

Adjusting for centre effects in the analysis of survival data from multicentre clinical trials

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Promoter: Catherine Legrand

Young Researchers' Day

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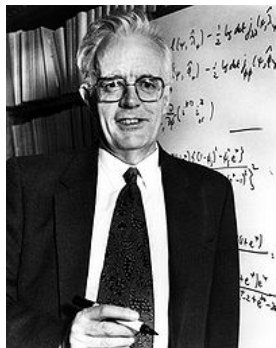
Proportional Hazards model

- ▶ PH model:

$$h_i(t) = h_0(t) \exp(\mathbf{x}'_i \boldsymbol{\beta}),$$

with $i = 1, \dots, n$;

- ▶ Fitted by maximising either the log-likelihood (parametric approach) or the partial log-likelihood (semi-parametric approach).



Assumption/Limitation: Given values for the covariates, event times are supposed to be independent.

The shared frailty model

The shared frailty model is an extension for clustered survival data of the Cox's model:

$$\begin{aligned}h_{ij}(t) &= h_0(t) \exp(\mathbf{x}'_{ij}\boldsymbol{\beta} + w_i) \\ &= h_0(t)u_i \exp(\mathbf{x}'_{ij}\boldsymbol{\beta})\end{aligned}$$

$$i = 1, \dots, s; \quad j = 1, \dots, n_i.$$

The frailty u_i is

- ▶ an unobservable realisation of a non-negative random variable U with p.d.f. $f(\cdot)$ —the frailty distribution;
- ▶ shared by all n_i subjects from cluster i ;
- ▶ used in order to adjust for dependence/heterogeneity among individuals/centres.

Assumption: Given values for the covariates, event times are supposed to be independent, conditional on the cluster.

Clustering survival data

cluster	experimental unit	survival time ¹	event indicator ²	covariate information
1	1	y_{11}	δ_{11}	\mathbf{x}'_{11}
1	2	y_{12}	δ_{12}	\mathbf{x}'_{12}
⋮	⋮	⋮	⋮	⋮
1	n_1	y_{1n_1}	δ_{1n_1}	\mathbf{x}'_{1n_1}
⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮
s	1	y_{s1}	δ_{s1}	\mathbf{x}'_{s1}
s	2	y_{s2}	δ_{s2}	\mathbf{x}'_{s2}
⋮	⋮	⋮	⋮	⋮
s	n_s	y_{sn_s}	δ_{sn_s}	\mathbf{x}'_{sn_s}

$${}^1Y_{ij} = \min(T_{ij}, C_{ij})$$

$${}^2\Delta_{ij} = I(T_{ij} \leq C_{ij})$$

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Frailty distributions

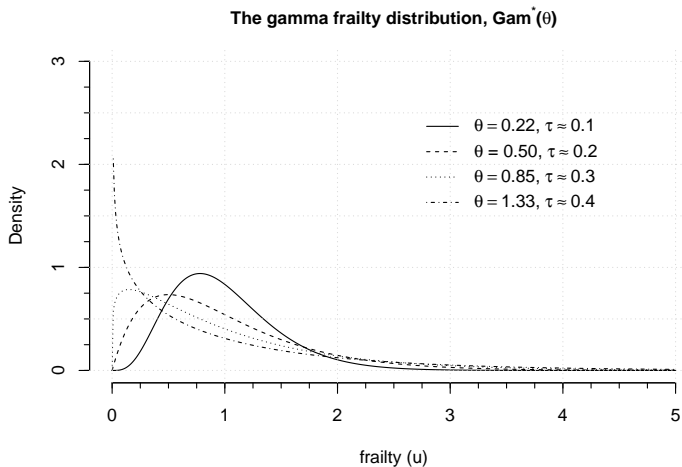
Various choices for $f(\cdot)$ have been proposed in the literature (Duchateau and Janssen, 2008, Chapter 4).

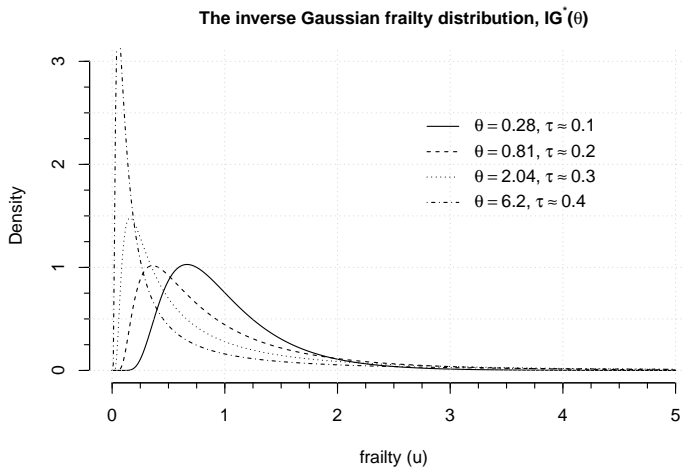
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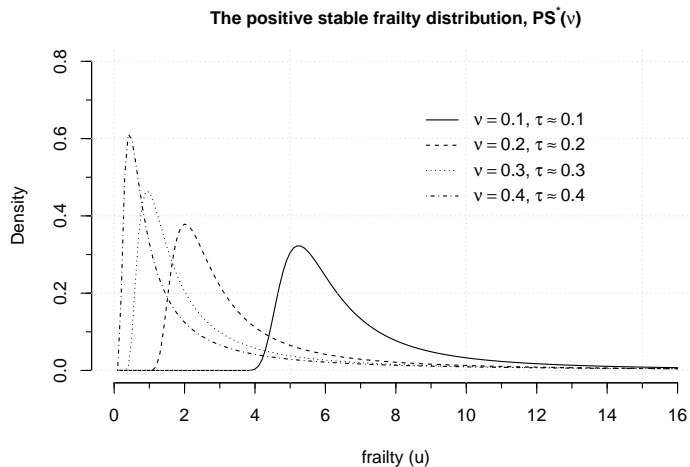
Frailty distributions

Different distributions have been proposed for the frailty term. In Chapter 2 the gamma distribution was introduced. In this chapter we discuss different frailty distributions that are proposed in the literature. Although the discussion in this chapter is rather technical (most of the results appeared in methodological journals), it is important to collect what is available in a detailed way. Indeed, in practice mainly the gamma distribution and the lognormal distribution are used to model the frailty term and most of the software limits the choice of the frailty distribution to these cases. But the right choice of the frailty distribution is of crucial importance to arrive at a good description of the dependence structure present in the data. Therefore, the choice of the frailty distribution is even more important as the choice of the distribution of the random effect(s) in mixed models since, in frailty models, the dependence between correlated observations changes over time and the frailty distribution dictates how the dependence changes. Few results are available on comparing models with different frailty distributions; more research is needed in this area.

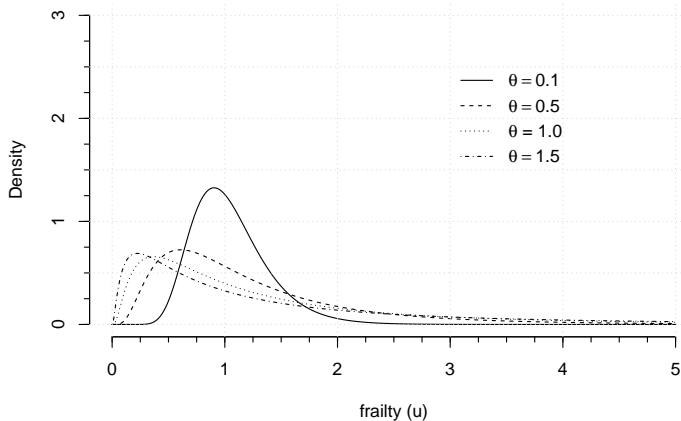
The general characteristics of frailty distributions are studied in detail in Section 4.1. We further discuss how the effect of particular frailty distributions on the survival and hazard function of individuals can be investigated by using the Laplace transform. Important global and local measures of dependence, such as Kendall's τ and the cross ratio function, are introduced in general terms. In Section 4.2 the gamma distribution is discussed in detail. The inverse Gaussian frailty distribution and the positive stable distribution are discussed in Sections 4.3 and 4.4, respectively. It is demonstrated that the positive stable distribution has specific and advantageous properties. For instance, the marginal model deduced from the conditional model still obeys the proportional hazards assumption. In Section 4.5, the power variance function family is discussed in general terms. This family contains the gamma, inverse Gaussian, and positive stable frailty. The compound Poisson distribution is discussed in Section 4.6. It allows a proportion of the population to be not susceptible for the event under consideration. This part of the population has







The log-normal frailty distribution, $LN(\theta)$



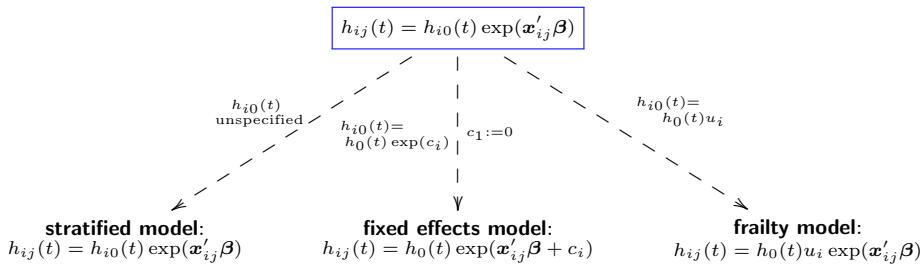
Note: there is no explicit evaluation of Kendall's τ .

Estimation techniques

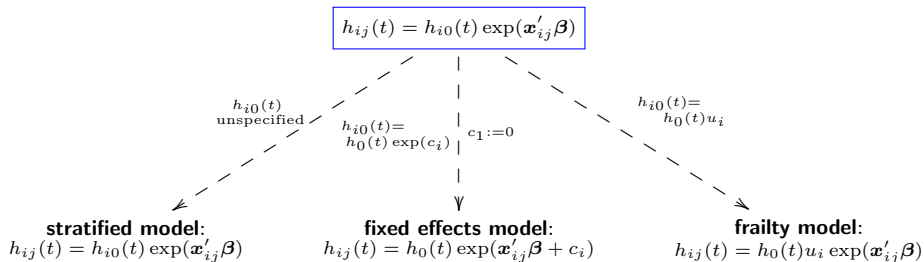
- ▶ Parametric approach:
 - (i) Select a parametric form for $h_0(\cdot)$ (e.g., Weibull),
 - (ii) Maximise the marginal log-likelihood;

- ▶ Semi-parametric approach:
 - (i) Let $h_0(\cdot)$ be unspecified,
 - (ii) EM algorithm, penalise log-likelihood approach, ...

Modelling clustered survival data



Modelling clustered survival data



Question: If primary interest centres on making inference on the treatment effect ($\exp(\beta_k)$), which methodology should be recommended?

Simulation study

Description

Table: Settings for the simulation study.

	parameter	notation	value(s)
	number of centres	s	15, 30, 300
	number of patients in each centre	$n_1 = \dots = n_s = n$	40, 20, 2
	total number of patients	$N = n \times s$	600
	accrual period in years	atime	3
	constant baseline yearly hazard	λ	0.23
	regression coefficient	β	0, -0.30
scenario A	follow-up period in years	ftime	10
	frailty distribution	$f(u_i)$	gamma
	heterogeneity parameter	θ	0.22
scenario B	follow-up period in years	ftime	7
	frailty distribution	$f(u_i)$	positive stable
	heterogeneity parameter	ν	0.3

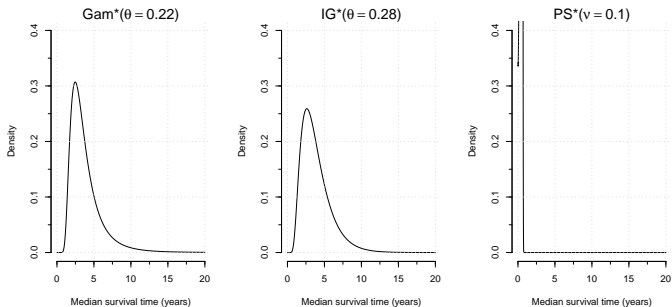
► Scenario A: $\tau = 0.1$ 

Figure: Probability density functions of the median survival time in the control group of centre i in which different frailty distributions induce dependence as measure by $\tau = 0.1$.

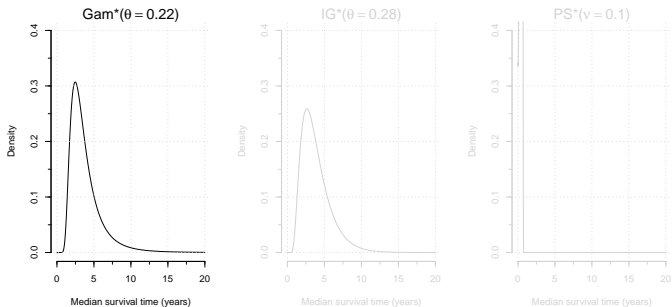
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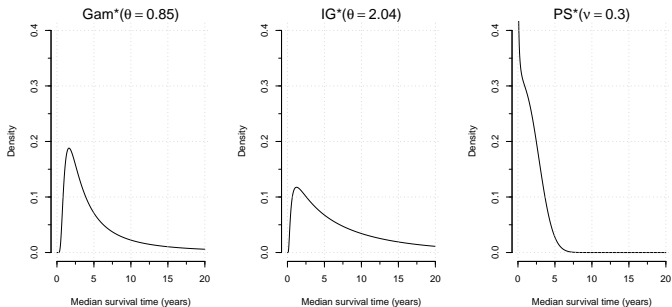
► Scenario B: $\tau = 0.3$ 

Figure: Probability density functions of the median survival time in the control group of centre i in which different frailty distributions induce dependence as measure by $\tau = 0.3$.

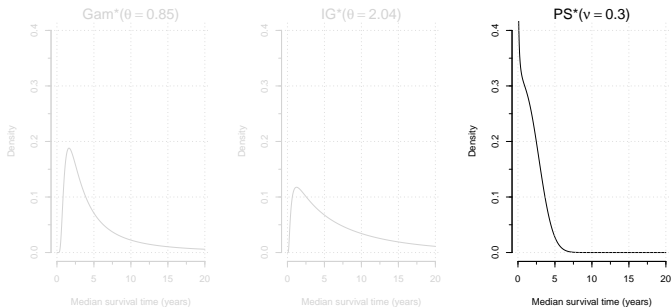
► Scenario B: $\tau = 0.3$ 

Figure: Probability density functions of the median survival time in the control group of centre i in which different frailty distributions induce dependence as measure by $\tau = 0.3$.

Results

Table: Unadjusted Cox's model

scenario	β	statistic	$N = 600$		
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$
A					
	$\beta = 0$	mean	-0.002	0.001	0.002
		std. dev.	0.086	0.087	0.088
		95% CI cov.	0.957	0.957	0.948
	$\beta = -0.30$	mean	-0.268	-0.267	-0.260
		std. dev.	0.093	0.093	0.092
		95% CI cov.	0.924	0.931	0.927
B					
	$\beta = 0$	mean	-0.007	0.002	-0.002
		std. dev.	0.085	0.085	0.086
		95% CI cov.	0.948	0.949	0.951
	$\beta = -0.30$	mean	-0.217	-0.206	-0.212
		std. dev.	0.087	0.086	0.086
		95% CI cov.	0.840	0.797	0.817

Table: Fixed effects Cox's model

scenario	β	statistic	$N = 600$		
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$
A	$\beta = 0$	mean	-0.005	-0.000	/
		std. dev.	0.088	0.094	/
		95% CI cov.	0.956	0.948	/
	$\beta = -0.30$	mean	-0.304	-0.315	/
		std. dev.	0.090	0.099	/
		95% CI cov.	0.954	0.934	/
B	$\beta = 0$	mean	-0.005	0.001	/
		std. dev.	0.091	0.093	/
		95% CI cov.	0.944	0.946	/
	$\beta = -0.30$	mean	-0.308	-0.309	/
		std. dev.	0.088	0.093	/
		95% CI cov.	0.962	0.939	/

Table: Stratified Cox's model

scenario	β	statistic	$N = 600$		
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$
A	$\beta = 0$	mean	-0.004	0.000	0.003
		std. dev.	0.087	0.092	0.162
		95% CI cov.	0.960	0.961	0.960
	$\beta = -0.30$	mean	-0.298	-0.302	-0.308
		std. dev.	0.090	0.098	0.171
		95% CI cov.	0.959	0.944	0.946
B	$\beta = 0$	mean	-0.005	0.001	0.001
		std. dev.	0.092	0.092	0.164
		95% CI cov.	0.944	0.956	0.955
	$\beta = -0.30$	mean	-0.303	-0.298	-0.307
		std. dev.	0.088	0.094	0.162
		95% CI cov.	0.962	0.944	0.966

Table: Parametric frailty models under scenario A

model	β	statistic	$N = 600$			
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$	
param. gamma frailty model	$\beta = 0$	mean	-0.005	-0.000	0.003	
		std. dev.	0.086	0.089	0.098	
		95% CI cov.	0.957	0.957	0.952	
	$\beta = -0.30$	mean	-0.298	-0.303	-0.296	
		std. dev.	0.088	0.095	0.105	
		95% CI cov.	0.959	0.946	0.948	
	param. inv. Gauss. frailty model	$\beta = 0$	mean	-0.005	-0.000	0.003
			std. dev.	0.086	0.089	0.098
			95% CI cov.	0.958	0.957	0.951
$\beta = -0.30$		mean	-0.298	-0.303	-0.296	
		std. dev.	0.088	0.095	0.105	
		95% CI cov.	0.961	0.945	0.947	
param. pos. stable frailty model		$\beta = 0$	mean	-0.005	-0.000	0.002
			std. dev.	0.086	0.090	0.096
			95% CI cov.	0.958	0.956	0.943
	$\beta = -0.30$	mean	-0.298	-0.302	-0.281	
		std. dev.	0.089	0.095	0.101	
		95% CI cov.	0.960	0.942	0.941	

Table: Semi-parametric frailty models under scenario A

model	β	statistic	$N = 600$		
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$
semi-param. gamma frailty model					
	$\beta = 0$	mean	-0.005	-0.000	0.003
		std. dev.	0.086	0.089	0.098
		95% CI cov.	0.956	0.956	0.951
	$\beta = -0.30$	mean	-0.299	-0.303	-0.297
		std. dev.	0.089	0.094	0.105
		95% CI cov.	0.959	0.943	0.944
semi-param. log-normal frailty model					
	$\beta = 0$	mean	-0.005	-0.000	0.003
		std. dev.	0.086	0.090	0.098
		95% CI cov.	0.957	0.957	0.950
	$\beta = -0.30$	mean	-0.298	-0.303	-0.296
		std. dev.	0.089	0.095	0.104
		95% CI cov.	0.958	0.945	0.947

Table: Parametric frailty models under scenario B

model	β	statistic	$N = 600$			
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$	
param. gamma frailty model	$\beta = 0$	mean	-0.005	0.001	-0.001	
		std. dev.	0.089	0.089	0.104	
		95% CI cov.	0.945	0.954	0.964	
	$\beta = -0.30$	mean	-0.302	-0.295	-0.261	
		std. dev.	0.086	0.089	0.102	
		95% CI cov.	0.957	0.944	0.947	
	param. inv. Gauss. frailty model	$\beta = 0$	mean	-0.005	0.001	0.000
			std. dev.	0.090	0.090	0.124
			95% CI cov.	0.946	0.955	0.955
$\beta = -0.30$		mean	-0.304	-0.300	-0.321	
		std. dev.	0.086	0.090	0.126	
		95% CI cov.	0.956	0.945	0.949	
param. pos. stable frailty model		$\beta = 0$	mean	-0.005	0.001	-0.001
			std. dev.	0.089	0.089	0.111
			95% CI cov.	0.947	0.955	0.960
	$\beta = -0.30$	mean	-0.303	-0.297	-0.301	
		std. dev.	0.086	0.089	0.111	
		95% CI cov.	0.957	0.947	0.956	

Table: Semi-parametric frailty models under scenario B

model	β	statistic	$N = 600$		
			$s = 15, n = 40$	$s = 30, n = 20$	$s = 300, n = 2$
semi-param. gamma frailty model					
	$\beta = 0$	mean	-0.005	0.001	-0.000
		std. dev.	0.089	0.090	0.114
		95% CI cov.	0.946	0.952	0.959
	$\beta = -0.30$	mean	-0.302	-0.296	-0.284
		std. dev.	0.086	0.090	0.111
		95% CI cov.	0.963	0.946	0.952
semi-param. log-normal frailty model					
	$\beta = 0$	mean	-0.006	0.001	-0.000
		std. dev.	0.089	0.090	0.121
		95% CI cov.	0.947	0.953	0.955
	$\beta = -0.30$	mean	-0.303	-0.298	-0.309
		std. dev.	0.086	0.090	0.118
		95% CI cov.	0.961	0.947	0.948

Conclusion

$$h_i(t) = h_0(t) \exp(\mathbf{x}'_i \boldsymbol{\beta})$$

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May fail to convergence when $s \gg n$;

May have under-coverage under censoring and with small or moderate centre sizes.

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