Simulating simple and complex survival data

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Outline

1. Background
2. Motivating dataset
3. Simulating survival times from standard distributions
4. A general algorithm for generating survival times
5. Discussion
Background

- Simulation studies are conducted to assess the performance of current and novel statistical models in pre-defined scenarios
- Guidelines for the reporting of simulation studies in medical research have been published (Burton et al., 2006)
- Many simulation studies involving survival data use the exponential or Weibull models
- Often in clinical trials and population based studies, at least one turning point in the baseline hazard function is observed
Motivating dataset

- webuse brcancer
- 686 women diagnosed with breast cancer in Germany
- 246 were randomised to receive hormonal therapy and 440 to receive a placebo
- Outcome of interest is recurrence-free survival, with 299 patients experiencing the event

Analysis
- Weibull proportional hazards model
- Flexible parametric model with 5 degrees of freedom
- Treatment included in both models
Fitted survival functions

Weibull model

Flexible parametric model

KM, no therapy

Predicted survival, no therapy

KM, hormonal therapy

Predicted survival, hormonal therapy
Fitted hazard functions

Weibull model

Flexible parametric model

- Predicted hazard, no therapy
- Predicted hazard, hormonal therapy
Bender et al. (2005) provided a simple and efficient method to simulate survival times from standard parametric distributions

\[ h(t|X) = h_0(t) \exp(X\beta), \quad H(t|X) = H_0(t) \exp(X\beta) \]

\[ S(t|X) = \exp[-H(t|X)], \quad F(t|X) = 1 - \exp[-H(t|X)] \]
If we let $T$ be the simulated survival time

$$F(T|X) = 1 - \exp[-H(T|X)] = u, \quad \text{where} \quad u \sim U(0, 1)$$

and

$$S(T|X) = 1 - u \quad \text{(or equivalently} \quad = u)$$

This can then simply be re-arranged and solved for $T$

$$T = H_0^{-1}[-\log(u) \exp(-X\beta)]$$
For example in Stata

```
. //simulate 1000 survival times
. set obs 1000
obs was 0, now 1000
. //set seed for reproducibility
. set seed 398894
. //get uniform draws, representing centiles
. gen u = runiform()
. //generated a binary treatment group indicator
. gen treatment = runiform()>0.5
. //Weibull baseline parameters
. local lambda = 0.1
. local gamma = 1.2
. //treatment effect
. local loghr = 0.7
. //simulate survival times from Weibull PH model
. gen stimes = (-log(u)/(`lambda´*exp(`loghr´*treatment))))^(1/`gamma´)
```
survsim (from SSC)

**survsim** `newvarname1 [newvarname2] [, options]`

- `distribution(exp|gomp|weib)`
- `lambda(#), gamma(#)`
- `covariates(varname # [varname #] ...)`
- `tde(varname # [varname #] ...)`
- `maxtime(#)`

. **survsim stime event, dist(weib) lambda(0.1) > gamma(1.2) cov(treatment 0.7)**
Recent use of survival simulation

- Paul Lambert and I recently proposed a general parametric framework for survival analysis, implemented in *stgenreg* (Crowther and Lambert, 2013b, 2014)
- Reviews raised questions about benefits/pitfalls compared to the Cox model
- We set out to compare the efficiency of the Kaplan-Meier estimate of survival with a parametric function using splines, when data is sparse in the right tail
Core of simulation program

. //simulate from a Weibull distribution
. survsim stime died, lambda(0.2) gamma(1.3) maxt(5)
. //censoring times
. gen cens = runiform()*6
. replace died = 0 if cens<stime
. replace stime = cens if cens<stime
. stset stime, f(died=1)
. //KM estimate
. sts gen s1 = s sells = se(lls) lb = lb(s) ub = ub(s)
. //Fit parametric model
. stgenreg, loghaz([xb]) xb(#rcs(df(3)))
. //Get predicted survival at 4 and 5 years
. range t45 4 5 2
. predict surv, survival timevar(t45) ci
## Results

**Table**: Bias and mean squared error of \( \log(-\log(S(t))) \) at 4 and 5 years.

<table>
<thead>
<tr>
<th>Time</th>
<th>Kaplan-Meier</th>
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<tbody>
<tr>
<td></td>
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<td>-0.0038</td>
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<tr>
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**Median # events = 101**

**Median # events in final year = 5**
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Median # events = 101
Median # events in final year = 5
Benefits of the Bender et al. (2005) approach

- Extremely easy to implement
- Quite often we simulate survival times and then apply Cox models → baseline hazard from which we simulate is irrelevant
- What if we wish to simulate from a more complex and biologically plausible underlying hazard function?
- There is a growing interest in parametric survival models (Royston and Lambert, 2011; Crowther and Lambert, 2014)
Limitations with simulating survival times from standard distributions with proportional hazards

\[ T = H_0^{-1}[− \log(u) \exp(−Xβ)] \]

- Must be able to integrate the hazard function in order to calculate the cumulative hazard function
- We then must be able to invert the cumulative hazard function to obtain the simulated survival time
Simulating from a more complex baseline hazard function

We can use a mixture of parametric distributions

\[ S_0(t) = pS_{01}(t) + (1 - p)S_{02}(t) \]  \hspace{1cm} (1)

For example a 2-component mixture Weibull

\[ S_0(t) = p \exp(-\lambda_1 t^{\gamma_1}) + (1 - p) \exp(-\lambda_2 t^{\gamma_2}) \]  \hspace{1cm} (2)

with \(0 \leq p \leq 1\), and \(\lambda_1, \lambda_2, \gamma_1, \gamma_2 > 0\)
\[ \lambda_1 = 1, \gamma_1 = 1.5, \lambda_2 = 1, \gamma_2 = 0.5, p = 0.5 \]

\[ \lambda_1 = 0.1, \gamma_1 = 3, \lambda_2 = 0.1, \gamma_2 = 1.6, p = 0.8 \]

\[ \lambda_1 = 1.4, \gamma_1 = 1.3, \lambda_2 = 0.1, \gamma_2 = 0.5, p = 0.9 \]

\[ \lambda_1 = 1.5, \gamma_1 = 0.2, \lambda_2 = 0.5, \gamma_2 = 0.1, p = 0.1 \]
Incorporating proportional hazards gives us a survival function

\[
S(t) = \left[ p \exp(-\lambda_1 t^{\gamma_1}) + (1 - p) \exp(-\lambda_2 t^{\gamma_2}) \right] \exp(X\beta)
\]  

(3)

This model is implemented in the `stmix` command from SSC. Attempting to apply the inversion method, gives

\[
S(t) = u, \quad \text{where} \quad u \sim U(0, 1)
\]  

(4)

which cannot be re-arranged to directly solve for \( t \).

To solve we can apply iterative root finding techniques, such as Newton-Raphson iterations, or Brent’s univariate root finder. I favour the latter, using `mm_root()` from Ben Jann’s `moremata` (Jann, 2005)
survsim

survsim newvarname1 [newvarname2] [, options]
  ▶ mixture
  ▶ distribution(exp|gomp|weib)
  ▶ lambdas(#), gammas(#)
  ▶ covariates(varname # [varname #] ...)
  ▶ maxtime(#)

. survsim stime event, mixture dist(weib)
> lambdas(0.1 0.2) gammas(1.2 0.5) p(0.3)
Simulating survival times when the cumulative hazard doesn’t have a closed form expression - joint model data

\[ h(t) = h_0(t) \exp [X \beta + \alpha m(t)] \]

where

\[ m(t) = \beta_0 + \beta_1 t \]

- To obtain the cumulative hazard function we require numerical integration
- We then require root finding techniques to solve for the simulated survival time, \( t \)
Numerical integration

\[
\int_{-1}^{1} g(x) \, dx = \int_{-1}^{1} W(x) g(x) \, dx \approx \sum_{i=1}^{m} w_i g(x_i)
\]

where \(W(x)\) is a known weighting function and \(g(x)\) can be approximated by a polynomial function.

\[
\int_{t_{0i}}^{t_i} h(x) \, dx = \frac{t_i - t_{0i}}{2} \int_{-1}^{1} h \left( \frac{t_i - t_{0i}}{2} x + \frac{t_{0i} + t_i}{2} \right) \, dx
\]

\[
\approx \frac{t_i - t_{0i}}{2} \sum_{i=1}^{m} w_i h \left( \frac{t_i - t_{0i}}{2} x_i + \frac{t_{0i} + t_i}{2} \right)
\]
survsim

survsim newvarname1 [newvarname2] [, options]
  ▶ [log]hazard()
  ▶ [log]cumhazard()
  ▶ nodes(#)
  ▶ covariates(varname # [varname #] ...)
  ▶ tde(varname # [varname #] ...)
  ▶ tdefunction()
  ▶ centol(#)
  ▶ maxtime(#)

. survsim stime event, hazard(0.1:*1.2:*t:^{(1.1:-1)})
Simulating survival data - recap

- Does $H_0(t)$ have a closed form expression?  
  Yes  No

- Can you solve for $T$ analytically?  
  Yes  No

- Numerically integrate to obtain $H_0(t)$, within iterative root finding to solve for $T$  
  (3) Yes  No

- Use iterative root finding to solve for simulated time, $T$  
  (2) Yes  No

- Apply method of Bender et. al. (2005)  
  (1) Yes  No

Figure: Schematic flow diagram of simulation techniques

Crowther and Lambert (2012)
General survival simulation

Given a well-defined hazard function, \( h(t) \), this two-stage algorithm involving
1. Numerical integration
2. Root-finding
provides a framework for general survival simulation which can incorporate:
   - Practically \textit{any} user-defined baseline hazard function
   - Time-varying covariates
   - Time-dependent effects
   - Delayed entry
   - Extends to competing risks, frailty etc.
Examples

- Fractional polynomial baseline

```
survsim stime event, logh(-18 :+ 7.3:*log(#t):-11.5:*#t:^0.5):*log(#t))
```
Examples

- Fractional polynomial baseline

```
survsim stime event, logh(-18 :+ 7.3:*log(#t):-11.5:*#t:\^0.5):*log(#t))
```

- Non-proportional hazards

```
survsim stime event, logh(-18 :+ 7.3:*log(#t):-11.5:*#t:\^0.5):*log(#t)) cov(trt -0.7) tde(trt 1) tdefunc(0.01:*t :+ 0.4:*log(t))
```
Examples

- **Joint model data (time-varying covariate)**

  ```stata
  . //Simulate 1000 survival times
  . set obs 1000
  
  . //Define the association between the biomarker and survival
  . local alpha = 0.25
  
  . //Generate the random intercept and random slopes
  . gen b0 = rnormal(0,1)
  . gen b1 = rnormal(1,0.5)
  
  . survsim stime event, loghazard(-2.3:+2:*#t:*-#t:^2:+0.12:*#t:^3 > :+ `alpha´:* (b0 :+ b1:* #t)) maxt(5)
  
  . //Generate observed biomarker values at times 0, 1, 2, 3, 4 years
  . gen id = _n
  
  . expand 5
  . bys id: gen meastime = _n-1
  
  . bys id: drop if meastime>=stime
  
  . //Generate observed biomarker values incorporating measurement error
  . gen response = b0 + b1*meastime + rnormal(0,0.5)
  ```
Practical advice

- Although computation time is often minimal, it may be of use to simulate your 1000 datasets, say, before applying any model fits.
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- Although computation time is often minimal, it may be of use to simulate your 1000 datasets, say, before applying any model fits
- With the numerical integration, it is important to assess the approximation by setting a seed and using an increasing number of quadrature points
We have described a general framework for the generation of survival data, incorporating any combination of complex hazard functions, time-dependent effects, time-varying covariates, delayed entry, random effects and covariates measured with error (Crowther and Lambert, 2013a).
Discussion

- We have described a general framework for the generation of survival data, incorporating any combination of complex hazard functions, time-dependent effects, time-varying covariates, delayed entry, random effects and covariates measured with error (Crowther and Lambert, 2013a)

- As the procedure relies on numerical integration, it is important to establish the consistency of the simulated survival times by setting a seed and using an increasing number of quadrature nodes
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Discussion

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▶ As the procedure relies on numerical integration, it is important to establish the consistency of the simulated survival times by setting a seed and using an increasing number of quadrature nodes

▶ You can also specify a user-defined [log] cumulative hazard function (Royston, 2012) (stsurvsim)

▶ Simulating from a fitted model (or observed censoring distribution) can be particularly useful (Royston, 2012)


B. Jann. MOREMATA: Stata module (Mata) to provide various functions. Statistical Software Components, Boston College Department of Economics, 2005.
