Supplementary material for "A Two-Stage Joint Model for Nonlinear Longitudinal Response and a Time-to-Event with Application in Transplantation Studies"

Magdalena Murawska [1,*], Dimitris Rizopoulos[1], and Emmanuel Lesaffre[1,2]

October 27, 2011

[1] *Department of Biostatistics, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands*
[2] *Biostatistical Centre, I-Biostat, Catholic University of Leuven, Belgium*
**e-mail:m.murawska@erasmusmc.nl*

1. Renal Resistance Data. Descriptives

The individual profiles for different types of donor and different regions are presented in Figure 2. It can be observed that there is some variability in the RR level at time zero, in asymptotes and also in the "slopes". After putting the kidney into the machine there is a rise of RR level for both H-B and N-H-B. This later stabilizes and appears to be almost constant. The same behavior is visible for the three donor regions. The mean profiles for different donor types and regions are presented in Figure 1. N-H-B have higher RR level as compared to the N-H-B donors. Donors from different regions have more less similar mean RR profiles with a bit higher RR mean initial value for Region 2 and the lowest asymptote for Region 1. There were not N-H-B donors from Region 2 present in the data set. Figure 3 presents the results from a nonlinear mixed model for the renal data.

2. Metropolis-Hastings algorithm

Metropolis-Hastings algorithm is a Markov chain Monte Carlo method for obtaining a sequence of random samples from a probability distribution for which direct sampling is not straightforward. The M-H algorithm is defined by two steps: a first step in which a proposal value is drawn from the candidate generating density and a second step in which the proposal value is accepted as the next iterate in the Markov chain according to the defined probability or rejected and then the next sampled value is taken to be the current value.

In order to sample form the posterior distribution for random effects for a particular individual i according to the algorithm described in Section 3.2 of the article in each step k we propose the density q for $\boldsymbol{\alpha}_i$. The proposal density was chosen to be a multivariate t distribution with 4 df, mean equal the Empirical Bayes estimate obtained from the nonlinear mixed model and variance-covariance matrix $\boldsymbol{D}$ also estimated from the nonlinear mixed model, additionally scaled by some parameter $Scale$. Before the start of the analysis the tuning parameter $Scale$ was calibrated in order to achieve the acceptance rate equal 0.5. We run 300 iterations for the calibration.
The procedure can be described as below:
Step 0 :

$$\boldsymbol{\alpha}_i^0 = EB(\boldsymbol{\alpha}_i)$$

Step K:

$$\boldsymbol{\alpha}_i^* \sim q(EB(\boldsymbol{\alpha}_i), Scale * \boldsymbol{D})(\text{proposition for } \boldsymbol{\alpha}_i)$$

Calculate acceptance-rejection criterion:

$$r_i = \frac{p(\boldsymbol{\alpha}_i^* \mid \boldsymbol{Y}_i, \boldsymbol{\theta}_y) q(\boldsymbol{\alpha}_i^{k-1}, Scale * \boldsymbol{D})}{p(\boldsymbol{\alpha}_i^{k-1} \mid \boldsymbol{Y}_i, \boldsymbol{\theta}_y) q(\boldsymbol{\alpha}_i^*, Scale * \boldsymbol{D})},$$

where $\boldsymbol{\theta}_y$ is the vector of fixed effects sampled using the estimates from the nonlinear mixed model.
Since the posterior distribution $p(\boldsymbol{\alpha}_i \mid \boldsymbol{Y}_i, \boldsymbol{\theta}_y)$ is unknown, we use the fact that:

$$p(\boldsymbol{\alpha}_i \mid \boldsymbol{Y}_i, \boldsymbol{\theta}_y) \propto p(\boldsymbol{Y}_i \mid \boldsymbol{\alpha}_i, \boldsymbol{\theta}_y) p(\boldsymbol{\alpha}_i),$$

and therefore the acceptance-rejection criterion takes the form:

$$r_i = \frac{p(\boldsymbol{Y}_i \mid \boldsymbol{\alpha}_i^*, \boldsymbol{\theta}_y) p(\boldsymbol{\alpha}_i^*) q(\boldsymbol{\alpha}_i^{k-1}, Scale * \boldsymbol{D})}{p(\boldsymbol{Y}_i \mid \boldsymbol{\alpha}_i^{k-1}, \boldsymbol{\theta}_y) p(\boldsymbol{\alpha}_i^{k-1}) q(\boldsymbol{\alpha}_i^*, Scale * \boldsymbol{D})}.$$

In above criterion $p(\boldsymbol{Y}_i \mid \boldsymbol{\alpha}_i, \boldsymbol{\theta}_y)$ is a Gaussian density for individual i with a mean being a nonlinear function of random and fixed effects $f(\boldsymbol{\alpha}_i, \boldsymbol{\theta}_y)$ and variance σ^2 estimated from the nonlinear mixed model. $p(\boldsymbol{\alpha}_i)$ is the multivariate normal distribution with mean zero and a scaled variance-covariance matrix $\boldsymbol{D}$.

Draw from uniform distribution:

$$u \sim U(0,1).$$

If $r_i \leq u$ (accept proposition $\boldsymbol{\alpha}_i^*$ for $\boldsymbol{\alpha}_i$):

$$\boldsymbol{\alpha}_i^k = \boldsymbol{\alpha}_i^*,$$

otherwise reject $\boldsymbol{\alpha}_i^*$:

$$\boldsymbol{\alpha}_i^k = \boldsymbol{\alpha}_i^{k-1}.$$

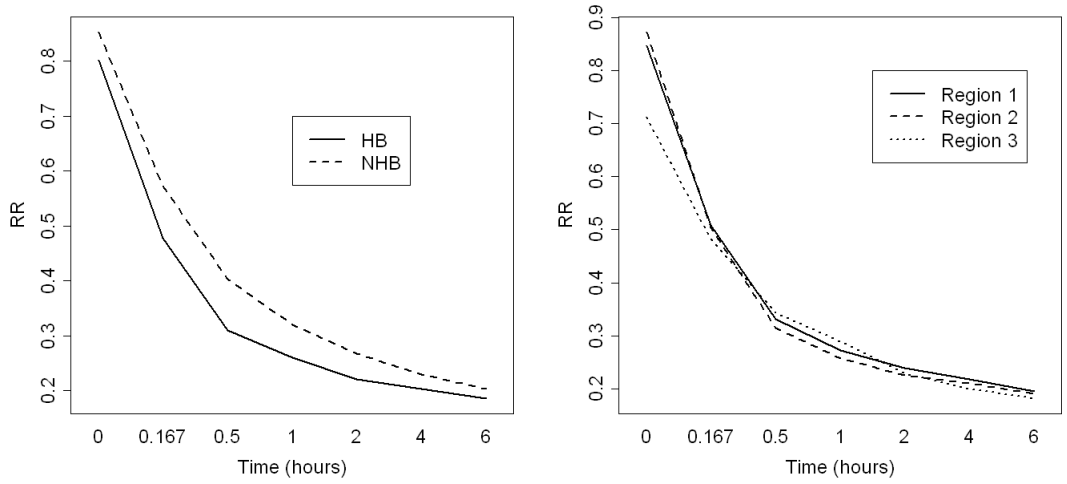
Since we always propose the q density around the EB estimates for $\boldsymbol{\alpha}_i$ this procedure is an independence version of Metropolis-Hastings algorithm.

3. Tables

Table 1: *Parameter estimates, standard errors and 95% credibility intervals from the longitudinal part of the joint fully Bayesian model with Weibull survival submodel*

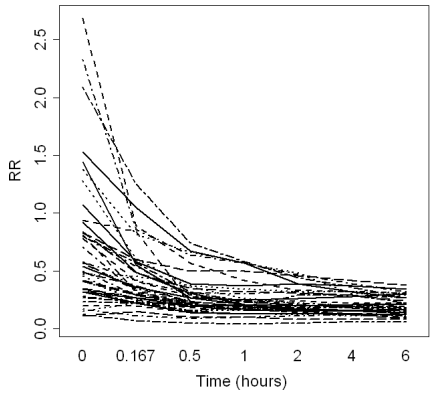
	RR			
Effect	Parameter	Estimate	SE	(95%HPD)
ϕ_1				
Constant	β_{10}	2.862	0.143	(2.582; 3.142)
Donor Age	β_{11}	0.011	0.004	(0.003; 0.018)
Donor Type (HB vs NHB)	β_{12}	-0.106	0.118	(-0.337; 0.125)
Donor Region 1 vs 3	β_{13}	-0.09	0.096	(-0.278; 0.098)
Donor Region 2 vs 3	β_{14}	-0.08	0.100	(-0.276; 0.116)
ϕ_2				
Constant	β_{20}	3.540	0.341	(2.872; 4.208)
Donor Age	β_{21}	0.004	0.008	(-0.011; 0.020)
Donor Type (HB vs NHB)	β_{22}	-0.080	0.196	(-0.464; 0.304)
Donor Region 1 vs 3	β_{23}	-0.094	0.314	(-0.709; 0.521)
Donor Region 2 vs 3	β_{24}	0.045	0.216	(-0.378; 0.468)
ϕ_3				
Constant	β_{30}	1.335	0.257	(0.831; 1.839)
Donor Age	β_{31}	0.009	0.009	(-0.009; 0.027)
Donor Type (HB vs NHB)	β_{32}	0.540	0.133	(0.279; 0.801)
Donor Region 1 vs 3	β_{33}	-0.234	0.127	(-0.483; 0.015)
Donor Region 2 vs 3	β_{34}	-0.070	0.147	(-0.358; 0.218)

4. Figures

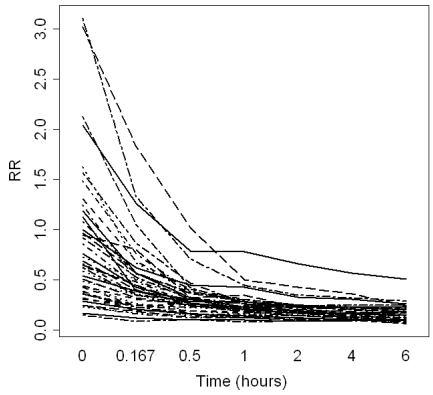


(a) (b)

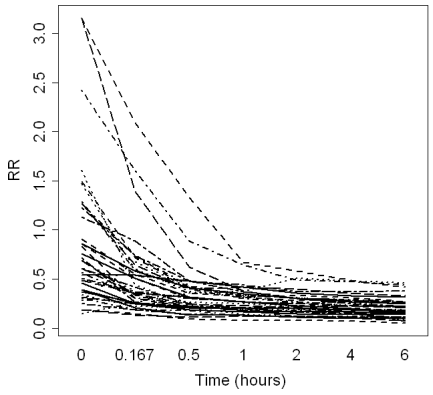
Fig. 1: *Mean profiles of Renal Resistance for the two type of donors: Herat-Beating (H-B) and Non-Heart-Beating (N-H-B) a) and 3 donor regions b)*



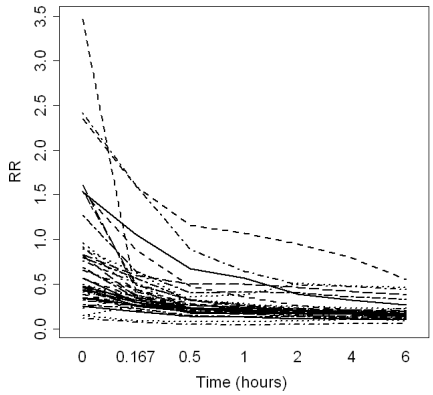
(a) *Region 1*



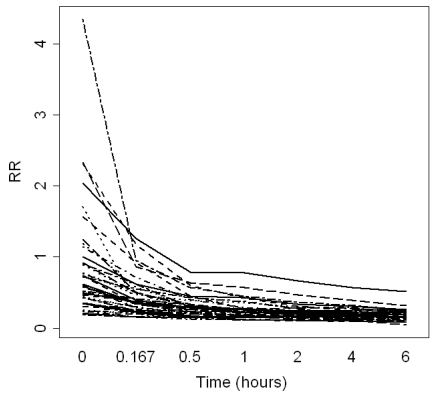
(b) *Region 2*



(c) *Region 3*

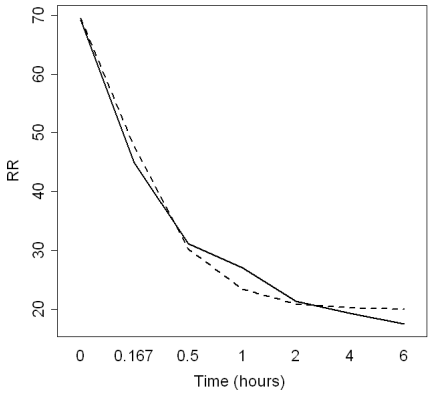


(d) *Heart Beating*

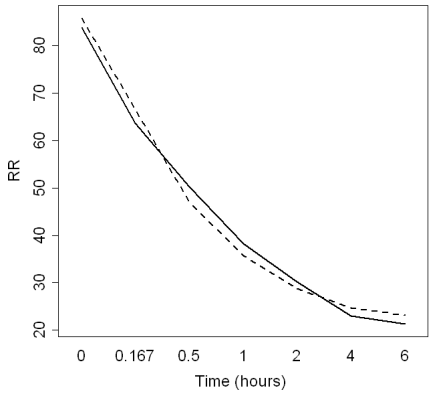


(e) *Non Heart Beating*

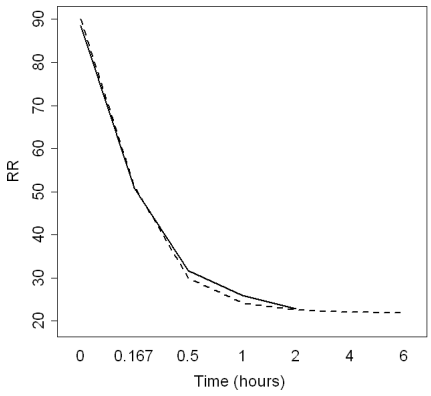
Fig. 2: *Individual profiles of renal resistance depending on donor region and donor type (50 sampled ind. in each subgroup)*



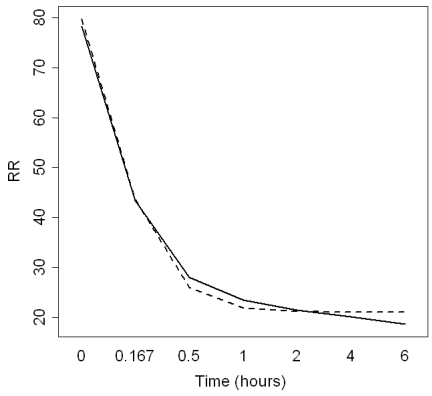
(a) *HB Region 1*



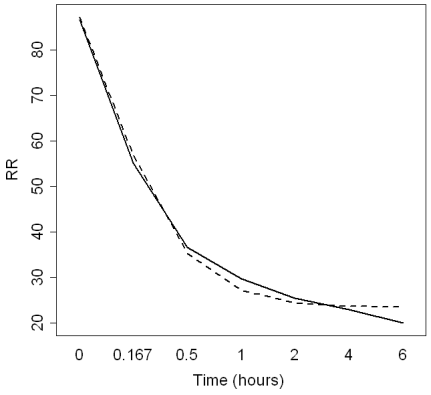
(b) *NHB Region 1*



(c) *HB Region 2*



(d) *HB Region 3*



(e) *NHB Region 3*

Fig. 3: *Mean original (solid) and fitted (dashed) RR profiles for both donor types and all donor regions*

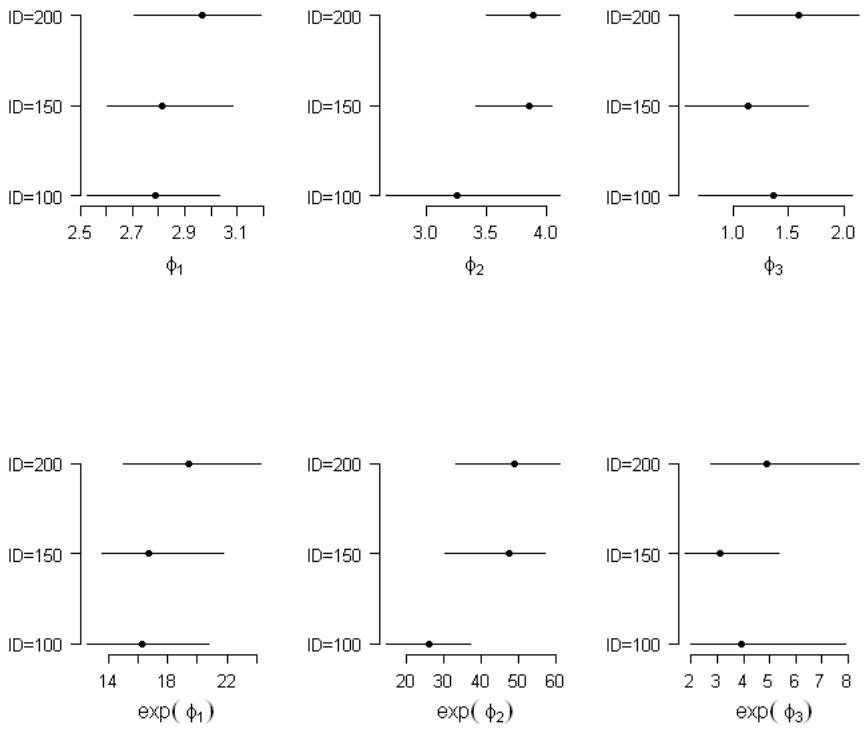


Fig. 4: *RR Parameter estimates from the nonlinear mixed model together with 25 % and 95% quartiles calculated using Monte Carlo method for arbitrary chosen individuals.*

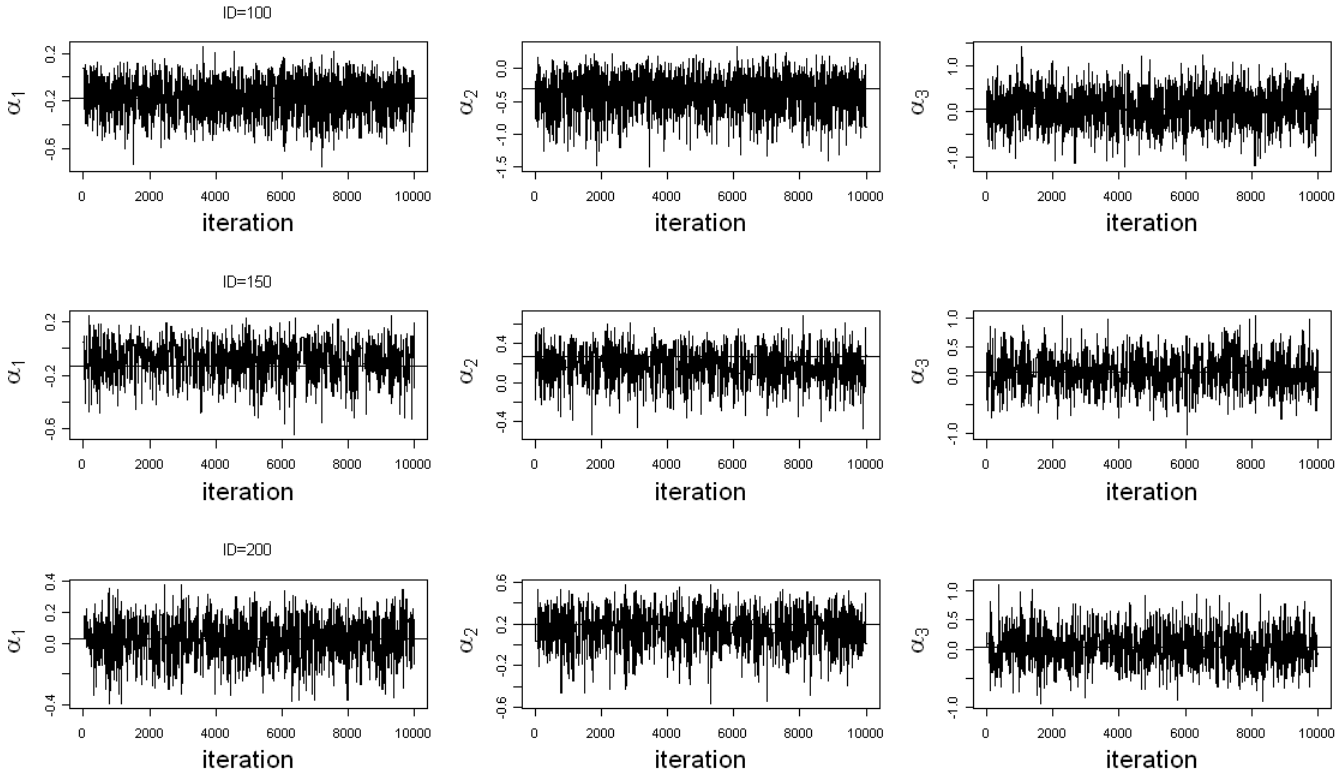


Fig. 5: *Random effects estimates together with EB (horizontal lines) estimates obtained from Monte Carlo sampling procedure for arbitrary chosen individuals.*