Joint modeling of longitudinal and survival data

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Motivation

Joint analysis

New Stata commands for joint analysis

Joint analysis of the PANSS data

Models with more flexible latent associations

Summary

Future work

Acknowledgement

References

- Many studies collect both longitudinal (measurements) data and survival-time data.
- Longitudinal (or panel, or repeated-measures) data are data in which a response variable is measured at different time points such as blood pressure, weight, or test scores measured over time.
- Survival-time or event history data record times until an event of interest such as times until a heart attack or times until death from cancer.

- In the absence of correlation between longitudinal and survival outcomes, each outcome can be analyzed separately.
- Longitudinal analyses include fitting linear mixed models.
- Survival analyses include fitting semiparametric (Cox) proportional hazards models or parametric survival models such as exponential and Weibull.
- When longitudinal and survival outcomes are related, they must be analyzed jointly to avoid potentially biased results.

Joint analyses are useful to:

- Account for informative dropout in the analysis of longitudinal data;
- Study effects of baseline covariates on longitudinal and survival outcomes; or
- Study effects of time-dependent covariates on the survival outcome.

In this presentation, I will concentrate on the first two applications.

- Consider Positive and Negative Symptom Scale (PANSS) data from a clinical trial comparing different drug treatmeans for schizophrenia (Diggle [1998]).
- We are interested in modeling the total score of the PANSS measurements, which is used to measure psychiatric disorder, over time for each of the drug treatments. The smaller the score the better.
- Six original treatments are combined into three: placebo, haloperidol (reference), and risperidone (novel therapy).
- For details about this study and its analyses, see Diggle (1998) and Henderson (2000).

- We consider a subset of the original data:

```
. use panss
(PANSS scores from a study of drug treatments for schizophrenia)

. describe

Contains data from panss.dta
  obs:           150                          PANSS scores from a study of
                                                drug treatments for
                                                schizophrenia
 vars:            11                          29 Aug 2016 12:07
 size:         3,150                          (_dta has notes)
-------------------------------------------------------------------------------
              storage   display    value
variable name   type    format     label      variable label
-------------------------------------------------------------------------------
id              int     %8.0g                 Patient identifier
panss0          int     %8.0g                 PANSS score at week 0
panss1          int     %8.0g                 PANSS score at week 1
panss2          int     %8.0g                 PANSS score at week 2
panss4          int     %8.0g                 PANSS score at week 4
panss6          int     %8.0g                 PANSS score at week 6
panss8          int     %8.0g                 PANSS score at week 8
treat           byte    %11.0g     treatlab   Treatment identifier:
                                                1=Haloperidol, 2=Placebo,
                                                3=Risperidone
```

```
nobs            byte    %8.0g                 Number of nonmissing
                                                measurements, between 1 and 6
droptime        float   %8.0g                 Imputed dropout time (weeks)
infdrop         byte    %14.0g     droplab    Dropout indicator:
                                                0=none or noninformative;
                                                1=informative
--------------------------------------------------------------------------------
Sorted by: id

. notes

_dta:
  1.  Subset of the data from a larger (confidential) randomized clinical trial
      of drug treatments for schizophrenia
  2.  Source:
      http://www.lancaster.ac.uk/staff/diggle/APTS-data-sets/PANSS_short_data.t
      > xt
  3.  PANSS (Positive and Negative Symptom Scale)
```

- Listing of a subset of the data:

```
. list id panss* treat if inlist(id,1,2,3,10,19,24,30,42), sepby(nobs) noobs

  +------------------------------------------------------------------------+
  | id   panss0   panss1   panss2   panss4   panss6   panss8         treat |
  |------------------------------------------------------------------------|
  |  1       91        .        .        .        .        .   Haloperidol |
  |  2       72        .        .        .        .        .       Placebo |
  |------------------------------------------------------------------------|
  |  3      108      110        .        .        .        .   Haloperidol |
  | 10       97      118        .        .        .        .       Placebo |
  | 19       81       71        .        .        .        .   Risperidone |
  |------------------------------------------------------------------------|
  | 24      127       98      152        .        .        .   Haloperidol |
  | 30       73       74       68        .        .        .       Placebo |
  | 42       75       92      117        .        .        .   Risperidone |
  +------------------------------------------------------------------------+
```

- Many patients withdrew from the study before completing the measurement schedule—of the 150 subjects, only 68 completed the study.

```
. misstable pattern panss*, freq bypattern

       Missing-value patterns
         (1 means complete)

              |   Pattern
    Frequency |  1  2  3  4    5
  ------------+------------------
              |
           68 |  1  1  1  1    1
              |
  1:          |
           16 |  1  1  1  1    0
  2:          |
           24 |  1  1  1  0    0
  3:          |
           19 |  1  1  0  0    0
  4:          |
           21 |  1  0  0  0    0
  5:          |
            2 |  0  0  0  0    0
  ------------+------------------
              |
          150 |
  Variables are  (1) panss1  (2) panss2  (3) panss4  (4) panss6  (5) panss8
```

- Over 40% of subjects specified the reason for dropout as “inadequate for response”, which suggests that the dropout may be informative.

```
. tabulate infdrop
      Dropout |
    indicator |      Freq.     Percent        Cum.
--------------+-----------------------------------
 None, noninf. |         87       58.00       58.00
   Informative |         63       42.00      100.00
--------------+-----------------------------------
         Total |        150      100.00
```

- Let's first perform standard longitudinal analysis assuming noninformative or random dropout.

```
. use panss_long
(PANSS scores from a study of drug treatments for schizophrenia)

. describe

Contains data from panss_long.dta
  obs:           900                          PANSS scores from a study of
                                                drug treatments for
                                                schizophrenia
 vars:             6                          29 Aug 2016 12:07
 size:         9,900                          (_dta has notes)
-------------------------------------------------------------------------------
              storage   display    value
variable name   type    format     label      variable label
-------------------------------------------------------------------------------
id              int     %8.0g                 Patient identifier
week            byte    %9.0g                 Time (weeks)
panss           int     %8.0g                 PANSS
treat           byte    %11.0g     treatlab   Treatment identifier:
                                                1=Haloperidol, 2=Placebo,
                                                3=Risperidone
nobs            byte    %8.0g                 Number of nonmissing
                                                measurements, between 1 and 6
panss_mean      float   %9.0g                 Observed means over time and
                                                treatment
-------------------------------------------------------------------------------
Sorted by: id  week
```

```
. list id week panss treat in 1/16, sepby(id)

     +--------------------------------+
     | id   week   panss        treat |
     |--------------------------------|
  1. |  1      0      91     Haloper. |
  2. |  1      1       .     Haloper. |
  3. |  1      2       .     Haloper. |
  4. |  1      4       .     Haloper. |
  5. |  1      6       .     Haloper. |
  6. |  1      8       .     Haloper. |
     |--------------------------------|
  7. |  2      0      72      Placebo |
  8. |  2      1       .      Placebo |
  9. |  2      2       .      Placebo |
 10. |  2      4       .      Placebo |
 11. |  2      6       .      Placebo |
 12. |  2      8       .      Placebo |
     |--------------------------------|
 13. |  3      0     108     Haloper. |
 14. |  3      1     110     Haloper. |
 15. |  3      2       .     Haloper. |
 16. |  3      4       .     Haloper. |
     +--------------------------------+
```

- Consider the following random-intercept model:

$$\texttt{panss}_{ij} = \boldsymbol{\beta}^L \mathbf{x}_{ij} + U_i + \epsilon_{ij} \tag{1}$$

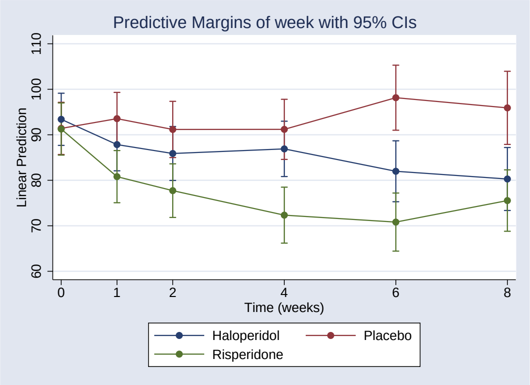
  with m subjects ($i = 1, 2, \ldots, m$) and n_i observations per subject ($j = 1, 2, \ldots, n_i$), where $\boldsymbol{\beta}^L \mathbf{x}_{ij}$ represents a saturated model with one coefficient for each `treat` and `week` combination.
- $U_i's \sim$ i.i.d. $N(0, \sigma_u^2)$ are random intercepts which induce dependence within subjects.
- $\epsilon_{ij}'s \sim$ i.i.d. $N(0, \sigma_e^2)$ are error terms.

- We use `xtreg, mle` to fit a simple random-intercept model by using maximum likelihood (ML) with fixed effects for each combination of treatment and time:

```
. xtset id
       panel variable:  id (balanced)

. xtreg panss i.treat##i.week, mle nolog

Random-effects ML regression                    Number of obs      =       685
Group variable: id                              Number of groups   =       150

Random effects u_i ~ Gaussian                   Obs per group:
                                                              min =         1
                                                              avg =       4.6
                                                              max =         6

                                                LR chi2(17)        =    105.58
Log likelihood  =   -2861.58                    Prob > chi2        =    0.0000

------------------------------------------------------------------------------
       panss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       treat |
    Placebo  |      -2.00       4.14    -0.48   0.629     -10.11        6.11
    Risper.  |      -2.14       4.14    -0.52   0.605     -10.25        5.97
             |
        week |
          1 |      -5.55       2.52    -2.21   0.027      -10.49      -0.62
          2 |      -7.51       2.62    -2.87   0.004      -12.64      -2.38
          4 |      -6.50       2.70    -2.40   0.016      -11.80      -1.20
          6 |     -11.42       3.06    -3.73   0.000      -17.41      -5.43
          8 |     -13.12       3.19    -4.12   0.000      -19.36      -6.88
            |
  treat#week |
  Placebo#1 |       7.70       3.56     2.16   0.031        0.72      14.68
  Placebo#2 |       7.28       3.80     1.91   0.056       -0.17      14.74
  Placebo#4 |       6.29       4.04     1.56   0.119       -1.63      14.21
  Placebo#6 |      18.17       4.50     4.03   0.000        9.34      26.99
  Placebo#8 |      17.63       4.96     3.56   0.000        7.92      27.35
  Risper.#1 |      -4.91       3.55    -1.38   0.167      -11.86       2.05
  Risper.#2 |      -6.02       3.68    -1.64   0.102      -13.24       1.19
  Risper.#4 |     -12.42       3.85    -3.23   0.001      -19.97      -4.87
  Risper.#6 |      -9.03       4.20    -2.15   0.032      -17.26      -0.79
  Risper.#8 |      -2.60       4.43    -0.59   0.558      -11.29       6.09
            |
       _cons |      93.40       2.92    31.93   0.000       87.67      99.13
--------------+----------------------------------------------------------------
    /sigma_u |      16.48       1.10                        14.47      18.78
    /sigma_e |      12.49       0.38                        11.76      13.26
         rho |       0.64       0.03                         0.57       0.70
-------------------------------------------------------------------------------
LR test of sigma_u=0: chibar2(01) = 353.11             Prob >= chibar2 = 0.000
```

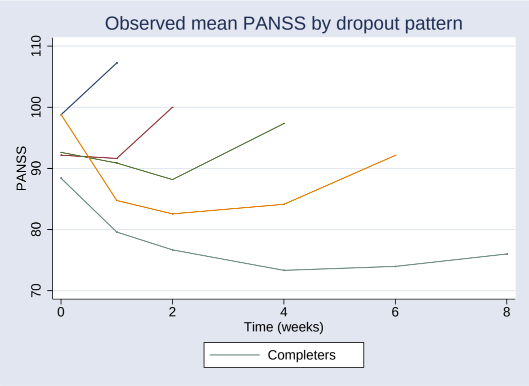
- All three groups demonstrate a decrease in mean PANSS score over time, at least in the first three weeks.

```
. quietly margins i.week, over(treat) predict(xb)
. marginsplot
  Variables that uniquely identify margins: week treat
```



- Given that many subjects dropped out of the study because of inadequate response, the observed decrease in PANSS scores may be due to the dropout of subjects with high PANSS scores.
- We can look at the observed mean profiles over time for each missing-value pattern, similarly to Figure 13.4 in Diggle et al. (2002).

```
. keep if nobs>1
(12 observations deleted)
. by week nobs, sort: egen panss_ptrn = mean(panss)
(205 missing values generated)
. qui reshape wide panss_ptrn, i(id week) j(nobs)
. twoway line panss_ptrn* week, sort legend(order(5 "Completers")) ///
>   title(Observed mean PANSS by dropout pattern) ytitle(PANSS)
```



- There is a steep increase in the mean PANSS score immediately prior to dropout for all dropout patterns except completers.
- This provides strong empirical evidence that dropout is related to PANSS scores and is thus informative (nonrandom).

- We may also be interested in a dropout process itself. For example, is there a difference between dropout rates because of "inadequate response" among groups?
- We can use standard methods of survival analysis to answer this question.
- We can treat dropout time as our analysis time and whether the dropout is because of inadequate response as our event of interest or failure.

- Data description:

```
. use panss_surv
(Dropout times for study of drug treatments for schizophrenia)

. describe

Contains data from panss_surv.dta
  obs:           150                          Dropout times for study of drug
                                                treatments for schizophrenia
 vars:             4                          29 Aug 2016 12:07
 size:         1,200                          (_dta has notes)
-------------------------------------------------------------------------------
              storage   display    value
variable name   type    format     label      variable label
-------------------------------------------------------------------------------
id              int     %8.0g                 Patient identifier
droptime        float   %8.0g                 Imputed dropout time (weeks)
infdrop         byte    %14.0g     droplab    Dropout indicator:
                                                0=none or noninfiormative;
                                                1=informative
treat           byte    %11.0g     treatlab   Treatment identifier:
                                                1=Haloperidol, 2=Placebo,
                                                3=Risperidone
-------------------------------------------------------------------------------
Sorted by: id
```

```
. list in 1/10

     ┌─────────────────────────────────────────────────┐
     │ id   droptime           infdrop          treat │
     ├─────────────────────────────────────────────────┤
  1. │  1        .704   None or noninf.       Haloper. │
  2. │  2         .74   None or noninf.        Placebo │
  3. │  3       1.121       Informative       Haloper. │
  4. │  4       1.224       Informative       Haloper. │
  5. │  5       1.303   None or noninf.       Haloper. │
     ├─────────────────────────────────────────────────┤
  6. │  6       1.541       Informative       Haloper. │
  7. │  7       1.983       Informative       Haloper. │
  8. │  8       1.035       Informative        Placebo │
  9. │  9       1.039   None or noninf.        Placebo │
 10. │ 10       1.116       Informative        Placebo │
     └─────────────────────────────────────────────────┘
```

- Cox proportional hazards model:

$$h_i(t|\texttt{treat}) = h_0(t)\exp(\beta_1^S 1.\texttt{treat}_i + \beta_2^S 2.\texttt{treat}_i + \beta_3^S 3.\texttt{treat}_i) \tag{2}$$

  where t is the dropout time `droptime` and $i = 1, 2, \ldots, m$.
- Baseline hazard $h_0(t)$ is left unspecified.
- A constant term β_0^S is absorbed into the baseline hazard.
- Coefficients β_1^S, β_2^S, and β_3^S model subject-specific hazards as a function of the treatment group. In general, covariates may also depend on time t.
- Subject-specific hazards are proportional.
- Exponentiated coefficients are hazard ratios.

- Declare survival-time data:

```
. stset droptime, failure(infdrop)

     failure event:  infdrop != 0 & infdrop < .
obs. time interval:  (0, droptime]
 exit on or before:  failure

------------------------------------------------------------------------------
        150  total observations
          0  exclusions
------------------------------------------------------------------------------
        150  observations remaining, representing
         63  failures in single-record/single-failure data
    863.624  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =     8.002
```

- Fit Cox model:

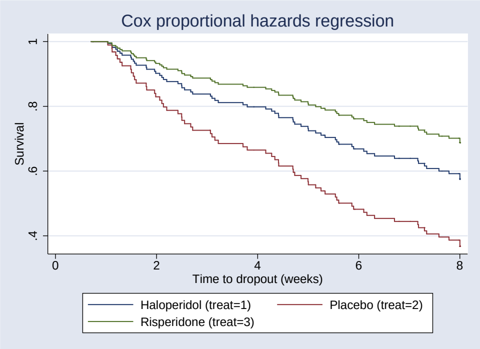
```
. stcox i.treat

         failure _d:  infdrop
   analysis time _t:  droptime

Iteration 0:   log likelihood = -293.97982
Iteration 1:   log likelihood = -288.97387
Iteration 2:   log likelihood = -288.86504
Iteration 3:   log likelihood = -288.86498
Refining estimates:
Iteration 0:   log likelihood = -288.86498

Cox regression -- Breslow method for ties

No. of subjects =          150                  Number of obs    =        150
No. of failures =           63
Time at risk    =  863.6239911
                                                LR chi2(2)       =      10.23
Log likelihood  =   -288.86498                  Prob > chi2      =     0.0060

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       treat |
    Placebo  |        1.81       0.53     2.04  0.041          1.02        3.21
    Risper.  |        0.68       0.24    -1.12  0.262          0.34        1.34
------------------------------------------------------------------------------
```

- Redisplay results as coefficient estimates (for later comparison):

```
. stcox, nohr

Cox regression -- Breslow method for ties

No. of subjects =          150                 Number of obs    =        150
No. of failures =           63
Time at risk    =  863.6239911
                                               LR chi2(2)       =      10.23
Log likelihood  =   -288.86498                 Prob > chi2      =     0.0060

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       treat |
    Haloper. |       0.00  (empty)
     Placebo |       0.59       0.29     2.04   0.041         0.02        1.16
     Risper. |      -0.39       0.35    -1.12   0.262        -1.07        0.29
------------------------------------------------------------------------------
```

- Plot survivor functions in three treatment groups:

```
. stcurve, survival at1(treat=1) at2(treat=2) at3(treat=3)
```



- The placebo group has the highest dropout rate due to inadequate response whereas the risperidone group has the lowest dropout rate.
- But dropout rates also depend on PANSS scores.

- Whether we are interested:
  - In the longitudinal analysis of PANSS trajectory over time in different groups,
  - In the survival analysis comparing dropout rates among the groups, or
  - In both types of analysis,

  we cannot perform them separately, given that the two outcomes may be correlated.
- We should consider joint analysis of these data.

- Joint analysis should be able to incorporate the specific features of longitudinal and survival data.
- Joint analysis should be equivalent to the corresponding separate analysis in the absence of an association between the longitudinal and survival outcomes.
- Tsiatis et al. (1995), Wulfsohn and Tsiatis (1997), and Henderson et al. (2000) considered a joint model that links the longitudinal and survival outcomes through a shared latent process.

- Let's fit a model that accounts for informative dropout.
- Consider the following joint random-intercept Cox model based on separate models (1) and (2):

$$\begin{aligned} \texttt{panss}_{ij} &= \beta^L \mathbf{x}_{ij} + U_i + \epsilon_{ij} \\ h_i(t) &= h_0(t) \exp(\beta^S \texttt{i.treat}_i + \gamma U_i) \end{aligned} \qquad (3)$$

- Random intercepts $U_i's$ are now shared between the two models and induce dependence between the longitudinal outcome `panss` and survival outcome `droptime`.
- More generally, I will refer to model (3) as a joint random-intercept Cox model, in which survival outcome is modeled semiparametrically using the Cox model.

- You can use forthcoming, user-written suite `jm` to perform joint analysis of longitudinal and survival data.
- Command `jmxtstset` declares your longitudinal and survival data.
- Command `jmxtstcox` fits joint random-intercept Cox models, similar to model (3).
- Command `jmxtstcurve` plots survivor, hazard, and cumulative hazard functions after `jmxtstcox`.
- Other Stata postestimation features such as `predict`, `test`, `nlcom`, `margins`, etc. are also available.

- To fit joint models using `jmxtstcox`, you must first declare your longitudinal and survival data using `jmxtstset`.
- Longitudinal and survival data are typically saved in different files. To perform estimation, all data should be in one file with longitudinal data saved in a long format (with multiple observations per subject saved in rows).
- `jmxtstset` provides a syntax that combines the two datasets and performs declaration, and provides a syntax that declares an already combined dataset.

- `jmxtstset` combines the syntaxes of `stset` and `xtset`.
- Syntax for the combined dataset:

```
. jmxtstset idvar timevar, xt(is_xt)|st(is_st) failure(failvar) [stsetopts]
```

is_xt and *is_st* are binary variables identifying longitudinal and survival observations, respectively; only one of them must be specified in the respective option.

- Syntax for separate datasets with survival dataset in memory:

```
. use survfile
. jmxtstset idvar timevar using longfile, st failure(failvar) [stsetopts]
```

- Syntax for separate datasets with longitudinal dataset in memory:

```
. use longfile
. jmxtstset idvar timevar using survfile, xt failure(failvar) [stsetopts]
```

- Command `jmxtstcox` performs estimation.
- It fits a random-intercept Cox model to the survival and longitudinal outcomes.
- `jmxtstcox` uses nonparametric ML to estimate model parameters. The estimation method is an expectation-maximization algorithm. The standard errors are obtained using the observed information matrix (Louis 1982).

- Command `gsem` (`help gsem`) can be used to fit joint models with flexible specification of latent processes, but in which survival outcome is modeled parametrically.
- User-written command `stjm` (Crowther et al. 2013) can be used to fit joint random-intercept and random-coefficient models. The survival outcome is again modeled parametrically, but flexible parametric survival models (Royston and Lambert 2011) are also supported.
- User-written command `jmxtstcox` currently supports only joint random-intercept models, but it allows to model the survival outcome semiparametrically, without any parametric assumptions for the baseline hazard.

- Let’s now analyze PANSS scores and dropout times jointly by fiting the random-intercept Cox model (3).
- The longitudinal data are saved in `panss_long.dta` and the survival data are saved in `panss_surv.dta`.
- We first use `jmxtstset` to combine survival and longitudinal datasets and to declare the combined data:

```
. use panss_surv
(Dropout times for study of drug treatments for schizophrenia)
. jmxtstset id droptime using panss_long, st failure(infdrop)
-----------------------------------LONGITUDINAL-------------------------------
                id:  id
          filename:  panss_long.dta
──────────────────────────────────────────────────────────────────────────────
      900  total observations
        0  exclusions
──────────────────────────────────────────────────────────────────────────────
      900  observations remaining
      150  subjects
```

```
-------------------------------------SURVIVAL---------------------------------
                id:  id
     failure event:  infdrop != 0 & infdrop < .
obs. time interval:  (droptime[_n-1], droptime]
 exit on or before:  failure

------------------------------------------------------------------------------
        150  total observations
          0  exclusions
------------------------------------------------------------------------------
        150  observations remaining, representing
        150  subjects
         63  failures in single-failure-per-subject data
    863.624  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =     8.002
```

- We now use `jmxtstcox` to fit the joint model:

```
. jmxtstcox (_xt: panss i.treat##i.week) (_st: i.treat), nolog
   longitudinal depvar:   panss
            failure _d:   infdrop
      analysis time _t:   droptime
Joint model of longitudinal and survival data
Breslow method for ties
Subject id: id                                   Total subjects    =        150
Longitudinal (_xt):                              Survival (_st):
No. of subjects = 150                            No. of subjects   =        150
No. of obs      = 685                            No. of obs        =        150
                                                 No. of failures   =         63
                                                 Time at risk      =     863.62
                                                 Wald chi2(19)     =     112.90
Observed log likelihood = -3194.739326           Prob > chi2       =     0.0000
```

```
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
panss        |
       treat |
     Placebo |      -2.00        4.16   -0.48   0.631      -10.16         6.16
     Risper. |      -2.14        4.16   -0.51   0.607      -10.30         6.02
             |
        week |
           1 |      -5.55        2.51   -2.21   0.027      -10.48        -0.63
           2 |      -7.24        2.61   -2.77   0.006      -12.36        -2.13
           4 |      -6.12        2.70   -2.27   0.023      -11.40        -0.83
           6 |     -10.61        3.05   -3.48   0.001      -16.59        -4.63
           8 |     -12.20        3.18   -3.84   0.000      -18.43        -5.97
             |
  treat#week |
   Placebo#1 |       7.69        3.55    2.17   0.030        0.73        14.66
   Placebo#2 |       7.65        3.79    2.02   0.044        0.22        15.09
   Placebo#4 |       7.03        4.03    1.75   0.081       -0.86        14.93
   Placebo#6 |      18.74        4.49    4.18   0.000        9.95        27.54
   Placebo#8 |      18.43        4.94    3.73   0.000        8.75        28.11
   Risper.#1 |      -4.91        3.54   -1.39   0.166      -11.84         2.03
   Risper.#2 |      -6.08        3.67   -1.65   0.098      -13.28         1.13
   Risper.#4 |     -12.30        3.84   -3.20   0.001      -19.83        -4.77
   Risper.#6 |      -9.12        4.19   -2.18   0.029      -17.33        -0.91
   Risper.#8 |      -2.82        4.42   -0.64   0.524      -11.48         5.85
             |
       _cons |      93.40        2.93   31.85   0.000       87.65        99.15
```

```
_t          |
      treat |
    Placebo |      0.77        0.34      2.23    0.026         0.09        1.44
    Risper. |     -0.49        0.39     -1.26    0.207        -1.26        0.27
------------+-------------------------------------------------------------------
     /gamma |      0.05        0.01                             0.04        0.07
------------+-------------------------------------------------------------------
  /sigma2_u |    281.22       37.30                           208.11      354.34
------------+-------------------------------------------------------------------
  /sigma2_e |    155.29        9.47                           136.73      173.85
--------------------------------------------------------------------------------
LR test of gamma = 0: chi2(1) = 37.41                 Prob >= chi2 =     0.0000
```

- The association parameter γ has an estimate of 0.05 with a 95% CI of (0.04, 0.07), which implies a positive association between PANSS scores and dropout times—the higher the PANSS score, the higher the chance of dropout.
- The LR test of no latent association (H_0: $\gamma = 0$) with $\chi^2_1 = 37.41$ provides strong evidence against a random-dropout model.

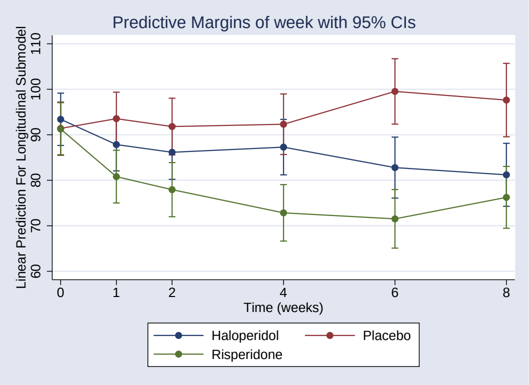
- The estimated random-intercept variance is slightly larger under the joint, informative dropout model.

Variable	inform	noninf
sigma2_u		
_cons	281.22	271.75
	37.30	36.19
	0.00	0.00
sigma2_e		
_cons	155.29	155.95
	9.47	9.55
	0.00	0.00

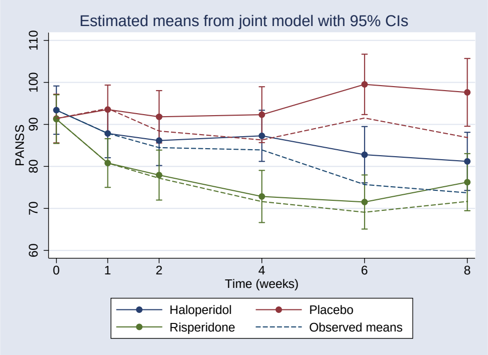
legend: b/se/p

- As with `xtreg`, we can compute and plot estimated mean PANSS profiles after `jmxtstcox`.

```
. qui margins i.week, over(treat) predict(xb xt)
. marginsplot
  Variables that uniquely identify margins: week treat
```



- We can overlay the estimated mean profiles with the observed mean profiles.



- The estimated mean profiles from the joint model are higher than the observed mean profiles because the former represent “dropout-free” profiles—subjects with high PANSS scores tend to drop out, which leads to lower observed mean values.

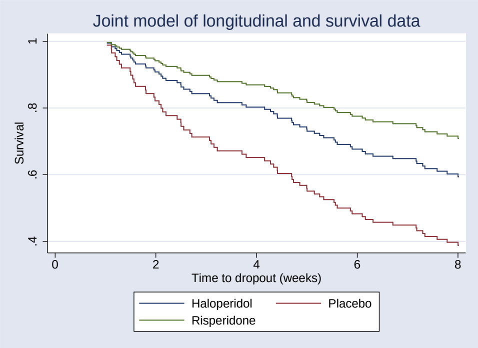
- We can compare estimates from joint and separate Cox models:

Variable	joint	stcox
treat		
Haloper.	(base)	(base)
Placebo	0.77	0.59
	0.34	0.29
	0.03	0.04
Risper.	-0.49	-0.39
	0.39	0.35
	0.21	0.26

legend: b/se/p

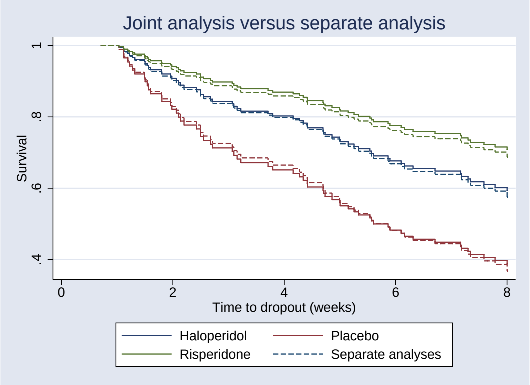
- We can plot marginal survivor functions of times to dropout in each group.

```
. jmxtstcurve, survival at1(treat=1) at2(treat=2) at3(treat=3)
```



- As with separate analysis, the placebo group has the highest "informative" dropout rate whereas the risperidone group has the lowest dropout rate.

- In fact, survival estimates from joint and separate analyses are similar:



- Random-intercept model (3) can be extended to allow for more flexible latent associations motivated by practice; see Henderson (2000) for details.
- For example, a joint random-coefficient Cox model additionally includes a random slope on time in the longitudinal model and an association through the random slope in the survival model.

$$\begin{aligned}\texttt{panss}_{ij} &= \boldsymbol{\beta}^{L}\mathbf{x}_{ij} + U_{1i} + \texttt{week} \times U_{2i} + \epsilon_{ij} \\ h_i(t) &= h_0(t)\exp(\boldsymbol{\beta}^{S}\texttt{i.treat}_i + \gamma_1 U_{1i} + \gamma_2 U_{2i}) \quad (4)\end{aligned}$$

- A joint random-trajectory Cox model extends the random-coefficient model (4) to include an entire stochastic longitudinal trajectory.

$$\begin{aligned}\texttt{panss}_{ij} &= \boldsymbol{\beta}^{L}\mathbf{x}_{ij} + U_{1i} + \texttt{week} \times U_{2i} + \epsilon_{ij} \\ h_i(t) &= h_0(t)\exp(\boldsymbol{\beta}^{S}\texttt{i.treat}_i + \gamma_1 U_{1i} + \gamma_2 U_{2i} + \gamma_3 W_i(t)) \\ W_i(t) &= U_{1i} + t \times U_{2i} \quad (5)\end{aligned}$$

- Semiparametric Cox submodels in (3), (4), and (5) can be replaced with a parametric survival model, if appropriate.
- For example, with an exponential model:

$$h_i(t) = t \exp(\beta^S \texttt{i.treat}_i + \gamma U_i) \tag{3a}$$

- Or, with a Weibull model:

$$h_i(t) = p t^{p-1} \exp(\beta^S \texttt{i.treat}_i + \gamma U_i) \tag{3b}$$

- Such parametric models can be fit using, for example, `gsem`, but software for the corresponding semiparametric models is not available yet.

- For example, a joint random-intercept model using gsem:

```
. gsem (panss <- i.treat##i.week U[id]@1)
> (droptime <- i.treat U[id]@gamma, family(weibull, failure(infdrop))
```

- A joint random-coefficient model:

```
. gsem (panss <- i.treat##i.week U1[id]@1 c.week#U2[id]@1)
> (droptime <- i.treat U1[id]@gamma1 U2[id]@gamma2,
>                    family(weibull, failure(infdrop))),
> covstructure(U1[id] U2[id], unstructured)
```

Summary

- Joint analysis of longitudinal and survival outcomes is necessary to obtain unbiased inference when the two outcomes are correlated.
- Joint analysis can be used, for example, 1) to evaluate effects of baseline covariates on longitudinal and survival outcomes, 2) to evaluate effects of time-dependent covariates on survival outcome; and 3) to account for informative dropout in longitudinal analysis.
- You can use user-written command `jmxtstcox` to fit a joint random-intercept Cox model.
- You can use `gsem` to fit joint models that can accommodate more flexible specifications of a latent process and noncontinuous longitudinal outcomes. The survival outcome, however, is modeled parametrically.
- Also see user-written command `stjm` for fitting flexible parametric joint models of longitudinal and survival data.

Future work

- Support of semiparametric Cox models with more flexible latent associations such as a random-coefficient model (4) and a random-trajectory model (5).
- Support of noncontinuous longitudinal outcomes including binary and count outcomes.
- Support of nonproportional hazards via transformation survival models (Zeng and Lin 2007).
- More postestiomation features such as dynamic predictions and model diagnostics for joint analysis of longitudinal and survival data.

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References

Crowther, M. J., Abrams, K. R., and P. C. Lambert. 2013. Joint modeling of longitudinal and survival data. *Stata Journal* 13: 165–184.

Diggle, P. J. 1998. Dealing with missing values in longitudinal studies. In Everitt, B. S., and G. Dunn. (eds.) *Recent Advances in the Statistical Analysis of Medical Data*. London: Arnold, pp. 203–228.

Diggle, P. J., P. Heagerty, K. Y. Liang, and S. L. Zeger. 2002. *Analysis of Longitudinal Data*. 2nd Ed. Oxford University Press.

References (cont.)

Henderson, R., P. Diggle, and A. Dobson. 2000. Joint modeling of longitudinal measurements and event time data. *Biostatistics* 4: 465–480.

Louis, T. A. 1982. Finding the observed information matrix when using the EM algorithm. *Journal of the Royal Statistical Society B.* 44: 226–233.

Royston, P., and P. C. Lambert. 2011. *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. College Station, TX: Stata Press.

References (cont.)

Tsiatis, A. A., V. DeGruttola, and M. S. Wulfsohn. 1995. Modeling the relationship of survival to longitudinal data measured with error: Applications to survival and CD4 counts in patients with AIDS. *Journal of the American Statistical Association* 90: 27–37.

Wulfsohn, M. S. and A. A. Tsiatis. 1997. A joint model for survival and longitudinal data measured with error. *Biometrics* 53: 330–339.

Zeng, D. and D. Y. Lin. 2007. Maximum likelihood estimation in semiparametric regression models with censored data (with discussion). *Journal of the Royal Statistical Society B*, 69, 507–564.