Assessment of health status over time by prevalence and weighted prevalence functions Interface in R

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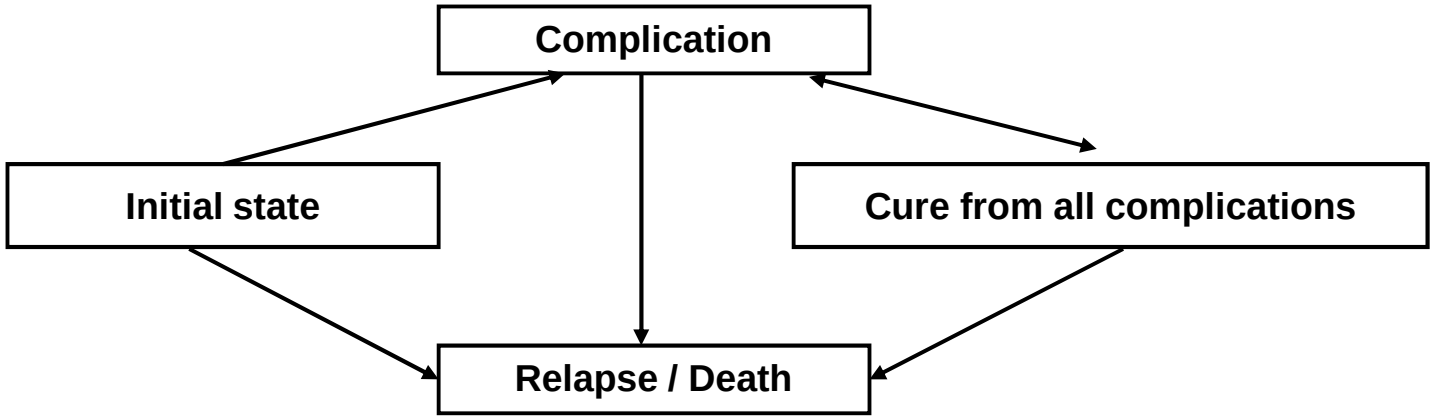
Context

- During treatment and follow-up, patients are exposed to a finite number of states depending on complications, relapse or death

- Possible states of patients during follow-up



- ➢ Worst grade method : frequency of patients who enter in the complication state (binary rate)

- ➢ Survival and Competing risks analysis : take into account time until event but only consider first event

Prevalence function
(Pepe, 1991)

- Take into account duration and possible repetitions of complications
- Defined as the probability of being in the complication state C_k at time t conditionally to be alive and relapse-free at this time

$$Q_k(t) = P\left[alive\ in\ C_k\ at\ t\ /\ alive\ and\ relapse-\ free\ at\ t\right]$$

- Prevalence function is estimated using combination of Kaplan-Meier survival function $\hat{S}_X(t)$ at time t

$$\hat{Q}_k(t) = \frac{\sum_{m=1}^{M}\left[\hat{S}^m_{CU}(t) - \hat{S}^m_{CT}(t)\right]}{\hat{S}_{RD}(t)}$$

- M : number of maximum entries in the complication state
- CT_m : time until entry into complication for the m^{th} time or until relapse or death
- CU_m : time until exit from complication for the m^{th} time or until relapse or death
- RD : time until relapse or death

Weighted Prevalence function (Lancar & Kramar , 1995)

- Defined as the sum of the prevalence function for each severity grade of complication with a respective weight $w_1 < w_2 < ... < w_K$

$$w\hat{Q}(t) = \sum_{k=1}^{K} w_k \hat{Q}_k(t)$$

- Weight vector needs to be fixed in advance
- Take into account the severity of the complication
- Interpretation is more difficult :
  - Results can be different according to the weights
  - Not a proportion of patients ($w\hat{Q}$ can be greater than 1)
- Comparison between groups :
  - Weigthed Kaplan Meier Statistical Test (Pepe , 1989)

R Functions

`main.preval.func` / `main.wpreval.func`

- Interface to estimate the prevalence and weighted prevalence functions

- Implementation of additional analysis elements
  - Descriptive statistics
  - Worst grade method
  - Survival analysis
  - Competing risks analysis
  - Bootstrap Confidence Intervals
  - Statistical Tests to compare estimations between groups

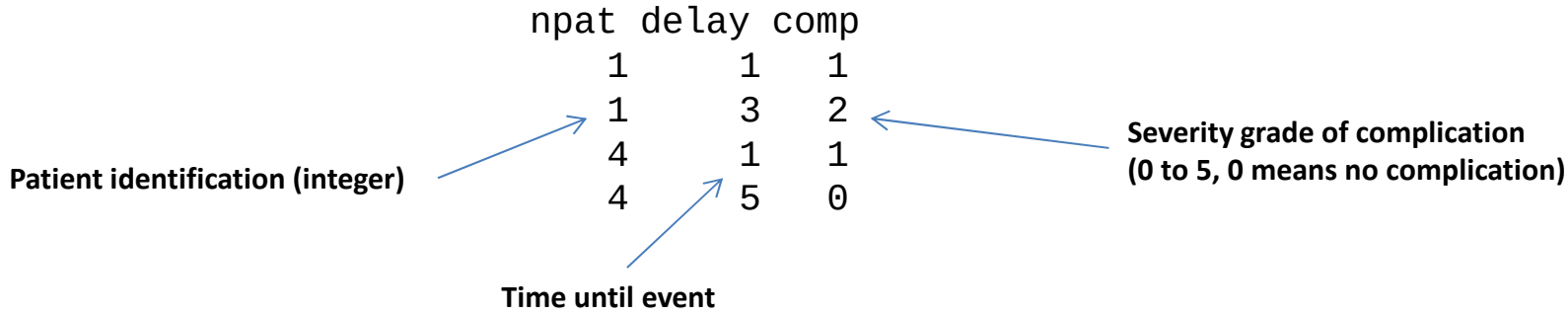
Prevalence & Weigthed Prevalence

- R packages needed to download
  - *survival*
  - *cmprsk*

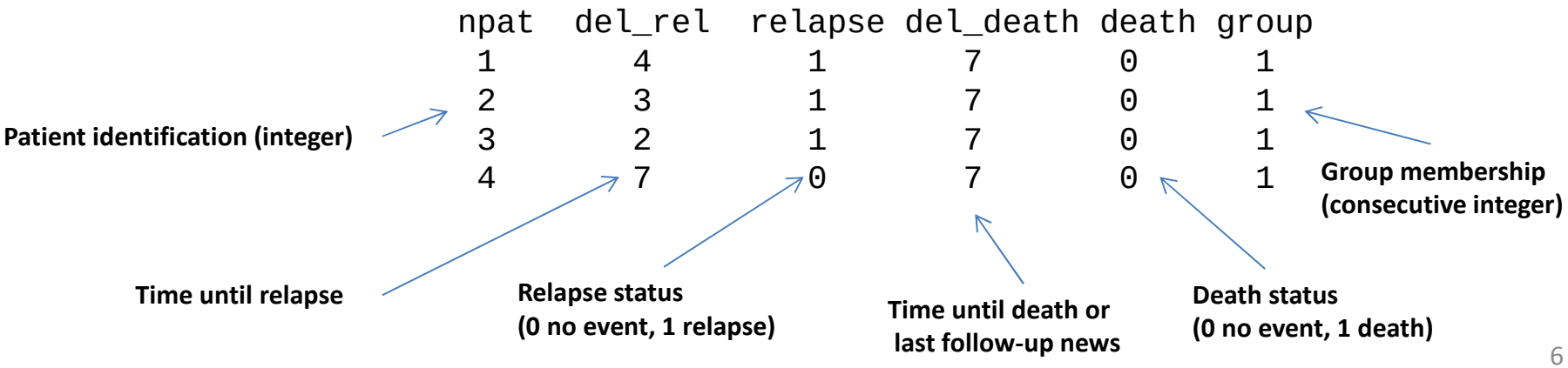
Inputs (1)

```
main.preval.func(visit,fu,gm,tmax,tp,met,N,export)
main.wpreval.func(visit,fu,gm,p,tmax,tp,met,N,export)
```

- `visit`: Data file containing information about patient's health state



- `fu` : Data file containing information about patient's follow-up



Inputs (2)

- `gm` : minimum severity grade taken into account (1 to 5)
- `p` : vector of weights (numerical vector)
- `tmax` : maximum delay taken into account
- `tp` : timepoint where estimations are displayed
- `met` : Statistical tests and 95% confidence intervals (logical vector)

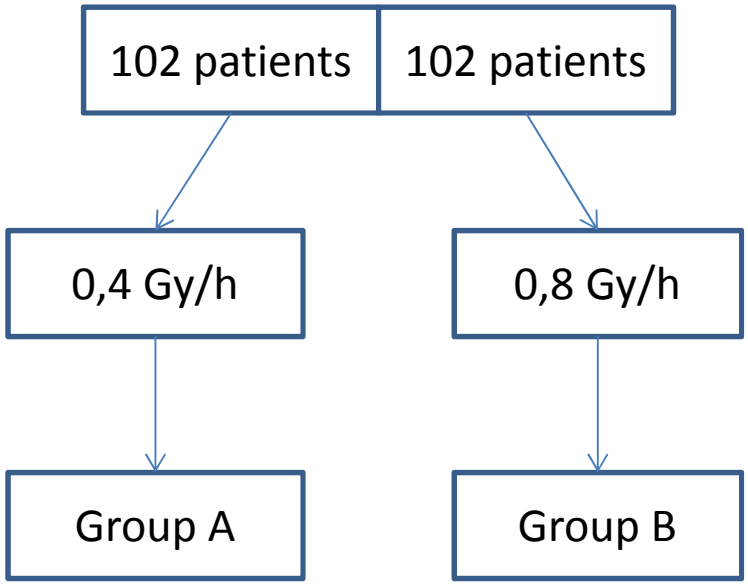
```
met = c([1],[2],[3]) with[.]= T or F
```

Bootstrap Test — **« Permutation » Test (Pepe , 1991)** — **Confidence Intervals**

- `N` : number of iterations in tests and confidence intervals computing (> 20)
- `export` : Export pdf graphic to the current work file (`T or F`)

Example

- Phase III trial comparing two low dose rates in brachytherapy
- 204 patients randomized between two groups :



→ **OBJECTIVE** : Evaluate type and severity of acute and chronic complications

Example : Inputs

```
main.preval.func(visit,fu,gm,tmax,tp,met,N,export)
main.wpreval.func(visit,fu,gm,p,tmax,tp,met,N,export)
```

- `visit` and `fu` files are imported as matrix under R
- `gm = 1` (`main.preval.func` : C_1 to C_5 are considered as the same state !)
- `p=c(1,2,3,4,5)`
- `tmax = 1825` : Study period equals to 5 years
- `tp = 730` : Estimation at 2 years
- `met = c(T,T,T)`: The two tests and confidence intervals are computed
- `N = 2000`
- `export = T` : pdf graphic is exported to the current work file

Example : Results

```
main.preval.func(visit,fu,1,1825,730,c(T,T,T),2000,T)
main.wpreval.func(visit,fu,1,1:5,1825,730,c(T,T,T),2000,T)
```

- Entitled

```
*********************************************************************
*              Prevalence analysis for transient events             *
*                     (B. Cabarrou & T. Filleron)                   *
*********************************************************************
* Institut CLaudius Regaud                                          *
* 20-24 rue du pont Saint Pierre                                    *
* 31052 Toulouse                                                    *
* France                                                            *
*********************************************************************
```

- Data check : Checking consistency on the data files and input parameters

```
+--------------------+
|     Data Check     |
+--------------------+

Data OK
```

Example : Results (2)

```
main.preval.func(visit,fu,1,1825,730,c(T,T,T),2000,T)
main.wpreval.func(visit,fu,1,1:5,1825,730,c(T,T,T),2000,T)
```

- Descriptive statistics

```
+----------------------------+
|   Descriptive statistics   |
+----------------------------+

    - Maximum delay taken into account : 1809
    - Minimum grade : 1
    - Weight vector :  "1" "2" "3" "4" "5"
```

Total		Group A	Group B
Number of subjects	204	102	102
Number of first entries in C	139	63	76
Total number of entries in C	166	70	96
Total number of exits to C	98	47	51
Number of RD	61	26	35
Number of subjects RD in C	26	9	17
Number of subjects RFS in C	42	14	28

Number of patients entered at least once in complication state

Total number of entries in complication state

Number of patients cured from all complications

Number of relapse or death

Number of patients who relapsed or died while in a complication state

Number of patients lost to follow-up while in a complication state

Example : Results (3)

```
main.preval.func(visit,fu,1,1825,730,c(T,T,T),2000,T)
main.wpreval.func(visit,fu,1,1:5,1825,730,c(T,T,T),2000,T)
```

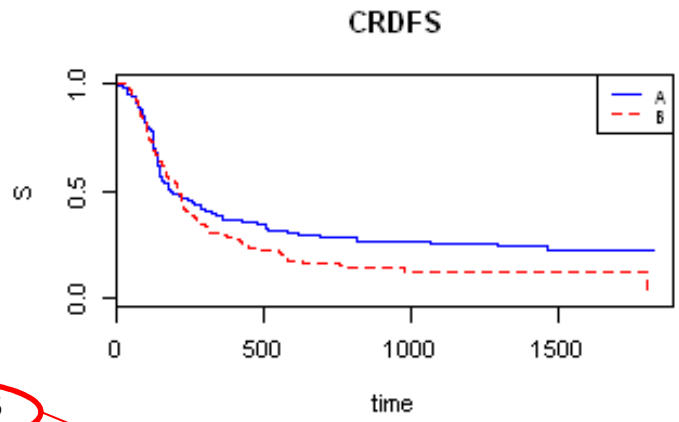
- Worst grade method : Comparison of patient's worst grade observed

```
 +----------------------------+
 |     Worst grade method     |
 +----------------------------+
                  Group A            Group B
Worst grade < gm       39 ( 38.2 %)      26 ( 25.5 %)
Worst grade >= gm      63 ( 61.8 %)      76 ( 74.5 %)

     - X² test    df = 1    p = 0.071
```

Not significant !

- Survival analysis : Complication Relapse Death Free Survival

```
+---------------------------------+
|              CRDFS              |
|   Toxicity or relapse or death  |
+---------------------------------+

     - CRDFS estimate at t = 730"

             Group A Group B
Estimation     0.283   0.160
Lower 95% CI   0.205   0.102
Upper 95% CI   0.390   0.250

     - Logrank test statistic = 2.348     p = 0.125
```



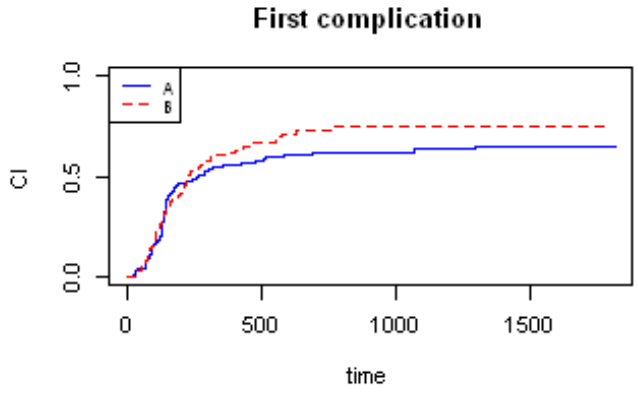
Not significant !

Example : Results (4)

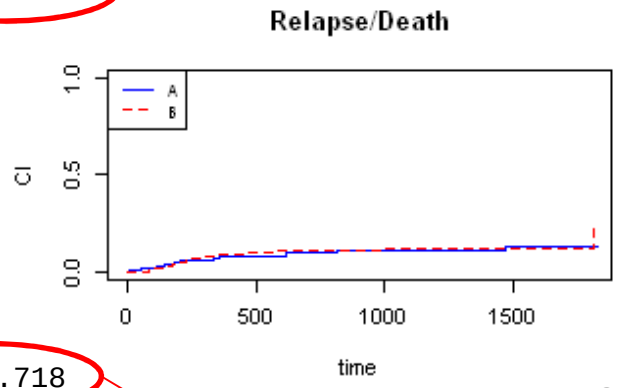
```
main.preval.func(visit,fu,1,1825,730,c(T,T,T),2000,T)
main.wpreval.func(visit,fu,1,1:5,1825,730,c(T,T,T),2000,T)
```

- Competing risks analysis

```
+-----------------------------------------------------------+
|        Cumulative incidence (Competing risks)             |
+-----------------------------------------------------------+

     - Cumulative Incidence of first complications

          + Estimate at t = 730

              Group A Group B
Estimation      0.624   0.731
Lower 95% CI    0.518   0.632
Upper 95% CI    0.713   0.808

          + Gray test statistic = 1.442      df = 1      p = 0.23

     - Cumulative Incidence of relapse/death

          + Estimate at t = 730

              Group A Group B
Estimation      0.093   0.109
Lower 95% CI    0.045   0.057
Upper 95% CI    0.162   0.180

          + Gray test statistic = 0.13      df = 1      p = 0.718
```



Not significant !



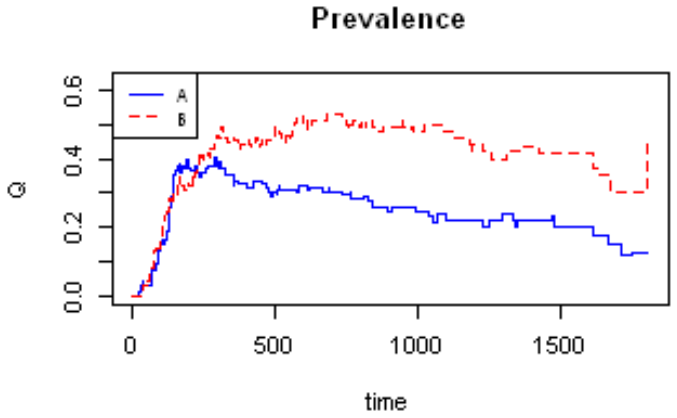
Not significant !

Example : Results (5)

```
main.preval.func(visit,fu,1,1825,730,c(T,T,T),2000,T)
main.wpreval.func(visit,fu,1,1:5,1825,730,c(T,T,T),2000,T)
```

- Prevalence analysis

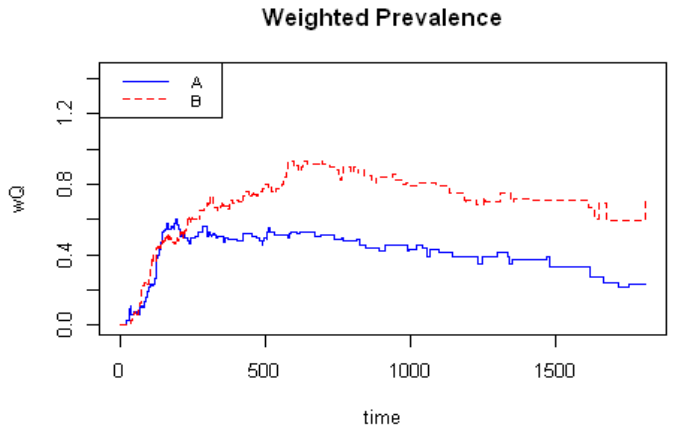
```
+----------------------------+
|         Prevalence         |
+----------------------------+

     - Prevalence estimate at t = 730

              Group A Group B
Estimation      0.305   0.528
Lower 95% CI    0.204   0.413
Upper 95% CI    0.414   0.642

     - WKM test statistic = 1452.22
```



`p.boot = 0.002  p.perm = 0.002` → **Significant !**

- Weighted Prevalence Analysis

```
+-----------------------------------+
|         Weighted Prevalence       |
+-----------------------------------+

     - Weighted Prevalence estimate at t = 730

              Group A Group B
Estimation      0.509   0.898
Lower 95% CI    0.325   0.682
Upper 95% CI    0.713   1.126

     - WKM test statistic : 2537.372
```



`p.boot = 0.002  p.perm = 0.004` → **Significant !**

In summary

- Two functions design for Quality Of Life Survival Adjusted analysis using Prevalence and Weighted Prevalence functions
- Both functions return list of objects in order to make additionnal analysis and graphics
- Take into account duration and possible transitions into the different states
- Non-parametric methods : Markov and semi-Markov assumptions are avoided
- Compare to QTWiST method, Markov and semi-Markov (Project QOLSA)

References

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- Gelber ED, Goldhirsch A, Castiglione M, Price K, Isley M, Coates A. Time without symptoms and toxicity (TWiST): a quality-of-life oriented endpoint to evaluate adjuvant therapy. *In: Salmon SE*, ed. Adjuvant therapy of cancer V. Orlando: Grune & Stratton, **1987**:455-65.

Thank your for your attention!