

Example 4 — Mixture cure models for survival data
[Description](#)[Remarks and examples](#)[References](#)[Also see](#)

Description

Cure models, or split-population models, are used to model survival data where a fraction of the population will never experience a failure. Mixture cure models represent the population as a combination of two types of individuals: a short-term survivor (noncured) group and a long-term survivor (cured) group. These models allow us to detect covariates associated with class membership (being cured or not) and to investigate the impact of covariates on the hazard for the noncured group as well.

In this example, we demonstrate how to fit a cure model as a two-component FMM with one component being a parametric survival model and one component being a point mass density that represents the cured group.

Remarks and examples

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Implantation of intraocular lenses is a common surgery used to treat cataracts. One possible complication after this procedure is calcification of the lenses. Some patients will experience calcification during the follow-up period and some will not. Just because patients have not experienced calcification during the follow-up period does not mean that they truly are cured. It is still possible that they might experience calcification after the follow-up period ends. Thus, the cured group must be considered right-censored, with some individuals not observed to have calcification possibly belonging to this group.

In the language of FMM, we have two latent groups: a cured group and a noncured group. We know that patients who experience calcification are members of the noncured group. We do not know which group that patients who remain healthy belong to. That is, some of the patients we observe as healthy are truly cured, whereas others are members of the noncured group who are right-censored because they happened to not experience calcification during the study.

With a mixture cure model, we can predict the probability that an individual who did not experience calcification during the study is noncured. Let π be the probability of being in the noncured group, and let $S_1(t)$ be the survivor function for the noncured group. For the noncured group, the time to failure is modeled with a parametric distribution accounting for right-censoring, such as exponential or Weibull. If we let $S(t)$ be the probability of not failing before time t for an individual in the population, our model is

$$S(t) = (1 - \pi) + \pi S_1(t)$$

To illustrate the model, we use the artificial dataset, `lenses.dta`, with some of the characteristics of the calcification study described in [Ma \(2009\)](#). About 46% of the patients did not have postsurgery calcification of lenses during the follow-up period. We will predict how many of those are likely to have calcification after the follow-up period.

In our model, $S_1(t)$ is a Weibull using a proportional hazards parameterization. The covariates of interest are patient's sex (`sex`), patient's age at implantation divided by 10 (`age10`), and incision length (`inclength`).

2 Example 4 — Mixture cure models for survival data

The variable `fail` in the dataset contains an indicator for failure (occurrence of calcification). When `fail = 1`, we know that an individual belongs to the noncured group. When `fail = 0`, the individual is observed as healthy, but we cannot say they are a member of the cured group.

We first use `stset` to declare the data to be survival-time data. We specify `t` as the variable that contains analysis time and `fail` as the variable that indicates failure; see [ST] `stset` for details.

```
. use https://www.stata-press.com/data/r17/lenses
(Simulated calcification data)
. stset t, failure(fail)
Survival-time data settings
      Failure event: fail!=0 & fail<.
Observed time interval: (0, t]
      Exit on or before: failure
```

```
      770 total observations
      0 exclusions
```

```
      770 observations remaining, representing
      415 failures in single-record/single-failure data
20,133.467 total analysis time at risk and under observation
                        At risk from t =      0
Earliest observed entry t =      0
                        Last observed exit t =    36
```

To model time-to-calcification in the noncured group, we fit a Weibull model for right-censored data where the dependent variable is the time variable. This includes the patients observed as noncured and those who appear healthy. To model the probability of being cured, we use a point mass density at `fail = 0` because this indicates that calcification was not observed. See [FMM] `fmm: pointmass` for details about the point mass distribution.

```
. fmm: (pointmass fail) (streg inclength i.sex age10, distribution(weibull))
(iteration log omitted)
Finite mixture model                                Number of obs = 770
Log likelihood = -1980.1495
```

| | Coefficient | Std. err. | z | P> z | [95% conf. interval] | |
|------------------|----------------|-----------|------|-------|----------------------|----------|
| 1.Class | (base outcome) | | | | | |
| 2.Class _cons | 1.01863 | .2703434 | 3.77 | 0.000 | .4887664 | 1.548493 |

```
Class:      2
Response:  _t
Model:      streg, dist(weibull)
No. of failures = 415
Time at risk = 20,133.47
```

| | Coefficient | Std. err. | z | P> z | [95% conf. interval] | |
|-----------------|-------------|-----------|-------|-------|----------------------|-----------|
| _t inclength | -.5922698 | .2273662 | -2.60 | 0.009 | -1.037899 | -.1466402 |
| sex | | | | | | |
| male | .3314051 | .1259957 | 2.63 | 0.009 | .0844581 | .5783522 |
| age10 | .1600672 | .032798 | 4.88 | 0.000 | .0957843 | .2243502 |
| _cons | -4.939691 | .940024 | -5.25 | 0.000 | -6.782104 | -3.097278 |
| /_t ln_p | .4683771 | .058332 | | | .3540485 | .5827056 |

The first table in the output shows the estimated coefficient on the logit scale for the class 2 (noncured group) probability. This probability is 0.73 [$\text{invlogit}(1.019) \approx 0.73$], which implies that the probability of being in the cured group is 0.27.

The second table presents the results for the Weibull regression model for the noncured group. We see that longer incisions decrease the hazard of calcification, while being male and being older increase the hazard of calcification.

We may want to know the probability that patients who have not experienced calcification will do so in the future. We can predict the posterior probability of being in class 2. We list the first 10 patients for the cured group.

```
. predict pprob2, classposterior class(2.Class)
. sort fail, stable
. list fail pprob2 in 1/10
```

| | fail | pprob2 |
|-----|------|----------|
| 1. | 0 | .2569577 |
| 2. | 0 | .4447927 |
| 3. | 0 | .3233174 |
| 4. | 0 | .4677424 |
| 5. | 0 | .4549083 |
| 6. | 0 | .4183038 |
| 7. | 0 | .3161573 |
| 8. | 0 | .4540032 |
| 9. | 0 | .2782425 |
| 10. | 0 | .5745969 |

We see that the posterior probability of having calcification in the future is over 50% for the last patient.

We generate an indicator variable `prfail` that takes on value 1 if the posterior probability of calcification is greater than 50% and zero otherwise. We construct a classification table where we tabulate our variable against the indicator of failure `fail`.

```
. generate prfail = pprob2 > .5
. tabulate prfail fail
```

| prfail | failed=1, didn't fail=0 | | Total |
|--------|----------------------------|-----|-------|
| | 0 | 1 | |
| 0 | 257 | 0 | 257 |
| 1 | 98 | 415 | 513 |
| Total | 355 | 415 | 770 |

Out of 355 individuals who did not experience calcification during the study, we estimate that 98 are more likely than not to have calcification in the future.

References

- Lambert, P. C. 2007. [Modeling of the cure fraction in survival studies](#). *Stata Journal* 7: 351–375.
- Ma, S. 2009. Cure model with current status data. *Statistica Sinica* 19: 233–249.

Also see

[FMM] **fmm** — Finite mixture models using the fmm prefix

[FMM] **fmm postestimation** — Postestimation tools for fmm