Grandes données de santé : méthodes et challenges

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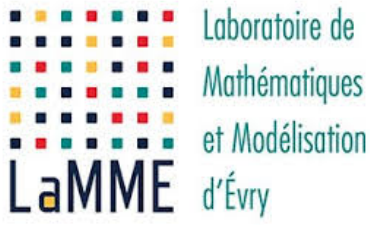


4 examples / 4 dimensions (1)

Clinic: Colo-rectal cancer

- Relapse free survival after tumor resection for colo-rectal cancer patients
- genomic and survival data for $\sim$500 patients

High-dimensional covariates

$$(n, p) \rightarrow (n, p)$$

4 examples / 4 dimensions (2)

Marketing: Monetization for free-to-play games

- Times of monetization for players until their giving-ups
- Several hours of game-play history for $\sim$1MM players

Large number of observations (individuals), time-dependent covariates

$$(n, p) \to \left(n, p, D\right)$$

4 examples / 4 dimensions (3)

Clinic : HEGP-APHP data warehouse

- Adverse events for patients in ARTEMIS cohort (hypertension)
- 25 years of medical history for $\sim$ 30000 patients

Large everything....

$$(n, p) \to \left(n, p, D, K\right)$$

4 examples / 4 dimensions (4)

Public health: SNIRAM data

- Adverse events in SNIRAM database
- 3 years history for $\sim$ 60 MM beneficiaries

Huge everything....

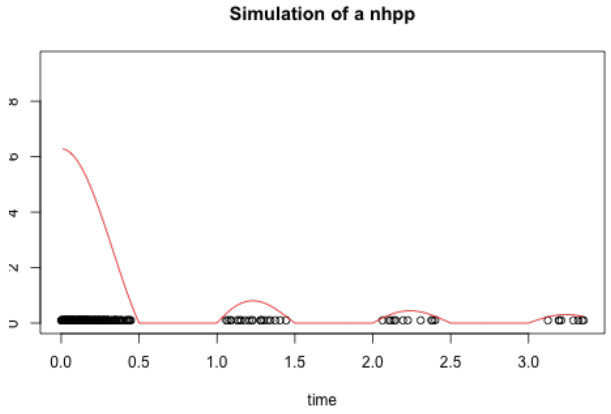
$$(n, p) \to \big(n, p, D, K\big)$$

Contents

Section: Time(s) to event(s) data, censoring and models

Time(s) to event(s) data

What are we observing ?



Time(s) to event(s) data

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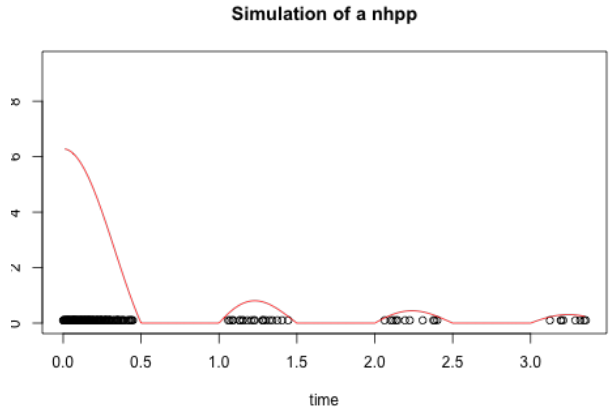
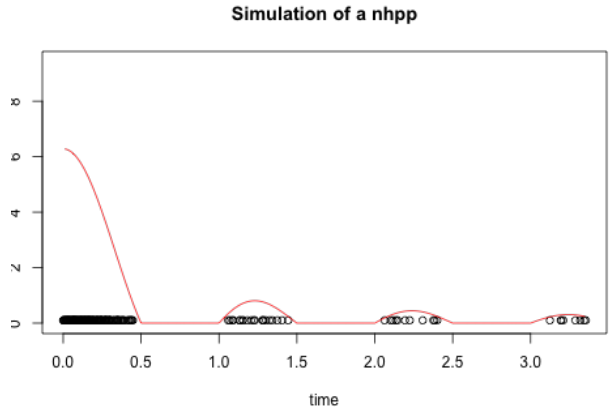


The higher the intensity, the more points we observe :

$$\lambda^\star(t) = \text{infinitesimal } \mathbb{P}(\text{event} \in [t, t + dt])$$

Time(s) to event(s) data

What are we observing ?



The higher the intensity, the more points we observe :

$$\lambda^\star(t) = \text{infinitesimal } \mathbb{P}(\text{event} \in [t, t + dt])$$

Construct a **counting process** $N^\star$ defined as

$$N^\star(t) = \text{number of observed events in } [0, t],$$

we'll say that $N^\star$ has intensity $\lambda^\star$.

One special case: at most one event

One event

Let T be a time of interest and construct

$$N^\star(t) = I(T \leq t)$$

Clinic: Colo-rectal cancer (with the CdR Saint Antoine - INSERM/UPMC)

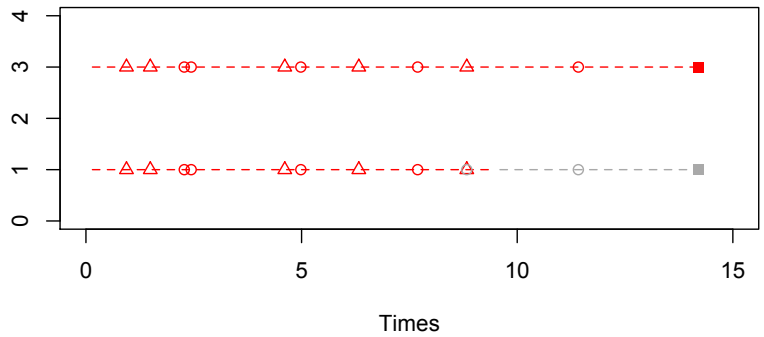
T is the time of recurrence of cancer

In this case

$$\lambda^\star(t) = \frac{f(t)}{1 - F(t)} = \text{infinitesimal } \mathbb{P}(T \in [t, t + dt] \mid T \geq t)$$

Censoring

We observe N only until a censoring C occurs.



Marketing: Monetization for free-to-play games

Times of monetization for players until their **giving-ups**

One special case: at most one event and censoring

Right censoring

Let

- T be a time of interest
- C a censoring time independent of T

We observe

$$T^C = T \wedge C \text{ and } \delta = \mathbb{1}(T \leq C).$$

In terms of counting processes, this is equivalent to observing

$$N(t) = \mathbb{1}(T^C \leq t, \delta = 1) \text{ and } Y(t) = \mathbb{1}(T^C \geq t).$$

Section: Covariates

Covariates

Time independent covariates

Clinic: Colo-rectal cancer
Genomic data

Public health: SNIRAM data
The gender of the beneficiary

Time dependent covariates

Monetization for games
The weapons the player owns

Public health: SNIRAM data
The drugs the beneficiary is on

We'll see that this implies that $n \to D \times n$.

Models for the intensity

We want the intensity to depend on the covariates at time t

$$\lambda^\star(t) \to \lambda^\star(t, X(t)).$$

The Cox model [Cox72]

$$\lambda^*(t) = \alpha^\star(t) \exp(X(t)\beta^\star)$$

Stanford Heart Transplant data [KP11]

Survival of patients on the waiting list for the Stanford heart transplant program.

- accept.dt: acceptance into program
- fustat: dead or alive
- surgery: prior bypass surgery
- age: age (in years)
- futime: follow-up time
- wait.time: time before transplant
- transplant: transplant indicator

```
##    accept.dt fustat surgery      age futime wait.time transplant
## 1 1967-11-15      1       0 30.84463     49        NA          0
## 2 1968-01-02      1       0 51.83573      5        NA          0
## 3 1968-01-06      1       0 54.29706     15         0          1
## 4 1968-03-28      1       0 40.26283     38        35          1
## 5 1968-05-10      1       0 20.78576     17        NA          0
## 6 1968-06-13      1       0 54.59548      2        NA          0
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##    accept.dt fustat surgery      age futime wait.time transplant
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```

Stanford Heart Transplant data [KP11] (2)

On transforme la variable `accept.dt` en gardant seulement l'année.

```
jasa = dplyr::mutate(jasa, accept.yr = year(ymd(accept.dt)))
jasa = dplyr::select(jasa,   fustat, surgery,age,futime,
                wait.time,transplant,accept.yr)

head(jasa)
```

```
##   fustat surgery      age futime wait.time transplant accept.yr
## 1      1       0 30.84463     49        NA          0      1967
## 2      1       0 51.83573      5        NA          0      1968
## 3      1       0 54.29706     15         0          1      1968
## 4      1       0 40.26283     38        35          1      1968
## 5      1       0 20.78576     17        NA          0      1968
## 6      1       0 54.59548      2        NA          0      1968
```

Example with time independent covariates

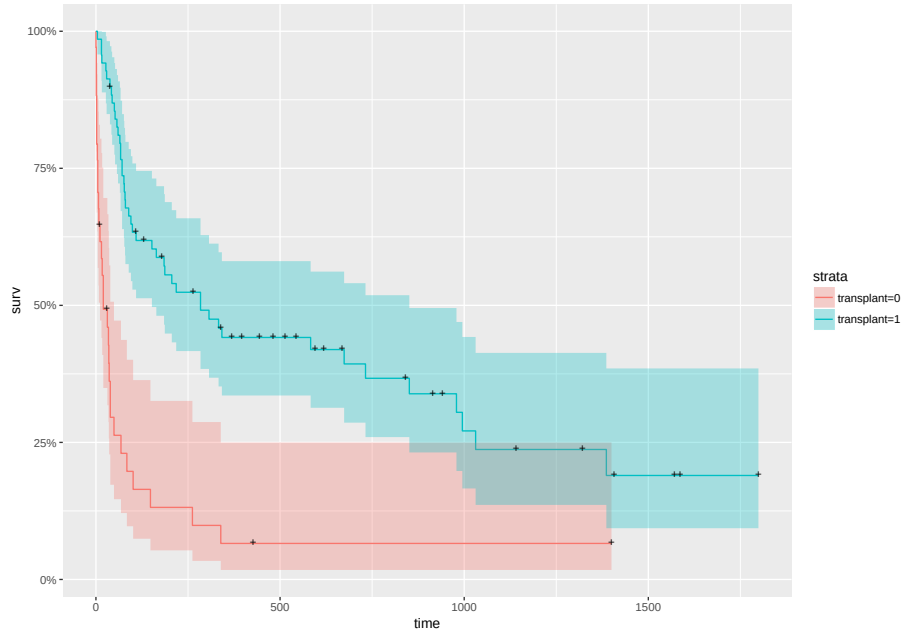
```
coxph(Surv(futime,fustat) ~ accept.yr + surgery + age, data = jasa)
```

```
## Call:
## coxph(formula = Surv(futime, fustat) ~ accept.yr + surgery +
##     age, data = jasa)
##
##               coef exp(coef) se(coef)     z     p
## accept.yr -0.1320    0.8764   0.0681 -1.94 0.053
## surgery   -0.6427    0.5259   0.3673 -1.75 0.080
## age        0.0276    1.0280   0.0134  2.06 0.039
##
## Likelihood ratio test=14.5  on 3 df, p=0.00226
## n= 103, number of events= 75
```

Example with time dependent covariates: false model

- transplant: transplant indicator $\rightarrow$ **time dependent covariate**

```
autoplot(survfit(Surv(futime,fustat) ~transplant , data = jasa))
```



"The key rule for time dependent covariates in a Cox model is simple and essentially the same as that for gambling: *you cannot look into the future*." [TCA17]

Example with time dependent covariates: false model (2)

```
coxph(Surv(futime,fustat) ~ surgery + transplant + age , data = jasa)
```

```
## Call:
## coxph(formula = Surv(futime, fustat) ~ surgery + transplant +
##     age, data = jasa)
##
##                coef exp(coef) se(coef)     z       p
## surgery    -0.4190    0.6577   0.3712 -1.13    0.26
## transplant -1.7171    0.1796   0.2785 -6.16 7.1e-10
## age         0.0589    1.0607   0.0150  3.91 9.1e-05
##
## Likelihood ratio test=45.9  on 3 df, p=6.11e-10
## n= 103, number of events= 75
```

A new format for time dependent covariates: start-stop

```
##     id start stop event transplant        age      year surgery
##     1     0   49     1          0 -17.155373 0.1232033       0
##     2     0    5     1          0   3.835729 0.2546201       0
##     3     0   15     1          1   6.297057 0.2655715       0
##     4     0   35     0          0  -7.737166 0.4900753       0
##     4    35   38     1          1  -7.737166 0.4900753       0
##     5     0   17     1          0 -27.214237 0.6078029       0
```

Notice that for individual 4, we have

- with the old format

```
##   fustat          age futime wait.time transplant
## 4      1     40.26283     38        35          1
```

- with the new format

```
##     id start stop event transplant
##     4     0   35     0          0
##     4    35   38     1          1
```

A new format for time dependent covariates: start-stop (2)

- False model

```
## coxph(formula = Surv(futime, fustat) ~ surgery + transplant +
##     age, data = jasa)
##
##                coef exp(coef) se(coef)     z       p
## surgery    -0.4190    0.6577   0.3712 -1.13    0.26
## transplant -1.7171    0.1796   0.2785 -6.16 7.1e-10
## age         0.0589    1.0607   0.0150  3.91 9.1e-05\end{itemize}
```

- Start-stop model

```
## coxph(formula = Surv(start, stop, event) ~ age + surgery +
##     transplant, data = jasa1)
##
##                coef exp(coef) se(coef)     z     p
## age           0.0306    1.0310   0.0139  2.20 0.028
## surgery      -0.7733    0.4615   0.3597 -2.15 0.032
## transplant    0.0141    1.0142   0.3082  0.05 0.964
```

Section: Estimation

The data

We observe for $i = 1, \ldots, n$ i.i.d.

$$\Big(X_i(s) Y_i(s), N_i(s), Y_i(s), s \leq \tau \Big)$$

and we want to learn the influence of X on $t \mapsto \lambda^*(t, X(t))$.

The likelihood

$$- \frac{1}{n} \sum_{i=1}^{n} \{ \int_{[0,\tau]} \log(\lambda(t, X_i(t))) dN_i(t) - \int_{[0,\tau]} Y_i(t) \lambda(t, X_i(t)) dt \}$$

$$= - \frac{1}{n} \sum_{i=1}^{n} \{ \sum_{T_{i,k}} \delta_{i,k} \log(\lambda(t, X_i(T_{i,k}))) - \int_{[0,\tau]} Y_i(t) \lambda(t, X_i(t)) dt \}$$

To ease the notation, I'll consider that each individual has a most one event

$$- \frac{1}{n} \sum_{i=1}^{n} \{ \delta_i \log(\lambda(t, X_i(T_i^C))) - \int_{[0,\tau]} Y_i(t) \lambda(t, X_i(t)) dt \}$$

Partial likelihood

In the Cox model[Cox72],

$$\lambda^*(t) = \alpha^\star(t) \exp(X(t)\beta^\star),$$

we can estimate $\beta^\star$ only with the partial likelihood (that's what `coxph` does)

$$\begin{aligned}
\ell_n^P(\beta) &= -\frac{1}{n}\sum_{i=1}^{n} \delta_i \log \frac{\exp(X_i(T_i^C)\beta)}{\frac{1}{n}\sum_{j:T_j^C \geq T_i^C} \exp(X_j(T_i)\beta)} \\
&= \frac{1}{n}\sum_{i=1}^{n} \delta_i \Big\{ - X_i(T_i^C)\beta + \log\Big(\sum_{j:T_j^C \geq T_i^C} \exp(X_j(T_i^C)\beta)\Big)\Big\}.
\end{aligned}$$

Large p

When p grows, one can consider to add a lasso penalty:

$$\ell_n^P(\beta) + \gamma \sum_{j=1}^{p} |\beta_j|$$

or an elastic-net penalty

$$\ell_n^P(\beta) + \gamma\big(\alpha \sum_{j=1}^{p} |\beta_j| + \frac{1-\alpha}{2} \sum_{j=1}^{p} |\beta_j|^2\big).$$

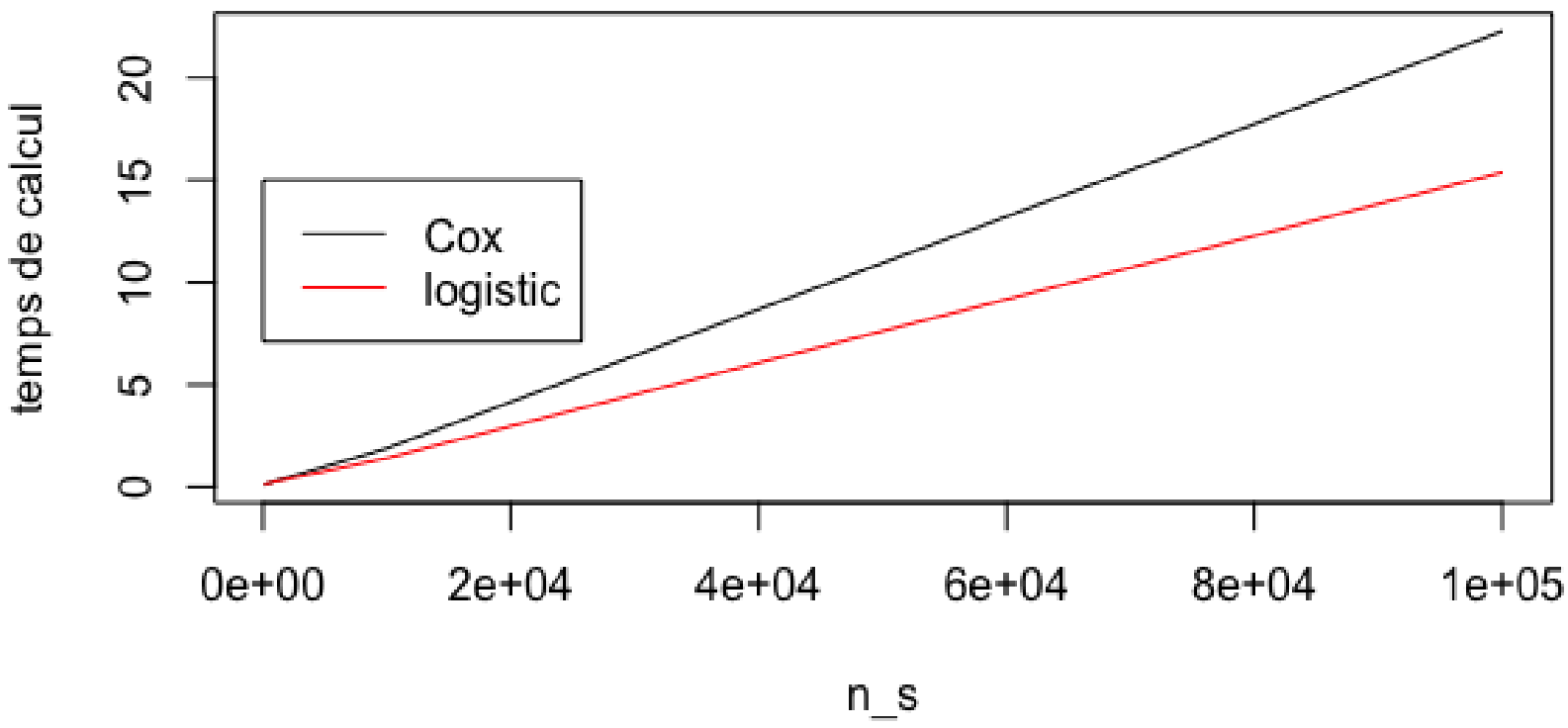
```
data("nki70")
model_matrix = model.matrix( ~ as.factor(Grade)  + . - Grade - 1
                              , data = nki70[3:77])

X = model_matrix[,-1]

elasticnet_solution = cv.glmnet(X,Surv(nki70$time, nki70$event),
        family = "cox" , alpha = 0.5,
        penalty.factor = c(rep(0,6),rep(1,70)))

coef(elasticnet_solution)
```

Few additional remarks

- For the selection,
  - see also“bo-lasso” ([Bac08]) and “stability selection” ([MB10])
  - multi-tests procedures ([DvdL08]) are developed for the Cox model in the package `multtest`
- In very large dimension, a ”screening” is mandatory
  - “Sure Independence Screening” ([FL08]) for Cox model in [ZL12]
  - others “screenings” in `ahaz`
  - or [TBF+12] and [EVR10], adapted to the Cox model in [TBF+12].
- They are other methods in high dimension: PCA, PLS (cf. [WT10]), Survival forest (cf. [IKG+10, IKCM11])

Section: Algorithmic challenges (n)

Timings: logistic regression vs Cox regression



Stochastic gradient descent

When n grows, stochastic algorithms are usually considered. For the logistic regression :

$$\ell_n(\beta) = \frac{1}{n}\sum_{i=1}^{n} \log(1 + \exp(-Y_i X_i \beta))$$

- Pick $i \sim \mathcal{U}[n]$
- update $\beta^{(t)}$

$$\beta^{(t+1)} = \beta^{(t)} - \eta_t \nabla_\beta \Big(\log(1 + \exp(-Y_i X_i \beta) \Big).$$

Problem : the partial losses are not adequate

- Partial likelihood

$$\begin{aligned}\ell_n^P(\beta) &= -\frac{1}{n}\sum_{i=1}^{n}\log\frac{\exp(X_i(T_i)\beta)}{\frac{1}{n}\sum_{j:T_j\geq T_i}\exp(X_j(T_i)\beta)}\\ &= \frac{1}{n}\sum_{i=1}^{n}\left(\ell_n^P(\beta)\right)_{(i)}\\ &= \frac{1}{n}\sum_{i=1}^{n}\Big\{-X_i(T_i)\beta+\log\Big(\sum_{j:T_j\geq T_i}\exp(X_j(T_i)\beta)\Big)\Big\}.\end{aligned}$$

- update $\beta^{(t)}$

$$\beta^{(t+1)} = \beta^{(t)} - \eta_t\nabla_\beta\Big(-X_i(T_i)\beta+\log\big(\sum_{j:T_j\geq T_i}\exp(X_j(T_i)\beta)\big)\Big).$$

1-step procedures and Poisson regression (1)

Likelihood

$$\sum_{i=1}^{n}\{\int_{[0,\tau]}\log(\lambda(t,X_i(t)\beta(t)))dN_i(t)-\int_{[0,\tau]}Y_i(t)\lambda(t,X_i(t)\beta(t))dt\}$$

$$=\sum_{i=1}^{n}\sum_{d=1}^{D}\{\int_{I_d}\log(\lambda(t,X_i(t)\beta(t)))dN_i(t)-\int_{I_d}Y_i(t)\lambda(t,X_i(t)\beta(t))dt\}$$

$$=\ldots$$

1-step procedures and Poisson regression (2)

$$\sum_{i=1}^{n}\sum_{d=1}^{D}\{\int_{I_d}\log(\alpha(t)\exp(X_i(t)\beta(t)))dN_i(t) - \int_{I_d} Y_i(t)\alpha(t)\exp(X_i(t)\beta(t))dt\}$$

Assuming that $X_i(t)$ is constant on small interval, and with sieves proposals, we get

$$\sum_{i=1}^{n}\sum_{d=1}^{D}\log(\alpha(I_d)\exp(X_i(I_d)\beta(I_d)))N_i(I_d) - |Y_i(I_d)|\alpha(I_d)\exp(X_i(I_d)\beta(I_d))$$

Poisson regression with $n \times D$ observations and $p \times D$ covariates ! But $n \times D$ and $p \times D$ are (very) large.

Example : simulated data

J'ai reproduit des données de santé de type pharmacovigilance. Elles contiennent des observations pour

- 10000 individus
- sur 5 ans avec une mesure par semaine.

On s'intéresse à la **survenue d'une pathologie**. On suspecte qu'un traitement augmente ce risque, proportionnellement à la dose cumulée reçue par l'individu. Chaque individu /bf commence (à un moment aléatoire sur les 5 ans) le traitement.
Les autres variables mesurées sont le sexe de l'individu et une variable continue (qui dans la simulation n'a pas d'influence sur le risque).
Pour chaque individu et chaque semaine soit $10000 \times 5 \times 52 = 2600000$ lignes de données.
Seuls 26 individus ont développé (au moins une fois) la pathologie.

Example : simulated data (2)

- l'identifiant de l'individu (`ind`)
- le numéro de la semaine (`week`)
- la dose cumulée (`cum_dose`)
- le sexe (`sex`)
- la variable continue (`var`)
- le nombre d'évènements survenus dans la semaine (`nevent`)
- une variable d'identification de la ligne (`id`)

```
##   ind week cum_dose sex        var nevent id
## 1   1    1        0   0  2.2712990      0  1
## 2   1    2        0   0 -0.4266551      0  2
## 3   1    3        0   0 -0.4064611      0  3
## 4   1    4        0   0 -0.7696531      0  4
## 5   1    5        0   0  1.7527771      0  5
## 6   1    6        0   0  1.1024576      0  6
```

Cases only study

Ordered statistics property of Poisson processes, see [Kin93]

In a Poisson regression model,

- when conditioning by the number of adverse events for each individuals with a least an event
- the number of events for each individual in each interval has a multinomial distribution.

This is known as **SCCS** (self-controlled case series), see http://statistics.open.ac.uk/sccs/r.htm.

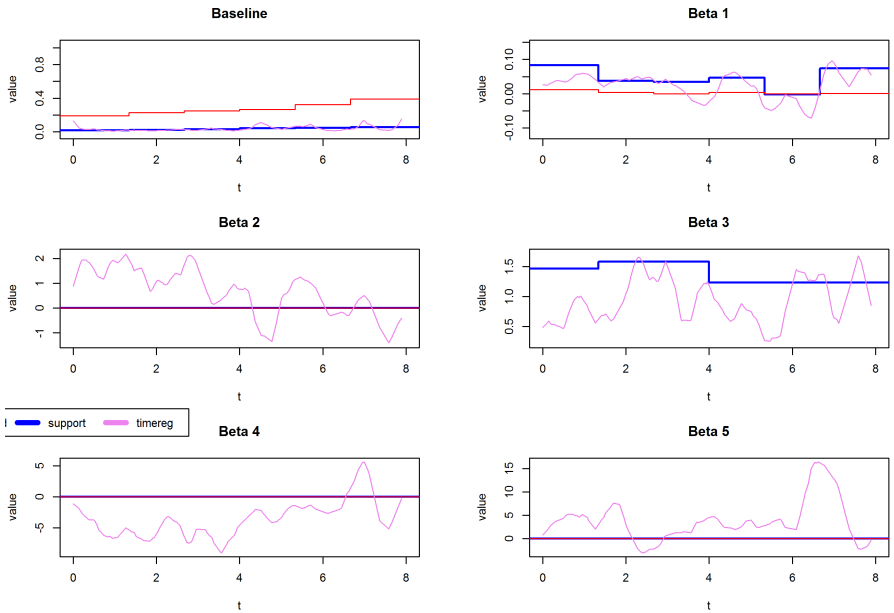
Section: Other challenges

Constant $\beta^\star$? Really ???

We considered that

$$\lambda^*(t) = \lambda^*(t, X(t)\beta^*).$$

But for long history (several years of data), we'd like $\beta^*(t)$!
This is possible but, in this case, $p \to D \times p$.



The K dimension

Clinic : HEGP-APHP data warehouse

- Adverse events for patients in ARTEMIS cohort (hypertension)
- 25 years of medical history for $\sim$ 30000 patients

Large everything....

$$(n, p) \to \big(n, p, D, K\big)$$

References I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