The Cox model: introduction and history

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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
1. Introduction

2. In 1972 . . .

3. ‘Regression Models and Life-Tables’
   - The Cox model
   - Insights
   - What was new

4. Trail of influence
   - The Discussion
   - The next 10 years
   - The next 20 years
   - Applications

5. Thanks
1. Introduction

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5. Thanks
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
If $T$ is a continuous positive random variable its probability distribution is equivalently specified by:

- the **density** function:
  \[
  f(t) = \lim_{\Delta t \to 0^+} \frac{Pr(t \leq T < t + \Delta t)}{\Delta t}
  \]

- the **survivor** function:
  \[
  S(t) = Pr(T \geq t)
  \]

- the **hazard** function:
  \[
  \lambda(t) = \lim_{\Delta t \to 0^+} \frac{Pr(t \leq T < t + \Delta t | t \leq T)}{\Delta t}
  \]
By the product law of probability, $S(t)$ is related to $\lambda(t)$:

$$S(t) = \lim_{k=0}^{r-1} \prod \left\{1 - \lambda(\tau_k)(\tau_{k+1} - \tau_k)\right\}$$

where:

- the limit is for $(\tau_{k+1} - \tau_k) \rightarrow 0$
- $0 < \tau_1 < \tau_2 < \ldots < \tau_r = t$ the interval endpoints
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$S(t)$ is the product of the conditional survival probabilities for infinitesimal intervals up to $t$

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")
Actuarial (Life-Table) estimation:

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

- **Actuarial (Life-Table) estimation:**
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  - survivor function estimated as the product of the conditional probabilities of surviving each interval: $\hat{S}(t_j) = \prod_{k<j} (1 - \hat{\lambda}_k)$

- **Product Limit estimation:**
  - exactly the same but defined for vanishingly small intervals
  - hence $\hat{\lambda}_j = \text{no. events / total no. persons at risk}$
  - 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 formulae 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
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)
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)

- **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
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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
“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”
Aims

- “The present paper is largely concerned with the extension of the results of Kaplan and Meier to the comparison of life tables...”

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The Cox model

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

$$\lambda(t; z) = \exp(z\beta) \lambda_0(t)$$

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

- **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** $\beta$ **is usually slight**
Observations:

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

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  - $\mathcal{R}(t)$ the set of individuals at risk at time $t$

- Originally estimation derived from a ‘conditional likelihood’

- This is the product of factors, one per event time $t(i)$:

$$\frac{\exp z(i) \beta}{\sum_{\ell \in \mathcal{R}(t(i))} \exp \{ z_{\ell} / \beta \}}$$
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conditional probabilities that the failure is on the individual as observed
‘Conditional log-likelihood’ then is:

\[ l (\beta) = \sum_{i=1}^{k} z_{(i)} \beta - \sum_{i=1}^{k} \log \left[ \sum_{\ell \in \mathcal{R}(t_{(i)})} \exp \{ z_{\ell} \beta \} \right] \]
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The score function:

\[ U_\xi(\beta) = \sum_{i=1}^{k} \{ z_\xi i - A_\xi i(\beta) \} \]

where \( A_\xi i(\beta) \) is the weighted average of \( z_\xi \) in \( \mathbb{R} \).
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Derivation was controversial
Is it a conditional likelihood?

\[
\frac{\exp(z_{(i)} \beta)}{\sum_{\ell \in \mathcal{R}(t_{(i)})} \exp\{z_{\ell} \beta\}}: \text{interpreted as cond. prob. that individual } (i) \text{ is the one failing at time } t_{(i)}, \text{ given that a failure occurs at } t_{(i)}
\]

- but it is given \(\mathcal{R}(t_{(i)})\)
- 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 \(I\) 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.
To deal with this the paper proposes two strategies:
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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(t; z) \, dt}{1 - \lambda(t; z) \, dt} = \frac{\lambda_0(t) \, dt}{1 - \lambda_0(t) \, dt} \exp(z\beta)
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where \(\lambda_0(t) = Pr(T \leq t + 1 | T > t)\) arbitrary
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Similar arguments lead to PLE
PO model \(\Rightarrow\) PH model as the intervals become infinitesimal
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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2. **Departures from proportionality:**
   - Formulation of both PH and PO allows for time varying explanatory variables
   - Special case: covariate generated from the interaction between a time fixed variable and time
   - This allows testing the proportional assumption
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2. **Departures from proportionality:**
   - formulation of both PH and PO allows for time varying explanatory variables
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   - This allows testing the proportional assumption

3. **Estimating failure time dsn:** generalization of the product limit estimation of $\lambda(t)$
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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
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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
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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
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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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5. Thanks
(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
2 – The next 10 years

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Interest in **semi-parametric models** exploded following PH model, prompting huge developments in theory (Bickel et al, 1998)

These developments are increasingly important in causal inference, missing data, *etc.* (Tsiatis, 2006)
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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?
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De Stavola/History · 8 March 2013
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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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)
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