R program for flexible Cox models including time-dependent (TD) and non-linear (NL) effects: CoxFlex

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March 10, 2021

R program

- R program and dataset used for the example in this tutorial are available at:

  https://github.com/mebeauchamp/CoxFlex

R program

- Function `CoxFlex` allows to estimate a Cox model ***with time-dependent (TD) and/or non-linear (NL) effects*** for ***one or several variables***
  - Can include variables without TD and NL effects

- `CoxFlex` can handle:

  a) *Time-invariant data* (one observation per subject)

id	time	dose	event
1	56	3.0	1
2	365	0.5	0
3	283	0	0

  b) *Time-dependent* (or time-varying) data (several observations per subject)

id	start	stop	dose	event
1	0	14	1.0	0
1	14	28	2.0	0
1	28	56	3.0	1
2	0	180	1.0	0
2	180	365	0.5	0

Data preparation

1. The data must be a **data frame**
2. The **first column of data *must* be a numeric ID variable** identifying the individuals (with the name of your choice)
3. **No missing data** are allowed (otherwise the function will crash)
4. All string characters or factors *must* be recorded as numeric values
   - E.g., gender (0, 1)

Data preparation

5. Categorical variables, with more than 2 categories, *must* be recorded as dummy variables
   - E.g., 4 age groups (<18, 18-39, 40-64, ≥65) with reference <18 (i.e. age.gr=1)

ID	age	age.gr	bin.age18.39	bin.age40.64	bin.age65
1	16	1	0	0	0
2	22	2	1	0	0
3	51	3	0	1	0
4	89	4	0	0	1
			age.gr=2	age.gr=3	age.gr=4

6. Negative values of continuous covariates are *not* a problem, as opposed to when using fractional polynomials

7. Include in dataset passed to `CoxFlex` *only* the variables used in the model. This will greatly improve the efficiency of the program.

Data preparation

8. <u>For time-varying data:</u>
   - Each line can be for time intervals with length of 1 (e.g. 1 day) or longer
   - The 'start' of a line must be the same as the 'stop' of the previous line (for the same subject), i.e. **no gap and no overlap in time intervals**
   - No intervals with 'start' = 'stop'

id	start	stop	dose	event
1	0	14	1.0	0
1	14	28	2.0	0
1	28	56	3.0	1
2	0	180	1.0	0
2	180	365	0.5	0

   - The 1st start value of each subject must be 0 (no delayed entry)

Data preparation

9. For time-invariant data (1 line per subject):
   - Make sure event time is > 0

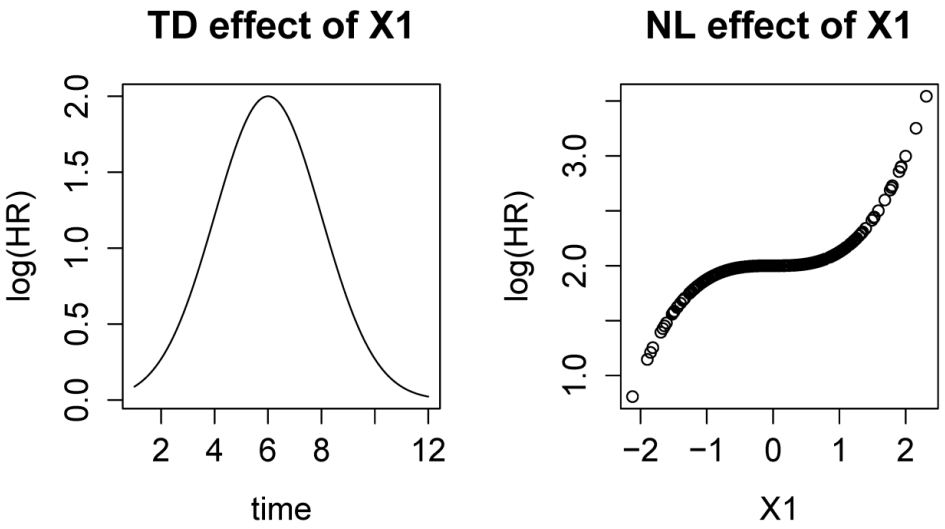
Example of a dataset (`dat`) with time-varying covariates (available with the R program)

Id	Event	Fup	Start	Stop	x1	x2	x3
1	0	2	0	1	-0.23549	1.541651	0.87255
1	1	2	1	2	-0.86123	-1.27724	0.87255
2	0	2	0	1	0.737676	-0.17344	1.959211
2	1	2	1	2	1.345106	-0.60027	1.959211
3	0	8	0	1	0.863421	1.182985	3.862302
3	0	8	1	2	0.914108	0.784081	3.862302
3	0	8	2	3	0.933757	-0.38651	3.862302
3	0	8	3	4	1.19725	-0.77683	3.862302
3	0	8	4	5	1.139094	1.371349	3.862302
3	0	8	5	6	0.518455	0.056261	3.862302
3	0	8	6	7	0.575675	-0.71817	3.862302
3	1	8	7	8	0.632166	0.67002	3.862302

Example

- 300 patients followed for up to 12 months
- $X_1(t)$, $X_2(t)$, $X_3(t)$ are continuous time-varying variables
- **True model** (data generated from it):
  - X_1: TD and NL effects
  - X_2 and X_3: constant-over-time and linear effects

$$\lambda(t|\, X_1(t), X_2(t), X_3(t)) = \lambda_0 \exp\{ \beta_1(t) g_1(X_1(t)) + \beta_2 X_2(t) + \beta_3 X_3(t) \}$$



Code

```
# Source the program in current R session (not a package yet):
source("C:/.../CoxFlex - 20200324 - to share.R")
   # No need to look at the code in this file

# Load data
load("C:/.../dat.RData")

head(dat)
  # Id Event Fup Start Stop          x1         x2        x3
  #  1     0   2     0    1 -0.2354852  1.5416514 0.8725503
  #  1     1   2     1    2 -0.8612346 -1.2772441 0.8725503
  #  2     0   2     0    1  0.7376760 -0.1734419 1.9592107
  #  2     1   2     1    2  1.3451063 -0.6002743 1.9592107
  #  3     0   8     0    1  0.8634209  1.1829845 3.8623023
  #  3     0   8     1    2  0.9141075  0.7840808 3.8623023
```

```
# Select only variables relevant for model estimation
dat.red <- dat[, c('Id','Event','Start','Stop','x1','x2','x3')]

# Check data are a data frame
is.data.frame(dat.red)
    # [1] TRUE

# Check the ID variable is numeric (must be 1st column)
is.numeric(dat.red[, 1])
    # [1] TRUE

# Display structure of data (all variables must be numeric)
str(dat.red)
 # 'data.frame':   2307 obs. of  7 variables:
 #  $ Id   : num  1 1 2 2 3 3 3 3 3 3 ...
 #  $ Event: num  0 1 0 1 0 0 0 0 0 0 ...
 #  $ Start: num  0 1 0 1 0 1 2 3 4 5 ...
 #  $ Stop : num  1 2 1 2 1 2 3 4 5 6 ...
 #  $ x1   : num  -0.235 -0.861 0.738 1.345 0.863 ...
 #  $ x2   : num  1.542 -1.277 -0.173 -0.6 1.183 ...
 #  $ x3   : num  0.873 0.873 1.959 1.959 3.862 ...

# Check no missing values in any variables used for the model
sum(is.na(dat.red))
    # [1] 0
```

Estimation of a *predefined* model with `CoxFlex`

```
m1 <- CoxFlex(data=dat.red, Type=c("Start","Stop","Event"),
              variables=c("x1","x2","x3"),
              TD=c(1,0,0), NL=c(1,0,0),
              m=1, p=2, knots=-999)
```

Arguments of the CoxFlex function:

- **`data`**: Your dataset (data frame). 1st column must be an ID variable of individuals.
- **`Type`**: Variables in data indicating the start and stop of time intervals, and the event (1=event, 0=censored).

  If time-invariant data: `Type=c("Time","Event")`.

  Start, Stop, and Time do *not* have to be integers.
- **`variables`**: Independent variables in the model
- **`TD`**: Indicate for each independent variable if the TD effect is modeled (0/1)
- **`NL`**: Indicate for each independent variable if the NL effect is modeled (0/1).
  Can be 1 only for continuous variables.

Estimation of a *predefined* model with CoxFlex

```
m1 <- CoxFlex(data=dat.red, Type=c("Start","Stop","Event"),
              variables=c("x1","x2","x3"),
              TD=c(1,0,0), NL=c(1,0,0),
              m=1, p=2, knots=-999)
```

Arguments of the CoxFlex function:

- **m**: Number of interior knots (the same for all TD and NL effects). By default `m=1`.
- **p**: Order of splines (the same for all TD and NL effects). By default `p=2`.
  - p=0: step functions
  - p=1: linear splines
  - p=2: quadratic splines
  - p=3: cubic splines
- **knots**: Position of interior knots. Default `knots=-999`, which indicates that the knots are automatically allocated.

  To specify the position of interior knots, specify a matrix with (length(variables)+1) rows by m columns. There is one row per variable (add NA if no NL effect for a variable) and one for time. E.g., for this model it could be:

  ```
  knots = matrix(c(-1,NA,NA,4), nrow=4, ncol=1).
  ```

Output of the model

```
# Type the name of the object of results to see the output
m1

$Partial_Log_Likelihood
[1] -1013.063

$Number_of_parameters
[1] 9

$Number_events
[1] 202

$Number_knots
[1] 1

$Degree_of_splines
[1] 2
```

The output
(more on next slides)

To calculate AIC use:

AIC =
-2 * `m1$Partial_Log_Likelihood`
`+ 2 * m1$Number_of_parameters`

```
$knots_covariates
         [,1]       [,2]       [,3]         [,4]
x1 -3.229684 -3.229684 -3.229684 -0.06910736
x2         NA         NA         NA           NA
x3         NA         NA         NA           NA
       [,5]     [,6]     [,7]
x1 3.687497 4.687497 5.687497
x2       NA       NA       NA
x3       NA       NA       NA

$knots_time
[1]  0  0  0  5 12 13 14
```

Position of interior and exterior knots, for each variable with a NL effect

Position of interior and exterior knots for time

```
$coefficients
       x1        x2        x3
       NA 0.3267542 0.1293491

$Standard_Error
[1]    NA 0.07258465 0.01504884

$coefficients_splines_NL
           x1 x2 x3
[1,] 0.000000 NA NA
[2,] 2.568096 NA NA
[3,] 2.445147 NA NA
[4,] 6.327139 NA NA

$coefficients_splines_TD
             x1 x2 x3
[1,]  0.5779502 NA NA
[2,]  1.3659911 NA NA
[3,]  1.5177027 NA NA
[4,] -0.4379260 NA NA
```

Coefficients (log hazard) and SE for variables *without* TD nor NL effects requested

Coefficients of splines for NL and TD effects requested:

3 splines for a NL effect (m+p):
First NL spline coefficient always set 0 for technical reasons.

4 splines for a TD effect (m+p+1).

```
$variables
[1] "x1" "x2" "x3"
```

```
$coef
[1] NA       NA       0.327     0.129

$var
[1] NA       NA       0.005329  0.000225

$pvalue
[1] 0.264    0.398    0.000     0.000
```

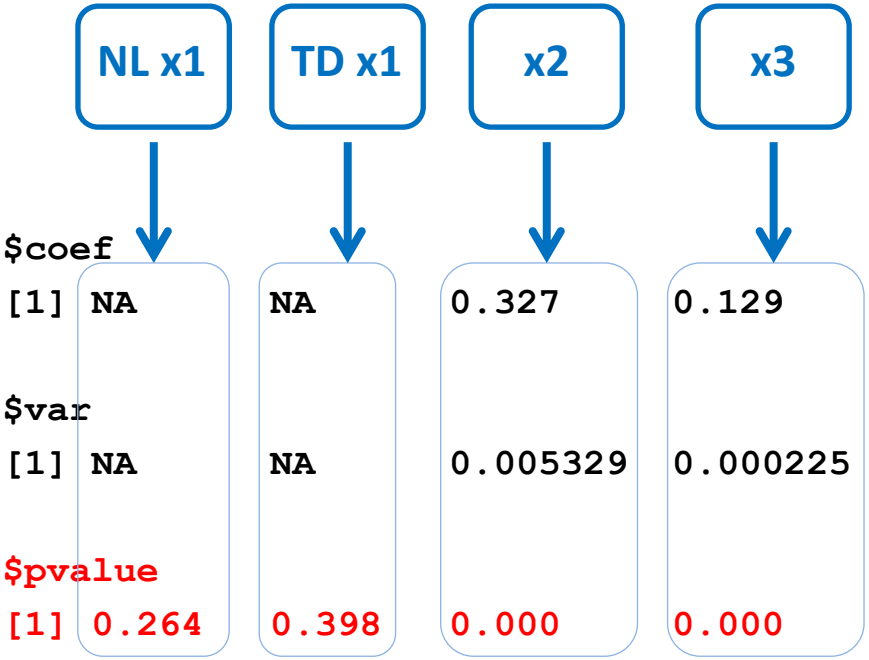
```
$variables
[1] "x1" "x2" "x3"
```

For each variable above, the values shown below are, respectively, for:

1) ***NL* effect (when applicable), and/or**
2) ***TD* effect (when applicable), or**
3) **"Standard" effect when no NL nor TD effects were requested.**

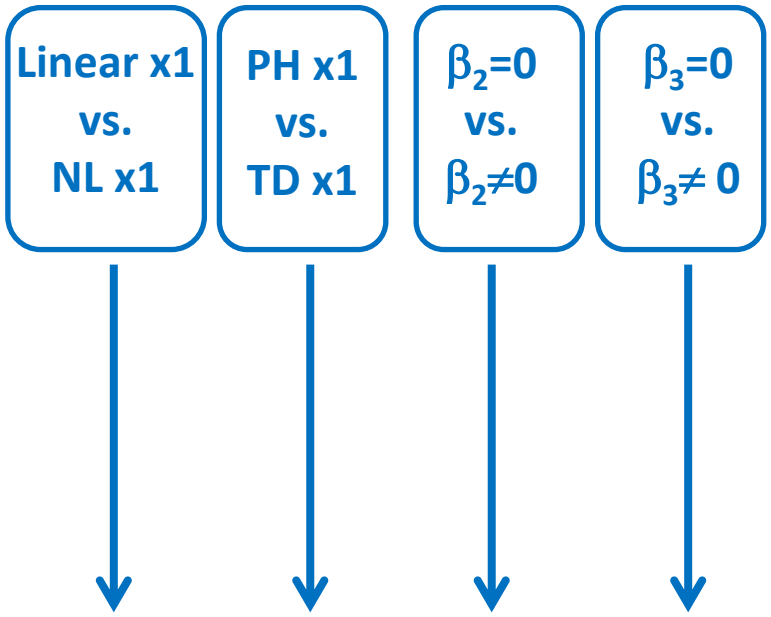
Then, move to the next variable.

For this model, the request was:
`variables=c("x1","x2","x3"), TD=c(1,0,0), NL=c(1,0,0)`
Therefore, the values reported below are for:



```
$variables
[1] "x1" "x2" "x3"
```

LRT testing:




```
$pvalue
[1] 0.264    0.398    0.000      0.000
```

NL and TD effects of x1 are non-significant. Does it mean x1 is not important?

Standard Cox PH model

```
library(survival)
m.cox <- coxph(Surv(Start, Stop, Event) ~ x1 + x2 + x3, data=dat.red)
m.cox
   #Call:
   #coxph(formula = Surv(Start, Stop, Event) ~ x1 + x2 + x3, data = dat.red)

   #    coef exp(coef) se(coef)    z       p
   #x1 0.401      1.49   0.0728 5.51 3.6e-08
   #x2 0.316      1.37   0.0721 4.38 1.2e-05
   #x3 0.136      1.15   0.0151 8.99 0.0e+00

   #Likelihood ratio test=89.1  on 3 df, p=0  n= 2307, number of events= 202

# Significant effect for x1, even though the NL and TD effects were not
# significant in the flexible model.
# Don't discard a variable because NL and/or TD effects are non-significant!

AIC(m.cox)
   # [1] 2037.618
BIC(m.cox)
   # [1] 2047.543
```

AIC/BIC for a model estimated with `CoxFlex`

```
# AIC
-2 * m1$Partial_Log_Likelihood + 2 * m1$Number_of_parameters
   # [1] 2044.127

# BIC
-2 * m1$Partial_Log_Likelihood +
  log(m1$Number_events) * m1$Number_of_parameters
   # [1] 2073.901

# Both AIC and BIC are higher (worse) than for standard Cox model,
# confirming the extra parameters to model NL and TD effects of x1 did
# not improve enough the fit to the data
```

Order of p-values in `$pvalue` for another example of model

- If the model requested in the CoxFlex function was:

```
variables=c("x1","x2","x3"), TD=c(0,1,0), NL=c(0,1,1)
```

- Then, the p-values in vector $pvalue would be for:
  - Significance of "standard" effect for x1 ($\beta_1 \neq 0$)
  - *NL* effect of x2
  - *TD* effect of x2
  - NL effect of x3

Plot the NL/TD effects

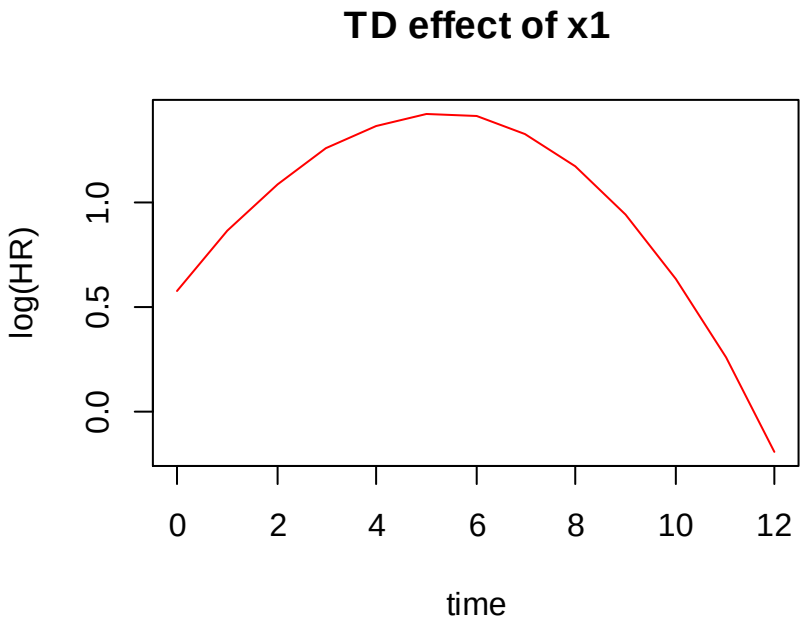
```
# To plot two graphs on top of each other
par(mfrow=c(2,1))
```

One variable at the time

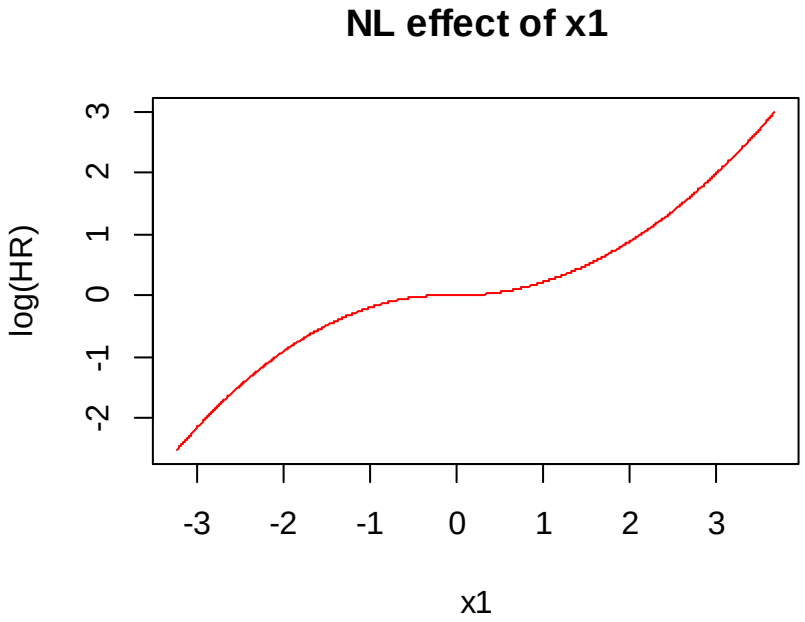
```
# Plot for TD effect of x1
plot.FlexSurv(model.FlexSurv=m1, variable="x1", TD=1, NL=0,
    col="red", xlab="time", ylab="log(HR)",
    main="TD effect of x1", type="l")
```

NL effect plotted with respect to *this reference value* of the variable (default 0)

```
# Plot for NL effect of x1
plot.FlexSurv(model.FlexSurv=m1, variable="x1", TD=0, NL=1, ref.value.NL=0,
    col="red", xlab="x1", ylab="log(HR)",
    main="NL effect of x1", type="l")
```



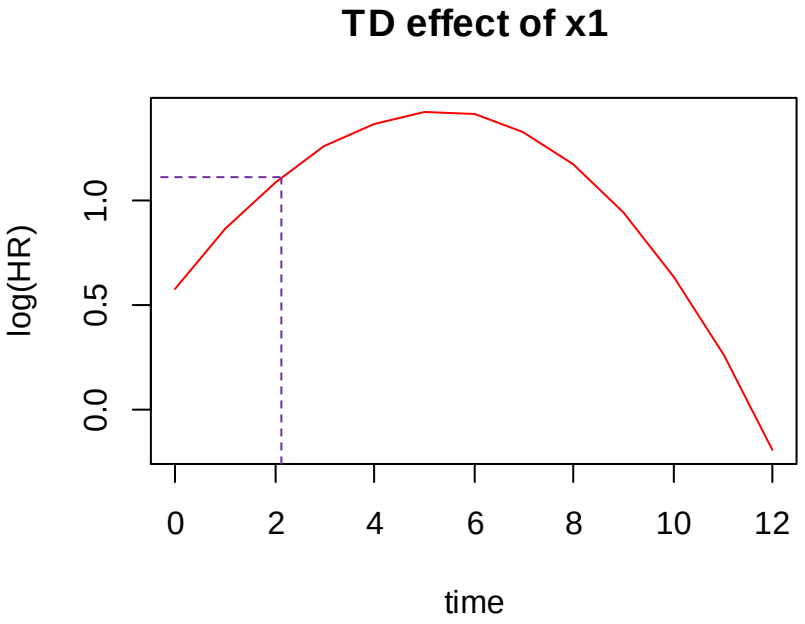
Shows how the *strength* of the effect of x1 varies over time.



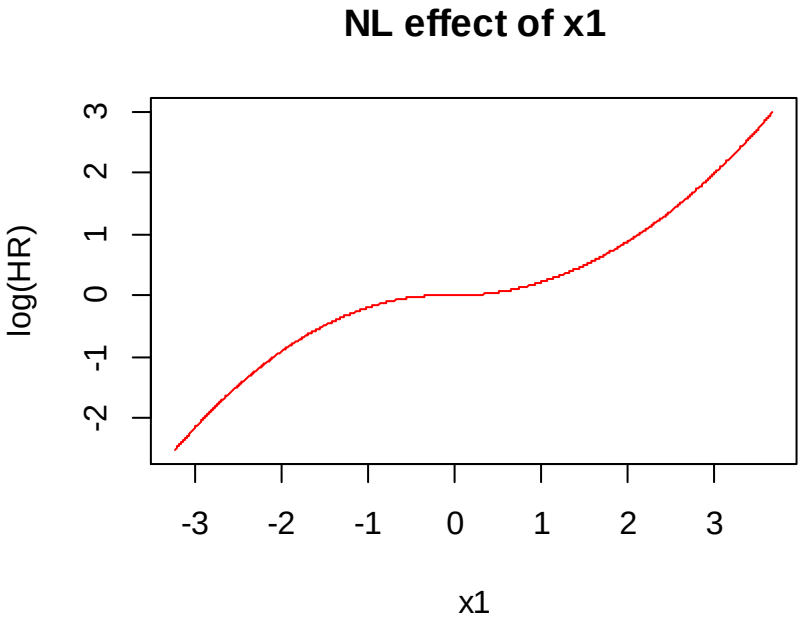
Shows the log(HR) comparing each value of x1 (numerator) to the reference value x1=0 (denominator)

However, in the *current model estimated*, TD and NL effects for x1 are *multiplied* by each other: $\beta_1(t) \cdot g_1(X_1(t))$

Consequently, *shapes* of NL and TD effects are good on these independent graphs, but *not* log(HR) on y axes

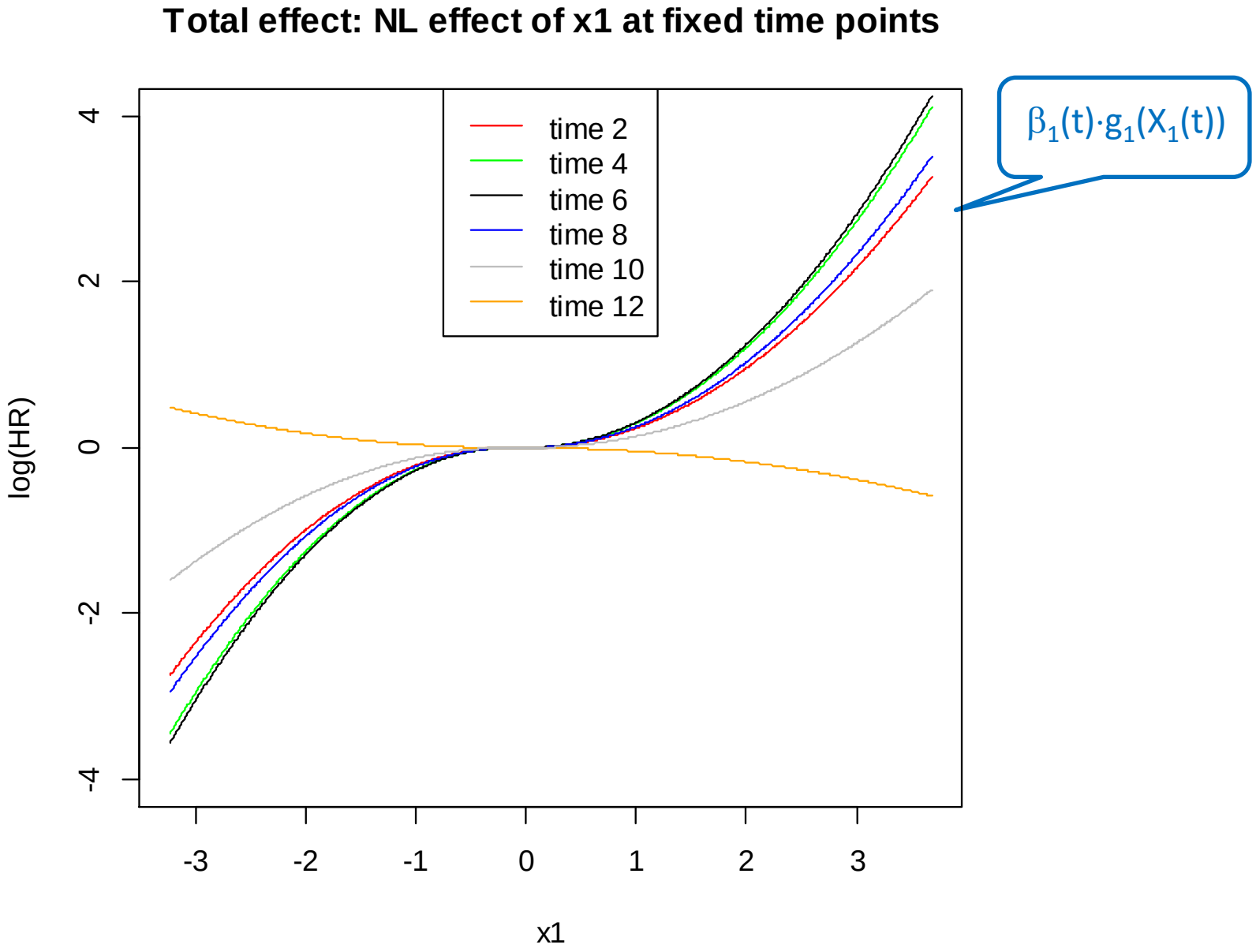


E.g., at *t*=2 the NL effect of x1 has to be multiplied by 1.1



NL effect at fixed time points (when a TD effect is also modeled)

```
par(mfrow=c(1,1))

plot.FlexSurv(m1, variable="x1", TD=1, NL=1, TimePoint=2, ref.value.NL=0,
    ylim=c(-4,4), xlab="x1", ylab="log(HR)", type="l", col="red",
    main="Total effect: NL effect of x1 at fixed time points")

lines.FlexSurv(m1, variable="x1", TD=1, NL=1, TimePoint=4, ref.value.NL=0,
    col="green")

lines.FlexSurv(m1, variable="x1", TD=1, NL=1, TimePoint=6, ref.value.NL=0,
    col="black")
lines.FlexSurv(m1, variable="x1", TD=1, NL=1, TimePoint=8, ref.value.NL=0,
    col="blue")
lines.FlexSurv(m1, variable="x1", TD=1, NL=1, TimePoint=12, ref.value.NL=0,
    col="gray")
lines.FlexSurv(m1, variable="x1", TD=1, NL=1, TimePoint=10, ref.value.NL=0,
    col="orange")

legend("top", c("time 2","time 4","time 6","time 8","time 10","time 12"),
    lty=c(1,1,1,1,1,1), col=c("red","green","black","blue","gray","orange"))
```


Total effect: NL effect of x1 at fixed time points
time 2
time 4
time 6
time 8
time 10
time 12
log(HR)
x1
-4
-2
0
2
4
-3
-2
-1
0
1
2
3
$\beta_1(t) \cdot g_1(X_1(t))$

Backward selection of NL/TD effects

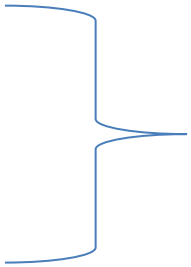
```
m2 <- backward_selection2(data=dat.red,
        Type=c("Start","Stop","Event"),
        variables=c("x1","x2","x3"), continuous=c(1,1,1),
        TD=c(0,0,0), NL=c(0,0,0),
        m=1, p=2, alpha_back=0.05, knots=-999)
```

Arguments of the backward_selection2 function:

- **`continuous`**: Indicate whether each variable is continuous (1=yes, 0=no)
- **`TD=1 / NL=1`**: Force TD/NL effect of corresponding variable
- **`TD=0 / NL=0`**: Do not force any effect (TD/NL effects are evaluated, and a variable may be excluded from final model)
- **`TD=-1 / NL=-1`**: Exclude TD/NL effect of corresponding variable (i.e. force the PH/LL effect)
- **`alpha_back`**: Alpha value used to select effects

Note: x1, x2, or x3 could be excluded from the final model

```
# Command to see model output for the final model
m2
$final_model$Partial_Log_Likelihood
[1] -999.011

$final_model$Number_of_parameters
[1] 5

$final_model$Number_events
[1] 202

$final_model$Number_knots
[1] 1

$final_model$Degree_of_splines
[1] 2

$final_model$knots_covariates
          [,1]        [,2]        [,3]     [,4]     [,5]     [,6]     [,7]
x1          NA          NA          NA       NA       NA       NA       NA
x2          NA          NA          NA       NA       NA       NA       NA
x3 0.04792073 0.04792073 0.04792073 0.846845 35.50922 36.50922 37.50922

$final_model$knots_time
[1]  0  0  0  5 12 13 14
```



Here, better likelihood, with fewer parameters, than the predefined model (-1013.063, with 9 parameters)

```
$final_model$coefficients
       x1        x2        x3
0.3743083 0.3481198        NA

$final_model$Standard_Error
[1] 0.07211582 0.07257598         NA

$final_model$coefficients_splines_NL
     x1 x2        x3
[1,] NA NA 0.0000000
[2,] NA NA 0.2563118
[3,] NA NA 7.4415084
[4,] NA NA 3.0269701

$final_model$coefficients_splines_TD
     x1 x2 x3
[1,] NA NA NA
[2,] NA NA NA
[3,] NA NA NA
[4,] NA NA NA
```

NL effect selected for x3,

but no TD effects

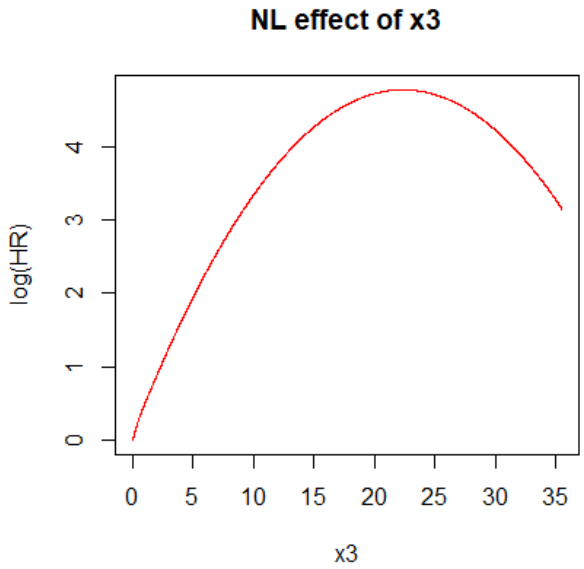
```
$final_model$variables
[1] "x1" "x2" "x3"

$final_model$coef
[1] 0.374 0.348    NA

$final_model$var
[1] 0.005184 0.005329       NA

$final_model$pvalue
[1] 0 0 0
```

Showing respectively, p-value for significance of:

- $\beta_1 = 0$ vs. $\beta_1 \neq 0$
- $\beta_2 = 0$ vs. $\beta_2 \neq 0$
- Linear x3 vs. NL x3

Model selected by backward selection

```
# AIC
-2 * m2$final_model$Partial_Log_Likelihood + 2 *
m2$final_model$Number_of_parameters
   # [1] 2008.022
   # Better than standard Cox (2037.6)

plot.FlexSurv(model.FlexSurv = m2$final_model, variable="x3", TD=0, NL=1,
          ref.value.NL = min(dat.red$x3),
          col="red", xlab="x3", ylab="log(HR)",
          main="NL effect of x3", type="l")
```



Problem: NL effect for continuous exposure with non-negative values & frequent 0 values

- Typical cases: Variable *X* with values ≥ 0 but with 0 for a majority of observations (i.e. median(*X*) = 0). E.g.,
  - Number of cigarettes per day, when > 50% of non-smokers
  - Drug dose, when subjects are often unexposed
- Problem for the estimation of a NL effect: the interior knot is placed at median(*X*) = 0, which is also min(*X*)
  - Spline estimation crashes because interior knot = one of the exterior knots
- The problem would also occur if median(*X*) = max(*X*)
- But *no problems* if only a TD effect is requested for *X*

Solution

1. Add a binary variable *Z* to indicate if *X* is 0 (*Z*=1) or not (*Z*=0)
2. Create a new variable *X.c:*
   - Center the *non-zero* values of original *X* at 0, i.e. subtract the mean of *non-zero X* values (say M) to each non-zero value of *X*
   - Keep *X.c*=0 when original *X*=0
   - ➢ Therefore, mean(*X.c*) = 0, but min(*X.c*) < 0
3. Run the model with:

   NL effect of *X.c* (excluding original *X*) + *Z* + all other covariates

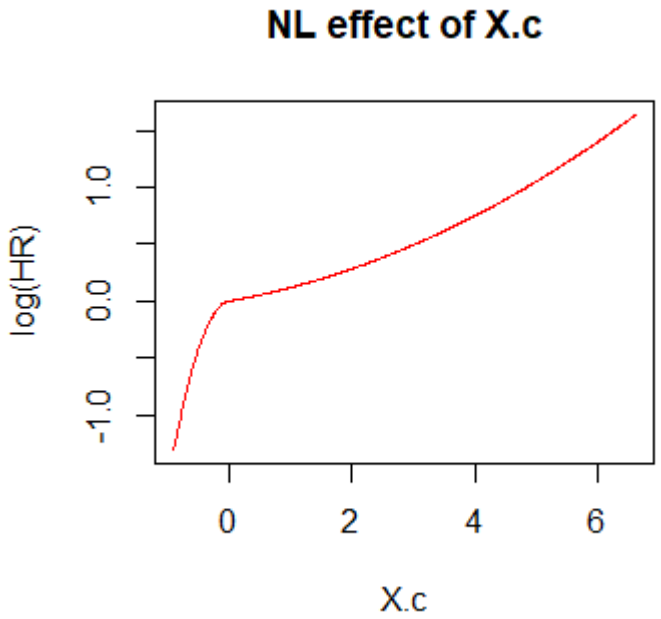
   - ➢ **Now, the NL effect describes the effect of non-zero values of *X*, while *Z* estimates the HR for the dose M vs. dose 0**

NOTES:

- Nothing prevents you to include TD effects of *X.c* and *Z* too

Code (on mock data)

```
M <- mean(dat.red$X[dat.red$X != 0])
dat.red$X.c <- ifelse(dat.red$X == 0, 0, dat.red$X - M)
mean(dat.red$X.c)   # Approximately 0

dat.red$Z <- ifelse(dat.red$X > 0, 1, 0)

m3 <- CoxFlex(data=dat.red, Type=c("Time","Event"),
              variables = c("X.c", "Z", "Age"),
              TD=c(1,1,0), NL=c(1,0,0),
              m=1, p=2, knots=-999)
```



References

References to cite:

- Abrahamowicz M, MacKenzie TA. Joint estimation of time-dependent and non-linear effects of continuous covariates on survival. *Statistics in Medicine* 2007;26(2):392-408.
- Wynant W, Abrahamowicz M. Impact of the model-building strategy on inference about nonlinear and time-dependent covariate effects in survival analysis. *Statistics in Medicine 2014; 33: 3318–3337.*

Examples of applications:

- Gagnon B, Abrahamowicz M, Xiao Y, Beauchamp ME, MacDonald N, Kasymjanova G, Kreisman H, Small D. Flexible modeling improves assessment of prognostic value of C-reactive protein in advanced non-small cell lung cancer. *British Journal of Cancer* 2010;102(7):1113-1122.
- Le Teuff G, Abrahamowicz M, Wynant W, Binquet C, Moreau M, Quantin C. Flexible modeling of disease activity measures improved prognosis of disability progression in relapsing-remitting multiple sclerosis. *J Clin Epidemiol* 2015;68(3):307-16.
- Isidean SD, Wang Y, Mayrand M-H, Ratnam S, Coutlée F, Franco EL, Abrahamowiz M, for the CCCaST Study Group. Assessing the time-dependence of prognostic values of cytology and human papillomavirus testing in cervical cancer screening. *Int J Cancer* 2019;144(10):2408-2418.

Help!

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