# Fitting Cox proportional-hazards model for interval-censored event-time data

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2021 Stata Webinar

## Outline

- What is interval-censored event-time data?
- Semiparametric Cox proportional hazards model for interval-censored event-time data
- Highlights of `stintcox` command
- Postestimation features of `stintcox` command
- Graphical assessment for proportional-hazards assumption
- Conclusion and future work

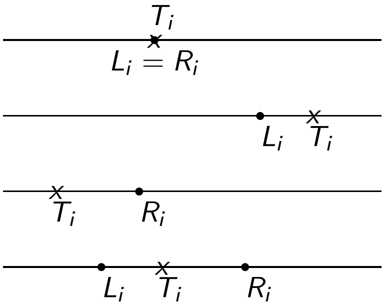
# What is interval-censored event-time data?

- The event of interest is not always observed exactly, but is known only to occur within some time interval. For example, cancer recurrence, time of COVID infection.
- Interval-censored event-time data arise in many areas, including medical, epidemiological, economic, financial, and sociological studies.
- Ignoring interval-censoring may lead to biased estimates.
- There are four types of censoring: left-censoring, right-censoring, interval-censoring, and no censoring.

# Types of censoring

Event time $T_i$ is not always exactly observed. $(L_i, R_i]$ denotes the interval in which $T_i$ is observed.

No censoring
$L_i = R_i = T_i$
Right-censoring
$(L_i, R_i = +\infty)$
Left-censoring
$(L_i = 0, R_i]$
Interval-censoring
$(L_i, R_i]$



# Types of interval-censored data

- Case I interval-censored data (**current status data**): occurs when subjects are observed only once, and we only know whether the event of interest occurred before the observed time. The observation on each subject is either left- or right-censored.
- Case II (**general**) interval-censored data: occurs when there are potentially two or more examination times for each study subject. The interval that brackets the event time of interest, the event-time interval, is recorded for each subject. The observation on each subject is one of left-, right-, or interval-censored.

# Methods for analyzing interval-censored data

- Simple imputation methods
- Nonparametric maximum-likelihood estimation
- Parametric regression models – `stintreg`
- **Semiparametric Cox proportional hazards model –** `stintcox`
- Bayesian analysis
- ...

# Semiparametric Cox proportional hazards model

- The Cox proportional hazards model was first introduced by Cox in 1972 and was used routinely to analyze uncensored and right-censored event-time data.

$$h(t;\mathbf{x}) = h_0(t)\exp(\beta_1 x_1 + \cdots + \beta_p x_p)$$

- It is also appealing for interval-censored data because it does not require parameterization of the baseline hazard function.
- Also, under the proportional-hazard assumption, the hazard ratios are constant over time.

# Cox model's challenge for interval-censored data

- Cox model is challenging for interval-censored event-time data because none of the event times are observed exactly. In particular, the traditional partial-likelihood approach is not applicable.
- Several authors have proposed spline methods to fit the Cox model to interval-censored data and those method have their limitations.
- The direct maximum-likelihood optimization using the Newton-Raphson algorithm is highly unstable.
- Zeng, Mao, and Lin (2016) developed a genuine EM algorithm for efficient nonparametric maximum-likelihood estimation (NPMLE) method to fit the Cox model for interval-censored data.

# A genuine model for `stintcox`

- Suppose that the observed data consist of $(t_{li}, t_{ui}, \mathbf{x}_i)$ for $i = 1, \ldots, n$, where $t_{li}$ and $t_{ui}$ define the observed time interval and $\mathbf{x}_i$ records covariate values for a subject $i$.
- Under the NPMLE approach, the baseline cumulative hazard function $H_0$ is regarded as a step function with nonnegative jumps $h_1, \ldots, h_m$ at $t_1, \ldots, t_m$, respectively, where $t_1 < \cdots < t_m$ are the distinct time points for all $t_{li} > 0$ and $t_{ui} < \infty$ for $i = 1, \ldots, n$.
- The observed-data likelihood function is

$$\prod_{i=1}^{n} \exp\left\{-\sum_{t_k \le t_{li}} h_k \exp(\mathbf{x}_i\boldsymbol{\beta})\right\}\left[1-\exp\left\{-\sum_{t_{li}<t_k\le t_{ui}} h_k \exp(\mathbf{x}_i\boldsymbol{\beta})\right\}\right]^{I(t_{ui}<\infty)} \quad (1)$$

# A genuine model for `stintcox` (cont.)

- Let $W_{ik}$ $(i = 1, \ldots, n; k = 1, \ldots, m)$ be independent latent Poisson random variables with means $h_k \exp(\mathbf{x}_i \beta)$. Define $A_i = \sum_{t_k \leq t_{li}} W_{ik}$ and $B_i = I(t_{ui} < \infty) \sum_{t_{li} < t_k \leq t_{ui}} W_{ik}$. The likelihood for the observed data $(t_{li}, t_{ui}, \mathbf{x}_i, A_i = 0, B_i > 0)$ is

$$\prod_{i=1}^{n} \prod_{t_k \leq t_{li}} \Pr(W_{ik} = 0) \Big\{ 1 - \Pr\Big( \sum_{t_{li} < t_k \leq t_{ui}} W_{ik} = 0 \Big) \Big\}^{I(t_{ui} < \infty)} \qquad (2)$$

- (1) and (2) are exactly equal. The maximization of a weighted sum of Poisson log-likelihood functions is strictly concave and has a closed-form solution for $h_k$'s.

# A genuine model for `stintcox` (cont.)

- We maximize (2) through an EM algorithm treating $W_{ik}$ as missing data.
  - In the E-step, we evaluate the posterior means of $W_{ik}$.
  - In the M-step, we update $\boldsymbol{\beta}$ and $h_k$ for $k = 1, \ldots, m$.
- This method allows a completely arbitrary baseline hazard distribution and results in consistent, asymptotically normal, and asymptotically efficient.

# stintcox highlights

stintcox fits semiparametric Cox proportional hazards models to interval-censored event-time data, which may contain right-censored, left-censored, or interval-censored observations.

- Fits current-status and general interval-censored data.
- Provides four methods for standard-error computation.
- Provides standard-error computation on replay.
- Provides options to control the tradeoff between the execution speed and accuracy of the results.
- Supports two ways to choose the time intervals to be estimated for baseline hazard contributions.
- Supports stratification.

# Basic Syntax

stintcox [ *indepvars* ], interval($t_l$ $t_u$)

- Option interval() is required and is used to specify two time variables that contain the endpoints of the event-time interval.
- *indepvars* is optional. You can fit a Cox model without any covariates.
- st setting the data is not necessary and will be ignored.
- stintcox currently only fits time-independent Cox model.

# Motivating example

## Modified Bangkok IDU Preparatory Study

- 1124 subjects were initially negative for HIV-1 virus.
- They were followed and tested for HIV approximately every four months.
- The event of interest was time to HIV-1 seropositivity.
- The exact time of HIV infection was not observed, but it was known to fall in intervals between blood tests with time variables `ltime` and `rtime`.
- We want to identify the factors that influence HIV infection. The covariates that we are interested in are centered age variable (`age_mean`), and history of drug injection before recruitment (`inject`).

# Motivating example

```
. list in 701/710
```

| | ltime | rtime | age_mean | inject |
|---|---|---|---|---|
| 701. | 41.049179 | . | -1.4617438 | Yes |
| 702. | 20.09836 | . | 3.5382562 | No |
| 703. | 40.918034 | . | 5.5382562 | No |
| 704. | 11.934426 | 16.065575 | 4.5382562 | No |
| 705. | 32.327869 | . | -10.461744 | Yes |
| 706. | 40.360657 | . | -5.4617438 | No |
| 707. | 39.901638 | . | -9.4617438 | No |
| 708. | 24.065575 | . | 7.5382562 | Yes |
| 709. | 28.163935 | 32.52459 | -7.4617438 | No |
| 710. | 0 | 16.196722 | 3.5382562 | Yes |

# First example

```
. stintcox age_mean i.inject, interval(ltime rtime)
note: using adaptive step size to compute derivatives.
Performing EM optimization (showing every 100 iterations):
Iteration 0:    log likelihood = -1086.2564
  (output omitted)
Iteration 299:  log likelihood = -601.53336
Computing standard errors: ................ done
Interval-censored Cox regression                      Number of obs      =  1,124
Baseline hazard: Reduced intervals                           Uncensored =      0
                                                         Left-censored =     41
                                                        Right-censored =    991
                                                        Interval-cens. =     92
                                                      Wald chi2(2)       =  11.18
Log likelihood = -601.53336                           Prob > chi2        = 0.0037
```

| | Haz. ratio | OPG std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| age_mean | .9657816 | .0124711 | -2.70 | 0.007 | .9416454 | .9905365 |
| inject | | | | | | |
| Yes | 1.590116 | .2847623 | 2.59 | 0.010 | 1.11942 | 2.25873 |

# Types of standard-error estimation in stintcox

- stintcox estimates VCE for regression coefficients using the profile log-likelihood, which is obtained by maximizing the likelihood by holding the regression coefficients fixed.

| **Type of VCE** | **Order of deriv.** | **Stepsize** |
|---|---|---|
| vce(opg[,stepsize(adaptive)]) | first-order | adaptive |
| vce(opg, stepsize(fixed [#])) | first-order | fixed |
| vce(oim[,stepsize(adaptive)]) | second-order | adaptive |
| vce(oim, stepsize(fixed [#])) | second-order | fixed |

# Types of standard-error estimation in stintcox

- The oim will generally provide more accurate results when there are sufficient data to estimate the second-order derivatives reliably.
- However, the oim may lead to a negative definite matrix of second-order derivatives, which is not invertible.
- The choice of the step size may also affect the estimates.
- In some cases, the search for adaptive step sizes may lead to step sizes that are too large or too small such that the VCE matrix becomes close to being singular. In that case, you may consider trying a different search method or using a fixed step size.

# Standard-error estimation example

- For small dataset or dataset with low proportions of interval-censored observations, the standard-error estimates may be more variable between different VCE methods. In that case, you may want to compare several VCE methods.
- `stintcox` provides `vce()` on replay so you can compare different VCE methods without rerunning the estimation command.

# Standard-error estimation example

```
. stintcox, vce(oim)
note: using adaptive step size to compute derivatives.
Computing standard errors: .................. done
Interval-censored Cox regression                         Number of obs     =  1,124
Baseline hazard: Reduced intervals                              Uncensored =      0
                                                             Left-censored =     41
                                                            Right-censored =    991
                                                            Interval-cens. =     92
                                                         Wald chi2(2)      =  11.18
Log likelihood = -601.53336                              Prob > chi2       = 0.0037
```

| | Haz. ratio | OIM std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| age_mean | .9657816 | .0121666 | -2.76 | 0.006 | .9422274 | .9899245 |
| inject | | | | | | |
| Yes | 1.590116 | .3285746 | 2.24 | 0.025 | 1.060572 | 2.384061 |

```
Note: Standard-error estimates may be more variable for small datasets and
      datasets with low proportions of interval-censored observations.
```

# Compare different standard-error estimations

- First, save the current estimation for later comparison.

```
. stintcox, saving(basehc, replace)
note: file basehc.dta not found; file saved.
. estimates store opg_adapt
```

- Run different vce() on replay and save the results

```
. stintcox, vce(oim, post)
  (output omitted)
. estimates store oim_adapt
. stintcox, vce(opg, stepsize(fixed) post)
  (output omitted)
. estimates store opg_fixed
. stintcox, vce(oim, stepsize(fixed) post)
  (output omitted)
. estimates store oim_fixed
```

# Compare different standard-error estimations

- Compare the results

```
. estimates table opg* oim*, b(%9.4f) se(%9.4f) t p
```

| Variable | opg_adapt | opg_fixed | oim_adapt | oim_fixed |
|---|---|---|---|---|
| age_mean | -0.0348 | -0.0348 | -0.0348 | -0.0348 |
| | 0.0129 | 0.0129 | 0.0126 | 0.0116 |
| | -2.70 | -2.70 | -2.76 | -3.00 |
| | 0.0070 | 0.0070 | 0.0057 | 0.0027 |
| inject | | | | |
| Yes | 0.4638 | 0.4638 | 0.4638 | 0.4638 |
| | 0.1791 | 0.1791 | 0.2066 | 0.1746 |
| | 2.59 | 2.59 | 2.24 | 2.66 |
| | 0.0096 | 0.0096 | 0.0248 | 0.0079 |

Legend: b/se/t/p

# favorspeed vs. favoraccuracy

- `stintcox` may become time consuming for large dataset.
- Options `favorspeed` and `favoraccuracy` control the tradeoff between the execution speed and accuracy of the results.
- `stintcox` uses less stringent convergence criteria when `favorspeed` is specified.

# favorspeed example

```
. stintcox age_mean i.inject, interval(ltime rtime) favorspeed
note: using fixed step size with a multiplier of 5 to compute derivatives.
note: using EM and VCE tolerances of 0.0001.
note: option noemhsgtolerance assumed.
Performing EM optimization (showing every 100 iterations):
Iteration 0:    log likelihood = -1086.2564
Iteration 31:   log likelihood = -602.62237
Computing standard errors: ..... done

Interval-censored Cox regression                     Number of obs     =  1,124
Baseline hazard: Reduced intervals                          Uncensored =      0
                                                         Left-censored =     41
                                                        Right-censored =    991
                                                        Interval-cens. =     92
                                                     Wald chi2(2)      =  11.19
Log likelihood = -602.62237                          Prob > chi2       = 0.0037
```

| | Haz. ratio | OPG std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| age_mean | .965774 | .012463 | -2.70 | 0.007 | .9416534 | .9905125 |
| inject | | | | | | |
| Yes | 1.591654 | .2848271 | 2.60 | 0.009 | 1.120794 | 2.260329 |

# reduced vs. full

- Option `reduced`, the default, specifies that the baseline hazard function be estimated using a reduced (innermost) set of time intervals. The innermost time intervals were originally used by Turnbull (1976) to estimate the survivor function for nonparametric estimation.
- Option `full` specifies that the baseline hazard function be estimated using all observed time intervals. This is the approach used by Zeng, Mao, and Lin (2016) and Zeng, Gao, and Lin (2017).
- Option `full` is more time consuming, but it may provide more accurate results.
- When the dataset is right-censored dataset, `full` is assumed.

# reduced vs. full example

```
. stintcox age_mean i.inject, interval(ltime rtime) full
note: using adaptive step size to compute derivatives.
Performing EM optimization (showing every 100 iterations):
Iteration 0:    log likelihood = -951.11659
  (output omitted)
Iteration 733:  log likelihood = -601.56204
Computing standard errors: ................ done
Interval-censored Cox regression                    Number of obs     =  1,124
Baseline hazard: All intervals                            Uncensored =      0
                                                       Left-censored =     41
                                                      Right-censored =    991
                                                      Interval-cens. =     92
                                                    Wald chi2(2)      =  11.18
Log likelihood = -601.56204                         Prob > chi2       = 0.0037
```

| | Haz. ratio | OPG std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| age_mean | .9657924 | .0124751 | -2.69 | 0.007 | .9416485 | .9905553 |
| inject | | | | | | |
| Yes | 1.590554 | .2849228 | 2.59 | 0.010 | 1.119616 | 2.259581 |

# Postestimation overview

`stintcox` provides several postestimation features after estimation:

- Predictions of hazard ratios, linear predictions, and standard errors
- Predictions of baseline survivor, baseline cumulative hazard, and baseline hazard contribution functions
- Prediction of martingale-like residuals
- Plots for survivor, hazard, and cumulative hazard function

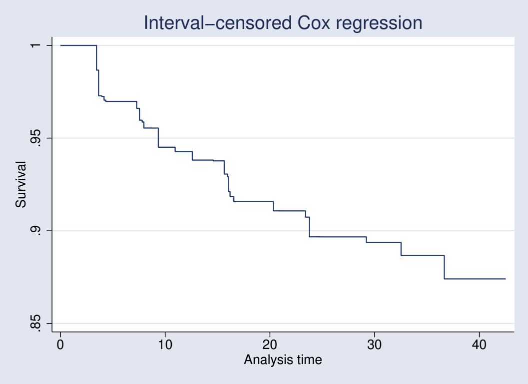
# Predict baseline survival functions

```
. stintcox age_mean i.inject, interval(ltime rtime)
  (output omitted)
. predict bs_l bs_u, basesurv
. list bs_l bs_u ltime rtime age inject in 300/310
```

| | bs_l | bs_u | ltime | rtime | age | inject |
|---|---|---|---|---|---|---|
| 300. | .8740674 | 0 | 40 | . | 36 | No |
| 301. | .9427818 | .9306043 | 11.967213 | 15.836065 | 21 | Yes |
| 302. | .9554337 | .9377201 | 8.1967211 | 15.180327 | 36 | Yes |
| 303. | .8740674 | 0 | 39.934425 | . | 40 | No |
| 304. | .8740674 | 0 | 39.47541 | . | 25 | No |
| 305. | .8740674 | 0 | 36.72131 | . | 40 | No |
| 306. | .8740674 | 0 | 39.934425 | . | 40 | Yes |
| 307. | .97047 | 0 | 4.2950821 | . | 34 | No |
| 308. | .8740674 | 0 | 39.737705 | . | 42 | No |
| 309. | .8740674 | 0 | 37.606556 | . | 30 | No |
| 310. | .8740674 | 0 | 39.967213 | . | 28 | No |

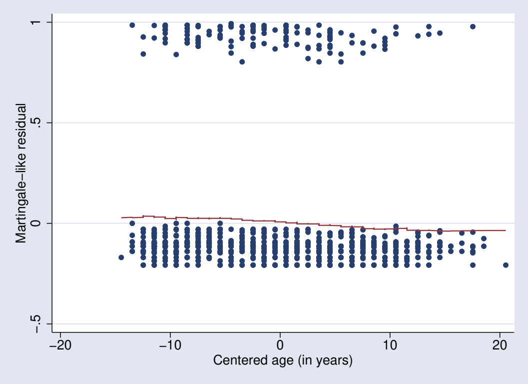
# Graph baseline survival functions

```
. stcurve, survival at(age_mean=0 inject=0)
```



# Assess functional form of a covariate

```
. stintcox i.inject, interval(ltime rtime)
  (output omitted)
. predict mg, mgale
. lowess mg age_mean, mean noweight title("") note("") m(o)
```



# Graphical check for proportional-hazards assumption

- `stintphplot` plots "log-log" survival plots for each level of a nominal or ordinal covariate. The proportional-hazard assumption is satisfied when the curves are parallel.
- `stintcoxnp` plots Turnbull's nonparametric and Cox predicted survival curves for each level of a categorical covariate. The closer the nonparametric estimates are to the Cox estimates, the less likely it is that the proportional-hazards assumption has been violated.
- You don't need to run `stintcox` before using those commands. `stintcox` has been called within those two commands.

## stintphplot basic syntax

stintphplot, interval($t_l$ $t_u$) by()

- Computes nonparametric estimates of the survivor function for each level of by() variable.

stintphplot, interval($t_l$ $t_u$) by() adjustfor()

- Fits a separate Cox model, which contains all covariates from the adjustfor() option, for each level of by() variable.

stintphplot, interval($t_l$ $t_u$) strata() adjustfor()

- Fits one stratified Cox model with all covariates from the adjustfor() option, then plots the estimated survivor function for each level of strata() variable.

# stintcoxnp basic syntax

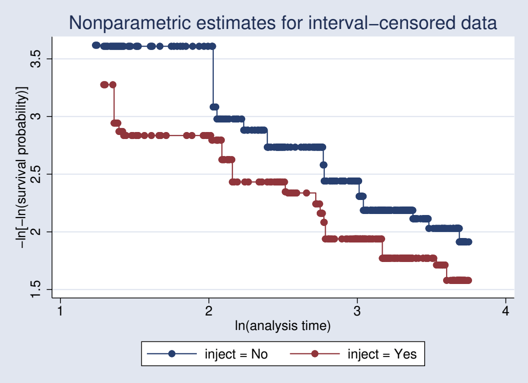
`stintcoxnp, interval(`$t_l$ $t_u$`) by() [separate]`

- The nonparametric and Cox predicted survivor functions are plotted for each level of `by()` variable.
- Option `separate` produces separate plots of nonparametric and Cox predicted survivor functions for each level of `by()` variable.

# Check PH-assumption for a model with a single covariate

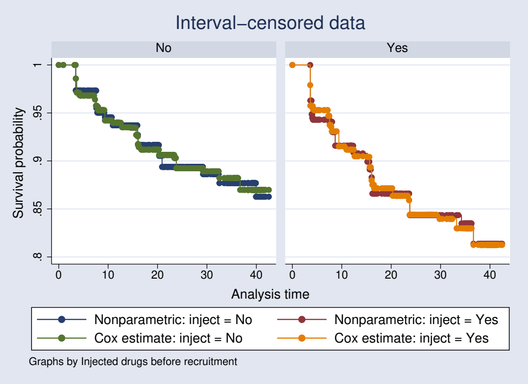
We want to check whether the PH-assumption holds for `inject`.

```
. stintphplot, interval(ltime rtime) by(inject)
Computing nonparametric estimates for inject = No ...
Computing nonparametric estimates for inject = Yes ...
```



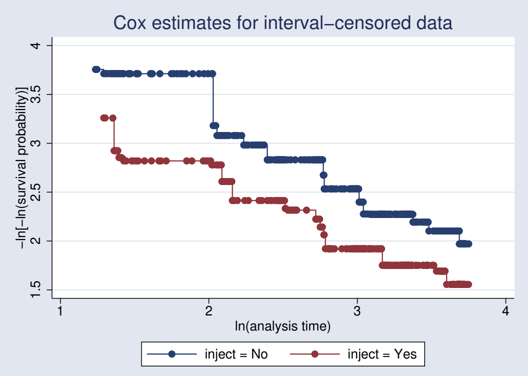
# Check PH-assumption for a model with a single covariate

```
. stintcoxnp, interval(ltime rtime) by(inject) separate
Computing nonparametric estimates ...
Computing Cox estimates ...
```



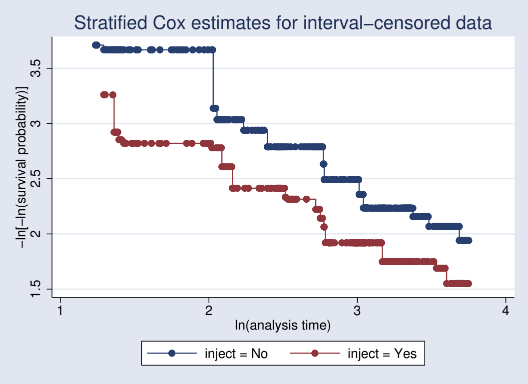
# Check PH-assumption for a model with multiple covariates

```
. stintphplot, interval(ltime rtime) by(inject) adjustfor(age_mean)
Fitting Cox model with covariates from option adjustfor()
for inject = No ...
Fitting Cox model with covariates from option adjustfor()
for inject = Yes ...
```



# Check PH-assumption for a stratified Cox model

```
. stintphplot, interval(ltime rtime) strata(inject) adjustfor(age_mean)
Fitting Cox model stratified on inject with covariates from option adjustfor()
...
```



# Conclusions

- Fit a genuine semiparametric Cox proportional-hazards model with time-independent covariates for two types of interval-censored data.
- Support different methods for standard-error computation.
- Support modeling of stratification.
- Support options to control the tradeoff between speed and accuracy.
- Support two ways to choose the time intervals to be estimated for baseline hazard function.
- Provide diagnostic measures, predictions, and much more after fitting the model.
- Provide graphical assessments for proportional-hazard assumption.

# More resources

https://www.stata.com/manuals/ststintcox.pdf
https://www.stata.com/manuals/ststintcoxpostestimation.pdf
https://www.stata.com/manuals/ststintcoxph-assumptionplots.pdf

# References

[1] B. W. Turnbull. "The empirical distribution function with arbitrarily grouped censored and truncated data". In: *Journal of the Royal Statistical Society, Series B* 38 (1976), pp. 290–295.

[2] D. Zeng, F. Gao, and D.Y. Lin. "Maximum likelihood estimation for semiparametric regression models with multivariate interval-censored data". In: *Biometrika* 104 (2017), pp. 505–525.

[3] D. Zeng, L. Mao, and D.Y. Lin. "Maximum likelihood estimation for semiparametric transformation models with interval-censored data". In: *Biometrika* 103 (2016), pp. 253–271.