The Cox model: introduction and history

Bianca L. De Stavola
Centre for Statistical Methodology
LSHTM

March 8, 2013

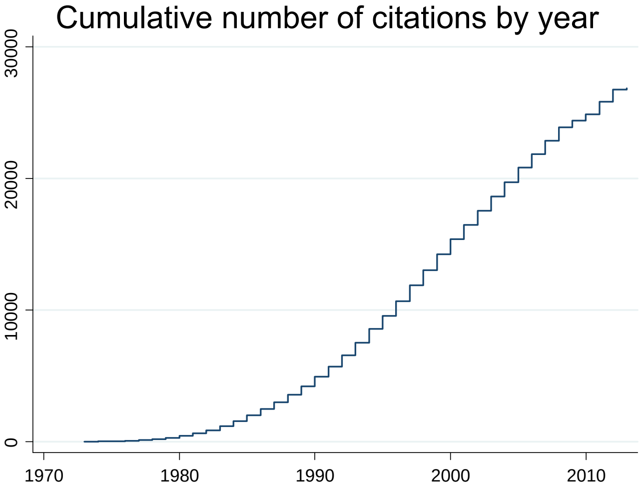
Introduction

Today is a celebration of an incredibly influential paper:

- the most cited paper in the whole history of JRSS
- the third most cited paper in medical journals
- it has a total of nearly 30,000 citations (according to Web of Science)
- and this is still increasing

Cumulative citations

Web of Science



Outline

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Setting

We are concerned with studying:

- individuals at risk of experiencing a failure after time T
- measured from a relevant origin and according to a relevant measurement scale
- difficulty if some are not observed until failure occurs, *i.e.* are censored
- crucially, censoring must be independent of the failure process

Definitions

If T is a continuous positive random variable its probability distribution is equivalently specified by:

- the density function:

$$f(t) = \lim_{\Delta t \to 0^+} \frac{Pr\left(t \leq T < t + \Delta t\right)}{\Delta t}$$

- the survivor function:

$$S(t) = Pr\left(T \geq t\right)$$

- the hazard function:

$$\lambda(t) = \lim_{\Delta t \to 0^+} \frac{Pr\left(t \leq T < t + \Delta t | t \leq T\right)}{\Delta t}$$

Survivor and hazard function

By the product law of probability, $S(t)$ is related to $\lambda(t)$:

$$S(t) = \lim \prod_{k=0}^{r-1} \{1 - \lambda(\tau_k)(\tau_{k+1} - \tau_k)\}$$

where:

- the limit is for $(\tau_{k+1} - \tau_k) \to 0$
- $0 < \tau_1 < \tau_2 < \ldots < \tau_r = t$ the interval endpoints

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construction of the likelihood depends on this

Known at the time

Three main analytical approaches:

1. Non-parametric estimation of $S(t)$
2. Parametric estimation of $S(t)$
3. Comparison of survivor functions ("the two-sample problem")

1 – Non-parametric estimation of $S(t)$

- Actuarial (Life-Table) estimation:
  - long tradition in demography
  - assuming hazard function piecewise constant over pre-specified intervals $\{t_j, t_{j+1}\}$, $\hat{\lambda}_j =$ no. events / total follow-up time
  - survivor function estimated as the product of the conditional probabilities of surviving each interval: $\hat{S}(t_j) = \prod_{k<j}\left(1 - \hat{\lambda}_k\right)$

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- Product Limit estimation:
  - exactly the same but defined for vanishingly small intervals
  - hence $\hat{\lambda}_j =$ no. events / total no. persons at risk
  - derived by Kaplan & Meier (1958) as a non-parametric MLE of $S(t)$
- Although both derived from ML arguments, asym. properties not developed until later (Breslow and Crowley, 1974)

2 – Parametric estimation of $S(t)$

- Exponential and Weibull often used (simple formulæ for $S(t)$ and $\lambda(t)$)
- Approach attractive because of physical interpretation, *e.g.*
  - multi-hit carcinogenesis theories lead to Weibull models (Armitage and Doll, 1954, 1961)
- Estimation via ML mostly derived assuming fixed censoring time (*e.g.* Bartholomew 1963 for exponential, Pike 1966 for Weibull)
- Inclusion of explanatory variables rare and with no censoring

3 – Comparing survivor functions: the two-sample problem

Generalizations of the Savage–Wilcoxon rank test to settings with censored data:

- Mantel (1966):
  - test based on difference between observed and expected events at each failure time
  - expectations come from the hypergeometric distribution
  - results combined as in the Mantel–Haenszel test (1959)

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  - test based on difference between observed and expected events at each failure time
  - expectations come from the hypergeometric distribution
  - results combined as in the Mantel–Haenszel test (1959)
- Peto and Peto (1972):
  - different derivation of the same comparison
  - named log-rank test
  - Note: paper read $<$ 2 months before "Regression models and life-tables"

Summary of methods prevalent in 1972

- Statistical theory for non-parametric estimation of $S(t)$ not yet fully formalized
- Inference for parametric estimation of $S(t)$: complex even with simple censoring mechanisms
- Comparison of survivor curves dealt with via significance tests (and only possible for categorical variables)
- Extension of parametric models to include explanatory variables not generally available with censoring

Outline

Regression Models and Life-Tables

Regression Models and Life-Tables

BY D. R. COX

Imperial College, London

[Read before the ROYAL STATISTICAL SOCIETY, at a meeting organized by the Research Section, on Wednesday, March 8th, 1972, Mr M. J. R. HEALY in the Chair]

SUMMARY

The analysis of censored failure times is considered. It is assumed that on each individual are available values of one or more explanatory variables. The hazard function (age-specific failure rate) is taken to be a function of the explanatory variables and unknown regression coefficients multiplied by an arbitrary and unknown function of time. A conditional likelihood is obtained, leading to inferences about the unknown regression coefficients. Some generalizations are outlined.

Read here in the Goldsmiths Lecture Theatre

Aims

- *"The present paper is largely concerned with the extension of the results of Kaplan and Meier to the comparison of life tables. . . "*
- *". . . and more generally to the incorporation of regression like arguments into life-table analysis"*
- it would be *"sensible to make a minimum of assumptions leading to a convenient analysis"*

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The Cox model

- Let $\mathbf{z} = z_1, z_2, \ldots, z_p$ be explanatory variables of interest
- Proportional hazards (PH) model defined as

$$\lambda(t; \mathbf{z}) = \exp(\mathbf{z}\boldsymbol{\beta})\, \lambda_0(t)$$

  - $\boldsymbol{\beta}$ vector of unknown parameters (of interest)
  - $\lambda_0(t)$ unknown arbitrary function (nuisance)
- $\lambda_0(t)$ describes the shape of the survival function
- $\exp(\mathbf{z}\boldsymbol{\beta})$ could be replaced by $h(\mathbf{z}, \boldsymbol{\beta})$

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- $\lambda_0(t)$ describes the shape of the survival function
- $\exp(\mathbf{z}\boldsymbol{\beta})$ could be replaced by $h(\mathbf{z}, \boldsymbol{\beta})$

> - *explore the consequences of allowing $\lambda_0(t)$ to be arbitrary*
> - *method to have sensible properties, whatever $\lambda_0(t)$*
> - *plausible loss of information about $\boldsymbol{\beta}$ is usually slight*

Estimation (1)

- Observations:
  - n individuals, k fail
  - independent censoring
  - failure times: $0 < t_{(1)} < t_{(2)} < \ldots < t_{(k)} < \infty$
  - $\Re(t)$ the set of individuals at risk at time t

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- Originally estimation derived from a ‘conditional likelihood’
- This is the product of factors, one per event time $t_{(i)}$:

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conditional probabilities that the failure is
on the individual as observed

Estimation (2)

- '**Conditional log-likelihood**' then is:

$$l(\beta) = \Sigma_{i=1}^{k} \mathbf{z}_{(i)}\beta - \Sigma_{i=1}^{k} \log\left[\Sigma_{\ell \in \Re\left(t_{(i)}\right)} \exp\left\{\mathbf{z}_{\ell}\beta\right\}\right]$$

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- The **score function**:

$$U_{\xi}(\boldsymbol{\beta}) = \Sigma_{i=1}^{k} \left\{z_{\xi i} - A_{\xi i}(\boldsymbol{\beta})\right\}$$

where $A_{\xi i}(\boldsymbol{\beta})$ is the weighted average of z_{ξ} in $\Re$

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Derivation was controversial

Is it a conditional likelihood?

- $\frac{\exp \mathbf{z}_{(i)}\boldsymbol{\beta}}{\sum_{\ell \in \Re\left(t_{(i)}\right)} \exp\{\mathbf{z}_\ell \boldsymbol{\beta}\}}$: interpreted as cond. prob. that individual (i) is the one failing at time $t_{(i)}$, given that a failure occurs at $t_{(i)}$
- but it is given $\Re(t_{(i)})$
- equivalent to conditioning on the history of the process up to t
- independent of times $\Rightarrow$ conditional probabilities for the ranks: $l(\beta)$ is marginal log lik. of the ranks (Kalbfleisch and Prentice, 1973)
- Cox (1975) calls it Partial Likelihood (PL) and shows max PLE consistent and asym. normal, with asym. covariance matrix estimated consistently (ordering of $t_{(i)}$ defines a nesting of conditioning events: U and $\Im$ derived cond. but hold uncond.)
- Tsiatis (1981) shows this more formally using empirical processes

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If there are tied events the PL is not appropriate.

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1. If few, a correction of the term contributing to the partial likelihood
2. If several, PH model replaced by a proportional odds (PO) model:

$$\frac{\lambda\left(t;\mathbf{z}\right)dt}{1-\lambda\left(t;\mathbf{z}\right)dt}=\frac{\lambda_0\left(t\right)dt}{1-\lambda_0\left(t\right)dt}\exp\left(\mathbf{z}\beta\right)$$

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Similar arguments lead to PLE

PO model $\Rightarrow$ PH model as the intervals become infinitesimal

Additional insights

Other insights, both methodological and relevant for applications:

1. Dealing with the two sample problem:
   - with PH model this becomes a comparison of $\lambda_0(t)$ and $e^{\beta_1}\lambda_0(t)$
   - score test from the PL for discrete times equivalent to Mantel's test and asym. equivalent to log-rank test
   - novelty: it can be applied to continuous exposures

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3. Estimating failure time dsn: generalization of the product limit estimation of $\lambda(t)$

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What was new

The paper is well known although maybe not so well read

- Aspects that are well known:
  - semi-parametric PH model and its estimation approach
  - ability to perform score tests for continuous exposures

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- Aspects that are well known:
  - semi-parametric PH model and its estimation approach
  - ability to perform score tests for continuous exposures
- Aspects that are not so well known:
  - checking of PH assumption
  - solutions for tied event times, including semi-parametric PO model for discrete times
  - estimation of cumulative failure time distribution
  - extension to multivariate T and links to the accelerated failure time models
  - physical versus empirical interpretation of the model

Outline

Methodological influences

Extremely influential paper methodologically on three ‘time scales’:

1. at the time origin: the Society discussion
2. in the next 10 years
3. in the following 20 years and beyond

Outline

1 – The Society Discussion

Highlights of that discussion:

1. Richard Peto: proposed an alternative approach to dealing with tied events
2. Jack Kalbfleish and Ross Prentice: raised questions regarding the 'conditional' likelihood
3. Norman Breslow: showed how the baseline cumulative hazard function could be estimated in a more natural way
4. Susannah Howard: showed how easily max. PL estimation could be performed

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2 – The next 10 years

(a) The development of the theory of partial likelihood

(b) The incorporation within counting processes theory:
- Andersen and Gill (1982) simplified and generalized the results on asym. properties of PLE using martingale theory for counting processes (from Aalen 1975)
- Indeed this viewpoint is required for an elegant derivation of these properties
- PH model played a key role for this powerful methodological development

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3 – The next 20 years and beyond

- Interest in semi-parametric models exploded following PH model, prompting huge developments in theory (Bickel et al, 1998)
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> Would we be using doubly robust methods, efficient g-estimation, targeted ML *etc.* had "Regression Models and Life-Tables" not been published?

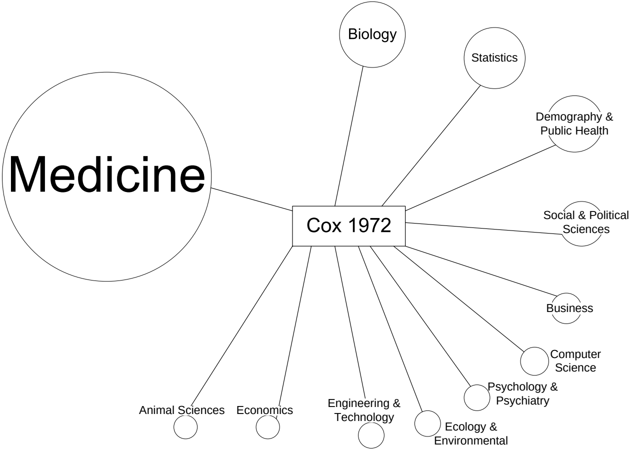
Outline

Applications

- The paper states that the proposed methodology will be for *"applications in industrial reliability studies and in medical statistics"*
- Was this a fair prediction?

Citations from Web of Science

Area proportional to number of citations



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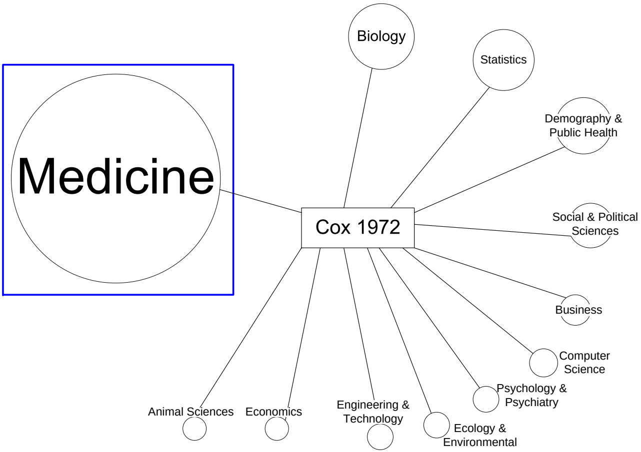

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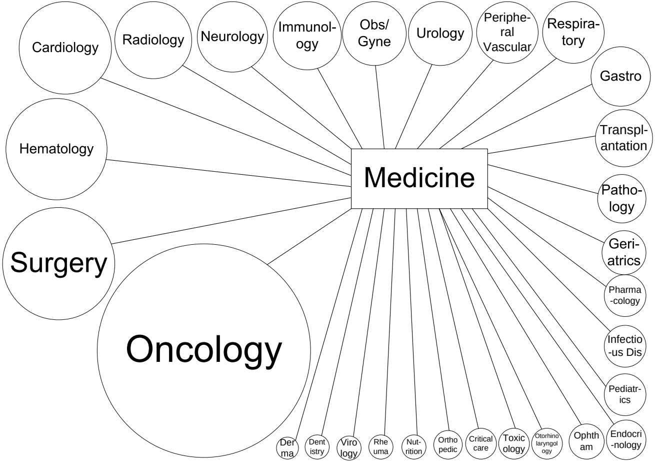

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Final thoughts

Votes of thanks aired on 8 March 1972:

> *As usual [David Cox's] statistical ideas are of both theoretical interest and great practical importance.*
>
> *(F. Downton)*

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(F. Downton)

. . . he has opened up new territories to common sense.

(R. Peto)

Sources

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