

# A boosting algorithm to extend first-hitting time models to a high-dimensional survival setting

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This master's thesis is submitted under the master's program *Modelling and Data Analysis*, with program option *Statistics and Data Analysis*, at the Department of Mathematics, University of Oslo. The scope of the thesis is 60 credits.

The front page depicts a section of the root system of the exceptional Lie group  $E_8$ , projected into the plane. Lie groups were invented by the Norwegian mathematician Sophus Lie (1842–1899) to express symmetries in differential equations and today they play a central role in various parts of mathematics.

# Abstract

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# Acknowledgements

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# Chapter 1

## Introduction and outline of the thesis

sec:intro

The analysis of survival data is an important part of biomedical statistics. Almost all modelling of survival data is done with the Cox regression model (Cox, 1972). Competing frameworks exist, but are not widely adopted. An important part of modern biomedical statistics is the ability to incorporate genetic data when modelling. Models lacking this ability suffer from less adoption. In the 1970s, a framework called first hitting time models was developed. It is a rich and flexible modelling framework where one models the process underlying an individual before it experiences an event. Practitioners wanting to use first hitting time models are at a loss of models where genetic data can easily be used. However, Cox regression makes assumptions which are not always true. Therefore there is a need for methods which are more flexible.

Genetic data is nowadays widely available, and typical data sets include gene expressions from genes numbering in the tens of thousands. Such data is an example of so-called high-dimensional data, because one can think of the genes from one individual as one point in a high-dimensional space where each gene spans one dimension. Somewhat counterintuitively, virtually all points in high-dimensional space will be far apart. This makes it difficult to generalize on the structure. It also makes it very easy for statistical models to overfit, i.e., to explain the variation in the data in a way that is not really true, and that would not carry over to unseen data of a similar kind. Furthermore, many classical statistical models are simply unable to use so many predictors, at least directly. Specifically, a scenario where the number of covariates  $p$ , is much larger than the number of predictors,  $n$ , which is often referred to as the  $p \gg n$  scenario.

In recent years, an algorithmical framework called gradient boosting has been very successful in  $p \gg n$  scenarios. It is a method that originated around 2000, in the field of machine learning. Friedman (2001) later connected it to a statistical view. Gradient boosting algorithms are iterative algorithms for performing penalized maximum likelihood estimation. About 20 years later, gradient boosting is still very much an active field of research, and various methods exist for model fitting. Most traditional gradient boosting algorithms are concerned with modelling one parameter. In more recent years, gradient boosting methods for regression of parameters beyond the mean have also been introduced.

In this thesis, we develop such a multidimensional gradient boosting algorithm, to fit an FHT model which depends on two parameters. There has to our knowledge been no attempt at developing any methods for first hitting time regression in a high-dimensional setting.

In chapter 2, we give an overview of survival data and existing models, primarily Cox regression. We then discuss first hitting time models and in particular a specific instance of such models, where a Wiener process is used. Chapter 3 introduces boosting, and reviews existing methods for modelling one parameter, before concluding with methods for estimating several parameters using boosting. In chapter 4, we derive such a multidimensional algorithm for fitting the FHT model discussed in chapter 2, which we call FHTBoost. Chapter 5 gives an overview of evaluation measures that we then use in subsequent chapters. In chapter 6 we perform a simulation study of FHTBoost, where we look at two high-dimensional survival data scenarios. Chapter 7 looks at a survival data set consisting children diagnosed with neuroblastoma. We estimate an FHT model and discuss the results, before we compare its predictive performance with that of a Cox regression performed on the same data. We conclude the thesis with discussion and remarks on possible future work.

High-dimensional survival analysis.

These days, genetic information is cheap. The cost of perform gene sequencing is very low, at the point where it is feasible to perform it on many patients.

The main goal of this thesis is to adapt first-hitting-time models for survival analysis to a high-dimensional setting. This will be done by implementing a gradient boosting algorithm.

We will estimate two parameters. To this end, we will review recent developments in gradient boosting for multidimensional likelihood functions.

In chapter 2, we will discuss first-hitting-time models.. We will first provide background on survival data and then briefly discuss Cox regression. The latter part of the chapter will be focused on first-hitting-time models. In chapter 3, we discuss gradient boosting methods. In chapter 4, we discuss a gradient boosting algorithm for first-hitting-time models. In chapter 5, we perform a simulation study. In chapter 6, we apply the developed algorithm on a real-life dataset with neuroblastoma patients, and compare it to Cox regression. Finally, chapter 7 summarizes and hints at future work.



## Chapter 2

# First-hitting-time models

### 2.1 Survival data

Time to event data are seen in many different contexts, including medicine, engineering, biology, and sociology. One considers a set of individuals  $i$ ,  $i = 1, 2, \dots, N$ , for which an event can happen. The term *survival data* is used to refer to time to event data where such events only can happen once. An overview of modelling of survival data can be found in for example Aalen et al. (2008). Although the term survival data sounds like it refers to deaths only, the event in question may be anything of interest. You might, for example, be a doctor performing a study of cancer patients, and monitoring them for possible relapse. In this case, the event is the relapse. Or, possibly, you are a demographer looking at all parents who have only one child, and you are monitoring the time that elapses before they have a second child. Clearly, to observe such data in real life, we must wait until the event actually happens. This might in some cases never happen, or it might take a very long time. Consider, for example, a clinical trial of  $N$  patients who have been treated for some disease, and where  $T_i$ ,  $i = 1, \dots, N$ , is the time until their relapse. Such a trial can only last a certain amount of time, say, until a time  $\tau$ . Luckily, not every patient relapses during that time, and so the actual time to their relapse,  $\tilde{T}_i$ , is not observed. We could throw away these observations without an observed event, and consider them irrelevant. But we at least know that these patients survived until time  $\tau$ . We therefore work with the concept of incomplete data, which we call *censored* survival data (Aalen et al., 2008).

subsec:survdata

#### 2.1.1 Independently censored survival data

The time-to-event  $\tilde{T}$  is a random variable of a non-negative domain. This time-to-event has a corresponding random variable  $W$  which represents the censoring time of the time-to-event. The observed, and possibly censored, survival time is

$$T = \min(\tilde{T}, W).$$

We also operate with a corresponding censoring indicator

$$D = \mathbf{I}(\tilde{T} = T),$$

which is 1 if the observed survival time is not censored, and 0 if it is. In the clinical trial example mentioned, the censoring time  $W$  would be the end of

the possible observation period of the trial, namely  $\tau$ . An important property of survival data is the concept of *independent censoring*, also called *random censoring*. We say that we have independent censoring if the censoring indicator  $D$  is independent of the time, meaning that

$$P(T|D) = P(T).$$

What we have so far called censored data is in truth *right-censored* survival data. Left-censoring is also possible, but we will not discuss it in this thesis, and so we continue to simply use the term “censoring.”

### 2.1.2 The survival function $S(t)$ , the hazard function $\alpha(t)$ , and their estimators

When studying censored survival data, we are interested in estimating the probability of surviving until time  $t$ , which is called the survival function, and is defined as

$$S(t) = \Pr(T > t) = 1 - \Pr(T \leq t) = 1 - F(t).$$

Here  $F(t)$  is the familiar cumulative distribution function. If the derivative of  $F(t)$  exists, we denote it  $f(t)$ , and then the lifetime  $T$  has probability distribution function (pdf)  $f(t)$ .

Another function we are interested in is the hazard function. This is the probability of the event happening at time  $t$ , conditioned on the event not having happened yet. More formally, the hazard function is defined as

$$\alpha(t) = \lim_{\epsilon \rightarrow 0} \frac{\Pr(T < t + \epsilon | T > t)}{\epsilon}.$$

Estimating the hazard function is hard, and we do not achieve the usual  $\sqrt{n}$  convergence.

Find and add citation.

It is, however, typically the function we are most interested in, as we will see later, in subsection 2.2.2. Note that by observing

$$\Pr(T < t + \epsilon | T > t) = \frac{\Pr(T < t + \epsilon, T > t)}{\Pr(T > t)} = \frac{F(t + \epsilon) - F(t)}{S(t)},$$

and inserting this into the hazard function we have the relation

$$\alpha(t) = \frac{1}{S(t)} \lim_{\epsilon \rightarrow 0} \frac{F(t + \epsilon) - F(t)}{\epsilon} = \frac{f(t)}{S(t)} = \frac{-S'(t)}{S(t)}, \quad (2.1)$$

{eq:hfs}

where the probability distribution function  $f(t)$  is obtained by its limit definition, and we note that  $S'(t)$  is the derivative of  $1 - F(t)$ , which is  $-f(t)$ . We further note that by interchanging the notation for derivation, we obtain

$$\alpha(t) = \frac{S'(t)}{S(t)} = \frac{\frac{dS}{dt}}{S(t)}. \quad (2.2)$$

{eq:alpha-diff}

By integrating the hazard from 0 to time  $t$ , we get the cumulative hazard function,

$$A(t) = \int_0^t \alpha(s) \, ds, \quad (2.3)$$

{eq:cumulative-hazard-1}

and we insert (2.2) into (2.3),

$$A(t) = - \int_0^t \frac{\frac{dS}{ds}}{S(s)} ds = - \int_0^t \frac{1}{S(s)} dS = -\log(S(t)), \quad (2.4)$$

{eq:cumulative-hazard}

which is an important relationship. Given survival data  $(t_i, d_i)_{i=1}^N$ , we introduce the *risk set*  $R(t)$ , which gives the set of all individuals at risk at time  $t$ ,

$$R(t) = \{i: t_i \geq t\}.$$

We further introduce the function  $Y(t)$ , which is equal to the number of individuals still at risk at time  $t$ ,

$$Y(t) = \#R(t) = \#\{i: t_i \geq t\},$$

where  $\#(\cdot)$  is the counting operator over a set. Note that  $Y(t)$  does not depend on the censoring indicators, since an individual is at risk at time  $t$  even though it turns out that it did not die, i.e., its censoring indicator  $d_i$  is 0. Estimating the survival function  $S(t)$  is usually done by the Kaplan-Meier estimator (Kaplan and Meier, 1958),

$$\hat{S}_{\text{KM}}(t) = \prod_{i: \{t_i \leq t\}} 1 - \frac{d_i}{Y(t_i)},$$

and the cumulative hazard function  $A(t)$  by the Nelson-Aalen estimator (Nelson, 1972; Aalen, 1978),

$$\hat{A}(t) = \sum_{i: \{t_i \leq t\}} \frac{d_i}{Y(t_i)}.$$

## 2.2 Classical inference approaches

### 2.2.1 Likelihood regression

Consider survival data  $(t_i, d_i)$ ,  $i = 1, 2, \dots, N$ , where  $t_i$  is the time to event of individual  $i$ , and  $d_i$  is a censoring indicator of the usual type, meaning it is 1 if the event has been observed, and 0 if not. To make inference on what affects the time to event, we need to consider covariates. Covariates are information about an individual. In medical applications, typical covariates are age, gender, disease status, as well as clinical measurements. Denote the covariates, i.e., the information, of an individual  $i$  by  $x_{i,1}, x_{i,2}, \dots, x_{i,p}$ , where  $p$  is the total number of pieces of information. We gather these in a vector  $\mathbf{x}_i = (x_{i,1}, x_{i,2}, \dots, x_{i,p})$ . We may now consider a data set of complete tuples of survival data with covariates,

$$D = (t_i, d_i, \mathbf{x}_i)_{i=1}^N. \quad (2.5)$$

{eq:surv-D}

Now, consider a survival time distribution

$$\psi(\boldsymbol{\beta}), \quad (2.6)$$

{eq:surv-time-dist}

which has a vector of regression parameters  $\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_p)$ , with one parameter  $\beta_j$ ,  $j = 1, 2, \dots, p$  corresponding to one covariate  $x_j$ . This distribution has a parameterized survival function

$$S(t|\boldsymbol{\beta}, \mathbf{x})$$

and a parameterized probability distribution function

$$f(t|\boldsymbol{\beta}, \mathbf{x}).$$

Given an observed dataset  $D$  (2.5), we wish to make inference on which covariates affect the survival time. One way to do this, having assumed a specific survival distribution  $\psi(\boldsymbol{\beta})$ , is to construct a so-called (joint) likelihood. The likelihood is a function of the parameters  $\boldsymbol{\beta}$  in the distribution, given the observed sample. The likelihood is maximized at the parameters which have the highest probability of yielding the observed sample. If all censoring indicators are 1, meaning all observations are actual events, we are in the usual statistical regression landscape. For each observation, its likelihood is the probability of observing its event at  $t_i$  given the parameters and the data,

$$f(t_i|\boldsymbol{\beta}, \mathbf{x}_i).$$

A typical assumption when setting up a (joint) likelihood is to assume that the conditional distribution of each observation is independent and identically distributed (*iid*), given the data. Hence the joint likelihood is the product of all the single likelihood contributions,

$$L(\boldsymbol{\beta}) = \prod_{i=1}^N f(t_i|\boldsymbol{\beta}, \mathbf{x}_i).$$

But we need to consider the case of censored survival data, and we wish to set up a joint likelihood for such a data set. Again assume that the observations  $D = \{\mathbf{x}_i, y_i\}_{i=1}^N$  are independent and identically distributed from a survival distribution  $\psi(\boldsymbol{\beta})$ . In the case of an uncensored observation  $i$ , meaning  $d_i = 1$ , the single contribution to the likelihood is

$$f(t_i|\boldsymbol{\beta}, \mathbf{x}_i) \tag{2.7} \quad \boxed{\text{\{eq:f\}}}$$

to the likelihood. If the event has not occurred, i.e. the observation is censored,  $d_i = 0$ . In this case, we do not have the actual lifetime, and so we cannot use the lifetime distribution, but we must instead use the survival distribution. After all, the fact that this individual is alive at time  $t_i$  is informative. Therefore this observation contributes

$$S(t_i|\boldsymbol{\beta}, \mathbf{x}_i) \tag{2.8} \quad \boxed{\text{\{eq:S\}}}$$

to the likelihood. Since an observation can only be either censored or not censored at the same time,  $d_i$  is either 0 or 1. This means that we can combine expressions (2.7) and (2.8) in a way that a single observation contributes the product

$$f(t_i|\mathbf{x}_i)^{d_i} S(t_i|\mathbf{x}_i)^{1-d_i}$$

to the likelihood. Since we assume the observations to be independent, the likelihood is, again, the product of the single complete contributions. The complete likelihood becomes

$$L(\boldsymbol{\beta}) = \prod_{i=1}^N f(t_i|\mathbf{x}_i, \boldsymbol{\beta})^{d_i} S(t_i|\mathbf{x}_i, \boldsymbol{\beta})^{1-d_i}. \tag{2.9} \quad \boxed{\text{\{eq:surv-lik\}}}$$



It is more convenient to work with the log likelihood,

$$\begin{aligned} l(\beta) &= \log L(\beta) \\ &= \sum_{i=1}^N [d_i \log f(t_i | \mathbf{x}_i, \beta) + (1 - d_i) \log S(t_i | \mathbf{x}_i, \beta)]. \end{aligned} \quad (2.10)$$

{eq:surv-log-lik-1}

Note that since  $A(t) = -\log S(t)$  and  $f(t) = \alpha(t)S(t)$ , see (2.4) and (2.1), respectively, (2.10) further simplifies to

$$l(\beta) = \sum_{i=1}^n [d_i \log \alpha(t_i | \mathbf{x}_i, \beta) - A(t_i | \mathbf{x}_i, \beta)].$$

For any survival distribution  $\psi(\beta)$  (2.6) for which either form of  $l(\beta)$  can be calculated, we can perform maximum likelihood estimation of its parameters.

subsec:ph-reg

### 2.2.2 Proportional hazards regression

In other fields of statistics, we are often most interested in modelling the probability distribution function and the cumulative distribution function. In survival analysis, however, we are typically more interested in modelling the hazard function. In this subsection, we consider the effect of covariates on the hazard function  $\alpha(\cdot)$ . How may we use a covariate vector  $\mathbf{x}$  in modelling the hazard rate? A very common model to choose here is a proportional hazards model, which assumes

$$\alpha(t | \mathbf{x}) = \alpha_0(t) r(\mathbf{x} | \beta), \quad (2.11)$$

{eq:PH}

where  $\alpha_0(t)$  is an *unspecified* baseline hazard function shared between all individuals, and  $r(\mathbf{x} | \beta)$  is a so-called relative risk function parameterized with regression coefficients  $\beta = (\beta_1, \dots, \beta_p)$ . We choose  $r(\mathbf{x})$  such that it is appropriately normalized, meaning  $r(\mathbf{0}) = 1$ . A crucial assumption here is that the effects of the covariates are fixed in time. In this setup, it turns out that we can do regression without specifying the baseline hazard. This is a major advantage, because we then do not have to think about modelling effects in time. Given data  $D = (t_i, d_i, \mathbf{x}_i)_{i=1}^N$ , we may set up a so-called partial likelihood (Cox, 1972).

The idea behind the partial likelihood is as follows. We have observed data  $D$  with at least some censoring indicators  $d_i$  equal to 1. In partial likelihood regression, we simply ignore the censored observations. Informally, the probability of the event happening at a time  $t$  for some individual  $j$  is the probability of an event happening to individual  $i$  at time  $t$ , divided by the total probability of an event happening at time  $t$ , the instantaneous probability of an event happening to that individual at that time, i.e., the hazard function of that individual at that time,

$$\frac{\Pr(\text{event happens to individual } i \text{ at time } t)}{\Pr(\text{event happens to any individual } j \text{ at time } t)}. \quad (2.12)$$

{eq:hazard-fractional-informal}

More formally, we look at the instantaneous probability of an event happening for the individual  $i$ , which is the hazard function  $\alpha(t | \mathbf{x}_i)$ . Thus the total probability of an event happening at time  $t$  is the sum of the hazard functions of all individuals in the risk set  $R(t)$ , which, again, is defined as

$$R(t) = \{i: t_i \geq t, i = 1, 2, \dots, n\}.$$

From all the uncensored observations, we know that events happened at times  $\{t_i: d_i = 1, i = 1, 2, \dots, N\}$ . Therefore, we can construct expressions for (2.12) at all the observed, uncensored, times. Inserting the probabilities into the informal expression in (2.12), an individual with an observed event at  $t_i$  contributes to the likelihood with

$$\frac{\alpha_0(t_i)r(\mathbf{x}_i)}{\sum_{j \in R(t_i)} \alpha_0(t_i)r(\mathbf{x}_j)}. \quad (2.13) \quad \boxed{\text{eq:hazard-fraction}}$$

Now, assuming that observations are independent and identically distributed, we say that the *partial likelihood* of the model given the observed data is the product of all ratios (2.13), namely

$$\text{pl}(\beta) = \prod_{i: d_i=1} \frac{\alpha_0(t_i)r(\mathbf{x}_i)}{\sum_{j \in R(t_i)} \alpha_0(t_i)r(\mathbf{x}_j)} = \prod_{i: d_i=1} \frac{\alpha_0(t_i)r(\mathbf{x}_i)}{\alpha_0(t_i) \sum_{j \in R(t_i)} r(\mathbf{x}_j)}. \quad (2.14) \quad \boxed{\text{eq:pl}}$$

In the expression above, (2.14), we rearrange the denominator such that the baseline hazard of individual  $i$ ,  $\alpha_0(t_i)$ , is moved out of the sum. This hazard depends on individual  $i$ , while the sum is a sum over all individuals  $j$ . It therefore cancels out, and we are left with just the relative risk functions,

$$\text{pl}(\beta) = \prod_{i: d_i=1} \frac{r(\mathbf{x}_i)}{\sum_{j \in R(t_i)} r(\mathbf{x}_j)}.$$

The fact that the baseline hazard cancels out is quite powerful. Even though proportional hazards regression is not fully parametric, the canceling means that we can model the effect of covariates in a fully parametric way, and without having to consider the baseline hazard.

Consider now possible choices for the relative risk function  $r(\mathbf{x})$ . The most common choice, by far, for  $r(\mathbf{x})$  is

$$r(\mathbf{x}) = \exp(\mathbf{x}^T \beta),$$

which leads to the famous Cox model (Cox, 1972). The Cox model is an attractive model because the value of the parameter  $\beta$  has a nice interpretation. Assume we have two observations with covariate vectors  $\mathbf{x}_1$  and  $\mathbf{x}_2$ , and that  $\mathbf{x}_2$  is equal to  $\mathbf{x}_1$  except for in element  $j$ , where  $x_{2j} = x_{1j} + 1$ . Then the ratio of the two hazard rates becomes

$$\frac{\exp(\mathbf{x}_2^T \beta)}{\exp(\mathbf{x}_1^T \beta)} = \exp((\mathbf{x}_2 - \mathbf{x}_1)^T \beta) = \exp(\beta_j).$$

Furthermore, if the two covariate vectors differ in more elements, say, that, each element in  $\mathbf{x}_2$  is one unit increased from each element in  $\mathbf{x}_1$ , we get that

$$\frac{\exp(\mathbf{x}_2^T \beta)}{\exp(\mathbf{x}_1^T \beta)} = \exp((\mathbf{x}_2 - \mathbf{x}_1)^T \beta) = \exp(\beta_1 + \beta_2 + \dots + \beta_p) = \exp(\beta_1) \exp(\beta_2) \dots \exp(\beta_p).$$

In other words, each unit increase in a covariate is a multiplicative factor in the hazard. Cox regression is used very much in applied research.

### 2.2.3 Issues with the proportional hazards assumption

When assuming (2.11), i.e.  $\alpha(t|\mathbf{x}) = \alpha_0(t)r(\mathbf{x}|\boldsymbol{\beta})$ , we are making a relatively strong assumption. Namely, we assume that the ratio between the hazard function of two individuals is the same *at all times*, because the part of  $\alpha(t|\mathbf{x})$  cancels out when we do regression, and because we assume that the covariate effects are constant in time, as  $r(\mathbf{x}|\boldsymbol{\beta})$  is not a function of time. This assumption goes under the name of the proportional hazards (PH) assumption. While, as we saw, this assumption greatly simplifies the inference, it is not necessarily satisfied in practice. In any case, it is very difficult to verify, in case of multivariate analysis, especially in high-dimensional contexts. In the literature, there exist alternative models, that do not require the PH assumption. One of these is Aalen's additive model, which is an example of additive hazard modelling. In Aalen's model, the hazard function takes the form

$$\alpha(t|\mathbf{x}) = \beta_0(t) + \beta_1(t)x_1(t) + \beta_2(t)x_2(t) + \dots + \beta_p(t)x_p(t),$$

where  $\beta_j(t), j = 1, \dots, p$  is the increase in the hazard at time  $t$  corresponding to a unit's increase in the  $j$ -th covariate. Another alternative model to the Cox model is the first hitting threshold model. In this thesis we will focus on the latter, focusing on the analysis of high-dimensional data. To our best knowledge, this is the first study which tries to combine FHT models and high-dimensional data.

### 2.2.4 Cox, proportional hazards, and variable selection

The PH assumption (2.11) is very often not valid. Consider survival data with two covariates  $x_1$  and  $x_2$ . With Cox regression, the hazard is

$$\alpha(t|x_{i,1}, x_{i,2}) = \alpha_0(t) \exp(\beta_1 x_{i,1} + \beta_2 x_{i,2}).$$

There is a model inconsistency problem here. If we only observe  $x_{i,1}$ , and calculate the hazard  $\alpha(t|x_{i,1})$ , then this will not be of Cox regression form, regardless of the distribution of  $x_2|x_1$ .

In addition, if there is perfect Cox structure given  $x_1$  alone, and perfect Cox structure given  $x_2$  alone, one almost never has a Cox model in the joint space  $(x_1, x_2)$ . That is, one almost never has the proportional hazards assumption actually satisfied. However, in practice, Cox regression is robust and tends to work well.

Find citation for this paragraph!

Given that Cox sometimes leaves us wanting of a more flexible and more theoretically plausible model, there is room for other models. One may attempt to start the model building task at a deeper level, taking biologically plausible assumptions about the background processes associated with life lengths. This is where first-hitting-time models come in.

## 2.3 First hitting time models

sec:FHT

So far we have done regression by modelling the log-likelihood  $l(\cdot)$  and the hazard rate  $\alpha(\cdot)$ . Therefore we have not thought much about how a time-to-event is *generated*, other than the fact that it arises from a survival distribution

$S(\cdot)$  with a corresponding hazard function  $\alpha(\cdot)$ . In this context, an individual is alive at one time. Slightly later, it is either still alive, or it may have died.

Instead, another way to approach survival analysis is to model the process which generates the survival data. We can imagine that each individual has an underlying stochastic process  $Y(t)$ , which we call a health process. When this health process reaches a barrier, or an end state, the individual dies. This is a conceptually appealing framework: Instead of just being a stochastic lifetime with a binary status of an event having happened or not or alive, it introduces the concept of distance to the event. We may call the time the health process hits the barrier or the end state the *first hitting time* (FHT) of a boundary or threshold state, by sample paths of a stochastic health process. This health process may be observable, but for most purposes it will be latent, i.e., unobservable.

Many types of time-to-death data may, in fact, be interpreted as FHTs. FHT models have a long history of application in diverse fields, including medicine and engineering. They have been used to describe the length of a hospital stay (Whitmore, 1975; Eaton and Whitmore, 1977), to model the duration of a strike (Lancaster, 1972), to estimate degradation in components (Whitmore, 1995), and to assess lung cancer risk in railroad workers (Lee et al., 2004).

Eaton and Whitmore (1977) discuss FHTs as a general model for hospital stay. Aalen and Gjessing (2001) provide an overview of much of this subject. Lawless (2011) provides a compact overview of the theory. Lee and Whitmore (2003) provides an overview of first hitting time models for survival and time-to-event data. There is a large literature dealing with theoretical and mathematical aspects of FHT models.

Models based on this view are called first hitting time models (FHT). FHT models were introduced in Whitmore (1986), see Lee and Whitmore (2006) for a complete overview. Note that these authors use the term threshold regression when referring to regression for first hitting time models. We have, following Caroni (2017), chosen to not use this term, as it is also used to refer to a well established, and quite different, topic in econometrics.

fht-idea

### 2.3.1 General idea

A first-hitting-time (FHT) model has two basic components:

1. A parent stochastic process  $\{Y(t), t \in \mathcal{T}, y \in \mathcal{Y}\}$ , with initial value  $Y(0) = y_0$ , where  $\mathcal{T}$  is the time space and  $\mathcal{Y}$  is the state space of the process.
2. A boundary set  $\mathcal{B}$ , where  $\mathcal{B} \subset \mathcal{Y}$ . This is at times also referred to as a barrier or a threshold, depending on which is most appropriate to the context.

The process  $\{Y(t)\}$  may have a variety of properties, such as one or many dimensions, the Markov property, continuous or discrete paths, and monotonic sample paths. Whether the sample path of the parent process is observable or latent (unobservable) is an important distinguishing characteristic of the FHT model. Latent (unobservable) processes are the most common by far. The boundary set  $\mathcal{B}$  may also have different features. The basic model assumes that



$\mathcal{B}$  is fixed in time. Some applications may require dependencies on time, i.e.,  $\mathcal{B}(t)$ , but this case will not be considered in this thesis, and so we write  $\mathcal{B}$ .

Taking the initial value  $Y(0) = y_0$  of the process to lie outside the boundary set  $\mathcal{B}$ , the *first hitting time* of  $\mathcal{B}$  is the random variable  $T$  defined as

$$T = \inf_t (t: Y(t) \in \mathcal{B}). \quad (2.15)$$

{eq:fht-t}

Thus, the first hitting time is the time when the stochastic process first encounters the boundary set  $\mathcal{B}$ . The boundary set defines a stopping condition for the process. Note that when the parent process is latent, there is no direct way of observing the FHT even in the state space of the process.

In some versions of the FHT model, there is no guarantee that the process  $\{Y(t)\}$  will reach the boundary set  $\mathcal{B}$ , so  $P(T < \infty) < 1$ . We will let  $T = \infty$  denote the absence of a finite hitting time with

$$P(T = \infty) = 1 - P(T < \infty). \quad (2.16)$$

{eq:T-is-infinity}

This condition is sometimes plausible and a desirable model feature. Two common concepts in survival analysis might lead to this. One is the case of competing risks. That is the case where an individual might die from not only one, but several causes, but we are only studying one of these. Naturally, then, we would not expect that all individuals die from the cause that we study, and hence  $P(T < \infty) < 1$ . The second concept is related to “cure models.” A cure model is a model where there are individuals with zero frailty, i.e., a nonsusceptible group (Aalen et al., 2008). Consult Maller and Zhou (1996) for more details.

### 2.3.2 Examples of first-hitting-time models

The parent stochastic process  $Y(t)$  may take many forms, from Wiener processes to Markov chains. Similarly, the boundary state may also take various forms. For example, it may be a fixed threshold in a Wiener process or an absorbing state in a Markov chain. The freedom in the choice of these quantities show how flexible the FHT framework is. The choice of boundary must fit the process, such that the boundary set is a subset of the state space. We will now briefly mention some examples of choices of health processes and corresponding boundaries, before focusing on the most studied case, which uses as a choice of health process the Wiener process. These examples are taken from Lee and Whitmore (2006).

1. *Bernoulli process and negative binomial first hitting time.* The number of trials  $S$  required to reach the  $m$ -th success in a Bernoulli process  $\{B_t, t = 1, 2, \dots\}$  has a negative binomial distribution with parameters  $m$  and  $p$ , where  $p$  is the success probability of each trial. To give this setup our standard representation, we consider a parent process

$$\{Y(t), t = 0, 1, 2, \dots\}$$

with initial value  $Y_0 = y_0 = m$  and let

$$Y_t = y_0 - B_t, t = 1, 2, \dots,$$

where  $\{B_t\}$  is the aforementioned Bernoulli process. The first hitting time is the first Bernoulli trial  $t = T$  for which  $Y_t$  equals 0. The number of rocket launches to get  $m$  satellites in orbit is an example of this FHT model.

2. *Gamma process and inverse gamma first hitting time.* Consider a parent process

$$\{Y(t), t \leq 0\}$$

with initial value  $Y(0) = y_0 > 0$ . Let

$$Y(t) = y_0 - Z(t),$$

where  $Z(t)$ ,  $t \leq 0$  is a gamma process with a scale parameter  $\beta$ , a shape parameter  $\alpha$  and a starting point  $Z(0) = 0$ . The first hitting time of the zero level in the parent process ( $Y = 0$ ) has an inverse gamma cumulative distribution function (cdf), defined by the identity

$$P(T > t) = P(Z(t) < y_0).$$

The identity follows from the fact that a gamma process has monotonic, nondecreasing sample paths. Computational routines for the gamma cdf allows the cdf of  $T$  to be computed readily. Singpurwalla (1995) and Lawless and Crowder (2004) consider the gamma process as a model for degradation. A gamma process is a good choice if we want a monotonic restriction on the movement of the health process (Lee and Whitmore, 2006). It might, for example, make sense if the health process is meant to model e.g. the breakdown of a structure.

3. *Poisson process and Erlang first hitting time.* The time  $S$  until the occurrence of the  $m$ -th event in a Poisson process

$$\{N(t), t \geq 0\}$$

with rate parameter  $\lambda$  has an Erlang distribution with parameters  $m$  and  $\lambda$ . Again, to give this setup our standard representation, we consider a parent process

$$\{Y(t), t \geq 0\}$$

with initial value  $Y(0) = y_0 = m$  and let  $Y(t) = y_0 - N(t)$ , where

$$\{N(t), t \geq 0\}$$

is the preceding Poisson process. The first hitting time is the earliest time  $t = S$  when  $Y(t) = 0$ . This FHT model is illustrated by the time to failure of an engineering system consisting of  $m$  components in parallel, having identical and independent exponential lifetimes, that are placed in service successively as failures occur.

We are to choose a stochastic process to model a person's health process. A person's health, although generally decreasing over longer periods of time, will fluctuate, at times going up, and at times going down. If we consider the health process to be analogous with a person's health, it therefore makes sense to use

a process which can both go up and down. Therefore the choice of a gamma process as the health process would not be appropriate.

The most usual setup for a first hitting time model is to have the health process be a Wiener process, and the boundary set be a fixed threshold level. This is attractive because it has closed-form probability and cumulative density functions, and its likelihood is computationally simple. There are also no restrictions on the movements of the process, meaning, it is non-monotonic. We will first give an introduction to the Wiener process.

subsec:wiener

### 2.3.3 Wiener process

Consider a continuous stochastic process  $W(t)$  defined for  $t \in [0, \infty)$ , taking values in  $\mathbb{R}$ , and with initial value  $W(0) = 0$ . If  $W$  has increments that are independent and normally distributed with

$$\mathbb{E}[W(s+t) - W(t)] = 0 \text{ and } \text{Var}[W(s+t) - W(t)] = s,$$

we call  $W$  a Wiener process. In other words, each increment has expectation 0 and has standard deviation proportional to the square root of the length of the time interval. The position of the process at time  $t$  always follows a Gaussian distribution  $N(0, \sqrt{t})$  (Aalen et al., 2008). To increase the flexibility of the Wiener process, we can introduce a new process  $Y$ ,

$$Y(t) = y_0 + \mu t + \sigma W(t), \quad (2.17)$$

{wiener}

which is called a Wiener process with initial value  $y_0$ , drift coefficient  $\mu$ , and diffusion coefficient  $\sigma$ . A good introduction to Wiener processes can be found in Cox and Miller (1965).

### 2.3.4 Wiener process as health process causes an inverse Gaussian first hitting time

If we choose the stochastic process to be a Wiener process with intercept and drift (2.17), and we let the boundary be the non-positive numbers,  $\mathcal{B} = (-\infty, 0]$ , then (2.15) becomes

$$T = \min_t (t : Y(t) < 0),$$

i.e. the first hitting time is the time it takes for the process to first reach a non-positive value. (Note that since the Wiener process is continuous, there is no difference between  $\leq$  and  $<$ . We therefore use  $<$  for convenience.) It can be shown that the first hitting time of such a Wiener process follows an inverse Gaussian distribution (Chhikara, 1988), with probability distribution function (pdf)

$$f(t|y_0, \mu, \sigma^2) = \frac{y_0}{\sqrt{2\pi\sigma^2 t^3}} \exp\left[-\frac{(\mu t + y_0)^2}{2\sigma^2 t}\right], \quad (2.18)$$

{eq:ig-pdf}

and cumulative distribution function (cdf)

$$F(t|\mu, \sigma^2, y_0) = \Phi\left[-\frac{\mu t + y_0}{\sqrt{\sigma^2 t}}\right] + \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left[\frac{\mu t - y_0}{\sqrt{\sigma^2 t}}\right]. \quad (2.19)$$

{eq:ig-cdf}

As previously discussed in subsection 2.3.1, it is possible that the process does not reach the boundary set and thus cause an event. In this case, this means

that the Wiener health process never reaches 0. This will happen if the drift  $\mu$  is positive. If so, the probability distribution function in (2.18) is improper, and the probability of the time not being finite is

$$\Pr(T = \infty) = 1 - \Pr(T < \infty) = 1 - \exp(-2 \cdot y_0 \cdot \mu), \quad (2.20)$$

{eq:P-inf-FHT}

see Cox and Miller (1965).

Since we in survival analysis prefer working with the survival function  $S(t) = 1 - F(t)$  rather than the cdf  $F(t)$ , we note that  $S(t)$  becomes

$$S(t|\mu, \sigma^2, y_0) = \Phi\left[\frac{\mu t + y_0}{\sqrt{\sigma^2 t}}\right] - \exp\left(-\frac{2y_0\mu}{\sigma^2}\right)\Phi\left[\frac{\mu t - y_0}{\sqrt{\sigma^2 t}}\right], \quad (2.21)$$

{eq:ig-surv}

where  $\Phi(x)$  is the cumulative distribution function of the standard normal,

$$\Phi(x) = \int_{-\infty}^x \phi(y) \, dy,$$

and  $\phi(x)$  is the pdf of the standard normal, defined as

$$\phi(x) = \frac{\exp(-x^2/2)}{\sqrt{2\pi}}.$$

Note that in (2.21) we used the fact that the cdf of the standard normal distribution is symmetric around 0, meaning that we were able to swap

$$1 - \Phi\left[-\frac{\mu t + y_0}{\sqrt{\sigma^2 t}}\right]$$

with

$$\Phi\left[\frac{\mu t + y_0}{\sqrt{\sigma^2 t}}\right].$$

Note that for the sake of brevity, when we talk about FHT from now on, we mean this particular FHT model, where the Wiener process is chosen as health process.

### 2.3.5 Effects of parameters in the Wiener process

Let us consider a a Wiener health process where its drift  $\mu$  is strictly negative, and not zero. Such a health process will reach 0 with certainty, such that  $P(T = \infty)$  (2.16) is 0. Clearly, for such a Wiener process, starting in  $y_0 > 0$  and with a downwards drift  $\mu < 0$ , the movement is markedly in the direction of zero. If the variance  $\sigma^2$  of the process is small in comparison to the drift, and the initial level is sufficiently large in comparison to  $\sigma^2$ , then the process  $Y(t)$  will move in an almost straight line, such that

$$Y(t) \approx y_0 + \mu t.$$

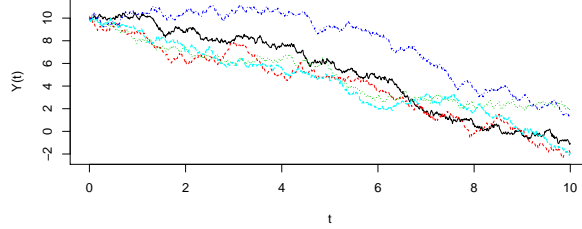
Consequently, the first hitting time will be a near-deterministic function of  $y_0$  and  $\mu$ , such that

$$T \approx -\frac{y_0}{\mu}.$$



plot:wiener

Figure 2.1: Example of 5 Wiener process paths with initial value  $y_0 = 10$  and drift  $\mu = -1$ .



This is quite visible in Figure 2.3.5, which shows examples of 5 Wiener process paths with diffusion parameter  $\sigma^2 = 1$ , initial value  $y_0 = 10$ , and drift  $\mu = -1$ . Furthermore, if the diffusion is relatively small, such that  $T \approx -y_0/\mu$ , then either increasing  $y_0$  or decreasing  $\mu$  will have the same outcome, namely a larger lifetime  $T$ . Conversely, either choice of decreasing the initial level or increasing the drift will cause a smaller lifetime  $T$ . If  $\sigma^2$  is relatively large compared to the drift, however, the diffusion part is more dominant and thus the hitting time is less predictable (Aalen et al., 2008).

## 2.4 Properties of the inverse Gaussian

### 2.4.1 Inverse Gaussian distribution and different parameterizations

The typical inverse Gaussian parameterization is.

Add this parameterization!

We will use ... This parameterization is not in the exponential family, and hence it is not a generalized linear model.

### 2.4.2 The inverse gaussian is overdetermined if the health process is latent

subsec:  
overdetermined

There are three parameters in the inverse Gaussian distribution, namely  $y_0, \mu$  and  $\sigma$ . We observe, however, that both the pdf  $f(t|y_0, \mu, \sigma^2)$  in (2.18) and the survival function  $S(t|\mu, \sigma^2, y_0)$  in (2.21) only depend on these parameters through the ratios  $\mu/\sigma$  and  $y_0/\sigma$ . Hence, in reality there are only two free parameters. In other words, we can without loss of generality fix one parameter. The conventional way to proceed is to set  $\sigma$  equal to 1 (Lee and Whitmore, 2006), and in this thesis we follow this convention.

### 2.4.3 The shape of the hazard function in the inverse Gaussian FHT model

From (2.1), we know that the hazard function can be seen as

$$\alpha(t) = f(t)/S(t).$$

If we plug in the inverse Gaussian versions of  $f(t)$  and  $S(t)$ , we would get a rather intractable expression. However, we can make some comments on its shape as it relates to different values of  $y_0$  and  $\mu$ . Consider the shape of the hazard rate in three different cases for the initial level  $y_0$ :

1. If  $y_0$  is close to zero, we essentially get a decreasing hazard rate.
2. If  $y_0$  is far from zero, however, we essentially get an increasing hazard rate.
3. If  $y_0$  is somewhat inbetween, we get a hazard rate which first increases and then decreases (Aalen et al., 2008).

These three examples are clearly observed in Figure ..., where we have plotted the hazard function arising from three FHT models. All three have drift as  $\mu = X$ . The first has  $y_0 = X$ , the second has  $y_0 = Y$ , and the third has  $y_0 = Z$ .

add figure!

In all three of these cases, the hazard function has a pronounced peak, which is dependent on both the initial level and the drift, of course. It is not as simple as the peak being at the mean lifetime, i.e.,  $y_0/\mu$ . Although the height of the peak will change both by changing both parameters, to simplify it a lot,  $y_0$  mostly impacts at what time the peak is, whereas  $\mu$  mostly affects the height of the peak. Regardless of the initial value, the hazard rate converges to the same limiting hazard, which is

$$\lim_{t \rightarrow \infty} \alpha(t) = \frac{1}{2} \left( \frac{\mu}{\sigma} \right)^2 = 0.5\mu^2,$$

as seen in Aalen et al. (2008). To get an intuitive feel for this, I have made an interactive website at [vegarsti.shinyapps.io/FHT\\_Hazard](http://vegarsti.shinyapps.io/FHT_Hazard)

Add plots and more explanation here.

#### 2.4.4 Comparison of hazard rates

It might be of particular interest to look at the ratio between two hazard rates. We might for example look at it when the drift  $\mu$  is the same, but the initial level  $y_0$  is different. Then the hazard ratio is strongly decreasing. This feature is the same phenomenon as that observed in frailty models, where the relative hazards often decline (Aalen et al., 2008).

Add plot and explain better.

It is also of interest to do the converse, that is, look at the hazard ratio when the initial level is the same, but the drift is different. The result here is quite different. The ratio of the hazards has a “bathtub” shape, which levels off at a later time (Aalen et al., 2008). Keep in mind here that levelling off means getting to proportional hazards. We see that the FHT framework with a Wiener process is a highly flexible parametric model for survival analysis. Indeed, much more flexible than Cox regression, since the hazard ratios in Cox are all confined to be constant over time.

Add plot here as well; also here see ABG page 402

subsec:IG-reg

## 2.5 Regression with first-hitting-time models

We may introduce effects from covariates by allowing  $\mu$  and  $y_0$  to depend on covariates  $\mathbf{x}$  and  $\mathbf{z}$ . A simple and much used model (Lee and Whitmore, 2006; Caroni, 2017) is to simply use the identity link function for the drift  $\mu$ ,

$$\mu(\boldsymbol{\beta}) = \boldsymbol{\beta}^T \mathbf{x} = \sum_{j=1}^p \beta_j x_j, \quad (2.22)$$

{eq:y0}

and to use the logarithm link function for the initial level  $y_0$ , since  $y_0$  must be positive in our framework,

$$y_0(\boldsymbol{\gamma}) = \exp(\boldsymbol{\gamma}^T \mathbf{z}) \Rightarrow \ln y_0(\boldsymbol{\gamma}) = \boldsymbol{\gamma}^T \mathbf{z} = \sum_{j=1}^d \gamma_j z_j. \quad (2.23)$$

{eq:mu}

Here  $\boldsymbol{\beta} \in \mathbb{R}^p$  and  $\boldsymbol{\gamma} \in \mathbb{R}^d$  are vectors of regression coefficients. Note that we use separate names for the vectors  $\mathbf{x}$  and  $\mathbf{z}$  corresponding to  $\mu$  and  $y_0$ , respectively. We may let these share none, some, or all elements.

Plugging in the pdf (2.18) and the survival function (2.21) into the log-likelihood (2.9), we get that the log-likelihood of a survival data set with the inverse gaussian FHT model, is

$$\begin{aligned} l(y_0, \mu, \sigma) = \sum_{i=1}^n d_i \left( \ln y_0 - \frac{1}{2} \ln(2\pi\sigma^2 t_i^3) - \frac{(\mu t_i + y_0)^2}{2\sigma^2 t_i} \right) \\ + (1 - d_i) \ln \left( \Phi \left( \frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}} \right) - \exp \left( -\frac{2y_0\mu}{\sigma^2} \right) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right). \end{aligned} \quad (2.24)$$

{eq:loglik}

### 2.5.1 Fitting an IG FHT model

At the moment, the standard for fitting an inverse gaussian FHT model to survival data is to use numerical likelihood maximization (Caroni, 2017). A few software packages for performing this maximization exist. For **R** (R Core Team, 2013), the **threg** package (Xiao et al., 2015). However, the software “only” performs unpenalized maximization likelihood estimation. In modern data sets, it is necessary to perform some sort of penalized or regularized estimation. It is also necessary to be able to perform variable selection, as in the case of using data sets containing genetic information, the number of covariates  $p$  will typically be far larger than the number of individual observations  $N$ . To the best of our knowledge, there does not exist any such method for FHT models.

### 2.5.2 Constructing survival probabilities based on estimates

Consider a case where we have performed estimation of an FHT model, such that we have estimated parameters  $\hat{y}_0$  and  $\hat{\mu}$ , which can be obtained by using the inverse link functions. Since we have a parametric expression for the survival function  $S(t)$  (2.21), we can construct parametric estimates of the survival probability at time  $t$ , by plugging in these estimates. Recall that  $\sigma^2$  is 1, so it is removed from the expression. We denote the estimated probability for  $\hat{S}(t)$ ,

$$\hat{S}(t|\hat{\mu}, \hat{y}_0) = \Phi[\hat{\mu}t + \hat{y}_0] - \exp(-2 \cdot \hat{y}_0 \cdot \hat{\mu}) \Phi[\hat{\mu}t - \hat{y}_0].$$

With an estimate of the probability of an individual at time  $t$ , we are for example able to use the Brier score to assess the predictive performance of the estimated model. We will discuss the Brier score later in the thesis, in section 5.3.

### 2.5.3 Combining clinical and genetic data in the inverse Gaussian FHT model

subsec:FHT-  
combine

Classical survival analysis models have considered a small number of predictors, and they have often been clinical variables. In recent years, much effort has been put into being able to use genetic information to make predictions of survival, and it has become cheap and feasible to obtain genetic data. Rather than only using genetic data in models, it would be best to be able to combine such data with clinical data and other types of data, which might typically be shown to be predictive. There exist various schemes for making such models in Cox regression settings, see e.g. Frigessi et al. (2007). It is, however, not straightforward to perform such a combination. If, for example, we simply merge the clinical data and genetic data into one group, and subsequently standardize the data, as we often need to do for proper model performance, then we might very well miss important effects of the genomic data. Some approaches used require tuning and weighting of parameters.

Ask Riccardo about this; he wrote something about this

The FHT model, however, lends itself nicely to combining clinical and genetic data. Especially if, as Aalen and Gjessing (2001) suggest, we make a priori splitting of covariates into two groups. One group is related to “fixed” covariates, e.g. genes, and the other group of covariates is related to “lifestyle,” e.g., indicators about smoking, or measurements, such as weight. If we incorporate this split of covariates in FHT models, it seems reasonable to let the initial level  $y_0$  of the health process be a function of the “fixed” covariates, while letting the drift  $\mu$  be a function of the “lifestyle” covariates. With the fact that the two groups relate to two separate parameters, they can be standardized separately, and thus we might more easily be able to extract explanatory power from both the genetic data and the clinical data.

## Chapter 3

# Gradient boosting

ch:boosting

Boosting is one of the most promising methodological approaches for data analysis developed in the last two decades (Mayr et al., 2014a). It has become a staple part of the statistical learning toolbox because it is a flexible tool for estimating interpretable statistical models. Boosting, however, originated as a black box algorithm in the fields of computational learning theory and machine learning, not in statistics.

Computer scientists Michael Kearns and Leslie Valiant, who were working on computational learning theory, posed the following question ((Kearns and Valiant, 1989)): Could any weak learner be transformed to become a strong learner? A weak learner, sometimes also simple or base learner, is a learner that has a low performance. For example, in the context of classification, a weak learner is one that performs only slightly better than random (uniform) chance. In the binary classification setting, it would only perform slightly better than a coin flip. Meanwhile, a strong learner should be able to perform in a near-perfect fashion, for example attaining high accuracy on a prediction task. We will first give a summary of the history of boosting, starting with AdaBoost (Freund and Schapire, 1996), an algorithm that proved that the answer to the original question above was yes. For a complete overview of the history of boosting, see Mayr et al. (2014a,b, 2017).

### 3.1 AdaBoost: From machine learning to statistical boosting

The original AdaBoost, also called Discrete AdaBoost (Freund and Schapire, 1996) is an iterative algorithm for constructing a binary classifier  $F(\cdot)$ . It was the first *adaptive* boosting algorithm, as it automatically adjusted its parameters to the data based on its performance. In the binary classification problem, we are given a set of observations

$$D = (\mathbf{x}_i, y_i)_{i=1}^N,$$

where  $\mathbf{x}_i \in \mathbb{R}^p$  is a vector of covariates, and  $y_i \in \{-1, 1\}$  is a binary response, i.e., positive or negative; yes or no. We want to find a rule which best separates these observations into the correct classes  $\{-1, 1\}$ , as well as being able to classify new, unseen observations  $\mathbf{x}_{\text{new}}$  of the same form. Some observations are hard to classify, whereas some are not. One way to look at binary classification

is to imagine the  $p$ -dimensional space of the observations  $\mathbf{x}$ , and think of the classifier as finding the hyperplane which best splits the observations into their corresponding label. Some observations are not at all close to the boundary, and so they are easily classified. Observations that are close to the boundary, however, are more problematic to classify. Freund and Schapire (1996) proposed that one could estimate several classifiers, and assign a weight  $\alpha_m$  to each classifier. By giving more weight to a more accurate classifier, a weighted sum of all of these classifications might be a good classification. It turns out that this is the case. We now give an explanation of the algorithm.

AdaBoost is an iterative algorithm. In a given step  $m$ , we use a weak learner  $h(\cdot)$  to estimate a classifier  $\hat{h}^{[m]}(\cdot)$ , that minimizes the weighted sum of misclassified points. Finally, based on the misclassification rate of this classifier, calculate a weight  $\alpha^{[m]}$  to assign to this classifier  $\hat{h}^{[m]}(\cdot)$ . Currently, the classifier is  $F_1(\cdot) = \alpha_1 h_1(\cdot)$ . Using this initial classifier, some points will be correctly classified, and some will be misclassified. We therefore increase the weights of the misclassified ones, and normalize the weights afterwards, to ensure that the sum of the weights is always the same. This results in the correctly classified observations having a reduced weight, and with misclassified observations having an increased weight, compared to their previous weights. In the next iteration, apply again a weak learner which minimizes the weighted sum of the observations, and reweight observations accordingly as before. Again, calculate a weight to give to this new classifier, and add it to the previous classifier, such that  $F_2(\cdot) = \alpha_1 h_1(\cdot) + \alpha_2 h_2(\cdot)$ . Continue iterating in this fashion until an iteration number  $m_{\text{stop}}$ . The resulting final classifier, the AdaBoost classifier, becomes

$$\hat{F}(\cdot) = F_{m_{\text{stop}}}(\cdot) = \sum_{m=1}^{m_{\text{stop}}} \alpha_m h_m(\cdot).$$

$\hat{F}(\cdot)$  is a linear combination of the weak classifiers. It is in essence a weighted majority vote of weak learners given the observations. See ... for a schematic overview of the algorithm.

The AdaBoost algorithm often carries out highly accurate prediction. In practice, it is often used with stumps, which are decision trees with one split. For example, Bauer and Kohavi (1999) report an average 27% relative improvement in the misclassification error for AdaBoost using stump trees, compared to the error attained with a single decision tree. They conclude that boosting not only reduces the variance in the prediction error from using different training data sets, but that it is also able to reduce the average difference between the predicted and the true class, i.e., the bias. Breiman (1998) supports this analysis. Because of its plug-and-play nature and the fact that it never seemed to overfit, which occurs when the learned classifier degrades in test error because of being too specialized on its training set, Breiman remarked that “boosting is the best off-the-shelf classifier in the world” (Hastie et al., 2009).

While originally developed for binary classification, boosting is now used to estimate the unknown quantities in more general statistical models and settings. We therefore extend our discussion to a more general statistical regression scheme. In its original formulation, the AdaBoost classifier does not have interpretable coefficients, and as such it is a so-called black-box algorithm. This means that we are unable to infer anything about the effect of different covariates.



In statistics, however, we are interested in models which are interpretable. In the rest of this chapter, we will discuss gradient boosting algorithms. We will start by defining the problem such algorithms try to solve, and introduce some notation. We will then explain the gradient descent algorithm, which is what inspired the origin of gradient boosting.

### 3.2 General model structure, setting, and chosen notation

The aim of statistical boosting algorithms is to estimate and select the effects in structured additive regression models. Consider a data set

$$D = \left( \mathbf{x}^{(i)}, \mathbf{y}^{(i)} \right)_{i=1}^N$$

containing the values of an outcome variable  $\mathbf{y}$  and predictor variables  $\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_p$ , forming covariate matrix  $\mathbf{X} = (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_p)$ . We assume that the samples  $i = 1, \dots, n$  are independently generated from an identical distribution over the joint space  $\mathcal{X} \times \mathcal{Y}$ . The input space of  $\mathbf{x}$  is a possibly high-dimensional  $\mathcal{X} \in \mathbb{R}^p$  and the output space is a low-dimensional space  $\mathcal{Y}$ . For the majority of applications, the output space  $\mathcal{Y}$  is one-dimensional, but we will explicitly allow for multidimensional outcome variables. Our objective is to model the relationship between  $\mathbf{y}$  and  $\mathbf{x}$  and to obtain an “optimal” prediction of  $\mathbf{y}$  given  $\mathbf{x}$ . To model the relationship, we will use an approach which very similar to the generalized additive model (GAM) approach (Hastie and Tibshirani, 1990). We will assume that the conditional outcome  $\mathbf{y}|\mathbf{x}$  follows some probability distribution function (pdf)

$$\psi(\mathbf{y}|\theta(\mathbf{x})), \tag{3.1}$$

{eq:psi}

where  $\theta$  is a parameter in the distribution function, typically related to the mean. We will at times refer to  $\psi$  as a prediction function, when we use it to estimate parameters. Further, we will model the distribution parameter  $\theta$  as a functional of the covariates  $\mathbf{X}$ , with conditional expectation given the observed value  $\mathbf{x}$  as

$$g(\mathbb{E}(\theta(\mathbf{x}))) = f(\mathbf{x}), \tag{3.2}$$

where  $g(\cdot)$  is a so-called link function and  $f(\cdot)$  is a predictor. We will discuss  $f(\cdot)$  shortly. We observe that if we use  $g^{-1}(\cdot)$ , i.e. the inverse of the link function, on this expression, we get

$$\mathbb{E}(\theta(\mathbf{x})) = g^{-1}(f(\mathbf{x})).$$

This means that the conditional expectation of  $\theta$  given the observed  $\mathbf{x}$  is a transformation of the additive predictor  $f(\mathbf{x})$  using the inverse of the link function. The link function will be chosen appropriately for the parameter  $\theta$  in the distribution  $\psi$ , and is typically used to constrain the domain of the parameter. For example, if we choose the logarithm as the link function, the inverse link function is the exponential function, meaning that

$$\mathbb{E}(\theta(\mathbf{x})) = \exp(f(\mathbf{x})), \tag{3.3}$$

which will constrain the expectation to be a positive number.

The predictor  $f(\cdot)$  can be modeled in many ways. A common model is to let it be an *additive* predictor, consisting of additive effects of single predictors. This is called a generalized additive model (GAM), and it is specified by

$$f(\mathbf{x}) = \beta_0 + f_1(x_1) + \dots + f_p(x_p), \quad (3.4)$$

{eq:gam}

where  $\beta_0$  is a common intercept and the functions  $f_j(x_j), j = 1, \dots, p$  are single predictors, which are partial effects of the variables  $x_j$ . The generic notation

$$f_j(x_j)$$

may represent different types of predictor effects, such as classical linear effects  $x_j\beta_j$ , smooth non-linear effects constructed via regression splines, spatial effects or random effects of the explanatory variable  $x_j$ , and so on. The component-wise effects will typically be built up by additive estimation of base-learners, and statistical boosting is one way to perform this additive estimation. Statistical boosting algorithms are one way to estimate such models. These algorithms typically estimate  $f(\mathbf{x})$  by estimating component-wise effects for each component  $j$ , and these are in turn built up by estimation of base-learners  $h_1(\cdot), \dots, h_p(\cdot)$ . We will discuss this more in Section 3.5, which introduces component-wise boosting.

We evaluate the fit of a model  $\phi$  and its additive predictor  $f(\cdot)$  by using a loss function  $\rho(y, f(\cdot))$ . The loss function is a measure of the discrepancy between the observed outcome  $\mathbf{y}$  and the additive predictor  $f(\cdot)$ . In machine learning and optimization, one usually talks of loss functions, and as the name suggests, we wish to minimize the loss. We will use the negative log-likelihood of the distribution of the response as a loss function because it is common in statistics (Mayr et al., 2014a). In these cases, the loss function, which works on one set of observations  $(\mathbf{x}_i, \mathbf{y}_i)$ , is

$$\rho(\mathbf{y}_i, \theta(\mathbf{x}_i)) = -\log \psi(\mathbf{y}_i | \theta(\mathbf{x}_i)),$$

since the likelihood of one observation is simply the distribution given the observed data. Note that there is a theoretical result stating that maximizing the log-likelihood is equivalent to minimizing the Kullback-Leibler Divergence, which is a measure of the difference between the distribution of the data itself and the assumed distribution  $\psi$ . This shows that, having assumed a distribution  $\psi$  for the responses, it is a good choice of loss function to use the log-likelihood of  $\psi$ .

### 3.2.1 Example of a model and corresponding loss function

subsec:model-  
example

Let us consider at a specific example of a distribution and a loss function. We have a dataset  $D = (\mathbf{x}_i, y_i)_{i=1}^N$  where the responses  $y_i$  are continuous and univariate. We further assume that the responses follow a normal distribution, conditioned on the data. Thus we wish to model the conditional mean  $\mu(\mathbf{x})$ , and so we use  $\mu$  instead of  $\theta$ . Since the responses are continuous and normal, we do not need any transformation of the additive predictor, which means that the link function is the identity function,

$$g(\mathbf{x}) = \mathbf{x}.$$

Further, it means that

$$\mathbb{E}(\mu(\mathbf{x})) = f(\mathbf{x}).$$

For a normally distributed observation  $y$ , the likelihood is the familiar pdf,

$$f(y|\mu, \sigma^2) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp \left\{ -\frac{(y - \mu)^2}{2\sigma^2} \right\},$$

and we derive the loss function  $\rho$  accordingly, yielding

$$\begin{aligned} \rho(y, \mu(\mathbf{x})) &= -\log f(y|\mu(\mathbf{x})) \\ &= \log(\sqrt{2\pi\sigma^2}) + \frac{(y - \mu(\mathbf{x}))^2}{2\sigma^2} \\ &\propto (y - \mu(\mathbf{x}))^2, \end{aligned}$$

which is the familiar  $L_2$  loss function. Note that since we will only model  $\mu(\cdot)$ , the loss function need not depend on  $\sigma^2$ . Similarly we have disregarded all proportionality constants. With all those parts in place, we can model the additive predictor  $f(\cdot)$ . One way to do this is by gradient boosting, which we will discuss soon.

### 3.2.2 Model selection and model assessment

Having chosen a distribution  $\psi$  and a loss function  $\rho$ , we wish to find the parameter  $\theta$  which minimizes the loss function of all unseen data

$$D_{\text{unseen}} = (\mathbf{X}, Y).$$

This means that we wish to minimize

$$\text{Err}(\theta) = \mathbb{E}_{Y, X} [\rho(Y, \theta(\mathbf{X}))]. \quad (3.5)$$

{eq:unseen-error}

However, we are unable to estimate this quantity, as we do not have access to all such unseen data. We therefore need a so-called *test set*

$$D_{\text{test}} = (\mathbf{x}_i, \mathbf{y}_i)_{i=1}^{N_{\text{test}}}.$$

We can then calculate a test error  $\text{Err}$  of a specific  $\theta$ , which is the mean of the loss using  $\theta$ , over all observations in the test set  $D_{\text{test}}$ ,

$$\text{Err}_{D_{\text{test}}}(\theta) = \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \rho(\mathbf{y}_i, \theta(\mathbf{x}_i)).$$

$\text{Err}_{D_{\text{test}}}$  is an estimate of  $\text{Err}$ , since  $D_{\text{test}}$  is a realization of unseen data. To ensure that  $\text{Err}_{D_{\text{test}}}$  is an unbiased estimate, we will not use any data from the test set to estimate  $\theta$ . To estimate  $\theta$ , we will therefore use a so-called *training set*, which we will denote

$$D_{\text{train}} = (\mathbf{x}_i, \mathbf{y}_i)_{i=1}^N.$$

We can calculate the training error  $\overline{\text{err}}(\theta)$ , also called the *in-sample error*, or the *empirical risk*, which similarly is the sum of the loss function over all observations in the training set,

$$\overline{\text{err}}(\theta) = \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \rho(\mathbf{y}_i, \theta(\mathbf{x}_i)).$$

Our goal will be to use gradient boosting to minimize  $??$ . To understand gradient boosting, we first need to understand the gradient descent algorithm.

### 3.3 Gradient descent

Suppose we are trying to minimize a differentiable multivariate function  $G: \mathbb{R}^n \rightarrow \mathbb{R}$ , where  $n \in \mathbb{N}$ . Gradient descent is a so-called greedy algorithm for finding the minimum of such a function  $G$ , and one which is quite simple and surprisingly effective. If all partial derivatives of  $G$  at a point

$$\mathbf{x}^{[0]} = (x_1^{[0]}, x_2^{[0]}, \dots, x_n^{[0]}) \in \mathbb{R}^n$$

exist, then the gradient of  $G$  at  $\mathbf{x}^{[0]}$  is the vector of all its partial derivatives at  $\mathbf{x}^{[0]}$ , namely

$$\nabla G(\mathbf{x}^{[0]}) = \left( \frac{\partial G(\mathbf{x}^{[0]})}{\partial x_1}, \frac{\partial G(\mathbf{x}^{[0]})}{\partial x_2}, \dots, \frac{\partial G(\mathbf{x}^{[0]})}{\partial x_n} \right).$$

The motivation behind the gradient descent algorithm is that in a small interval around the point  $\mathbf{x}_0$ ,  $G$  is most decreasing in the direction of the negative gradient at that point. Therefore, if we take a small step slightly in the direction of the negative gradient at  $\mathbf{x}^{[0]}$ , which we denote  $\mathbf{g}^{[0]}$ , from  $\mathbf{x}^{[0]}$  to a new value  $\mathbf{x}^{[1]}$ , we end up with a slightly lower function value: The new function value  $G(\mathbf{x}^{[1]})$  will be less than  $G(\mathbf{x}^{[0]})$ . The algorithm is greedy because it always goes in a direction which is immediately better. The length  $a^{[1]}$  of this small step is found by a line search, i.e., by finding the step length which gives the best  $G(\mathbf{x}^{[1]})$ , where then the new point is

$$\mathbf{x}^{[1]} = \mathbf{x}^{[0]} + a^{[1]} \cdot \mathbf{g}^{[0]}.$$

By repeating this procedure  $m_{\text{stop}}$  number of times, the point  $\mathbf{x}^{[m_{\text{stop}}]}$  will yield a minimum value of  $G(\cdot)$ . The number of iterations  $m_{\text{stop}}$  is decided by stopping when the decrease in function value is smaller than some pre-specified threshold  $\epsilon > 0$ ,

$$m_{\text{stop}} = \min_m G(\mathbf{x}^{[m-1]}) - G(\mathbf{x}^{[m]}) < \epsilon.$$

With sufficiently small steps, gradient descent will always converge, albeit possibly to a local minimum. For a schematic overview of the algorithm, see Algorithm 1.

The gradient descent algorithm is surprisingly robust. Even though it may converge to a local minimum, it often seems to find good solutions globally. This is likely related to research which has found that in high-dimensional spaces, most minima are not minima, but in fact, saddlepoints masquerading as local minima (Dauphin et al., 2014). This means that the size of the improvements in the function value  $G(\cdot)$  will slow since the gradient will be small at this saddlepoint. When using a gradient descent method one typically sets a threshold  $\epsilon$  at which the algorithm terminates when the gradient becomes smaller than the threshold, as we did. However if the algorithm continues for a long enough time, then the multivariate gradient descent search should be able to continue to decrease the function value after it “escapes” the saddle point.

algo:grad-desc

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**Algorithm 1** Gradient descent
 

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We wish to minimize  $G(\mathbf{x})$ , i.e. solve  $\min_{\mathbf{x}} G(\mathbf{x})$ , where  $G$  is a multivariate function  $G: \mathbb{R}^n \rightarrow \mathbb{R}$ .

1. Start with an initial guess  $\mathbf{x}^{[0]} \in \mathbb{R}^n$ , for example  $\mathbf{x}^{[0]} = \mathbf{0}$ , and set the number of iterations  $m$  to 0.

grad-desc-iter

2. Increase the iteration number  $m$  by 1.

3. Calculate the direction to step in, i.e., the derivative at the current point,

$$\mathbf{g}^{[m-1]} = -\nabla G(\mathbf{x}^{[m-1]}).$$

4. Solve the line search to find the best step length  $a^{[m]}$ ,

$$a^{[m]} = \underset{a}{\operatorname{argmin}} \mathbf{x}^{[m-1]} + a \cdot \mathbf{g}^{[m-1]}.$$

5. The step in iteration  $m$  becomes

$$\mathbf{h}_m = a^{[m]} \cdot \mathbf{g}^{[m-1]}.$$

6. Let  $\mathbf{x}^{[m]} = \mathbf{x}^{[m-1]} + \mathbf{h}^{[m-1]}$ .

7. Decide if the algorithm should terminate by checking if the decrease in function value is smaller than the pre-specified threshold,

$$G(\mathbf{x}^{[m-1]}) - G(\mathbf{x}^{[m]}) < \epsilon.$$

If this is true, set the number of iterations  $m_{\text{stop}}$  to  $m$ , and go to the next step of the algorithm. If not, go to step 2.

8. The resulting minimum point for  $G(\cdot)$  is

$$\mathbf{x}^{[m_{\text{stop}}]} = \mathbf{x}^{[0]} + \sum_{m=1}^M \mathbf{h}^{[m]}.$$


---

### 3.4 The gradient boosting approach

#### 3.4.1 Direct gradient descent on the loss function

In a seminal paper, Friedman (2001) developed an iterative algorithm for fitting a predictor  $f(\mathbf{x})$ , and he called the algorithm gradient boosting. He showed that AdaBoost performs this algorithm for a particular loss function, namely the exponential loss function. See Hastie et al. (2009) for a good demonstration of Friedman's argument. With this, Friedman provided a way of viewing boosting through a statistical lens, and connected the successful machine learning approach to the world of statistical modelling.

The key idea of gradient boosting is to iteratively fit the different predictors with simple functions (base-learners) and combine the estimates into a predictor. The base-learners are in particular fitted to the negative gradient of the loss function.

Consider data as in the example in subsection 3.2.1. We have covariate vectors  $\mathbf{x}_i$  and continuous responses  $y_i$ , where  $i = 1, 2, \dots, N$ . We assume that the conditional response  $y_i$ , given  $\mathbf{x}_i$ , follows a distribution  $\psi(\theta)$  with a parameter  $\theta$ , which we will let depend on  $\mathbf{x}_i$ , i.e.,  $\theta(\mathbf{x}_i)$ . Based on the distribution  $\psi$ , we derive a loss function  $\rho$ , as seen in Subsection 3.2.1. We wish to estimate the  $\hat{\theta}(\cdot)$  that minimizes the training error, the empirical risk over the observed training data set

$$\underset{\hat{\theta}}{\operatorname{argmin}} \bar{\operatorname{err}}(\theta) = \underset{\hat{\theta}}{\operatorname{argmin}} \frac{1}{N} \sum_{i=1}^N \rho(\mathbf{y}_i, \theta(\mathbf{x}_i)).$$

We can think of the empirical risk  $\bar{\operatorname{err}}(\theta)$  as a multivariate function  $\bar{\operatorname{err}}(\boldsymbol{\theta})$ , where the variables of the function are the parameter values of  $\theta$  at each point  $\mathbf{x}_i$ ,

$$\boldsymbol{\theta}(\mathbf{x}) = (\theta(\mathbf{x}_1), \theta(\mathbf{x}_2), \dots, \theta(\mathbf{x}_N)).$$

These are plugged into the loss function for their corresponding observations, i.e.,

$$\bar{\operatorname{err}}(\boldsymbol{\theta}(\mathbf{x})) = \bar{\operatorname{err}}(\theta(\mathbf{x}_1), \theta(\mathbf{x}_2), \dots, \theta(\mathbf{x}_N)) = \frac{1}{N} \sum_{i=1}^N \rho(\mathbf{y}_i, \theta(\mathbf{x}_i)).$$

In this view,  $\bar{\operatorname{err}}$  is a multivariate function  $\bar{\operatorname{err}}: \mathbb{R}^N \rightarrow \mathbb{R}$ . We can therefore use gradient descent (see the previous section) directly on this function. To do so, we consider  $\hat{\theta}(\mathbf{x}_i)$  as a sum

$$\hat{\theta}(\mathbf{x}_i) = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} f^{[m]}(\mathbf{x}_i),$$

where the first term,  $\beta_0$ , is an initial guess which is common for all  $\mathbf{x}_i$ , and the remaining  $\{\hat{f}^{[m]}(\mathbf{x}_i)\}_{m=1}^M$  function values are increments – steps, or boosts. The initial guess  $\beta_0$  should be the constant which minimizes the loss function  $\rho$ , e.g. the maximum likelihood constant in cases where the loss function is a negative log-likelihood.



To perform gradient descent on the  $\overline{\text{err}}(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N)$ , we need to calculate its negative gradient. The negative partial derivative for each observation has the same structure, namely

$$-\frac{\partial}{\partial \theta(\mathbf{x}_i)} \rho(y_i, \theta(\mathbf{x}_i)).$$

Thus the gradient  $\nabla \overline{\text{err}}(\boldsymbol{\theta})$ , which we will denote  $\mathbf{u}$ , and call generalized residuals, becomes

$$\mathbf{u} = (u_i)_{i=1}^N = \left( -\frac{\partial}{\partial \theta(\mathbf{x}_i)} \rho(y_i, \hat{\theta}(\mathbf{x}_i)) \right)_{i=1}^N.$$

Since we now know how to calculate the gradient of a vector of estimated function values, we can construct an algorithm for performing gradient descent on the loss function. We initialize  $\hat{\theta}^{[0]}(\mathbf{x}_i)$  to  $\beta_0$  for all  $\mathbf{x}_i$ , where  $\beta_0$  is found by

$$\beta_0 = \underset{c}{\text{argmin}} \overline{\text{err}}(c).$$

We then iterate. In a step  $m > 0$ , we calculate the negative gradient  $\mathbf{u}^{[m-1]}$ , and perform a gradient descent step in the direction  $\mathbf{u}^{[m-1]}$ . The gradient descent step is

$$\hat{\theta}^{[m]}(\mathbf{x}_i) = \hat{\theta}^{[m-1]}(\mathbf{x}_i) + a^{[m]} \cdot u_i^{[m-1]},$$

for each observation  $\mathbf{x}_i$ . Thus in vector form, the step is

$$\hat{\boldsymbol{\theta}}^{[m]}(\mathbf{x}) = \hat{\boldsymbol{\theta}}^{[m-1]}(\mathbf{x}) + a^{[m]} \cdot \mathbf{u}^{[m-1]},$$

where the step length  $a^{[m]}$  is found by a line search, as before. After  $m_{\text{stop}}$  number of steps, we will have converged to a solution  $\hat{\boldsymbol{\theta}}^{[m_{\text{stop}}]}$ ,

$$\hat{\boldsymbol{\theta}}^{[m_{\text{stop}}]} = \hat{\theta}^{[m_{\text{stop}}]}(\mathbf{x}_1), \hat{\theta}^{[m_{\text{stop}}]}(\mathbf{x}_2), \dots, \hat{\theta}^{[m_{\text{stop}}]}(\mathbf{x}_N),$$

which is a minimizer for the loss function  $\overline{\text{err}}$ . This nonparametric approach would reduce the error of each data point. However, it will not generalize to a similar data set where one observes different data points, since we only considers the points  $\mathbf{x}_i$  in the training set. We therefore need to do something else, and this is the functional gradient descent algorithm.

### 3.4.2 Functional Gradient Boosting

sec:FGD

In the nonparametric approach from the previous subsection, we are only looking at the observed data points, and not at neighboring points in  $\mathcal{X}$  space. We have to keep in mind that although we are optimizing the empirical risk over a specific data set, we are actually trying to minimize the expected value (3.5), i.e.,

$$\text{Err}(\theta) = \mathbb{E}_{Y, \mathbf{X}} [\rho(Y, \theta(\mathbf{X}))],$$

over all possible values of  $\mathbf{X}$  and  $Y$  in the joint distribution. In addition, we wish to have an interpretable model. Therefore, we must impose smoothness to neighboring points in the  $\mathcal{X}$  space. We can do this by choosing steps of (parameterized) *functions* instead of steps of function *values*, which is what we did in the previous subsection. Therefore, since the solutions are parameterized functions, and we are performing gradient descent, the approach by Friedman

(2001) develops a *functional* gradient descent (FGD) algorithm, a gradient descent search in parameter space. We now consider the estimate  $\hat{\theta}$  to be a function which takes values in  $\mathcal{X}$ ,

$$\hat{\theta}(\mathbf{x}) = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} f^{[m]}(\mathbf{x}),$$

and it is composed of sums of an initial value  $\beta_0$ , and steps  $\{f^{[m]}\}_{m=1}^{m_{\text{stop}}}$ . What is new is that now each  $f^{[m]}(\mathbf{x})$  is a parameterized function which we will estimate. Since  $\theta$  is now a parameterized function, we do not consider the training error  $\overline{\text{err}}(\theta)$  to be a function of  $N$  individual function parameter values  $\theta(\mathbf{x}_i)$ ,  $i = 1, \dots, N$ , but rather just a function of  $\theta$ . Hence, to derive the negative gradient of an estimate  $\hat{\theta}$ , i.e., we must differentiate the loss function  $\rho$  with respect to  $\theta$  instead of  $\theta(\mathbf{x}_i)$ . The generalized residuals, or the negative gradient, then become

$$\mathbf{u} = \left( -\frac{\partial}{\partial \theta} \rho(y_i, \hat{\theta}(\mathbf{x}_i)) \right)_{i=1}^N.$$

Then we iterate, let us say, at each step  $m > 0$  first calculating the generalized residuals of the previous iteration,

$$\mathbf{u}^{[m-1]} = \left( -\frac{\partial}{\partial \theta} \rho(y_i, \hat{\theta}^{[m-1]}(\mathbf{x}_i)) \right)_{i=1}^N,$$

like we have seen before. Here we insert the model from the previous step,  $\hat{\eta}^{[m-1]}$ . We now perform a gradient descent step. However, we now constrain ourselves to steps which are functions of a base learner

$$\langle (\cdot),$$

to ensure smoothness and generalizability, as discussed above.

A base learner is a class of functions  $\langle$  which is regularized, and often a simple effect of a parameter  $\beta$ . Typical examples are linear least squares, stumps (trees with one split; see Bühlmann and Hothorn (2007) and Hastie et al. (2009)), and splines with a few degrees of freedom. There are several reasons to use simple base learners in each step. One is that there often exists fast methods for estimating a single base learner. Therefore there will be little computational cost in each step. Secondly, there is more to gain by combining simple learners, rather than combining complex learners. If we want to use complex learners, it is better to use another algorithm.

To take the steepest gradient in a functional sense, we must choose the realization of the base learner class  $\langle$  that produces the function  $\hat{h}^{[m]}$  that is *most parallel* to  $\mathbf{u}^{[m-1]}$ . Another way of looking at it is that it is the member of the base learner function class  $h$  that is most correlated with  $\mathbf{u}^{[m-1]}$  over the data distribution. This it means that  $\hat{h}^{[m]}$  is the best approximation of the generalized residuals  $\mathbf{u}^{[m-1]}$  by using  $h(\cdot)$  to approximate with. Equivalently,  $\hat{h}^{[m]}$  is the projection of the generalized residuals onto the space spanned by the base learner function class. We obtain  $\hat{h}_m$  by fitting the base learner  $\langle$  to the generalized residuals. The specific method of fitting will depend on the base learner. If, for example, the base learner is a linear regressor, then the base learner will be

$$\hat{h}^{[m]} = \left( \mathbf{u}^{[m-1]} \right)^T \hat{\beta}^{[m]},$$

where the parameter is found by

$$\hat{\beta}^{[m]} = \left( \left( \mathbf{u}^{[m-1]} \right)^T \mathbf{u}^{[m-1]} \right)^{-1} \left( \mathbf{u}^{[m-1]} \right)^T \mathbf{y}.$$

Having estimated the base learner, we do a line search to find the appropriate step length to use in order to minimize the loss function the most,

$$a^{[m]} = \underset{a}{\operatorname{argmin}} \overline{\operatorname{err}} \left( \hat{\theta}^{[m-1]} + a \cdot \hat{h}^{[m]} \right).$$

We add the estimated learner times the step length to the current model, obtaining

$$\hat{\theta}^{[m]}(\cdot) \leftarrow \hat{\theta}^{[m-1]}(\cdot) + a^{[m]} \hat{h}^{[m]}(\cdot).$$

We iterate this procedure until some stopping criterion. The convention that has emerged is to specify a number of iterations  $m_{\text{stop}}$ . This is the most important tuning parameter, and we will discuss it in the next subsection. The resulting model

$$\hat{\theta}_{\text{FGD}}(\cdot) = \hat{\theta}^{[m_{\text{stop}}]}(\cdot)$$

has the additive structure that we discussed earlier, namely

$$\hat{\theta}(\mathbf{x}) = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} f^{[m]}(\mathbf{x}),$$

where each

$$f^{[m]}(\cdot) = a^{[m]} \cdot \hat{h}^{[m]}(\cdot).$$

This structure is a direct effect of the gradient descent algorithm, as the aggregation of base learners is strictly additive: In every iteration, small increments are added to the additive predictor. For a schematic overview of this algorithm, see Algorithm 2.

The algorithm just described calculates error terms in each iteration, and performs functional gradient descent on them. It is a very general framework, and it only requires a data set, a differentiable loss function, and a base learner. It is therefore quite straightforward to derive specific algorithms to use for specific models: It is just a matter of plugging in a chosen loss function and deriving its negative gradient. This gives great flexibility. We will now discuss the tuning parameters of the algorithm, which are very important to achieve good performance.

### 3.4.3 Tuning parameters

#### 3.4.3.1 Step length

In the original generic functional gradient boosting algorithm, Algorithm 2, the step length  $a_m$  for each iteration is found through a line search, as in gradient descent. Friedman (2001) says that fitting the data too closely may be counterproductive, and result in overfitting. This has indeed proven to be true since then. To combat the overfitting, we must constrain the fitting procedure. This constraint is called regularization. Friedman therefore, later in the paper, proposes to regularize each step in the algorithm by a common learning rate,

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**Algorithm 2** Gradient boosting, or, generic Functional Gradient Descent (FGD)

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algo:fgd

1. Start with a data set  $D = \{x_i, y_i\}_{i=1}^N$  and a chosen loss function  $\rho(y, \theta(x))$ , for which we wish to minimize the empirical risk, i.e., the loss function evaluated on the samples,

$$\hat{\theta} = \operatorname{argmin}_{\theta} \overline{\text{err}}(\theta) = \operatorname{argmin}_{\theta} \sum_{i=1}^n \rho(y_i, \theta(x_i)).$$

2. Set iteration counter  $m$  to 0. Initialize the additive predictor by setting  $\hat{f}_0(\cdot)$  to a constant  $\beta_0$ . This constant should be the maximizer of the loss function,

$$\beta_0(\cdot) = \operatorname{argmin}_c \overline{\text{err}}(c),$$

and it can be found e.g. through numerical maximization.

3. Specify a base learner class  $h$ , e.g. linear least squares.
4. Increase  $m$  by 1.
5. Compute the generalized residuals (the negative gradient vector) of the previous iteration,

$$\mathbf{u}^{[m-1]} = \left( -\frac{\partial}{\partial \theta} \rho(y_i, \hat{\theta}^{[m-1]}(x_i)) \right)_{i=1}^N$$

6. Fit base learner  $h$  to the generalized residuals  $\mathbf{u}$  to obtain a fitted version  $\hat{h}^{[m]}$ .

algo-fgd-step-line

7. Find best step length for  $a^{[m]}$  by a line search:

$$a^{[m]} = \operatorname{argmin}_a \overline{\text{err}} \left( \hat{\theta}^{[m-1]} + a \cdot \hat{h}^{[m]} \right).$$

algo-fgd-step-last-loop

8. Update the current estimated  $\theta$ ,

$$\hat{\theta}^{[m]}(\cdot) \leftarrow \hat{\theta}^{[m-1]}(\cdot) + a^{[m]} \cdot \hat{h}^{[m]}(\cdot).$$

9. Repeat steps 4 to 8 (inclusive) until the iteration number  $m$  is  $m_{\text{stop}}$ .

10. Finally, return the estimated

$$\hat{\theta}_{\text{FGD}}(\cdot) = \hat{\theta}^{[m_{\text{stop}}]}(\cdot) = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} a^{[m]} \hat{h}^{[m]}(\cdot).$$


---

$\nu \in (0, 1]$ . As we will see, most modern boosting algorithms omit the step of the line search entirely, i.e. step 7 in Algorithm 2, instead using only a fixed learning rate/step length  $\nu$ . The choice of this step length is not of critical importance as long as it is sufficiently small (Schmid and Hothorn, 2008), i.e., it produces sufficient shrinkage, but the convention is to use  $\nu = 0.1$  (Mayr et al., 2014a). This reduces the complexity of the algorithm, and it reduces the number of tuning parameters to 1, namely the number of iterations  $m_{\text{stop}}$ . There is a tradeoff between the number of iterations  $m_{\text{stop}}$  and the size of the step length  $\nu$ . We will now discuss the number of iterations.

subsec:  
iterations

### 3.4.3.2 Number of iterations

With a fixed step length (learning rate), the main tuning parameter for gradient boosting is the number of iterations  $m_{\text{stop}}$  that are performed before the algorithm is stopped. Its value is critical: If  $m_{\text{stop}}$  is too small, the model will underfit and it cannot fully incorporate the influence of the effects on the response and will consequently have poor performance. On the other hand, too many iterations will result in overfitting, leading to poor generalization. We know that we have overfitting if the estimated model  $\hat{\theta}$  causes a high value of the test error  $\text{Err}(\hat{\theta})$ . It is easiest to notice overfitting if we continually calculate the test error as the model complexity increases. The model complexity will increase with the number of steps. The normal behaviour is that the test error will first decrease for a number of iterations, but then it will start to increase again. The training error  $\overline{\text{err}}$ , on the other hand, will continue to decrease, so it is important to monitor by calculating test error. The number of iterations is a very important tuning parameter. We will discuss it more in-depth in Section 3.6.

## 3.5 High dimensions and component-wise gradient boosting

sec:component

### 3.5.1 Problems in high dimensions

In modern biomedical statistics, it is crucial to be able to handle high-dimensional data. In some situations, a data set consists of more predictors  $p$  than observations  $N$ . When  $p$  is much larger than  $N$  ( $p \gg N$ ), we talk about high-dimensional settings. In order to address the issue of analyzing high-dimensional data sets, a variety of regression techniques have been developed over the past years. Many of these techniques are characterized by a built-in mechanism for regularization. Regularization is a way to reduce the complexity of a model.

### 3.5.2 Regularization

In methods with built-in regularization, shrinkage of coefficient estimates or selection of relevant predictors is carried out *simultaneously* with the estimation of the model parameters. Both shrinkage and variable selection will typically improve prediction accuracy: In case of shrinkage, coefficient estimates tend to have a slightly increased bias but a decreased variance, while in case of variable selection, overfitting the data is avoided by selecting only the most informative

predictors. For instance if we are to use a least squares base learner which uses all  $p$  dimensions, we see that it is infeasible: The matrix which must be inverted is singular when the number of predictors  $p$  is larger than the number of observations  $N$ . For other models, it might be possible to estimate parameters for each predictor, but it would very easily result in overfitting. This is due to the “curse of dimensionality,” which states that in high-dimensional space, virtually all points are very far apart. Since the points are far apart, there are a vast number of ways that the variation can be explained, and very few of these will capture a generalized structure. Similarly, for variable selection, typical regimes such as *forward stepwise variable selection* are infeasible to carry out, because it requires refitting all covariates in each new step, and it might be necessary to carry out a lot of steps. It is also clearly impossible to perform an exhaustive search of all combinations, as the number of models will suffer from the combinatorial explosion, i.e. that the number of models increases incredibly fast as the number of predictors  $p$  increases. Note that regularization is not only useful in the high-dimensional data setting, but also tends to improve prediction accuracy in low-dimensional settings where  $p \leq N$ .

### 3.5.3 The component-wise boosting approach

Component-wise gradient boosting is an algorithm which works very well in these settings. In fact, Bühlmann believes that it is mainly in the case of high-dimensional predictors that boosting has a substantial advantage over classical approaches (Bühlmann, 2006). The component-wise approach was first proposed in (Bühlmann and Yu, 2003), and component-wise boosting is a very active field of research (Bühlmann, 2006; Mayr et al., 2014a,b, 2017). The key idea of the component-wise approach to gradient boosting is to add the effect of only one variable at a time, instead of adding a small effect from all variables, as is the case in the generic FGD algorithm (Algorithm 2).

Consider yet again the case where we have a data set  $D = (\mathbf{x}_i, y_i)_{i=1}^N$ , where  $\mathbf{x}_i \in \mathbb{R}^p$  are covariate vectors of a high dimension  $p$ , and  $N$  is the number of observations. Specifically, we are in a setting where  $p > N$ . We want to find the parameter  $\theta$  which minimizes the empirical risk of a chosen loss function  $\rho$  on the data set,

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \overline{\operatorname{err}}(\theta) = \underset{\theta}{\operatorname{argmin}} \sum_{i=1}^n \rho(y_i, \theta(\mathbf{x}_i)),$$

where the parameter  $\theta$  is a predictor  $\theta: \mathbb{R}^p \rightarrow \mathbb{R}$ . However, we will now let  $\theta$  be an additive predictor, meaning it is a sum of partial effects of covariates,

$$\theta(\mathbf{x}) = \beta_0 + \sum_{j=1}^p f_j(x_j).$$

These partial effects of the covariates will be estimated by component-wise learners in an iterative fashion.

### 3.5.4 The component-wise boosting algorithm

The structure of the component-wise boosting algorithm is very much the same as the generic functional gradient boosting algorithm (Algorithm 2), but



with some additional steps. As mentioned, instead of using a base learner which incorporates all predictors, we use a set  $\mathcal{H}$  of base learners consisting of a separate base learner for each component of the covariates. The learners typically share the same structure, i.e., are they are the same base learner, only using different covariates, but it is not necessarily the case. For example, if we use a linear least squares model as base learners, the set of base learners would be

$$\mathcal{H} = \{h_1(\mathbf{x}; \beta_1) = \beta_1 x_1, h_2(\mathbf{x}; \beta_2) = \beta_2 x_2, \dots, h_p(\mathbf{x}; \beta_p) = \beta_p x_p\}.$$

The initialization of the algorithm is the same as in the FGD algorithm: We first initialize the additive predictor  $\hat{\theta}^{[0]}$  to a constant  $\beta_0$ . We then iterate. In a given iteration  $m$ , we first construct the generalized residuals, by calculating the negative gradient. Here we insert the additive predictor from the previous step, namely  $\hat{\theta}^{[m-1]}$ ,

$$\mathbf{u}^{[m-1]} = \left( -\frac{\partial}{\partial \theta} \rho(y_i, \hat{\theta}(\mathbf{x}_i)) \right)_{i=1}^N.$$

Note that this calculation is exactly like in the generic gradient boosting algorithm. While the generic FGD algorithm here only estimated a single base learner, in the component-wise we estimate all base learners separately. We obtain  $p$  estimated functions

$$\hat{h}_1^{[m]}(\cdot), \hat{h}_2^{[m]}(\cdot), \dots, \hat{h}_p^{[m]}(\cdot).$$

These estimated functions can again be viewed as approximations of the negative gradient vector, or equivalently the projection of the negative gradient vector onto the space spanned by the component-wise base learner. However, these are projections onto only one dimension of the covariate space. We wish to reduce the error  $\overline{\text{err}}$  as much as possible, and so we select the covariate which has a corresponding estimated base learner which explains as much as possible of the variation in  $\mathbf{u}^{[m-1]}$ . To select the best-fitting base-learner, we select the one with the smallest residual sum of squares error

$$j^{[m]} = \underset{j \in \{1, 2, \dots, p\}}{\operatorname{argmin}} \sum_{i=1}^N \left( u_i - \hat{h}_j^{[m]} \right)^2.$$

Note that this makes sense from a linear algebra perspective: Choosing the one with minimal RSS means that we choose the one with the smallest projection error, or the one with the most signal. We add this best-fitting base-learner  $\hat{h}_{j^{[m]}}^{[m]}$  to the current model, with a pre-specified step length of  $\nu$ , again typically set to 0.1, for the purpose of regularization. Hence the model after iteration  $m$  is

$$\hat{\theta}^{[m]}(\cdot) \leftarrow \hat{\theta}^{[m-1]}(\cdot) + \nu \cdot \hat{h}_{j^{[m]}}^{[m]}.$$

Seen from a component-wise perspective, we update the predictor of the selected component,

$$\hat{f}_{j^{[m]}}^{[m]}(\cdot) \leftarrow \hat{f}_{j^{[m]}}^{[m-1]}(\cdot) + \nu \cdot \hat{h}_{j^{[m]}}^{[m]},$$

and for all other components  $j \in \{j : j \neq j^{[m]}, j = 1, 2, \dots, p\}$ , the update in iteration  $m$  is simply to keep the predictor from the last iteration

$$\hat{f}_j^{[m]}(\cdot) \leftarrow \hat{f}_j^{[m-1]}.$$

We continue iterating until the iteration number  $m$  reaches the pre-specified stopping iteration  $m_{\text{stop}}$ . We will discuss selection of  $m_{\text{stop}}$  in Section 3.6. The final additive predictor becomes

$$\hat{\theta} = \hat{\theta}^{[m_{\text{stop}}]} = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} \hat{h}_{j^{[m]}}^{[m]}(\cdot).$$

Note that any base-learner  $h_j$  can be selected at multiple iterations. The partial effect of the variable  $x_j$  is the sum of the estimated corresponding base learner in all iterations where it was selected. Hence each  $\hat{\theta}_j^{[m_{\text{stop}}]}(x_j)$  can be seen as i.e.,

$$\hat{\theta}_j(x_j) = \sum_{m=1}^{m_{\text{stop}}} \nu \cdot \hat{h}_j^{[m]}(x_j) \mathbf{I}(j^{[m]} = j),$$

where  $\mathbf{I}(\cdot)$  is an indicator function. Hence the resulting additive predictor is a sum of component-wise predictors in the GAM form of

$$\hat{\eta}(\mathbf{x}) = \beta_0 + \sum_{j=1}^p \hat{f}_j(x_j).$$

For a schematic overview of the algorithm, see Algorithm 3.

### 3.5.5 Component-wise boosting performs data-driven variable selection

sec:variable-  
selection

Stopping the algorithm before every base-learner was at least selected once effectively excludes all non-selected base-learners, and thus also the corresponding covariates, from the final model. The algorithm is therefore able to perform variable selection and model fitting simultaneously. Furthermore, early stopping shrinks effect estimates toward zero (Bühlmann and Hothorn, 2007; De Bin, 2016), similar to  $L_1$ -penalized regression such as the lasso (Tibshirani, 1996; Efron et al., 2004). Shrinkage of effect estimates lead to a lower variance and therefore to more stable and accurate predictions (Efron, 1975; Copas, 1983; Hastie et al., 2009).

In other words, if the number of iterations  $m_{\text{stop}}$  is small enough, the component-wise gradient boosting algorithm will carry out automatic variable selection. In particular the base learners applied to irrelevant variables will never be considered in the updating step, and therefore many of the covariates in  $\mathbf{x}$  will not be a part of the final model. Some predictors will have more explanatory power, or signal, than others, and so they will be selected more often. This is because some predictors are more correlated with the output than others. We will now discuss the tuning parameter  $m_{\text{stop}}$ .

## 3.6 Selecting the iteration number $m_{\text{stop}}$

sec:stop

As we have mentioned in subsection 3.4.3.2, the crucial tuning parameter in boosting is the number of iterations,  $m_{\text{stop}}$ . Stopping a boosting procedure early enough will lead to variable selection and shrinks the parameter estimates toward zero, compared to if the algorithm was to run to convergence. In the case

algo: component-wise

**Algorithm 3** Component-wise gradient boosting

---

1. Start with a data set  $D = \{x_i, y_i\}_{i=1}^N$  and a chosen loss function  $\rho(y, \theta(x))$ , for which we wish to minimize the empirical risk, i.e., the loss function evaluated on the samples,

$$\hat{\theta} = \underset{\theta}{\operatorname{argmin}} \overline{\operatorname{err}}(\theta) = \underset{\theta}{\operatorname{argmin}} \frac{1}{N} \sum_{i=1}^N \rho(y_i, \theta(x_i)).$$

2. Set iteration counter  $m$  to 0. Specify a step length  $\nu$ . Initialize the additive predictor by setting  $\hat{f}_0(\cdot)$  to a constant  $\beta_0$ . This constant should be the maximizer of the loss function,

$$\beta_0(\cdot) = \underset{c}{\operatorname{argmin}} \overline{\operatorname{err}}(c),$$

and it can be found e.g. through numerical maximization.

3. Specify a set of base learners  $\mathcal{H} = \{h_1(\cdot), \dots, h_p(\cdot)\}$ , where each  $h_j$  is univariate and takes column  $j$  of  $\mathbf{X}$ .

first-step

4. Increase  $m$  by 1.
5. Compute the negative gradient vector, i.e., the generalized residuals after the previous iteration of the boosted model,

$$\mathbf{u}^{[m-1]} = \left( -\frac{\partial}{\partial \theta} \rho(y_i, \hat{\theta}(x_i)) \right)_{i=1}^N.$$

6. For each base learner  $h_j \in \mathcal{H}, j = 1, \dots, p$ , estimate  $\hat{h}_j^{[m]}$  by fitting  $(\mathbf{x}_i, u_i)_{i=1}^N$  using the base learner  $h_j(\cdot)$ . We obtain

$$\hat{h}_1^{[m]}(\cdot), \hat{h}_2^{[m]}(\cdot), \dots, \hat{h}_p^{[m]}(\cdot).$$

7. Select the best-fitting component  $j^{[m]}$ , i.e., with lowest RSS,

$$j^{[m]} = \underset{j \in \{1, 2, \dots, p\}}{\operatorname{argmin}} \sum_{i=1}^N \left( u_i - \hat{h}_j^{[m]} \right)^2.$$

last-step

8. Update the current model with the best-fitting model from the current iteration

$$\hat{\theta}^{[m]}(\cdot) \leftarrow \hat{\theta}^{[m-1]}(\cdot) + \nu \cdot \hat{h}_{j^{[m]}}^{[m]}(\cdot).$$

9. Repeat steps 4 to 8 (inclusive) until the iteration number  $m$  is  $m_{\text{stop}}$ .
10. Return the final boosted additive predictor

$$\hat{\theta}(\cdot) = \hat{\theta}^{[m_{\text{stop}}]}(\cdot) = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} \nu \cdot \hat{h}_{j^{[m]}}^{[m]}(\cdot)$$


---

of  $p < N$ , with  $m \rightarrow \infty$ , the parameters in boosting will converge towards the maximum likelihood estimates (De Bin, 2016), i.e., minimizing the in-sample error. We are, on the other hand, interested in minimizing the test error  $\text{Err}(\theta)$  with respect to  $\theta$ . When using a gradient boosting algorithm, we do so on a data set  $D$ . We choose an appropriate loss function, we specify base learners, and we specify a learning rate. When these four factors are fixed, the parameter path will be deterministic. This means that running the boosting algorithm the same number of steps  $m$  several times will lead to the same  $\hat{\theta}^{[m]}$ . There is no randomness in the estimates. This is quite obvious if we think about it, because at any given step, the algorithm selects the component and learner which leads to the best decrease in training error, and there is nothing random in that. The point of this is that we can view the test error of an estimated boosting model  $\hat{\theta}^{[m]}$  as a function of the number of iterations used to produce it, i.e.,

$$\text{Err}(m) = \text{Err}(\hat{\theta}^{[m]}). \quad (3.6)$$

{test-error-m}

There exists an  $m$  which minimizes  $\text{Err}(m)$ . Many authors state that the algorithm should be stopped early, but do not go further into the details. What we want is therefore a good method for approximating  $\text{Err}(m)$ . This can be done in a number of ways. Common model selection criteria such as the Akaike Information Criteria (AIC) may be used, however the AIC is dependent on estimates of the model's degrees of freedom. Initial versions of boosting used it, but practice showed that AIC-based stopping rules lead to overfitting (Mayr et al., 2012b). For  $L_2$ Boost, Bühlmann and Hothorn (2007) suggest that  $\text{df}(m) = \text{trace}(B_m)$  is a good approximation. Here  $B_m$  is the hat matrix resulting from the boosting algorithm. This was, however, shown by Hastie (2007) to always underestimate the actual degrees of freedom. Mayr et al. (2012b) propose a sequential stopping rule using subsampling. However this is computationally very expensive and not really used in practice. None of these rules, in other words, are optimal to use. Instead, cross-validation, a general and very common method for selection of tuning parameters in statistics, is what is used in almost all cases, both in practice and in research (Mayr et al., 2014a,b, 2017). Cross-validation is flexible and easy to implement. It is somewhat computationally demanding, because it requires several full runs of the boosting algorithm, but it is otherwise quite simple. We now give an explanation of this procedure.

### 3.6.1 K-fold cross-validation

subsec:K-fold

K-fold cross-validation (Lachenbruch and Mickey, 1968), or simply cross-validation, is a general method commonly used for selection of penalty or tuning parameters because it approximates the test error. In cross-validation, the data are randomly split into  $K$  roughly equally sized folds. For a given fold  $k$ , all folds except  $k$  act as the training data in estimating the model. We often say that the  $k$ -th fold is left out. The resulting model is then evaluated on the unseen data, namely the observations belonging to fold  $k$ . This procedure is repeated for all  $k = 1, \dots, K$ . An estimate of the test error is obtained by averaging over the test errors evaluated in each left-out fold. Let  $\kappa(k)$  be the set

of indices for fold  $k$ . The cross-validated estimate for a given  $m$  then becomes

$$\text{CV}(m) = \frac{1}{K} \sum_{k=1}^K \sum_{i \in \kappa(k)} \rho(y_i, \hat{y}_i^{-\kappa(k)}).$$

$\text{CV}(m)$  is an estimate of the training error of gradient boosting as a function of the iteration number  $m$  (3.6). For each iteration  $m$ , we calculate the estimate of the cross-validated prediction error  $\text{CV}(m)$ . We choose  $m_{\text{stop}}$  to be the minimizer of this error,

$$m_{\text{stop}} = \underset{m}{\operatorname{argmin}} \text{CV}(m).$$

Typical values for  $K$  are 5 or 10, but in theory one can choose any number. The extreme case is  $K = N$ , called leave-one-out cross-validation, where all but one observation is used for training and the model is evaluated on the observation that was left out. In this case, the outcome is deterministic, since there is no randomness when dividing into folds.

### 3.6.2 Stratified cross-validation

When dividing an already small number of survival data observations into  $K$  folds, we might risk getting folds without any observed deaths, or in any case, very few. In stratified cross validation, we do not divide the folds entirely at random, but rather, try to divide the data such that there is an equal amount of uncensored data in each fold. As before, let  $\kappa(k)$  be the set of indices for fold  $k$ . Divide the observed data into  $K$  folds, as with usual cross validation, to get an index set  $\kappa_{\delta=1}(k)$  for a given  $k$ . Similarly, divide the censored data into  $K$  folds, obtaining  $\kappa_{\delta=0}(k)$ . Finally,  $\kappa(k)$  is the union of these sets:  $\kappa(k) = \kappa_{\delta=1}(k) \cup \kappa_{\delta=0}(k)$ . For a detailed description of 10-fold cross-validation issues in the presence of censored data, see Kohavi (1995).

### 3.6.3 Repeated cross-validation

subsec: repeated-  
cv

The randomness inherent in the cross-validation splits has an effect on the resulting  $m_{\text{stop}}$ . This is true for boosting in general, but it is especially true for real-life survival data, because such data sets typically have small effective sample sizes (number of observed events). We can easily imagine that we can end up with quite different values for  $m_{\text{stop}}$  for two different splits of the data, depending on which folds the events end up in. It has been very effectively demonstrated that the split of the folds has a large impact on the choice of  $m_{\text{stop}}$  (Seibold et al., 2018). To reduce the impact of this issue, Seibold et al. (2018) suggest to repeat the cross-validation scheme a few times and average the results. They show that repeating the cross-validation procedure even only 5 times effectively averages out the randomness. In other words, we divide the data into  $K$  folds, and repeat this  $J$  times. Now let  $\kappa(j, k)$  be the  $k$ -th fold in the  $j$ -th split. We end up with a new estimate for the prediction error,

$$\text{RCV}(m) = \frac{1}{J} \sum_{j=1}^J \frac{1}{K} \sum_{k=1}^K \sum_{i \in \kappa(j, k)} \rho(y_i, \hat{y}_i^{-\kappa(j, k)}).$$

Again,  $\text{RCV}(m)$  is also an estimate of (3.6), but with less variance due to averaging several results. As before, we choose  $m_{\text{stop}}$  to be the minimizer of this error,

$$m_{\text{stop}} = \underset{m}{\operatorname{argmin}} \text{RCV}(m).$$

To carry out this in practice when using a boosting algorithm, we let the boosting algorithm run for  $m = 1$  to  $m = M$ , where  $M$  is a large number that we are sure will result in an overfitted model. Thus we ensure that we find the minimizing  $m$ , and not a local minimum.

### 3.7 Multidimensional boosting

A limitation of the boosting methods we have described so far, as well as of  $L_1$ -penalized estimation such as the lasso method (Tibshirani, 1996), is that they are designed for statistical problems involving a one-dimensional prediction function. By only considering such functions, we are restricted to estimating models which only model a single quantity of interest, which is almost always the mean. In many applications, modelling only one parameter will not be sufficient (Kneib, 2013). We want to be able to estimate more general models, in which more quantities, e.g. the drift and the threshold of the models described in section 2.3, can be explained by covariates. To properly estimate such an FHT model, we therefore need a more general gradient boosting algorithm which is able to estimate several parameters. Typical examples of multidimensional estimation problems are classification with multiple outcome categories and regression models for count data. Another example is estimating models in the GAMLSS family (Rigby and Stasinopoulos, 2005). GAMLSS, which refer to “generalized additive models for location, scale and shape,” are a family of models that relates not only the mean, but all parameters of the outcome distribution to the available covariates. GAMLSS are in this sense an extension of GAM models (Hastie and Tibshirani, 1990). A gradient boosting algorithm called *gamboostLSS* was developed for boosting such models (Mayr et al., 2012a). The algorithm framework used in *gamboostLSS* is inspired by the multidimensional boosting algorithm first introduced in Schmid et al. (2010). We will here explain the *gamboostLSS* algorithm, as presented in Mayr et al. (2012a).

### 3.8 Cyclical *gamboostLSS*

sec:gamlssboost

A key feature of the GAMLSS model family is that every parameter of the conditional response distribution is modelled by its own predictor and associated link function. Traditional GAMs (Hastie and Tibshirani, 1990) are typically restricted to modelling the conditional mean of the response variable, and treats possible other distributional parameters as fixed. GAMLSS, on the other hand, allows for regression of each distribution parameter on the covariates. Common distribution parameters are location, scale, skewness and kurtosis, but degrees of freedom (of a  $t$ -distribution) and zero inflation probabilities can be modelled as well (Mayr et al., 2012a). Thus, in the GAMLSS approach, the full conditional distribution of a multiparameter model is related to a set of predictor variables of interest. Similarly to in GAMs, in GAMLSS the structure of each predictor is assumed to be additive. Hence a wide variety of functional predictors can

be included in each predictor. Examples include non-parametric terms based on penalized splines, varying-coefficient terms and spatial and subject-specific terms for repeated measurements. The estimation of GAMLSS coefficients is usually based on penalized likelihood maximization; for details on fitting procedures, see Rigby and Stasinopoulos (2005).

### 3.8.1 GAMLSS

The GAMLSS model class assumes observations  $y_i$  for  $i = 1, 2, \dots, n$  that are conditionally independent given a set of covariates and after having accounted for spatiotemporal effects. The conditional density

$$\psi(y_i|\boldsymbol{\theta}(x_i)), \quad (3.7) \quad \boxed{\{\text{gamlss-density}\}}$$

may depend on  $K$  distribution parameters

$$\boldsymbol{\theta}_i = (\theta_{i,1}, \theta_{i,2}, \dots, \theta_{i,K})^T.$$

Each distribution parameter  $\theta_k, k = 1, 2, \dots, K$  is modelled by its own additive predictor  $\eta_k$  and depends additively on the covariates.  $\theta_k$  is linked to its predictor by a known monotonic link function

$$g_k(\cdot).$$

Letting  $p_k$  be the number of covariates to be used for distribution parameter  $\theta_k$ ,

$$x_{k,1}, x_{k,2}, \dots, x_{k,p_k}$$

are the covariates in the model of the parameter  $\theta_k$ . A GAMLSS is given by the equations

$$\eta_k := g_k(\theta_k) = \beta_{k,0} + \sum_{j=1}^{p_k} f_{k,j}(x_{k,j}),$$

for all  $k = 1, 2, \dots, K$ . Here  $\beta_{k,0}$  is the intercept for distribution parameter  $\theta_k$ , and  $f_{k,j}$  represents the type of effect that covariate  $j$  has on the distribution parameter  $\theta_k$ , through the link function. In the case of a simple linear regression learner, a component-wise effect of component  $j$  on distribution parameter  $\theta_k$  would be

$$f_{k,j}(x_{k,j}) = x_{k,j}\beta_{k,j},$$

where  $\beta_{k,j}$  is a parameter to be estimated. Finally,  $\eta_k$  is the additive predictor for  $\theta_k$ . Note that a GAMLSS reduces to a GAM (Hastie and Tibshirani, 1990) in the case where the distribution parameter vector is a scalar

$$\boldsymbol{\theta}_i = \theta_i = \mu_i,$$

i.e., the conditional mean of observation  $i$ . For parametric models, the unknown quantities of a GAMLSS can be estimated by maximizing the log-likelihood of an observed data set of  $n$  observations of the conditional density (3.7). The log-likelihood contribution for one sample is

$$\log\{\psi(\boldsymbol{\theta}(x_i)|y_i)\},$$



$\hat{\theta}$  will be a functional which works on the covariate vector  $\mathbf{x}$ . Hence the total log-likelihood is

$$l(\boldsymbol{\theta}) = \sum_{i=1}^N \log(\psi(\boldsymbol{\theta}(x_i)|y_i)),$$

Denoting estimates of the prediction functions as  $\hat{\eta}_k$ , estimates of the distribution parameters  $\boldsymbol{\theta}$  are then obtained from transforming back via the inverse link functions,

$$\hat{\theta}_k = g_k^{-1}(\hat{\eta}_{\theta_k}),$$

for all  $k = 1, 2, \dots, K$ , i.e.,  $\hat{\boldsymbol{\theta}} = (\theta_1, \theta_2, \dots, \theta_K)$  is an estimate of  $\boldsymbol{\theta}$ . After the original GAMLSS paper (Rigby and Stasinopoulos, 2005), a penalized likelihood approach based on modified versions of the backfitting algorithm for GAM estimation was developed by the same authors (Stasinopoulos and Rigby, 2007). Later, however, a gradient boosting algorithm, called *gamboostLSS*, was developed (Mayr et al., 2012a). The algorithm *gamboostLSS* uses a strategy for multidimensional boosting proposed by Schmid et al. (2010). Thomas et al. (2018) later coined the term “cyclical” to describe it and here we use this notation.

### 3.8.2 The *gamboostLSS* algorithm

The main idea of the cyclical multidimensional boosting algorithm is to have a boosting step for each parameter  $k$  in each iteration, and to successively update the predictors in each iteration. We cycle through all parameter dimensions in each boosting iteration. In every dimension  $k$ , we carry out one boosting iteration. This boosting iteration can in principle be the same as in the generic FGD algorithm (2), i.e., to estimate a full base learner which incorporates all covariates. The *gamboostLSS* algorithm (Mayr et al., 2012a), however, uses the component-wise base learner strategy, introduced in section 3.5. This allows for model fitting in high-dimensional contexts. To use the gradient boosting approach for a multidimensional prediction function, we need to have existing partial derivatives of the loss function with respect to each predictor. Again since we are doing a gradient descent step, we as usual use the *negative* derivative. These negative partial derivatives are

$$-\frac{\partial}{\partial \eta_k} \rho(y_i, \boldsymbol{\eta}(x_i)) = \frac{\partial}{\partial \eta_k} \log(\psi(y_i|\boldsymbol{\theta}(x_i))),$$

for all  $k = 1, 2, \dots, K$ . As in previous algorithms, we use these negative derivatives to construct generalized residual vectors. In this multidimensional approach, we now have  $K$  partial derivatives, and so we construct  $K$  different generalized residual vectors  $\mathbf{u}_k$ ,  $k = 1, 2, \dots, K$ . For a specific distribution parameter  $\theta_k$ , we construct a generalized residual vector by computing the negative derivative with respect to each additive predictor  $\eta_k$ , and inserting the current estimate  $\hat{\boldsymbol{\eta}}$ , evaluated at each observation  $(x_i, y_i)_{i=1}^n$ . This yields

$$\begin{aligned} \mathbf{u}_k &= (u_{k,1}, u_{k,2}, \dots, u_{k,N}) \\ &= \left( -\frac{\partial}{\partial \eta_k} \rho(y_i, \hat{\boldsymbol{\eta}}(x_i)) \right)_{i=1}^N. \end{aligned}$$

Like in other gradient boosting algorithms, we need base learners. We specify component-wise base learners for *each* distribution parameter. In principle, these might be different, but one usually chooses the same type for all, only letting the base learners differ in which component and which parameter they affect. In other words, in general we have a set of base learners

$$\mathcal{H}_k = \{h_{k,1}, h_{k,2}, \dots, h_{k,p_1}\}$$

for each  $k = 1, 2, \dots, K$ . As before, we use the base learners to estimate possible updates of the model based on single predictors, and we choose the one that improves the model the most.

The initialization of the algorithm is done analogously to the regular boosting method, by setting each parameter to a constant. These constants should be those that jointly maximize the log-likelihood. We find the optimal constant  $c_k$  for each distribution parameter, and then initialize the estimate of each predictor  $\eta_k$  as

$$\hat{\eta}_k^{[0]} = \beta_{k,0} = c_k,$$

for each  $k = 1, 2, \dots, K$ . In the  $k$ -th step of iteration  $m$ , i.e. after having cycled through until component  $k$ , the estimated vector of additive predictors is denoted  $\hat{\boldsymbol{\eta}}_{k-1}^{[m]}$ , and it is

$$\hat{\boldsymbol{\eta}}_{k-1}^{[m]} = \left( \hat{\eta}_1^{[m]}, \hat{\eta}_2^{[m]}, \dots, \hat{\eta}_{k-1}^{[m]}, \hat{\eta}_k^{[m-1]}, \hat{\eta}_{k+1}^{[m-1]}, \dots, \hat{\eta}_K^{[m-1]} \right).$$

Here the additive predictors of the preceding parameter dimensions,  $1, 2, \dots, k-1$ , have been updated in the current iteration  $m$ . Hence they are denoted with the current iteration, as  $\hat{\eta}_1^{[m]}, \hat{\eta}_2^{[m]}$ , until  $\hat{\eta}_{k-1}^{[m]}$ . The following dimensions  $k+1, \dots, K$  have not been updated in iteration  $m$ , and hence they are denoted with iteration  $m-1$ :

$$\hat{\eta}_{k+1}^{[m-1]}, \hat{\eta}_{k+2}^{[m-1]}, \dots, \text{until } \hat{\eta}_K^{[m-1]}.$$

We are in this step going to update dimension  $k$ , i.e., going from  $\hat{\eta}_k^{[m-1]}$  to  $\hat{\eta}_k^{[m]}$ . We calculate a vector of generalized residuals for dimension  $k$  by calculating the  $k$ -th partial derivative and inserting the current estimated vector of additive predictors  $\hat{\boldsymbol{\eta}}_{k-1}^{[m]}$ , and evaluating it at the observations  $x_1, x_2, \dots, x_N$ . This yields the generalized residual vector

$$\begin{aligned} \mathbf{u}_k^{[m-1]} &= (u_{k,1}^{[m-1]}, u_{k,2}^{[m-1]}, \dots, u_{k,N}^{[m-1]}) \\ &= \left( -\frac{\partial}{\partial \eta_k} \rho(\hat{\eta}_1^{[m]}(\mathbf{x}_i), \hat{\eta}_2^{[m]}(\mathbf{x}_i), \dots, \hat{\eta}_{k-1}^{[m]}(\mathbf{x}_i), \hat{\eta}_{k+1}^{[m-1]}(\mathbf{x}_i), \dots, \hat{\eta}_K^{[m-1]}(\mathbf{x}_i)) \right)_{i=1}^N \\ &= \left( -\frac{\partial}{\partial \eta_k} \rho(y, \hat{\boldsymbol{\eta}}_{k-1}^{[m]}(\mathbf{x}_i)) \right)_{i=1}^N. \end{aligned}$$

Again, like in a regular component-wise boosting algorithm, we fit all component-wise base learners separately to this residual vector  $\mathbf{u}_k^{[m-1]}$ . Of these learners, select the best fitting component  $j_k^{[m]}$  like previously, by selecting the estimated learner which fits best according to RSS,

$$j_k^{[m]} = \underset{j \in \{1, 2, \dots, p_k\}}{\operatorname{argmin}} \sum_{i=1}^N \left( u_{k,i}^{[m-1]} - \hat{h}_{k,j}^{[m]} \right)^2.$$

We update the additive predictor in dimension  $k$  by the usual

$$\hat{f}_k^{[m]} \leftarrow \hat{f}_k^{[m-1]} + \nu \cdot \hat{h}_{j_k^{[m]}}^{[m]}(\cdot).$$

A schematic representation of the updating process using this algorithm in a given iteration  $m$  follows:

$$\begin{aligned} & \frac{\partial}{\partial \eta_1} \rho \left( y, \eta_1^{[m-1]}, \eta_2^{[m-1]}, \eta_3^{[m-1]}, \dots, \eta_{K-1}^{[m-1]}, \eta_K^{[m-1]} \right) \xrightarrow{\text{calculate}} \mathbf{u}_1^{[m-1]} \xrightarrow{\text{fit and update}} \hat{f}_1^{[m]} \\ & \frac{\partial}{\partial \eta_2} \rho \left( y, \hat{\eta}_1^{[m]}, \hat{\eta}_2^{[m-1]}, \hat{\eta}_3^{[m-1]}, \dots, \hat{\eta}_{K-1}^{[m-1]}, \hat{\eta}_K^{[m-1]} \right) \xrightarrow{\text{calculate}} \mathbf{u}_2^{[m-1]} \xrightarrow{\text{fit and update}} \hat{f}_2^{[m]} \\ & \frac{\partial}{\partial \eta_3} \rho \left( y, \hat{\eta}_1^{[m]}, \hat{\eta}_2^{[m]}, \hat{\eta}_3^{[m-1]}, \dots, \hat{\eta}_{K-1}^{[m-1]}, \hat{\eta}_K^{[m-1]} \right) \xrightarrow{\text{calculate}} \mathbf{u}_3^{[m-1]} \xrightarrow{\text{fit and update}} \hat{f}_3^{[m]} \\ & \dots \\ & \frac{\partial}{\partial \eta_{K-1}} \rho \left( y, \hat{\eta}_1^{[m]}, \hat{\eta}_2^{[m]}, \hat{\eta}_3^{[m]}, \dots, \hat{\eta}_{K-1}^{[m-1]}, \hat{\eta}_K^{[m-1]} \right) \xrightarrow{\text{calculate}} \mathbf{u}_{K-1}^{[m-1]} \xrightarrow{\text{fit and update}} \hat{f}_{K-1}^{[m]} \\ & \frac{\partial}{\partial \eta_K} \rho \left( y, \hat{\eta}_1^{[m]}, \hat{\eta}_2^{[m]}, \hat{\eta}_3^{[m]}, \dots, \hat{\eta}_{K-1}^{[m]}, \hat{\eta}_K^{[m-1]} \right) \xrightarrow{\text{calculate}} \mathbf{u}_K^{[m-1]} \xrightarrow{\text{fit and update}} \hat{f}_K^{[m]} \end{aligned}$$

For a schematic overview of this cyclical multidimensional boosting algorithm, see Algorithm 4. Note that this algorithm resembles the backfitting strategy of Hastie and Tibshirani (1986). In both backfitting and this multidimensional boosting strategy, components are updated successively by using estimates of the other components as offset values. In backfitting, a completely new estimate of  $f^*$  is determined in every iteration. In gradient boosting, however, the estimates are only slightly modified in each iteration.

### 3.8.3 Tuning parameters

The main tuning parameters in the cyclical multidimensional gradient boosting algorithm are the stopping iterations  $\mathbf{m}_{\text{stop}} = m_{\text{stop},1}, \dots, m_{\text{stop},K}$ . As in the one-dimensional gradient boosting algorithm, we should not let the algorithm run until convergence, since that will lead to overfitting, and we want to have a low test error. We therefore need to find estimates of the stopping iterations by cross-validation (Schmid et al., 2010). However, to properly tune these parameters, it is necessary to perform a multidimensional search, which is usually done by implementing a so-called grid search. One divides the search space into a multidimensional grid, obtaining tuples of configurations. On each tuple, we should use cross-validation, as usual, and the next subsection explains the procedure.

### 3.8.4 Grid search cross-validation in gradient boosting

To find a vector of length  $K$  of optimal iterations  $\mathbf{m}_{\text{stop}} = m_{\text{stop},1}, \dots, m_{\text{stop},K}$ , we perform a  $K$ -dimensional grid search. We must first specify a minimum and maximum number of iterations for each parameter. Call these  $m_{k,\min}$  and  $m_{k,\max}$ , respectively. We then divide this one-dimensional search space into a finite grid with  $N_k$  points, such that we obtain

$$m_{k,\min} = m_{k,1} < m_{k,2} < \dots < m_{k,N_k-1} < m_{k,N_k} = m_{k,\max},$$

grid-search

algo:multi-  
cyclical

---

**Algorithm 4** Multidimensional cyclical component-wise gradient boosting
 

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1. Start with a data set  $D = \{\mathbf{x}_i, y_i\}_{i=1}^N$  and a chosen loss function  $\rho(y, \boldsymbol{\eta}(\mathbf{x}))$ , for which we wish to minimize the empirical risk, i.e., the loss function evaluated on the samples,

$$\hat{\boldsymbol{\eta}} = \underset{\boldsymbol{\eta}}{\operatorname{argmin}} \overline{\operatorname{err}}(\boldsymbol{\eta}) = \underset{\boldsymbol{\eta}}{\operatorname{argmin}} \sum_{i=1}^n \rho(y_i, \boldsymbol{\eta}(\mathbf{x}_i)).$$

2. Initialize iteration counter  $m$  to 0. Initialize additive predictors to constants  $\boldsymbol{\beta}_0 = (\beta_{1,0}, \beta_{2,0}, \dots, \beta_{K,0})$ , e.g. to those that jointly maximize the training error,

$$\boldsymbol{\beta}_0 = \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \overline{\operatorname{err}}(\boldsymbol{\beta}).$$

initialization

3. Specify a set of base learners  $\mathcal{H}_k$  for each predictor  $\theta_k$ , for  $k = 1, \dots, K$ . Specify a step length  $\nu$ .

cyclic-proper-  
first

4. Increase  $m$  by 1.

5. Set  $k$  to 0.

cyclic-first

6. Increase  $k$  by 1.

7. If  $m > m_{\text{stop},k}$ , go to step 6. Otherwise compute the negative partial derivative  $-\frac{\partial \rho}{\partial \eta_k}$  and evaluate at  $\hat{\boldsymbol{\eta}}_{k-1}^{[m]}(x_i), i = 1, \dots, N$ , yielding the negative gradient vector

$$\mathbf{u}_k^{[m-1]} = \left( -\frac{\partial}{\partial \eta_k} \rho(y_i, \hat{\boldsymbol{\eta}}_{k-1}^{[m]}(x_i)) \right)_{i=1}^N$$

8. Fit the negative gradient vector  $\mathbf{u}_k^{[m-1]}$  to each of the  $p_k$  components of  $\mathbf{X}$  separately, using each component's respective base learner. This yields  $p_k$  vectors of predicted values,

$$\hat{h}_{k,1}^{[m]}, \hat{h}_{k,2}^{[m]}, \dots, \hat{h}_{k,p_k}^{[m]}.$$

9. Select the component of  $\mathbf{x}$  with the best-fitting base learner, according to RSS,

$$j_k^{[m]} = \underset{j \in \{1, 2, \dots, p\}}{\operatorname{argmin}} \sum_{i=1}^N \left( u_{k,i} - \hat{h}_{k,j}^{[m]} \right)^2.$$

10. Update the predictor for parameter  $k$  in component  $j^{[m]}$  by

$$\hat{\eta}_{k,j_k}^{[m]} \leftarrow \hat{\eta}_{k,j_k}^{[m-1]} + \nu \cdot \hat{h}_{j_k}^{[m]},$$

where  $\nu$  is the real-valued step-length factor specified in step 3. For all other components, meaning each  $j \in \{j \neq j_k^{[m]}, j = 1, 2, \dots, p_k\}$ , set the predictor to the one from the previous iteration,

$$\hat{\eta}_{k,j}^{[m]} \leftarrow \hat{\eta}_{k,j}^{[m-1]}.$$

cyclic-last

11. If  $k < K$ , go to step 6. If not, update the full model,  $\hat{\boldsymbol{\eta}}^{[m]} \leftarrow \hat{\boldsymbol{\eta}}^{[m]}$ .
  12. If  $m < \max(m_{\text{stop},1}, \dots, m_{\text{stop},K})$ , go to step 4. If not, return  $\hat{\boldsymbol{\eta}}^{[m]}$ .
-

again for each  $k = 1, 2, \dots, K$ . The total search space is the cartesian product of all of these grids. We illustrate with an example. Let  $K = 3$ , and  $m_{k,\min} = 1$  and  $m_{k,\max} = 10$  for all  $k$ , and finally divide each grid into 10 points, i.e.,  $N_1 = N_2 = N_3 = 10$ . The total search grid will consist of  $N_1 \cdot N_2 \cdot N_3 = 10^3 = 10000$  tuples of configurations of  $\mathbf{m}$ , enumerated below:

$$\begin{aligned}
 & (m_{1,1}, m_{2,1}, m_{3,1}) \\
 & (m_{1,1}, m_{2,1}, m_{3,2}) \\
 & \dots \\
 & (m_{1,1}, m_{2,1}, m_{3,10}) \\
 & (m_{1,1}, m_{2,2}, m_{3,1}) \\
 & \dots \\
 & (m_{1,1}, m_{2,2}, m_{3,10}) \\
 & \dots \\
 & (m_{1,10}, m_{2,10}, m_{3,10}).
 \end{aligned}$$

We want to find the best configuration  $\mathbf{m}$ , i.e., we want to find the minimum of the hyperplane of cross-validated errors  $CV(\mathbf{m})$ . Like in subsection 3.6.1, we must calculate the estimate of the cross-validated prediction error for each given configuration  $\mathbf{m}$ , obtaining the prediction error  $CV(\mathbf{m})$ . We choose  $\mathbf{m}_{\text{stop}}$  to be the minimizer of this error,

$$\mathbf{m}_{\text{stop}} = \underset{\mathbf{m}}{\operatorname{argmin}} CV(\mathbf{m}).$$

Using boosting, we may obtain estimates of  $CV(\mathbf{m})$  for all  $\mathbf{m}$  by fixing all but one of the parameters and perform a typical boosting run. If we fix all but one of the parameters in the vector  $\mathbf{m} = (m_{1,i_1}, m_{2,i_2}, m_{3,i_3})$ , where  $m_{k,\min} \leq i_k \leq m_{k,\max}$  for all  $k = 1, 2, 3$ , say, we fix  $m_{1,i_1}$  and  $m_{2,i_2}$ . This is due to the way boosting algorithms work, since for any given iteration  $M$ , we also automatically obtain all boosted estimates for all iterations less than  $M$ , as long as we have access to the boosted parameters of each iteration. Consider again the example. We now let the first two parameters in the example be fixed for each boosting run. While the search grid consist of  $N_1 \cdot N_2 \cdot N_3$  tuples, considering the first two parameters as fixed, we only need to do  $N_1 \cdot N_2$  boosting runs, and in each run set the maximum number of possible iterations in the boosting algorithm for the third component to be  $m_{\max,3}$ . This means that we consider all configurations of the first two parameters in  $\mathbf{m}$ , i.e.,

$$\begin{aligned}
 & (m_{1,1}, m_{1,2}) \\
 & (m_{1,1}, m_{2,2}) \\
 & \dots \\
 & (m_{1,1}, m_{10,2}) \\
 & (m_{2,1}, m_{1,2}) \\
 & \dots \\
 & (m_{2,1}, m_{10,2}) \\
 & \dots \\
 & (m_{10,2}, m_{10,2}),
 \end{aligned}$$

and do a boosting run for each such. Like in subsection 3.6.1, we choose

$$\mathbf{m}_{\text{stop}} = \underset{\mathbf{m}}{\operatorname{argmin}} \operatorname{CV}(\mathbf{m}),$$

where

$$\operatorname{CV}(\mathbf{m}) = \sum_{k=1}^K \sum_{i \in \kappa(k)} \rho(y_i, \hat{y}_i^{-\kappa(k)}),$$

i.e., the cross-validated test error, as usual, which is an estimate of the test error  $\operatorname{Err}(\mathbf{m})$ . Note here also that we will need to perform repeated cross-validation as in subsection , to reduce the variance of the  $\mathbf{m}_{\text{stop}}$  estimate.

subsec: repeated-cv

### 3.9 Noncyclical component-wise multidimensional boosting algorithm

In the cyclical algorithm seen previously in Algorithm 4, the different  $m_{\text{stop},j}$  parameters are not independent of each other, and hence they have to be jointly optimized. As we saw in the previous subsection (3.8.4), the usually applied *grid search* for such parameters scales exponentially with the number of parameters  $K$ . This can quickly become very demanding computationally. Thomas et al. (2018) develop a new algorithm for fitting GAMLSS models, in which only one scalar tuning parameter  $m_{\text{stop}}$  is needed because only one parameter is chosen in each boosting iteration. Thomas et al. (2018) call their new algorithm “noncyclical.” Compared to the cyclical algorithm in *gamboostLSS* (Mayr et al., 2012a), this noncyclical algorithm obtains faster variable tuning and equal prediction results on simulation studies carried out (Thomas et al., 2018). We will now explain the necessary adjustments that this algorithm makes.

#### 3.9.1 Gradients are not comparable across parameters

In the cyclical algorithm, we always boost all parameters in the same iteration. Therefore we do not need to choose between parameters. However, if we want to choose one parameter in each boosting iteration, we need to be able to find out which of the parameters would lead to the best increase in performance in this iteration. We are already doing this for choosing which component-wise learner to use for each parameter  $\theta_k$ . We choose the base learner with the best residual-sum-of-squares (RSS), with respect to the negative gradient vector  $u_k^{[m-1]}$ . We called this the inner loss. We cannot naïvely extend this criterion to compare between two parameters, say,  $\theta_1$  and  $\theta_2$ , because the parameters have different scales (Thomas et al., 2018), and therefore (in general) the scale of their respective generalized residual vectors will not be comparable. It is simply not the case that the parameter with the least RSS causes the best decrease in loss. We therefore need a different comparison method is needed to compare between parameters. In the noncyclical algorithm, we still choose the component-wise base learner which best fits according to the RSS, for each parameter  $\theta_k$ ,

$$\hat{h}_{k,j}(\cdot).$$

After having done so, we calculate the potential improvement in the loss function, which we denote  $\Delta\rho_k$ ,

$$\Delta\rho_k = R\left(\hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{k,j_k^{[m]}}\right),$$

where  $\hat{\boldsymbol{\eta}}^{[m-1]}$  is the current vector of additive predictors. After calculating the improvement  $\Delta\rho_k$  of each parameter  $k = 1, 2, \dots, K$ , we find out which parameter leads to the best increase. We call this  $k^{[m]}$  and it is

$$k^{[m]} = \underset{k \in \{1, 2, \dots, K\}}{\operatorname{argmin}} \Delta\rho_k.$$

We incorporate only the best-fitting learner corresponding for that parameter into the full boosting model, so the model after iteration  $m$  is

$$\hat{\boldsymbol{\eta}}^{[m]} \leftarrow \hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{k^{[m]}, j_{k^{[m]}}}^{[m]}(\cdot).$$

For all  $k \in \{k: k \neq k^{[m]}, k = 1, 2, \dots, K\}$  we do not update their parameter  $\theta_k$ ,

$$\hat{\eta}_k^{[m]} \leftarrow \hat{\eta}_k^{[m-1]}.$$

### 3.9.2 Criterion for selecting component-wise learner

In the previous subsection, we used RSS, or what we called the inner loss. It makes sense to use this because we choose the component with the best explanation of the error terms. It is, however, not the same criterion that is used to choose between parameters, which might be problematic. Thomas et al. (2018) therefore propose using the loss function  $\rho$  directly to choose between component-wise learners as well. They call this the “outer loss.” In this case, when choosing a component-wise learner for parameter  $k$ , we choose the learner that minimizes the outer loss function, i.e.,

$$j^{[m]} = \underset{j}{\operatorname{argmin}} \overline{\operatorname{err}}\left(\hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{k,j}^{[m]}\right)$$

The individual component-wise learners are still estimated by their usual method, i.e., calculating the negative gradient of the generalized residuals and using the base learner to estimate the models. A schematic overview of the algorithm is given in algorithm 5.

### 3.9.3 Advantages with noncyclical

For the noncyclical algorithm, the fact that the optimal number of boosting steps,  $m_{\text{stop}}$ , is always a scalar value, is a major advantage. Finding this tuning parameter can be done fairly quickly with standard cross validation schemes, and most importantly, it scales with the number of parameters. We therefore choose to use the noncyclical version to construct a gradient boosting algorithm for the FHT model discussed in chapter 2.



algo:multi-  
noncyclical

**Algorithm 5** Multidimensional noncyclical component-wise gradient boosting

1. Start with a data set  $D = \{\mathbf{x}_i, y_i\}_{i=1}^N$  and a chosen loss function  $\rho(y, \boldsymbol{\eta}(\mathbf{x}))$ , for which we wish to minimize the empirical risk, i.e., the loss function evaluated on the samples,

$$\hat{\boldsymbol{\eta}} = \underset{\boldsymbol{\eta}}{\operatorname{argmin}} \overline{\operatorname{err}}(\boldsymbol{\eta}) = \underset{\boldsymbol{\eta}}{\operatorname{argmin}} \sum_{i=1}^n \rho(y_i, \boldsymbol{\eta}(\mathbf{x}_i)).$$

2. Initialize iteration counter  $m$  to 0. Initialize additive predictors to constants  $\boldsymbol{\beta}_0 = (\beta_{1,0}, \beta_{2,0}, \dots, \beta_{k,0})$ , e.g. to those that jointly maximize the training error,

$$\boldsymbol{\beta}_0 = \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \overline{\operatorname{err}}(\boldsymbol{\beta}).$$

3. Specify a set of base learners  $\mathcal{H}_k$  for each dimension  $k = 1, \dots, K$ . Specify a step length  $\nu$ .

noncyclic-step-  
first-loop

4. Increase  $m$  by 1 and set  $k$  to 0.

5. Increase  $k$  by 1.

6. Compute the negative partial derivative  $-\frac{\partial \rho}{\partial \eta_k}$  and evaluate at  $\hat{\boldsymbol{\eta}}^{[m-1]}(\mathbf{x}_i), i = 1, \dots, N$ , yielding negative gradient vector

$$\mathbf{u}_k^{[m-1]} = \left( -\frac{\partial}{\partial \eta_k} \rho(y_i, \hat{\boldsymbol{\eta}}^{[m-1]}(\mathbf{x}_i)) \right)_{i=1}^N$$

7. Fit the negative gradient vector  $\mathbf{u}_k^{[m-1]}$  to each of the  $p_k$  components of  $\mathbf{X}$  separately, using each component's respective base learner. This yields  $p_k$  vectors of predicted values,  $\left\{ \hat{h}_{k,j}^{[m]} \right\}_{j=1}^{p_k}$ .

8. Select the best fitting base learner for  $k$ ,  $\hat{h}_{k,j^{[m]}}^{[m]}$ , either by

- the inner loss, i.e., the RSS of the base-learner fit w.r.t the negative gradient vector

$$j^{[m]} = \underset{j \in 1, \dots, p_k}{\operatorname{argmin}} \sum_{i=1}^N \left( u_{k,i} - \hat{h}_{k,j}(\mathbf{x}_i) \right)^2$$

- the outer loss, i.e., the loss function after the potential update,

$$j^{[m]} = \underset{j \in 1, \dots, p_k}{\operatorname{argmin}} \overline{\operatorname{err}} \left( \hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{k,j} \right)$$

9. Compute the possible improvement of this update regarding the outer loss,

$$\Delta \rho_k = \overline{\operatorname{err}} \left( \hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{k,j^{[m]}} \right)$$

10. Select the  $k$  with boosted predictor that improves training error most,

$$k^{[m]} = \underset{k \in 1, \dots, K}{\operatorname{argmin}} \Delta \rho_k.$$

Update the additive predictor for this parameter,

$$\hat{\boldsymbol{\eta}}_{k^{[m]}}^{[m]}(\cdot) \leftarrow \hat{\boldsymbol{\eta}}_{k^{[m]}}^{[m-1]} + \nu \cdot \hat{h}_{k^{[m]},j^{[m]}}(\cdot),$$

11. If  $m < m_{\text{stop}}$ , go to step 4. If not, return  $\hat{\boldsymbol{\eta}}^{[m_{\text{stop}}]}(\cdot)$ .



## Chapter 4

# FHTBoost: A multidimensional component-wise gradient boosting algorithm for survival data

ch:FHTboost

In this chapter, we propose a component-wise boosting algorithm for fitting the inverse Gaussian first hitting time (FHT) model to survival data. The algorithm is designed to be especially fit for use with both clinical and genomic data. We work with survival data sets with  $N$  observations,

$$D = (\mathbf{x}_i, \mathbf{z}_i, t_i, d_i)_{i=1}^N.$$

Here  $t_i$  is a possibly right-censored event time,  $d_i$  is an indicator variable which is 1 if  $t_i$  is an actually observed event time, and 0 if it is right-censored. For simplicity later, we denote the response data

$$y_i = (t_i, d_i).$$

Further, we have covariate vectors  $\mathbf{x}_i$  and  $\mathbf{z}_i$ , which will be related to the inverse Gaussian parameters  $y_0$  and  $\mu$ , respectively.  $\mathbf{x}_i$  is defined as

$$\mathbf{x}_i = (x_{i,1}, x_{i,2}, \dots, x_{i,p_1}). \quad (4.1)$$

$\mathbf{z}_i$  is defined as

$$\mathbf{z}_i = (z_{i,1}, z_{i,2}, \dots, z_{i,p_2}). \quad (4.2)$$

Typically the number of dimensions  $p_1$  of  $\mathbf{x}_i$  is high (in particular,  $p_1$  is much larger than  $n$ ,  $p_1 \gg n$ ), and the number of dimensions  $p_2$  of  $\mathbf{z}_i$  is relatively small, and in particular,  $p_2 < N$ . However, the dimensions  $p_1$  and  $p_2$  can be any size. There are theoretical arguments for this particular combination of the high and low-dimensional vectors and parameters, which we have discussed earlier in subsection 2.5.3.

### 4.1 Setting

#### 4.1.1 Additive predictors etc

The first-hitting-time model with Wiener processes, as shown, leads to inverse Gaussian lifetimes. The probability distribution function (pdf) for this distri-

*SURVIVAL DATA*  
bution is given in (2.18), and its cumulative distribution function is given in (2.19). The log likelihood is given in (2.24). We repeat it here. It depends on  $y_0$  and  $\mu$ , and  $\sigma$  is in practice set to 1 to avoid overparameterization (see subsection 2.4.2).

$$l(y_0, \mu | y_i) = \sum_{i=1}^n d_i \left( \ln y_0 - \frac{1}{2} \ln(2\pi t_i^3) - \frac{(\mu t_i + y_0)^2}{2t_i} \right) + (1 - d_i) \ln \left( \Phi \left( \frac{\mu t_i + y_0}{\sqrt{t_i}} \right) - \exp(-2y_0\mu) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{t_i}} \right) \right).$$

We wish to use a similar setup as the GAMLSS. We will therefore model the parameters through additive predictors  $\boldsymbol{\eta}$ , consisting of components  $\eta_1$  and  $\eta_2$ , which we relate by link functions. We denote the  $K = 2$  distribution parameters as

$$\boldsymbol{\theta} = (\theta_1, \theta_2)^T = (y_0, \mu)^T. \quad (4.3)$$

We relate the parameters to the additive predictors to use the usual link functions

$$g_1(y_0) = \ln(y_0) \quad (4.4)$$

and

$$g_2(\mu) = \mu, \quad (4.5)$$

and we further relate the additive predictors to covariates. The additive predictors for an individual  $i$  are defined as

$$\eta_{1,i} := \ln(y_{0,i}) = \boldsymbol{\beta}^T \mathbf{x}_i = \beta_0 + \sum_{j=1}^{p_1} x_{j,i} \beta_j \quad (4.6)$$

and

$$\eta_{2,i} := \mu_i = \boldsymbol{\gamma}^T \mathbf{z}_i = \gamma_0 + \sum_{j=1}^{p_2} z_{j,i} \gamma_j, \quad (4.7)$$

and we denote both as  $\boldsymbol{\eta}_i = (\eta_{1,i}, \eta_{2,i})$ .

We are going to build up these additive predictors by means of gradient boosting. Each

### 4.1.2 Loss function

Since we have a probability distribution, we should use the negative of the corresponding log likelihood as our loss function. For an observation numbered  $i$  and with parameter vector

$$\boldsymbol{\theta}(\mathbf{x}_i, \mathbf{z}_i) = (y_0(\mathbf{x}_i), \mu(\mathbf{z}_i)),$$

the loss function is

$$\rho(y_i, \hat{\boldsymbol{\theta}}(\mathbf{x}_i, \mathbf{z}_i)) = -l(\hat{y}_{0,i}, \hat{\mu}_i | y_i).$$

Given an estimated additive predictor  $\hat{\boldsymbol{\eta}}$ , we calculate the corresponding estimated distribution parameters by transforming the additive predictors via the inverse of their link functions. Thus,

$$y_0 = \theta_1 = g_1^{-1}(\eta_1) = \exp(\eta_1), \quad (4.8)$$

and

$$\mu = \theta_2 = g_2^{-2}(\eta_2) = \eta_2. \quad (4.9)$$

This means that as a function of the additive predictors, the loss function is

$$\rho(y, \boldsymbol{\eta}) = -l(\exp(\eta_1), \eta_2).$$

To use the gradient boosting algorithm, we need to compute the negative gradient of the loss function, i.e., the negative of the derivative. The negative partial derivative of the loss function is equal to the (positive) derivative of the (positive) log-likelihood function, with regard to each parameter. These are

$$-\frac{\partial}{\partial \eta_1} \rho(y_i, \boldsymbol{\theta}) = \frac{\partial}{\partial \eta_1} l(\exp(\eta_1), \eta_2) = f_1 \quad (4.10)$$

and

$$-\frac{\partial}{\partial \eta_2} \rho(y_i, \boldsymbol{\theta}) = \frac{\partial}{\partial \eta_2} l(\exp(\eta_1), \eta_2) = f_2. \quad (4.11)$$

See Appendix for the full details.

We can now apply the component-wise multidimensional boosting algorithm shown in the previous chapter. We choose to use the noncyclical variant as this leads to equally good results and is less computationally intensive to tune, due to a one-dimensional stopping parameter search, as stated in Schmid et al. (2010).

More details here!

## 4.2 Initialization via maximum likelihood estimate

To ensure proper estimation of  $\eta_1$  and  $\eta_2$ , we need to compute the intercepts  $\beta_0$  and  $\gamma_0$ , which capture the general, average effect of the covariates. If analytical relationships or formulas exist, such as taking the average of a Gaussian distributed variable in an ordinary regression setting, their computation would be straightforward. In lieu of such known formulas, a reasonable method to use is to perform numerical maximization of the log-likelihood, treating the log likelihood as a function of

$$\boldsymbol{\beta}_0 = (\beta_0, \gamma_0)$$

only. Hence the offsets are estimated to be

$$\hat{\boldsymbol{\beta}} = \underset{\boldsymbol{\beta}}{\operatorname{argmin}} \overline{\operatorname{err}}(\boldsymbol{\beta}).$$

To do this in practice, we use the routine called `nlm`, which belongs to the base package of R.

Find citation for R programming language!

## 4.3 The FHTBoost algorithm

algo: fhtboost

1. Given a survival data set  $D = (\mathbf{x}_i, \mathbf{z}_i, t_i, d_i)_{i=1}^N$ , where for each observation  $i$ ,  $\mathbf{x}_i$  is a vector of clinical measurements,  $\mathbf{z}_i$  a vector of gene expressions,  $t_i$  is the possibly right-censored survival time, and  $d_i$  is the censoring indicator. (If  $\mathbf{X}$  and/or  $\mathbf{Z}$  are not normalized, do this.) We wish to estimate the  $\hat{\boldsymbol{\eta}}$  that minimizes the training error in  $m_{\text{stop}}$  number of iterations,

$$\hat{\boldsymbol{\eta}} = \underset{\boldsymbol{\eta}}{\operatorname{argmin}} \overline{\operatorname{err}}(\boldsymbol{\eta})$$

2. Set iteration counter  $m$  to 0. Initialize additive predictors  $\hat{\boldsymbol{\eta}} = (\hat{\eta}_1, \hat{\eta}_2)$  to  $\hat{\beta}_0 = (\hat{\beta}_0, \hat{\gamma}_0)$ , by finding maximum likelihood constants through numerical maximization,

$$\hat{\beta} = \underset{\beta}{\operatorname{argmin}} \overline{\operatorname{err}}(\beta).$$

algostep:FHT-  
base-learner

3. Specify linear least squares base learners:

$$\begin{aligned}\mathcal{H}_1 &= \{h_{1,j}\}_{j=1}^{p_1} = \{x_j \beta_j\}_{j=1}^{p_1}, \\ \mathcal{H}_2 &= \{h_{2,j}\}_{j=1}^{p_1} = \{z_j \gamma_j\}_{j=1}^{p_2}\end{aligned}$$

algostep:FHT-  
init

4. Increase  $m$  by 1.

5. Compute the negative partial derivative  $-\frac{\partial \rho}{\partial \hat{\eta}_1}$  and evaluate at  $\hat{\boldsymbol{\eta}}^{[m-1]}(\mathbf{x}_i, \mathbf{z}_i)$ ,  $i = 1, \dots, N$ , yielding negative gradient vector

$$\mathbf{u}_1^{[m-1]} = \left( -\frac{\partial}{\partial \hat{\eta}_1} \rho(y_i, \hat{\boldsymbol{\eta}}^{[m-1]}(\mathbf{x}_i, \mathbf{z}_i)) \right)_{i=1}^N \quad (4.12)$$

6. Fit the negative gradient vector to each of the  $p_1$  components of  $\mathbf{X}$  (i.e. to each base learner) separately, using the base learners specified in step 3, so i.e., fitting

$$\hat{\beta}_j^{[m]} = (\mathbf{x}_j^T \mathbf{x}_j)^{-1} \mathbf{x}_j^T \mathbf{u}_1^{[m-1]}$$

7. Select the best fitting base learner,  $\hat{h}_{1,j_1^{[m]}}$ , by the inner loss, i.e., the RSS of the base-learner fit w.r.t the negative gradient vector

$$j_1^{[m]} = \underset{j \in 1, \dots, p_1}{\operatorname{argmin}} \sum_{i=1}^N \left( u_{1,i}^{[m-1]} - \hat{h}_{1,j}^{[m]}(u_{1,i}^{[m-1]}) \right)^2. \quad (4.13)$$

8. Compute the possible improvement of this update regarding the outer loss,

$$\Delta \rho_1 = \overline{\operatorname{err}} \left( \hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{1,j_1^{[m]}}^{[m]} \right) \quad (4.14)$$

9. Compute the negative partial derivative  $-\frac{\partial \rho}{\partial \hat{\eta}_2}$  and evaluate at  $\hat{\boldsymbol{\eta}}^{[m-1]}(\mathbf{x}_i, \mathbf{z}_i)$ ,  $i = 1, \dots, N$ , yielding negative gradient vector

$$\mathbf{u}_1^{[m-1]} = \left( -\frac{\partial}{\partial \hat{\eta}_1} \rho(y_i, \hat{\boldsymbol{\eta}}^{[m-1]}(\mathbf{x}_i, \mathbf{z}_i)) \right)_{i=1}^N \quad (4.15)$$

10. Fit the negative gradient vector to each of the  $p_2$  components of  $\mathbf{Z}$  (i.e. to each base learner) separately, using the base learners specified in step 3, so i.e., fitting

$$\hat{\gamma}_j^{[m]} = (\mathbf{z}_j^T \mathbf{z}_j)^{-1} \mathbf{z}_j^T \mathbf{u}_2^{[m-1]}$$

11. Select the best fitting base learner,  $\hat{h}_{2,j_2}^{[m]}$ , by the inner loss, i.e., the RSS of the base-learner fit w.r.t the negative gradient vector

$$j_2^{[m]} = \operatorname{argmin}_{j \in 1, \dots, p_2} \sum_{i=1}^N \left( u_{2,i}^{[m-1]} - \hat{h}_{2,j}(u_{2,i}^{[m-1]}) \right)^2.$$

12. Compute the possible improvement of this update regarding the outer loss,

$$\Delta \rho_2 = \overline{\text{err}} \left( \hat{\boldsymbol{\eta}}^{[m-1]} + \nu \cdot \hat{h}_{2,j_2}^{[m]} \right)$$

algostep:FHT-end

13. Find which parameter should be included in the model,

$$k^{[m]} = \operatorname{argmin}_{k \in \{1, 2\}} \Delta \rho_k.$$

Include this component in the final model, by updating its additive predictor,

$$\hat{\eta}_{k^{[m]}}^{[m]} = \hat{\eta}_{k^{[m]}}^{[m-1]} + \nu \cdot \hat{h}_{k^{[m]}, j^{[m]}}^{[m]}(x),$$

while for the other component  $k \neq k^{[m]}$ , set the additive predictor for this iteration to be the same as previous iteration

$$\hat{\eta}_k^{[m]} = \hat{\eta}_k^{[m-1]}.$$

14. If  $m < m_{\text{stop}}$ , go to step 4. If not, return

$$\hat{\boldsymbol{\eta}}(\cdot) = \hat{\boldsymbol{\eta}}_{m_{\text{stop}}}(\cdot) = \beta_0 + \sum_{m=1}^{m_{\text{stop}}} \boldsymbol{\eta}^{[m]}(\cdot).$$

## 4.4 Small example

subsec:algo-  
example

Let us now consider a small example where we draw survival times from an inverse Gaussian FHT distribution, and confirm that FHTBoost recovers the maximum likelihood parameters. Let parameter vectors be

$$\boldsymbol{\beta} = (2, 0.1, 0.2)$$

and

$$\boldsymbol{\gamma} = (-1, -0.1, 0.1)$$

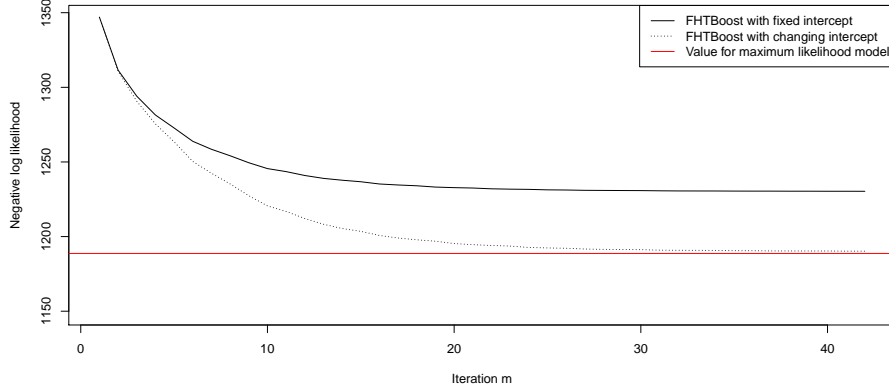
We let the design matrices be  $\mathbf{X} = (\mathbf{x}_1, \mathbf{x}_2)$  and  $\mathbf{Z} = (\mathbf{z}_1, \mathbf{z}_2)$ , where all covariate vectors are drawn from  $N(0, 1)$ . We simulate data using Algorithm 6 in section 6.2, with censoring times  $w_i$  being drawn from a distribution  $\exp(0.1)$ . We thus end up with a survival data set

$$D = (\mathbf{x}_i, \mathbf{z}_i, t_i, d_i)_{i=1}^N.$$



Figure 4.1: Negative log-likelihood for the boosting algorithm with both fixed and iteratively changing intercept, as a function of iteration number  $m$

fig:boosting-ML



We estimate  $\hat{\beta}$  and  $\hat{\gamma}$  using FHTBoost. Figure 4.1 shows a plot of the negative log likelihood of the data (in-sample loss) as a function of the iteration number  $m$ . The solid black line shows negative log-likelihood for FHTBoost with a fixed intercept, i.e., the algorithm in the previous subsection. With a fixed intercept, we only estimate the intercepts  $\hat{\beta}_0$ ,  $\hat{\gamma}_0$  before we begin iterating, and so these intercepts are not changed in any of the boosting iterations. The red line shows the negative of the maximum likelihood, obtained through numerical maximization of the joint maximum likelihood. We can see in the figure 4.1 that it quite clearly does not reach the maximum likelihood value, which is the solid red horizontal line. The maximum likelihood intercepts are  $\hat{\beta}_{1,0}^{\text{ML}} = 1.98$  and  $\hat{\beta}_{2,0}^{\text{ML}} = -1.02$ , while running the boosting algorithm for  $m_{\text{stop}} = 42$  iterations produces estimates of the intercepts as  $\hat{\beta}_0^{[m_{\text{stop}}]} = 1.68$  and  $\hat{\gamma}_0^{[m_{\text{stop}}]} = -0.71$ , respectively.

We therefore see that to achieve the maximum likelihood, we have to modify the algorithm to incorporate updates in the intercepts while boosting. To change the intercept in each boosting iteration, we can perform a new numerical maximization after each boosting step. This means to perform the same kind of numerical maximization as is done initially, at the beginning of each iteration, using now the estimated additive predictors as offsets. We denote the initially estimated intercept  $\hat{\beta}_{1,0}$  as  $\hat{\beta}_{1,0}^{[0]}$ . The intercepts in the additive predictors now become sums of boosted intercepts,

$$\hat{\beta}_0 = \hat{\beta}_0^{[0]} + \sum_{m=1}^{m_{\text{stop}}} \hat{\beta}_0^{[m]}, \quad (4.16)$$

and

$$\hat{\gamma}_0 = \hat{\gamma}_0^{[0]} + \sum_{m=1}^{m_{\text{stop}}} \hat{\gamma}_0^{[m]}. \quad (4.17)$$

Here each  $\hat{\beta}_0^{[m]}$  and  $\hat{\gamma}_0^{[m]}$  are calculated in the intercept estimated in step  $m$  of the boosting algorithm.

Table 4.1: Parameter values of a model which reaches ML

table:ML

	$\beta_0$	$\beta_1$	$\beta_2$	$\gamma_0$	$\gamma_1$	$\gamma_2$
Maximum likelihood estimate	1.98	0.10	0.21	-1.03	-0.09	0.12
FHTBoost with fixed intercept	1.68	0.10	0.18	-0.72	-0.06	0.09
FHTBoost with changing intercept	1.97	0.10	0.18	-1.02	-0.09	0.12

When introducing *changing* intercepts, the algorithm was successful in recovering the maximum likelihood value and parameters. See table 4.1 for the estimated parameter values, and graphically, in figure 4.1, where the convergence is plotted as a function of the number of boosting iterations.

In mboost, they seem to change the offset while boosting. This must surely be a problem others have encountered while deriving boosting algorithms.

## 4.5 FHTBoost algorithm with changing intercept

subsec:FHT-intercept

algo:fhtboost-with-intercept

We modify algorithm 4.3, where step 13 is replaced by this step, where we incorporate changing intercepts for the additive predictors in each boosting iteration.

13. Find which parameter should be included in the model,

$$k^{[m]} = \underset{k \in \{1,2\}}{\operatorname{argmin}} \Delta \rho_k.$$

Include this component in the final model, by updating its additive predictor,

$$\hat{\eta}_{k^{[m]}}^{[m]} = \hat{\eta}_{k^{[m]}}^{[m-1]} + \nu \cdot \hat{h}_{k^{[m]}, j^{[m]}}^{[m]}(x),$$

while for the other component  $k \neq k^{[m]}$ , set the additive predictor for this iteration to be the same as previous iteration

$$\hat{\eta}_k^{[m]} = \hat{\eta}_k^{[m-1]}.$$

Find the best numerical constant to add to the intercept of the selected additive learner,

$$c = \underset{c}{\operatorname{argmin}} \overline{\operatorname{err}} \left( \hat{\eta}^{[m]} + c \right) \quad (4.18)$$

Add this  $c$  to the selected parameter

$$\hat{\beta}_{k^{[m]},0} \leftarrow \hat{\beta}_{k^{[m]},0} + c. \quad (4.19)$$

## 4.6 Conclusion thoughts choices

Write a conclusion from the example: The algorithm with updating intercept seems better, as it should not be shrunk towards 0 (Hastie et al., 2009).



## Chapter 5

# Evaluation measures

In this chapter, we will explain different evaluation measures which we will use to assess different aspects of models, later in the thesis.

### 5.1 Assessing model fit with difference in deviance between an estimated model and a null model

sec:deviance

To comparing the performance of two models of the same kind, e.g., two different estimated FHT models, we can calculate their difference in deviance.

#### 5.1.1 Deviance

In general, the deviance of an FHT model with covariate vectors  $\beta$  and  $\gamma$ , which we concatenate as

$$\theta = (\beta, \gamma),$$

is

$$\text{dev}(\theta) = 2 \cdot l(\theta),$$

where  $l(\theta)$  is the log-likelihood value attained by an FHT model with covariate vector  $\theta$ . As we know, the better the model fit of  $\theta$ , the higher the value of  $l(\theta)$ . Deviance is used in the generalized linear models (GLM) framework, where there exist general results related to the deviance. These results, which we will not go into here, are the reason why there is a factor of 2 in the deviance. This factor does not matter for us, but we will use it to adhere to convention.

#### 5.1.2 Difference in deviance

Consider two FHT models  $\hat{\theta}_1$  and  $\hat{\theta}_2$ , where  $\hat{\theta}_1$  is a less complex model, i.e., it has fewer, or possibly smaller, covariates than  $\hat{\theta}_2$ . The difference in deviance between  $\hat{\theta}_1$  and  $\hat{\theta}_2$ , which we denote  $d$ , is simply the deviance of the more complex model,  $\hat{\theta}_2$ , subtracted from the deviance of the less complex model,  $\hat{\theta}_1$ ,

$$d = \text{dev}(\hat{\theta}_1) - \text{dev}(\hat{\theta}_2) = 2 \cdot l(\hat{\theta}_1) - 2 \cdot l(\hat{\theta}_2) = 2 \left( l(\hat{\theta}_1) - l(\hat{\theta}_2) \right).$$

Since a more complex model should achieve a higher log-likelihood, we expect the difference of deviance to be negative if the model is a good fit to the data. For our purposes, the difference of deviance is a measure of how much the estimated model improves on a model with no covariates, a so-called null model.

### 5.1.3 Null model

A model which incorporates no covariate information is called a *null model*, and it will behave the same, no matter the covariate information it is given. A null model thus acts as a baseline to which we can compare our estimated model. If an estimated model does not explain the variation of the data better than the null model, and consequently the chosen model is not a good model fit.

In our case, when using FHTBoost, the null model is an FHT model which only contains the intercepts in the covariate vectors. In our procedure, before we start the boosting iterations, we find the maximum likelihood intercepts of the covariate vectors,  $\beta_0$  and  $\gamma_0$ . These are found by numerically maximizing the likelihood of the training set. This is the model we would get if we performed FHTBoost with 0 iterations. The covariate vectors of the null model, i.e., the covariate vectors before starting boosting, are thus vectors containing only the intercepts, and all other elements being 0:

$$\hat{\beta}_{\text{train}}^{[0]} = (\overbrace{\hat{\beta}_0^{[0]}, 0, 0, \dots, 0}^{\text{length } p_1})$$

and

$$\hat{\gamma}_{\text{train}}^{[0]} = (\overbrace{\hat{\gamma}_0^{[0]}, 0, 0, \dots, 0}^{\text{length } p_2}).$$

For simplicity of notation, we again denote the concatenated vector of these as

$$\hat{\theta}_{\text{train}}^{[0]} = (\hat{\beta}_{\text{train}}^{[0]}, \hat{\gamma}_{\text{train}}^{[0]}).$$

Similarly, an estimated model, which is estimated by using FHTBoost on the training set with  $m_{\text{stop}}$  steps, has covariate vectors

$$\hat{\beta}_{\text{train}}^{[m_{\text{stop}}]} = (\hat{\beta}_0^{[m_{\text{stop}}]}, \hat{\beta}_1^{[m_{\text{stop}}]}, \hat{\beta}_2^{[m_{\text{stop}}]}, \dots, \hat{\beta}_{p_1}^{[m_{\text{stop}}]})$$

and

$$\hat{\gamma}_{\text{train}}^{[m_{\text{stop}}]} = (\hat{\gamma}_0^{[m_{\text{stop}}]}, \hat{\gamma}_1^{[m_{\text{stop}}]}, \hat{\gamma}_2^{[m_{\text{stop}}]}, \dots, \hat{\gamma}_{p_2}^{[m_{\text{stop}}]}).$$

Again let their concatenation be denoted

$$\hat{\theta}_{\text{train}}^{[m_{\text{stop}}]} = (\hat{\beta}_{\text{train}}^{[m_{\text{stop}}]}, \hat{\gamma}_{\text{train}}^{[m_{\text{stop}}]}).$$

To avoid overfitting, we calculate the log-likelihood values on data from a separate test set, for reasons we have discussed previously. A model estimated on the training set,  $\hat{\theta}_{\text{train}}$ , has a likelihood on the test set of

$$l^{\text{test}}(\hat{\theta}_{\text{train}}) = \sum_{i=1}^{N_{\text{test}}} \rho(y_i, \hat{\theta}). \quad (5.1)$$

Hence the difference in deviance between a fitted model and the null model containing no covariates is

$$d = 2 \left( l^{\text{test}}(\hat{\theta}_{\text{train}}^{[0]}) - l^{\text{test}}(\hat{\theta}_{\text{train}}^{[m_{\text{stop}}]}) \right).$$

The performance of the estimated model  $\hat{\theta}_{\text{train}}^{[m_{\text{stop}}]}$  is good when  $d$  is small, meaning “very negative.” We may still end up with a *positive* difference of deviance. This means that the null model achieved a higher log-likelihood value than the fully estimated model, which is opposite of what we would expect. This is the typical effect of overfitting, where the model “follows” too much random variability in the training set, and hence performs badly on the test set.

sec:variable-  
selection

## 5.2 Variable selection measures

As shown in section 5.2, a component-wise gradient boosting algorithm, like FHTBoost, performs data-driven variable selection. The two major objectives of a component-wise gradient boosting algorithm is to perform selection of variables, and shrinkage of variables. We may wish to measure the first of these two, namely the effectiveness of the variable selection. We will, however, not in this section be able to discuss the shrinkage as well. One way to measure the variable selection is to treat it as a classification problem. In this view, correctly selecting a true variable (adding this variable to the boosting model) is an instance of correct classification. In this section we discuss such classification measures.

### 5.2.1 Terminology

We denote a variable selected by the algorithm as “positive,” or  $P$  for short, and a variable that is not selected as “negative,” or  $N$  for short. Since we know which variables actually affect the response, we know how many of the variables selected are selected correctly, in the sense that they are selected and they have an effect. We call these “true positives,” or  $TP$  for short. Similarly, we know which variables do not affect the response, and hence we can calculate the number of non-informative variables which were not selected, i.e., true negative, or  $TN$  for short. Furthermore, we say that selected variables which in truth do not have an effect, are false positives ( $FP$ ). Similarly, false negatives ( $FN$ ) are variables which do have an effect, but which were not selected in the boosting model. We now give explain three such metrics that we will use to determine how well a model performs variable selection.

### 5.2.2 Classification measures

**Sensitivity** measures the proportion of the selected variables which are informative. The ideal sensitivity is 1, whereas the worst possible sensitivity is 0.

$$\text{Sensitivity} = \frac{TP}{P} \tag{5.2} \quad \boxed{\text{\{eq:sensitivity\}}}$$

**Specificity** measures the proportion of variables *not* selected which were not informative. The ideal specificity is 1, and the worst is 0.

$$\text{Specificity} = \frac{TN}{N} \tag{5.3} \quad \boxed{\text{\{eq:specificity\}}}$$

**False discovery rate** measures the proportion of selected variables which are in truth not informative. The ideal false discovery rate is 0, and the worst is 1.

Furthermore, we might note that if the rate is above 0.5, then there are more false positives than true positives in the variable selection.

$$\text{FDR} = \frac{FP}{FP + TP} \quad (5.4)$$

{eq:accuracy}

### 5.3 Evaluating survival prediction with the Brier score

sec:brier

The Brier score (Brier, 1950) was first introduced as a way to measure the accuracy of weather forecasts, and later translated into survival analysis (Graf et al., 1999). Let us first consider, for ease of presentation, a survival data case where there is

#### 5.3.1 Brier score on uncensored survival data

Consider a test set of  $N_{\text{test}}$  individuals. For all observations  $i = 1, \dots, N_{\text{test}}$ , the test set contains an observed survival time  $t_i$ , and a covariate vector  $\mathbf{x}_i$ . The estimated survival probability of individual  $i$  at time  $t^*$  is

$$\hat{S}(t^*|\mathbf{x}_i), \quad (5.5)$$

{eq:phat}

where the prediction function  $\hat{S}(t^*|\mathbf{x}_i)$  is obtained from an FHT model. The Brier score aims to evaluate how well  $\hat{S}(t^*|\mathbf{x}_i)$  (5.5) is able to predict the event status of individual  $i$  at a given time  $t^*$ , namely

$$I(t_i > t^*). \quad (5.6)$$

The error made in predicting the event status for a patient in the test set can be given as

$$\begin{aligned} BS(t^*) &= \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \left( I(t_i > t^*) - \hat{S}(t^*|\mathbf{x}_i) \right)^2 \\ &= \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \left[ \hat{S}(t^*|\mathbf{x}_i)^2 I(t_i \leq t^*) + (1 - \hat{S}(t^*|\mathbf{x}_i))(I(t_i > t^*)) \right]. \end{aligned}$$

In the first formulation, the Brier score is similar to a residual-sum-of-squares (RSS) measure, since we sum the squared error between the observed event and the estimated probability. In the second formulation, we see that the  $BS(t^*)$  measure is the average of the Brier score of events that have occurred before time  $t^*$ , and events that have not yet occurred. In the case of censored data, however, the above is not enough.

#### 5.3.2 Brier score on censored survival data

The Brier score was consequently adapted to handle censored survival times by Graf et al. (1999). A crucial assumption is that the censored survival times have the independent censoring property (see subsection 2.1.1). They showed that the loss of information due to censoring can be accounted for by using an



inverse probability of censoring weighting (Graf et al., 1999). This version of the Brier score for censored data is defined as

$$BS^c(t^*) = \frac{1}{N} \sum_{i=1}^N \left[ \frac{\hat{S}(t^*|\mathbf{x}_i)^2 I(t_i \leq t^*, \delta_i = 1)}{\hat{G}(t_i)} + \frac{(1 - \hat{S}(t^*|\mathbf{x}_i))^2 (I(t_i > t^*))}{\hat{G}(t^*)} \right]. \quad (5.7)$$

{eq:brier}

Here  $\hat{G}(\cdot)$ , defined as

$$\hat{G}(t) = \prod_{i \in \bar{R}(t)} \left( 1 - \frac{1 - \delta_i}{\sum_{i=1}^N Y_i(t)} \right),$$

is the Kaplan-Meier estimate of the *censoring distribution* (Bøvelstad and Borgan, 2011), and where further  $Y_i(t)$  is an indicator of whether individual  $i$  is at risk at time  $t$ , and where  $\bar{R}(t)$  is the set of individuals *not* at risk at time  $t$ , i.e.,

$$\bar{R}(t) = \{i: t_i < t, i = 1, 2, \dots, N\}.$$

If we look closely at (5.7), we see that the  $BS^c(t^*)$  measure is a weighted average of the Brier score of events having happened at or before time  $t^*$ , and the events that have not yet occurred.

### 5.3.3 Integrated Brier score

subsec:  
integrated-brier

The Brier score  $BS^c(\cdot)$  (5.7) only considers a given timepoint. We might also be interested in a time interval, say, from time  $t_{\text{start}}$  to time  $t_{\text{end}}$ . The integrated Brier score is simply the Brier score integrated over this time interval,

$$\text{IBS}(t_{\text{start}}, t_{\text{end}}) = \frac{1}{t_{\text{end}} - t_{\text{start}}} \int_{t_{\text{start}}}^{t_{\text{end}}} BS^c(t) dt.$$

This can be seen as the average Brier score over this interval. In practice, we can obtain  $\text{IBS}(t_{\text{start}}, t_{\text{end}})$  by computing the Brier score 5.7 over a grid of time points  $t \in [t_{\text{start}}, t_{\text{end}}]$ , and then numerically integrating these. If we have survival times  $t_1, \dots, t_N$ , we can calculate an approximation of  $\text{IBS}(t_1, t_N)$ ,

$$\widehat{\text{IBS}}(t_1, t_N) \approx \frac{1}{t_N - t_1} \sum_{j=1}^{N-1} BS^c(t_j) \cdot (t_{j+1} - t_j).$$



## Chapter 6

# Simulation study

After developing FHTBoost (see chapter 4), we wish to verify that it works, i.e. that it has predictive power and selects correct variables. Not only that, but we wish to see which of the two versions of the algorithm works best, namely the fixed intercept version and the version with an iteratively changing intercept.

One way to verify that a statistical estimation method works, is to test it on simulated data. Simulation studies are used for many different purposes, but a particularly common purpose is to simulate survival data from the “true model” (in this case, our first-hitting-time model), for which we know the true values of the parameters. We can then use our developed method to estimate these parameters, and see how well it recovers the true parameters in the final model, and how well the model fits the simulated data. The model should fit the simulated data well, because the data generating mechanism *is* the model. In this chapter, we simulate data, use FHTBoost to estimate models, and assess the performance of these models. The boosting algorithm has two main purposes: Selection of variables, and minimizing test error. To assess the test/generalization error, we calculate the difference of deviance on the test set. To assess variable selection, we look at some well known metrics.

### 6.1 Simulation design

In this chapter we describe two scenarios, a highly correlated scenario and an uncorrelated scenario. The purpose of each scenario is to first generate survival data from an FHT mechanism, based on known true parameters, then use FHTBoost to estimate the parameters of the model, and then finally to assess the model’s performance on this data. In both scenarios, we generate a high-dimensional covariate matrix  $\mathbf{X}$  consisting of covariate vectors

$$\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_{p_1}, \quad (6.1)$$

which is supposed to mimic gene expression data. We also have a low-dimensional covariate matrix  $\mathbf{Z}$ , which similarly consist of covariate vectors

$$\mathbf{z}_1, \mathbf{z}_2, \dots, \mathbf{z}_{p_2}, \quad (6.2)$$

and which is supposed to mimic clinical measurements. The motivation for this dichotomy is discussed in subsection 2.5.3. We link each covariate to a

parameter in a parameter vector. We let  $\mathbf{X}$  correspond to  $\beta$ , and  $\mathbf{Z}$  correspond to  $\gamma$ . This allows us to test the variable selection performance of FHTBoost. In each parameter vector, we set only a small number of parameters to a non-zero value, and we set all the rest to zero. Thus only a very small number of covariates will have an effect. Given these parameter vectors and covariate matrices, we calculate a specific  $y_{0,i}$  and a specific  $\mu_i$  for each individual  $i$ , where  $i = 1, 2, \dots, N$ , and where  $N$  is the size of the data set. From the FHT perspective, discussed previously in section 2.3.1 and onward, these are parameters representing the health process of each individual. To reiterate, an individual  $i$  has a stochastic health process, specifically a Wiener process with an initial level  $y_{0,i}$  and a drift  $\mu_i$ . When the health process hits 0, it causes the event for the individual. Since the FHT of a Wiener with health level  $y_{0,i}$  and drift  $\mu$  is  $\text{IG}(y_{0,i}, \mu_i)$ , then also the individual's lifetime follows this distribution  $\text{IG}(y_{0,i}, \mu_i)$ . This relationship allows us to easily draw a lifetime for each individual from its respective inverse Gaussian distribution.

It is important to evaluate an estimated model's performance on a separate and unseen test set. Each training set will be generated by drawing  $N = 500$  individuals as described above, with a specific seed. Since we are simulating, it is simple to generate a test set by drawing from a unique seed. We are therefore also able to decide the size of the test set. We set  $N_{\text{test}} = 1000$  observations.

We generate  $B \approx 500$  data sets by drawing survival data according to algorithm 6. In each data set there are  $N = 500$  observations. We treat each data set as a separate training data set. To estimate a model based on a training set, we first perform repeated 5-fold cross validation procedure (see subsection 3.6.1), with 5 repeats. As shown in subsection 3.4.3.2, this provides a reasonably variance reduced estimate of  $m_{\text{stop}}$  (near the "true"  $m_{\text{stop}}$ ). We then estimate a model based on the entire training set, by running FHTBoost with  $m_{\text{stop}}$  number of iterations.

To simulate the covariate matrices  $X$  and  $Z$  we will use Algorithm 7, which is a method for simulating clinical and gene data together. We specify the different correlations for the covariate matrices. We specify the true parameter vectors,  $\beta$  and  $\gamma$ . For each scenario, we create  $B$  data sets. For each of these, we estimate FHT parameters using FHTBoost.

For each data set  $D_b$ , we first draw data (with a specific seed to ensure reproducibility). We do this by drawing covariate matrices  $\mathbf{X}$ ,  $\mathbf{Z}$  from Algorithm 7. Then we combine these with the true covariate matrices to get vectors  $\mathbf{y}_0$  and  $\mu$  of initial value of the health process, and drift, respectively. Then we draw from the Inverse Gaussian distribution according to Algorithm 6, obtaining  $N$  right-censored lifetimes, i.e.,  $N$  tuples  $(t_i, d_i)_{i=1, \dots, N}$ . With these tuples, then, we can do a run with the FHT boosting algorithm. We first use repeated K-fold cross-validation to find the optimal number of boosting steps,  $m_{\text{stop}}$ . Then we estimate the model on the whole of this training set. Then we validate this model on a test set of size  $N_{\text{test}}$ . The data here are drawn in the exact same manner as the training data, again with a specific seed for reproducibility. We first discuss the algorithms we use to generate FHT survival data.

## 6.2 Simulation of survival data from an IG FHT distribution

sec:simulate-IG-data

We wish to simulate survival times  $(t_i)_{i=1}^N$  with censoring. We first draw  $N$  uncensored survival times  $\{\tilde{t}_i\}_{i=1}^N$  from a survival time distribution  $f(\cdot)$ . If this distribution has a closed form probability distribution function, we can draw from it directly, and this is the case for us. To implement censoring of the data, we draw censoring times  $w_i \sim f(\cdot), i = 1, \dots, N$  from some other lifetime distribution where the parameters do *not* depend on covariates. Thus the observed survival times are

$$t_i = \min(\tilde{t}_i, w_i), \quad (6.3)$$

as we have seen before. The corresponding censoring indicator,  $d_i$ , is then set equal to 1 if the actual survival time was observed, i.e., if  $t_i < w_i$ . We end up with a data set

$$D = (\mathbf{x}_i, \mathbf{z}_i, t_i, d_i)_{i=1}^N. \quad (6.4)$$

Note that this procedure simulates censored time under independent censoring, since indeed the censoring times are independent of the survival times. See 6 for a schematic overview of the algorithm.

## 6.3 Generating correlated clinical and gene expression data

To create a realistic scenario where we have data looking like gene expression data and clinical data, we need to define a proper correlation structure. We can draw covariate matrices from a normal distribution with a suitable covariance matrix.

We consider a scenario where we have a covariate matrix  $X$  consisting of  $p$  gene expressions, and a covariate matrix  $Z$  consisting of  $d$  clinical measurements. We can imagine that some of the genes in  $X$  are highly correlated. One way to imagine this is to imagine that we have blocks of genes, where inside one block, the genes are highly correlated, whereas genes in one block are not correlated to other genes. In addition, one block of genes might affect a block of clinical variables as well.

We specify a number of blocks  $B$ . A given block  $b, b = 1, 2, \dots, B$ , contains a certain number of genes,  $G_b$ , which are correlated to each other. It also contains a certain number of clinical measurements,  $C_b$ . These measurements are correlated to each other, and to the genes in the block.

After setting up the block structure, we

Finish this

There are three types of correlations. 1. Within each block of genes. Defaults to 0 for genes not belonging to any block. 2. Between clinical predictors in each pathway 3. Between the clinical and molecular predictors in each pathway

Algorithm 7 contains a schematic overview.

algo:FHT-sim

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**Algorithm 6** Generating survival data from Inverse Gaussian FHT distribution
 

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1. Obtain the design matrices  $\mathbf{X}$ ,  $\mathbf{Z}$  and the true parameter vectors  $\boldsymbol{\beta}$  and  $\boldsymbol{\gamma}$ .
2. Specify a censoring time distribution.
3. Calculate the distribution parameters  $y_0$  and  $\mu$  using the link functions,

$$y_0 = \exp(\boldsymbol{\beta}^T \mathbf{X}) = \exp \left( \beta_0 + \sum_{j=1}^p \beta_j x_j \right),$$

$$\mu = \boldsymbol{\gamma}^T \mathbf{Z} = \gamma_0 + \sum_{j=1}^d \gamma_j z_j.$$

4. Draw  $N$  uncensored survival times  $(\tilde{t}_i)_{i=1}^N$  from  $\text{IG}(\boldsymbol{\mu}, \mathbf{y}_0)$ , where

$$\tilde{t}_i \sim \text{IG}(\mu_i, \mathbf{y}_{0,i}).$$

5. Draw  $N$  censoring times  $(w_i)_{i=1}^N$  from the censoring time distribution specified in step 2.
6. Right censor the survival times by choosing

$$t_i = \min(\tilde{t}_i, w_i).$$

The censoring indicator on whether observation  $i$  was observed or not is then

$$d_i = I(t_i = \tilde{t}_i).$$

7. The simulated data set is  $D = (t_i, d_i)_{i=1}^N$ .
- 

algo:clinical-sim

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**Algorithm 7** Generating correlated clinical and gene expression data
 

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1. Lorem ipsum.
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## 6.4 Scenarios

### 6.4.1 Scenario 1: Uncorrelated case

We generate a data set of size  $N_{\text{scenario}} = 500$ , and parameter vectors of size 10000 and 15, respectively. We let  $\beta$  be a large vector of size  $p = 10001$ , and  $\gamma$  be a small vector of size  $d = 16$ . We first discuss the size of the parameter effects. The parameter vector  $\beta$  is linked to the initial level  $y_0$  by an exponential link function. Consequently, each parameter effect is *multiplicative* instead of additive. A large gene expression value can therefore potentially cause a large change in  $y_0$ . Since there are 35 elements of  $\beta$  which are informative, there is a reasonable chance of such extreme values occurring in  $y_0$ . Because of this, we had trouble setting up simulations in which there was much signal from the underlying parameter vector. Therefore we choose 0.1 for the informative parameter effects  $\beta_j, j = 1, 2, \dots, 35$ . The parameter sizes on the drift might also appear rather small, at 0.1, but this effect is linear with time. By having a relatively low effect per time unit, we ensure that the lifetimes are not too short. These two considerations in mind made us achieve a decent simulation setup. Specifically, we set the intercept term in  $\beta$  to be 2.0, and the following  $p_1 = 35$  elements to be 0.1. We set all other elements to 0. For  $\gamma$ , we set the intercept term to be -1. In similar fashion as in  $\beta$ , we let the first 5 elements in  $\gamma$  have a non-zero value of -0.1, while we set the remaining 10 elements to 0. Hence, the true parameter vectors are

$$\beta = \left( 2.0, \underbrace{0.1, 0.1, \dots, 0.1}_{\text{length 35}}, \underbrace{0, 0, \dots, 0}_{\text{length 9965}} \right)$$

$$\gamma = \left( -1.0, \underbrace{0.1, 0.1, \dots, 0.1}_{\text{length 5}}, \underbrace{0, 0, \dots, 0}_{\text{length 10}} \right)$$

We draw  $X$  and  $Z$  from Algorithm 7 for drawing clinical and gene data, with  $B = 0$  blocks. We specify that all correlations are 0, meaning no covariate correlates with any other. We generate  $B = 500$  data sets from this algorithm, where we set the seed at the beginning of each simulation. Having now a data set  $D_b$ , we run cross validation on this data set to find the optimal iteration number  $m_{\text{stop}}$ . We then run a boosting algorithm with  $m_{\text{stop}}$  steps on the training set, to estimate parameters. We will discuss the results in the next section, but we first describe the other scenario.

### 6.4.2 Scenario 2: Correlated

Consider now a scenario where we wish to have high correlation. We have blocks of genes which are correlated, meaning the genes comprising one are correlated. Furthermore, we let the genes in a block of genes be correlated with a (smaller) block of clinical measurements. Finally, the clinical measurements are correlated. All these correlations are set to 0.7. The main purpose of the algorithm is to specify the covariance matrix before drawing the data.

There are three types of correlations. 1. Within each block of genes. Defaults to 0 for genes not belonging to any block. 2. Between clinical predictors in each pathway 3. Between the clinical and molecular predictors in each pathway

Table 6.1: Difference of deviance results for FHTBoost, uncorrelated case

	Updating	Fixed
Mean	-92.0	-130.1
Standard deviation	41.8	40.7
Minimum	-233.6	-255.2
Maximum	7.2	-5.7

table: uncorrelated- deviance
-------------------------------------

## 6.5 Results

After having estimated an FHT model on the training set, we assess the performance of the model on the test set. We calculate the difference of deviance. To assess the variable selection of the model, we calculate metrics for the variables selected based on the training set. We count  $TP$ , the number of informative covariates which were selected in the estimated boosting model, and  $TN$ , the number of non-informative covariates which were selected in the model. Based on these numbers, we calculate the metrics discussed in Section 5.2, namely Sensitivity, Specificity and False Discovery Rate. Let us now consider the results of each scenario.

### 6.5.1 Scenario 1: Uncorrelated case

#### 6.5.1.1 Test set performance/model fit

The most evident result is that, in contrast to our expectation, the fixed intercept version of FHTBoost seems to perform on average better than that with updating intercept (see Table 6.5). The mean difference of deviance on the updating intercept version is -92.0, while it is -130.1 on the fixed intercept version. Despite the large variability (see min, max and standard deviation in Table 6.5) in the distributions of the difference of deviance results, the difference between the fixed intercept and the changing intercept are noticeable. This is perhaps most apparent in Figure 6.1. In addition, the fixed intercept version always performs better than the null model, while there are a few cases in which the updating intercept version does not (Table 6.5, row "min", and Figure 6.1). In other words, all models estimated using the fixed intercept version performed better than their null models, whereas this is not the case for the version with a changing intercept. This can be a consequence of overfitting. Moving the intercept allows the model to fit the training data too well. We now consider the variable selection metrics.

#### 6.5.1.2 Variable selection

Let us contrast the two versions of FHTBoost in terms of variable selection as well. This scenario has 35 informative gene covariates and 5 informative clinical covariates. Since the changing intercept version has a rather low number of iterations, with a mean of 15.8, it is usually impossible to get anywhere near perfect on these metrics, as at most one new parameter is selected in each iteration, and we have 40 informative covariates in total from the two vectors. Since the covariate vector is estimated on the training data, a likely explanation is that the changing intercept captures more of the variation in the training



Figure 6.1: Boxplot for difference in deviance for the two intercept variants, non-correlated scenario

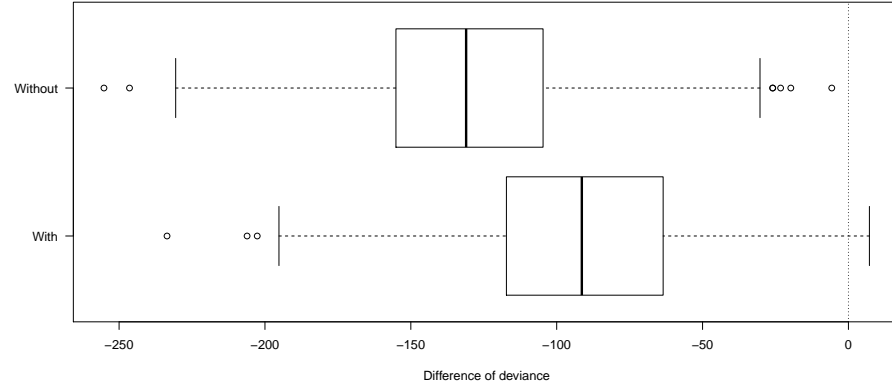
fig:simulation-  
uncorrelated-  
deviances-  
boxplot

Table 6.2: High dimensional (genomic) part: Performance of FHTBoost in terms of variable selection, uncorrelated case

	Updating		Fixed	
	Mean	Standard error	Mean	Standard error
Sensitivity	0.190	(0.090)	0.452	(0.162)
Specificity	1.000	(0.000)	0.997	(0.002)
FDR	0.310	(0.176)	0.613	(0.144)

table:  
uncorrelated-y0

Table 6.3: Low dimensional (clinical) part: Performance of FHTBoost in terms of variable selection, uncorrelated case

	Updating		Fixed	
	Mean	Standard error	Mean	Standard error
Sensitivity	0.741	(0.232)	0.958	(0.099)
Specificity	0.943	(0.110)	0.638	(0.291)
FDR	0.091	(0.144)	0.375	(0.192)

table:  
uncorrelated-mu

data. In doing so, there is less variation to be explained by the covariates, and hence the boosting algorithm will start to overfit more quickly.

Furthermore, we are considering the sensitivity and specificity on both covariate vectors at the same time. Since we are only selecting a covariate for either  $\beta$  or  $\gamma$ , these scores will depend on each other.

Consider first the result of the version in which the intercept is changed in each step. Both covariate vectors have a very high specificity, which measures the amount of true negatives which are correctly classified as negatives, i.e., not selected. The changing intercept version has a mean specificity of 1.00. It also has a mean false discovery rate of 0.316. Thus there is about a one in three chance that it selects a variable which is not actually informative. The sensitivity, i.e., the ratio of correctly selected informative variables, has a mean of only 0.190. This means that a large proportion of the informative covariates

Table 6.4: Optimal iteration number  $m_{\text{stop}}$  results for FHTBoost, uncorrelated case

	Updating	Fixed
Mean	15.8	63.8
Standard deviation	6.4	26.5
Minimum	2	2
Maximum	39	160

table: uncorrelated- mstop
----------------------------------

Table 6.5: Difference of deviance results for FHTBoost, correlated case

	Updating	Fixed
Mean	-57.8	-58.8
Standard deviation	47.2	46.1
Minimum	-203.4	-223.1
Maximum	87.6	73.5

table: uncorrelated- deviance
-------------------------------------

are not selected. For  $\gamma$ , which is related to the clinical covariates, a much higher specificity is attained, with a mean of 0.943. Even though the parameter effects on the drift are rather small, the informative covariates are often correctly selected. Furthermore, the false discovery rate here is very low, with a mean of 0.091.

Now consider the results of the fixed intercept version. For the  $\beta$  covariate vector, a higher proportion of informative covariates are selected, with a mean sensitivity of 0.452. The mean specificity is 0.997. Simultaneously, a larger mean false discovery rate of 0.613 is not good: This means that more than half of all selected variables should be expected to be false positives. At the same time, a very good sensitivity is achieved on the  $\gamma$  covariate vector, with a mean of 0.958, and a good specificity with a mean of 0.638. The false discovery rate on  $\gamma$  is slightly above one in three, with a mean of 0.375.

### 6.5.1.3 Summary

Summarize

## 6.5.2 Scenario 2: Correlated case

We now consider the results for the correlated simulation study.

### 6.5.2.1 Test set performance/model fit

We observe that the mean deviance is very slightly better for the fixed intercept version, and with better extreme values, both minimum and maximum. See Figure 6.2 for a boxplot of these deviances. However, it is very close, so it is difficult to say that there is any difference in the model fit for these two versions.

### 6.5.2.2 Variable selection

We now consider the variable selection metrics. We first look at the covariate vector  $\beta$ , which affects the initial level  $y_0$ , and which is related to “genomic”

Figure 6.2: Boxplot for difference in deviance for the two intercept variants, correlated scenario

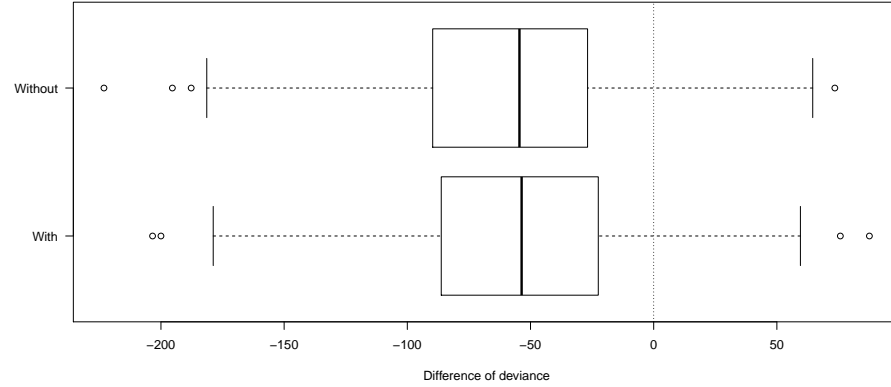
fig:simulation-  
correlated-  
deviances-  
boxplot

Table 6.6: High dimensional (genomic) part: Performance of FHTBoost in terms of variable selection, correlated case

	Updating		Fixed	
	Mean	Standard error	Mean	Standard error
Sensitivity	0.157	(0.084)	0.204	(0.081)
Specificity	0.999	(0.000)	0.998	(0.001)
FDR	0.439	(0.218)	0.652	(0.181)

table:  
correlated-y0

variables. The fixed intercept version is slightly better with regards to sensitivity, with a mean of 0.204 versus a mean of 0.157 for the changing intercept version. So selecting informative variables, This does come at the cost of a higher false discovery rate, with a mean as high as 0.652. Here the changing intercept version has a mean of 0.439. The specificity score is almost perfect in both cases.

We now consider the “clinical” covariates, used in  $\gamma$  and related to the drift  $\mu$ . The changing intercept version performs quite a lot worse here than the fixed intercept version, overall. It achieves a mean sensitivity of 0.273, while the fixed intercept version achieves 0.625. However, the changing intercept then achieves a mean of 0.831 for specificity, where the fixed intercept version attains 0.537. For the false discovery rate, the fixed intercept has a slightly higher mean, at 0.507, whereas the changing intercept version has a mean of 0.454.

For this scenario, as well, we see that the fixed intercept version has a higher optimal iteration number. The mean  $m_{\text{stop}}$  is 50 with a fixed intercept, compared to a mean of 19.5 for the changing intercept version. Again this necessarily means that more variables are selected, and that coefficients from the changing intercept version will be more shrunk.

Table 6.7: Low dimensional (clinical) part: Performance of FHTBoost in terms of variable selection, correlated case

	Updating		Fixed	
	Mean	Standard error	Mean	Standard error
Sensitivity	0.273	(0.187)	0.625	(0.245)
Specificity	0.831	(0.139)	0.537	(0.236)
FDR	0.454	(0.250)	0.507	(0.130)

table: correlated-mu
-------------------------

Table 6.8: Optimal iteration number  $m_{\text{stop}}$  results for FHTBoost, correlated case

	Updating	Fixed
Mean	20.0	51.1
Standard deviation	12.1	24.4
Minimum	2	2
Maximum	65	148

table: correlated-mstop
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### 6.5.2.3 Conclusion

In conclusion, while the fixed intercept version also here selects more true positive variables, it comes at a cost of selecting more false positives. If we use the deviance to assess which one is best, then the fixed intercept version is the better one here as well.

## 6.6 Discussion

In general, we see that FHTBoost is able to estimate FHT models which achieve good performance, on data generated from a true FHT mechanism. The performance achieved is especially high for the uncorrelated scenario. As we have discussed, the variable selection has trade offs. The fixed intercept version selects more true positives, but it also selects more false positives. It does seem to be worth it, in the end, since it achieves a better generalization error in the form of a lower difference of deviance. The results are also good in the highly correlated scenario. Since this is a much more realistic scenario, we should give more weight to the results attained in it. If so, it is difficult to make a conclusive statement on which version is better, as the results are very similar in the highly correlated scenario. However, to narrow down the scope of the analysis in the next chapter, we will decide to only use the fixed intercept version, as we at least cannot say that it is not better than the changing intercept version.

## Chapter 7

# Application on real data

In the simulation study in the previous chapter, we contrasted the fixed intercept version and the updating intercept version of FHTBoost. In general, FHTBoost seems to provide a decent model for correlated, realistic survival data, with average difference of deviance much smaller than 0, meaning that including covariates increases model fit. We now evaluate its performance in a real data example. In particular, we consider data from Oberthuer et al. (2008), consisting of data from patients diagnosed with neuroblastoma. The dataset includes a relatively small number of patients, with information on two clinical covariates and around 10 000 gene expressions. We use FHTBoost on this data to estimate an FHT model, and assess its performance. Finally, we compare the predictive power of FHTBoost to CoxBoost, which is a method to estimate a Cox regression model using a boosting framework (see, e.g., Binder and Schumacher (2008)).

### 7.1 Neuroblastoma

We consider survival data from Oberthuer et al. (2008), consisting of patients diagnosed with neuroblastoma. Neuroblastoma is a malignant pediatric tumor that accounts for about 8% of all childhood cancers. One of the hallmarks of the disease is its contrasting biological behavior, which results in diverse clinical courses ranging from spontaneous regression to rapid and fatal tumor progression despite intensive treatment.

In recent years, several markers have been reported to offer valuable prognostic information. These markers are routinely determined by the current German neuroblastoma clinical trial NB2004 to stratify patients into groups of high risk (50%) or low risk (50%) of disease. Therapeutic strategies vary according to these risk categories, and they range from a wait-and-see approach for those in the low risk group to intensive treatment for the high-risk group. However, common clinical experience suggests that such risk classification is still suboptimal for a substantial number of patients.

Originally, the data consist of two separate data sets: A larger training set, collected in Germany, and a smaller test set, collected in several countries. The training set consists of 256 patients of the German Neuroblastoma Trials NB90-NB2004, where the patients were diagnosed between 1989 and 2004. The test set is an independent set of 120 patients from national trials in several

countries (including 29 from Germany). Due to a low number of events in the NB2004 low risk group, and following Bøvelstad et al. (2009), we merge the “training set” and the “test set” into one data set. Hence, in total, the data consists of 362 patients suffering from neuroblastoma. There are 9978 gene expressions measurements, comprised of those measurements that are in probes from both the “training set” and the “test set.” From each patient, we have information on their risk group according to the current German neuroblastoma trial, as well as the patient’s age at diagnosis. In this data set, 89 out of the 362 observations have missing values. We remove all of these observations, and are left with a data set of 273 individuals with full observations. Finally, for each individual we have the possibly censored survival time. This survival time was defined as time from diagnosis to first recurrence, and was censored at 5 years. 42 of the 273 children experienced a recurrence within the follow up, which is a proportion of 31.5%. Of these, 86 children were classified as having high-risk, while the remaining 187 were not. The risk indicator is coded as a binary variable, where low risk is coded as 0, and high risk as 1.

Due to the lack of data, Bøvelstad et al. (2009) generated 50 random splits of training and test sets from the merged data set. We do the same, and generate 100 random splits times. First, however, we report the analyses of one single (the first) split of train and test data, to give an example of how to interpret the results.

## 7.2 Single split

The data are split in a training set (2/3) and test set (1/3), stratified by the event status. The training set consists of 182 patients, where 28 are observed events. The test set consists of 91, where 14 are observed events. The data are standardized.

### 7.2.1 Cross-validation on training set

As has been shown previously, cross-validation should be repeated with different division of folds, as this reduces variance in the estimate of  $m_{\text{stop}}$ . We perform a (10 times) repeated 5-fold cross validation to find the optimal number of iterations. Note in Figure 7.1 the impact of running the 5-fold cross-validation in a repeated fashion: We would not have selected the same  $m_{\text{stop}}$  in all of the 10 single 5-fold cross-validations. We find  $m_{\text{stop}} = 20$  to be optimal, i.e., the minimizing iteration number. It is down as the red vertical line in Figure 7.1. Each dotted gray line in the figure is the sum of the negative log-likelihood of a model trained on 4 folds and applied to the last fold, as a function of the iteration number  $m$ , while the solid black line is the mean of these 10 gray lines. As we can see, in this example the boosting algorithm, in contrast to the original AdaBoost, eventually overfits, so it is important to select the number of boosting stpes by cross-validation.

### 7.2.2 Results

We run the boosting algorithm with  $m_{\text{stop}}$  iterations, to estimate the model parameters on the entire training set. We now discuss the results of the parameters obtained from FHTBoost.

Figure 7.1: Repeated 5-fold cross validation on training set generated from neuroblastoma data set (Oberthuer et al., 2008). The grey lines refer to the cross validation error for a single 5-fold CV implementation, the black line is the average of 10 such replications. The red vertical line highlights the best value for the number of boosting steps.

fig:  
neuroblastoma-cv

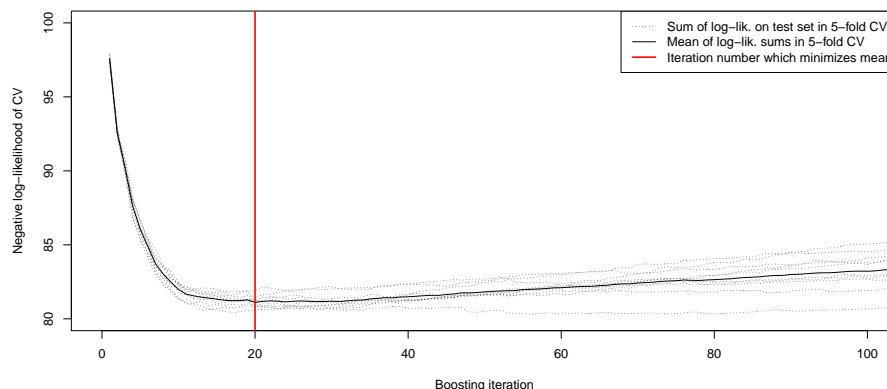


Table 7.1: Estimated FHT null model on neuroblastoma (Oberthuer et al., 2008)

tab:  
neuroblastoma-  
intercepts

	Value
$\beta_0$	0.692
$\gamma_0$	0.077

### 7.2.2.1 Null model interpretation

We first look at the intercepts, reported in Table 7.1, basically the parameters of the null model. The estimated intercept for the gene data,  $\beta_0$ , is 0.692. Remember that in the FHT model, the vector  $\beta$  corresponds to the initial level  $y_0$  of the health process, through the log link function. The null model, without any covariate effects, therefore has a  $y_0$  of  $\exp(0.692) = 1.998$ . The intercept  $\gamma_0$  corresponding to the clinical data is estimated to be 0.077. This means that the health process with the FHT interpretation that arises from our estimation is a Wiener process with a relatively small initial level of 1.998, and with a *positive* drift, albeit slightly, of 0.077. Recall from section 2.3.3 that a Wiener process  $W(t)$  has variance equal to its time  $t$ . The large variability of the process relative to its starting point means there is still a significant chance of recurrence of neuroblastoma. The resulting health process is

$$Y(t) = 1.998 + W(t) \cdot 0.077t,$$

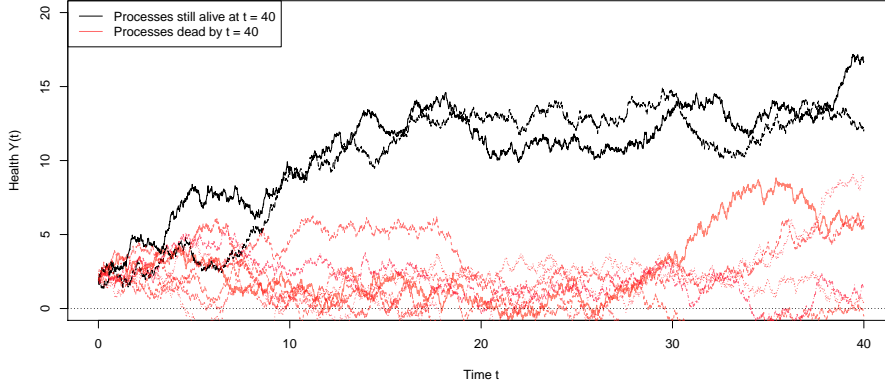
where  $W(t) \sim N(0, \sqrt{t})$ , i.e.,

$$Y(t) \sim N(1.998 + 0.077t, \sqrt{t}).$$

To get a feeling of the variability of  $Y(t)$ , and potential trajectories of such a process, we plot 10 realizations of this process in Figure 7.2. Of these particular

Figure 7.2: Curves for 10 randomly generated Wiener processes with parameters  $y_0 = 1.998$  and  $\mu = 0.077$ , corresponding to the estimated null model from the neuroblastoma data set (Oberthuer et al., 2008).

fig:  
neuroblastoma-  
wien



10 processes, 8 processes at some point go below 0. These are given a red color in figure 7.2. In the FHT interpretation, then, these health processes would cause an event, or rather, a recurrence of the neuroblastoma cancer in the child. To get a better estimate of the proportion of health processes not hitting the death state, we need to sample more processes. We sampled 10000, and 6221 of these went below 0 within  $t = 40$ , i.e., a proportion of 0.378 did not experience recurrence.

[Check time here ... and in paper](#)

In section 2.3, specifically in equation (2.20), we stated the probability of an IG FHT lifetime not ending, i.e., the cure rate. We will have a non-zero cure rate if the drift is positive, like we have here in our null model. We calculate the cure rate for our estimated null model, obtaining

$$\begin{aligned} \Pr(T = \infty) &= 1 - \Pr(T < \infty) = 1 - \exp(-2 \cdot y_0^{[0]} \cdot \mu^{[0]}) \\ &= 1 - \exp(-2 \cdot 1.998 \cdot 0.077) = 0.265, \end{aligned}$$

meaning about three in four should have a recurrence during their lifetime. For this training set, 28 out of 182 are observed events, meaning only 0.154 have experienced a recurrence. Note that this is with a medium follow-up on patients of 4.5 years. It is still a bit off from the cure rate obtained from the estimated null model, but our model does predict a non-zero proportion of long-term survivors, which is good.

Consider the fact that the initial level  $y_0$  is quite low. Since we are looking at when, if ever, a neuroblastoma patient will have a recurrence after a surgery, this initial level of the Wiener process is the health level of a patient at surgery. The health of such a child is presumably quite precarious, as neuroblastoma is a malignant cancer. Therefore it makes sense that the initial level  $y_0$  of the child's health process is quite low. Furthermore, the fact that the drift  $\mu$  is positive also makes sense. Since the individuals in the study are young children, and we are looking at a timeframe that does not comprise the length of a typical human



life, the health level of most children should indeed increase after the surgery. However, as mentioned, and as clinicians experience, the survival probability of patients vary, even among those specified as high-risk. We therefore must look at estimated covariates to understand variability.

### 7.2.2.2 Estimated covariate effects

Let us further look at estimated covariate effects in Table 7.2 and Table 7.3. We first observe that the boosting algorithm has included both clinical covariates into the model, and it has included 8 genes. Remember that we centered each column of the covariate matrices, such that the mean across all individuals is (approximately) 0 for each covariate  $j$ . For the gene expressions, this is not particularly important with regards to interpretation, as the scale of these do not lend themselves easily to interpretation. However, to properly consider the interpretation of the estimated parameters for to the clinical measurements, we should consider these on their original scale. For example, the covariate corresponding to risk, namely  $\gamma_1$ , is originally either 0 or 1, depending on the covariate. After standardizing, these are -0.677 and 1.472, respectively. The most striking result here is the large parameter corresponding to risk. We calculate the drift parameter for those individuals designated as high-risk, and it is

$$\mu_{\text{high-risk}}^{[0]} = 0.077 - 0.189 \cdot 1.472 = -0.202.$$

Whereas for those designated as low and intermediate risk, it is

$$\mu_{\text{low-risk}}^{[0]} = 0.077 - 0.189 \cdot -0.677 = 0.205.$$

So the drift for those with high risk is negative, while it is positive for low risk. Since age is standardized, these two drift covariates should be the mean drift parameters for each of the groups. We can first check to see if this holds true for all individuals within the risk groups. The effect of age is negative, which means that there is some downward effect on the drift as the child's age increases. This negative effect could also potentially lead to low-risk individuals having an estimated negative drift, if the child is sufficiently old. This is, however, not the case. The effect of age is so small as to not impact the sign of the drift. Because the maximum standardized age is 4.193, the age contribution to drift is bounded below by

$$-0.029 \cdot 4.193 = -0.122.$$

Similarly, there are no high-risk individuals for which the drift will be positive, since the minimum standardized age is -0.724, and so the effect of age is bounded above by

$$-0.029 \cdot 0.724 = 0.021.$$

Hence, crucially, this means that the model predicts that *all* high-risk individuals will eventually have a recurrence of neuroblastoma cancer. This seems to resonate with the fact that these children are indeed characterized as having a high risk of recurrence. Those not designated as high-risk, on the other hand, have a non-zero probability of not experiencing recurrence. We calculate it using the formula seen previously, namely

$$1 - \exp(-2 \cdot y_0^{[0]} \cdot \mu_{\text{low-risk}}^{[0]}) = 1 - \exp(-2 \cdot 1.998 \cdot 0.205) = 0.559.$$

Table 7.2: Results of estimated clinical coefficients on neuroblastoma data (Oberthuer et al., 2008).

Clinical covariate	$\gamma_j$ (full)	$\gamma_j$ (clinical only)
Risk	-0.189	-0.268
Age	-0.029	0

tab:oberthuer-  
gamma

Table 7.3: Results of estimated gene coefficients on neuroblastoma data (Oberthuer et al., 2008).

Gene $j$	$\beta_j$ (full)	$\beta_j$ (genomic only)
Gene 49	-0.010	0
Gene 1447	-0.069	-0.047
Gene 3191	0	-0.051
Gene 2442	0.012	0
Gene 4447	0	-0.062
Gene 5307	0	0
Gene 5527	-0.073	-0.098
Gene 5725	-0.009	0
Gene 6532	-0.011	0
Gene 6701	0.015	0
Gene 6901	0.011	0

tab:oberthuer-  
beta

Table 7.4: Difference of deviance results.

Boosting type	Difference of deviance
Full	-95.2
Clinical ( $y_0$ ) only	-14.5
Genetic ( $\mu$ ) only	-104.4

tab:deviances

We should therefore expect, based on the estimated model, that more than half of the low-risk patients should recover. We can also consider the gene covariates.

We observe that 8 genes have been selected in 20 boosting iterations (see Table 7.3). Some effects are estimated to be positive, some to be negative. Again, the gene expression measurements have been centered and scaled. However, a larger parameter does not necessarily mean that the effect of this gene is in general larger than others, as that still depends on the distribution of these. It is more difficult here to say how much the genomic data helps in explaining the variance.

Why???

Check Riccardo's comments on table here

### 7.2.3 Difference of deviance on the test set

The test set consists of 91 individuals, of which 14 have experienced recurrence. We calculate the difference in deviance for the estimated FHT model, as seen in Section 5.1. Recall that the performance of a model is good when the difference

in deviance is small (i.e. negative with a large absolute value). We obtain a difference of deviance on -95.2. It means that under the assumption that the FHT model is true, a lot of variation is explained by covariates.

### 7.3 Comparing a clinical-genetic model to clinical-only and genetic-only models

Bøvelstad et al. (2009) analysed the neuroblastoma data and compared different statistical methods to combine clinical and genomic data in Cox models. As mentioned in subsection 2.5.3, the FHT model lends itself easily to combining genomic and clinical data, and this holds for FHTBoost as well. There is also a straightforward way to only use one kind of covariates, i.e., only clinical covariates or only genetic covariates. To do this, we can use the cyclical version of the algorithm, where we boost both parameters in each step, but each has its own tuning parameter. This lets us fix the number of boosting steps of the parameter not to be boosted to 0. In other words, we make a genomic version of FHTBoost, or  $y_0$ -only version of FHTBoost, by only boosting the initial level  $y_0$ . This version of FHTBoost has  $m_{\text{stop},1}$ , corresponding to  $\mu$ , fixed at 0, while we perform cross-validation in the usual way to find the optimal  $m_{\text{stop},2}$ , corresponding to  $y_0$ . Similarly, the clinical version fixes  $m_{\text{stop},2}$  at 0, and tunes the other,  $m_{\text{stop},1}$ , corresponding to  $\mu$ . In this way, we can compare the performance of our model across the genetic and clinical data, in a similar way as in Bøvelstad et al. (2009).

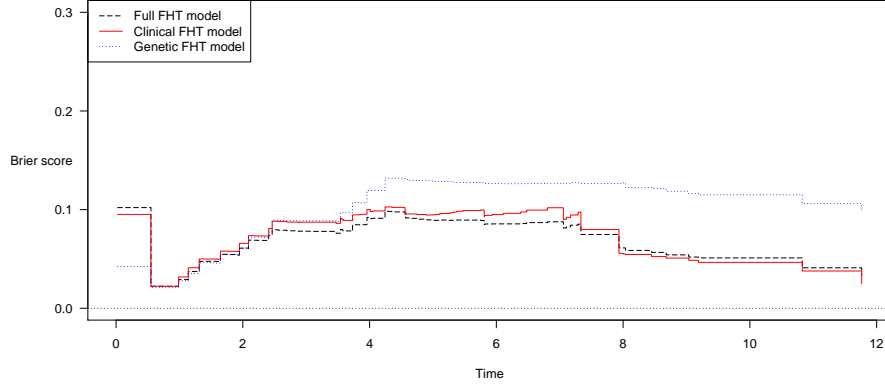
We do the estimation and the test set calculation, and we get the difference of deviance results shown in Table 7.4. We see here, in fact, that in this specific case the full model is beaten by the genomic model, with difference of deviance of -95.2 and -104.4, respectively.

Furthermore, we calculate the Brier scores (Section 5.3) of these models on the test set, see Figure 7.3. Interestingly, the full FHT model is quite consistently better than the genomic model, even though it achieves a worse difference of deviance. Furthermore, the Brier score of the full FHT model is mostly equal to the clinical one, except in the middle, where it is somewhat better. It is perhaps easiest to compare the performance if we have a number, and we get that by calculating the integrated Brier score, explained in subsection 5.3.3, and which is effectively the average Brier score over a given range of time, in this case the times from the entire test set.

We find that the integrated Brier score for the full FHT model is 0.0679, while the estimated FHT null model achieves 0.1226, which is almost the double. Note, however that large part of the additional error refers to the right part of the error curve (see Figure 7.3), where the computations are more unstable due to the reduced number of events (larger proportion of censored data). And the genomic model attains an integrated Brier score of 0.1015, while the clinical attains 0.0708.

Figure 7.3: Brier scores for FHT models.

fig:brier-FHT



## 7.4 Comparison with the Cox model

We compared our model with the Cox model (see subsection 2.2.2) as implemented in `CoxBoost()`, setting

$$\lambda = N \frac{1 - \nu}{\nu}, \quad (7.1)$$

{eq:lambda-nu}

Add citation for CoxBoost!!!!!!

as suggested in De Bin (2016), where  $N$  is the number of individuals in the data set on which the estimator is applied, and  $\nu$  is the step length mentioned in the various boosting algorithms in Chapter 3, which we by convention always set to 0.1.

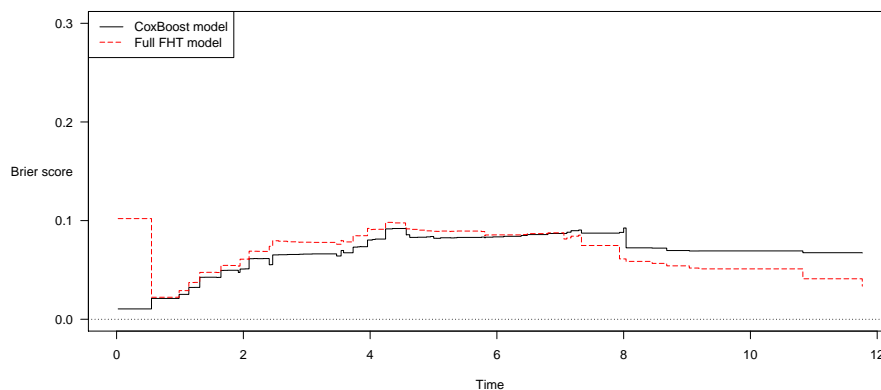
We calculate the Brier score for these models (again, see Section 5.3 for an explanation). Consider now a comparison of the Brier score for the full FHT model and the Cox model, which can be seen in Figure 7.4. We can see that the Cox model performs better at the beginning, but at the end, the FHT model has better predictive performance. We calculate the integrated Brier score (seen in subsection 5.3.3). We find that the integrated Brier score for the full FHT model is 0.0679, while the estimated CoxBoost model attains 0.0673, i.e., almost entirely the same. For reference, the estimated FHT null model achieves 0.1226, which is almost the double.

## 7.5 Analysis of 100 train/test splits

Bøvelstad et al. (2009) generated 50 random splits of training and test sets from the data, to see the distribution. We now generate 100 splits of training and test sets, in the same manner. We first estimate parameters based on the training set, and then calculate the model's difference of deviance, on the test set, using the parameters estimated on the training set.

Figure 7.4: Brier scores for Cox and both.

fig:brier-cox-both



### 7.5.1 Difference of deviance results

We now consider the difference of deviance across all 100 splits of training and test sets. The main measure of interest is the mean of difference of deviance. It is -47.217 for the full model, and -19.890 for the clinical model, and -35.533 for the genomic model. See Figure 7.5 for a boxplot comparing these. Interestingly, the median for the clinical model is -21.600, while it is 4.009 for the genomic. So the median of the clinical model is lower than the median of the genomic model, but the *mean* of the clinical model is higher than the mean of the genomic model. Since the mean is more sensitive to extreme values, and more extreme negative values than extreme positive values will here push the mean more down, than the median will be. It seems, therefore, that the genomic model sometimes achieves very good performance with regard to the difference of deviance. The clinical model, on the other hand, often does not achieve that high of a deviance, but it is more stable.

### 7.5.2 Integrated Brier scores results

We now calculate the integrated Brier scores for all 100 splits, for all of the mentioned methods. A boxplot can be seen in Figure 7.6. For the FHT models, the full model performs best on average, with a mean of 0.0737, the clinical has 0.0791, genomic 0.0987. For reference, the FHT null model, using only the maximum likelihood intercepts, gets 0.1185. We might at least be relieved by the fact that the full model performs best, since it is able to incorporate all information. This also shows that the model should be a good fit for survival data such as what we have used here.

The FHT models are, however, beaten by boosted Cox regression models. The regular Cox model has a mean of 0.0692, while the mandatory Cox model has 0.0574.

Figure 7.5: Boxplot for difference in deviance for different variants of the FHT model.

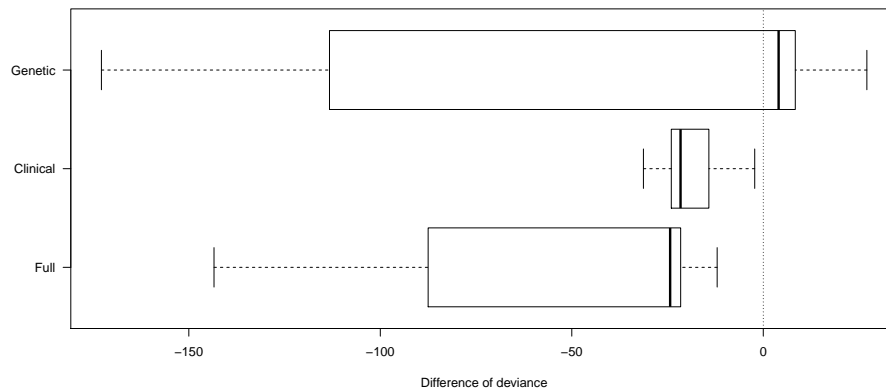


fig:  
neuroblastoma-  
deviances

Figure 7.6: Boxplot of integrated Brier scores.

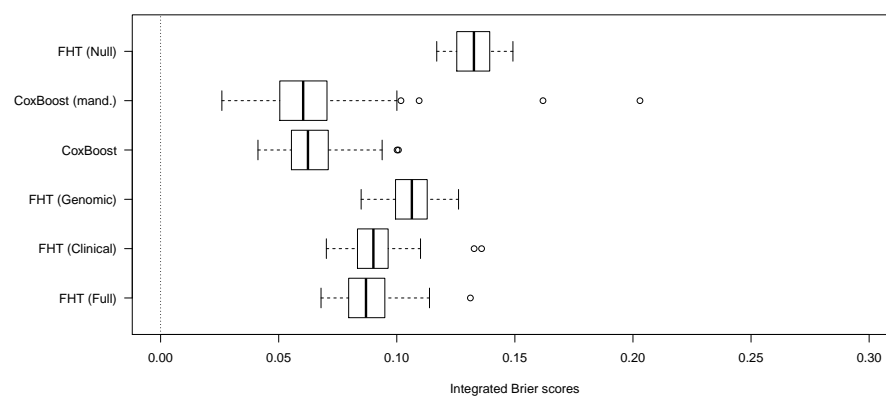


fig:  
neuroblastoma-  
integrated-brier

## Chapter 8

# Discussion and future work

sec:discussion

Future work.

One fruitful extension of FHTBoost is to add other base learners. We might try using regularized splines to achieve more.





# Appendices



## Appendix A

### Appendix 1: Differentiating the IG FHT

appendix

First we have the likelihood,

$$L(y_0, \mu) = \prod_{i=1}^n \left( \frac{y_0}{\sqrt{2\pi\sigma^2 t_i^3}} \exp \left[ -\frac{(y_0 + \mu t_i)^2}{2\sigma^2 t_i} \right] \right)^{\delta_i} \times \left[ 1 - \Phi \left( -\frac{y_0 + \mu t_i}{\sqrt{\sigma^2 t_i}} \right) - \exp \left( -\frac{2y_0\mu}{\sigma^2} \right) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right]^{1-\delta_i}, \quad (\text{A.1})$$

with respect to parameters  $\mu$ , and  $y_0$ . First, note that for any cumulative distribution function  $F$  that is symmetric around 0, and for  $x \in \mathbb{R}$ ,

$$F(x) = 1 - (1 - F(x)) = 1 - F(-x), \quad (\text{A.2})$$

and so in particular,

$$\Phi(x) = 1 - (1 - \Phi(x)) = 1 - \Phi(-x), \quad (\text{A.3})$$

and thus we can rewrite (A.1) as

$$L(y_0, \mu) = \prod_{i=1}^n \left( \frac{y_0}{\sqrt{2\pi\sigma^2 t_i^3}} \exp \left[ -\frac{(y_0 + \mu t_i)^2}{2\sigma^2 t_i} \right] \right)^{\delta_i} \times \left[ \Phi \left( \frac{y_0 + \mu t_i}{\sqrt{\sigma^2 t_i}} \right) - \exp \left( -\frac{2y_0\mu}{\sigma^2} \right) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right]^{1-\delta_i}. \quad (\text{A.4})$$

It is easier to work with the log likelihood, so we take the log of (A.4) and get

$$l(y_0, \mu) = \sum_{i=1}^n \delta_i \left( \ln y_0 - \frac{1}{2} \ln(2\pi\sigma^2 t_i^3) - \frac{(y_0 + \mu t_i)^2}{2\sigma^2 t_i} \right) + (1 - \delta_i) \ln \left( \Phi \left( \frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}} \right) - \exp \left( -\frac{2y_0\mu}{\sigma^2} \right) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right) \quad (\text{A.5})$$

To make things easier, let us introduce some intermediate functions here. Let

$$\ln f_i(y_0, \mu) = \ln y_0 - \frac{1}{2} \ln(2\pi\sigma^2 t_i^3) - \frac{(y_0 + \mu t_i)^2}{2\sigma^2 t_i} \quad (\text{A.6})$$

and

$$S_i(y_0, \mu) = \Phi\left(\frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}}\right) - \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right). \quad (\text{A.7})$$

So we get

$$l(y_0, \mu) = \sum_{i=1}^n \delta_i \ln f_i(y_0, \mu) + (1 - \delta_i) \ln S_i(y_0, \mu) \quad (\text{A.8})$$

Thus we see that the partial derivatives are

$$\frac{\partial}{\partial y_0} l(y_0, \mu) = \sum_{i=1}^n \delta_i \frac{\partial}{\partial y_0} \ln f_i(y_0, \mu) + (1 - \delta_i) \frac{\frac{\partial}{\partial y_0} S_i(y_0, \mu)}{S_i(\theta)} \quad (\text{A.9})$$

and

$$\frac{\partial}{\partial \mu} l(y_0, \mu) = \sum_{i=1}^n \delta_i \frac{\partial}{\partial \mu} \ln f_i(y_0, \mu) + (1 - \delta_i) \frac{\frac{\partial}{\partial \mu} S_i(y_0, \mu)}{S_i(\theta)} \quad (\text{A.10})$$

We take these one by one

$$\frac{\partial}{\partial y_0} \ln f_i(y_0, \mu) = \frac{1}{y_0} - \frac{y_0 + \mu t_i}{\sigma^2 t_i} \quad (\text{A.11})$$

$$\frac{\partial}{\partial \mu} \ln f_i(y_0, \mu) = -\frac{y_0 + \mu t_i}{\sigma^2} \quad (\text{A.12})$$

$$\begin{aligned} \frac{\partial}{\partial y_0} S_i(y_0, \mu) &= \frac{1}{\sqrt{\sigma^2 t_i}} \phi\left(\frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}}\right) + \frac{2\mu}{\sigma^2} \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \\ &\quad + \frac{1}{\sqrt{\sigma^2 t_i}} \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \end{aligned} \quad (\text{A.13})$$

$$\begin{aligned} \frac{\partial}{\partial \mu} S_i(y_0, \mu) &= \frac{t_i}{\sqrt{\sigma^2 t_i}} \phi\left(\frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}}\right) + \frac{2y_0}{\sigma^2} \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \\ &\quad - \frac{t_i}{\sqrt{\sigma^2 t_i}} \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \end{aligned} \quad (\text{A.14})$$

Hence

$$\begin{aligned} &\frac{\partial}{\partial y_0} l(y_0, \mu) \\ &= \sum_{i=1}^n \left( \delta_i \left( \frac{1}{y_0} - \frac{y_0 + \mu t_i}{\sigma^2 t_i} \right) + (1 - \delta_i) \left[ \frac{1}{\sqrt{\sigma^2 t_i}} \phi\left(\frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}}\right) + \frac{2\mu}{\sigma^2} \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \right. \right. \\ &\quad \left. \left. + \frac{1}{\sqrt{\sigma^2 t_i}} \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \right] \left[ \Phi\left(\frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}}\right) - \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left(\frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}}\right) \right]^{-1} \right) \end{aligned} \quad (\text{A.15})$$

and

$$\begin{aligned}
& \frac{\partial}{\partial \mu} l(y_0, \mu) \\
&= \sum_{i=1}^n \left( \delta_i \left( -\frac{y_0 + \mu t_i}{\sigma^2} \right) + (1 - \delta_i) \left[ \frac{t_i}{\sqrt{\sigma^2 t_i}} \phi \left( \frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}} \right) + \frac{2y_0}{\sigma^2} \exp \left( -\frac{2y_0 \mu}{\sigma^2} \right) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right. \right. \\
&\quad \left. \left. - \frac{t_i}{\sqrt{\sigma^2 t_i}} \exp \left( -\frac{2y_0 \mu}{\sigma^2} \right) \phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right] \left[ \Phi \left( \frac{\mu t_i + y_0}{\sqrt{\sigma^2 t_i}} \right) - \exp \left( -\frac{2y_0 \mu}{\sigma^2} \right) \Phi \left( \frac{\mu t_i - y_0}{\sqrt{\sigma^2 t_i}} \right) \right]^{-1} \right) \\
&\hspace{15em} (\text{A.16})
\end{aligned}$$



# Bibliography

aalen1978	Aalen, O. (1978). Nonparametric inference for a family of counting processes. <i>Ann. Statist.</i> , 6(4):701–726.
ABG	Aalen, O., Borgan, O., and Gjessing, H. (2008). <i>Survival and Event History Analysis: A Process Point of View</i> . Statistics for Biology and Health. Springer New York.
aalengjessing2001	Aalen, O. O. and Gjessing, H. K. (2001). Understanding the shape of the hazard rate: a process point of view (with comments and a rejoinder by the authors). <i>Statist. Sci.</i> , 16(1):1–22.
bauer-kohavi	Bauer, E. and Kohavi, R. (1999). An empirical comparison of voting classification algorithms: Bagging, boosting, and variants. <i>Machine Learning</i> , 36(1):105–139.
BinderSchumacher2008	Binder, H. and Schumacher, M. (2008). Adapting prediction error estimates for biased complexity selection in high-dimensional bootstrap samples. <i>Statistical applications in genetics and molecular biology</i> , 7 1:Article12.
bovelstad2009	Bøvelstad, H. M., Nygård, S., and Borgan, Ø. (2009). Survival prediction from clinico-genomic models - a comparative study. <i>BMC Bioinformatics</i> , 10(1):413.
breiman1998	Breiman, L. (1998). Arcing classifier (with discussion and a rejoinder by the author). <i>Ann. Statist.</i> , 26(3):801–849.
brier1950	Brier, G. W. (1950). Verification of Forecasts expressed in terms of probability. <i>Monthly Weather Review</i> , 78(1):1–3.
bovelstadborgan	Bøvelstad, H. M. and Borgan, Ø. (2011). Assessment of evaluation criteria for survival prediction from genomic data. <i>Biometrical Journal</i> , 53(2):202–216.
buhlmann2006	Bühlmann, P. (2006). Boosting for high-dimensional linear models. <i>Ann. Statist.</i> , 34(2):559–583.
buhlmann2007	Bühlmann, P. and Hothorn, T. (2007). Boosting algorithms: Regularization, prediction and model fitting. <i>Statist. Sci.</i> , 22(4):477–505.
buhlmann-yu	Bühlmann, P. and Yu, B. (2003). Boosting with the l2 loss. <i>Journal of the American Statistical Association</i> , 98(462):324–339.
caroni2017	Caroni, C. (2017). <i>First Hitting Time Regression Models</i> . John Wiley & Sons, Inc.

chhikara1988

Chhikara, R. (1988). *The Inverse Gaussian Distribution: Theory: Methodology, and Applications*. Statistics: A Series of Textbooks and Monographs. Taylor & Francis.

copas1983

Copas, J. B. (1983). Regression, prediction and shrinkage. *Journal of the Royal Statistical Society. Series B (Methodological)*, 45(3):311–354.

cox1965

Cox, D. and Miller, H. (1965). *The theory of stochastic processes*. Wiley publications in statistics. Wiley.

cox-model

Cox, D. R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society. Series B (Methodological)*, 34(2):187–220.

saddlepoints

Dauphin, Y. N., Pascanu, R., Gulcehre, C., Cho, K., Ganguli, S., and Bengio, Y. (2014). Identifying and attacking the saddle point problem in high-dimensional non-convex optimization. In *Proceedings of the 27th International Conference on Neural Information Processing Systems - Volume 2*, NIPS’14, pages 2933–2941, Cambridge, MA, USA. MIT Press.

DeBin2016

De Bin, R. (2016). Boosting in cox regression: a comparison between the likelihood-based and the model-based approaches with focus on the r-packages coxboost and mboost. *Computational Statistics*, 31(2):513–531.

eaton-whitmore

Eaton, W. W. and Whitmore, G. A. (1977). Length of stay as a stochastic process: A general approach and application to hospitalization for schizophrenia. *The Journal of Mathematical Sociology*, 5(2):273–292.

efron1975

Efron, B. (1975). Biased versus unbiased estimation. *Advances in Mathematics*, 16(3):259 – 277.

efron2004

Efron, B., Hastie, T., Johnstone, I., and Tibshirani, R. (2004). Least angle regression. *Ann. Statist.*, 32(2):407–499.

adaboost

Freund, Y. and Schapire, R. E. (1996). Experiments with a new boosting algorithm. In *Proceedings of the Thirteenth International Conference on International Conference on Machine Learning*, ICML’96, pages 148–156, San Francisco, CA, USA. Morgan Kaufmann Publishers Inc.

friedman2001

Friedman, J. H. (2001). Greedy function approximation: A gradient boosting machine. *Ann. Statist.*, 29(5):1189–1232.

bovelstad2007

Frigessi, A., Størvold, H., Bøvelstad, H., Aldrin, M., Borgan, Ø., Lingjærde, O., and Nygård, S. (2007). Predicting survival from microarray data—a comparative study. *Bioinformatics*, 23(16):2080–2087.

graf

Graf, E., Schmoor, C., Sauerbrei, W., and Schumacher, M. (1999). Assessment and comparison of prognostic classification schemes for survival data. *Statistics in Medicine*, 18(17-18):2529–2545.

hastie2007

Hastie, T. (2007). Comment: Boosting algorithms: Regularization, prediction and model fitting. *Statist. Sci.*, 22(4):513–515.

hastie1986

Hastie, T. and Tibshirani, R. (1986). Generalized additive models. *Statist. Sci.*, 1(3):297–310.



gam-book	Hastie, T. and Tibshirani, R. (1990). <i>Generalized Additive Models</i> . Chapman & Hall/CRC Monographs on Statistics & Applied Probability. Taylor & Francis.
ESL	Hastie, T., Tibshirani, R., and Friedman, J. (2009). <i>The Elements of Statistical Learning: Data Mining, Inference, and Prediction</i> . Springer series in statistics. Springer.
kaplan-meier	Kaplan, E. L. and Meier, P. (1958). Nonparametric estimation from incomplete observations. <i>Journal of the American Statistical Association</i> , 53(282):457–481.
kearnsvaliant	Kearns, M. and Valiant, L. G. (1989). Cryptographic limitations on learning boolean formulae and finite automata. In <i>Proceedings of the Twenty-first Annual ACM Symposium on Theory of Computing</i> , STOC '89, pages 433–444, New York, NY, USA. ACM.
kneib2013	Kneib, T. (2013). Beyond mean regression. <i>Statistical Modelling</i> , 13(4):275–303.
kohavi	Kohavi, R. (1995). A study of cross-validation and bootstrap for accuracy estimation and model selection. In <i>Proceedings of the 14th International Joint Conference on Artificial Intelligence - Volume 2</i> , IJCAI'95, pages 1137–1143, San Francisco, CA, USA. Morgan Kaufmann Publishers Inc.
lachenbruch	Lachenbruch, P. A. and Mickey, M. R. (1968). Estimation of error rates in discriminant analysis. <i>Technometrics</i> , 10(1):1–11.
lancaster	Lancaster, T. (1972). A stochastic model for the duration of a strike. <i>Journal of the Royal Statistical Society. Series A (General)</i> , 135(2):257–271.
lawless2011	Lawless, J. (2011). <i>Statistical Models and Methods for Lifetime Data</i> . Wiley Series in Probability and Statistics. Wiley.
lawless2004	Lawless, J. and Crowder, M. (2004). Covariates and random effects in a gamma process model with application to degradation and failure. <i>Lifetime Data Analysis</i> , 10(3):213–227.
leewhitmore2004a	Lee, M.-L. and Whitmore, G. A. (2003). First hitting time models for lifetime data. <i>Handbook of Statistics</i> , 23:537–543.
leewhitmore2006	Lee, M.-L. T. and Whitmore, G. A. (2006). Threshold regression for survival analysis: Modeling event times by a stochastic process reaching a boundary. <i>Statist. Sci.</i> , 21(4):501–513.
leewhitmore2004	Lee, M. T., Whitmore, G. A., Laden, F., Hart, J. E., and Garshick, E. (2004). Assessing lung cancer risk in railroad workers using a first hitting time regression model. <i>Environmetrics</i> , 15(5):501–512.
maller1996survival	Maller, R. and Zhou, X. (1996). <i>Survival Analysis with Long-Term Survivors</i> . Wiley Series in Child Care and Protection. Wiley.
mayr14a	Mayr, A., Binder, H., Gefeller, O., and Schmid, M. (2014a). The evolution of boosting algorithms. from machine learning to statistical modelling. <i>Methods of Information in Medicine</i> , 53(6):419–427.

mayr14b	Mayr, A., Binder, H., Gefeller, O., and Schmid, M. (2014b). Extending statistical boosting. an overview of recent methodological developments. <i>Methods of Information in Medicine</i> , 53(6):428–435.
gamboostlss-paper	Mayr, A., Fenske, N., Hofner, B., Kneib, T., and Schmid, M. (2012a). Generalized additive models for location, scale and shape for high dimensional data—a flexible approach based on boosting. <i>Journal of the Royal Statistical Society. Series C (Applied Statistics)</i> , 61(3):403–427.
mayr-hofner	Mayr, A., Hofner, B., and Schmid, M. (2012b). The importance of knowing when to stop. a sequential stopping rule for component-wise gradient boosting. <i>Methods of Information in Medicine</i> , 51(2):178–186.
mayr17	Mayr, A., Hofner, B., Waldmann, E., Hepp, T., Meyer, S., and Gefeller, O. (2017). An update on statistical boosting in biomedicine. <i>Computational and Mathematical Methods in Medicine</i> , 2017:1–12.
nelson	Nelson, W. (1972). Theory and applications of hazard plotting for censored failure data. <i>Technometrics</i> , 14(4):945–966.
oberthuer-data	Oberthuer, A., Kaderali, L., Kahlert, Y., Hero, B., Westermann, F., Berthold, F., Brors, B., Eils, R., and Fischer, M. (2008). Subclassification and individual survival time prediction from gene expression data of neuroblastoma patients by using caspar. <i>Clinical cancer research : an official journal of the American Association for Cancer Research</i> , 14:6590–6601.
Rlang	R Core Team (2013). <i>R: A Language and Environment for Statistical Computing</i> . R Foundation for Statistical Computing, Vienna, Austria.
gamlss	Rigby, R. A. and Stasinopoulos, D. M. (2005). Generalized additive models for location, scale and shape. <i>Journal of the Royal Statistical Society. Series C (Applied Statistics)</i> , 54(3):507–554.
schmid-hothorn	Schmid, M. and Hothorn, T. (2008). Boosting additive models using component-wise p-splines. <i>Comput. Stat. Data Anal.</i> , 53(2):298–311.
schmid	Schmid, M., Potapov, S., Pfahlerberg, A., and Hothorn, T. (2010). Estimation and regularization techniques for regression models with multidimensional prediction functions. <i>Statistics and Computing</i> , 20(2):139–150.
seibold	Seibold, H., Bernau, C., Boulesteix, A.-L., and De Bin, R. (2018). On the choice and influence of the number of boosting steps for high-dimensional linear cox-models. <i>Computational Statistics</i> , 33(3):1195–1215.
singpurwalla1995	Singpurwalla, N. D. (1995). Survival in dynamic environments. <i>Statist. Sci.</i> , 10(1):86–103.
gamlssR	Stasinopoulos, D. M. and Rigby, R. A. (2007). Generalized additive models for location scale and shape (gamlss) in r. <i>Journal of Statistical Software</i> , 023(i07).
thomas2018	Thomas, J., Mayr, A., Bischl, B., Schmid, M., Smith, A., and Hofner, B. (2018). Gradient boosting for distributional regression: faster tuning and improved variable selection via noncyclical updates. <i>Statistics and Computing</i> , 28(3):673–687.

lasso	Tibshirani, R. (1996). Regression shrinkage and selection via the lasso. <i>Journal of the Royal Statistical Society. Series B (Methodological)</i> , 58(1):267–288.
whitmore1975	Whitmore, G. A. (1975). The inverse gaussian distribution as a model of hospital stay. <i>Health services research</i> , 10:297–302.
whitmore1986	Whitmore, G. A. (1986). First-passage-time models for duration data: Regression structures and competing risks. <i>Journal of the Royal Statistical Society. Series D (The Statistician)</i> , 35(2):207–219.
whitmore1995	Whitmore, G. A. (1995). Estimating degradation by a wiener diffusion process subject to measurement error. <i>Lifetime Data Analysis</i> , 1(3):307–319.
threg	Xiao, T., Whitmore, G., He, X., and Lee, M.-L. (2015). The r package threg to implement threshold regression models. <i>Journal of Statistical Software, Articles</i> , 66(8):1–16.