Lecture 9

Monday, November 13, 2023 10:00

BIOS522_Slides9

BIOS 522: Survival Analysis Methods

Lecture 9:

Parametric regression models

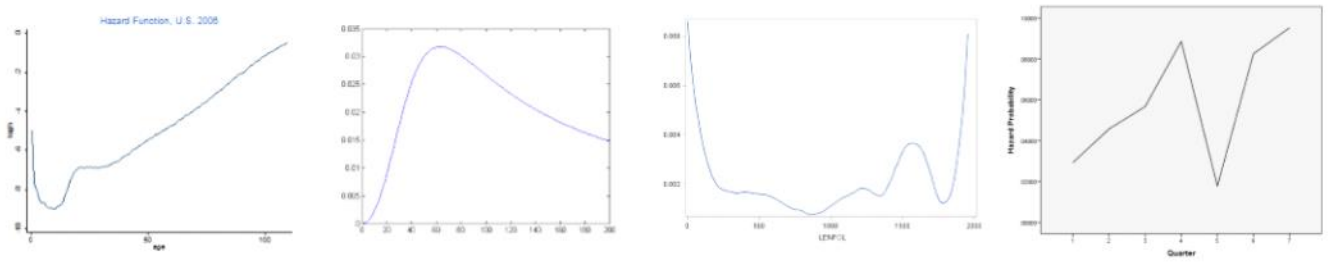
Semiparametric regression

dependent variable is a function

- Cox proportional hazards regression

$$h_i(t) = h_0(t)\exp(\beta_1 X_{i1} + \cdots + \beta_k X_{ik})$$

- $h_0(t)$ can take any of an infinite number of shapes



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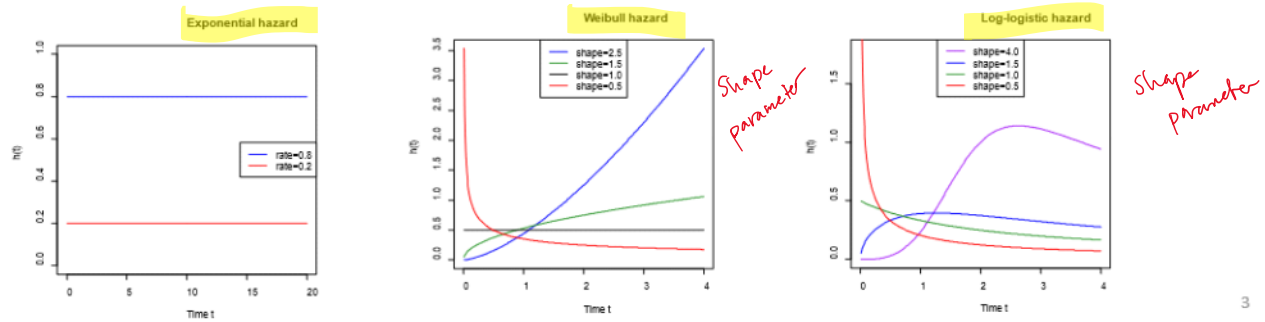
Parametric regression

- Parametric proportional hazards regression

$$h_i(t) = h_0(t)\exp(\beta_1 X_{i1} + \cdots + \beta_k X_{ik})$$

Baseline hazard

- $h_0(t)$ takes the shape of a pre-specified distribution



Shape parameter

Shape parameter

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Parametric PH model structure

- Exponential PH model

$$h_i(t) = \lambda_0 \exp(\beta_1 X_{i1} + \cdots + \beta_1 X_{ik})$$

- Weibull PH model

$$h_i(t) = \lambda_0 \gamma_0 (\lambda_0 t)^{\gamma_0 - 1} \exp(\beta_1 X_{i1} + \cdots + \beta_1 X_{ik})$$

multiplies the hazard fxn

Coefficients for parametric PH

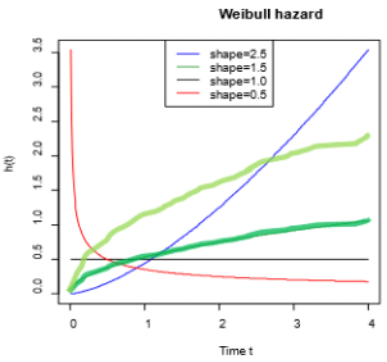
- *Example:* Weibull proportional hazards model

rate & shape parameters

$$h_i(t) = \lambda_0 \gamma_0 (\lambda_0 t)^{\gamma_0 - 1} \exp(\beta_1 X_{i1} + \cdots + \beta_k X_{ik})$$

β's are log hazard ratios

- Estimate **log hazard ratios**:
  - $\hat{\beta}_1, \ldots, \hat{\beta}_k$
- Estimate **reference group parameters**:
  - Weibull rate $\hat{\lambda}_0$, Weibull shape $\hat{\gamma}_0$



Recall: Likelihood fxn for right-censored data:

but now also include rate & shape parameters

$$L(\lambda_0, \gamma_0, \beta_1, \ldots, \beta_k) = \prod_{i=1}^{n} [h(T_i^* | \lambda_0, \gamma_0, \beta_1, \ldots, \beta_k)]^{\delta_i} S(T_i^* | \lambda_0, \gamma_0, \beta_1, \ldots, \beta_k)$$

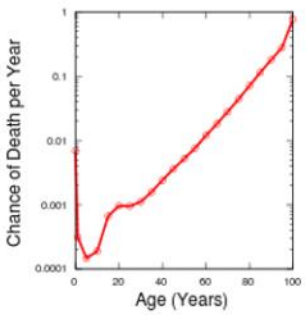
Another option for parametric PH models

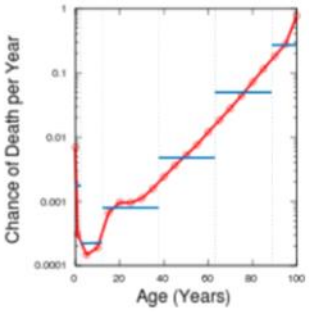
Piecewise exponential model

$$h_i(t) = h_0(t)\exp(\beta_1 X_{i1} + \cdots + \beta_k X_{ik})$$

Can model more complex shapes

- The baseline hazard function $h_0(t)$ is modeled as constant within intervals





Cut points/Pieces don't have to be the same width

Saying there's a constant hazard within each interval

$$h_0(t) = \begin{cases} \lambda_1 = 0.002 & 0 \le t < 2 \\ \lambda_2 = 0.0003 & 2 \le t < 15 \\ \lambda_3 = 0.0009 & 15 \le t < 38 \\ \lambda_4 = 0.005 & 38 \le t < 65 \\ \lambda_5 = 0.05 & 65 \le t < 85 \\ \lambda_6 = 0.5 & t \ge 85 \end{cases}$$

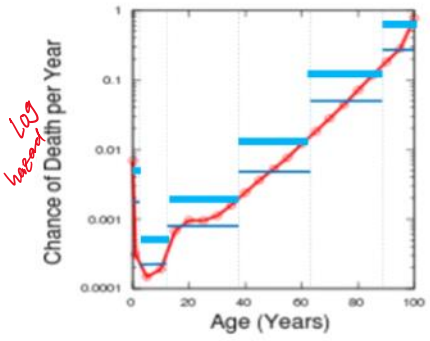
As many (hazards) parameters as there are intervals

Estimation for parametric PH

- *Example:* piecewise exponential model

$$h_i(t) = h_0(t)\exp(\beta_1 X_{i1} + \cdots + \beta_k X_{ik})$$

- Estimate **log hazard ratios**:
  - $\hat{\beta}_1, \ldots, \hat{\beta}_k$
- Estimate **reference group parameters**:
  - Hazard rates $\hat{\lambda}_1, \ldots, \hat{\lambda}_6$



RESEARCH ARTICLE Open Access

Piecewise exponential models to assess the influence of job-specific experience on the hazard of acute injury for hourly factory workers

Jessica Kubo[1*], Mark R Cullen[2], Linda Cantley[3], Martin Slade[3], Baylah Tessier-Sherman[3], Oyebode Taiwo[3] and Manisha Desai[1]

Goal: To define an approach for studying the relationship between experience and risk of injury for different occupations.

Population: Data set of 81,301 hourly production workers of a global aluminum company at 207 facilities.

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Outcome variable: Time in months from the start of a particular job **to injury on that job**.

Non-injured employees were censored at the earliest of the following: change of job within the corporation, death, termination from the company, or the end of the observation period.

Predictor variables:

Age at job initiation, overall company tenure at job initiation, gender, race, physical demand of the job, union status of the plant, plant type, and socio-demographic characteristics.

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Statistical analysis: Sought to model the hazard of injury as a function of time on the job (i.e. experience). The main parameter of interest was the **baseline hazard itself**. They wanted to assess whether the hazard for injury changes with experience (is the hazard constant over time?). Thus, a Cox PH was not appropriate.

Compared several models:

- Exponential PH model (constant baseline hazard)
- Weibull PH model
- A piecewise exponential model with one cut point at 12 months
- A piecewise exponential model with one data-driven* cut point

* Yielded the largest likelihood value

Results: Figure 2 compares model-predicted survival functions and KM estimate for a test set chosen from 81,301 employees

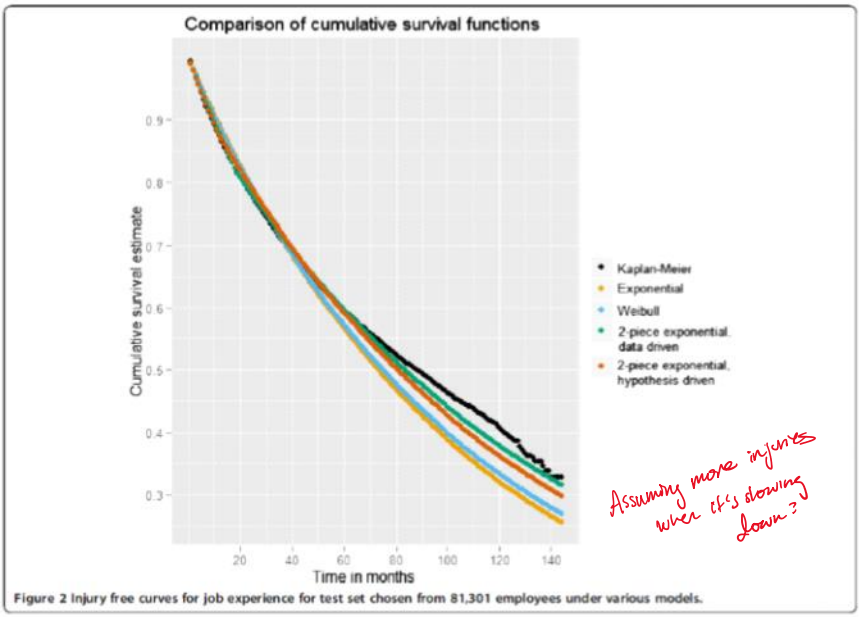
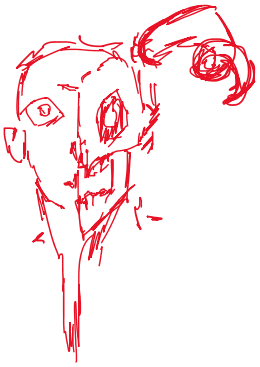


Figure 2 Injury free curves for job experience for test set chosen from 81,301 employees under various models.

Results: Table 5 reports results for the 2-piece exponential model with 19 month cut point

Table 5 Results from CC and MI frailty models for 2-piece exponential model with 19 month cut point (data-driven model)

	Complete case analysis (N=33 427 jobs for 13 427 employees)		*Multiple imputation (N=191 692 jobs for 81 301 employees)*	
	HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*
0-19 Months (inexperienced period)	1.41 (1.35, 1.47)	<.001	1.33 (1.29, 1.36)	<.001
Male gender	0.62 (0.57, 0.68)	<.001	0.71 (0.68, 0.73)	<.001
Non-White	1.08 (0.99, 1.17)	0.070	0.97 (0.93, 1.00)	0.067
First job at company	0.88 (0.79, 0.98)	0.017	0.90 (0.88, 0.93)	<.001
Age at start of job	0.98 (0.98, 0.99)	<.001	0.99 (0.98, 0.99)	<.001
Physical demand	1.25 (1.21, 1.29)	<.001	1.26 (1.24, 1.29)	<.001
Smelter plant	1.24 (1.17, 1.32)	<.001	1.30 (1.24, 1.36)	<.001
Union plant	1.16 (1.04, 1.28)	0.006	1.30 (1.23, 1.38)	<.001
Original plant	1.01 (0.83, 1.22)	0.942	1.57 (1.50, 1.65)	<.001



Accelerated failure time models

- AFT model:

e.g. surviving twice as long or half as long

$$T_i = e^{\alpha_1 X_{i1} + \cdots + \alpha_k X_{ik}} T_0$$

Covariates operate to lengthen or shorten survival time

Survival time random variable in the reference group

Accelerated failure time models

Requires that you set a distribution. Define it here like this

- AFT model (written another way):

$$S_i(t) = S_0\left(e^{-(\alpha_1 X_{i1} + \cdots + \alpha_k X_{ik})} t\right)$$

Survival function in the reference group

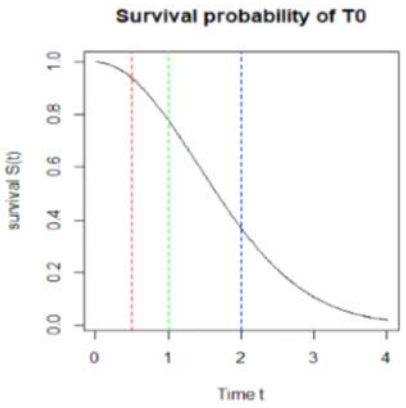
Covariates operate to "speed up" or "slow down" time

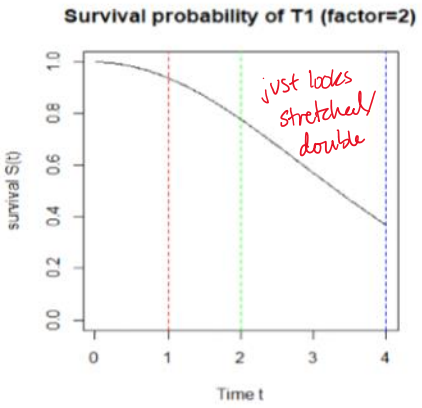
We could assume weibull, exponential etc.

Accelerated failure time models

- Consider two groups, defined by $X_i = 1$ vs. $X_i = 0$
- If the **acceleration factor** $\exp(\alpha) = 2$, then:

Extend time by double





People with $X_i = 1$...

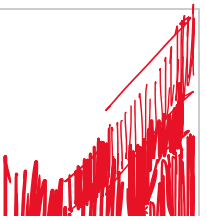
Live twice as long

$$T_1 = \exp(\alpha)$$
$$= 2T_0$$

"Age half as fast"

$$S_1(t) = S_0(e^{-\alpha}t)$$
$$= S_0(0.5t)$$

Inference for the AFT model



Inference for the AFT model

Coefficient	Acceleration factor	Survival in group 1 versus group 0
$\alpha > 0$	$\exp(\alpha) > 1$	Increased survival; age slower
$\alpha = 0$	$\exp(\alpha) = 1$	No difference in survival
$\alpha < 0$	$\exp(\alpha) < 1$	Decreased survival; age faster

- Null hypothesis H_0
  - Covariate has no effect on survival
  - The acceleration factor $\exp(\alpha_j) = 1$
  - Equivalently, the coefficient $\alpha_j = 0$

Don't have hazard ratios; we have acceleration factors instead

Acceleration factors ≠ hazard ratios

Coefficient	Acceleration factor	Survival in group 1 versus group 0
$\alpha > 0$	$\exp(\alpha) > 1$	Increased survival; age slower
$\alpha = 0$	$\exp(\alpha) = 1$	No difference in survival
$\alpha < 0$	$\exp(\alpha) < 1$	Decreased survival; age faster

flipped

Coefficient	Hazard ratio	Survival in group 1 versus group 0
$\beta > 0$	$\exp(\beta) > 1$	Decreased survival; higher hazard
$\beta = 0$	$\exp(\beta) = 1$	No difference in survival
$\beta < 0$	$\exp(\beta) < 1$	Increased survival; lower hazard

Acceleration factors ≠ hazard ratios

- In general, AFT and PH models are different
  - Log-logistic AFT model ≠ log-logistic PH model
- For some *particular* parametric distributions, the models are related
  - Exponential AFT model is also a PH model
  - Weibull AFT model is also a PH model

} part of HW assignment

- *Acceleration factors are not just inverted hazard ratios**

* exception = exponential AFT model

Prediction with the AFT model

- Given our acceleration factor(s) $\hat{\alpha}_1, \ldots, \hat{\alpha}_k$ and our fitted reference group parameters $\hat{\lambda}_0$ and $\hat{\gamma}_0$, making **predictions** with the AFT model is easy
- For any set of covariates, we can quickly generate predictions for $S_i(t), h_i(t), H_i(t)$, median survival time, mean survival time, etc.
- *More in today's activity…*

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

Goal: Estimate efficacy of **oseltamivir** (Tamiflu) for alleviation of influenza symptoms

Population: Meta-analysis of nine randomized, placebo-controlled trials of 75 mg twice a day oseltamivir in adults. Total data set included **4328 patients**.

Eligible patients were within 36 hours of symptom onset, with fever and at least two influenza symptoms.

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Outcome variable: The primary outcome was **time to alleviation of all symptoms** (all seven influenza symptoms scored as absent or mild) and remained so for at least 21.5 hours

The **time origin** was time of first study drug intake.

Predictor variables: **Trial arm.**

- Clinical trial.
- Age (<65 yrs, ≥65 yrs).
- Risk status (based on age, presence of chronic illness).
- Time from influenza onset to randomization (<24 hrs, ≥24 hrs).
- Symptom score at randomization.
- Virus type (influenza A or B).

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Statistical analysis: **Two sets of analyses were conducted:**

1. Using the **intention-to-treat population**, including all trial participants who received at least one dose of study drug.
2. Using the **intention-to-treat infected population**, including all trial participants as above + confirmed to be influenza-infected.

"For time to alleviation of all symptoms, we initially assessed Kaplan-Meier plots by treatment group and we obtained a treatment effect estimate (time ratio) from a **log-logistic accelerated failure time model, adjusted for trial**. We did not use proportional hazards models because **non-proportionality of hazards was evident**.

We estimated treatment differences in median time to alleviation of symptoms adjusted for trial along with **bootstrap confidence intervals** (2000 repetitions, stratified by trial and treatment group)."

Results: **Figure 1** reports the acceleration factor (time ratio) for each trial and overall in the **intention-to-treat infected population**.

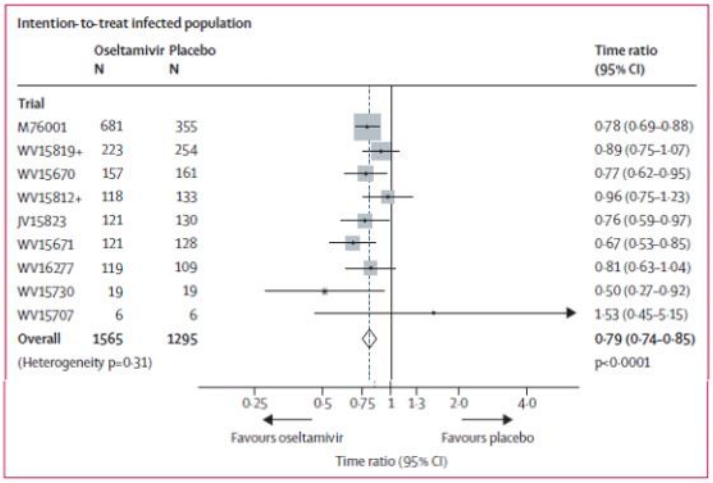

Figure 1: **Fixed effect meta-analysis for time to alleviation of all symptoms**
The overall time ratio is calculated from an accelerated failure time model adjusted for trial.

Abstract: "In the intention-to-treat infected population, we noted a **21% shorter time to alleviation of all symptoms** for oseltamivir versus placebo recipients (**time ratio 0.79,** 95% CI 0.74-0.85; p<0.0001).

The median times were **97.5 h** for oseltamivir and **122.7 h** for placebo groups (difference -25.2 h, 95% CI -36.2 to -16.0)."

Figure 2 assessed the overall fit of the model by comparing Kaplan-Meier curves and AFT predictions.

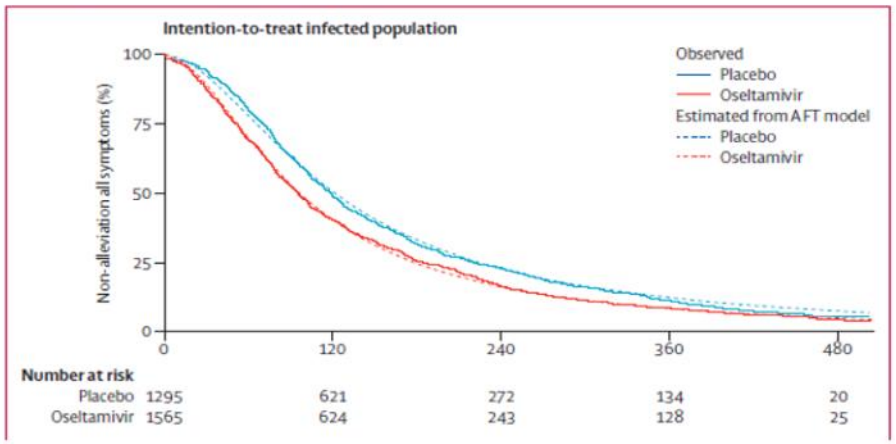

Figure 2: **Overall Kaplan-Meier curves and estimated survival curves from AFT model (adjusted for trial) by treatment group for time to alleviation of all symptoms in all trials combined**
AFT=accelerated failure time.

Results: "The accelerated failure time model provided a good fit to the data (figure 2)."

Conclusion: Oseltamivir in adults with influenza **accelerates time to clinical symptom alleviation**, supporting the beneficial effect of this widely used drug

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Cox PH model	**Parametric regression models**
(+) **Widely used** in the literature	(-) Less commonly used in the literature
(+) **Flexible baseline hazard function**; no pre-specification required!	(-) Necessary to pre-specify shape of baseline hazard function
(+) Model fits even if baseline hazard function dies not have a parametric shape	(-) Baseline hazard function may fit poorly and negatively impact the model; need to **justify your assumptions**!
(-) Slightly less efficient (larger standard errors) when a parametric model fits well	(+) **Slightly more efficient** (smaller standard errors) when parametric model fits well
(-) Unstable when data are sparse	(+) When **data are sparse**, these gains in efficiency are more noticeable
(-) We use this model to study hazard ratios only, not the actual hazard functions	(+) This model is better suited to **study the shape of the hazard functions**, not just the hazard ratios
(-) Need specialized estimators (e.g. Breslow estimator) to use model to predict survival	(+) Straightforward to use model to **predict survival**
(-) May not be well-suited to complex settings	(+) Can be generalized to **model complex settings**, like jointly modeling several correlated survival outcomes

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