PLSC 504 - Fall 2017
Cure Models

October 10, 2017

Cure Models

Standard models (e.g.):

$$h(T_i|\mathbf{X}_i,\beta) = \frac{f(T_i|\mathbf{X}_i,\beta)}{S(T_i|\mathbf{X}_i,\beta)}$$

assume:

$$\int_0^\infty f(t)\,dt = 1 \;\forall\; i.$$

All observations will (eventually) experience the event of interest.

Mixture Cure Model

Assume (unobserved):

$$Y_i = \begin{cases} 1 \text{ for observations that will eventually fail,} \\ 0 \text{ for those that will not.} \end{cases}$$

For observations with $Y = 1$:

$$\begin{aligned} f(T_i|\mathbf{X}_i, \beta, Y_i = 1) &= g(T|\mathbf{X}_i, \beta) \\ F(T_i|\mathbf{X}_i, \beta, Y_i = 1) &= G(T|\mathbf{X}_i, \beta) \end{aligned}$$

For observations with $Y = 0$, $f(T)$ and $F(T)$ are undefined.

Mixture Cure Model (continued)

Define:

$$\Pr(Y_i = 1) = \delta_i.$$

Overall survival is then just:

$$S_i(T) = (1 - \delta_i) + \delta_i[1 - G_i(t)]$$

Mixture Cure Model: Likelihood

Then for $C_i = 1$:

$$\begin{aligned} L_i | C_i = 1 &= \Pr(Y_i = 1) \Pr(T_i = t | Y_i = 1, \mathbf{X}_i, \beta) \\ &= \delta_i g(T_i | \mathbf{X}_i, \beta) \end{aligned}$$

For $C_i = 0$:

$$\begin{aligned} L_i | C_i = 0 &= \Pr(Y_i = 0) + \Pr(Y_i = 1) \Pr(T_i > t_i | Y_i = 1, \mathbf{X}_i, \beta) \\ &= (1 - \delta_i) + \delta_i [1 - G(T_i | \mathbf{X}_i, \beta)] \end{aligned}$$

Mixture Cure Model: Likelihood

Implies:

$$\mathbf{L} = \prod_{i=1}^{N} \left[\delta_i g(T_i|\mathbf{X}_i, \beta)\right]^{C_i} \left\{(1-\delta_i) + \delta_i \left[1 - G(T_i|\mathbf{X}_i, \beta)\right]\right\}^{(1-C_i)}$$

and:

$$\begin{aligned} ln\mathbf{L} &= \sum_{i=1}^{N} C_i \left\{\ln(\delta_i) + \ln\left[g(T_i|\mathbf{X}_i, \beta)\right]\right\} \\ &\quad + (1-C_i)\ln\left\{(1-\delta_i) + \delta_i \left[1 - G(T_i|\mathbf{X}_i, \beta)\right]\right\} \end{aligned}$$

Mixture Cure Model: Specification

Typically:

$$\delta_i = \frac{\exp(\mathbf{Z}_i\gamma)}{1 + \exp(\mathbf{Z}_i\gamma)}$$

or:

$$\delta_i = \Phi(\mathbf{Z}_i\gamma).$$

Identified even if $\mathbf{Z} \equiv \mathbf{X}$.

Non-Mixture Cure Model (e.g. Sposto 2002)

$N_i =$ number of pre-cancerous cell clusters, with:

$$N_i \sim \text{Poisson}(\lambda).$$

Pr(Cure) is:

$$\pi_i = \Pr(N_i = 0).$$

Time to cancer onset for cluster j of observation i is:

$$Z_{ij} \sim F(t),\ j = \{1, 2, ...N_i\}.$$

Non-Mixture Cure Model (continued)

Survival to first onset:

$$S(t) = \pi^{F(t)}$$

with hazard function:

$$h(t) = -\ln(\pi) f(t)$$

which reflects the fact that $\int_0^\infty h(t)dt = -\ln(\pi)$.

Non-Mixture Cure Model (continued)

Rewritten $S(t)$:

$$S(t) = \exp[\ln(\pi)F(t)].$$

Assuming:

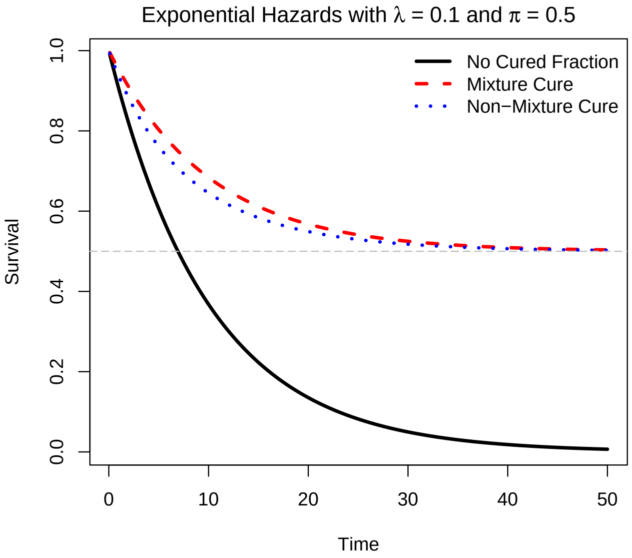
$$\pi_i = \exp[-\exp(\mathbf{X}_i\beta)]$$

we get:

$$S(t) = \exp\{[-\exp(\mathbf{X}_i\beta)]F(t)\}.$$

which is the Cox.

Mixture vs. Non-Mixture Models



Discrete-Time Cure Models

- Parametric / Cox $\longrightarrow$ Poisson
- Mixture Cure Model $\longrightarrow$ Zero-Inflated Poisson
- Non-Mixture Cure Model $\longrightarrow$ "Hurdle" Poisson

Software

R

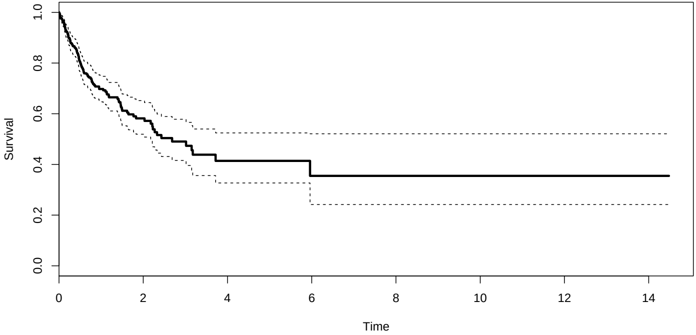
- `smcure` (semiparametric mixture models via EM)
- `semicure` (same; old)
- `nltm` (various; see Tsodikov 2003)
- `CR`, `NPHMC` (power analysis for cure models)

Stata

- `strsmix` and `strsnmix` (general parametric mixture & non-mixture cure models)
- `cureregr` (an old version)
- `lncure` (log-normal cure model)
- `spsurv` (discrete-time cure model)
- `zip / zinb` (discrete-time kludge)

A Simulated Example

```
> set.seed=7222009
> X<-rnorm(500)
> Z<-rbinom(500,1,0.5)
> T<-rweibull(500,shape=1.2,scale=1/(exp(0.5+1*X)))
> C<-rbinom(500,1,(0.4-0.3*Z))
> S<-Surv(T,C)
```



Cox Models

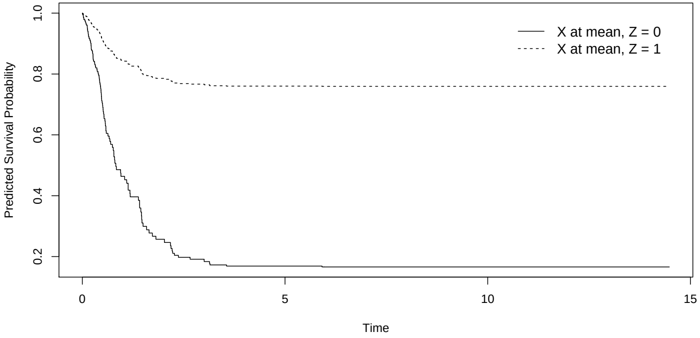
```
> coxph(S~X)
Call:
coxph(formula = S ~ X)

  coef exp(coef) se(coef)    z p
X 1.05      2.85    0.124 8.44 0

Likelihood ratio test=77.7  on 1 df, p=0  n= 500, number of events= 130


> coxph(S~X+Z)
Call:
coxph(formula = S ~ X + Z)

   coef exp(coef) se(coef)    z       p
X  1.08     2.956    0.122  8.9 0.0e+00
Z -1.59     0.204    0.230 -6.9 5.4e-12

Likelihood ratio test=140  on 2 df, p=0  n= 500, number of events= 130
```

Cure Model

```
> cure.fit<-smcure(S~X,cureform=~Z,data=data.cure,model="ph")

Program is running..be patient... done.

Call:
smcure(formula = S ~ X, cureform = ~Z, data = data.cure, model = "ph")

Cure probability model:
            Estimate Std.Error Z value Pr(>|Z|)
(Intercept)      1.6      0.39     4.1  3.4e-05
Z               -2.8      0.41    -6.7  2.5e-11


Failure time distribution model:
  Estimate Std.Error Z value Pr(>|Z|)
X      1.1      0.14     8.1  6.7e-16
```

An Interesting Plot

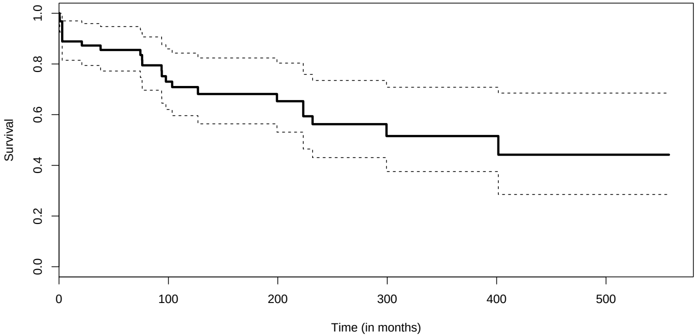
```
> cure.hat<-predictsmcure(cure.fit,c(rep(mean(X),times=2)),
                          c(0,1),model="ph")

> cure.pic<-plotpredictsmcure(cure.hat,type="S",model="ph")
```



An Example: Ceasefire Durability

Data are a subset used in Fortna (2004) (full data are here).

- $N = 63$
- Non-time-varying



Ceasefires: Cox Model

```
> CF.cox<-coxph(CF.S~tie+imposed+lndeaths+contig+onedem+twodem,
              data=CF,method="efron")
> CF.cox

Call:
coxph(formula = CF.S ~ tie + imposed + lndeaths + contig + onedem +
    twodem, data = CF, method = "efron")

            coef exp(coef) se(coef)      z       p
tie        1.845     6.327    0.557  3.314 0.00092
imposed    0.210     1.233    0.594  0.353 0.72000
lndeaths  -0.135     0.874    0.193 -0.699 0.48000
contigyes  2.898    18.143    0.948  3.058 0.00220
onedem     3.423    30.648    1.144  2.991 0.00280
twodem    -0.723     0.485    1.209 -0.598 0.55000

Likelihood ratio test=36.8  on 6 df, p=0.00000197  n= 63, number of events= 23
```

(hours of fiddling...)

A Typical Result

```
> CF.cure1.fit<-smcure(CF.S~tie+lndeaths+imposed,
                       cureform=~contig,data=CF,model="ph",
                       link="logit",emmax=500)

Program is running..be patient... done.

Call:
smcure(formula = CF.S ~ tie + lndeaths + imposed, cureform = ~contig,
    data = CF, model = "ph", link = "logit", emmax = 500)

Cure probability model:
            Estimate Std.Error Z value Pr(>|Z|)
(Intercept)     -3.4      12.4   -0.27     0.79
contig           2.1       7.4    0.28     0.78

Failure time distribution model:
         Estimate Std.Error Z value Pr(>|Z|)
tie          2.05      4.06    0.50     0.61
lndeaths    -0.37      0.34   -1.10     0.27
imposed      0.97      2.40    0.41     0.68
There were 50 or more warnings (use warnings() to see the first 50)
```

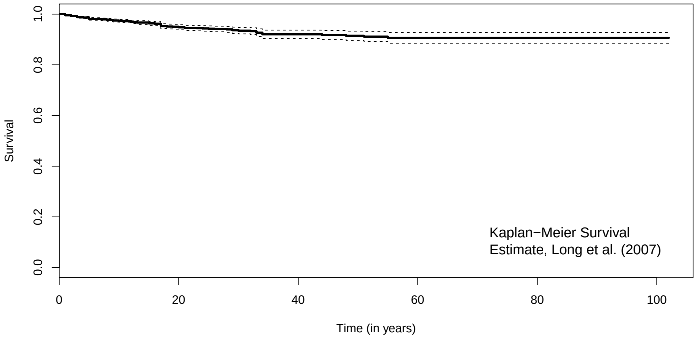
From Svolik (2008)

Consolidation status model[b]				
GDP per capita	2.121***	—	2.045***	2.121***
	(0.586)	—	(0.555)	(0.586)
GDP growth	−0.014	—	−0.048	−0.014
	(0.227)	—	(0.246)	(0.227)
Military (vs. *Not independent*)	−4.061**	—	−3.985**	−4.061**
	(1.895)	—	(1.857)	(1.895)
Civilian (vs. *Not independent*)	−0.421	—	−0.549	−0.421
	(1.097)	—	(1.067)	(1.097)
Monarchy (vs. *Not independent*)	−20.158	—	−15.844	−13.965
	(2888.609)	—	(680.185)	(891.870)
Parliamentary (vs. *Mixed*)	2.231	—	2.290	2.231
	(2.230)	—	(2.326)	(2.230)
Presidential (vs. *Mixed*)	−8.310**	—	−8.186**	−8.310**
	(3.958)	—	(4.035)	(3.958)
Intercept	−6.144**	—	−5.920**	−6.145**
	(2.646)	—	(2.644)	(2.647)

Another Example: Peace Duration

Long, Nordstrom and Baek (2007 *JOP*)

- Peace duration among allies
- Time-varying dyadic data, 1816-2001 ($NT = 57,819$)



Cox Model (replicating LNB)

```
> LNB.cox<-coxph(LNB.S~relcap+major+jdem+border+wartime+s_wt_glo+
              medarb+noagg+arbcom+organ+milinst+cluster(dyad),
              data=LNB,method="breslow")
> LNB.cox
Call:
coxph(formula = LNB.S ~ relcap + major + jdem + border + wartime +
    s_wt_glo + medarb + noagg + arbcom + organ + milinst + cluster(dyad),
    data = LNB, method = "breslow")


           coef exp(coef) se(coef) robust se      z        p
relcap   -1.431     0.239    0.614     0.683 -2.096 0.036000
major     1.137     3.118    0.241     0.280  4.064 0.000048
jdem     -0.987     0.373    0.367     0.380 -2.600 0.009300
border    1.931     6.897    0.190     0.206  9.378 0.000000
wartime  -0.359     0.699    0.367     0.467 -0.768 0.440000
s_wt_glo -0.284     0.752    0.332     0.355 -0.802 0.420000
medarb   -0.367     0.693    0.285     0.306 -1.202 0.230000
noagg    -0.463     0.630    0.126     0.152 -3.051 0.002300
arbcom    1.306     3.690    0.325     0.316  4.133 0.000036
organ     0.353     1.423    0.280     0.285  1.236 0.220000
milinst  -0.373     0.689    0.187     0.177 -2.101 0.036000
```

Cure Models

(hours of fiddling...)

```
> LNB.cure<-smcure(LNB.altS~relcap+major+jdem+border+wartime+s_wt_glo+
                   medarb+noagg+arbcom+organ+milinst,
                   cureform=~border,model="ph",data=LNB)

Program is running..be patient...
```

Cure Models (Stata Remix)

```
. stset count1, id(episode) f(buofmzmid==1)
. gen h0=0
. strsmix major jdem border wartime, bhazard(h0) distribution(weibull) link(logistic) k1
> (relcap major jdem border wartime s_wt_glo medarb noagg arbcom organ milinst)

                                                  Number of obs   =      57819
                                                  Wald chi2(4)    =      36.82
Log likelihood = -793.21263                       Prob > chi2     =     0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
pi           |
       major |  -7.921296   3.764002    -2.10   0.035     -15.2986   -.5439877
        jdem |  -.6177566   .7656096    -0.81   0.420    -2.118324    .8828107
      border |  -1.943181   .3786093    -5.13   0.000    -2.685241    -1.20112
     wartime |   2.583909   1.051959     2.46   0.014     .5221065    4.645711
       _cons |   2.659179   .3980719     6.68   0.000     1.878972    3.439385
-------------+----------------------------------------------------------------
ln_lambda    |
      relcap |  -1.408332   .7129111    -1.98   0.048    -2.805613   -.0110523
       major |  -1.232928    .395653    -3.12   0.002    -2.008394   -.4574626
        jdem |   -1.69796   .4596442    -3.69   0.000    -2.598846   -.7970736
      border |   1.224114   .2622007     4.67   0.000     .7102103    1.738018
     wartime |     .42086   .4072876     1.03   0.301     -.377409    1.219129
    s_wt_glo |   -.274703   .3579769    -0.77   0.443    -.9763249    .4269188
      medarb |  -.8221547   .3503126    -2.35   0.019    -1.508755   -.1355545
       noagg |    -.68365   .1465971    -4.66   0.000     -.970975   -.3963251
      arbcom |   1.667284   .4562532     3.65   0.000     .7730438    2.561524
       organ |   .9298395   .3595899     2.59   0.010     .2250563    1.634623
     milinst |  -.4428979   .2251323    -1.97   0.049    -.8841491   -.0016468
       _cons |  -2.060399   .7260061    -2.84   0.005    -3.483344   -.6374528
-------------+----------------------------------------------------------------
ln_gamma     |
       _cons |   .0969349   .0733007     1.32   0.186    -.0467319    .2406018
------------------------------------------------------------------------------
```

Some Lessons

Cure models...

- ...Powerful
- ...Intuitive
- ...Temperamental
- ...Ask a lot of your data