

# Cox Model With Time Varying Covariates

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## Introduction

The Cox Proportional Hazards Model is an important model in *event history and survival analysis*. One important aspect of the Cox Model is its ability to include *time varying covariates*, covariates whose value changes over time.

The example below draws heavily from—but is slightly adapted from—the Stata `help stcox` file.

## Get Data

```
. use https://www.stata-press.com/data/r17/drugtr2, clear // simulated drug data
```

Per the Stata documentation:

“Consider a dataset consisting of 45 observations on recovery time from walking pneumonia. Recovery time (in days) is recorded in the variable `time`, and there are measurements on the covariates `age`, `drug1`, and `drug2`, where `drug1` and `drug2` interact a choice of treatment with initial dosage level. The study was terminated after 30 days, so those who had not recovered by that time were censored (`cured = 0`).”

## stset The Data

```
. stset time, failure(cured) // set up data for survival analysis
Survival-time data settings
      Failure event: cured!=0 & cured<.
Observed time interval: (0, time]
      Exit on or before: failure
```

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|    |                    |  |
|----|--------------------|--|
| 45 | total observations |  |
| 0  | exclusions         |  |

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|       |   |    |
|-------|---|----|
| 45    | observations remaining, representing              |    |
| 36    | failures in single-record/single-failure data     |    |
| 677.9 | total analysis time at risk and under observation |    |
|       | At risk from t =                                  | 0  |
|       | Earliest observed entry t =                       | 0  |
|       | Last observed exit t =                            | 30 |

## Model 1: Drugs Are *Time Invariant* Covariates

```
. stcox age drug1 drug2 // Cox model
      Failure _d: cured
      Analysis time _t: time
Iteration 0:   log likelihood = -116.54385
Iteration 1:   log likelihood = -102.77311
Iteration 2:   log likelihood = -101.92794
Iteration 3:   log likelihood = -101.92504
Iteration 4:   log likelihood = -101.92504
Refining estimates:
Iteration 0:   log likelihood = -101.92504
Cox regression with Breslow method for ties
No. of subjects =    45                Number of obs =    45
No. of failures =    36
Time at risk    = 677.9
Log likelihood = -101.92504            LR chi2(3)    = 29.24
                                      Prob > chi2    = 0.0000
```

| _t    | Haz. ratio | Std. err. | z     | P> z  | [95% conf. interval] |          |
|-------|------------|-----------|-------|-------|----------------------|----------|
| age   | .8759449   | .0253259  | -4.58 | 0.000 | .8276873             | .9270162 |
| drug1 | 1.008482   | .0043249  | 1.97  | 0.049 | 1.000041             | 1.016994 |
| drug2 | 1.00189    | .0047971  | 0.39  | 0.693 | .9925323             | 1.011337 |

```
. est store M1 // store estimates
```

## Model 2: Drugs Are *Time Varying* Covariates

```
. stcox age, tvc(drug1 drug2) // Cox model
      Failure _d: cured
      Analysis time _t: time
Iteration 0:   log likelihood = -116.54385
Iteration 1:   log likelihood = -104.50191
Iteration 2:   log likelihood = -103.87961
Iteration 3:   log likelihood = -103.87525
Iteration 4:   log likelihood = -103.87525
Refining estimates:
Iteration 0:   log likelihood = -103.87525
Cox regression with Breslow method for ties
No. of subjects =    45                Number of obs =    45
No. of failures =    36
Time at risk    = 677.9
Log likelihood = -103.87525            LR chi2(3)    = 25.34
                                      Prob > chi2    = 0.0000
```

| _t    | Haz. ratio | Std. err. | z     | P> z  | [95% conf. interval] |          |
|-------|------------|-----------|-------|-------|----------------------|----------|
| main  |            |           |       |       |                      |          |
| age   | .8786593   | .0250789  | -4.53 | 0.000 | .8308552             | .9292139 |
| tvc   |            |           |       |       |                      |          |
| drug1 | 1.000272   | .000335   | 0.81  | 0.416 | .9996161             | 1.000929 |
| drug2 | .9998618   | .000364   | -0.38 | 0.704 | .9991486             | 1.000576 |

Note: Variables in tvc equation interacted with \_t.

```
. est store M2 // store estimates
```

## Model 3: Drugs Are *Time Varying Covariates* (Manually Specified)

```
. generate id=_n // multiple record data needs an id

. streset, id(id) // `streset` the data
-> stset time, id(id) failure(cured)
Survival-time data settings
    ID variable: id
    Failure event: cured!=0 & cured<.
    Observed time interval: (time[_n-1], time]
    Exit on or before: failure
```

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```
45 total observations
0 exclusions
```

---

```
45 observations remaining, representing
45 subjects
36 failures in single-failure-per-subject data
677.9 total analysis time at risk and under observation
                                     At risk from t =      0
                                     Earliest observed entry t =      0
                                     Last observed exit t =     30
```

```
. stsplot, at(failures) // split data at each recovery time
(31 failure times)
(812 observations (episodes) created)

. generate drug1emt = drug1 * _t // manual interaction of drug1 and time

. generate drug2emt = drug2 * _t // manual interaction of drug2 and time

. stcox age drug1emt drug2emt // Cox model
    Failure _d: cured
    Analysis time _t: time
    ID variable: id
Iteration 0: log likelihood = -116.54385
Iteration 1: log likelihood = -104.50191
Iteration 2: log likelihood = -103.87961
Iteration 3: log likelihood = -103.87525
Iteration 4: log likelihood = -103.87525
Refining estimates:
Iteration 0: log likelihood = -103.87525
Cox regression with Breslow method for ties
No. of subjects = 45                      Number of obs = 857
No. of failures = 36
Time at risk = 677.9
LR chi2(3) = 25.34
Log likelihood = -103.87525               Prob > chi2 = 0.0000
```

| _t       | Haz. ratio | Std. err. | z     | P> z  | [95% conf. interval] |
|----------|------------|-----------|-------|-------|----------------------|
| age      | .8786593   | .0250789  | -4.53 | 0.000 | .8308552 .9292139    |
| drug1emt | 1.000272   | .000335   | 0.81  | 0.416 | .9996161 1.000929    |
| drug2emt | .9998618   | .000364   | -0.38 | 0.704 | .9991486 1.000576    |

```
. est store M3 // store estimates
```

## Nice Table of Estimates to Compare Models

```
. est table M1 M2 M3, star equations(1)
```

| Variable | M1            | M2            | M3            |
|----------|---------------|---------------|---------------|
| #1       |               |               |               |
| age      | -.13245204*** | -.12935802*** | -.12935802*** |
| drug1    | .00844606*    |               |               |
| drug2    | .00188866     |               |               |
| drug1emt |               |               | .0002724      |
| drug2emt |               |               | -.00013819    |
| tvc      |               |               |               |
| drug1    |               | .0002724      |               |
| drug2    |               | -.00013819    |               |

Legend: \* p<0.05; \*\* p<0.01; \*\*\* p<0.001