Abstract. In many applications of the Cox model the proportional hazards assumption is not plausible. In these cases, the solution to non-proportional hazards usually consists of modeling the effect of the variable of interest as well as the interaction effect of this variable with some function of time. Although Stata provides a handy command to implement this interaction in \texttt{stcox}, it does not allow the typical visualizations using \texttt{stcurve} if \texttt{stcox} was estimated with the \texttt{tvc()} option. In this article, I provide a short workaround which enables to estimate the survival function after \texttt{stcox} with time-dependent coefficients. I introduce and describe a new program \texttt{scurve tvc} which automates this procedure and which allows users to easily visualize survival functions for models with time-varying effects.

Keywords: \texttt{s0001}, \texttt{scurve tvc}, \texttt{stcox}, \texttt{tvc()}, \texttt{stcurve}, \texttt{sts generate}, Cox model, proportional hazards, time-varying coefficients, survival function

1 Overview

In many disciplines, the time-varying effects of variables in duration analyses are of substantive interest (Box-Steffensmeier et al. 2003; Giolo et al. 2012; Nilsson and Nivre 2013). Assume that a cancer treatment \( x \) had short-term benefits, but long-term treatment would cause side-effects which eventually deteriorate a patients health situation. In this scenario, we would like to know if the long-term side-effects outweigh the short-term benefits. This would be the case if after a certain time, fewer people which received the treatment had survived compared to patients who did not receive treatment \( x \). The comparison of these groups could be achieved with the respective survivor functions for each group (Putter et al. 2003). Calculating these estimates requires a short workaround, since Stata does not provide a build-in solution to plot the survival function with time-varying coefficients. I provide a solution below.

In the case that all covariates have constant effects, it is straightforward to calculate the survivor function for different scenarios, based on the estimated coefficients as well as the baseline survival functions (Kalbfleisch and Prentice 2002; Cleves et al. 2010). Let \( h_0(t) \) be the baseline hazard function. In the Cox model, the hazard function for an individual \( i \) with covariates \( x \) is then asserted to be

\[
h(t|x_i) = h_0(t) \exp(x_i \beta)
\]
Survival functions after `stcox` with `tvc()`

From this we can calculate the cumulative hazard function:

\[
H(t|x_i) = \int_0^t h(u|x_i) \, du = \exp(x_i \beta) \int_0^t h_0(u) \, du = \exp(x_i \beta) H_0(t)
\]  

(2)

Since the survivor function can be calculated from the cumulative hazard function, we get:

\[
S(t|x_i) = \exp(-\exp(x_i \beta) H_0(t)) = S_0(t)^{-\exp(x_i \beta)}
\]  

(3)

In the case of time-varying effects, this calculation becomes more complicated. To allow for a changing effect, an interaction of the variable with some function of time can be included as a time-varying covariate. If the function \( f(t) \) by which the effect varies with time is known, the effect can easily be modeled. Consider a variable \( z \) with such a time-varying effect. If we enter the interaction of \( z \) with time as a time-varying covariate, the hazard can be written as

\[
h(t|z_i) = h_0(t) \exp(z_i \gamma + z_i f(t) \delta) = h_0(t) \exp(z_i [\gamma + f(t) \delta]) = h_0(t) \exp(z_i \beta_i)
\]  

(4)

While this easily accounts for the time-varying effect, the calculation of the survival function becomes more complicated. Once the predictor variables in the model are interacted with time, the linear combination of predictors \( z_i \beta_i \) depends on time and remains in the integral in (2).

Below, I provide an example how to estimate these survivor functions in Stata. Thereafter, I describe the new program `scurve_tvc` which automates this procedure.

2 Estimating survival functions with `tvc()`

Consider a case with a binary treatment variable \( x \) and a binary confounder called `control`, whereby the effect of \( x \) changes over time. The following code generates duration data for this setting, whereby the observations are censored after 30 observations (cf. Crowther and Lambert [2012]). The data come from the following exponential duration model:

\[
h(t|x_i) = \exp(ln(0.05) - 0.9x_i + 0.6ln(t)x_i + 1.5control_i)
\]
. gen control=(runiform()>0.5)
. survsim ftime, cov(x -.9 control 1.5) tde(x .6) distribution(exponential) ///
> lambda(.05)
. gen failure=(ftime<=30)
. replace ftime=30 if ftime>30
(65 real changes made)
. stset ftime, failure(failure)
    failure event: failure != 0 & failure < .
    obs. time interval: (0, ftime]
    exit on or before: failure

1000 total observations
0 exclusions

1000 observations remaining, representing
935 failures in single-record/single-failure data
9693.849 total analysis time at risk and under observation
at risk from t = 0
earliest observed entry t = 0
last observed exit t = 30

To model the time-dependent effect, users of Stata could draw on stcox and the tvc() option. Unfortunately, however, Stata is unable to estimate survival functions in the presence of time-dependent effects.

. stcox x control, tvc(x) texp(ln(_t)) nohr nolog
    failure _d: failure
    analysis time _t: ftime
Cox regression -- no ties
No. of subjects = 1,000 Number of obs = 1,000
No. of failures = 935
Time at risk = 9693.849402
LR chi2(3) = 468.86
Log likelihood = -5468.3546 Prob > chi2 = 0.0000

|   _t | Coef. Std. Err. z P>|z| [95% Conf. Interval] |
|-------|--------|--------|---------|----------------------|
| main  | x      | -.931918 | .132382 | -7.04 | 0.000 | -1.191382 | -.672454 |
| control | 1.464325 | .0768318 | 19.06 | 0.000 | 1.313737 | 1.614912 |
| tvc   | x      | .6156235 | .065858 | 9.35 | 0.000 | .4865441 | .7447028 |

Note: Variables in tvc equation interacted with ln(_t).
. capture noisily stcurve, survival at(x=1) at(x=0)
this post-estimation command is not allowed after estimation with tvc();
see tvc note for an alternative to the tvc() option
In a randomized clinical trial, the results for both groups are easily compared using e.g. the Kaplan-Meier survival estimates. However, if our data stems from observational studies and requires us to adjust for a larger number of covariates, this comparison is no longer useful. Moreover, we might want to predict the survival function for different subgroups to assess the relative success of an intervention in different contexts (cf. Putter et al. 2005). In this case, a manual workaround can help us to get the intuition how the two groups evolve over time as well as how the effect differs across subgroups in our sample. Below, I outline this workaround using the example data.

First, we need to estimate the time varying coefficient manually:

```
. gen id=_n
. stset ftime, id(id) failure(failure)
    id: id
    failure event: failure != 0 & failure < .
    obs. time interval: ([ftime[_n-1], ftime]
    exit on or before: failure

1000    total observations
  0    exclusions

    1000    observations remaining, representing
    1000    subjects
    935    failures in single-failure-per-subject data
    9693.849    total analysis time at risk and under observation
    at risk from t = 0
    earliest observed entry t = 0
    last observed exit t = 30

. stsplit, at(failures)
     (935 failure times)
     (497,420 observations (episodes) created)

. generate x_t = x*ln(_t)

. stcox x x_t control, nolog nohr
    failure _d: failure
    analysis time _t: ftime
    id: id

Cox regression -- no ties
No. of subjects = 1,000    Number of obs = 498,420
No. of failures = 935
Time at risk = 9693.849402
LR chi2(3) = 468.86    Prob > chi2 = 0.0000

|         _t | Coef.  | Std. Err. | z    | P>|z|  | [95% Conf. Interval] |
|-----------|--------|-----------|------|------|----------------------|
| x         | -.9319 | .1323     | -7.04| 0.000| -.191382 - .672454   |
| x_t       | .6156  | .0659     | 9.35 | 0.000| .486541 .7447028    |
| control   | 1.4643 | .0768     | 19.06| 0.000| 1.313737 1.614912   |
```
We could now use the `stcurve` command, but setting $x_t$ to some value would ignore the fact that this variable is not constant, but rather varies with time. Hence, we need to proceed with the manual workaround and grab the stored coefficient estimates:

```
. matrix b=e(b)
```

We now use `sts generate` (or alternatively `predict` with the option `basehc`) to store the estimated hazard component, $\Delta H(t_j) = H(t_j) - H(t_{j-1})$, adjusting all variables to zero. Smoothing the variable `baseline` would generate an estimate of the baseline hazard function. The cumulative function of the variable will give us an estimate of the baseline cumulative hazard function.

```
. sts generate baseline=h, adjust(x x_t control)
```

Here, however, we are interested in a comparison of the survival function for four different scenarios: $x=1$ and `control`=0, $x=0$ and `control`=0, $x=1$ and `control`=1, $x=0$ and `control`=1. Since the effect of $x$ varies with time, we cannot simply calculate the function from the baseline cumulative hazard or survival function. We therefore calculate the scenario-specific hazard contribution based on Kalbfleisch and Prentice (2002, 114ff.).

$$
\Delta H(t_j|x_i) = [1 - (1 - \Delta H(t_j))]^{\exp(x_i\beta)}
$$  \hspace{1cm} (5)

By summing up these values, we approximate the cumulative hazard function for each scenario. From this, we can calculate the estimated survival function.

$$
S(t_j|x_i) = \exp[-\sum \Delta H(t_j|x_i)]
$$  \hspace{1cm} (6)

The workaround implements these steps as follows:

```
. preserve
  . sort _t
  . collapse (mean) baseline, by(_t)
  .
  . *scenario 1: x=1 and control=0
    . gen b_x_nocontrol = 1-(1-baseline)^exp(b[1,1]+b[1,2]*ln(_t))
(1 missing value generated)
    . gen H_x_nocontrol = sum(b_x_nocontrol)
    . gen S_x_nocontrol = exp(-H_x_nocontrol)
  .
  . *scenario 2: x=0 and control=0
    . gen b_nox_nocontrol = baseline
(1 missing value generated)
    . gen H_nox_nocontrol = sum(b_nox_nocontrol)
    . gen S_nox_nocontrol = exp(-H_nox_nocontrol)
```

Survival functions after stcox with tvc().

*scenario 3: x=1 and control=1
  gen b_x_control = 1-(1-baseline)^exp(b[1,1]+b[1,2]*ln(_t)+b[1,3])
  (1 missing value generated)
  gen H_x_control = sum(b_x_control)
  gen S_x_control = exp(-H_x_control)

*scenario 4: x=0 and control=1
  gen b_nox_control = 1-(1-baseline)^exp(b[1,3])
  (1 missing value generated)
  gen H_nox_control = sum(b_nox_control)
  gen S_nox_control = exp(-H_nox_control)

keep S_x_nocontrol S_nox_nocontrol S_x_control S_nox_control _t
rename _t _tx
save my_surv_curve, replace
(note: file my_surv_curve.dta not found)

This data can now be merged with the original data and plotted using simple line plots. Figure 1 compares the workaround estimates against Kaplan-Meier estimates for each scenario. The individual graphs were combined with the user-written program grcileg. The graph demonstrates that the estimated survival functions are in reasonable agreement with the non-parametric Kaplan-Meier estimates for each scenario.
Figure 1: Comparing Kaplan-Meier survival estimates against estimated survivor function using the workaround.

3 The program `scurve_tvc`

The procedure is automated in the ado-file `scurve_tvc`. The program estimates a Cox model with time-varying coefficients from which it estimates, saves and plots the estimated survival function for as user-specified scenario. I describe the syntax, options and an illustrative example below.
3.1 Syntax

\texttt{scurve\_tvc [if] [in] , generate(newvarname)\hspace{1cm} at(varname \ [# [varname \ # \ldots \ ]]) tvc(varlist) texp(string) \ [ replace ties(string) shared(varname) strata(varname) graph plotopts(string)]}

3.2 Description

\texttt{scurve\_tvc} fits \texttt{stcox} with time-varying effects and calculates the survival curve for specific covariate values.

\texttt{generate(newvarname)} creates the variable \texttt{newvarname} to store the estimated survival curve. If \texttt{strata()} is specified, \texttt{scurve\_tvc} creates one variable for each stratum. The corresponding analysis time variable, which allows to plot the results, is saved in a new variable called \texttt{tscurve}.

\texttt{at(varname \ [# \ldots \ ])} specifies the covariates included in the model and the values for which the survival curve should be calculated.

\texttt{tvc(varlist)} specifies the covariates with time-varying coefficients. The variables in \texttt{tvc()} must also appear in \texttt{at()}. \texttt{scurve\_tvc} will automatically \texttt{stsplit} the data at failure times to ensure a correctly estimated model. See \texttt{help tvc note} for more information.

\texttt{texp(string)} specifies the function of analysis time according to which the effect varies with time. For example, specifying \texttt{texp(ln(t))} would cause the variables with time-varying coefficients to be multiplied by the logarithm of analysis time.

3.3 Options

\texttt{replace} existing variable(s) with the new estimates.

\texttt{ties(string)} specifies the option how \texttt{stcox} handles tied failure times. See \texttt{help stcox} for details.

\texttt{shared(varname)} specifies a shared-frailty ID variable. See \texttt{help stcox} for details.

\texttt{strata(varname)} specifies a strata ID variables. See \texttt{help stcox} for details.

\texttt{graph} plots the predicted survival curve. If \texttt{strata()} is specified, the survival estimates for each stratum will be plotted.

\texttt{plotopts(string)} enables to customize the plot using options allowed with \texttt{twoway line}. 

\textit{Survival functions after \texttt{stcox} with \texttt{tvc()}}
### 3.4 Example

Similar to the example above, consider a case with a binary treatment variable \( x \), a binary confounder called \( \text{control1} \) and a continuous confounder called \( \text{control2} \), whereby the effect of \( x \) changes over time. The following code generates duration data for this setting, whereby the observations are censored after 30 observations (cf. Crowther and Lambert 2012). The data come from the following Weibull duration model:

\[
h(t|x_i) = 1.3t^{1.3-1}\exp(ln(0.05) - 0.9x_i + 0.6ln(t)x_i - 1.3\text{control1}_i - 0.4\text{control2}_i)
\]

```stata
. clear
. set seed 581265456
. set obs 1000
   number of observations (_N) was 0, now 1,000
. gen x=(runiform()>0.5)
. gen control1=(runiform()>0.5)
. gen control2=rnormal()
.
. survsim ftime, cov(x -.9 control1 -1.3 control2 -.4) tde(x .6) ///
   distribution(weibull) lambda(.05) gamma(1.3)
. gen failure=(ftime<30)
. replace ftime=30 if ftime>30
   (109 real changes made)
.
. gen id=_n
.
. stset ftime, id(id) failure(failure)
   id: id
   failure event: failure != 0 & failure < .
   obs. time interval: (ftime[_n-1], ftime]
   exit on or before: failure

1000  total observations
   0  exclusions

1000  observations remaining, representing
1000  subjects
891  failures in single-failure-per-subject data
13122.843  total analysis time at risk and under observation
at risk from t = 0
earliest observed entry t = 0
last observed exit t = 30
```

Assume that \( x \) is a cancer treatment from which we know that it causes severe long-term side-effects. Hence, we would want to know under which circumstances the treatment is beneficial and whether the survival functions cross at a certain point in time. In this case, we can use \texttt{scurve} and \texttt{tv} to estimate a Cox model in which the effect of \( x \) varies with time and predict the estimated survival function for a specific scenario, here \( x=1 \), \( \text{control1}=0 \) and \( \text{control2}=0 \):
Survival functions after *stcox* with *tvc()*

. scurve_tvc, gen(S_x) at(x 1 control1 0 control2 0) tvc(x) texp(ln(_t)) replace
(note: variable S_x not found)

Dataset has been temporarily split at failure times
(891 failure times)
(493,614 observations (episodes) created)

The estimation is based on the following Cox Proportional Hazards Model:

\[
\begin{align*}
\text{failure} \_d & : \text{failure} \\
\text{analysis time} \_t & : \text{ftime} \\
\text{id} & : \text{id}
\end{align*}
\]

Iteration 0: log likelihood = -5506.5059
Iteration 1: log likelihood = -5299.4786
Iteration 2: log likelihood = -5298.9218
Iteration 3: log likelihood = -5298.9218
Refining estimates:
Iteration 0: log likelihood = -5298.9218

Cox regression -- no ties

| _t       | Coef. | Std. Err. | z     | P>|z|   |  [95% Conf. Interval] |
|----------|-------|-----------|-------|-------|-----------------------|
| x        | -.99  | .197      | -5.04 | 0.00  | -1.38 to -.61        |
| control1 | -1.23 | .074      | -16.61| 0.00  | -1.38 to -1.09       |
| control2 | -.39  | .035      | -10.99| 0.00  | -.46 to -.32         |
| _x_t     | .64   | .086      | 7.40  | 0.00  | .48 to .81           |

Note: tvc-interactions denoted by \_varname\_t were interacted with ln(_t).

We repeat the same process, but this time for the scenario with \(x=0\). We then plot this variable against the corresponding analysis time stored in the new variable \_tscurve. Figure 2 shows that for the specified scenarios, the survival curves cross after about 9 time units. Hence, the negative side-effects of treatment \(x\) outweigh its benefits after this time.

. quietly scurve_tvc, gen(S_nox) at(x 0 control1 0 control2 0) tvc(x) texp(ln(_t)) replace
. label var S_x "x=1"
. label var S_nox "x=0"
. twoway line S_x S_nox _tscurve, c(J J) scheme(sj) title(""") xtitle("Analysis time") ytitle("Probability of survival") ylab(0(.2)1)

If the user is interested in a single scenario only, using the option *graph* as well as *plotopts()* will automatically produces a graph for the scenario specified in *at()*.
Often, however, we are interested in a comparison of different scenarios, similar to Putter et al. (2005). Hence, we can use scurve_tvc to estimate the survival functions for $x=0$ and $x=1$ at various values of the remaining covariates. In the hypothetical cancer treatment example, this might imply calculating the estimated survival probabilities for specific patient characteristics with different risk-levels. We can then plot the estimated survival functions for each scenario to transparently communicate the estimated survival probabilities and highlight potential trade-offs for treatments with time-varying effects.

Figure 3 provides these estimates for four scenarios. The substantive interpretation for our hypothetical cancer treatment implies that the treatment $x$ is ineffective and even harmful for low and moderate risk patients. However, high risk patients profit from the procedure. The graphical representation therefore helps to communicate the complex results from the model with non-proportional hazards very clearly and intuitively.

To highlight that the procedure accurately captures the data generating process, Figure 3 shows the analytically calculated, true survival functions and compares these to the estimates from scurve_tvc. The plot indicates that the results are in close agreement with underlying data generating process.

4 Conclusion

This paper demonstrates how to estimate survival functions from Cox models with time-varying coefficients. The code is automated in the program scurve_tvc. The procedure allows to visualize the predictions of models with non-proportional hazards and enables to effectively communicate model predictions for different covariate scenarios to
Survival functions after `stcox with tvc()`

Figure 3: Comparing true, analytically calculated survivor functions (left) for the simulated data with empirical estimates calculated with `scurve_tvc` (right).
a broader audience.

5 References


About the authors

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