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► **To cite this version:**

Virginie Rondeau, Yassin Mazroui, Audrey Mauguen, Juan Ramon Gonzalez. FrailtyPack: An R Package for the Analysis of Correlated Survival Data with Frailty Models Using Penalized Likelihood or Parametrical Estimation. 1ères Rencontres R, Jul 2012, Bordeaux, France. hal-00717543

HAL Id: hal-00717543

<https://hal.science/hal-00717543>

Submitted on 13 Jul 2012

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FrailtyPack: An R Package
for the Analysis of Correlated Survival Data with Frailty Models
Using Penalized Likelihood or Parametrical Estimation

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Mots clefs : Statistic, Frailty models, clustered data, recurrent events

Frailty models are extensions of the Cox proportional hazards model which is the most popular model in survival analysis. In many clinical applications, the study population needs to be considered as a heterogeneous sample or as a cluster of homogeneous groups of individuals such as families or geographical areas. Sometimes, due to lack of knowledge or for economical reasons, some covariates related to the event of interest are not measured. The frailty approach is a statistical modelling method which aims to account for the heterogeneity caused by unmeasured covariates. It does so by adding random effects which act multiplicatively on the hazard function.

FrailtyPack is an R package¹ which allows to fit four types of frailty models, for left-truncated and right-censored data, adapted to most survival analysis issues. The aim of this talk is to present the new version of the R package **FrailtyPack**, which is available from the Comprehensive R Archive Network at <http://CRAN.R-project.org/>, and the various new models proposed. It depends on the R `survival` package.² The initial version of this package³ was proposed for a simple shared frailty model, and was developed for more general frailty models.⁴ The shared frailty model⁵ can be used, when observations are supposed to be clustered into groups. The nested frailty model⁶ is most appropriate, when there are two levels of hierarchical clustering. However, several relapses (recurrent events) are likely to increase the risk of death, thus the terminal event is considered as an informative censoring. Using a joint frailty model, it is possible to fit jointly the two hazard functions associated with recurrent and terminal events,⁷ when these events are supposed to be correlated. The additive frailty model⁸ is more adapted to study both heterogeneity across trial and treatment-by-trial heterogeneity (for instance meta-analysis or multicentric datasets study). We show how a simple multi-state frailty model can be used to study semi-competing risks while fully taking into account the clustering (in ICU) of the

data and the longitudinal aspects of the data, including left truncation and right censoring.⁹ We included recently parametric hazard functions and prediction methods. Depending on the models, stratification and time-dependent covariates are allowed or not.

The frailty models discussed in recent literature present several drawbacks. Their convergence is too slow, they do not provide standard errors for the variance estimate of the random effects and they can not estimate smooth hazard function. `FrailtyPack` use a non-parametric penalized likelihood estimation, and the smooth estimation of the baseline hazard functions is provided by using an approximation by splines.

`FrailtyPack` was first written in Fortran 77 and was implemented for the statistical software R. We will present the models that `FrailtyPack` can fit and the estimation method, then we will describe all the functions and the arguments of `FrailtyPack`. Finally epidemiological illustrations will be provided using `FrailtyPack` functions. `FrailtyPack` is improved regularly in order to add new developments around frailty models.

References

- [1] R Development Core Team. *R: A Language and Environment for Statistical Computing*.
- [2] T. Therneau. *survival: A Package for Survival Analysis in S*, 2012. R package version 2.36-12.
- [3] V. Rondeau and J.R. Gonzalez. frailtypack: A computer program for the analysis of correlated failure time data using penalized likelihood estimation. *Computer Methods and Programs in Biomedicine*, 80(2):154–164, 2005.
- [4] V. Rondeau, Y. Mazroui, A. Mauguen, A. Diakite, and JR Gonzalez. FRAILTYPACK: An R package for General frailty models using a semi-parametrical penalized likelihood estimation or a parametrical estimation, 2012. R package version 2.2-22.
- [5] V. Rondeau, D. Commenges, and P. Joly. Maximum penalized likelihood estimation in a gamma-frailty model. *Lifetime Data Analysis*, 9(2):139–153, 2003.
- [6] V. Rondeau, L. Filleul, and P. Joly. Nested frailty models using maximum penalized likelihood estimation. *Statistics in Medicine*, 25(23):4036–4052, 2006.
- [7] V. Rondeau, S. Mathoulin-Pelissier, H. Jacqmin-Gadda, V. Brouste, and P. Soubeyran. Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics*, 8(4):708–721, 2007.
- [8] V. Rondeau, S. Michiels, B. Liqueur, and J.P. Pignon. Investigating trial and treatment heterogeneity in an individual patient data meta-analysis of survival data by means of the penalized maximum likelihood approach. *Statistics in Medicine*, 27(11):1894–1910, 2008.
- [9] B. Liqueur, J.F. Timsit, and V. Rondeau. Investigating hospital heterogeneity with a multi-state frailty model: application to nosocomial pneumonia disease in intensive care units. *BMC medical reserach methodology*, In press, 2012.