

Models In Epidemiology And Biostatistics
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Assessment of the Proportional Hazards Assumption

Graphical : The Log Log Plot

We know that proportional hazards means models like:

$$\log h(t) = \log h_0(t) + \sum_{j=1}^k \beta_j x_j \quad \text{or equivalently} \quad \log H(t) = \log H_0(t) + \sum_{j=1}^k \beta_j x_j$$

If the hazard functions are proportional, then the cumulative hazard functions are proportional and vice versa.

We can recall that $H(t) = -\log S(t)$ and so:

$$\log[-\log S(t)] = \log[-\log S_0(t)] + \sum_{j=1}^k \beta_j x_j$$

Let us consider a [crude] model for a dichotomous exposure which then gives us:

$$\log[-\log S_0(t)] + \beta_1 E$$

If we graph $\log[-\log S_0(t)]$ versus [analysis] time and $\log[-\log S_0(t)] + \beta_1$ versus [analysis] time on the same graph, we can see that the two curves are the same apart from the vertical shift β_1 . We call this graphing on the log log scale. So graphing the logarithm of the negative of the logarithm of the modelled survival curves has this simple form of a one curve and a vertically shifted version of the curve. Such a visual is an implication of the model.

Now consider the construction of such curves without the proportional hazards assumption. One could, for this example, construct separate Nelson Allen estimates of the 2 curves:

$-\log S_0(t)$ and $-\log S_1(t)$ and then graph $\log[-\log S_0(t)]$ versus [analysis] time along with $\log[-\log S_1(t)]$ versus [analysis] time. If these curves cannot be viewed as merely vertically shifted versions of each other, then we [visual] evidence against the proportional hazards assumption.

We can extend this approach to models with

- a) more than two exposure groups
- b) a dichotomous exposure and a small set of other explanatory variables analogous to a stratified analysis

In principle, one then views each of the estimated curves [on the log log scale as above] and attempts to see trouble.

One can consider models that include a measured variable like [centred actual] age A included additively like those that imply:

$$\log[-\log S_0(t)] + \beta_1 E + \beta_2 A$$

Choosing $A=0$ and then graphing the two curves on the log log scale again gives the vertical shift.

We can separately fit $\log[-\log S_{0i}(t)] + \beta_2 A$ for each exposure group [a model allowing for exposure specific baseline hazard] and then graph the two estimated curves [on the log log scale] for each exposure group [and set at say $A = 0$]. We then get a visual assessment of proportional hazards for the two exposure groups after 'adjusting' for age A . Unfortunately, this approach does not assess whether proportional hazards applies to age. Rather, this approach still assumes the assumption applies to age.

Again, in principle, we can extend this approach to:

- a) more than two exposure groups
- b) more than one additive measured variable
- c) combinations of exposure groups, other groups and additive measure variables

We are then assessing whether the proportional hazards assumption applies to the groups with additive 'adjustment' but not whether the assumption applies to the 'adjustment' variables.

We can explore some of these ideas:

```
use drugtr
stcox drug age, nohr
stcox age, strata(drug) nohr
stphplot, by(drug) adjust(age)
streg drug age, dist(weib) nohr
```

Stata's default is to graph the negative of the log of the negative of the log of estimated survivor functions versus the log of time. You can choose options [noneg, nolnt] to change from the defaults. In this example, the two 'curves' are quite straight. This suggests not just proportional hazards but Weibull hazards as well.

$$\log H(t) = \log \lambda + p \log(t) + \beta_1 E + \beta_2 A$$

These two curves then have approximately the same slope [which would estimates of negative p].

Log Log plots need not be lines. We are looking for the vertical shifts of one baseline cumulative hazard on the log scale.

Graphical: Residuals

Schoenfeld [1980, 1982] developed sets of residuals that provide a graphical assessment of the proportional hazards assumption. Each set of residuals can be considered for each time fixed explanatory variable. If there are 'trends' in these residuals when graphed versus analysis time, we obtain graphical evidence against proportional hazards for that variable. Grambsch and Therneau [1994] provided a quite unified view for these graphical assessments. Scatterplots smoothers and transformations of the analysis time axis provide incisive tools to aid in this assessment.

```
use drugtr
stcox drug age, nohr
estat phtest, plot(drug)
estat phtest, plot(age)
```

```
estat phtest, log plot(age)
estat phtest, rank plot(age)
```

Tests of Significance

In order to assess the trends, we can consider a regression of each of these sets of residuals [discussed above] on [possibly transformed] analysis time. For each time fixed variable and [possibly] a range of transformations of analysis time, we can obtain a p-value. So there can be many p-values in play here. Some authors propose considering just a single omnibus test for each transformation of analysis time. Inevitably, there are assumptions for these tests. These assumptions allow the use of an estimated overall (pooled) variance–covariance matrix in the equations. These tests have been shown to be fairly robust to departures from these assumptions. Nevertheless, some authors recommend such assessments with [suitably] stratified models. Again, one can be faced with many p-values, many graphs and sometimes mixed messages.

```
estat phtest, detail
estat phtest, rank detail
estat phtest, log detail

use leukemia
sts test treatment2
sts graph, by(treatment2)
stphplot, by(treatment2) adj(wbc2 wbc3)
stcox treatment2 wbc2 wbc3, nohr
estat phtest, detail
```

Assessment in Discrete Time

Since analysis is Logistic regression or CLogLog Regression, one can, in principle, use the usual model fitting process methods with either individual Wald tests or LR tests.

Returning to the study of Wheaton et al, we could consider a model which retains the time varying 'pd' but assesses a gender specific baseline hazard.

```
use wheaton_pp.dta
gen af=age_18*female
gen a2f=age_18sq*female
gen a3f=age_18cub*female
logit event age_18 af age_18sq a2f age_18cub a3f pd female
```