Stratification in the Cox model

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Today’s topic is the use of stratification in Cox regression

There are two main purposes of stratification:

- It is useful as a diagnostic for checking the proportional hazards assumption
- It offers a way of extending the Cox model to allow for non-proportionality with respect to some covariates
To illustrate these concepts, we will look at a classic survival data set, the VA lung cancer data (veteran in the survival package).

The data comes from a clinical trial carried out by the Veterans’ Administration on male veterans with advanced, inoperable lung cancer.

In the trial, patients were randomized to receive either a standard chemotherapy or an experimental chemotherapy, and the primary endpoint was the time until death.
A number of covariates which potentially affect survival were also recorded:

- **karno**: The Karnofsky score, a way of quantifying the patient’s overall baseline status, with $\geq 70$ denoting that the patient is able to care for themselves, $40 - 60$ meaning that the patient requires assistance and regular medical care, and $10 - 30$ meaning that the patient is hospitalized.

- **diagtime**: Time in months from diagnosis to randomization.

- **age**: Age in years at randomization.

- **prior**: Indicator for whether the patient had received prior therapy.

- **celltype**: Type of tumor (small cell, large cell, squamous, adenocarcinoma).
Kaplan-Meier

- Checking the proportional hazards assumption
- Fitting stratified Cox models

Survival plot showing two curves labeled "Standard" and "Test".
Cox results

- Adeno vs. squamous: Hazard ratio < 0.0001
- Small vs. squamous: Hazard ratio < 0.01
- Large vs. squamous: Hazard ratio 0.16
- Treatment: Hazard ratio 0.16
- Prior: Hazard ratio 0.76
- Diagnosis Time: Hazard ratio 0.99
- Age: Hazard ratio 0.35
- Karnofsky: Hazard ratio < 0.0001

Hazard ratio

0.6 1 1.6 2.7 4.5 7.4
Consider the following as a way to assess the proportional hazards assumption: rather than including a term in the model as a covariate, we will estimate separate baseline hazards $\hat{\Lambda}_{01}, \hat{\Lambda}_{02}, \ldots$, for each level of the covariate.

If the baseline hazards appear proportional, then it is reasonable to model the term in the regular manner.
Because proportionality is difficult to assess by visual inspection, it is common to plot $\log \hat{\Lambda}_0$:

$$\Lambda_i(t) = \Lambda_0(t) \exp(\eta_i)$$

$$\log \Lambda_i(t) = \log \Lambda_0(t) + \eta_i$$

An alternative, known as the *Andersen plot*, is to plot $\hat{\Lambda}_{01}$ versus $\hat{\Lambda}_{02}$; under proportional hazards this should be a straight line with slope $\exp(\eta)$. 

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Treatment (Version 1)

![Graph showing log(Λ(t)) over time for Standard and Test treatments. The graph indicates that the hazard rates are similar between the two treatments.]
Treatment (Version 2) ($\hat{\beta} = 0.29$)
Treatment (Version 3, the Andersen plot)
Introduction

Checking the proportional hazards assumption

Fitting stratified Cox models

Cell type

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Karnofsky

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Remarks

- Treatment appears broadly proportional except for very short-term survival
- Proportional hazards appears questionable with respect to cell type
- Karnofsky status also appears non-proportional, with the variable losing relevance over time (which makes sense)
The stratified Cox model

- What should we do in the presence of variables with non-proportional effects?
  - One remedy is to allow for different baseline hazards for each level of the variable:

\[
\lambda_{ij}(t) = \lambda_{0j}(t) \exp(x_i^T \beta),
\]

where \( \lambda_{ij}(t) \) is the hazard function for the \( i \)th subject, who belongs to the \( j \)th stratum.

- The model may seem complex, but is entirely straightforward in the likelihood framework, as we can simply combine likelihoods across strata:

\[
L(\beta) = \prod_j L_j(\beta)
\]
Furthermore,

\[ \ell(\beta) = \sum_j \ell_j(\beta) \]

\[ u(\beta) = \sum_j u_j(\beta) \]

\[ I(\beta) = \sum_j I_j(\beta) ,\]

so estimation, the Newton-Raphson algorithm, and inference are all straightforward as well: we simply have to sum the contributions from each stratum.
The survival package makes it easy to fit stratified Cox models through the use of the strata function:

```r
fit <- coxph(S ~ trt + karno + ... + strata(celltype))
```

`summary(fit)` will then provide a summary for all the parametric terms (trt, karno, ...), but not celltype.

`survfit(fit)` will estimate $K$ different baseline hazard functions, one for each stratum (here, $K = 4$).
Standard treatment, wait 12 months, age 40, no prior treatment
Stratified Cox models are a useful extension of the standard Cox models to allow for covariates with non-proportional hazards.

A minor drawback is that stratifying unnecessarily (i.e., even though the PH assumption is met) reduces estimation efficiency, although the loss is typically very small.

A larger limitation of stratification is that it becomes messy with continuous variables and with multiple stratification variables, as there is no way to impose an additive structure.
The other primary limitation of stratified models is that there is no way to carry out inference for the stratification variables. For example, stratification is commonly used to aggregate results across multi-center studies, because comparing these sites is typically not of interest. Stratification is less useful in dealing with non-proportionality with respect to treatment – we are definitely interested in estimating the effect of treatment, and although we can obtain descriptive measures by estimating baseline coefficients, confidence intervals and tests are lacking. In such cases, a more satisfying approach is to directly model the changing effect of the predictor over time, a topic we will cover in a future lecture.