Absolute risk integration using penalized logistic regression

Jesse Islam

2/27/2020

Popular methods in time-to-event analysis

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  - Cox Regression
- When we want the absolute risk:
  - Breslow estimator
  - Parametric models

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. [2]

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- They believe the stepwise nature is the reason, as it reduces interpretability. [2]
- Want to easily model non-proportional hazards. [2]
- A streamlined approach for reaching a **smooth absolute risk** curve. [2]

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.

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SUPPORT dataset (knaus)

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- **Study to Understand Prognoses and Preferences for Outcomes and Risks Treatments**
- Design: Prospective cohort study.
- Setting: 5 academic care centers in the United States.
- Participants: 9105 hospitalized.
- Follow-up-time: 5.56 years.
- 68% incidence rate.

SUPPORT manual imputation (knaus)

- Notorious for missing data

Baseline Variable	Normal Fill-in Value
Bilirubin	1.01
BUN	6.51
Creatinine	1.01
PaO2/FiO2 ratio (pafi)	333.3
Serum albumin	3.5
Urine output	2502
White blood count	9 (thousands)

Table 1: Suggested imputation values. [3]

SUPPORT automated imputation

- Mice imputation package (R)

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2. logreg(Logistic Regression) – For Binary Variables (with 2 levels)
3. polyreg(Bayesian polytomous regression) – For Factor Variables ($>=$ 2 levels)

Removed variables (knaus)

- Hospital Charges.

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- Surrogate activities of daily living.

Variable overview (knaus)

- **Response variables**

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  - Physiological variables. (11)

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  - Activities of daily living. (2)
  - Previous model findings. (8)

Original SUPPORT analysis (knaus)

- Determined SUPPORT prognostic model on phase I (4301 individuals).

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- Tested on Phase II (4028 individuals).

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- Tested on Phase II (4028 individuals).
- Both on the scale of 180 days.

Original SUPPORT analysis (knaus)

- Write out complicated model?????

SUPPORT question

- How does their model perform over 5.56 years?

SUPPORT question

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- Absolute Risk comparison.

Analysis Process

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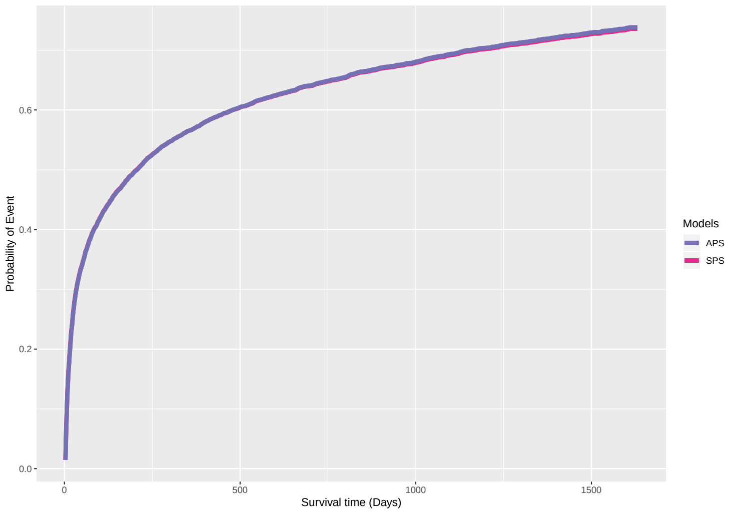
- All models is trained on 80% of the observations.

Analysis Process

1. Impute
2. Compare SPS and APS over ~5.56 years using absolute risk curves.
3. Compare to Kaplan-Meier curve
4. Compare to full model (excluding SPS and APS)

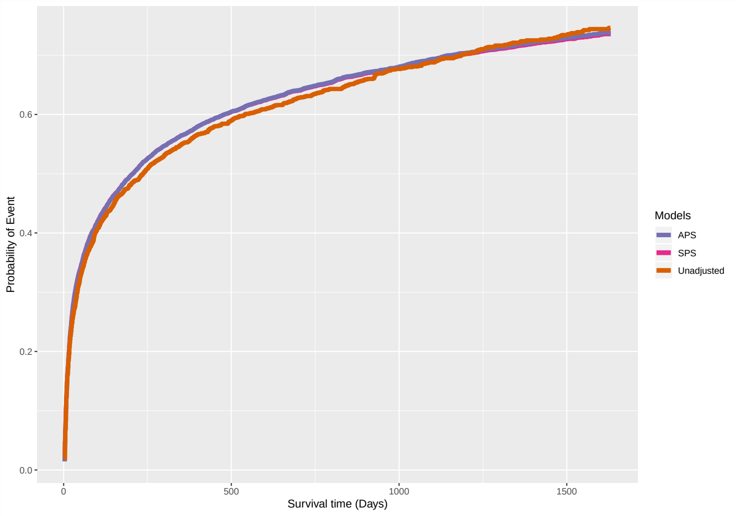
- All models is trained on 80% of the observations.
- Remaining observations are used to generate comparative absolute risk curves.

SPS vs APS

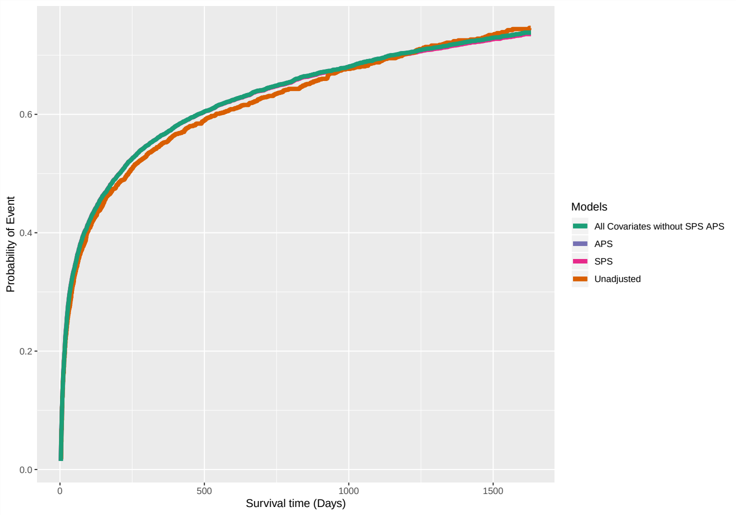


Probability of Event
0.0
0.2
0.4
0.6
0
500
1000
1500
Survival time (Days)
Models
APS
SPS

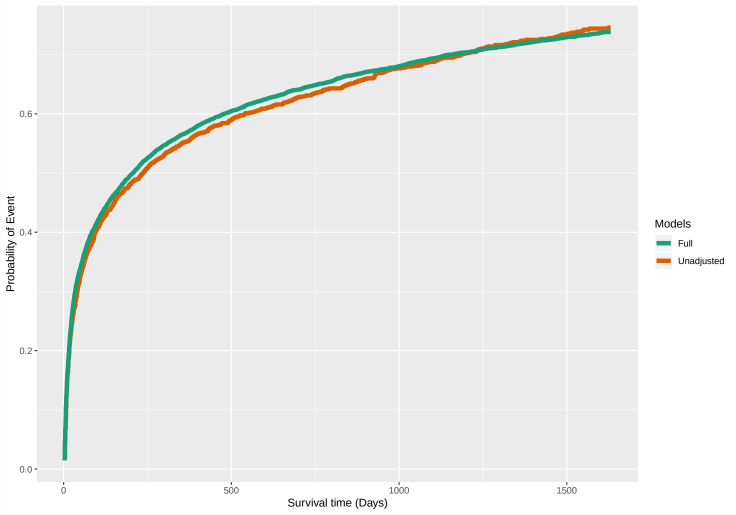
SPS vs. Kaplan-Meier



All covariates vs. physiology scores vs unadjusted



Chosen absolute risk comparisons



Chosen absolute risk comparisons: conclusion

- Linear associations without physiology scores perform similarly to physiology scores alone.

Casebase sampling overview

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Casebase sampling overview

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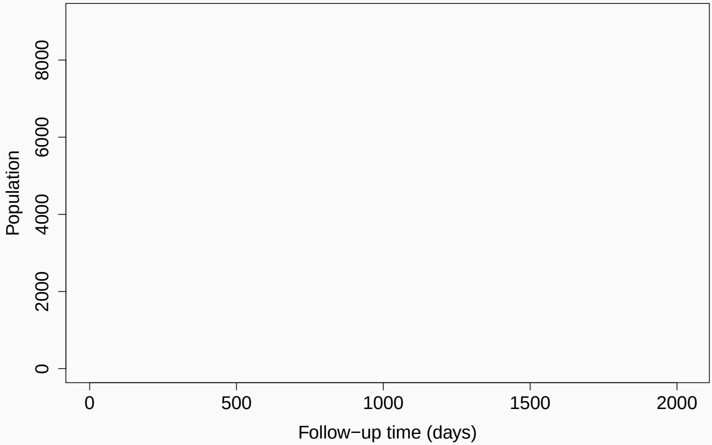
- Casebase is parametric, and allows different parametric fits by incorporation of the time component.
- Package contains an implementation for generating *population-time* plots.

Casebase: Sampling



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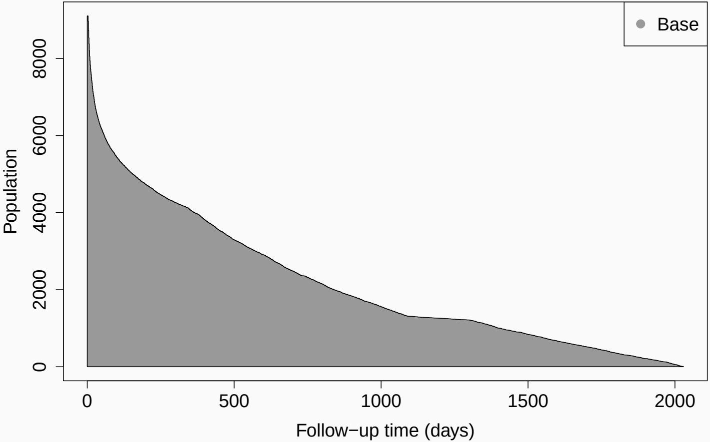

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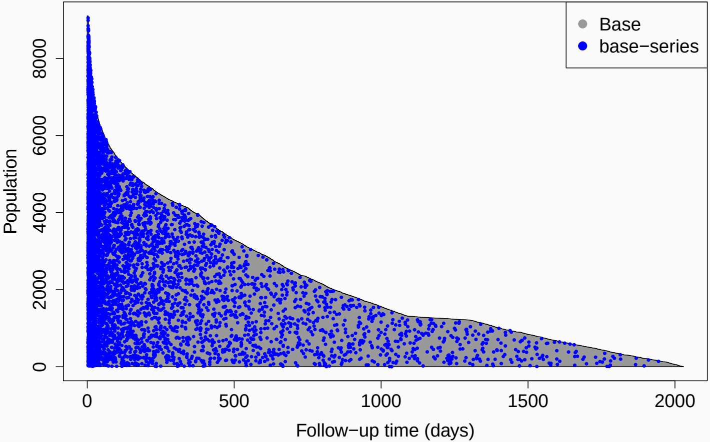

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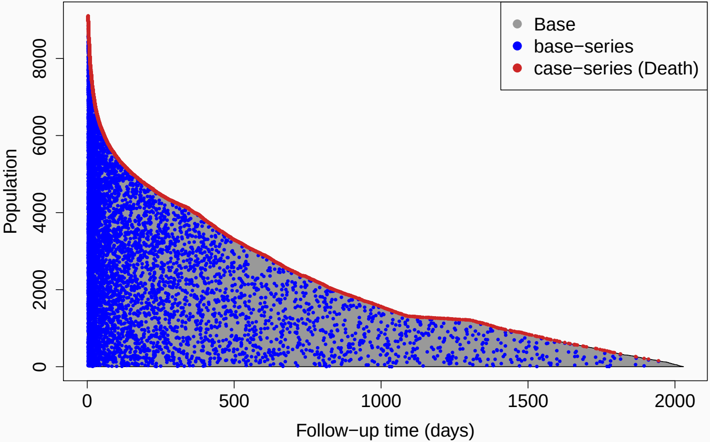

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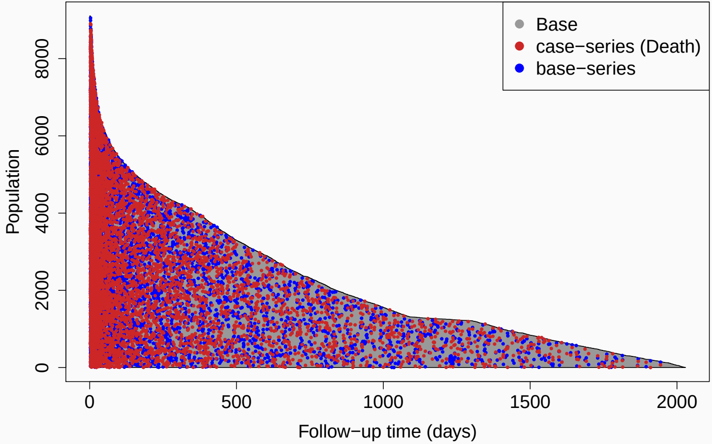

Casebase: Sampling

$$e^L = \frac{Pr(Y = 1|x, t)}{Pr(Y = 0|x, t)} = \frac{h(x, t) * B(x, t)}{b[B(x, t)/B]} = \frac{h(x, t) * B}{b}$$

- $L = \beta X$

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- B = Base.
- *B(x,t)* = Risk-set for survival time t.

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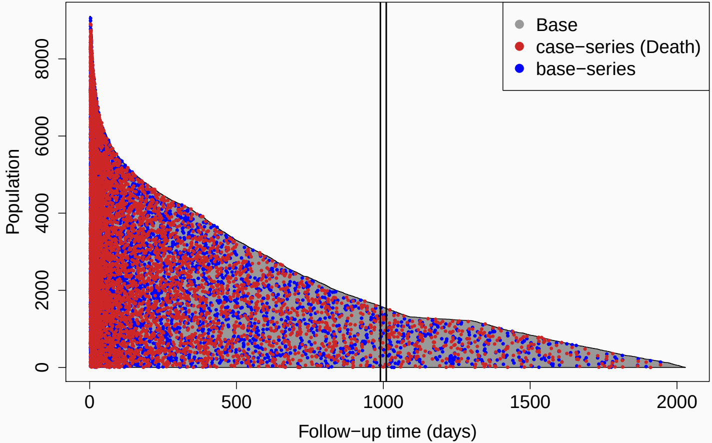

log-odds = log hazard

$$e^L = \frac{\hat{h}(x,t) * B}{b}$$

$$\hat{h}(x,t) = \frac{b * e^L}{B}$$

$$log(\hat{h}(x,t)) = L + log(\frac{b}{B})$$

Maximum log-likelihood [1]

$$log(l(\beta)) = \sum_{i=1}^{N}(\sum_{k=0}^{K} x_{ik}\beta_k) - n_i log(1 + e^{\sum_{k=0}^{K} x_{ik}\beta_k})$$

Maximum log-likelihood, with offset

$$log(l(\beta)) = \sum_{i=1}^{N}(\sum_{k=0}^{K} x_{ik}\beta_k + log(\frac{b}{B})) - n_i log(1 + e^{\sum_{k=0}^{K} x_{ik}\beta_k + log(\frac{b}{B})})$$

Maximum log-likelihood, with offset and lasso

$$log(l(\beta)) = \sum_{i=1}^{N} (\sum_{k=0}^{K} x_{ik}\beta_k + log(\frac{b}{B})) - n_i log(1 + e^{\sum_{k=0}^{K} x_{ik}\beta_k + log(\frac{b}{B})}) - \lambda ||\beta||$$

Casebase: Parametric families

- We can now fit models of the form:

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

Casebase: Parametric families

- We can now fit models of the form:

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

- 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

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

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

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

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

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

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- *h(x,u)*= Hazard function
- Lets use the weibull hazard

models to be compared

- Recall: Case study to demonstrate regularization using our method.

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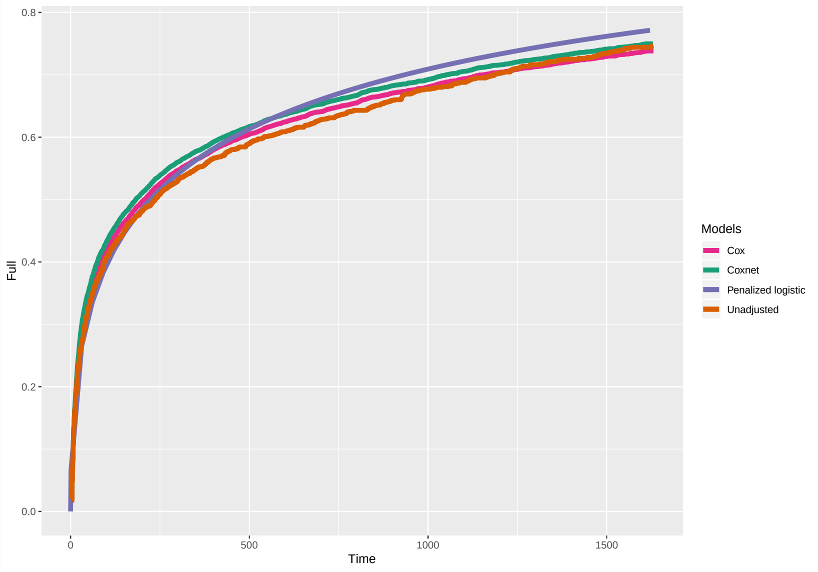
models to be compared

- Recall: Case study to demonstrate regularization using our method.
- **unadjusted**: (death, time) ~ 1
- **Cox**: (death, time) ~ βX
- **Coxnet**: (death, time) ~ $\beta X <$–Lasso
- **Penalized logistic**: death ~ log(time) + $\beta X <$–Lasso

Survival comparison



Future work

- IPA score

Future work

- IPA score
- Survival GWAS

References 1

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Tutorial and Slides

\begin{center} Tutorial:

http://sahirbhatnagar.com/casebase/

Slides:

https://github.com/Jesse-Islam/ATGC_survival_presentation_Feb.27.2020

Questions? \end{center}