A flexible approach to time-to-event data analysis using case-base sampling

Jesse Islam
McGill University

July 11, 2019

Motivating example

- Meet Justin.

Motivating example

- Meet Justin.
    - Age: 56

Motivating example

- Meet Justin.
    - Age: 56
    - Worried about his prostate.

Motivating example

- Meet Justin.
    - Age: 56
    - Worried about his prostate.
    - What is Justin's two year risk of death due to prostate cancer?

Popular methods in time-to-event analysis

- In disease etiology, we tend to make use of the proportional hazards hypothesis.

Popular methods in time-to-event analysis

- In disease etiology, we tend to make use of the proportional hazards hypothesis.
    - Cox Regression

Popular methods in time-to-event analysis

- In disease etiology, we tend to make use of the proportional hazards hypothesis.
    - Cox Regression
- When we want the absolute risk:

Popular methods in time-to-event analysis

- In disease etiology, we tend to make use of the proportional hazards hypothesis.
    - Cox Regression
- When we want the absolute risk:
    - Parametric models

Popular methods in time-to-event analysis

- In disease etiology, we tend to make use of the proportional hazards hypothesis.
  - Cox Regression
- When we want the absolute risk:
  - Parametric models
  - Breslow estimator

Motivations for a new method

- Julien and Hanley found that survival analysis rarely produces prognostic functions, even though the software is widely available in cox regression packages. [1]

Motivations for a new method

- Julien and Hanley found that survival analysis rarely produces prognostic functions, even though the software is widely available in cox regression packages. [1]
- They believe the stepwise nature is the reason, as it reduces interpretability. [1]

Motivations for a new method

- Julien and Hanley found that survival analysis rarely produces prognostic functions, even though the software is widely available in cox regression packages. [1]
- They believe the stepwise nature is the reason, as it reduces interpretability. [1]
- Want to easily model non-proportional hazards. [1]

Motivations for a new method

- Julien and Hanley found that survival analysis rarely produces prognostic functions, even though the software is widely available in cox regression packages. [1]
- They believe the stepwise nature is the reason, as it reduces interpretability. [1]
- Want to easily model non-proportional hazards. [1]
- A streamlined approach for reaching a **smooth absolute risk** curve. [1]

Dr. Cox's perspective

Reid: How do you feel about the cottage industry that's grown up around it [the Cox model]?
Cox: Don't know, really. In the light of some of the further results one knows since, I think I would normally want to tackle problems parametrically, so I would take the underlying hazard to be a Weibull or something. I'm not keen on nonparametric formulations usually.
Reid: So if you had a set of censored survival data today, you might rather fit a parametric model, even though there was a feeling among the medical statisticians that that wasn't quite right.
Cox: That's right, but since then various people have shown that the answers are very insensitive to the parametric formulation of the underlying distribution [see, e.g., Cox and Oakes, Analysis of Survival Data, Chapter 8.5]. And if you want to do things like predict the outcome for a particular patient, it's much more convenient to do that parametrically.

European Randomized Study of Prostate Cancer Screening (ERSPC) Data

- ~150 000 men ages 55-69. [4]

The European Randomized Study of Screening for Prostate Cancer – Prostate Cancer Mortality at 13 Years of Follow-up

Fritz H. Schröder[1], **Jonas Hugosson**[2], **Monique J. Roobol**[1], **Teuvo L.J. Tammela**[3], **Marco Zappa**[4], **Vera Nelen**[5], **Maciej Kwiatkowski**[6,7], **Marcos Lujan**[8,9], **Lissa Määttänen**[10], **Hans Lilja**[11,12,13], **Louis J. Denis**[14], **Franz Recker**[6], **Alvaro Paez**[15,16], **Chris H. Bangma**[1], **Sigrid Carlsson**[2,11], **Donella Puliti**[4], **Arnauld Villers**[17], **Xavier Rebillard**[18], **Matti Hakama**[10,19], **Ulf-Hakan Stenman**[20], **Paula Kujala**[21], **Kimmo Taari**[22], **Gunnar Aus**[23], **Andreas Huber**[24], **Theo van der Kwast**[25], **Ron H.N. van Schaik R**[26], **Harry J. de Koning**[27], **Sue M. Moss**[28], **Anssi Auvinen**[19], and **for the ERSPC Investigators**

European Randomized Study of Prostate Cancer Screening (ERSPC) Data

- ~150 000 men ages 55-69. [4]
- Examined effects screening has on death due to prostate cancer. [4]

The European Randomized Study of Screening for Prostate Cancer – Prostate Cancer Mortality at 13 Years of Follow-up

Fritz H. Schröder[1], **Jonas Hugosson**[2], **Monique J. Roobol**[1], **Teuvo L.J. Tammela**[3], **Marco Zappa**[4], **Vera Nelen**[5], **Maciej Kwiatkowski**[6,7], **Marcos Lujan**[8,9], **Lissa Määttänen**[10], **Hans Lilja**[11,12,13], **Louis J. Denis**[14], **Franz Recker**[6], **Alvaro Paez**[15,16], **Chris H. Bangma**[1], **Sigrid Carlsson**[2,11], **Donella Puliti**[4], **Arnauld Villers**[17], **Xavier Rebillard**[18], **Matti Hakama**[10,19], **Ulf-Hakan Stenman**[20], **Paula Kujala**[21], **Kimmo Taari**[22], **Gunnar Aus**[23], **Andreas Huber**[24], **Theo van der Kwast**[25], **Ron H.N. van Schaik R**[26], **Harry J. de Koning**[27], **Sue M. Moss**[28], **Anssi Auvinen**[19], and **for the ERSPC Investigators**

ERSPC Data

```r
head(casebase::ERSPC)
```

PatientID	ScrArm	Follow.Up.Time	DeadOfPrCa
1	1	0.003	0
2	0	1.038	1
3	1	7.966	1
4	0	11.975	1
5	1	14.910	0

Recall

- **Using the ERSPC dataset and casebase, we will determine Justin's absolute risk for death by prostate cancer.**

Casebase Overview

1. Clever sampling.

Casebase Overview

1. Clever sampling.
2. Allows a parametric fit using *logistic regression*.

Casebase Overview

1. Clever sampling.
2. Allows a parametric fit using *logistic regression*.

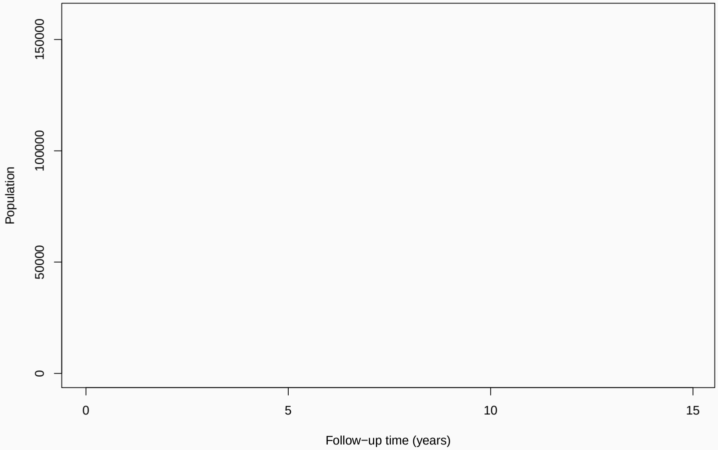
- Casebase is parametric, and allows different parametric fits by incorporation of the time component.

Casebase Overview

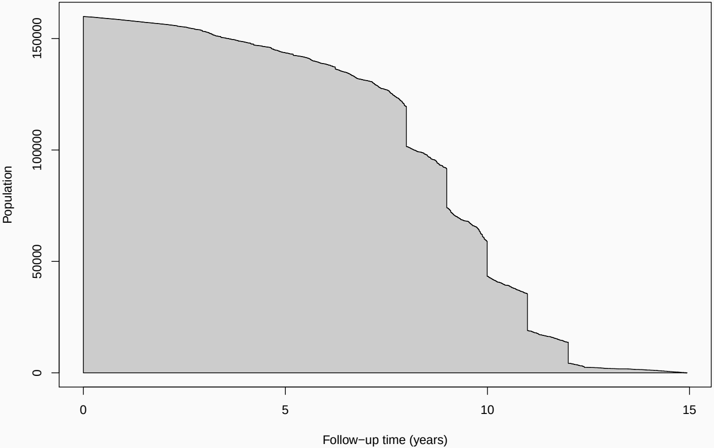
1. Clever sampling.
2. Allows a parametric fit using *logistic regression*.

- Casebase is parametric, and allows different parametric fits by incorporation of the time component.
- Package contains an implementation for generating *population-time* plots.

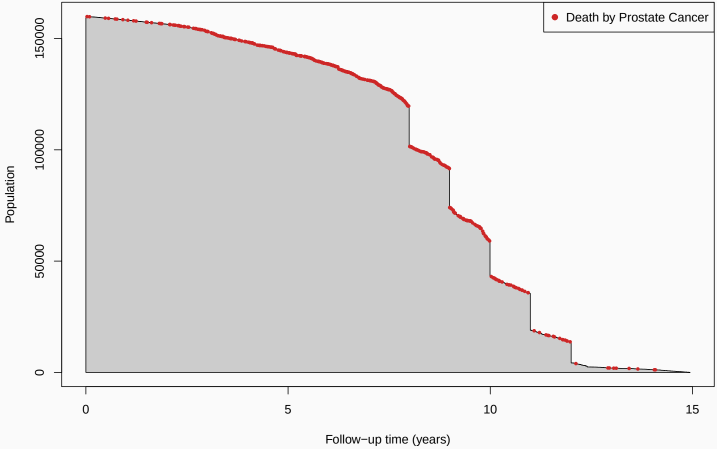
Casebase: Sampling [5]



Casebase: Sampling [5]

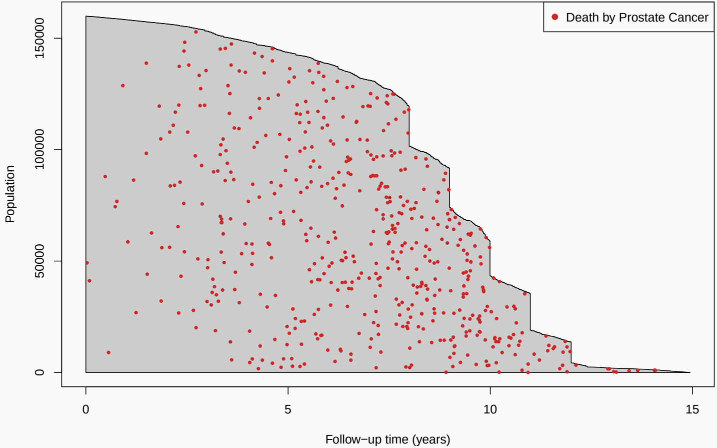


Casebase: Sampling [5]

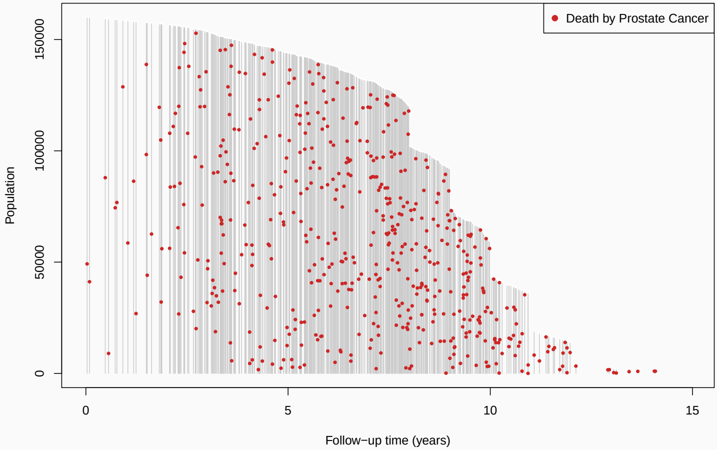


Casebase: Sampling

```r
casebase::popTime(Data,Event,Time)
```



Casebase: Sampling [3]



Casebase: Parametric families

- We can now fit models of the form: [1]

$$log(h(t;\alpha,\beta)) = g(t;\alpha) + \beta X$$

Casebase: Parametric families

- We can now fit models of the form: [1]

$$log(h(t;\alpha,\beta)) = g(t;\alpha) + \beta X$$

- By changing the function $g(t;\alpha)$, we can model different parametric families easily:

Casebase: Parametric models

Exponential: $g(t; \alpha)$ is equal to a constant

```
casebase::fitSmoothHazard(status ~ X1 + X2)
```

Gompertz: $g(t; \alpha) = \alpha t$

```
casebase::fitSmoothHazard(status ~ time + X1 + X2)
```

Weibull: $g(t; \alpha) = \alpha log(t)$

```
casebase::fitSmoothHazard(status ~ log(time) + X1 + X2)
```

Death by prostate cancer: hazard ratios

```r
casebase::fitSmoothHazard(DeadOfPrCa~ log(Follow.Up.Time)+
                            ScrArm, data=ERSPC, ratio = 100)
```

```
Call:
glm(formula = formula, family = binomial, data = sampleData)

Deviance Residuals: 
    Min       1Q   Median       3Q      Max  
-0.2693  -0.1715  -0.1348  -0.0908   4.5189  

Coefficients:
                    Estimate Std. Error z value Pr(>|z|)    
(Intercept)         -9.46535    0.15812 -59.862   <2e-16 ***
log(Follow.Up.Time)  1.08124    0.08264  13.084   <2e-16 ***
ScrArm              -0.20833    0.08859  -2.352   0.0187 *  
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 6059.0  on 54539  degrees of freedom
Residual deviance: 5794.1  on 54537  degrees of freedom
AIC: 5800.1

Number of Fisher Scoring iterations: 8
```

ERSPC Hazard comparison

Model	Hazard Ratio	Std.Error
Cox	0.801	1.092
Gompertz	0.802	1.093
Exponential	0.810	1.092
Weibull	0.797	1.093

Absolute Risk

- We have parametric hazard models now.

Absolute Risk

- We have parametric hazard models now.
- To get the absolute risk, we need to evaluate the following equation in relation to the hazard:

$$CI(x, t) = 1 - e^{-\int_0^t h(x,u)du}$$

Absolute Risk

- We have parametric hazard models now.
- To get the absolute risk, we need to evaluate the following equation in relation to the hazard:

$$CI(x,t) = 1 - e^{-\int_0^t h(x,u)du}$$

- *CI(x,t)*= Cumulative Incidence (Absolute Risk)

Absolute Risk

- We have parametric hazard models now.
- To get the absolute risk, we need to evaluate the following equation in relation to the hazard:

$$CI(x,t) = 1 - e^{-\int_0^t h(x,u)du}$$

- *CI(x,t)*= Cumulative Incidence (Absolute Risk)
- *h(x,u)*= Hazard function

Absolute Risk

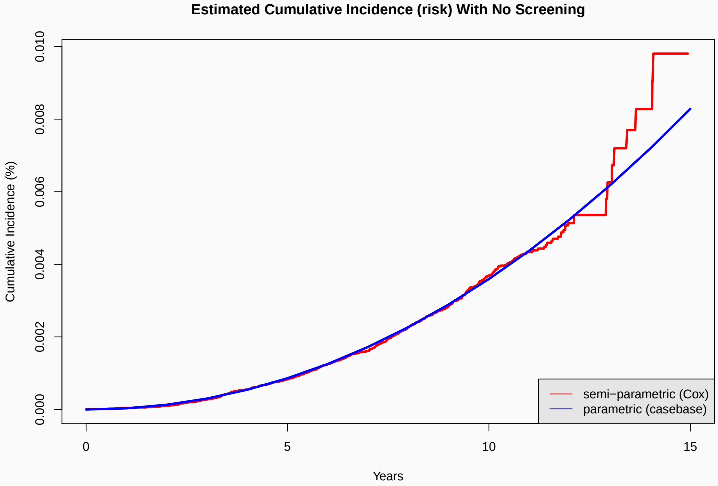
- We have parametric hazard models now.
- To get the absolute risk, we need to evaluate the following equation in relation to the hazard:

$$CI(x,t) = 1 - e^{-\int_0^t h(x,u)du}$$

- *CI(x,t)*= Cumulative Incidence (Absolute Risk)
- *h(x,u)*= Hazard function
- Lets use the weibull hazard.

Casebase: Absolute Risk comparison

```
casebase::absoluteRisk(fit, time=2, covariate_profile)
```



Summary

- Casebase sampling permits the use of GLMs and the tools associated with them

Summary

- Casebase sampling permits the use of GLMs and the tools associated with them
- The casebase package contains tools to generate:

Summary

- Casebase sampling permits the use of GLMs and the tools associated with them
- The casebase package contains tools to generate:
    - Population-Time plots

Summary

- Casebase sampling permits the use of GLMs and the tools associated with them
- The casebase package contains tools to generate:
    - Population-Time plots
    - Hazard functions

Summary

- Casebase sampling permits the use of GLMs and the tools associated with them
- The casebase package contains tools to generate:
    - Population-Time plots
    - Hazard functions
    - Absolute Risk

Summary

- Casebase sampling permits the use of GLMs and the tools associated with them
- The casebase package contains tools to generate:
    - Population-Time plots
    - Hazard functions
    - Absolute Risk
- Flexible fits through splines.

Summary

- Casebase sampling permits the use of GLMs and the tools associated with them
- The casebase package contains tools to generate:
  - Population-Time plots
  - Hazard functions
  - Absolute Risk
- Flexible fits through splines.
- Casebase can deal with competing risks.

References 1

1.Hanley, James A, and Olli S Miettinen. 2009. “Fitting Smooth-in-Time Prognostic Risk Functions via Logistic Regression.” *The International Journal of Biostatistics 5 (1)*.

2.Saarela, Olli. 2015. “A Case-Base Sampling Method for Estimating Recurrent Event Intensities.” *Lifetime Data Analysis*. Springer, 1–17

3.Saarela, Olli. Case-Base Sampling for Fitting and Validating Prognostic Models. 8 Nov. 2014, www.fields.utoronto.ca/programs/scientific/14-15/biomarker/slides/saarela.pdf.

References 2

4.Schroder FH, et al., for the ERSPC Investigators.Screening and Prostate-Cancer Mortality in a Randomized European Study. *N Engl J Med* 2009;360:1320-8.

5.Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007 Aug;40(4):381-7. doi: 10.1038/sj.bmt.1705727.

6.Turgeon, M. (2017, June 10). Retrieved May 05, 2019, from https://www.maxturgeon.ca/slides/MTurgeon-2017-Student-Conference.pdf

Tutorial and Slides

Tutorial:

http://sahirbhatnagar.com/casebase/

Slides:

https://github.com/Jesse-Islam/UseR–CaseBase-Presentation

Questions?

APPENDIX

Competing Risks

- Current methods:

Competing Risks

- Current methods:
  - Fine-Gray

Competing Risks

- Current methods:
    - Fine-Gray
    - Kaplan-Meier

Competing Risks

- Current methods:
    - Fine-Gray
    - Kaplan-Meier
- Proposed method:

Competing Risks

- Current methods:
    - Fine-Gray
    - Kaplan-Meier
- Proposed method:
    - Case-Base

Competing Risks: Data

- Two diseases:

```r
head(casebase::bmtcrr)
```

D	Status	ftime
ALL	2	0.67
AML	1	9.50
ALL	0	131.77
ALL	2	24.03

Competing Risks: Data

- Two diseases:
    - Acute Lymphoblastic Leukemia (ALL)

```r
head(casebase::bmtcrr)
```

D	Status	ftime
ALL	2	0.67
AML	1	9.50
ALL	0	131.77
ALL	2	24.03

Competing Risks: Data

- Two diseases:
  - Acute Lymphoblastic Leukemia (ALL)
  - Acute Myeloblastic Leukemia (AML)

```r
head(casebase::bmtcrr)
```

D	Status	ftime
ALL	2	0.67
AML	1	9.50
ALL	0	131.77
ALL	2	24.03

Competing Risks: Data

- Two diseases:
  - Acute Lymphoblastic Leukemia (ALL)
  - Acute Myeloblastic Leukemia (AML)
- Contains a competing event.

```
head(casebase::bmtcrr)
```

D	Status	ftime
ALL	2	0.67
AML	1	9.50
ALL	0	131.77
ALL	2	24.03

Competing Risks: Absolute Risk

```
fit_cb <- casebase::fitSmoothHazard(Status ~ ftime
                                      + ... , data =
                                      bmtcrr)
risk_cb <- absoluteRisk(fit_cb, Time, Newdata)
```

Competing Risks: Absolute Risk