde{S})$  in **fig-car-R7**) from these point predictions (Figure 21.3 (a)) is relatively simple and well-known with accessible off-shelf software. At the very least, one can assume a constant hazard rate between predictions and cast them into a step function (Figure 21.3 (b)). This is a fairly common assumption and is usually valid as bin-width decreases. Alternatively, the point predictions can be smoothed into a continuous function with off-shelf software, for example with polynomial local regression smoothing (Figure 21.3 (c)) or generalised linear smoothing (Figure 21.3 (d)). Whichever method is chosen, the survival function is now non-increasing right-continuous and the (R7) reduction is complete.

#### 21.5.1.7 R8) Deterministic Survival $\rightarrow$ Probabilistic Classification

Predicting a deterministic survival time from the multi-label classification predictions is relatively straightforward and can be viewed as a discrete analogue to (C3) (Section 21.4.3). For the discrete hazard representation, one can simply take the predicted time-point for an individual to be time at which the predicted hazard probability is highest however this could easily be problematic as there may be multiple time-points at which the predicted hazard equals 1. Instead it is cleaner to first cast the hazard to a pseudo-survival probability (Section 21.5.1.6) and then treat both representations the same.

Let  $\tilde{S}_i$  be the predicted multi-label survival probabilities for an observation  $i$  such that  $\tilde{S}_i(\tau)$  corresponds with  $\hat{P}(Y_{i;\tau} = 1)$  for label  $\tau \in \mathcal{K}$  where  $Y_{i;\tau}$  is defined in Section 21.5.1.2 and  $\mathcal{K} = \{1, \dots, K\}$  is the set of labels for which to make predictions. Then the survival time transformation is defined by

$$T_2(\tilde{S}_i) = \inf\{\tau \in \mathcal{K} : \tilde{S}_i(\tau) \leq \beta\}$$

for some  $\beta \in [0, 1]$ .

This is interpreted as defining the predicted survival time as the first time-point in which the predicted probability of being alive drops below a certain threshold  $\beta$ . Usually  $\beta = 0.5$ , though this can be treated as a hyper-parameter for tuning. This composition can be utilised even if predictions are not non-increasing, as only the first time the predicted survival probability drops below the threshold is considered. With this composition the (R8) reduction is now complete.



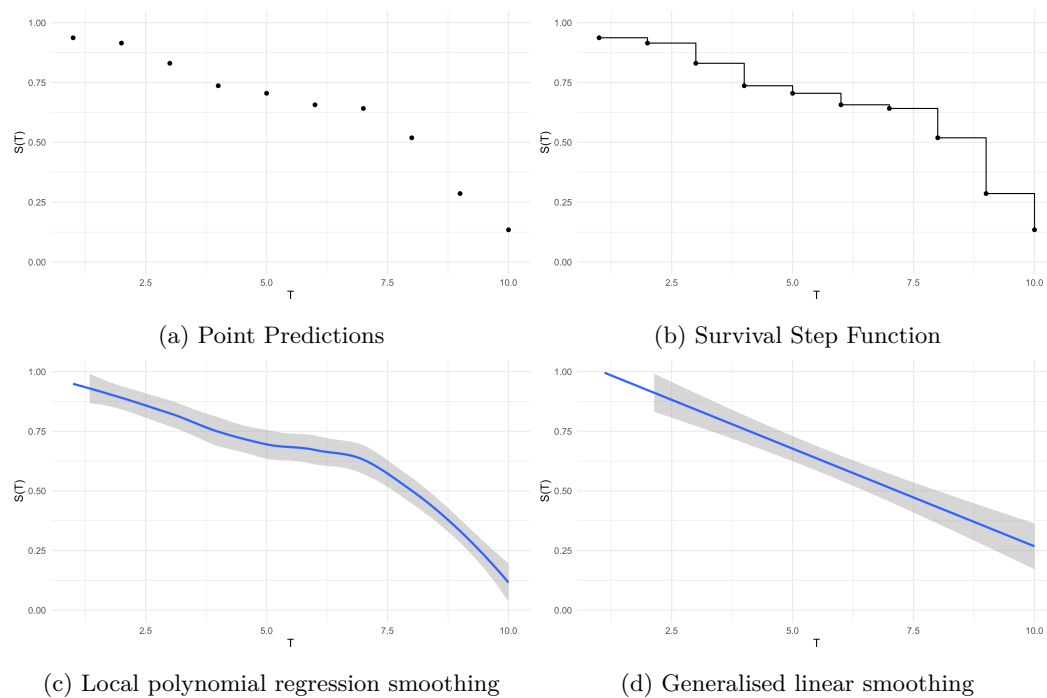


Figure 21.3: Survival function as a: point prediction (a), step function assuming constant risk (b), local polynomial regression smoothing (c), and generalised linear smoothing (d). (c) and (d) computed with [ggplot2](#) (Wickham 2016).

---

## 21.6 Conclusions

This chapter introduced composition and reduction to survival analysis and formalised specific strategies. Formalising these concepts allows for better quality of research and most importantly improved transparency. Clear interface points for hyper-parameters and compositions allow for reproducibility that was previously obfuscated by unclear workflows and imprecise documentation for pipelines.

Additionally, composition and reduction improves accessibility. Reduction workflows vastly increase the number of machine learning models that can be utilised in survival analysis, thus opening the field to those whose experience is limited to regression or classification. Formalisation of workflows allows for precise implementation of model-agnostic pipelines as computational objects, as opposed to functions that are built directly into an algorithm without external interface points.

Finally, predictive performance is also increased by these methods, which is most prominently the case for the survival model averaging compositor (C4) (as demonstrated by RSFs).

All compositions in this chapter, as well as (R1)-(R6), have been implemented in [mlr3proba](#) with the [mlr3pipelines](#) (M. Binder et al. 2019) interface. The reductions to classification will be implemented in a near-future update. Additionally the [discSurv](#) package (Welchowski and Schmid 2019) will be interfaced as a [mlr3proba](#) pipeline to incorporate further discrete-time strategies.

The compositions (C1) and (C3) are included in the benchmark experiment in R. E. B. Sonabend (2021) so that every tested model can make probabilistic survival distribution predictions as well as deterministic survival time predictions. Future research will benchmark all the pipelines in this chapter and will cover algorithm and model selection, tuning, and comparison of performance. Strategies from other papers will also be explored.

## 22

---

### *Competing Risks Pipelines*

TODO (150-200 WORDS)

**!** Page coming soon!

**We are working on this page and it will be available soon!**



## 23

---

### *Discrete Time Survival Analysis*

---

TODO (150-200 WORDS)

**!** Page coming soon!

**We are working on this page and it will be available soon!**



## 24

---

# *Connections to Poisson Regression and Processes*

---

TODO (150-200 WORDS)

! Page coming soon!

We are working on this page and it will be available soon!





## *Connections to Regression and Imputation*

---

TODO (150-200 WORDS)

! Major changes expected!

**This page is a work in progress and major changes will be made over time.**

---

TODO

- I think all these sections should have examples in implemented models, e.g., here we can point to SVM models and some neural nets
- We can also point to neural nets that use reduction to essentially just predict the linear predictor via regression or to use pseudovalues
- Add pseudovalues
- Add prediction of the observed outcome (not survival) time

---

This is a data-level SOC that transforms survival data to regression data by either removing censored observations or ‘imputing’ survival times. This composition is frequently incorrectly utilised (Section 21.3.3) and therefore more detail is provided here than previous compositions. Note that the previous compositions were prediction-level transformations that occur after a survival model makes a prediction, whereas this composition is on a data-level and can take place before model training or predicting.

In Statistics, there are only two methods for removing ‘missing’ values: deletion and imputation; both of these have been attempted for censoring.

Censoring can be beneficial, harmful, or neutral; each will affect the data differently if deleted or imputed. Harmful censoring occurs if the reason for censoring is negative, for example drop-out due to disease progression. Harmful censoring indicates that the true survival time is likely soon after the censoring time. Beneficial censoring occurs if censoring is positive, for example drop-out due to recovery. This indicates that the true survival time is likely far from the censoring time. Finally neutral censoring occurs when no information can be gained about the true survival time from the censoring time. Whilst the first two of these can be considered to be dependent on the outcome, neutral censoring is often the case when censoring is independent of the outcome conditional on the data, which is a standard assumption for the majority of survival models and measures.

### 25.0.0.1 Deletion `#{sec-redux-regr-del}`

Deletion is the process of removing observations from a dataset. This is usually seen in ‘complete case analysis’ in which observations with ‘missingness’, covariates with missing values, are removed from the dataset. In survival analysis this method is somewhat riskier as the subjects to delete depend on the outcome and not the features. Three methods are considered, the first two are a more brute-force approach whereas the third allows for some flexibility and tuning.

#### Complete Deletion

Deleting all censored observations is simple to implement with no computational overhead. Complete deletion results in a smaller regression dataset, which may be significantly smaller if the proportion of censoring is high. If censoring is uninformative, the dataset is suitably large and the proportion of censoring suitably low, then this method can be applied without further consideration. However if censoring is informative then deletion will add bias to the dataset, although the ‘direction’ of bias cannot be known in advance. If censoring is harmful then censored observations will likely have a similar profile to those that died, thus removing censoring will artificially inflate the proportion of those who survive. Conversely if censoring is beneficial then censored observations may be more similar to those who survive, thus removal will artificially inflate the proportion of those who die.

#### Omission

Omission is the process of omitting the censoring indicator from the dataset, thus resulting in a regression dataset that assumes all observations experienced the event. Complete deletion results in a smaller dataset of dead patients, omission results in no sample size reduction but the outcome may be incorrect. This reduction strategy is likely only justified for harmful censoring. In this case the true survival time is likely close to the censoring time and therefore treating censored observations as dead may be a fair assumption.

#### IPCW

If censoring is conditionally-outcome independent then deletion of censored events is possible by using Inverse Probability of Censoring Weights (IPCW). This method has been seen several times throughout this book in the context of models and measures. It has been formalised as a composition technique by Vock *et al.* (2016) (Vock et al. 2016) although their method is limited to binary classification. Their method weights the survival time of uncensored observations by  $w_i = 1/\hat{G}_{KM}(T_i)$  and deletes censored observations, where  $\hat{G}_{KM}$  is the Kaplan-Meier estimate of the censoring distribution fit on training data. As previously discussed, one could instead consider the Akritas (or any other) estimator for  $\hat{G}_{KM}$ .

Whilst this method does provide a ‘safer’ way to delete censored observations, there is not a necessity to do so. Instead consider the following weights

$$w_i = \frac{\Delta_i + \alpha(1 - \Delta_i)}{\hat{G}_{KM}(T_i)} \quad (25.1)$$

where  $\alpha \in [0, 1]$  is a hyper-parameter to tune. Setting  $\alpha = 1$  equally weights censored and uncensored observations and setting  $\alpha = 0$  recovers the setting in which censored observations are deleted. It is assumed  $\hat{G}_{KM}$  is set to some very small  $\epsilon$  when  $\hat{G}_{KM}(T_i) = 0$ . When  $\alpha \neq 0$  this becomes an imputation method, other imputation methods are now discussed.

### 25.0.0.2 Imputation

Imputation methods estimate the values of missing data conditional on non-missing data and other covariates. Whilst the true value of the missing data can never be known, by carefully conditioning on the ‘correct’ covariates, good estimates for the missing value can be obtained to help prevent a loss of data. Imputing outcome data is more difficult than imputing covariate data as models are then trained on ‘fake’ data. However a poor imputation should still be clear when evaluating a model as testing data remains un-imputed. By imputing censoring times with estimated survival times, the censoring indicator can be removed and the dataset becomes a regression dataset.

#### Gamma Imputation

Gamma imputation (D. Jackson et al. 2014) incorporates information about whether censoring is harmful, beneficial, or neutral. The method imputes survival times by generating times from a shifted proportional hazards model

$$h(\tau) = h_0(\tau) \exp(\eta + \gamma)$$

where  $\eta$  is the usual linear predictor and  $\gamma \in \mathbb{R}$  is a hyper-parameter determining the ‘type’ of censoring such that  $\gamma > 0$  indicates harmful censoring,  $\gamma < 0$  indicates beneficial censoring, and  $\gamma = 0$  is neutral censoring. This imputation method has the benefit of being tunable as  $\gamma$  is a hyper-parameter and there is a choice of variables to condition the imputation. No independent experiments exist studying how well this method performs, nor discussing the theoretical properties of the method.

#### MRL

The Mean Residual Lifetime (MRL) estimator has been previously discussed in the context of SVMs (Section 16.2). Here the estimator is extended to serve as an imputation method. Recall the MRL function,  $MRL(\tau|\hat{S}) = \int_{\tau}^{\infty} \hat{S}(u) du / \hat{S}(\tau)$ , where  $\hat{S}$  is an estimate of the survival function of the underlying survival distribution (e.g.  $\hat{S}_{KM}$ ). The MRL is interpreted as the expected remaining survival time after the time-point  $\tau$ . This serves as a natural imputation strategy where given the survival outcome  $(T_i, \Delta_i)$ , the new imputed time  $T'_i$  is given by

$$T'_i = T_i + (1 - \Delta_i)MRL(T_i|\hat{S})$$

where  $\hat{S}$  would be fit on the training data and could be an unconditional estimator, such as Kaplan-Meier, or conditional, such as Akritas. The resulting survival times are interpreted as the true times for those who died and the expected survival times for those who were censored.

#### Buckley-James

Buckley-James (Buckley and James 1979) is another imputation method discussed earlier ([?@sec-surv-ml-models-boost](#)). The Buckley-James method uses an iterative procedure to impute censored survival times by the conditional expectation given censoring times and covariates (Z. Wang and Wang 2010). Given the survival tuple for an outcome  $(T_i, \Delta_i)$ , the new imputed time  $T'_i$  is

$$T'_i = \begin{cases} T_i, & \Delta_i = 1 \\ X_i \hat{\beta} + \frac{1}{\hat{S}_{KM}(e_i)} \sum_{e_i < e_k} \hat{p}_{KM}(e_k) e_k & \Delta_i = 0 \end{cases}$$

where  $\hat{S}_{KM}$  is the Kaplan-Meier estimator of the survival distribution estimated on training data and with associated pmf  $\hat{p}_{KM}$  and  $e_i = T_i - X_i\hat{\beta}$  where  $\hat{\beta}$  are estimated coefficients of a linear regression model fit on  $(X_i, T_i)$ . Given the least squares approach, more parametric assumptions are made than other imputation methods and it is more complex to separate model fitting from imputation. Hence, this imputation may only be appropriate on a limited number of data types.

### Alternative Methods

Other methods have been proposed for ‘imputing’ censored survival times though with either less clear discussion or to no benefit. Multiple imputation by chained equations (MICE) has been demonstrated to perform well with covariate data and even outcome data (in a non-survival setting). However no adaptations have been developed to incorporate censoring times into the imputation and therefore is less informative than Gamma imputation.

Re-calibration of censored survival times (Vinzamuri, Li, and Reddy 2017) uses an iterative update procedure to ‘re-calibrate’ censoring times however the motivation behind the method is not sufficiently clear to be of interest in general survival modelling tasks outside of the authors’ specific pipelines.

Finally parametric imputation is defined by making random draws from truncated probability distributions and adding these to the censoring time (P. Royston 2001; Patrick Royston, Parmar, and Altman 2008). Whilst this method is arguably the simplest method and will lead to a sufficiently random sample, i.e. not one skewed by the imputation process, in practice the randomness leads to unrealistic results, with some imputed times being very far from the original censoring times and some being very close.

#### 25.0.0.3 The Decision to Impute or Delete

Deletion methods are simple to implement and fast to compute however they can lead to biasing the data or a significant sample reduction if used incorrectly. Imputation methods can incorporate tuning and have more relaxed assumptions about the censoring mechanism, though they may lead to over-confidence in the resulting outcome and therefore add bias into the dataset. In some cases, the decision to impute or delete is straightforward, for example if censoring is uninformative and only few observations are censored then complete deletion is appropriate. If it is unknown if censoring is informative then this can crudely be estimated by a benchmark experiment. Classification models can be fit on  $\{(X_1, \Delta_1), \dots, (X_n, \Delta_n)\}$  where  $(X_i, \Delta_i) \in \mathcal{D}_{train}$ . Whilst not an exact test, if any model significantly outperforms a baseline, then this may indicate censoring is informative. This is demonstrated in (**tab-car-predcens?**), in which a logistic regression outperforms a featureless baseline in correctly predicting if an observation is censored when censoring is informative, but is no better than the baseline when censoring is uninformative.

Table 25.1: Estimating censoring dependence by prediction. **Sim1** is informative censoring and **Sim7** is uninformative. Logistic regression is compared to a featureless baseline with the Brier score with standard errors. Censoring can be significantly predicted to 95% confidence when informative (**Sim1**) but not when uninformative (**Sim7**).

| Data        | Baseline          | Logistic Regression |
|-------------|-------------------|---------------------|
| <b>Sim1</b> | 0.20 (0.14, 0.26) | 0.02 (0.01, 0.03)   |
| <b>Sim7</b> | 0.19 (0.14, 0.24) | 0.16 (0.13, 0.19)   |

# 26

---

## *Advanced Methods*

---

TODO (150-200 WORDS)

! Page coming soon!

**We are working on this page and it will be available soon!**



## Part V

# Extensions and Outlook





## *Common problems in survival analysis*

---

! Page coming soon!

We are working on this page and it will be available soon!

---

### 27.1 Evaluation and prediction

- Which time points to make predictions for?
-



## *Survival Software*

---

TODO (150-200 WORDS)

**!** Page coming soon!

**We are working on this page and it will be available soon!**



## 29

---

### *What's next for MLSA?*

---

TODO (150-200 WORDS)

! Page coming soon!

**We are working on this page and it will be available soon!**

Get more context

See Chapter 21 for useful context.

Differences in measures

See Chapter 7 to learn about the differences between survival measures.

Learn more about the C-index

See Chapter 1 to learn more about the C-index.

C-index

Read Chapter 1 to learn about the C-index



---

## ***Exercises***

---

TODO (150-200 WORDS)

**!** Page coming soon!

**We are working on this page and it will be available soon!**





---

## References

---

- Aalen, Odd. 1978. “Nonparametric Inference for a Family of Counting Processes.” *The Annals of Statistics* 6 (4): 701–26.
- Abner, Erin L, Richard J Charnigo, and Richard J Kryscio. 2013. “Markov chains and semi-Markov models in time-to-event analysis.” *Journal of Biometrics & Biostatistics Suppl* 1 (e001): 19522. <https://doi.org/10.4172/2155-6180.S1-e001>.
- Akritas, Michael G. 1994. “Nearest Neighbor Estimation of a Bivariate Distribution Under Random Censoring.” *Ann. Statist.* 22 (3): 1299–1327. <https://doi.org/10.1214/aos/1176325630>.
- Andersen, Per Kragh, Mette Gerster Hansen, and John P. Klein. 2004. “Regression Analysis of Restricted Mean Survival Time Based on Pseudo-Observations.” *Lifetime Data Analysis* 10 (4): 335–50. <https://doi.org/10.1007/s10985-004-4771-0>.
- Andres, Axel, Aldo Montano-Loza, Russell Greiner, Max Uhlich, Ping Jin, Bret Hoehn, David Bigam, James Andrew Mark Shapiro, and Norman Mark Kneteman. 2018. “A novel learning algorithm to predict individual survival after liver transplantation for primary sclerosing cholangitis.” *PLOS ONE* 13 (3): e0193523. <https://doi.org/10.1371/journal.pone.0193523>.
- Antolini, Laura, Patrizia Boracchi, and Elia Biganzoli. 2005. “A time-dependent discrimination index for survival data.” *Statistics in Medicine* 24 (24): 3927–44. <https://doi.org/10.1002/sim.2427>.
- Avati, Anand, Tony Duan, Sharon Zhou, Kenneth Jung, Nigam H. Shah, and Andrew Ng. 2020. “Countdown Regression: Sharp and Calibrated Survival Predictions.” In *Proceedings of Machine Learning Research*, 145—155. <https://proceedings.mlr.press/v115/avati20a.html> <http://arxiv.org/abs/1806.08324>.
- Bakker, Bart, Tom Heskes, Jan Neijt, and Bert Kappen. 2004. “Improving Cox survival analysis with a neural-Bayesian approach.” *Statistics in Medicine* 23 (19): 2989–3012. <https://doi.org/10.1002/sim.1904>.
- Becker, Marc, Lennart Schneider, and Sebastian Fischer. 2024. “Hyperparameter Optimization.” In *Applied Machine Learning Using mlr3 in R*, edited by Bernd Bischl, Raphael Sonabend, Lars Kotthoff, and Michel Lang. CRC Press. [https://mlr3book.mlr-org.com/hyperparameter\\_optimization.html](https://mlr3book.mlr-org.com/hyperparameter_optimization.html).
- Bello, Ghalib A, Timothy J W Dawes, Jinming Duan, Carlo Biffi, Antonio de Marvao, Luke S G E Howard, J Simon R Gibbs, et al. 2019. “Deep-learning cardiac motion analysis for human survival prediction.” *Nature Machine Intelligence* 1 (2): 95–104. <https://doi.org/10.1038/s42256-019-0019-2>.
- Bennett, Steve. 1983. “Analysis of survival data by the proportional odds model.” *Statistics in Medicine* 2 (2): 273–77. <https://doi.org/https://doi.org/10.1002/sim.4780020223>.
- Beyersmann, Jan, Arthur Allignol, and Martin Schumacher. 2012. *Competing Risks and Multistate Models with R*. Use R! New York: Springer.
- Biganzoli, E M, F Ambrogi, and P Boracchi. 2009. “Partial logistic artificial neural networks (PLANN) for flexible modeling of censored survival data.” In *2009 International Joint Conference on Neural Networks*, 340–46. <https://doi.org/10.1109/IJCNN.2009.5178824>.
- Biganzoli, Elia, Patrizia Boracchi, Luigi Mariani, and Ettore Marubini. 1998. “Feed forward

- neural networks for the analysis of censored survival data: a partial logistic regression approach." *Statistics in Medicine* 17 (10): 1169–86. [https://doi.org/10.1002/\(SICI\)1097-0258\(19980530\)17:10%3C1169::AID-SIM796%3E3.0.CO;2-D](https://doi.org/10.1002/(SICI)1097-0258(19980530)17:10%3C1169::AID-SIM796%3E3.0.CO;2-D).
- Binder, Harald, and Martin Schumacher. 2008. "Allowing for mandatory covariates in boosting estimation of sparse high-dimensional survival models." *BMC Bioinformatics* 9 (1): 14. <https://doi.org/10.1186/1471-2105-9-14>.
- Binder, Harold. 2013. "CoxBoost: Cox models by likelihood based boosting for a single survival endpoint or competing risks." CRAN.
- Binder, Martin, Florian Pfisterer, Bernd Bischl, Michel Lang, and Susanne Dandl. 2019. "mlr3pipelines: Preprocessing Operators and Pipelines for 'mlr3'." CRAN. <https://cran.r-project.org/package=mlr3pipelines>.
- Bischl, Bernd, Raphael Sonabend, Lars Kotthoff, and Michel Lang, eds. 2024. *Applied Machine Learning Using mlr3 in R*. CRC Press. <https://mlr3book.mlr-org.com>.
- Bishop, Christopher M. 2006. *Pattern recognition and machine learning*. Springer.
- Blanche, Paul, Jean-François Dartigues, and Hélène Jacqmin-Gadda. 2013. "Review and comparison of ROC curve estimators for a time-dependent outcome with marker-dependent censoring." *Biometrical Journal* 55 (5): 687–704. <https://doi.org/10.1002/bimj.201200045>.
- Blanche, Paul, Aurélien Latouche, and Vivian Viallon. 2012. "Time-dependent AUC with right-censored data: a survey study," October. [https://doi.org/10.1007/978-1-4614-8981-8\\_11](https://doi.org/10.1007/978-1-4614-8981-8_11).
- Bland, J Martin, and Douglas G. Altman. 2004. "The logrank test." *BMJ (Clinical Research Ed.)* 328 (7447): 1073. <https://doi.org/10.1136/bmj.328.7447.1073>.
- Bou-Hamad, Imad, Denis Larocque, and Hatem Ben-Ameur. 2011. "A review of survival trees." *Statist. Surv.* 5: 44–71. <https://doi.org/10.1214/09-SS047>.
- Bower, Hannah, Michael J Crowther, Mark J Rutherford, Therese M.-L. Andersson, Mark Clements, Xing-Rong Liu, Paul W Dickman, and Paul C Lambert. 2019. "Capturing simple and complex time-dependent effects using flexible parametric survival models: A simulation study." *Communications in Statistics - Simulation and Computation*, July, 1–17. <https://doi.org/10.1080/03610918.2019.1634201>.
- Breiman, Leo. 1996. "Bagging Predictors." *Machine Learning* 24 (2): 123–40. <https://doi.org/10.1023/A:1018054314350>.
- Breiman, Leo, and Philip Spector. 1992. "Submodel Selection and Evaluation in Regression. The X-Random Case." *International Statistical Review / Revue Internationale de Statistique* 60 (3): 291–319. <https://doi.org/10.2307/1403680>.
- Brier, Glenn. 1950. "Verification of forecasts expressed in terms of probability." *Monthly Weather Review* 78 (1): 1–3.
- Buckley, Jonathan, and Ian James. 1979. "Linear Regression with Censored Data." *Biometrika* 66 (3): 429–36. <https://doi.org/10.2307/2335161>.
- Buhlmann, Peter. 2006. "Boosting for high-dimensional linear models." *Ann. Statist.* 34 (2): 559–83. <https://doi.org/10.1214/009053606000000092>.
- Buhlmann, Peter, and Torsten Hothorn. 2007. "Boosting Algorithms: Regularization, Prediction and Model Fitting." *Statist. Sci.* 22 (4): 477–505. <https://doi.org/10.1214/07-STS242>.
- Bühlmann, Peter, and Bin Yu. 2003. "Boosting With the L2 Loss." *Journal of the American Statistical Association* 98 (462): 324–39. <https://doi.org/10.1198/0162145030000125>.
- Casalicchio, Giuseppe, and Lukas Burk. 2024. "Evaluation and Benchmarking." In *Applied Machine Learning Using mlr3 in R*, edited by Bernd Bischl, Raphael Sonabend, Lars Kotthoff, and Michel Lang. CRC Press. [https://mlr3book.mlr-org.com/chapters/chapter3/evaluation\\_and\\_benchmarking.html](https://mlr3book.mlr-org.com/chapters/chapter3/evaluation_and_benchmarking.html).
- Chambless, Lloyd E, and Guoqing Diao. 2006. "Estimation of time-dependent area under

- the ROC curve for long-term risk prediction.” *Statistics in Medicine* 25 (20): 3474–86. <https://doi.org/10.1002/sim.2299>.
- Chen, Tianqi, Tong He, Michael Benesty, Vadim Khotilovich, Yuan Tang, Hyunsu Cho, Kailong Chen, et al. 2020. “xgboost: Extreme Gradient Boosting.” CRAN. <https://cran.r-project.org/package=xgboost>.
- Chen, Yen-Chen, Wan-Chi Ke, and Hung-Wen Chiu. 2014. “Risk classification of cancer survival using ANN with gene expression data from multiple laboratories.” *Computers in Biology and Medicine* 48: 1–7. <https://doi.org/10.1016/j.compbiomed.2014.02.006>.
- Chen, Yifei, Zhenyu Jia, Dan Mercola, and Xiaohui Xie. 2013. “A Gradient Boosting Algorithm for Survival Analysis via Direct Optimization of Concordance Index.” Edited by Lev Klebanov. *Computational and Mathematical Methods in Medicine* 2013: 873595. <https://doi.org/10.1155/2013/873595>.
- Ching, Travers. 2015. “Cox-Nnet.” <https://github.com/lanagarmire/cox-nnet>.
- Ching, Travers, Xun Zhu, and Lana X Garmire. 2018. “Cox-nnet: An artificial neural network method for prognosis prediction of high-throughput omics data.” *PLOS Computational Biology* 14 (4): e1006076. <https://doi.org/10.1371/journal.pcbi.1006076>.
- Choodari-Oskoei, Babak, Patrick Royston, and Mahesh K. B. Parmar. 2012. “A simulation study of predictive ability measures in a survival model I: Explained variation measures.” *Statistics in Medicine* 31 (23): 2627–43. <https://doi.org/10.1002/sim.4242>.
- Ciampi, Antonio, Sheila A Hogg, Steve McKinney, and Johanne Thiffault. 1988. “REC-PAM: a computer program for recursive partition and amalgamation for censored survival data and other situations frequently occurring in biostatistics. I. Methods and program features.” *Computer Methods and Programs in Biomedicine* 26 (3): 239–56. [https://doi.org/10.1016/0169-2607\(88\)90004-1](https://doi.org/10.1016/0169-2607(88)90004-1).
- Ciampi, Antonio, Johanne Thiffault, Jean Pierre Nakache, and Bernard Asselain. 1986. “Stratification by stepwise regression, correspondence analysis and recursive partition: a comparison of three methods of analysis for survival data with covariates.” *Computational Statistics and Data Analysis* 4 (3): 185–204. [https://doi.org/10.1016/0167-9473\(86\)90033-2](https://doi.org/10.1016/0167-9473(86)90033-2).
- Clevert, Djork-Arné, Thomas Unterthiner, and Sepp Hochreiter. 2015. “Fast and accurate deep network learning by exponential linear units (elus).” *arXiv Preprint arXiv:1511.07289*.
- Collett, David. 2014. *Modelling Survival Data in Medical Research*. 3rd ed. CRC.
- Collins, Gary S., Joris A. De Groot, Susan Dutton, Omar Omar, Milensu Shanyinde, Abdelouahid Tajar, Merryn Voysey, et al. 2014. “External validation of multivariable prediction models: A systematic review of methodological conduct and reporting.” *BMC Medical Research Methodology* 14 (1): 1–11. <https://doi.org/10.1186/1471-2288-14-40>.
- Colosimo, Enrico, Flávio Ferreira, Maristela Oliveira, and Cleide Sousa. 2002. “Empirical comparisons between Kaplan-Meier and Nelson-Aalen survival function estimators.” *Journal of Statistical Computation and Simulation* 72 (4): 299–308. <https://doi.org/10.1080/00949650212847>.
- Cortes, Corinna, and Vladimir Vapnik. 1995. “Support-Vector Networks.” *Machine Learning* 20: 273–97. <https://doi.org/10.1007/BF00994018>.
- Cox, D. R. 1972. “Regression Models and Life-Tables.” *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 34 (2): 187–220.
- . 1975. “Partial Likelihood.” *Biometrika* 62 (2): 269–76. <https://doi.org/10.1080/03610910701884021>.
- Cui, Lei, Hansheng Li, Wenli Hui, Sitong Chen, Lin Yang, Yuxin Kang, Qirong Bo, and Jun Feng. 2020. “A deep learning-based framework for lung cancer survival analysis with biomarker interpretation.” *BMC Bioinformatics* 21 (1): 112. <https://doi.org/10.1186/s12859-020-02000-0>.

- 1186/s12859-020-3431-z.
- Data Study Group Team. 2020. “Data Study Group Final Report: Great Ormond Street Hospital.” <https://doi.org/10.5281/zenodo.3670726>.
- Dawid, A P. 1984. “Present Position and Potential Developments: Some Personal Views: Statistical Theory: The Prequential Approach.” *Journal of the Royal Statistical Society. Series A (General)* 147 (2): 278–92. <https://doi.org/10.2307/2981683>.
- Dawid, A Philip. 1986. “Probability Forecasting.” *Encyclopedia of Statistical Sciences* 7: 210—218.
- Dawid, A Philip, and Monica Musio. 2014. “Theory and Applications of Proper Scoring Rules.” *Metron* 72 (2): 169–83. <https://arxiv.org/abs/arXiv:1401.0398v1>.
- Demler, Olga V, Nina P Paynter, and Nancy R Cook. 2015. “Tests of calibration and goodness-of-fit in the survival setting.” *Statistics in Medicine* 34 (10): 1659–80. <https://doi.org/10.1002/sim.6428>.
- Demšar, Janez. 2006. “Statistical comparisons of classifiers over multiple data sets.” *Journal of Machine Learning Research* 7 (Jan): 1–30.
- Dietterich, Thomas G. 1998. “Approximate Statistical Tests for Comparing Supervised Classification Learning Algorithms.” *Neural Computation* 10 (7): 1895–1923. <https://doi.org/10.1162/089976698300017197>.
- Efron, Bradley. 1988. “Logistic Regression, Survival Analysis, and the Kaplan-Meier Curve.” *Journal of the American Statistical Association* 83 (402): 414–25. <https://doi.org/10.2307/2288857>.
- Evers, Ludger, and Claudia-Martina Messow. 2008. “Sparse kernel methods for high-dimensional survival data.” *Bioinformatics* 24 (14): 1632–38.
- Faraggi, David, and Richard Simon. 1995. “A neural network model for survival data.” *Statistics in Medicine* 14 (1): 73–82. <https://doi.org/10.1002/sim.4780140108>.
- Faraggi, David, R Simon, E Yaskil, and A Kramar. 1997. “Bayesian Neural Network Models for Censored Data.” *Biometrical Journal* 39 (5): 519–32. <https://doi.org/10.1002/bimj.4710390502>.
- Fernández, Tamara, Nicolas Nicolás Rivera, and Yee Whye Teh. 2016. “Gaussian Processes for Survival Analysis.” In *Advances in Neural Information Processing Systems*. Vol. 29. Nips. Curran Associates, Inc. <http://arxiv.org/abs/1611.00817> <https://proceedings.neurips.cc/paper/2016/file/ef1e491a766ce3127556063d49bc2f98-Paper.pdf>.
- Fleming, Thomas R, Judith R O’Fallon, Peter C O’Brien, and David P Harrington. 1980. “Modified Kolmogorov-Smirnov Test Procedures with Application to Arbitrarily Right-Censored Data.” *Biometrics* 36 (4): 607–25. <https://doi.org/10.2307/2556114>.
- Foss, Natalie, and Lars Kotthoff. 2024. “Data and Basic Modeling.” In *Applied Machine Learning Using mlr3 in R*, edited by Bernd Bischl, Raphael Sonabend, Lars Kotthoff, and Michel Lang. CRC Press. [https://mlr3book.mlr-org.com/data\\_and\\_basic\\_modeling.html](https://mlr3book.mlr-org.com/data_and_basic_modeling.html).
- Fotso, Stephane. 2018. “Deep Neural Networks for Survival Analysis Based on a Multi-Task Framework.” *arXiv Preprint arXiv:1801.05512*, January. <http://arxiv.org/abs/1801.05512>.
- Fouodo, Cesaire J K, I König, C Weihs, A Ziegler, and M Wright. 2018. “Support vector machines for survival analysis with R.” *The R Journal* 10 (July): 412–23.
- Freund, Yoav, and Robert E Schapire. 1996. “Experiments with a new boosting algorithm.” In. Citeseer.
- Friedman, Jerome. 1999. “Stochastic Gradient Boosting.” *Computational Statistics & Data Analysis* 38 (March): 367–78. [https://doi.org/10.1016/S0167-9473\(01\)00065-2](https://doi.org/10.1016/S0167-9473(01)00065-2).
- Friedman, Jerome H. 2001. “Greedy Function Approximation: A Gradient Boosting Machine.” *The Annals of Statistics* 29 (5): 1189–1232. <http://www.jstor.org/stable/2699986>.

- Friedman, Michael. 1982. "Piecewise exponential models for survival data with covariates." *The Annals of Statistics* 10 (1): 101–13.
- Fritsch, Stefan, Frauke Guenther, and Marvin N. Wright. 2019. "neuralnet: Training of Neural Networks." CRAN. <https://cran.r-project.org/package=neuralnet>.
- Gelfand, Alan E, Sujit K Ghosh, Cindy Christiansen, Stephen B Soumerai, and Thomas J McLaughlin. 2000. "Proportional hazards models: a latent competing risk approach." *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 49 (3): 385–97. <https://doi.org/https://doi.org/10.1111/1467-9876.00199>.
- Gensheimer, Michael F., and Balasubramanian Narasimhan. 2018. "A Simple Discrete-Time Survival Model for Neural Networks," 1–17. <https://doi.org/arXiv:1805.00917v3>.
- Gensheimer, Michael F, and Balasubramanian Narasimhan. 2019. "A scalable discrete-time survival model for neural networks." *PeerJ* 7: e6257.
- Georgousopoulou, Ekavi N, Christos Pitsavos, Christos Mary Yannakoulia, and Demosthenes B Panagiotakos. 2015. "Comparisons between Survival Models in Predicting Cardiovascular Disease Events : Application in the ATTICA Study ( 2002-2012 )." *Journal of Statistics Applications & Probability* 4 (2): 203–10.
- Gerds, Thomas A, and Martin Schumacher. 2006. "Consistent Estimation of the Expected Brier Score in General Survival Models with Right-Censored Event Times." *Biometrical Journal* 48 (6): 1029–40. <https://doi.org/10.1002/bimj.200610301>.
- Giunchiglia, Eleonora, Anton Nemchenko, and Mihaela van der Schaar. 2018. "Rnn-surv: A deep recurrent model for survival analysis." In *International Conference on Artificial Neural Networks*, 23–32. Springer.
- Gneiting, Tilmann, and Adrian E Raftery. 2007. "Strictly Proper Scoring Rules, Prediction, and Estimation." *Journal of the American Statistical Association* 102 (477): 359–78. <https://doi.org/10.1198/016214506000001437>.
- Goli, Shahrbanoo, Hossein Mahjub, Javad Faradmal, Hoda Mashayekhi, and Ali-Reza Soltanian. 2016. "Survival Prediction and Feature Selection in Patients with Breast Cancer Using Support Vector Regression." Edited by Francesco Pappalardo. *Computational and Mathematical Methods in Medicine* 2016: 2157984. <https://doi.org/10.1155/2016/2157984>.
- Goli, Shahrbanoo, Hossein Mahjub, Javad Faradmal, and Ali-Reza Soltanian. 2016. "Performance Evaluation of Support Vector Regression Models for Survival Analysis: A Simulation Study." *International Journal of Advanced Computer Science and Applications* 7 (June). <https://doi.org/10.14569/IJACSA.2016.070650>.
- Gompertz, Benjamin. 1825. "On the Nature of the Function Expressive of the Law of Human Mortality, and on a New Mode of Determining the Value of Life Contingencies." *Philosophical Transactions of the Royal Society of London* 115: 513–83.
- Gönen, Mithat, and Glenn Heller. 2005. "Concordance Probability and Discriminatory Power in Proportional Hazards Regression." *Biometrika* 92 (4): 965–70.
- Good, I J. 1952. "Rational Decisions." *Journal of the Royal Statistical Society. Series B (Methodological)* 14 (1): 107–14. <http://www.jstor.org/stable/2984087>.
- Gordon, Louis, and Richard A Olshen. 1985. "Tree-structured survival analysis." *Cancer Treatment Reports* 69 (10): 1065–69.
- Graf, Erika, Claudia Schmoor, Willi Sauerbrei, and Martin Schumacher. 1999. "Assessment and comparison of prognostic classification schemes for survival data." *Statistics in Medicine* 18 (17-18): 2529–45. [https://doi.org/10.1002/\(SICI\)1097-0258\(19990915/30\)18:17/18%3C2529::AID-SIM274%3E3.0.CO;2-5](https://doi.org/10.1002/(SICI)1097-0258(19990915/30)18:17/18%3C2529::AID-SIM274%3E3.0.CO;2-5).
- Graf, Erika, and Martin Schumacher. 1995. "An Investigation on Measures of Explained Variation in Survival Analysis." *Journal of the Royal Statistical Society. Series D (The Statistician)* 44 (4): 497–507. <https://doi.org/10.2307/2348898>.
- Greenwell, Brandon, Bradley Boehmke, Jay Cunningham, and. GBM Developers. 2019.



- “gbm: Generalized Boosted Regression Models.” CRAN. <https://cran.r-project.org/package=gbm>.
- Gressmann, Frithjof, Franz J. Király, Bilal Mateen, and Harald Oberhauser. 2018. “Probabilistic supervised learning.” <https://doi.org/10.1002/iub.552>.
- Habibi, Danial, Mohammad Rafiei, Ali Chehrei, Zahra Shayan, and Soheil Tafaqodi. 2018. “Comparison of Survival Models for Analyzing Prognostic Factors in Gastric Cancer Patients.” *Asian Pacific Journal of Cancer Prevention : APJCP* 19 (3): 749–53. <https://doi.org/10.22034/APJCP.2018.19.3.749>.
- Haider, Humza, Bret Hoehn, Sarah Davis, and Russell Greiner. 2020. “Effective ways to build and evaluate individual survival distributions.” *Journal of Machine Learning Research* 21 (85): 1–63.
- Han, Ilkyu, June Hyuk Kim, Heeseol Park, Han-Soo Kim, and Sung Wook Seo. 2018. “Deep learning approach for survival prediction for patients with synovial sarcoma.” *Tumor Biology* 40 (9): 1010428318799264. <https://doi.org/10.1177/1010428318799264>.
- Han, Kyunghwa, and Inkyung Jung. 2022. “Restricted Mean Survival Time for Survival Analysis: A Quick Guide for Clinical Researchers.” *Korean Journal of Radiology* 23 (5): 495–99. <https://doi.org/10.3348/kjr.2022.0061>.
- Harrell, F E Jr, K L Lee, R M Califf, D B Pryor, and R A Rosati. 1984. “Regression modelling strategies for improved prognostic prediction.” *Statistics in Medicine* 3 (2): 143–52. <https://doi.org/10.1002/sim.4780030207>.
- Harrell, Frank E., Robert M. Califf, and David B. Pryor. 1982. “Evaluating the yield of medical tests.” *JAMA* 247 (18): 2543–46. <http://dx.doi.org/10.1001/jama.1982.03320430047030>.
- Harrell, Frank E., Kerry L. Lee, and Daniel B. Mark. 1996. “Multivariable Prognostic Models: Issues in Developing Models, Evaluating Assumptions and Adequacy, and Measuring and Reducing Errors.” *Statistics in Medicine* 15: 361–87. [https://doi.org/10.1002/0470023678.ch2b\(i\)](https://doi.org/10.1002/0470023678.ch2b(i)).
- Hastie, Trevor, Robert Tibshirani, and Jerome Friedman. 2001. *The Elements of Statistical Learning*. Springer New York Inc.
- Heagerty, Patrick J., Thomas Lumley, and Margaret S. Pepe. 2000. “Time-Dependent ROC Curves for Censored Survival Data and a Diagnostic Marker.” *Biometrics* 56 (2): 337–44. <https://doi.org/10.1111/j.0006-341X.2000.00337.x>.
- Heagerty, Patrick J., and Yingye Zheng. 2005. “Survival Model Predictive Accuracy and ROC Curves.” *Biometrics* 61 (1): 92–105. <https://doi.org/10.1111/j.0006-341X.2005.030814.x>.
- Henderson, and Velleman. 1981. “Building multiple regression models interactively.” *Biometrics* 37: 391—411.
- Herrmann, Moritz, Philipp Probst, Roman Hornung, Vindi Jurinovic, and Anne-Laure Boulesteix. 2021. “Large-scale benchmark study of survival prediction methods using multi-omics data.” *Briefings in Bioinformatics* 22 (3). <https://doi.org/10.1093/bib/bbaa167>.
- Hielscher, Thomas, Manuela Zucknick, Wiebke Werft, and Axel Benner. 2010. “On the Prognostic Value of Gene Expression Signatures for Censored Data BT - Advances in Data Analysis, Data Handling and Business Intelligence.” In, edited by Andreas Fink, Berthold Lausen, Wilfried Seidel, and Alfred Ultsch, 663–73. Berlin, Heidelberg: Springer Berlin Heidelberg.
- Hosmer, David W, and Stanley Lemeshow. 1980. “Goodness of fit tests for the multiple logistic regression model.” *Communications in Statistics-Theory and Methods* 9 (10): 1043–69.
- Hosmer Jr, David W, Stanley Lemeshow, and Susanne May. 2011. *Applied survival analysis: regression modeling of time-to-event data*. Vol. 618. John Wiley & Sons.
- Hothorn, Torsten, Peter Buehlmann, Thomas Kneib, Matthias Schmid, and Benjamin

- Hofner. 2020. “mboost: Model-Based Boosting.” CRAN. <https://cran.r-project.org/package=mboost>.
- Hothorn, Torsten, Peter Bühlmann, Sandrine Dudoit, Annette Molinaro, and Mark J Van Der Laan. 2005. “Survival ensembles.” *Biostatistics* 7 (3): 355–73. <https://doi.org/10.1093/biostatistics/kxj011>.
- Hothorn, Torsten, Kurt Hornik, and Achim Zeileis. 2006. “Unbiased Recursive Partitioning: A Conditional Inference Framework.” *Journal of Computational and Graphical Statistics* 15 (3): 651—674.
- Hothorn, Torsten, and Berthold Lausen. 2003. “On the exact distribution of maximally selected rank statistics.” *Computational Statistics & Data Analysis* 43 (2): 121–37. [https://doi.org/10.1016/S0167-9473\(02\)00225-6](https://doi.org/10.1016/S0167-9473(02)00225-6).
- Hothorn, Torsten, Berthold Lausen, Axel Benner, and Martin Radespiel-Tröger. 2004. “Bagging survival trees.” *Statistics in Medicine* 23 (1): 77–91. <https://doi.org/10.1002/sim.1593>.
- Hothorn, Torsten, and Achim Zeileis. 2015. “partykit: A Modular Toolkit for Recursive Partytioning in R.” *Journal of Machine Learning Research* 16: 3905–9. <http://jmlr.org/papers/v16/hothorn15a.html>.
- Huang, Shigao, Jie Yang, Simon Fong, and Qi Zhao. 2020a. “Artificial intelligence in cancer diagnosis and prognosis: Opportunities and challenges.” *Cancer Letters* 471: 61–71. <https://doi.org/https://doi.org/10.1016/j.canlet.2019.12.007>.
- . 2020b. “Artificial intelligence in cancer diagnosis and prognosis: Opportunities and challenges.” *Cancer Letters* 471: 61–71. <https://doi.org/https://doi.org/10.1016/j.canlet.2019.12.007>.
- Hung, Hung, and Chin-Tsang Chiang. 2010. “Estimation methods for time-dependent AUC models with survival data.” *The Canadian Journal of Statistics / La Revue Canadienne de Statistique* 38 (1): 8–26. <http://www.jstor.org/stable/27805213>.
- Hurvich, Clifford M, and Chih-Ling Tsai. 1979. “Comparison of Four Tests for Equality of Survival Curves in the Presence of Stratification and Censoring.” *Biometrika* 66 (3): 419–28. <https://doi.org/10.1093/biomet/76.2.297>.
- Ishwaran, By Hemant, Udaya B Kogalur, Eugene H Blackstone, and Michael S Lauer. 2008. “Random survival forests.” *The Annals of Statistics* 2 (3): 841–60. <https://doi.org/10.1214/08-AOAS169>.
- Ishwaran, Hemant, Eugene H Blackstone, Claire E Pothier, and Michael S Lauer. 2004. “Relative Risk Forests for Exercise Heart Rate Recovery as a Predictor of Mortality.” *Journal of the American Statistical Association* 99 (467): 591–600. <https://doi.org/10.1198/016214504000000638>.
- Ishwaran, Hemant, and Udaya B Kogalur. 2018. “randomForestSRC.” <https://cran.r-project.org/package=randomForestSRC>.
- Jackson, Christopher. 2016. “flexsurv: A Platform for Parametric Survival Modeling in R.” *Journal of Statistical Software* 70 (8): 1–33.
- Jackson, Dan, Ian R. White, Shaun Seaman, Hannah Evans, Kathy Baisley, and James Carpenter. 2014. “Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation.” *Statistics in Medicine* 33 (27): 4681–94. <https://doi.org/10.1002/sim.6274>.
- Jager, Kitty J, Paul C van Dijk, Carmine Zoccali, and Friedo W Dekker. 2008. “The analysis of survival data: the Kaplan–Meier method.” *Kidney International* 74 (5): 560–65. <https://doi.org/https://doi.org/10.1038/ki.2008.217>.
- James, Gareth, Daniela Witten, Trevor Hastie, and Robert Tibshirani. 2013. *An introduction to statistical learning*. Vol. 112. New York: Springer.
- Jing, Bingzhong, Tao Zhang, Zixian Wang, Ying Jin, Kuiyuan Liu, Wenze Qiu, Liangru Ke, et al. 2018. “RankDeepSurv.” <https://github.com/sysucc-ailab/RankDeepSurv>.

- , et al. 2019. “A deep survival analysis method based on ranking.” *Artificial Intelligence in Medicine* 98: 1–9. <https://doi.org/https://doi.org/10.1016/j.artmed.2019.06.001>.
- Johnson, Brent A, and Qi Long. 2011. “Survival ensembles by the sum of pairwise differences with application to lung cancer microarray studies.” *Ann. Appl. Stat.* 5 (2A): 1081–101. <https://doi.org/10.1214/10-AOAS426>.
- Kalbfleisch, J. D., and R. L. Prentice. 1973. “Marginal likelihoods based on Cox’s regression and life model.” *Biometrika* 60 (2): 267–78. <https://doi.org/10.1093/biomet/60.2.267>.
- Kalbfleisch, John D, and Ross L Prentice. 2011. *The statistical analysis of failure time data*. Vol. 360. John Wiley & Sons.
- Kamarudin, Adina Najwa, Trevor Cox, and Ruwanthi Kolamunnage-Dona. 2017. “Time-dependent ROC curve analysis in medical research: Current methods and applications.” *BMC Medical Research Methodology* 17 (1): 1–19. <https://doi.org/10.1186/s12874-017-0332-6>.
- Kaplan, E. L., and Paul Meier. 1958. “Nonparametric Estimation from Incomplete Observations.” *Journal of the American Statistical Association* 53 (282): 457–81. <https://doi.org/10.2307/2281868>.
- Katzman, Jared L, Uri Shaham, Alexander Cloninger, Jonathan Bates, Tingting Jiang, and Yuval Kluger. 2018. “DeepSurv: personalized treatment recommender system using a Cox proportional hazards deep neural network.” *BMC Medical Research Methodology* 18 (1): 24. <https://doi.org/10.1186/s12874-018-0482-1>.
- Katzman, Jared, Uri Shaham, Alexander Cloninger, Jonathan Bates, Tingting Jiang, and Yuval Kluger. 2016. “Deep Survival: A Deep Cox Proportional Hazards Network,” June.
- Kent, John T., and John O’Quigley. 1988. “Measures of dependence for censored survival data.” *Biometrika* 75 (3): 525–34. <https://doi.org/10.1093/biomet/75.3.525>.
- Khan, Faisal M., and Valentina Bayer Zubek. 2008. “Support vector regression for censored data (SVRc): A novel tool for survival analysis.” *Proceedings - IEEE International Conference on Data Mining, ICDM*, 863–68. <https://doi.org/10.1109/ICDM.2008.50>.
- Kim, Minyoung, and Vladimir Pavlovic. 2018. “Variational Inference for Gaussian Process Models for Survival Analysis.” *UAI*, 435–45.
- Király, Franz J., Markus Löning, Anthony Blaom, Ahmed Guecioueur, and Raphael Sonabend. 2021. “Designing Machine Learning Toolboxes: Concepts, Principles and Patterns.” *arXiv*, January. <http://arxiv.org/abs/2101.04938>.
- Király, Franz J, Bilal Mateen, and Raphael Sonabend. 2018. “NIPS - Not Even Wrong? A Systematic Review of Empirically Complete Demonstrations of Algorithmic Effectiveness in the Machine Learning and Artificial Intelligence Literature.” *arXiv*, December. <http://arxiv.org/abs/1812.07519>.
- Kirmani, S N U A, and Ramesh C Gupta. 2001. “On the Proportional Odds Model in Survival Analysis.” *Annals of the Institute of Statistical Mathematics* 53 (2): 203–16. <https://doi.org/10.1023/A:1012458303498>.
- Klein, John P, and Melvin L Moeschberger. 2003. *Survival analysis: techniques for censored and truncated data*. 2nd ed. Springer Science & Business Media.
- Kohavi, Ron. 1995. “A study of cross-validation and bootstrap for accuracy estimation and model selection.” *Ijcai* 14 (2): 1137–45.
- Korn, Edward L., and Richard Simon. 1990. “Measures of explained variation for survival data.” *Statistics in Medicine* 9 (5): 487–503. <https://doi.org/10.1002/sim.4780090503>.
- Korn, Edward L, and Richard Simon. 1991. “Explained Residual Variation, Explained Risk, and Goodness of Fit.” *The American Statistician* 45 (3): 201–6. <https://doi.org/10.2307/2684290>.
- Kvamme, Håvard. 2018. “Pycox.” <https://pypi.org/project/pycox/>.
- Kvamme, Håvard, Ørnulf Borgan, and Ida Scheel. 2019. “Time-to-event prediction with



- neural networks and Cox regression.” *Journal of Machine Learning Research* 20 (129): 1–30.
- Land, Walker H, Xingye Qiao, Dan Margolis, and Ron Gottlieb. 2011. “A new tool for survival analysis: evolutionary programming/evolutionary strategies (EP/ES) support vector regression hybrid using both censored / non-censored (event) data.” *Procedia Computer Science* 6: 267–72. <https://doi.org/https://doi.org/10.1016/j.procs.2011.08.050>.
- Langford, John, Paul Mineiro, Alina Beygelzimer, and Hal Daume. 2016. “Learning Reductions that Really Work.” *Proceedings of the IEEE* 104 (1).
- Lao, Jiangwei, Yinsheng Chen, Zhi-Cheng Li, Qihua Li, Ji Zhang, Jing Liu, and Guangtao Zhai. 2017. “A Deep Learning-Based Radiomics Model for Prediction of Survival in Glioblastoma Multiforme.” *Scientific Reports* 7 (1): 10353. <https://doi.org/10.1038/s41598-017-10649-8>.
- Lawless, Jerald F, and Yan Yuan. 2010. “Estimation of prediction error for survival models.” *Statistics in Medicine* 29 (2): 262–74. <https://doi.org/10.1002/sim.3758>.
- LeBlanc, Michael, and John Crowley. 1992. “Relative Risk Trees for Censored Survival Data.” *Biometrics* 48 (2): 411–25. <https://doi.org/10.2307/2532300>.
- . 1993. “Survival Trees by Goodness of Split.” *Journal of the American Statistical Association* 88 (422): 457–67. <https://doi.org/10.2307/2290325>.
- Lee, Changhee, William Zame, Jinsung Yoon, and Mihaela 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). <https://doi.org/10.1609/aaai.v32i1.11842>.
- Lee, Donald K K, Ningyuan Chen, and Hemant Ishwaran. 2019. “Boosted nonparametric hazards with time-dependent covariates.” <https://arxiv.org/abs/arXiv:1701.07926v6>.
- Li, Liang, Tom Greene, and Bo Hu. 2018. “A simple method to estimate the time-dependent receiver operating characteristic curve and the area under the curve with right censored data.” *Statistical Methods in Medical Research* 27 (8): 2264–78. <https://doi.org/10.1177/0962280216680239>.
- Liang, Hua, and Guohua Zou. 2008. “Improved AIC Selection Strategy for Survival Analysis.” *Computational Statistics & Data Analysis* 52 (5): 2538–48. <https://doi.org/10.1016/j.csda.2007.09.003>.
- Liestol, Knut, Per Kragh Andersen, and Ulrich Andersen. 1994. “Survival analysis and neural nets.” *Statistics in Medicine* 13 (12): 1189–1200. <https://doi.org/10.1002/sim.4780131202>.
- Lundberg, Scott M, and Su-In Lee. 2017. “A Unified Approach to Interpreting Model Predictions.” *Advances in Neural Information Processing Systems* 30.
- Lundin, M, J Lundin, H B Burke, S Toikkanen, L Pylkkänen, and H Joensuu. 1999. “Artificial Neural Networks Applied to Survival Prediction in Breast Cancer.” *Oncology* 57 (4): 281–86. <https://doi.org/10.1159/000012061>.
- Luxhoj, James T., and Huan Jyh Shyr. 1997. “Comparison of proportional hazards models and neural networks for reliability estimation.” *Journal of Intelligent Manufacturing* 8 (3): 227–34. <https://doi.org/10.1023/A:1018525308809>.
- Ma, Shuangge, and Jian Huang. 2006. “Regularized ROC method for disease classification and biomarker selection with microarray data.” *Bioinformatics (Oxford, England)* 21 (January): 4356–62. <https://doi.org/10.1093/bioinformatics/bti724>.
- Mani, D R, James Drew, Andrew Betz, and Piew Datta. 1999. “Statistics and data mining techniques for lifetime value modeling.” In *Proceedings of the Fifth ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, 94–103.
- Mariani, L, D Coradini, E Biganzoli, P Boracchi, E Marubini, S Pilotti, B Salvadori, et al. 1997. “Prognostic factors for metachronous contralateral breast cancer: A comparison of the linear Cox regression model and its artificial neural network extension.” *Breast Can-*

- cer Research and Treatment* 44 (2): 167–78. <https://doi.org/10.1023/A:1005765403093>.
- Mayr, Andreas, Benjamin Hofner, and Matthias Schmid. 2016. “Boosting the discriminatory power of sparse survival models via optimization of the concordance index and stability selection.” *BMC Bioinformatics* 17 (1): 288. <https://doi.org/10.1186/s12859-016-1149-8>.
- Mayr, Andreas, and Matthias Schmid. 2014. “Boosting the concordance index for survival data—a unified framework to derive and evaluate biomarker combinations.” *PloS One* 9 (1): e84483–83. <https://doi.org/10.1371/journal.pone.0084483>.
- McKinney, Scott Mayer, Marcin Sieniek, Varun Godbole, Jonathan Godwin, Natasha Antropova, Hutan Ashrafian, Trevor Back, et al. 2020. “International evaluation of an AI system for breast cancer screening.” *Nature* 577 (7788): 89–94. <https://doi.org/10.1038/s41586-019-1799-6>.
- Meinshausen, Nicolai, and Peter Bühlmann. 2010. “Stability selection.” *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 72 (4): 417–73. <https://doi.org/10.1111/j.1467-9868.2010.00740.x>.
- Moghimidehkordi, Bijan, Azadeh Safaee, Mohamad Amin Pourhoseingholi, Reza Fatemi, Ziauddin Tabeie, and Mohammad Reza Zali. 2008. “Statistical Comparison of Survival Models for Analysis of Cancer Data.” *Asian Pacific Journal of Cancer Prevention* 9: 417–20.
- Molnar, Christoph. 2019. *Interpretable Machine Learning*. <https://christophm.github.io/interpretable-ml-book/>.
- Murphy, Allan H. 1973. “A New Vector Partition of the Probability Score.” *Journal of Applied Meteorology and Climatology* 12 (4): 595–600. [https://doi.org/10.1175/1520-0450\(1973\)012%3C0595:ANVPOT%3E2.0.CO;2](https://doi.org/10.1175/1520-0450(1973)012%3C0595:ANVPOT%3E2.0.CO;2).
- N. Venables, W, and B D. Ripley. 2002. *Modern Applied Statistics with S*. Springer. <http://www.stats.ox.ac.uk/pub/MASS4>.
- Nadeau, Claude, and Yoshua Bengio. 2003. “Inference for the Generalization Error.” *Machine Learning* 52 (3): 239–81. <https://doi.org/10.1023/A:1024068626366>.
- Nair, Vinod, and Geoffrey E Hinton. 2010. “Rectified linear units improve restricted boltzmann machines.” In *Proceedings of the 27th International Conference on Machine Learning (ICML-10)*, 807–14.
- Nasejje, Justine B, Henry Mwambi, Keertan Dheda, and Maia Lesosky. 2017. “A comparison of the conditional inference survival forest model to random survival forests based on a simulation study as well as on two applications with time-to-event data.” *BMC Medical Research Methodology* 17 (1): 115. <https://doi.org/10.1186/s12874-017-0383-8>.
- Nelson, Wayne. 1972. “Theory and Applications of Hazard Plotting for Censored Failure Data.” *Technometrics* 14 (4): 945–66.
- Nezhad, Milad Zafar, Najibesadat Sadati, Kai Yang, and Dongxiao Zhu. 2019. “A Deep Active Survival Analysis approach for precision treatment recommendations: Application of prostate cancer.” *Expert Systems with Applications* 115: 16–26. <https://doi.org/https://doi.org/10.1016/j.eswa.2018.07.070>.
- Ng, Ryan, Kathy Kornas, Rinku Sutradhar, Walter P. Wodchis, and Laura C. Rosella. 2018. “The current application of the Royston-Parmar model for prognostic modeling in health research: a scoping review.” *Diagnostic and Prognostic Research* 2 (1): 4. <https://doi.org/10.1186/s41512-018-0026-5>.
- Oh, Sung Eun, Sung Wook Seo, Min-Gew Choi, Tae Sung Sohn, Jae Moon Bae, and Sung Kim. 2018. “Prediction of Overall Survival and Novel Classification of Patients with Gastric Cancer Using the Survival Recurrent Network.” *Annals of Surgical Oncology* 25 (5): 1153–59. <https://doi.org/10.1245/s10434-018-6343-7>.
- Ohno-Machado, Lucila. 1996. “Medical applications of artificial neural networks: connectionist models of survival.” Stanford University Stanford, Calif.
- . 1997. “A COMPARISON OF COX PROPORTIONAL HAZARDS AND ARTIFI-

- CIAL NEURAL NETWORK MODELS FOR MEDICAL PROGNOSIS The theoretical advantages and disadvantages of using different methods for predicting survival have seldom been tested in real data sets [ 1 , 2 ]. Althou.” *Comput. Biol. Med* 27 (1): 55–65.
- Patel, Katie, Richard Kay, and Lucy Rowell. 2006. “Comparing proportional hazards and accelerated failure time models: An application in influenza.” *Pharmaceutical Statistics* 5 (3): 213–24. <https://doi.org/10.1002/pst.213>.
- Peters, Andrea, and Torsten Hothorn. 2019. “ipred: Improved Predictors.” CRAN. <https://cran.r-project.org/package=ipred>.
- Pölsterl, Sebastian. 2020. “scikit-survival: A Library for Time-to-Event Analysis Built on Top of scikit-learn.” *Journal of Machine Learning Research* 21 (212): 1—6. <http://jmlr.org/papers/v21/20-729.html>.
- Probst, Philipp, Anne-Laure Boulesteix, and Bernd Bischl. 2019. “Tunability: Importance of Hyperparameters of Machine Learning Algorithms.” *Journal of Machine Learning Research* 20 (53): 1–32. <http://jmlr.org/papers/v20/18-444.html>.
- Puddu, Paolo Emilio, and Alessandro Menotti. 2012. “Artificial neural networks versus proportional hazards Cox models to predict 45-year all-cause mortality in the Italian Rural Areas of the Seven Countries Study.” *BMC Medical Research Methodology* 12 (1): 100. <https://doi.org/10.1186/1471-2288-12-100>.
- Qi, Jiezh. 2009. “Comparison of Proportional Hazards and Accelerated Failure Time Models.” PhD thesis.
- R., Cox, and Snell J. 1968. “A General Definition of Residuals.” *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 30 (2): 248–75.
- Rahman, M. Shafiqur, Gareth Ambler, Babak Choodari-Oskooei, and Rumana Z. Omar. 2017. “Review and evaluation of performance measures for survival prediction models in external validation settings.” *BMC Medical Research Methodology* 17 (1): 1–15. <https://doi.org/10.1186/s12874-017-0336-2>.
- Rasmussen, C. E., and C. K. I. Williams. 2004. *Gaussian processes for machine learning*. Vol. 14. 2. <https://doi.org/10.1142/S0129065704001899>.
- Reid, Nancy. 1994. “A Conversation with Sir David Cox.” *Statistical Science* 9 (3): 439–55. <https://doi.org/10.1214/aos/1176348654>.
- Ridgeway, Greg. 1999. “The state of boosting.” *Computing Science and Statistics* 31: 172–181.
- Rietschel, Carl, Jinsung Yoon, and Mihaela van der Schaar. 2018. “Feature Selection for Survival Analysis with Competing Risks using Deep Learning.” *arXiv Preprint arXiv:1811.09317*.
- Rindt, David, Robert Hu, David Steinsaltz, and Dino Sejdinovic. 2022. “Survival Regression with Proper Scoring Rules and Monotonic Neural Networks,” March. <http://arxiv.org/abs/2103.14755>.
- Ripley, Brian D, and Ruth M Ripley. 2001. “Neural networks as statistical methods in survival analysis.” In *Clinical Applications of Artificial Neural Networks*, edited by Richard Dybowski and Vanya Gant, 237–55. Cambridge: Cambridge University Press. <https://doi.org/DOI: 10.1017/CBO9780511543494.011>.
- Ripley, R M, A L Harris, and L Tarassenko. 1998. “Neural network models for breast cancer prognosis.” *Neural Computing & Applications* 7 (4): 367–75. <https://doi.org/10.1007/BF01428127>.
- Royston, P. 2001. “The Lognormal Distribution as a Model for Survival Time in Cancer, With an Emphasis on Prognostic Factors.” *Statistica Neerlandica* 55 (1): 89–104. <https://doi.org/10.1111/1467-9574.00158>.
- Royston, Patrick, and Douglas G. Altman. 2013. “External validation of a Cox prognostic model: Principles and methods.” *BMC Medical Research Methodology* 13 (1). <https://doi.org/10.1186/1471-2288-13-33>.

- Royston, Patrick, Mahesh K B Parmar, and Douglas G Altman. 2008. "Visualizing Length of Survival in Time-to-Event Studies: A Complement to Kaplan–Meier Plots." *JNCI: Journal of the National Cancer Institute* 100 (2): 92–97. <https://doi.org/10.1093/jnci/djm265>.
- Royston, Patrick, and Mahesh K. B. Parmar. 2002. "Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects." *Statistics in Medicine* 21 (15): 2175–97. <https://doi.org/10.1002/sim.1203>.
- Royston, Patrick, and Willi Sauerbrei. 2004. "A new measure of prognostic separation in survival data." *Statistics in Medicine* 23 (5): 723–48. <https://doi.org/10.1002/sim.1621>.
- Sashegyi, Andreas, and David Ferry. 2017. "On the Interpretation of the Hazard Ratio and Communication of Survival Benefit." *The Oncologist* 22 (4): 484–86. <https://doi.org/10.1634/theoncologist.2016-0198>.
- Saul, Alan D. 2016. "Gaussian Process Based Approaches for Survival Analysis." University of Sheffield.
- Schemper, Michael, and Robin Henderson. 2000. "Predictive Accuracy and Explained Variation in Cox Regression." *Biometrics* 56: 249–55. <https://doi.org/10.1002/sim.1486>.
- Schmid, Matthias, Thomas Hielscher, Thomas Augustin, and Olaf Gefeller. 2011. "A Robust Alternative to the Schemper-Henderson Estimator of Prediction Error." *Biometrics* 67 (2): 524–35. <https://doi.org/10.1111/j.1541-0420.2010.01459.x>.
- Schmid, Matthias, and Torsten Hothorn. 2008a. "Boosting additive models using component-wise P-splines." *Computational Statistics & Data Analysis* 53 (2): 298–311.
- . 2008b. "Flexible boosting of accelerated failure time models." *BMC Bioinformatics* 9 (February): 269. <https://doi.org/10.1186/1471-2105-9-269>.
- Schmid, Matthias, and Sergej Potapov. 2012. "A comparison of estimators to evaluate the discriminatory power of time-to-event models." *Statistics in Medicine* 31 (23): 2588–2609. <https://doi.org/10.1002/sim.5464>.
- Schwarzer, Guido, Werner Vach, and Martin Schumacher. 2010. "Estimation of prediction error for survival models." *Statistics in Medicine* 29 (2): 262–74. [https://doi.org/10.1002/\(SICI\)1097-0258\(20000229\)19:4%3C541::AID-SIM355%3E3.0.CO;2-V](https://doi.org/10.1002/(SICI)1097-0258(20000229)19:4%3C541::AID-SIM355%3E3.0.CO;2-V).
- Segal, Mark Robert. 1988. "Regression Trees for Censored Data." *Biometrics* 44 (1): 35–47.
- Seker, H, M O Odetayo, D Petrovic, R N G Naguib, C Bartoli, L Alasio, M S Lakshmi, G V Sherbet, and O R Hinton. 2002. "An artificial neural network based feature evaluation index for the assessment of clinical factors in breast cancer survival analysis." In *IEEE CCECE2002. Canadian Conference on Electrical and Computer Engineering. Conference Proceedings (Cat. No.02CH37373)*, 2:1211–1215 vol.2. <https://doi.org/10.1109/CCECE.2002.1013121>.
- Seker, Huseyin, Michael O Odetayo, Dobrila Petrovic, Raouf N G Naguib, C Bartoli, L Alasio, M S Lakshmi, and G V Sherbet. 2002. "Assessment of nodal involvement and survival analysis in breast cancer patients using image cytometric data: statistical, neural network and fuzzy approaches." *Anticancer Research* 22 (1A): 433–38. <http://europepmc.org/abstract/MED/12017328>.
- Shivaswamy, Pannagadatta K., Wei Chu, and Martin Jansche. 2007. "A support vector approach to censored targets." In *Proceedings - IEEE International Conference on Data Mining, ICDM*, 655–60. <https://doi.org/10.1109/ICDM.2007.93>.
- Sonabend, Raphael. 2020. "survivalmodels: Models for Survival Analysis." CRAN. <https://raphaels1.r-universe.dev/ui#package:survivalmodels>.
- . 2022. "Scoring rules in survival analysis," December. <http://arxiv.org/abs/2212.05260>.
- Sonabend, Raphael Edward Benjamin. 2021. "A Theoretical and Methodological Frame-

- work for Machine Learning in Survival Analysis: Enabling Transparent and Accessible Predictive Modelling on Right-Censored Time-to-Event Data.” PhD, University College London (UCL). <https://discovery.ucl.ac.uk/id/eprint/10129352/>.
- Sonabend, Raphael, Andreas Bender, and Sebastian Vollmer. 2022. “Avoiding C-hacking when evaluating survival distribution predictions with discrimination measures.” Edited by Zhiyong Lu. *Bioinformatics* 38 (17): 4178–84. <https://doi.org/10.1093/bioinformatics/btac451>.
- Sonabend, Raphael, Franz J Király, Andreas Bender, Bernd Bischl, and Michel Lang. 2021. “mlr3proba: an R package for machine learning in survival analysis.” Edited by Jonathan Wren. *Bioinformatics* 37 (17): 2789–91. <https://doi.org/10.1093/bioinformatics/btab039>.
- Sonabend, Raphael, Florian Pfisterer, Alan Mishler, Moritz Schauer, Lukas Burk, Sumantrak Mukherjee, and Sebastian Vollmer. 2022. “Flexible Group Fairness Metrics for Survival Analysis.” In *DSHealth 2022 Workshop on Applied Data Science for Healthcare at KDD2022*. <http://arxiv.org/abs/2206.03256>.
- Song, Xiao, and Xiao-Hua Zhou. 2008. “A semiparametric approach for the covariate specific ROC curve with survival outcome.” *Statistica Sinica* 18 (July): 947–65.
- Spooner, Annette, Emily Chen, Arcot Sowmya, Perminder Sachdev, Nicole A Kochan, Julian Trollor, and Henry Brodaty. 2020. “A comparison of machine learning methods for survival analysis of high-dimensional clinical data for dementia prediction.” *Scientific Reports* 10 (1): 20410. <https://doi.org/10.1038/s41598-020-77220-w>.
- Spruance, Spotswood L, Julia E Reid, Michael Grace, and Matthew Samore. 2004. “Hazard ratio in clinical trials.” *Antimicrobial Agents and Chemotherapy* 48 (8): 2787–92. <https://doi.org/10.1128/AAC.48.8.2787-2792.2004>.
- Srivastava, Nitish, Geoffrey Hinton, Alex Krizhevsky, Ilya Sutskever, and Ruslan Salakhutdinov. 2014. “Dropout: a simple way to prevent neural networks from overfitting.” *The Journal of Machine Learning Research* 15 (1): 1929–58.
- Stasinopoulos, Mikis, Bob Rigby, Vlasios Voudouris, and Daniil Kiose. 2020. “gamlss.add: Extra Additive Terms for Generalized Additive Models for Location Scale and Shape.” CRAN. <https://cran.r-project.org/package=gamlss.add>.
- Street, W Nick. 1998. “A Neural Network Model for Prognostic Prediction.” In *Proceedings of the Fifteenth International Conference on Machine Learning*. San Francisco.
- Therneau, Terry M. 2015. “A Package for Survival Analysis in S.” <https://cran.r-project.org/package=survival>.
- Therneau, Terry M., and Beth Atkinson. 2019. “rpart: Recursive Partitioning and Regression Trees.” CRAN.
- Therneau, Terry M., and Elizabeth Atkinson. 2020. “Concordance.” <https://cran.r-project.org/web/packages/survival/vignettes/concordance.pdf>.
- Therneau, Terry M., Patricia M. Grambsch, and Thomas R. Fleming. 1990. “Martingale-based residuals for survival models.” *Biometrika* 77 (1): 147–60. <https://doi.org/10.1093/biomet/77.1.147>.
- Tsoumakas, Grigorios, and Ioannis Katakis. 2007. “Multi-Label Classification: An Overview.” *International Journal of Data Warehousing and Mining* 3 (3): 1–13. <https://doi.org/10.4018/jdwm.2007070101>.
- Tutz, Gerhard, and Harald Binder. 2007. “Boosting Ridge Regression.” *Computational Statistics & Data Analysis* 51 (February): 6044–59. <https://doi.org/10.1016/j.csda.2006.11.041>.
- Tutz, Gerhard, and Matthias Schmid. 2016. *Modeling Discrete Time-to-Event Data*. Springer Series in Statistics. Cham: Springer International Publishing. <https://doi.org/10.1007/978-3-319-28158-2>.
- Uno, Hajime, Tianxi Cai, Michael J. Pencina, Ralph B. D’Agostino, and L J Wei. 2011.



- “On the C-statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data.” *Statistics in Medicine* 30 (10): 1105–17. <https://doi.org/10.1002/sim.4154>.
- Uno, Hajime, Tianxi Cai, Lu Tian, and L J Wei. 2007. “Evaluating Prediction Rules for t-Year Survivors with Censored Regression Models.” *Journal of the American Statistical Association* 102 (478): 527–37. <http://www.jstor.org/stable/27639883>.
- Ushey, Kevin, J J Allaire, and Yuan Tang. 2020. “reticulate: Interface to 'Python'.” CRAN. <https://cran.r-project.org/package=reticulate>.
- Vakulenko-Lagun, Bella, Micha Mandel, and Rebecca A. Betensky. 2020. “Inverse Probability Weighting Methods for Cox Regression with Right-Truncated Data.” *Biometrics* 76 (2): 484–95. <https://doi.org/10.1111/biom.13162>.
- Van Belle, Vanya, Kristiaan Pelckmans, Johan A K Suykens, and Sabine Van Huffel. 2008. “Survival SVM: a practical scalable algorithm.” In *Proceedings of the 16th European Symposium on Artificial Neural Networks (ESANN)*, 89–94.
- Van Belle, Vanya, Kristiaan Pelckmans, Johan A. K. Suykens, and Sabine Van Huffel. 2007. “Support Vector Machines for Survival Analysis.” In *In Proceedings of the Third International Conference on Computational Intelligence in Medicine and Healthcare*. 1.
- Van Belle, Vanya, Kristiaan Pelckmans, Sabine Van Huffel, and Johan A. K. Suykens. 2011. “Support vector methods for survival analysis: A comparison between ranking and regression approaches.” *Artificial Intelligence in Medicine* 53 (2): 107–18. <https://doi.org/10.1016/j.artmed.2011.06.006>.
- Van Houwelingen, Hans C. 2000. “Validation, calibration, revision and combination of prognostic survival models.” *Statistics in Medicine* 19 (24): 3401–15. [https://doi.org/10.1002/1097-0258\(20001230\)19:24%3C3401::AID-SIM554%3E3.0.CO;2-2](https://doi.org/10.1002/1097-0258(20001230)19:24%3C3401::AID-SIM554%3E3.0.CO;2-2).
- . 2007. “Dynamic prediction by landmarking in event history analysis.” *Scandinavian Journal of Statistics* 34 (1): 70–85. <https://doi.org/10.1111/j.1467-9469.2006.00529.x>.
- Vehtari, Aki, and Heikki Joensuu. 2013. “A Gaussian processes model for survival analysis with time dependent covariates and interval censoring.” [https://users.aalto.fi/~sim\\$ave/VehtariJoensuu\\_GIST\\_CT\\_timing\\_poster\\_2013.pdf](https://users.aalto.fi/~sim$ave/VehtariJoensuu_GIST_CT_timing_poster_2013.pdf).
- Vinzamuri, Bhanukiran, Yan Li, and Chandan K. Reddy. 2017. “Pre-processing censored survival data using inverse covariance matrix based calibration.” *IEEE Transactions on Knowledge and Data Engineering* 29 (10): 2111–24. <https://doi.org/10.1109/TKDE.2017.2719028>.
- Vock, David M, Julian Wolfson, Sunayan Bandyopadhyay, Gediminas Adomavicius, Paul E Johnson, Gabriela Vazquez-Benitez, and Patrick J O'Connor. 2016. “Adapting machine learning techniques to censored time-to-event health record data: A general-purpose approach using inverse probability of censoring weighting.” *Journal of Biomedical Informatics* 61: 119–31. <https://doi.org/https://doi.org/10.1016/j.jbi.2016.03.009>.
- Volinsky, Chris T, and Adrian E Raftery. 2000. “Bayesian Information Criterion for Censored Survival Models.” *International Biometric Society* 56 (1): 256–62.
- Wang, Hong, and Gang Li. 2017. “A Selective Review on Random Survival Forests for High Dimensional Data.” *Quantitative Bio-Science* 36 (2): 85–96. <https://doi.org/10.22283/qbs.2017.36.2.85>.
- Wang, Ping, Yan Li, and Chandan K. Reddy. 2019. “Machine Learning for Survival Analysis.” *ACM Computing Surveys* 51 (6): 1–36. <https://doi.org/10.1145/3214306>.
- Wang, Zhu. 2019. “bujar: Buckley-James Regression for Survival Data with High-Dimensional Covariates.” CRAN. <https://cran.r-project.org/package=bujar>.
- Wang, Zhu, and C Y Wang. 2010. “Buckley-James Boosting for Survival Analysis with High-Dimensional Biomarker Data.” *Statistical Applications in Genetics and Molecular Biology* 9 (1). <https://doi.org/https://doi.org/10.2202/1544-6115.1550>.
- Wei, L J. 1992. “The Accelerated Failure Time Model: A Useful Alternative to the Cox

- Regression Model in Survival Analysis.” *Statistics in Medicine* 11: 1871–79.
- Welchowski, Thomas, and Matthias Schmid. 2019. “discSurv: Discrete Time Survival Analysis.” CRAN. <https://cran.r-project.org/package=discSurv>.
- Wickham, Hadley. 2016. *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. <https://ggplot2.tidyverse.org>.
- Wright, Marvin N., and Andreas Ziegler. 2017. “ranger: A Fast Implementation of Random Forests for High Dimensional Data in C++ and R.” *Journal of Statistical Software* 77 (1): 1—17.
- Xiang, Anny, Pablo Lapuerta, Alex Ryutov, Jonathan Buckley, and Stanley Azen. 2000. “Comparison of the performance of neural network methods and Cox regression for censored survival data.” *Computational Statistics & Data Analysis* 34 (2): 243–57. [https://doi.org/https://doi.org/10.1016/S0167-9473\(99\)00098-5](https://doi.org/https://doi.org/10.1016/S0167-9473(99)00098-5).
- Yang, Yanying. 2010. “Neural Network Survival Analysis.” PhD thesis, Universiteit Gent.
- Yasodhara, Angeline, Mamatha Bhat, and Anna Goldenberg. 2018. *Prediction of New Onset Diabetes after Liver Transplant*.
- Zare, Ali, Mostafa Hosseini, Mahmood Mahmoodi, Kazem Mohammad, Hojjat Zeraati, and Kourosh Holakouie Naieni. 2015. “A Comparison between Accelerated Failure-time and Cox Proportional Hazard Models in Analyzing the Survival of Gastric Cancer Patients.” *Iranian Journal of Public Health* 44 (8): 1095–1102. <https://doi.org/10.1007/s00606-006-0435-8>.
- Zhang, Yucheng, Edriss M Lobo-Mueller, Paul Karanicolas, Steven Gallinger, Masoom A Haider, and Farzad Khalvati. 2020. “CNN-based survival model for pancreatic ductal adenocarcinoma in medical imaging.” *BMC Medical Imaging* 20 (1): 11. <https://doi.org/10.1186/s12880-020-0418-1>.
- Zhao, Lili, and Dai Feng. 2020. “Deep Neural Networks for Survival Analysis Using Pseudo Values.” *IEEE Journal of Biomedical and Health Informatics* 24 (11): 3308–14. <https://doi.org/10.1109/JBHI.2020.2980204>.
- Zhou, Zheng, Elham Rahme, Michal Abrahamowicz, and Louise Pilote. 2005. “Survival Bias Associated with Time-to-Treatment Initiation in Drug Effectiveness Evaluation: A Comparison of Methods.” *American Journal of Epidemiology* 162 (10): 1016–23. <https://doi.org/10.1093/aje/kwi307>.
- Zhu, Wan, Longxiang Xie, Jianye Han, and Xiangqian Guo. 2020. “The Application of Deep Learning in Cancer Prognosis Prediction.” *Cancers* 12 (3): 603. <https://doi.org/10.3390/cancers12030603>.
- Zhu, X, J Yao, and J Huang. 2016. “Deep convolutional neural network for survival analysis with pathological images.” In *2016 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 544–47. <https://doi.org/10.1109/BIBM.2016.7822579>.

---

## *Index*

---

ggplot2, 151  
discSurv, 145, 152  
mlr3pipelines, 152  
mlr3proba, 135, 140, 152  
renv, 5