Compound Cox: univariate feature selection and compound covariates for predicting survival

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We developed "*compound.Cox*" R package

Emura T, Matsui S, Chen HY (2019),
Computer Methods and Programs in Biomedicine
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Tools

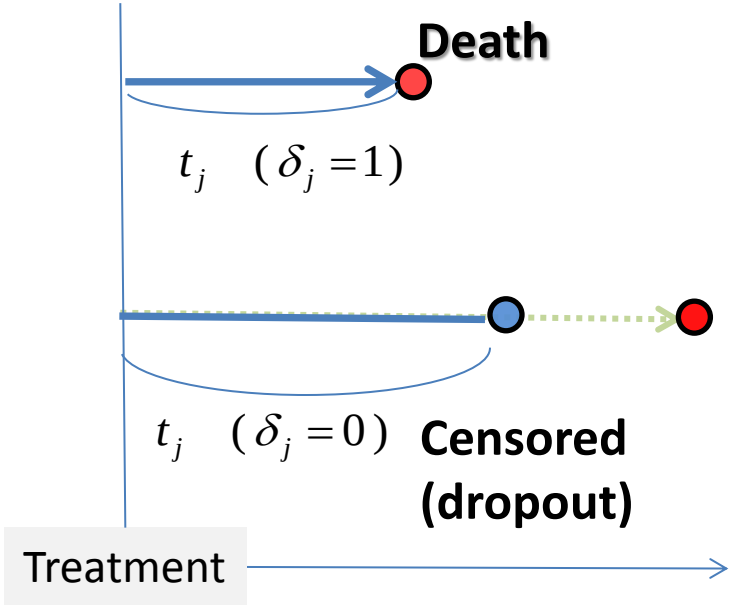
- **Lung cancer data**
- **Feature selection**
- **Multiple tests**
- **Predictor calculation**
- **Prediction error (CVL)**
- **False discovery rate (FDR)**
- **Copula methods**

- Survival Data（right-censored）

t_i : time-to-death or censoring

$$\delta_i = \begin{cases} 1 & \text{if death} \\ 0 & \text{if censoring} \end{cases}$$

$$\mathbf{x}_i = (x_{i1}, ..., x_{ip})', \quad \text{possibly} \quad p > n$$



t_i	δ_i	x_{i1}	x_{i2}	x_{i3}	x_{i4}		x_{i127}	$x_{i,128}$
Time-to-event	Censor	AP3S1	APMAP	ARHGAP28	CXCL12	……..	ASB7	B4GALT5
1650	0	-0.52	1.12	-0.37	1.30	……	0.354	-1.015
30	1	-0.18	-0.69	-0.93	1.28	……	0.026	0.38
⋮	⋮					……		
1800	1	-1.08	0.70	-0.29	-0.529	……	-0.50	-1.09

Short Survival

High Expression

P-value<0.05, but….

Errors in multiple tests

- **α=0.05 is the error rate of ONLY one test**

  100 tests ➔ $0.05 \times 100 = 5$ rejections

  (False Discoveries)

In statistical process control (Montgomery 2009)

- **3-sigma** rule, ***α*=0.0023**
- set ***α*** to be **ARL=370**

In design of microarray experiments (Simon 2001)

- ***α*=0.001,** one error in 1000 tests
- Set ***α*** to be **FDR=0.20**

Summary of today's material

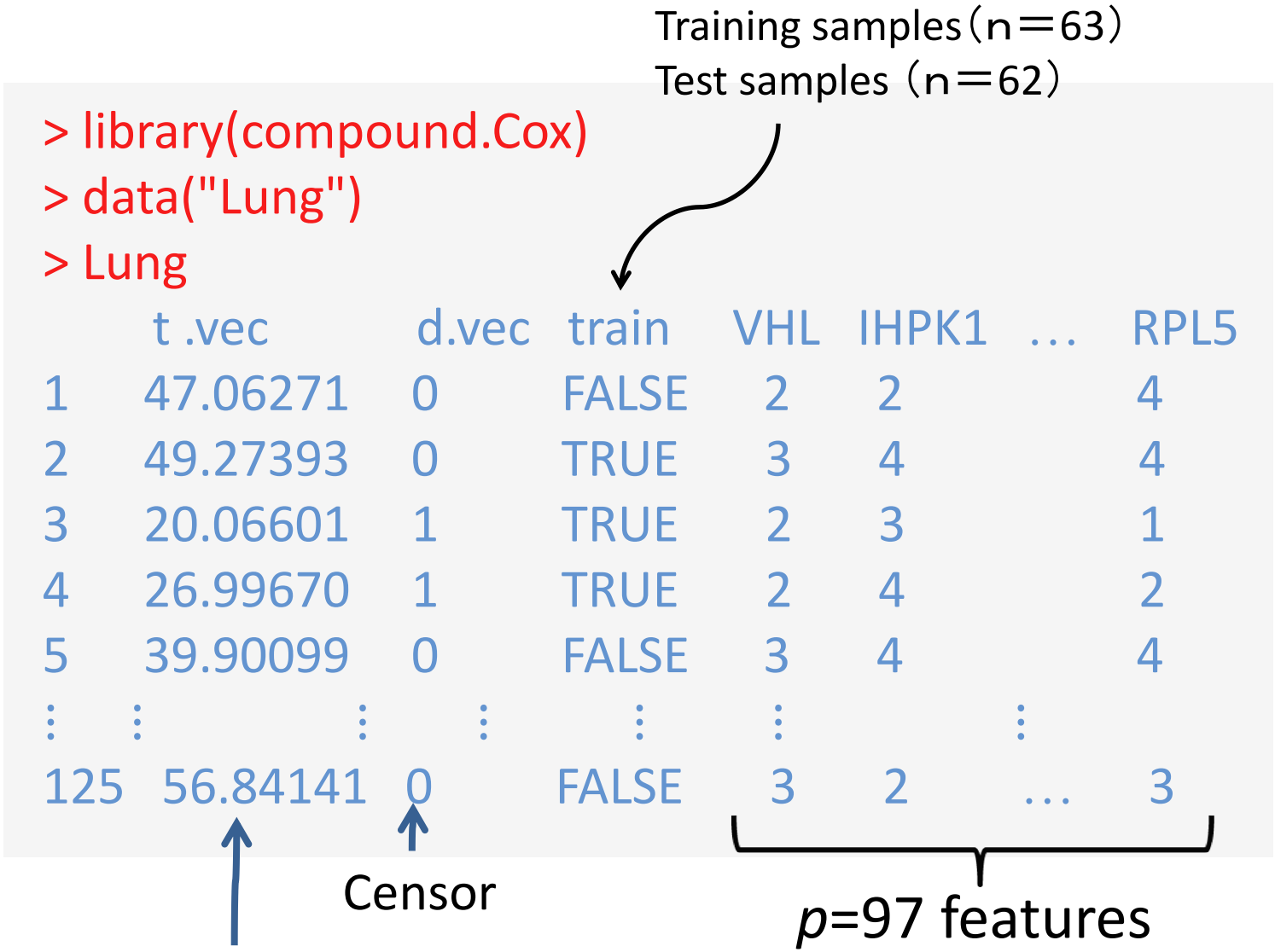
- "death" may be unobservable
  ➔ Deal with ***censoring (or dropout)***
  Tool: Cox's partial likelihood (Cox 1972)

- A ***large*** number of features
  ➔ Select a subset of ***features***
  Tool: Multiple significance tests
  Tool: False discovery rate (Witten & Tibshirani 2010)

- A multigene predictor
  Tool: Tukey's compound covariate
  (Tukey 1993; Shyr and Kim 2003; Matsui 2006; Emura et al. 2012)

- Prediction error via ***cross-validation***
  Tool: Cross-validated likelihood (CVL) (Matsui 2006)

Lung cancer data in *Lung* object



Univariate Cox regression

T = Survival time

x_j = j-th feature

Proportional hazards model (Cox 1972)

$$\Pr(t \le T < t + dt \mid T \ge t, x_j) = h_0(t) \exp(\beta_j x_j) dt$$

Partial likelihood estimator (Cox regression)

$$\hat{\beta}_j = \arg\max \ell_j(\beta_j)$$

$$\ell_j(\beta_j) = \sum_{i=1}^{n} \delta_i \left[\beta_j x_{ij} - \log \left(\sum_{\ell \in R_i} \exp(\beta_j x_{\ell j}) \right) \right]$$

$$SE(\hat{\beta}_j) = [-\partial^2 \ell_j(\beta_j) / \partial \beta_j^2]^{-1/2}$$

Univariate significance tests

$$H_{oj}: \beta_j = 0 \quad \text{vs.} \quad H_{1j}: \beta_j \neq 0$$

(1) Wald test:

Z-value: $z_j = \hat{\beta}_j / SE(\hat{\beta}_j) \sim N(0,1)$

P-value: $P_j = \Pr(|Z| > |z_j|)$

(2) Score test:

$$S_j = \sum_{i=1}^{n} \delta_i \left(x_{ij} - \bar{x}_j(t_i) \right) \qquad V_j = Var(S_j) = \sum_{i=1}^{n} \delta_i \left(\bar{x}_j^2(t_i) - (\bar{x}_{ij}(t_i))^2 \right)$$

Z-value: $z_j = S_j / \sqrt{V_j} \sim N(0,1)$

P-value: $P_j = \Pr(|Z| > |z_j|)$

-Simple algebraic computation

Multiple score tests via matrix

- Z-values: $\mathbf{Z} = \mathbf{S} / \mathbf{V}^{1/2}$

$$\mathbf{S} = \boldsymbol{\delta}'(\mathbf{X} - \mathbf{S}^{(1)} / \mathbf{S}^{(0)})$$

$$\mathbf{V} = \boldsymbol{\delta}'(\mathbf{S}^{(2)} / \mathbf{S}^{(0)} - (\mathbf{S}^{(1)} / \mathbf{S}^{(0)})^2)$$

$$\boldsymbol{\delta} = (\, \delta_1, \ldots, \delta_n \,)'$$

$\mathbf{S}^{(k)}$ is a $n \times p$ matrix with elements $S_{ij}^{(k)}$

$$S_{ij}^{(k)} = \sum_{\ell : t_\ell \geq t_i} x_{\ell j}^k \quad \text{for} \quad k = 0,\ 1 \text{ or } 2, \text{ and} \quad j = 1, \ldots,\ p$$

This computing technique is **new**
and implemented in *compound.Cox* package

Whole algorithms

Step 1: Test $H_{oj}: \beta_j = 0$ vs. $H_{1j}: \beta_j \neq 0$

Select a feature (via P-value < 0.05)

Step 2 : Critical evaluation of selected features

（1）False Discovery Rate (FDR) small enough ?

（2）Cross-validated Likelihood (CVL) high enough ?

Step 3 : Compound covariate predictor

Z-value: $z_1 x_1 + z_2 x_2 + \cdots + z_p x_q$

ß-value: $\hat{\beta}_1 x_1 + \hat{\beta}_2 x_2 + \cdots + \hat{\beta}_q x_q$

Step 4 : Test the predictor by independent test samples

"*compound.Cox*" performs the whole algorithms

uni.selection( )

features（$n \times p$ matrix）

Survival Time

Censor

P-value

```
> uni.selection(t.vec,d.vec,X.mat,K=20,P.value=0.05,score=FALSE,permutation=TRUE) ## Wald test
$beta
ANXA5       DLG2        ZNF264      DUSP6       CPEB4       LCK         STAT1
-1.0876762  1.3215044   0.5473276   0.7524497   0.5891676   -0.8447389  -0.5844262
RNF4        IRF4        STAT2       HGF         ERBB3       NF1         FRAP1
0.6463635   0.5176704   0.5849869   0.5086750   0.5509026   0.4715235   -0.7696768
MMD         HMMR
0.9151541   0.5156711
```

Regression coefficients

$$\hat{\beta}_j = \arg\max \ell(\beta_j)$$

$Z ⇐Z -value

.....

$P ⇐P-value

.....

```
$CVL
-98.66365
```

CVL: Cross-validation

```
$FDR
P.value * (No. of genes)    Permutation
0.3031250                   0.3128125
```

⇐FDR: False Discovery Rate

We selected **16 features** (P<0.05), but…

```
> uni.selection(t.vec,d.vec,X.mat,K=20,P.value=0.05,score=FALSE,permutation=TRUE)
$beta
ANXA5      DLG2      ZNF264     DUSP6      CPEB4      LCK        STAT1
-1.087     1.321     0.547      0.752      0.589      -0.844     -0.584
RNF4       IRF4      STAT2      HGF        ERBB3      NF1        FRAP1
0.646      0.517     0.584      0.5086     0.550      0.471      -0.769
MMD        HMMR
0.915      0.515
```

- **Q1: Is there any FALSE feature?**
  ⇒ Compute FDR（False discovery rate）
- **Q2: Is "P-value < 0.05" optimal ?**
  ⇒ Compute CVL（Cross-validated likelihood)
- **Q3: Beta unbiased ?**
  ⇒ Adjust the bias of beta by a copula method

False Discovery Rate (FDR)

FDR= Proportion of false rejection

= $E[f/16]$, where f is unknown

	Rejected	**Accepted**
ß≠0	16-f	
ß=0	f	
	$q=16$	$p=97$

➔ **FDR** and $E[f]$ can be estimated by a permutation method（Witten & Tibshirani 2010）

Random *M* permutations（Witten & Tibshirani 2010）

$$\mathrm{FDR} = \frac{\text{The expected number of false rejections}}{\text{The number of rejections}}$$

$$= \frac{\frac{1}{M}\sum_{m=1}^{M}\sum_{j=1}^{p} I(P_j^{(m)} < P)}{\sum_{j=1}^{p} I(P_j < P)}$$

$P_j^{(m)}$ is the P-value for testing $H_{0j}: \beta_j = 0$ vs. $H_{1j}: \beta_j \neq 0$

- **FDR does not guarantee predictive ability**

  （small FDR  high prediction ability）

CVL（Cross-validated likelihood)

: predictive capability of selected features

$$CVL = \sum_{k=1}^{K} \{ \ell(\hat{\gamma}_{-k}) - \ell_{-k}(\hat{\gamma}_{-k}) \},$$

where $\hat{\gamma}_{-k} = \arg\max_{\gamma} \ell_{-k}(\gamma)$,

CVL= - (Allen's PRESS)
for Gaussian likelihood & uncensored data (Allen 1974)

Test-data Likelihood ➔

$$\ell(\gamma) = \sum_i \delta_i \left[\gamma \mathrm{CC}_{i,-k} - \log \left\{ \sum_{\ell \in R_i} \exp\left(\gamma \mathrm{CC}_{\ell,-k} \right) \right\} \right],$$

Training-data likelihood ➔

$$\ell_{-k}(\gamma) = \sum_{i \in \Im_{-k}} \delta_i \left[\gamma \mathrm{CC}_{i,-k} - \log \left\{ \sum_{\ell \in R_i \cap \Im_{-k}} \exp\left(\gamma \mathrm{CC}_{\ell,-k} \right) \right\} \right],$$

High CVL ➡ High prediction (classification) capability

Matsui 2006 ; Emura, Matsui and Chen 2019

$$\begin{bmatrix} t_1, \delta_1, x_{11}, x_{12}, \ldots\ldots\ldots\ldots, x_{1p} \\ \vdots \\ t_n, \delta_n, x_{n1}, x_{n2}, \ldots\ldots\ldots\ldots, x_{np} \end{bmatrix}$$: survival data with n samples

⇓ ***Step 1***: Divide between "testing" vs. "training" samples

$$\begin{bmatrix} t_1, \delta_1, x_{11}, x_{12}, \ldots\ldots\ldots\ldots, x_{1p} \\ \vdots \\ \text{------} \\ \vdots \\ t_n, \delta_n, x_{n1}, x_{n2}, \ldots\ldots\ldots\ldots, x_{np} \end{bmatrix}$$

$\left.\begin{matrix} \\ \\ \\ \end{matrix}\right\}$ $\frac{n}{K}$ testing samples, $i \in \Im_k$

$\left.\begin{matrix} \\ \\ \\ \end{matrix}\right\}$ $n - \frac{n}{K}$ training samples, $i \in \Im_{-k}$

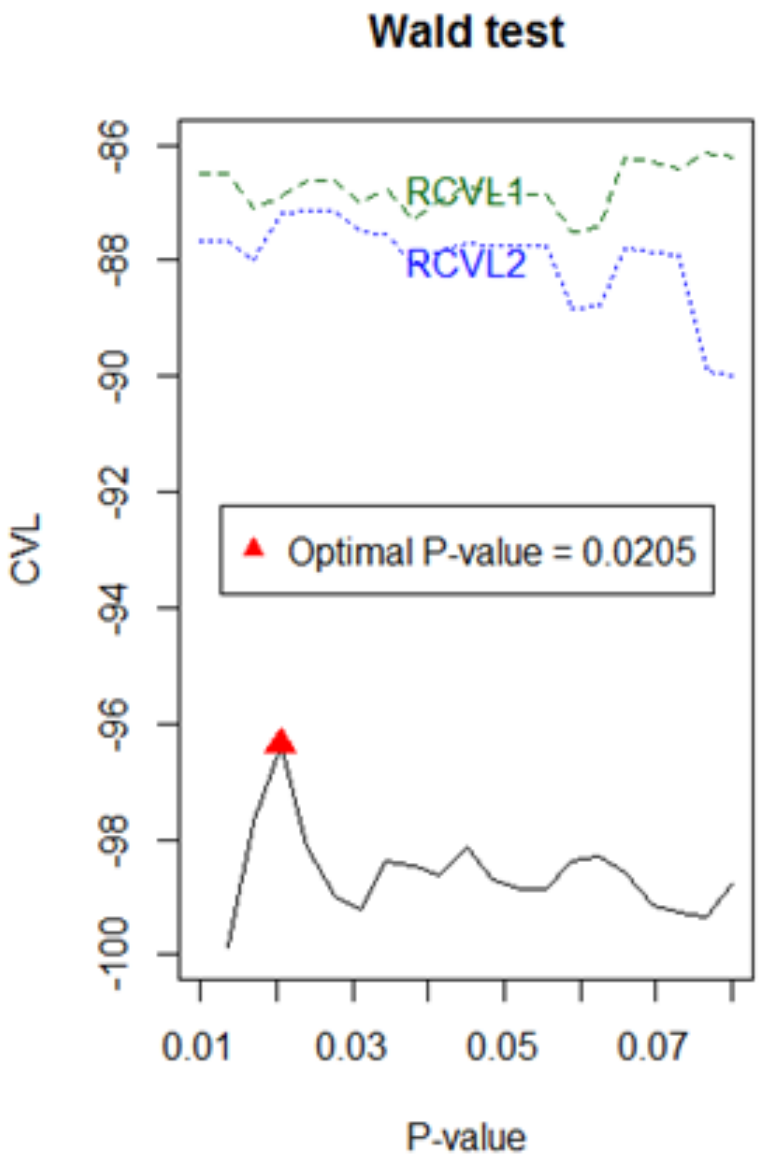
⇓ ***Step 2***: Feature Selection & Prediction (P-values < P)

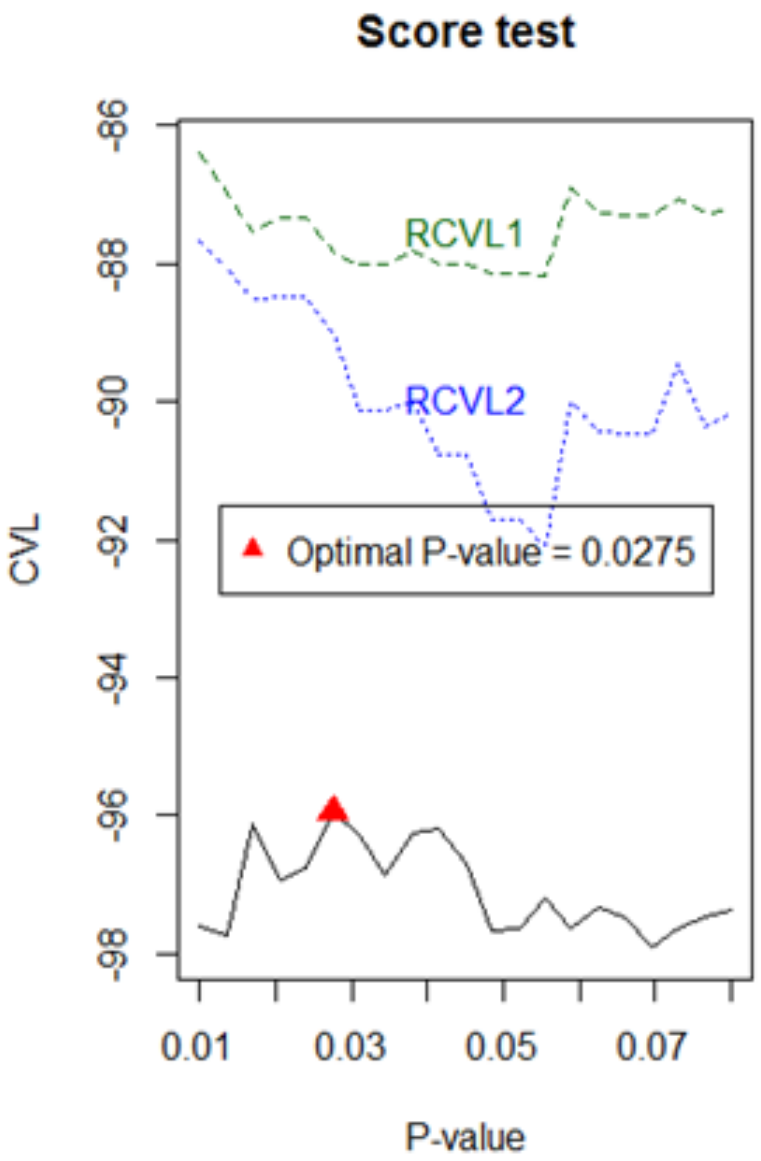
$$\begin{bmatrix} t_1, \delta_1, \mathrm{CC}_{1,-k} \\ \vdots \\ t_m, \delta_m, \mathrm{CC}_{m,-k} \end{bmatrix}, \quad \mathrm{CC}_{i,-k} = w_{1,-k} x_{i1} + w_{2,-k} x_{i2} + \cdots + w_{q,-k} x_{iq}, \quad i \in \Im_{-k}$$

⇓ ***Step 3***: Average (Predicted likelihood - Baseline)

$$CVL = \sum_{k=1}^{K} \{ \ell(\hat{\gamma}_{-k}) - \ell_{-k}(\hat{\gamma}_{-k}) \}$$

The optimal **P-value threshold** by the CVL plot





Optimal Wald tests (P< 0.0205)
➔ Select 7 features (genes)

```
> uni.selection(t.vec,d.vec,X.mat,K=20, P.value=0.0205,score=FALSE)
$beta
ANXA5       DLG2        ZNF264      DUSP6       CPEB4       LCK         STAT1
-1.0876762  1.3215044   0.5473276   0.7524497   0.5891676   -0.8447389  -0.5844262

$CVL  -96.37303
```

↑CVL

FDR=0.0205×97/7=0.29（29%）

Optimal score tests P <0.0275)
➔ Select 10 features (genes)

```
> uni.selection(t.vec,d.vec,X.mat,K=20, P.value=0.0275,score=TRUE)
$Z
ANXA5       DLG2        ZNF264      DUSP6       CPEB4       LCK         STAT1       STAT2
-3.363578   3.111772    2.814363    2.710854    2.538888    -2.511423   -2.445038   2.369334
RNF4        IRF4
2.345912    2.231286
⋮
$CVL    -95.95690
```

↑CVL

FDR=0.0275×97/10=0.30（30%）

Prediction & Classification

- **Selected Features**; $(x_1, \ldots, x_q)$

  e.g. $q = 10$ in the score tests

- **Compound Covariate**:

$$\mathbf{CC} = w_1 x_1 + \cdots + w_p x_q$$

Wald test: $(w_1, \ldots, w_q) = (\hat{\beta}_1, \ldots, \hat{\beta}_q)$

Score test: $(w_1, \ldots, w_q) = (z_1, \ldots, z_q)$

- Classification **CC** < *c* ➡ Good prognosis (Long survival)

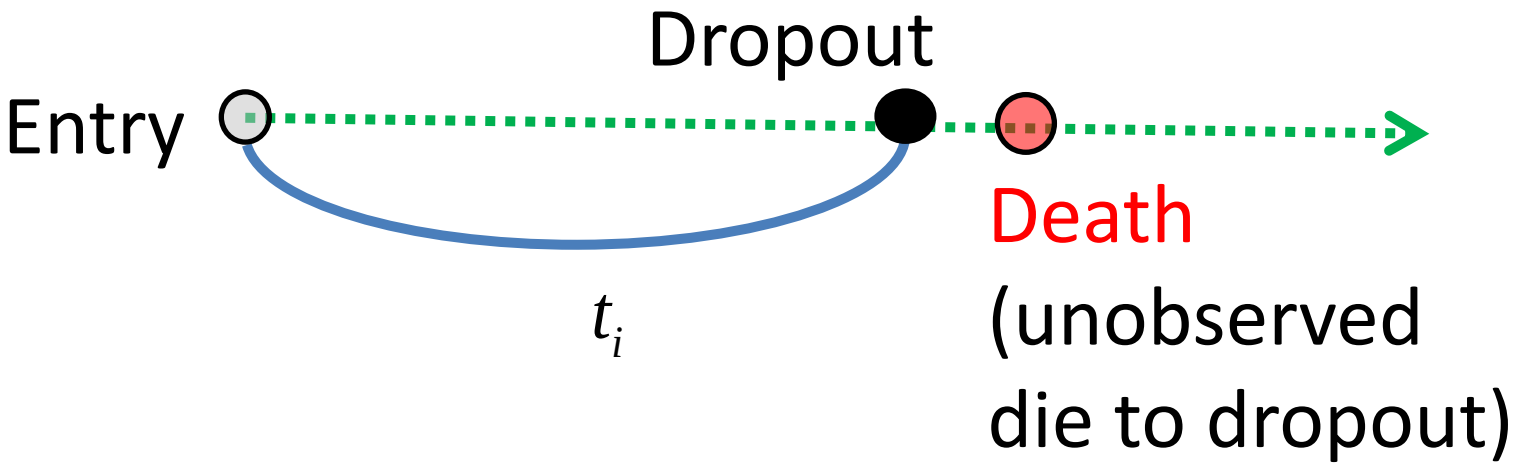
  CC > *c* ➡ Poor prognosis (Short survival)

⬆ cut-off value

Are weights (beta) unbiased?

Many dropout censors before death

➡ Dependence between censoring and death



Estimate $\hat{\beta}_j = \arg\max \ell_j(\beta_j)$ is biased

Model of Dependent Censoring

T = Survival (death) time

U = Censoring (dropout) time

x_j = *j-th feature*

C_α = Copula; α = copula parameter

⇓ Joint survival function

$$\Pr(T_i > t, U_i > u \mid x_{ij}) = C_\alpha\{\Pr(T_i > t \mid x_{ij}), \Pr(U_i > u \mid x_{ij})\}$$

$$\Pr(T_i > t \mid x_{ij}) = \exp\{-\Lambda_{0j}(t) e^{\beta_j x_{ij}}\}$$

Effect of j-th feature on T

⇑ Marginal survival function

Estimation under dependent censoring

Semi-parametric MLE (Emura and Chen 2016)

$$\ell(\beta_j, \gamma_j, \Lambda_{0j}, \Gamma_{0j} \mid \alpha)$$

$$= \sum_i \delta_i [\beta_j x_{ij} + \log \eta_{1ij}(t_i; \beta_j, \gamma_j, \Lambda_{0j}, \Gamma_{0j} \mid \alpha) + \log d\Lambda_{0j}(t_i)]$$

$$+ \sum_i (1-\delta_i)[\gamma_j x_{ij} + \log \eta_{2ij}(t_i; \beta_j, \gamma_j, \Lambda_{0j}, \Gamma_{0j} \mid \alpha) + \log d\Gamma_{0j}(t_i)]$$

$$- \sum_i \Phi_\alpha[\exp\{-\Lambda_{0j}(t_i)e^{\beta_j x_{ij}}\}, \exp\{-\Gamma_{0j}(t_i)e^{\gamma_j x_{ij}}\}],$$

Computed by "*compound.Cox*" R package

$$(\hat{\beta}_j(\alpha), \hat{\gamma}_j(\alpha), \hat{\Lambda}_{0j}(\alpha), \hat{\Gamma}_{0j}(\alpha))$$

Compute weight w_j the CC

Survival prediction

1. **Optimal Wald（7 features）:**

$$\mathbf{CC}= \hat{\beta}_1 x_{i1} + \cdots + \hat{\beta}_7 x_{i7}$$

2. **Optimal score（10 features）:**

$$\mathbf{CC}= z_1 x_{i1} + \cdots + z_{10} x_{i10}$$

3. **Optimal Wald + copula（7 features）:**

$$\mathbf{CC}= \hat{\beta}_1(\hat{\alpha}) x_{i1} + \cdots + \hat{\beta}_7(\hat{\alpha}) x_{i7}$$

4. **Optimal score + copula（10 features ）:**

$$\mathbf{CC}= \hat{\beta}_1(\hat{\alpha}) x_{i1} + \cdots + \hat{\beta}_{10}(\hat{\alpha}) x_{i10}$$

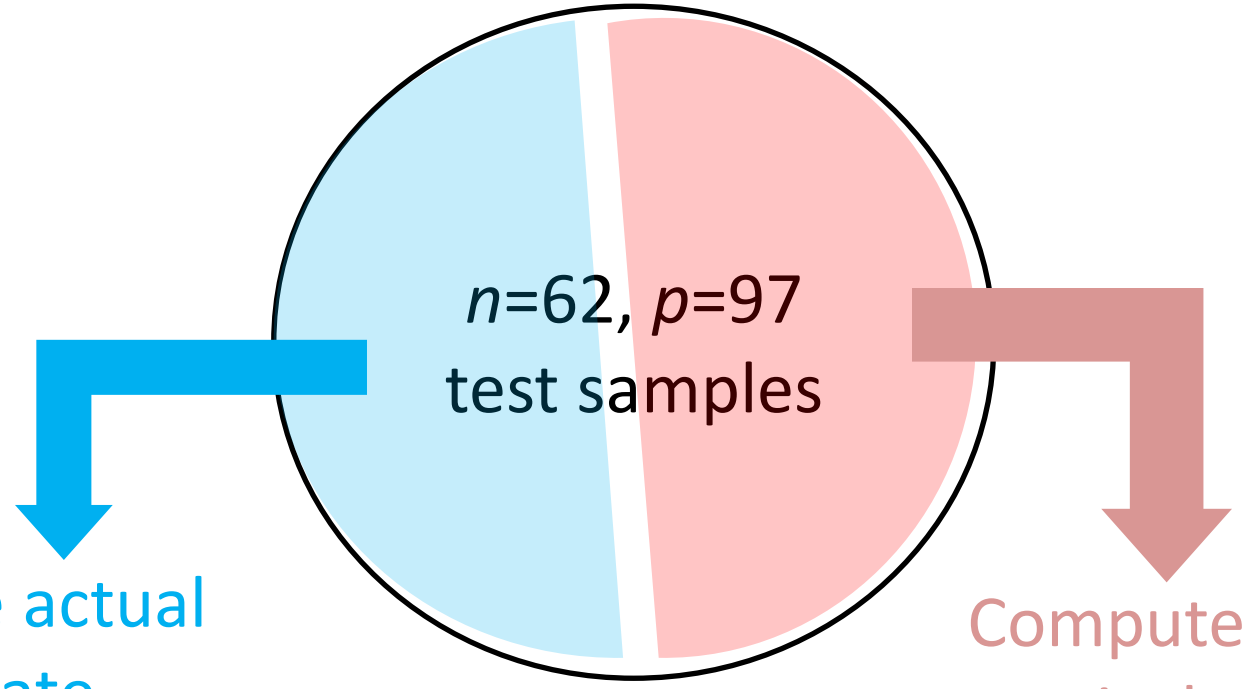
$CC < c$ ➡ Good prognosis（High survival rate）

$CC > c$ ➡ Poor prognosis（Low survival rate）

Classify the **test** samples（n=62）

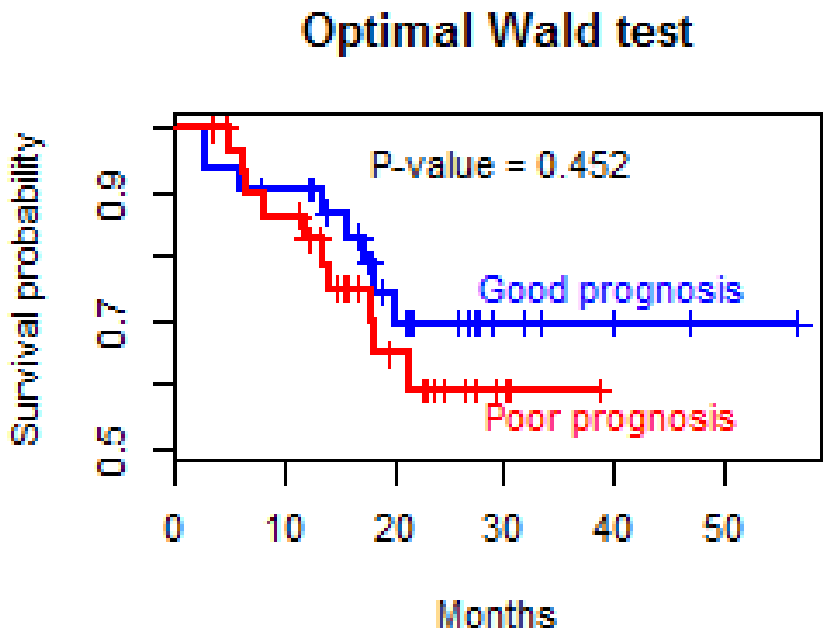
Class 1；Good prognosis（Low CC）

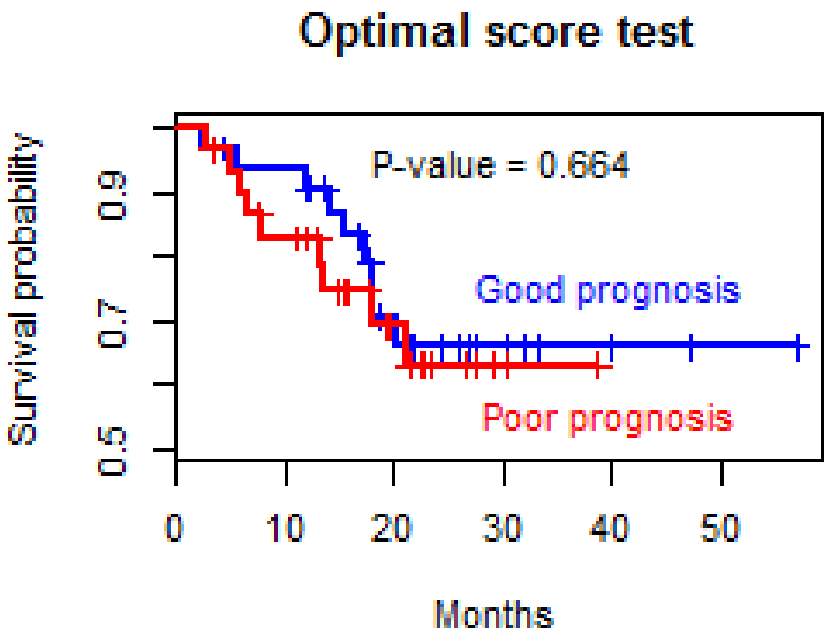
Class 2: Poor prognosis（High CC）

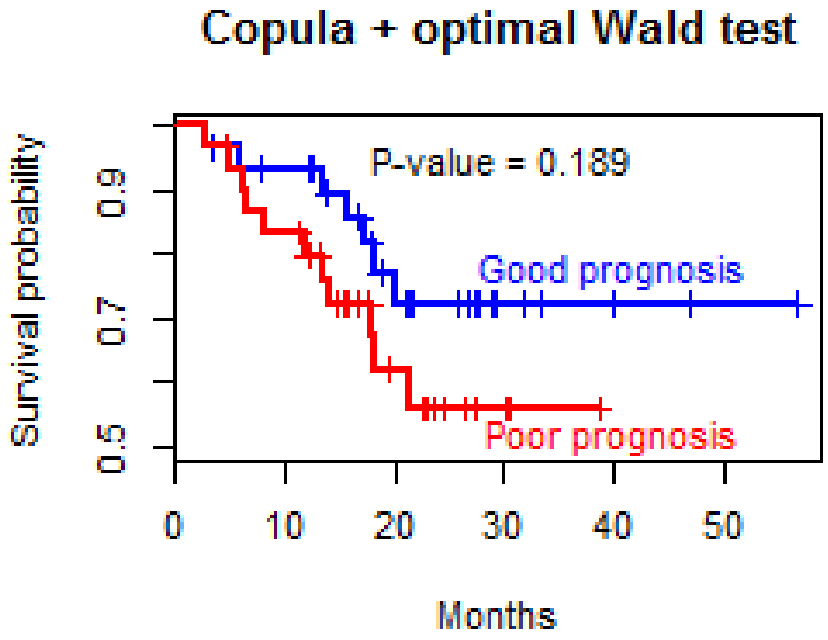


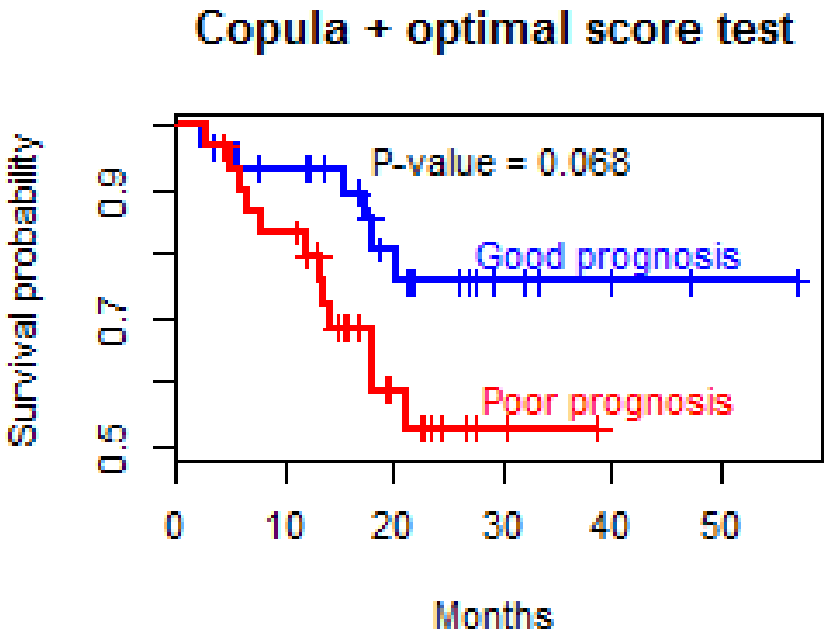
Compute actual survival rate (KM survival curve)

Compute actual survival rate (KM survival curve)


Optimal Wald test
P-value = 0.452
Good prognosis
Poor prognosis
Survival probability
0.5
0.7
0.9
0
10
20
30
40
50
Months


Optimal score test
P-value = 0.664
Good prognosis
Poor prognosis
Survival probability
0.5
0.7
0.9
0
10
20
30
40
50
Months


Copula + optimal Wald test
P-value = 0.189
Good prognosis
Poor prognosis
Survival probability
0.5
0.7
0.9
0
10
20
30
40
50
Months


Copula + optimal score test
P-value = 0.068
Good prognosis
Poor prognosis
Survival probability
0.5
0.7
0.9
0
10
20
30
40
50
Months

Summary

- **An R package "*compound.Cox*"**
  - **Multiple tests** for feature selection

    ≠ likelihood-based method (e.g., stepwise, Lasso)
  - **Compound covariate** for prediction

    (**Test** ➔ **selection** ➔ **prediction**) in a coherent way

  - **Matrix computation** of score tests

    (a number of tests done in a single matrix $\mathbf{Z} = \mathbf{S} / \mathbf{V}^{1/2}$)
- **Implemented the evaluation measures:**
  - Predictive capability (CVL） Matsui (2006)
  - False discovery rate (FDR) Witten and Tibshirani（2010）
- **Copula model to deal with dependent censoring**
  - improve prediction accuracy

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