**Performance of two formal tests based on martingales residuals to check the proportional hazard assumption and the functional form of the prognostic factors in flexible parametric excess hazard models**

Coraline Danieli, Nadine Bossard, Laurent Roche, Aurélien Belot, Zoé Uhry, Hadrien Charvat, Laurent Remontet and the CENSUR Working Survival Group

**In this document readme, we present the programs that we need to obtain the results of the table 1 and table 3 of the paper.**
**Furthermore, we gave the code for the PH test for the analysis of dataset with big sample size.**

We will first give 2 examples of the programs execution order to obtain the size of the PH test for 500 patients and the power of the FF test in case of low non-linearity for 2000 patients. For the example concerning the PH test, we gave the graph of the score processes over time for the first dataset and for the example concerning the FF test, we gave the graph of the cumulative martingale residuals over the range of the values of the covariate of interest *age* for the first dataset.
Then, we will describe the folder \reviewer.

CONTENTS

# 1 Programs execution order to obtain the size of the PH test for 500 patients

## 1.1 Generating the simulated data with a linear and proportional effect of age

*Main program*

**...\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\500_patients\Generation_Donnees_lin_ph.r**

*Functions and objects called through this main program*

...\Review\Simulations\Fonctions\...: Programs used for the design of the data, the generation of time to death due to cancer and time to death due to other causes

...\Review\Simulations\MUA\...: Life tables

...\Review\Simulations\Parametres_Theoriques\colon_TxBase\parametre_theorique\...: Theoretical parameters used for the excess baseline hazard

...\Review\Simulations\Parametres_Theoriques\lin_ph_colon\parametre_theorique\...: Theoretical parameters used to simulate the linear and proportional effect of age

The simulated datasets can be found in this folder:

...\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\500_patients\ListDataSimulation.lin.ph.RData

## 1.2 Running the PH test on the simulated datasets and plotting the results

*Main program*

**...\Review\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\500_patients\My_Test_PH_SigmaNum.r**

*Functions called through this main program*

...\Review\Test_PH_nsim1000\Fonctions\...

The results can be found in this folder:

...\Review\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\500_patients\res.RData

...\Review\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\500_patients\ Graphe.bmp

# 2 Programs execution order to obtain the power of the FF test in case of low non-linearity for 2000 patients

## 2.1 Generating the simulated data with a low non-linear and proportional effect of age

*Main program*

**...\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients\Generation_Donnees_nlin_ph.r**

*Functions and objects called through this main program*

- ...\Review\Simulations\Fonctions\...: Programs used for the design of the data, the generation of time to death due t cancer and time to death due to other causes
- ...\Review\Simulations\MUA\...: Life tables
- ...\Review\Simulations\Parametres_Theoriques\colon_TxBase\parametre_theorique\...: Theoretical parameters used for the excess baseline hazard
- ...\Review\Simulations\Parametres_Theoriques\nlin_ph_colon\parametre_theorique\...: Theoretical parameters used to simulate the a low non-linear and proportional effect of age

The simulated datasets can be found in this folder:

...\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients\ListDataSimulation.lin.ph.RData

## 2.2 Running the PH test on the simulated datasets and plotting the results

*Main program*

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients\My_Test_FF_SigmaNum.r**

*Functions called through this main program*

...\Review\Test_FF_nsim1000\Fonctions\...

The results can be found in this folder:

...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients\res.RData

...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients\Graphe.bmp

# 3 Description of the folder \review\simulations\

**...\Review\Simulations\Fonctions :** Functions used to simulate the data

cDataDesign.pourDiffusion.NLIN.r : First step (data design) to generate the survival data with non-linear effect of age

cDataDesign.pourDiffusion.r : First step (data design) to generate the survival data with linear and proportional effect of age and linear and non-proportional effect of age

cdatasimulation.PourDiffusion.r : Second step to generate the survival data (generation of the time to death due to cancer and the time to death due to other causes)

ListModeles.r : Models used to simulate the data or to analyze the data

**...\Review\Simulations\MUA :** Lifetable (dataframe format and ratetable format)

**..\Review\Simulations\Parametres_Theoriques :** Theoretical parameters used in simulations obtained from real data

### 3.1 Programs

**...\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\500_patients\Generation_Donnees_lin_ph.r**

**...\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\1000_patients\Generation_Donnees_lin_ph.r**

**...\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\2000_patients\Generation_Donnees_lin_ph.r**

Programs used to generate the data with a linear and proportional effect of age with 500 patients, 1,000 patients and 2,000 patients respectively

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\500_patients\Generation_Donnees_lin_nph.r**

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\1000_patients\Generation_Donnees_lin_nph.r**

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\2000_patients\Generation_Donnees_lin_nph.r**

Programs used to generate the data with a linear and low non-proportional effect of age with 500 patients, 1,000 patients and 2,000 patients respectively

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Fort_1000\500_patients\Generation_Donnees_lin_nph.r**

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Fort_1000\1000_patients\Generation_Donnees_lin_nph.r**

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Fort_1000\2000_patients\Generation_Donnees_lin_nph.r**

Programs used to generate the data with a linear and strong non-proportional effect of age with 500 patients, 1,000 patients and 2,000 patients respectively

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Moyen_1000\500_patients\ Generation_Donnees_lin_nph.r**

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Moyen_1000\1000_patients\ Generation_Donnees_lin_nph.r**

**...\Review\Simulations\lin_nph_lambda0.colon_NPH_Moyen_1000\2000_patients\ Generation_Donnees_lin_nph.r**

Programs used to generate the data with a linear and medium non-proportional effect of age with 500 patients, 1,000 patients and 2,000 patients respectively

# 4 Description of the folder \review\Test_PH_nsim1000 (table 1 of the paper)

## 4.1 Programs for the size of the PH test

Need of the functions contained in (...\Review\Test_PH_nsim1000\Fonctions)

**...\Review\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\500_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the size of the PH test with 500 patients

This programs needs simulated data with a linear and proportional effect of age with 500 patients (\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\500_patients).

**...\Review\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\1000_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the size of the PH test with 1000 patients

This program needs simulated data with a linear and proportional effect of age with 1000 patients (\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\1000_patients).

**...\Review\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\2000_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the size of the PH test with 2000 patients

This program needs simulated data with a linear and proportional effect of age with 2000 patients (\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\2000_patients).

## 4.2 Programs for the Power of the PH test

Need of the functions contained in (...\Review\Test_PH_nsim1000\Fonctions)

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Faible_1000\500_patients**

**My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 500 patients

This program needs simulated data with a linear and low non-proportional effect of age with 500 patients (\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\500_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Faible_1000\1000_patients**

**My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 1000 patients

This program needs simulated data with a linear and low non-proportional effect of age with 1000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\1000_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Faible_1000\2000_patients**

**My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 2000 patients

This program needs simulated data with a linear and low non-proportional effect of age with 2000 patients.

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\2000_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Fort_1000\500_patients**

**My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 500 patients

This program needs simulated data with a linear and high non-proportional effect of age with 500 patients (\Review\Simulations\lin_nph_lambda0.colon_NPH_Fort_1000\500_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Fort_1000\1000_patients\ My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 1000 patients

This program needs simulated data with a linear and high non-proportional effect of age with 1000 patients (\Review\Simulations\lin_nph_lambda0.colon_NPH_Fort_1000\1000_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Fort_1000\2000_patients\ My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 2000 patients

This program needs simulated data with a linear and high non-proportional effect of age with 2000 patients (\Review\Simulations\lin_nph_lambda0.colon_NPH_Fort_1000\2000_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Moyen_1000\500_patients\ My_Test_PH_SigmaNum.r**

: Programs used to estimate the power of the PH test with 500 patients

This program needs simulated data with a linear and medium non-proportional effect of age with 500 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Moyen_1000\500_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Moyen_1000\1000_patients \ My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 1000 patients

This program needs simulated data with a linear and medium non-proportional effect of age with 1000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Moyen_1000\1000_patients).

**...\Review\Test_PH_nsim1000\lin_nph_lambda0.colon_NPH_Moyen_1000\2000_patients \ My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 2000 patients

This program needs simulated data with a linear and medium non-proportional effect of age with 2000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Moyen_1000\2000_patients).

# 5 Description of the folder \review\Test_FF_nsim1000 (table 1 of the paper)

## 5.1 Programs for the Size of the FF test

Need of the functions contained in (...\Review\Test_FF\Fonctions)

**...\Review\Test_FF_nsim1000\lin_ph_lambda0.colon_0.02_2000\500_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the size of the FF test with 500 patients

This program needs simulated data with a linear and proportional effect of age with 500 patients (\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\500_patients).

**...\Review\Test_FF_nsim1000\lin_ph_lambda0.colon_0.02_2000\1000_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the size of the FF test with 1000 patients

This program needs simulated data with a linear and proportional effect of age with 1000 patients (\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\1000_patients).

**...\Review\Test_FF_nsim1000\lin_ph_lambda0.colon_0.02_2000\2000_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the size of the FF test with 2000 patients

This program needs simulated data with a linear and proportional effect of age with 2000 patients (\Review\Simulations\lin_ph_lambda0.colon_0.02_2000\2000_patients).

## 5.2 Programs for the power of the FF test

need of the functions contained in (...\Review\Test_FF_nsim1000\Fonctions)

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Faible_1000\500_patients\ My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 500 patients

This program needs simulated data with a linear and low non-proportional effect of age with 500 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\500_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Faible_1000\1000_patients \ My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 1000 patients

This program needs simulated data with a linear and low non-proportional effect of age with 1000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\1000_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients \ My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 2000 patients

This program needs simulated data with a linear and low non-proportional effect of age with 2000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Fort_1000\500_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 500 patients

This program needs simulated data with a linear and high non-proportional effect of age with 500 patients (\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Fort_1000\500_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Fort_1000\1000_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 1000 patients

This program needs simulated data with a linear and high non-proportional effect of age with 1000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Fort_1000\1000_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Fort_1000\2000_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 2000 patients

This program needs simulated data with a linear and high non-proportional effect of age with 2000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Fort_1000\2000_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Moyen_1000\500_patients**

**My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 500 patients

This program needs simulated data with a linear and medium non-proportional effect of age with 500 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Moyen_1000\500_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Moyen_1000\1000_patients\ My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 1000 patients

This program needs simulated data with a linear and medium non-proportional effect of age with 1000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Moyen_1000\1000_patients).

**...\Review\Test_FF_nsim1000\nlin_ph_lambda0.colon_NLIN_Moyen_1000\2000_patients\ My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 2000 patients

This program needs simulated data with a linear and medium non-proportional effect of age with 2000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Moyen_1000\2000_patients).

# 6 Description of the folder \review\additional_results (table 3 of the paper)

## 6.1 Programs for the size of the FF test in case of misspecification concerning the PH effect of the covariate age

**...\Review\Additional_Results\alpha_FF_sc2\500_patients\ My_Test_FF_SigmaNum.r**

Programs used to estimate the size of the FF test with 500 patients in case of misspecification of the PH effect of the covariate age

This program needs simulated data with a linear and low non-proportional effect of age with 500 patients (\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\500_patients).

**...\Review\Additional_Results\alpha_FF_sc2\1000_patients\My_Test_FF_SigmaNum.r**

Programs used to estimate the size of the FF test with 1000 patients in case of misspecification of the PH effect of the covariate age

This program needs simulated data with a linear and low non-proportional effect of age with 1000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\1000_patients).

**...\Review\Additional_Results\alpha_FF_sc2\2000_patients\My_Test_FF_SigmaNum.r**

Programs used to estimate the size of the FF test with 2000 patients in case of misspecification of the PH effect of the covariate age

This program needs simulated data with a linear and low non-proportional effect of age with 2000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\2000_patients).

## 6.2 Programs for the size of the PH test in case of misspecification concerning the FF of the covariate age

**...\Review\Additional_Results\alpha_PH_sc5\500_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the size of the PH test with 500 patients in case of misspecification of the FF of the covariate age

This program needs simulated data with low non-linear and proportional effect of age with 500 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\500_patients).

**...\Review\Additional_Results\alpha_PH_sc5\1000_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the size of the PH test with 1000 patients in case of misspecification of the FF of the covariate age

This program needs simulated data with low non-linear and proportional effect of age with 1000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\1000_patients).

**...\Review\Additional_Results\alpha_PH_sc5\2000_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the size of the PH test with 2000 patients in case of misspecification of the FF of the covariate age

This program needs simulated data with low non-linear and proportional effect of age with 2000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients).

## 6.3 Programs for the Power of the FF test while over-parameterizing the PH effect of the covariate age

**...\Review\Additional_Results\beta_FF_sc8\500_patients\My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 500 patients while over-parameterizing the PH effect of the covariate age.

This program needs simulated data with a low non-linear and proportional effect of age with 500 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\500_patients).

**...\Review\Additional_Results\beta_FF_sc8\1000_patients\My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 1000 patients while over-parameterizing the PH effect of the covariate age.

This program needs simulated data with a low non-linear and proportional effect of age with 1000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\1000_patients).

**...\Review\Additional_Results\beta_FF_sc8\2000_patients\My_Test_FF_SigmaNum.r**

Programs used to estimate the power of the FF test with 2000 patients while over-parameterizing the PH effect of the covariate age.

This program needs simulated data with a low non-linear and proportional effect of age with 2000 patients

(\Review\Simulations\nlin_ph_lambda0.colon_NLIN_Faible_1000\2000_patients).

## 6.4 Programs for the Power of the PH test while over-parameterizing the FF of the covariate age

**...\Review\Additional_Results\beta_PH_sc7\500_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 500 patients while over-parameterizing the FF of the covariate age.

This program needs simulated data with a linear and a low non-proportional effect of age with 500 patients (\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\500_patients).

**...\Review\Additional_Results\beta_PH_sc7\1000_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 1000 patients while over-parameterizing the FF of the covariate age.

This program needs simulated data with a linear and a low non-proportional effect of age with 1000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\1000_patients).

**...\Review\Additional_Results\beta_PH_sc7\2000_patients\My_Test_PH_SigmaNum.r**

Programs used to estimate the power of the PH test with 2000 patients while over-parameterizing the FF of the covariate age.

This program needs simulated data with a linear and a low non-proportional effect of age with 2000 patients

(\Review\Simulations\lin_nph_lambda0.colon_NPH_Faible_1000\2000_patients).

# 7 Description of the folder \review\big_sample_size

This folder contains code for the PH test, code that was updated the last few days (7/14/2016) and which allows the analysis of datasets with big sample size (example here on 1 dataset with 100,000)

## 7.1 Generating the simulated data with a linear and proportional effect of age

*Main program*

**...\Review\big_sample_size\simulations\lin_ph_lambda0.colon_0.02_2000\100000_patients\Generation_Donnees_lin_ph.r**

*Functions and objects called through this main program*

- ...\ Review\big_sample_size\simulations\Fonctions\...: Programs used for the design of the data, the generation of time to death due to cancer and time to death due to other causes
- ...\Review\ big_sample_size\Simulations\MUA\...: Life tables

...\Review\big_sample_size\Simulations\Parametres_Theoriques\colon_TxBase\parametre_theorique\....: Theoretical parameters used for the excess baseline hazard

...\Review\big_sample_size\Simulations\Parametres_Theoriques\lin_ph_colon\parametre_theorique\...: Theoretical parameters used to simulate the linear and proportional effect of age

The simulated datasets can be found in this folder:

...\Review\big_sample_size\simulations\lin_ph_lambda0.colon_0.02_2000\100000_patients\ListDataSimulation.lin.ph.RData

## 7.2 Running the PH test on the simulated dataset with 100,00 patients

*Main program*

**...\Review\big_sample_size\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\100000_patients\temps_exe_new3.r**

*Functions called through this main program*

...\Review\big_sample_size\Test_PH_nsim1000\Fonctions\...

The results can be found in this folder:

\Test_PH_nsim1000\lin_ph_lambda0.colon_0.02_2000\100000_patients\temps_exe_new3.lis