Recurrent event survival analysis

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Introduction

Recurrent event: event occurs more than once per subject over follow-up time.

Examples:

- multiple relapses from remission for leukemia patients
- repeated heart attacks
- recurrence of bladder cancer tumors
- deteriorating episodes of visual acuity

Two different approaches:

- recurrent events are treated as identical
  $\rightarrow$ Counting Process (CP) approach
  $\hookrightarrow$ leukemia and heart attack examples
- recurrent events are not treated as identical: event order important or different disease categories
  $\rightarrow$ Stratified Cox (SC) model approach
  $\hookrightarrow$ degeneration of visual acuity example

For bladder cancer example both approaches could be appropriate.

Counting Process approach

Example of data layout

Subj	Interval Number	Time Start	Time Stop	Event Status	Treatment Group
Al	1	0	3	1	1
Al	2	3	9	1	1
Al	3	9	21	1	1
Al	4	21	23	0	1
Hal	1	0	3	1	0
Hal	2	3	15	1	0
Hal	3	15	25	1	0
Sal	1	0	17	1	0
Mal	1	0	12	0	1

Differences between recurrent and nonrecurrent event data

- nonrecurrent event:
  $\rightarrow$the subjects remain in the risk set until the time of failure or censorship
  $\rightarrow$ different lines of data comes from differente subjects and are therefore treated as independent
- recurrent event:
  $\rightarrow$the subjects remain in the risk set until last interval is completed (i.e. last failure time or censorship)
  $\rightarrow$ we assume that the lines are independent even if some come from the same subject

Ordered failure time and risk set information for first 26 subjects

Ordered failure times $t_{(j)}$	# in risk set n_j	# failed m_j	# censored in $[t_{(j)}, t_{(j+1)})$	Subject ID #s for outcomes in $[t_{(j)}, t_{(j+1)})$
0	26	-	1	1
1	25	1	1	2,18
2	24	2	0	19,25
3	24	4	1	3,13,14,16,26
5	23	1	0	9
6	23	2	0	6,26
7	23	1	1	4,15
8	22	1	0	26
9	22	1	0	14
10	22	2	2	5,6,12,15
12	20	2	1	7,10,26
15	19	2	0	12,16
16	19	3	0	10,13,15
17	19	1	3	8,9,10,25
21	16	1	0	14
22	16	1	0	25
23	16	1	3	11,12,13,14
24	12	1	0	15
25	11	2	0	16,20
26	10	1	2	17,18,19
28	7	1	4	20,21,22,23,24
30	3	1	2	24,25,26

For simplicity, we consider the three variables tx, num and size as time independent.
We also assume that they satisfy the PH assumptions and that there is no interaction between the variables

$\rightarrow$ Cox PH model for bladder cancer study:

$$h(t, X) = h_0(t) \exp\left[\beta \text{ tx} + \gamma_1 \text{ num} + \gamma_2 \text{ size}\right]$$

Partial likelihood function: $L = L_1 \times L_2 \times \cdots \times L_{22}$
Considering the case when there is only one subject failing at time $t_{(j)}$:

$$\begin{aligned} L_j &= P\left[\text{failing at } t_{(j)} | \text{survival up to } t_{(j)}\right] \\ &= \frac{\exp(\beta\ \text{tx}_{[j]} + \gamma_1\ \text{num}_{[j]} + \gamma_2\ \text{size}_{[j]})}{\sum_{s \in R(t_{(j)})} \exp(\beta\ \text{tx}_s + \gamma_1\ \text{num}_s + \gamma_2\ \text{size}_s)} \end{aligned}$$

Until now we considered each line of data to be independent, but we know that some data come from the same subject.
Robust estimation takes care of this assuming that there may be some correlation between different lines.
The robust estimation adjusts the variance of the estimated coefficients as follows:

$$\widehat{J}_n(\hat{\theta})^{-1}\widehat{V}_n(\hat{\theta})\widehat{J}_n(\hat{\theta})^{-1}$$

where

$$\widehat{V}_n(\theta) = \sum_{i=1}^{n} \nabla l_n(\theta)(\nabla l_n(\theta))^T, \text{ an estimator of } V_n(\theta) = Var_g\left(\nabla l_n(\theta)\right)$$

$$\widehat{J}_n(\theta) = \sum_{i=1}^{n} \nabla^2 l_n(\theta), \text{ an estimator of } J_n(\theta) = -E_g\left(\nabla^2 l_n(\theta)\right)$$

because:

$$\sqrt{n}(\hat{\theta}_n - \theta^*) \xrightarrow{D} \text{Normal}(0, J_1(\theta^*)^{-1}V_1(\theta^*)J_1(\theta^*)^{-1})$$

Test for interaction:

```
> fit <- coxph(Surv(start,end,event)~tx+size+num, data=bladder)
Call:
coxph(formula = Surv(start, end, event) ~ tx + size + num, data = bladder)

        coef exp(coef) se(coef)      z       p
tx   -0.4116     0.663   0.1999 -2.059 0.03900
size -0.0411     0.960   0.0703 -0.584 0.56000
num   0.1637     1.178   0.0478  3.426 0.00061

Likelihood ratio test=14.7  on 3 df, p=0.00213  n=190



> fit1 <- coxph(Surv(start,end,event)~tx+size+num+ size*tx+num*tx)
Call:
coxph(formula = Surv(start, end, event) ~ tx + size + num + size *
    tx + num * tx)

             coef exp(coef) se(coef)      z     p
tx       -0.356408      0.70   0.4684 -0.761 0.450
size     -0.000874      1.00   0.0795 -0.011 0.990
num       0.085195      1.09   0.0785  1.086 0.280
tx:size  -0.300562      0.74   0.1808 -1.663 0.096
tx:num    0.166948      1.18   0.1018  1.639 0.100

Likelihood ratio test=21.1  on 5 df, p=0.000759  n=190
> p.value <- 1-pchisq(21.1-14.7,2)
> p.value
[1] 0.0407622
```

```
> fit <- coxph(Surv(start,end,event)~tx+size+num, data=bladder)
Call:
coxph(formula = Surv(start, end, event) ~ tx + size + num, data = bladder)

        coef exp(coef) se(coef)      z       p
tx   -0.4116     0.663   0.1999 -2.059 0.03900
size -0.0411     0.960   0.0703 -0.584 0.56000
num   0.1637     1.178   0.0478  3.426 0.00061

Likelihood ratio test=14.7  on 3 df, p=0.00213  n=190

Confidence interval = (exp(-0.4116-1.96*0.1999),exp(-0.4116+1.96*0.1999)) = (0.4478,0.9804)



> fitrobust=coxph(Surv(start,end,event)~tx+size+num,robust=TRUE)
Call:
coxph(formula = Surv(start, end, event) ~ tx + size + num, robust = TRUE)

        coef exp(coef) se(coef) robust se      z     p
tx   -0.4116     0.663   0.1999    0.2304 -1.787 0.074
size -0.0411     0.960   0.0703    0.0750 -0.548 0.580
num   0.1637     1.178   0.0478    0.0644  2.540 0.011

Likelihood ratio test=14.7  on 3 df, p=0.00213  n=190

Confidence interval = (exp(-0.4116-1.96*0.2304),exp(-0.4116+1.96*0.2304)) = (0.4218,1.0408)
```

Stratified Cox approach

We can not always assume indepence between recurrent events of the same subject:
$\rightarrow$ event order is important
$\rightarrow$ disease categories are different

In this case we need a different approach
$\rightarrow$ stratified Cox model
here the strata are the time interval numbers

We consider three startified Cox approaches:

Conditional 1: the data layout is the same as in the CP

id	int	event	start	stop	tx	num	size
10	1	1	0	12	0	1	1
10	2	1	12	16	0	1	1
10	3	0	16	18	0	1	1

Conditional 2: start times are always zero, and stop times are the length of the time intervals

id	int	event	start	stop	tx	num	size
10	1	1	0	12	0	1	1
10	2	1	0	4	0	1	1
10	3	0	0	2	0	1	1

Marginal: in the data layout we don't have the start times. For each subject we have as many lines as the subject which experienced the most events

id	int	event	stime	tx	num	size
10	1	1	12	0	1	1
10	2	1	16	0	1	1
10	3	0	18	0	1	1
10	4	0	18	0	1	1

Example

Three subjects: Molly, Holly and Polly

ID	Status	Stratum	Start (days)	Stop (days)	tx
M	1	1	0	100	1
M	1	2	100	105	1
H	1	1	0	30	0
H	1	2	30	50	0
P	1	1	0	20	0
P	1	2	20	60	0
P	1	3	60	85	0

For the first stratum, the risk set is the same for all three methods

$t_{(j)}$	n_j	$R(t_{(j)})$
0	3	M,H,P
20	3	M,H,P
30	2	M,H
100	1	M

For the other strata, the risk set will differ depending on the method.
We consider now the risk sets for the second stratum.

In Conditional 1, the time until the first event influences the risk set for later events

$t_{(j)}$	n_j	$R(t_{(j)})$
20	1	P
30	2	H,P
50	2	H,P
60	1	P
100	1	M
105	1	M

In Conditional 2, the time until the first event doesn't influence the following events since the clock determining who is at risk gets reset to 0 after each event

$t_{(j)}$	n_j	$R(t_{(j)})$
0	3	M,H,P
5	3	M,H,P
20	2	H,P
40	1	P

In Marginal, every subject is at risk since time zero

$t_{(j)}$	n_j	$R(t_{(j)})$
0	3	M,H,P
50	3	M,H,P
60	2	M,P
105	1	M

For the marginal approach we also show the table of stratum 3

$t_{(j)}$	n_j	$R(t_{(j)})$
0	3	M,H,P
85	2	M,P

The no-interaction stratified Cox model for the bladder cancer example is:

$$h_g(t, X) = h_{0g}(t) \exp\left[\beta \text{ tx} + \gamma_1 \text{ num} + \gamma_2 \text{ size}\right]$$

g=1,2,3,4

The interaction stratified Cox model for the bladder cancer example is:

$$h_g(t, X) = h_{0g}(t) \exp\left[\beta_g \text{ tx} + \gamma_{1g} \text{ num} + \gamma_{2g} \text{ size}\right]$$

g=1,2,3,4

We want to test the interaction between the strata with an LR test. The null hypothesis is H_0:

$$\beta_1 = \beta_2 = \beta_3 = \beta_4 \equiv \beta$$
$$\gamma_{11} = \gamma_{12} = \gamma_{13} = \gamma_{14} \equiv \gamma_1$$
$$\gamma_{21} = \gamma_{22} = \gamma_{23} = \gamma_{24} \equiv \gamma_2$$

As for the CP approach, we use the robust estimation also for the other three approaches.

R output for Conditional 1 model

```
> fitcon1 <- coxph(Surv(start,end,event)~tx+size+num+strata(interval), robust=TRUE)
Call:
coxph(formula = Surv(start, end, event) ~ tx + size + num + strata(interval),
    robust = TRUE)

        coef exp(coef) se(coef) robust se      z     p
tx   -0.3335     0.716   0.2162    0.2227 -1.497 0.130
size -0.0085     0.992   0.0728    0.0728 -0.117 0.910
num   0.1196     1.127   0.0533    0.0624  1.917 0.055
```

```
> fitcon1.int <- coxph(Surv(start,end,event)~tx*strata(interval)+size*strata(interval)+
  num*strata(interval),robust=TRUE)
Call:
coxph(formula = Surv(start, end, event) ~ tx * strata(interval) +
    size * strata(interval) + num * strata(interval), robust = TRUE)

                                  coef exp(coef) se(coef) robust se       z      p
tx                             -0.5260     0.591   0.3158    0.3152 -1.6685 0.0950
tx:strata(interval)interval=2   0.0221     1.022   0.5145    0.5529  0.0401 0.9700
tx:strata(interval)interval=3   0.6666     1.948   0.7435    0.5800  1.1493 0.2500
tx:strata(interval)interval=4   0.5763     1.779   0.8524    0.6254  0.9216 0.3600
tx:strata(interval)interval=5       NA        NA   0.0000    0.0000      NA     NA

> -0.5260+0.0221 = -0.5039
> -0.5260+0.6666 = 0.1406
> -0.5260+0.5763 = 0.0503
```

R output for Conditional 2 model

```
> fitcon2 <- coxph(Surv(rep(0,191),end-start,event)~tx+size+num+strata(interval),robust=TRUE)
Call:
coxph(formula = Surv(rep(0, 191), end - start, event) ~ tx +
    size + num + strata(interval), robust = TRUE)

         coef exp(coef) se(coef) robust se      z      p
tx   -0.27900     0.757   0.2073    0.2173 -1.284 0.2000
size  0.00742     1.007   0.0700    0.0695  0.107 0.9100
num   0.15805     1.171   0.0519    0.0560  2.823 0.0048
```

```
>fitcon2.int <- coxph(Surv(rep(0,191),end-start,event)~tx*strata(interval)+
 size*strata(interval)+num*strata(interval),robust=TRUE)
Call:
coxph(formula = Surv(rep(0, 191), end - start, event) ~ tx *strata(interval) +
    size * strata(interval) + num * strata(interval), robust = TRUE)

                                   coef exp(coef) se(coef) robust se       z      p
tx                              -0.5260     0.591   0.3158    0.3152 -1.6685 0.0950
tx:strata(interval)interval=2    0.2550     1.290   0.5136    0.5216  0.4890 0.6200
tx:strata(interval)interval=3    0.7363     2.088   0.6342    0.7215  1.0204 0.3100
tx:strata(interval)interval=4    0.3055     1.357   0.7129    0.7289  0.4191 0.6800
tx:strata(interval)interval=5        NA        NA   0.0000    0.0000      NA     NA
```

```
> -0.5260+0.2550 = -0.271
> -0.5260+0.7363 = 0.2103
> -0.5260+0.3055 = -0.2205
```

R output for marginal model

```
> fitcon3 <- coxph(Surv(stime,event)~tx+size+num+strata(interval),robust=TRUE, data=marginal.bladder)
Call:
coxph(formula = Surv(stime, event) ~ tx + size + num + strata(interval),
    data = marginal.bladder, robust = TRUE)

        coef exp(coef) se(coef) robust se      z       p
tx   -0.5848     0.557   0.2011    0.1926 -3.037 2.4e-03
size -0.0516     0.950   0.0697    0.0648 -0.796 4.3e-01
num   0.2103     1.234   0.0468    0.0455  4.618 3.9e-06
```

```
> fitcon3.int <- coxph(Surv(stime,event)~tx*strata(interval)+size*strata(interval)+num*strata(interval),
robust=TRUE, data=marginal.bladder)
Call:
coxph(formula = Surv(stime, event) ~ tx * strata(interval) +
    size * strata(interval) + num * strata(interval), data = marginal.bladder,
    robust = TRUE)

                                  coef exp(coef) se(coef) robust se      z      p
tx                             -0.5260     0.591   0.3158    0.3152 -1.669 0.0950
tx:strata(interval)interval=2  -0.1063     0.899   0.5042    0.4848 -0.219 0.8300
tx:strata(interval)interval=3  -0.1725     0.842   0.5578    0.5254 -0.328 0.7400
tx:strata(interval)interval=4  -0.1095     0.896   0.6573    0.5888 -0.186 0.8500

> -0.5260-0.1063 = -0.6323
> -0.5260-0.1725 = -0.6985
> -0.5260-0.1095 = -0.6355
```

Summarizing our results we obtain:

	Int Str1 $\widehat{\beta}_1$ (RSE)	Int Str2 $\widehat{\beta}_2$ (RSE)	Int Str3 $\widehat{\beta}_3$ (RSE)	Int Str4 $\widehat{\beta}_4$ (RSE)	No int $\widehat{\beta}$ (RSE)
CP	-	-	-	-	-0.4116 (0.2304)
C1	-0.5260 (0.3152)	-0.5039 (0.5529)	0.1406 (0.5800)	0.0503 (0.6254)	-0.3335 (0.2227)
C2	-0.5260 (0.3152)	-0.2710 (0.5216)	0.2103 (0.7215)	-0.2205 (0.7289)	-0.2790 (0.2173)
M	-0.5260 (0.3152)	-0.6323 (0.4848)	-0.6985 (0.5254)	-0.6355 (0.5888)	-0.5848 (0.1926)

Which approach is in general the best?
It depends!

- if the order of the events is not important
  $\rightarrow$ the CP model
- if the order of the events is important
  $\rightarrow$ one of the stratified model
  - if the time interval of interest is the time from study entry
    $\rightarrow$ conditional 1 model
  - if the time interval of interest is the time between two events
    $\rightarrow$ conditional 2 model
  - if there are different types of events
    $\rightarrow$ marginal model

In our bladder cancer example:

- We prefer the counting process, because the events seems to be independent
- If we have to choose one of the three stratified Cox model approaches, we would prefer the conditional 1 approach because the events are all of the same type and the time of interest is the time from study entry, in particular the no interaction model

```
LR test for no-interaction Conditional 1 = 6.51  on 3 df

LR test for Conditional 1 = 14.5  on 12 df

> 1-pchisq(14.5-6.51,9) = 0.5351543
```

What can we conclude about tx?
We consider the CP and the no-interaction Conditional 1 approaches:

	Counting process	Conditional 1
Parameter estimate	-0.4116	-0.3335
Robust standard error	0.2304	0.2227
p-value	0.074	0.130
Hazard ratio	0.663	0.716
95% confidence interval	(0.4218,1.0408)	(0.4584,1.1162)

From the R output we can not conclude that tx is effective.

Parametric approach using frailty

We consider now a parametric approach using shared frailty, where the data layout is the same as for the counting process approach:

$$h_k(t \mid \alpha, X_{jk}) = \alpha_k h(t \mid X_{jk})$$

where:

$$\alpha \sim \Gamma(1, \theta)$$

$$\mathrm{h(t} \mid X_{jk}) = \exp(\beta_0 + \beta_1 \mathrm{tx}_{jk} + \beta_2 \mathrm{num}_{jk} + \beta_3 \mathrm{size}_{jk}) p t^{p-1}$$

is the Weibull PH model.

The term *shared* frailty indicates that each subject shares the same level of frailty.

The shared frailty adjusts the standard errors of the estimated coefficients (as the robust estimation) and moreover can have an impact on the estimated coefficients themselves.

Weibull regression (PH form)
Gamma shared frailty
Log likelihood = −184.73658

_t	Coef.	Std. Err.	z	P > |z|
tx	−.458	.268	−1.71	0.011
num	.184	.072	2.55	0.327
size	−.031	.091	−0.34	0.730
_cons	−2.952	.417	−7.07	0.000
/ln_p	−.119	.090	−1.33	0.184
/ln_the	−.725	.516	−1.40	0.160
p	.888	.080		
1/p	1.13	.101		
theta	.484	.250		

Likelihood ratio test of theta = 0:
chibar(01) = 7.34
Prob >= chibar2 = 0.003

```
Confidence interval = (exp(-0.458-1.96*0.268),exp(-0.458+1.96*0.268))
                    = (0.3741,1.0696)
```

Survival curves

Survival to a kth event with $k \geq 1$:

$$S_k(t) = P(T_k > t)$$

where T_k is the survival time up to the occurence of the kth event

There are two possible versions of such a plot:

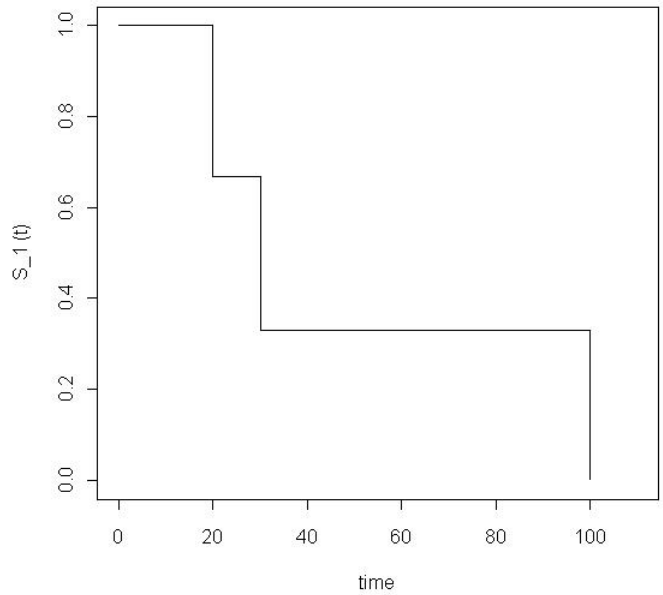
- Conditional 2 with T_{kc} = time from the (k-1)th to kth event, restricting data to subjects with k-1 events
- Marginal with T_{km} = time from study entry to kth event, ignoring previous events

Recall the example of Molly, Holly and Polly

ID	Status	Stratum	Start (days)	Stop (days)	tx
M	1	1	0	100	1
M	1	2	100	105	1
H	1	1	0	30	0
H	1	2	30	50	0
P	1	1	0	20	0
P	1	2	20	60	0
P	1	3	60	85	0

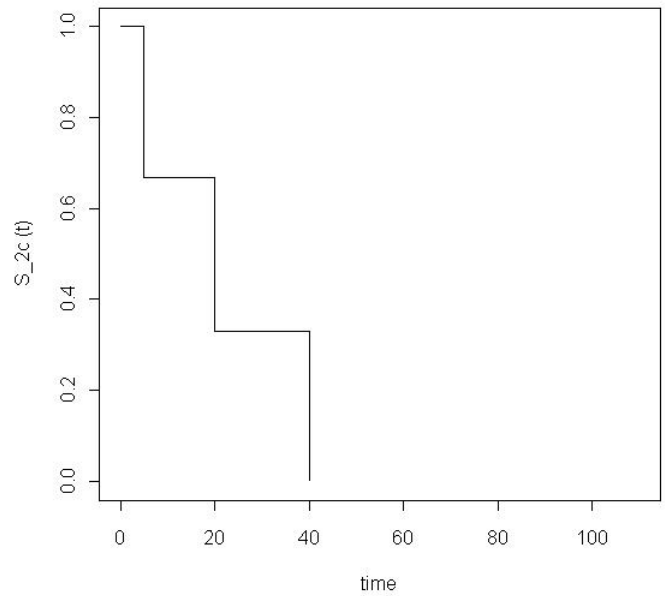
Survival plot for survival to the first event

$t_{(j)}$	n_j	m_j	q_j	$R(t_{(j)})$	$S_1(t_{(j)})$
0	3	0	0	M,H,P	1.00
20	3	1	0	M,H,P	0.67
30	2	1	0	M,H	0.33
100	1	1	0	M	0.00



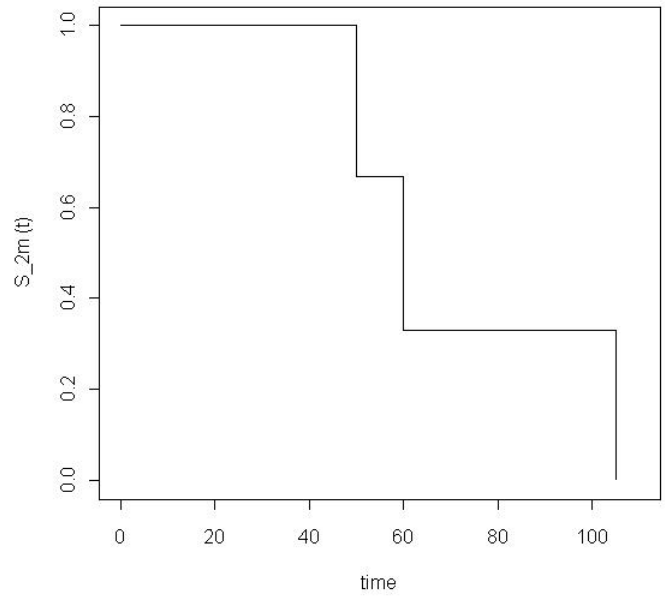
Conditional survival plot for survival to the second event

$t_{(j)}$	n_j	m_j	q_j	$R(t_{(j)})$	$S_1(t_{(j)})$
0	3	0	0	M,H,P	1.00
5	3	1	0	M,H,P	0.67
20	2	1	0	H,P	0.33
40	1	1	0	P	0.00



Marginal survival plot for survival to the second event

$t_{(j)}$	n_j	m_j	q_j	$R(t_{(j)})$	$S_1(t_{(j)})$
0	3	0	0	M,H,P	1.00
50	3	1	0	M,H,P	0.67
60	2	1	0	M,P	0.33
105	1	1	0	M	0.00



Summary

- Counting process approach
  - all the events are considered as independent
  - robust estimation
- Stratified Cox approach
  - Conditional 1: data layout same as CP
  - Conditional 2: start times zero, stop times length of interval
  - Marginal: only stop times, same number of lines for each subject
- Parametric approach using frailty
- Survival curves