

Boosting the First-Hitting-Time Regression Model

Vegard Stikbakke

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CHAPTER 1

Introduction

sec:intro

In this thesis, we work with boosting for regression in the first-hitting-time model. First-hitting-time is a model in survival analysis which serves as an alternative to the proportional hazards model, typically known as Cox regression. Developments in FHT regression are relatively recent, and there has to our knowledge been no attempt at tackling it in the high-dimensional case, in which boosting is an appropriate choice of method.

CHAPTER 2

First hitting time regression models

2.1 Survival analysis and time-to-event models

sec:survival

In many fields, it is interesting to consider the lifetime of some entity. A lifetime ends when an event occurs. We are usually interested in inferring things about this lifetime, and what it depends upon. In medical fields, this is called survival analysis, while in engineering it is called reliability analysis. In the former case, we consider the lifetime of patients or the length of a hospital stay after some treatment. In the latter, we consider, e.g., the time before a component of a system breaks and must be replaced.

The time-to-event T is a continuous, non-negative random variable $T \sim f(t)$, $t > 0$, for some probability density function f . We are particularly interested in two things related to T :

1. The survival function $S(t)$ – the probability of an individual having survived until time t . Note that $S(t) = 1 - F(t)$, where F is the cumulative density function of f .
2. The hazard function $h(t)$ – the probability of the event happening at time t . Note that this is conditional on surviving until time t , and is defined as $h(t) = \frac{f(t)}{S(t)}$.

Regression

sec:surv-reg

To find out anything interesting, we need to be able to do regression on covariates. Given a sample of n independent observations $\{t_i, \mathbf{x}_i, \delta_i, i = 1, \dots, n\}$, where individual i has covariates \mathbf{x}_i , lifetime t_i and censoring indicator $\delta_i, i = 1, \dots, n$, which is 1 if the event has happened, and 0 if not. From Caroni 2017, p. 10, the likelihood is given by

$$L(\boldsymbol{\theta}|\mathbf{x}_1, \dots, \mathbf{x}_n) = \prod_{i=1}^n f(t_i|\mathbf{x}_i, \boldsymbol{\theta})^{\delta_i} S(t_i|\mathbf{x}_i, \boldsymbol{\theta})^{1-\delta_i} \quad (2.1)$$

{eq:surv-lik}

Proportional hazards

The most used method for doing regression on survival data is the Cox proportional hazards (PH) regression. It is based on an assumption that is often

2. First hitting time regression models

called the PH property or the PH assumption, namely that

$$h(t|x) = h_0(t)g(\mathbf{x}), \quad (2.2)$$

where $h_0(t)$ is a baseline hazard function.

more about baseline hazard?

This property states that at any two time points t_1 and t_2 , the ratio between the hazard functions of any two \mathbf{x}_1 and \mathbf{x}_2 will be the same:

$$\frac{h(t_1|x_1)}{h(t_1|x_2)} = \frac{h(t_2|x_1)}{h(t_2|x_2)} \quad (2.3)$$

This is a strong assumption to make, and it will rarely be the case in practice (Lee and Whitmore 2010). However, many times Cox regression will work well in practice.

how to rephrase?

really? or argue why!

2.2 The first hitting time model

sec: fht

Revisiting the examples of the two lifetime settings, it may in both cases be natural to imagine that the event happens as a process reaches a threshold. Then one way to model the time-to-event is to model the process itself, and look at the time it takes for the process to reach this threshold, at which point the event is triggered. Lee and Whitmore 2006 is a thorough review on the first hitting time model, and Caroni 2017 is a book which covers many aspects of it. We continue by describing the first hitting time model.

An first hitting time model has two main components.

1. A stochastic process $\{Y(t), t \in \mathcal{T}, y \in \mathcal{Y}\}$, with $Y(0) = y_0$.
2. A boundary set, $B \subset \mathcal{Y}$, where $y_0 \notin B$

The first hitting time is the first time the process reaches the boundary set. Formally, the first hitting time is a stochastic variable S , which is defined as

$$S = \inf\{t: Y(t) \in B\}$$

Typically, one will consider a process with boundary $B = 0$. The event then occurs if and when the process $\{Y\}$ reaches 0 at $y(S)$. Note that it is possible that $P(S < \infty) < 1$.

what did you say about this again?

justify

The first hitting time model is conceptually appealing and does not require the PH assumption, and is hence more flexible. In fact, the PH model may be obtained by constructing the first hitting time model in a specific way (Lee and Whitmore 2010).

Different choices of processes lead to different kinds of distributions for the first hitting time. We now look at a common choice of the process.

Wiener process

sec: wiener

The Wiener process, also known as the standard Brownian motion process, is a process which is continuous in time and space, and has the properties (Caroni 2017, p. 61) that

2.3. First hitting time regression based on underlying Wiener process

- $Y(t)$ has independent increments, such that $Y(t_2) - Y(t_1)$ and $Y(t_4) - Y(t_3)$ are independent for any disjoint intervals, and
- for any interval (t_1, t_2) ,

$$Y(t_2) - Y(t_1) \sim N(\mu(t_2 - t_1), \sigma^2(t_2 - t_1)).$$

This is a process which will both increase and decrease. However, if we want a monotonic restriction on the movement of the process, we may use a gamma process.

Gamma process

The gamma process is suitable for modelling a process which we would require to be monotonic, typically a physical degradation, i.e. where the damage cannot mend itself, unlike a patient's health. The first-hitting-time that arises from the gamma process is inverse gamma. (Lee and Whitmore 2006, p. 503.)

[make this into a separate section?]

inline

Other choices of processes include Markov chain state models, the Bernoulli process, and the Ornstein-Uhlenbeck process.

2.3 First hitting time regression based on underlying Wiener process

The first hitting time of the Wiener process (section 2.2) follows an inverse Gaussian distribution (derivation in Chhikara 1988, pp. 23-29):

also derive more clearly in appendix?

$$f(t|y_0, \mu, \sigma^2) = \frac{y_0}{\sqrt{2\pi\sigma^2 t^3}} \exp\left[-\frac{(y_0 + \mu t)^2}{2\sigma^2 t}\right] \quad (2.4)$$

{eq:fht-ig}

If μ is positive, $Y(t) \leq 0$ is not certain to occur. Note also that this model is over-parameterized, because Y has an arbitrary scale, so we can without loss of generality set $\sigma^2 = 1$.

more!

While μ and y_0 have simple interpretations in terms of the underlying process, they do not in terms of the lifetime distribution. The mean lifetime is $\frac{y_0}{|\mu|}$, and the variance is $\frac{y_0}{|\mu|^3}$. (Caroni 2017, p. 62.)

The cumulative distribution function of the FHT is (from Xiao et al. 2015, p. 7)

$$F(t|\mu, \sigma^2, y_0) = \Phi\left[-\frac{y_0 + \mu t}{\sqrt{\sigma^2 t}}\right] + \exp\left(-\frac{2y_0\mu}{\sigma^2}\right) \Phi\left[\frac{\mu t - y_0}{\sqrt{\sigma^2 t}}\right], \quad (2.5)$$

{eq:cumulative}

where $\Phi(x)$ is the cumulative of the standard normal, i.e.,

$$\Phi(x) = \int_{-\infty}^x \exp(-y^2/2)/\sqrt{2\pi} \, dy. \quad (2.6)$$

2. First hitting time regression models

Regression

We may introduce effects from covariates by allowing μ and y_0 to depend on covariates \mathbf{x} . Suitable models are

$$\begin{aligned}\mu &= \beta^T \mathbf{x} \\ \ln y_0 &= \gamma^T \mathbf{z}\end{aligned}\tag{2.7}$$

{eq:coeffs}

where β and γ are vectors of regression coefficients. Note that we may let \mathbf{x} and \mathbf{z} share none, some, or all elements.

2.4 Likelihood

sec:lik

In section 2.1, we stated the likelihood of lifetime regression models in (2.1). For an inverse gaussian FHT this then becomes (inserting (2.4) and (2.5) into (2.1), and since $S(t) = 1 - F(t)$)

$$\begin{aligned}L(\theta|\mathbf{x}_1, \dots, \mathbf{x}_n) &= \left(\frac{y_0}{\sqrt{2\pi\sigma^2 t^3}} \exp \left[-\frac{(y_0 + \mu t)^2}{2\sigma^2 t} \right] \right)^{\delta_i} \\ &\times \left[1 - \Phi \left(-\frac{y_0 + \mu t}{\sqrt{\sigma^2 t}} \right) - \exp \left(-\frac{2y_0\mu}{\sigma^2} \right) \Phi \left(\frac{\mu t - y_0}{\sqrt{\sigma^2 t}} \right) \right]^{1-\delta_i}\end{aligned}\tag{2.8}$$

{eq:fht-lik}

Since we let $\sigma^2 = 1$, this simplifies to

$$\begin{aligned}L(\theta|\mathbf{x}_1, \dots, \mathbf{x}_n) &= \left(\frac{y_0}{\sqrt{2\pi t^3}} \exp \left[-\frac{(y_0 + \mu t)^2}{2t} \right] \right)^{\delta_i} \\ &\times \left[1 - \Phi \left(-\frac{y_0 + \mu t}{\sqrt{t}} \right) - \exp(-2y_0\mu) \Phi \left(\frac{\mu t - y_0}{\sqrt{t}} \right) \right]^{1-\delta_i}\end{aligned}\tag{2.9}$$

We can now substitute the covariates in (2.7) into this. To find optimal parameters, we use numerical maximum likelihood methods. However, this is only feasible in the low-dimensional case, since it will optimize the entire parameter space at once. Therefore it is necessary to develop methods which can deal with high-dimensional cases. That is what we intend to do in the main part of the thesis.

is this correct?

2.5 The threg package

There exists an R package **threg** for fitting regression with inverse gaussian FHT, described in Xiao et al. 2015. We provide a small example here, which is the one described in the help pages of the package.

```
1 library(threg)
2 data("lkr")
3 lkr$f.treatment2=factor(lkr$treatment2)
4 # head(lkr)
5 fit <- threg(Surv(weeks, relapse) ~ f.treatment2|f.treatment2,
6             data=lkr)
```

Which provides the following output

Call:

```
threg(formula = Surv(weeks, relapse) ~ f.treatment2 | f.treatment2,
      data = lkr)
```

	coef	se(coef)	z	p
lny0: (Intercept)	2.0097844	0.1705141	11.786620	0.0e+00
lny0: f.treatment21	-1.2739233	0.2441633	-5.217504	1.8e-07
mu: (Intercept)	-0.5886165	0.1340126	-4.392246	1.1e-05
mu: f.treatment21	0.5888365	0.1535081	3.835866	1.3e-04

Log likelihood =-104.64, AIC =217.28

Here we fit an inverse gaussian FHT model where

$$\ln y_0 = \mu = \beta_0 + \beta_1 I(\text{treatment2} = 1)$$

What the **threg** function in the package of the same name does, is essentially to set up the log likelihood and use the numerical optimization function **nlm** to find the optimal parameters.

Recreating

We recreate the above example in plain R code.

```
1 library(threg)
2 data("lkr")
3 lkr$f.treatment2=factor(lkr$treatment2)
4 fit <- threg(Surv(weeks, relapse) ~ f.treatment2|f.treatment2,
5             data=lkr)
6
7 library(dplyr)
8 #tbl <- select(.data=lkr, weeks, relapse, f.treatment2)
9 tbl <- data.frame(lkr$weeks, lkr$relapse, lkr$f.treatment2,
10                 row_names = c("weeks", "relapse", "f.treatment2"))
11 names(tbl)[names(tbl) == "lkr.weeks"] <- "weeks"
12 names(tbl)[names(tbl) == "lkr.relapse"] <- "relapse"
13 names(tbl)[names(tbl) == "lkr.f.treatment2"] <- "f.treatment2"
14
15 to_optimize <- function(params) {
16   total_loglikelihood <- 0
17
18   gamma <- params[1:2]
19   beta <- params[3:4]
20
21   for (i in 1:n) {
22     tbl_i <- tbl[i, ]
23     event <- tbl_i$relapse
24     t_i <- tbl_i$weeks
25     is_treated <- as.integer(tbl_i$f.treatment2)-1
26     X_i <- c(1, is_treated)
27     y0_i <- exp(sum(gamma*X_i))
28     mu_i <- sum(beta*X_i)
```


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```
28   log_f_i <- log(y0_i) - 0.5*log(2*pi*t_i^3) - ((y0_i +
      mu_i*t_i)^2)/(2*t_i)
29   log_S_i <- log(1 - pnorm(-(y0_i+mu_i*t_i)/sqrt(t_i)) -
      exp(-2*y0_i*mu_i)*pnorm((mu_i*t_i-y0_i)/sqrt(t_i)))
30   loglik_i <- event*log_f_i + (1 - event)*log_S_i
31   total_loglikelihood <- total_loglikelihood + loglik_i
32 }
33 return(-total_loglikelihood)
34 }
35
36 params_from_threg <- c(2.0098, -1.2739, -0.5886, 0.5886)
37 threg_value <- -to_optimize(params_from_threg)
38
39 initial_params <- c(1, 1, 1, 1)
40
41 best <- nlm(to_optimize, initial_params)
42 params_from_best <- best$estimate
43 best_value <- -best$minimum
44 print(best_value)
45 print(threg_value)
```

We can also inspect the parameters we found and see that we did indeed find the optimal parameters.

Appendices

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