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Identifying latent subgroups using regularized mixture cure models to develop risk stratification systems in cancer: Illustration using the hdcuremodels R package

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Survival models

- The Cox proportional hazards (PH) model is the most frequently used method for assessing the effect of a covariate on a time-to-event outcome and assumes:
    - independence of time-to-event;
    - failure and censoring times are independent given covariates (non-informative censoring);
    - hazard ratio is constant over time; and
    - all subjects will experience the event of interest $[S(t = \infty) = 0]$.
- When modeling time to relapse, some patients may:
    - experience "cure" and therefore are "immune" to the event
    - whereas others are susceptible to the event.

Survival models

- The Cox model is known to yield inaccurate estimates of the hazard and survival when cured subjects are in the risk set [1].
- Recall, the Cox PH model assumes the same risk or hazard of an event throughout the entire follow-up period for all subjects. This is violated when cured subjects are in the dataset.
- Moreover, when a cured fraction exists in the sample being modeled but is ignored, the survival function $S(t)$ is no longer proper because $S(t = \infty) \neq 0$.
- Although we don't observe "cure," various methods have been proposed for estimating the cure fraction [2].
- Methods that account for the proportion cured separately from the latency of susceptibles (AKA, time-to-event among those susceptible - that is, those who will experience the event) are called mixture cure models.

Notation

- We let $i = 1, \ldots, N$ index subjects in our dataset.
- $T_i^\star$ is the time until the event of interest for subject i.
- If $T^\star$ is subject to right censoring, we observe $T_i = \min(T_i^\star, C_i)$ where C_i is the censoring time.
- Thus

$$\delta_i = \begin{cases} 1 & \text{if } T_i \leq C_i \\ 0 & \text{otherwise.} \end{cases}$$

- Therefore we only observe T_i and δ_i, the time-to-event or time to last follow-up, and whether or not the event of interest occurred.

Notation

- If $\delta_i = 1$ we know the subject was uncured or susceptible.
- If $\delta_i = 0$ the subject either was cured or would have experienced the event if followed longer.
- Thus, we do not observe who is cured but they are usually censored observations, and those having long-term survival for which $P(T = \infty) = 1 - p$.
- Provided sufficiently long follow-up, the cure fraction, or probability of a cure, has been taken to be the Kaplan-Meier estimate of survival beyond the last observed event [3] or the limit of the cancer-specific survival distribution [4].

Mixture Models

- Consider that the population consists of K independent subgroups.
- Let $f(t)$ be a probability density function of the survival time T for the population.
- The finite mixture form is

$$f(t) = \sum_{k=1}^{K} p_k f_k(t)$$

where $p_1, \ldots, p_K$ represents the proportion of subjects in sub-population K where $\sum_{k=1}^{K} p_k = 1$ and $f_1(t), \ldots, f_K(t)$ are the K component densities.

Mixture Cure Models

- Let p_c = proportion "immunes" or cured subjects ($Y = 0$)
- Let p_u = proportion "susceptibles" or uncured subjects ($Y = 1$)
- $K = 2$ so $p_c + p_u = 1$.
- Let $S_u(t) = P(T > t|Y = 1)$ and $S_c(t) = P(T > t|Y = 0)$ then

$$S(t) = p_c S_c(t) + p_u S_u(t)$$

Notice $S_c(t) = P(T > t|Y = 0) = 1$

- Let $p = P(Y = 1)$ so that $(1 - p) = P(Y = 0)$ such that

$$S(t) = (1 - p) + pS_u(t)$$

- The latency or time-to-event $S_u(t)$ for susceptibles can be modeled using either
  - parametric [5, 6, 7];
  - non-parametric [8]; or
  - semi-parametric methods [9].

Mixture cure models (MCM)

- The mixture structure allows one to investigate the effect of covariates on two components of the model: incidence (susceptible versus cured) and latency (time-to-event for susceptibles).

$$S(t|\mathbf{x},\mathbf{w}) = (1 - p(\mathbf{x})) + p(\mathbf{x})S_u(t,\mathbf{w}|Y = 1)$$

- Example: The density of a Weibull distributed variable is $f(t) = \lambda\alpha(\lambda t)^{\alpha-1}\exp[-(\lambda t)^{\alpha}]$ where the shape α and scale λ parameters are both > 0.
- Letting the hazard depend on covariates, we replace λ^{α} with $\lambda^{\alpha}\exp(\boldsymbol{\beta}^{\top}\mathbf{w})$ such that

$$f(t|\mathbf{w}) = \lambda\alpha(\lambda t)^{\alpha-1}\exp(\boldsymbol{\beta}^{\top}\mathbf{w})\exp\left(-(\lambda t)^{\alpha}\exp(\boldsymbol{\beta}^{\top}\mathbf{w})\right).$$

Mixture cure models (MCM)

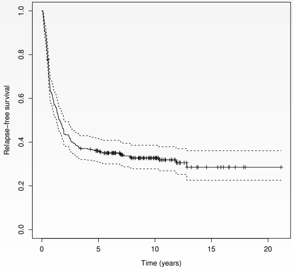
- The incidence component, $p(\mathbf{x})$, is usually modeled using logistic regression.
- We replace $p(\mathbf{x})$ with $\exp(b_0 + \mathbf{b}^\top \mathbf{x})/(1 + \exp(b_0 + \mathbf{b}^\top \mathbf{x}))$.
- The Weibull MCM likelihood consists of $p(\mathbf{x})$ and $f(t|\mathbf{w})$.
- The set of parameters for the Weibull MCM is $\boldsymbol{\theta} = (b_0, \mathbf{b}, \boldsymbol{\beta}, \alpha, \lambda)$.
- The exponential mixture cure model is a special case of the Weibull where $\alpha = 1$.
- $\boldsymbol{\theta} = (b_0, \mathbf{b}, \boldsymbol{\beta})$ for the semi-parametric mixture cure model.

Mixture cure models

- Mixture cure models assume:
  - independence of time-to-event;
  - failure and censoring times are independent given covariates (non-informative censoring);
  - some subjects will not experience the event of interest; and
  - there is sufficient follow-up time.
- Farewell (1982) [5] cautions that there should be strong scientific evidence that two sub-populations are present.
- Maller and Zhou (1996) [7] provided
  - an inferential procedure for assessing whether the proportion immunes > 0.
  - an inferential procedure for assessing whether there is sufficient follow-up.

hdcuremodels: Data example

```
> library(hdcuremodels)
> library(survival)
> dim(amltrain)
[1] 306 322
> dim(amltest)
[1]  40 322
> km <- survfit(Surv(cryr, relapse.death) ˜ 1, data = amltrain)
> plot(km, mark.time = TRUE, xlab = "Time (years)",
+  ylab = "Relapse-free survival")
```



hdcuremodels: Assessing MCM assumptions

```
> cure_estimate(km)
[1] 0.2853081
> nonzerocure_test(km)
$proportion_susceptible
[1] 0.7146919

$proportion_cured
[1] 0.2853081

$p.value
[1] "< 0.001"

$time_95_percent_of_events
[1] 5.294299
> sufficient_fu_test(km)
       p.value Nn   N
1 4.825325e-06 12 306
```

Penalized Mixture Cure Models*

```
> args(curegmifs)
function (formula, data, subset, x.latency = NULL, model = "weibull",
    penalty.factor.inc = NULL, penalty.factor.lat = NULL, epsilon = 0.001,
    thresh = 1e-05, scale = TRUE, maxit = 10000, inits = NULL,
    verbose = TRUE, ...)

> args(cureem)
function (formula, data, subset, x.latency = NULL, model = "cox",
    penalty = "lasso", penalty.factor.inc = NULL,
    penalty.factor.lat = NULL,
    thresh = 0.001, scale = TRUE, maxit = NULL, inits = NULL,
    lambda.inc = 0.1, lambda.lat = 0.1, gamma.inc = 3, gamma.lat = 3,
    ...)
```

* `cureem` uses the E-M algorithm [10]; curegmifs uses the GMIFS algorithm [11]

Penalized Mixture Cure Models

```
> coxem <-cureem(Surv(cryr, relapse.death) ~ ., data = amltrain,
+               x.latency = amltrain, model = "cox",
+               lambda.inc=0.009993, lambda.lat=0.02655)

> fitgmifs <- curegmifs(Surv(cryr, relapse.death) ~ ., data = amltrain,
+               x.latency = amltrain, model = "weibull", maxit = 20000)
```

Penalized Mixture Cure Models

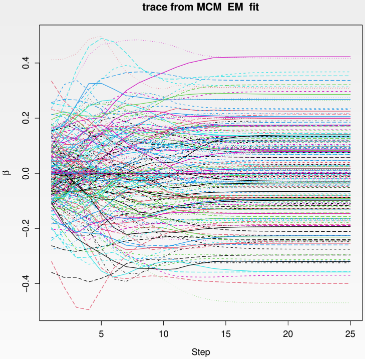
```
> args(cv_cureem)
function (formula, data, subset, x.latency = NULL, model = "cox",
    penalty = "lasso", penalty.factor.inc = NULL, penalty.factor.lat = NULL
    fdr.control = FALSE, fdr = 0.2, grid.tuning = FALSE, thresh = 0.001,
    scale = TRUE, maxit = NULL, inits = NULL, lambda.inc.list = NULL,
    lambda.lat.list = NULL, nlambda.inc = NULL, nlambda.lat = NULL,
    gamma.inc = 3, gamma.lat = 3, lambda.min.ratio.inc = 0.1,
    lambda.min.ratio.lat = 0.1, n_folds = 5, measure.inc = "c",
    one.se = FALSE, cure_cutoff = 5, parallel = FALSE, seed = NULL,
    verbose = TRUE, ...)

> args(cv_curegmifs)
function (formula, data, subset, x.latency = NULL, model = "weibull",
    penalty.factor.inc = NULL, penalty.factor.lat = NULL, fdr.control = FAL
    fdr = 0.2, epsilon = 0.001, thresh = 1e-05, scale = TRUE,
    maxit = 10000, inits = NULL, n_folds = 5, measure.inc = "c",
    one.se = FALSE, cure_cutoff = 5, parallel = FALSE, seed = NULL,
    verbose = TRUE, ...)
```

hdcuremodels: Generic functions

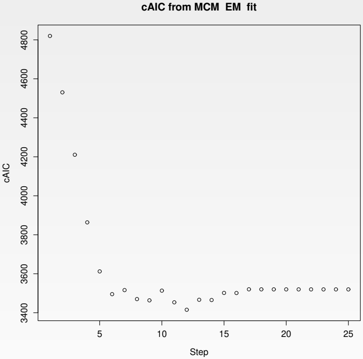
```
> print(coxem)
 [1] "b_path"      "beta_path"   "b0_path"     "logLik.inc"
 [5] "logLik.lat"  "x.incidence" "x.latency"   "y"
 [9] "model"       "scale"       "method"      "call"
[13] "cv"
> summary(coxem)
Mixture cure model fit using the EM algorithm
at step    =  25 logLik     =  -1113.552
at step    =  12 AIC        =  2634.476
at step    =  12 mAIC        =  5510.632
at step    =  12 cAIC        =  3415.284
at step    =  12 BIC        =  3382.917
at step    =  12 mBIC        =  5423.137
at step    =  12 EBIC        =  3777.815
```

hdcuremodels: Generic functions

```
> plot(coxem)
```



```
> plot(coxem, type = "cAIC")
```

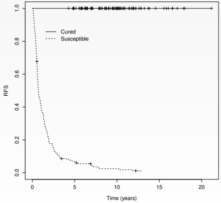


hdcuremodels: Generic functions

```
> coef.cAIC <- coef(coxem, model.select = "cAIC")
> coef.12 <- coef(coxem, model.select = 12)
> names(coef.cAIC)
[1] "b0"       "beta_inc" "beta_lat"
> coef.cAIC$b0
[1] 1.638612
> sum(coef.cAIC$beta_inc != 0)
[1] 112
> sum(coef.cAIC$beta_lat != 0)
[1] 88
```

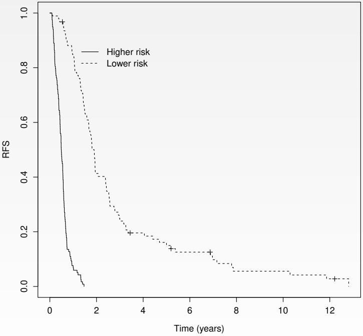
hdcuremodels: Generic functions

```
> train.predict <- predict(coxem, model.select = "cAIC")
> names(train.predict)
[1] "p.uncured"      "linear.latency" "latency.risk"
> head(train.predict$p.uncured)
[1] 0.95394997 0.89003059 0.94182718 0.76070954 0.18856553 0.04190272
> head(train.predict$linear.latency)
[1] -0.8706797 -0.4249528 -1.3281981 -1.3928568  0.9210771 -2.8833691
> head(train.predict$latency.risk)
[1] "low risk"  "low risk"  "low risk"  "low risk"  "high risk" "low risk"
> p_group <- ifelse(train.predict$p.uncured < 0.50, "Cured", "Susceptible")
> km.cured <- survfit(Surv(cryr, relapse.death) ~ p_group, data = amltrain)
> plot(km.cured, mark.time = TRUE, lty = c(1,2), xlab="Time (years)", ylab = "RFS")
> legend(c(.9, .1), legend = c("Cured", "Susceptible"), lty = c(1, 2), bty = "n")
```



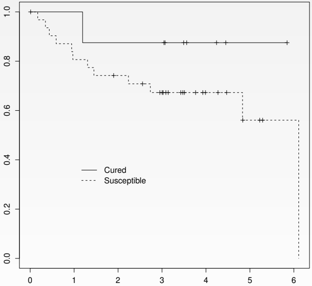
hdcuremodels: Generic functions

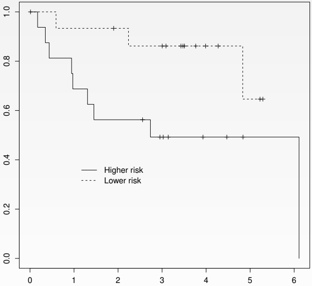
```
> km.suscept <- survfit(Surv(cryr, relapse.death) ~ train.predict$latency.risk,
+  data = amltrain, subset = (p_group == "Susceptible"))
> plot(km.suscept, mark.time = TRUE, lty = c(1,2), xlab = "Time (years)",
+ ylab="RFS")
> legend(c(.9, .1), legend = c("Higher risk", "Lower risk"), lty = c(1,2),
+ bty = "n")
```



hdcuremodels: Generic functions

```
> test.predict <- predict(coxem, newdata = amltest, model.select = "cAIC")
> test_p_group <- ifelse(test.predict$p.uncured < 0.50, "Cured", "Susceptible")
> km.cured.test <- survfit(Surv(cryr, relapse.death) ~ test_p_group, data = amltest)
> plot(km.cured.test, mark.time = TRUE, lty = c(1, 2))
> legend(c(.4, .1), legend = c("Cured", "Susceptible"), lty = c(1,2), bty = "n")
> km.suscept.test <- survfit(Surv(cryr, relapse.death) ~ test.predict$latency.risk, data = amltest,
+ subset = (test_p_group == "Susceptible"))
> plot(km.suscept.test, mark.time = TRUE, lty = c(1,2))
> legend(c(.4, .1), legend = c("Higher risk", "Lower risk"), lty = c(1, 2), bty = "n")
```





hdcuremodels: Generic functions

- The outcome for `cutoff` $= \tau$ is defined as

$$Y_i = \begin{cases} 0 \text{ if } T_i > \tau \\ 1 \text{ if } T_i \leq \tau \text{ and } \delta_i = 1 \\ \text{missing if } T_i \leq \tau \text{ and } \delta_i = 0 \end{cases} .$$

- The mean score imputation AUC lets $Y_i = 1 - \hat{p}(\mathbf{x}_i)$ for those subjects with a missing outcome [12].
- The C-statistic for MCMs was adapted to weight patients by their outcome (cured, susceptible, censored) [13].

```
> AUC(coxem, model.select = "cAIC")
[1] 0.9690409
> AUC(coxem, newdata = amltest, model.select = "cAIC")
[1] 0.8049214
> concordance_mcm(coxem, model.select = "cAIC")
[1] 0.8546535
> concordance_mcm(coxem, newdata = amltest, model.select = "cAIC")
[1] 0.6987875
```

Contributions⋆

- Our `hdcuremodels` R package can be used to model a censored time-to-event outcome in the presence of a cure fraction
- Our `hdcuremodels` R package can handle a high-dimensional covariate space
- Our `hdcuremodels` R package does not require the same variables to be included in the incidence and latency portions of the model
- Our `hdcuremodels` R package includes relevant functions for testing MCM assumptions
- As previously demonstrated [11], our GMIFS and E-M algorithms outperformed existing methods in terms of variable selection and prediction

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