

Cox FR LRT: a Gene-based Association Method for Censored Traits Via Functional Regressions

Ruzong Fan and Qi Yan, NICHD/NIH and University of Pittsburgh

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1 Overview

This document describes a R package to implement Cox FR LRT statistics proposed in Fan et al. (2015). The Cox FR LRT refers to Cox Functional Regression Likelihood Test, based on fixed effect Cox proportional hazard models using functional regression to perform gene-based association analysis of survival traits while adjusting for covariates. Section 2 briefly describes the installation of the program. Section 3 explains how to run the program using one example. Section 4 offers explanation of the results and warnings to use the programs. Section 5 provides some suggestions and parameter choices for real data analysis.

The theoretical basis for this program is given in our research papers in **References**. Please refer to the reference if you use the program in any published work. In case of suggestions and questions and/or problems, you can contact us via e-mail (fanr@mail.nih.gov).

2 Download and Installation

The package is written in R. First of all, download R function codes “FLM_survival.fixed_model.R”, “FLM_survival.beta_smooth_only.R”, and example files of “SeqMeta.example.R” from FLM_surv.zip. Put the files in a directory you may access.

3 How to Run the Program

The analysis needs libraries fda, MASS, Matrix, survival, and seqMeta in R package. Make sure to install them before running our codes. Open the “SeqMeta.example.R” file on an R Console in a PC

window. Change the paths leading to the directories of the package “FLM_survival_fixed_model.R” and “FLM_survival_beta_smooth_only.R” on your computer. Then, you may run the program. The following results are from “R i386 3.1.2”.

```
> rlt
```

	Gene	Cox FR LRT:fixed_b	Cox FR LRT:fixed_f	Cox FR LRT:beta_b	Cox FR LRT:beta_f
1	gene1	0.513947018	0.69067099	0.513947018	0.69067099
2	gene10	0.258871305	0.86395941	0.258871305	0.86395941
.....					
99	gene98	0.914683907	0.94941898	0.914683907	0.94941898
100	gene99	0.852615284	0.60316073	0.852615284	0.60316073

4 Explanation of the Results and Warnings

As shown in the Section 3, our program can output 4 p -values of Cox FR LRT statistics. Cox FR LRT:fixed_b and Cox FR LRT:fixed_f are from “flm_surv_fixed_model (...)” function in the R codes “FLM_survival_fixed_model.R”, by b-spline and Fourier spline basis functions, respectively. Cox FR LRT:beta_b and Cox FR LRT:beta_f are from “flm_surv_beta_smooth_only (...)” function of “FLM_survival_beta_smooth_only.R”, by b-spline and Fourier spline basis functions, respectively.

5 Suggestions and Parameters for Real Data Analysis

In this documentation, we present two R functions to perform gene-based association analysis of survive traits. In practice, one may use one of them for data analysis. One may use either B-spline or Fourier spline basis functions. For “flm_surv_fixed_model (...)” function of “FLM_survival_fixed_model.R” and base = “bspline”, we suggest the following parameters

```
order = 4
```

```
bbasis = 10
```

```
gbasis = 10
```

For “`flm_surv_fixed_model ( ... )`” function of “`FLM_survival_fixed_model.R`” and `base = "fspline"`, we suggest the following parameters

```
order = 4
```

```
fbasis = 11
```

```
gbasis = 11
```

For “`flm_surv_beta_smooth_only ( ... )`” function of “`FLM_survival_beta_smooth_only.R`” and `base = "bspline"`, we suggest the following parameters for a data analysis

```
order = 4
```

```
basis = 10
```

For “`flm_surv_beta_smooth_only ( ... )`” function of “`FLM_survival_beta_smooth_only.R`” and `base = "fspline"`, we suggest the following parameters

```
order = 4
```

```
basis = 11
```

6 References

1. Fan RZ, Wang YF, Mills JL, Wilson AF, Bailey-Wilson JE, and Xiong MM (2013) Functional linear models for association analysis of quantitative traits. *Genetic Epidemiology*, 37:726-742.
2. Fan RZ, Wang YF, Mills JL, Carter TC, Lobach I, Wilson AF, Bailey-Wilson JE, Weeks DE, and Xiong MM (2014) Generalized functional linear models for case-control association studies. *Genetic Epidemiology*, 38:622-637.
3. Fan RZ, Wang YF, Qi Y, Ding Y, Weeks DE, Lu ZH, Ren HB, Cook RJ, Xiong MM and Chen W (2015) Gene-based association analysis for censored traits via functional regressions. *Genetic Epidemiology*, revision submitted.