Joint Frailty Model of Recurrent and Terminal Events in ...

## Appendix. A.

In this appendix, we explain the structure of full likelihood

$$L(O \mid \omega_i) = \prod \int L(O_i \mid \omega_i) g(\omega_i) d\omega_i$$
, where

 $L_i(\lambda_0(.), h_0(.), \beta, \beta^*, \alpha, \theta) = L_i(O) \quad \text{for subject}$ i and  $(j = 1, 2, ..., n_i)$  such as,  $\delta_{(i, n_i + 1)} = 0$ .

1) we calculated the conditional likelihood for the patients who do not experience the occurrence of disease and observing death (ni = 0,  $\Delta_i = 1$ ), we have:

$$S_i^R(t_i \mid \omega_i) = \exp(-\omega_i \sum_{j=1}^{n_i+1} \int_{T_i(j-1)}^{T_{ij}} Y_i(t)\lambda_i(t)dt),$$
  
$$S_i^D(t_i^* \mid \omega_i) = \exp(-\omega_i \int_0^{T_i^*} Y_i(t)h_i(t)dt)$$

$$\begin{split} L_{i1} &= (1 - p_i) S_i^{R}(\mathbf{t}_i \mid \boldsymbol{\omega}_i, \mathbf{Y}_i = 1) \times \\ h_i(\mathbf{t}_i \mid \boldsymbol{\omega}_i, \mathbf{Y}_i = 1)^{\Delta_i} \times S_i^{D}(\mathbf{t}_i \mid \boldsymbol{\omega}_i, \mathbf{Y}_i = 1), \end{split}$$

1) We consider  $\omega_i : G(\frac{1}{\theta}, \frac{1}{\theta})$  with probability density  $\omega^{(\frac{1}{\theta}-1)} \exp(-\omega/2)$ 

$$f(\omega) = \frac{\omega^{\sqrt{\theta^{-1}}} \exp(-\omega/\theta)}{\Gamma(1/\theta)\theta^{(\frac{1}{\theta})}}$$

The contribution of marginal likelihood is obtained by integrating out the random effect  $(\sigma_i)$ .

$$L_{i1}(\mathbf{O} \mid \omega_{i}) = \frac{(1-\mathbf{p}_{i}) \times (\mathbf{h}_{i}(t_{i}^{*}))^{\Delta_{i}}}{\theta^{\frac{1}{\theta}} \Gamma(\frac{1}{\theta})} \times \int_{0}^{\infty} (\omega_{i}^{(\Delta_{i}+\frac{1}{\theta}-1)} \exp(-\omega_{i} \sum_{j=1}^{n_{i+1}} \int_{T_{i}(j-1)}^{T_{ij}} Y_{i}(t) \lambda_{i}(t) dt - \omega_{i} \int_{0}^{T_{i}^{*}} Y_{i}(t) \mathbf{h}_{i}(t) dt) - \frac{\omega_{i}}{\theta}) d\omega_{i}$$

In situation 2, we have subjects that experience the recurrent event  $n_i > 0$  and observing death  $\Delta_i = 1$ . The contribution of marginal likelihood for individual *i* can write:

$$L_{i2}(\mathbf{O} \mid \omega_{i}) = \frac{(1-p_{i}) \times \prod_{j=1}^{n_{i}+1} \lambda(t_{ij})^{\delta_{ij}} \times (\mathbf{h}_{i}(t_{i}^{*}))^{\Delta_{i}}}{\theta^{(1/\theta)} \Gamma(\frac{1}{\theta})} \times \int_{0}^{\infty} (\omega^{(\Delta_{i}+n_{i}+\frac{1}{\theta}-1)} \times \exp(-\omega_{i} \sum_{j=1}^{n_{i}+1} \int_{T_{i}(j-1)}^{T_{ij}}) X_{i}(t) \lambda_{i}(t) dt - \omega_{i} \int_{0}^{\infty} Y_{i}(t) \mathbf{h}_{i}(t) dt) - \frac{\omega_{i}}{\theta} d\omega_{i}$$

In situation 3, we have subjects that experience the recurrent event  $n_i > 0$  but no observing death  $\Delta_i = 0$ . the contribution of marginal likelihood for individual *i* can write: Joint Frailty Model of Recurrent and Terminal Events in ...

$$L_{i3}(\mathbf{O}) = \frac{(1-p_i) \times \prod_{j=1}^{n_i+1} \lambda(t_{ij})^{\delta_{ij}}}{\theta^{\binom{1}{j}} \Gamma(\frac{1}{\beta})} \times \int_{0}^{\infty} (\omega^{(n_i+\frac{1}{\theta}-1)}) \times \exp(-\omega_i \sum_{j=1}^{n_i+1} \int_{T_{i(j-1)}}^{T_{ij}} Y_i(t) \lambda_i(t) dt - \omega_i \int_{0}^{T_i^*} Y_i(t) h_i(t) dt) - \frac{\omega_i}{\theta} d\omega_i$$

In situation 4, we have subjects that experience  
neither recurrence nor death from the disease  
$$(n_i = 0, \Delta_i = 0).$$

$$L_{i4}(\mathbf{O}) = \frac{\mathbf{p}_i + (1 - p_i)}{\theta^{(\frac{1}{\theta})} \Gamma(\frac{1}{\theta})} \times \int_{0}^{\infty} (\omega^{(\frac{1}{\theta} - 1)} \times \exp(-\omega_i \sum_{j=1}^{n_i + 1} \int_{T_{i(j-1)}}^{T_{ij}} Y_i(t) \lambda_i(t) dt - \omega_i$$
$$\int_{0}^{T_i^*} Y_i(t) \mathbf{h}_i(t) dt - \frac{\omega_i}{\theta} d\omega_i$$

The marginal likelihood calculated by multiplying of the four marginal contribution of likelihood for subject *i* as follow

$$L(O_{i} | \omega_{i}) = L_{i1}^{I(n_{i}=0,\Delta_{i}=1)}$$
$$L_{i2}^{I(n_{i}=1,\Delta_{i}=1)}$$
$$L_{i3}^{I(n_{i}=1,\Delta_{i}=0)}$$
$$L_{i4}^{I(n_{i}=0,\Delta_{i}=0)}$$

We can obtain full log likelihood by sum of the four marginal contribution of log-likelihood for subject i as follow

$$l(O) = \sum_{i=1}^{4} l_i(O)$$

We can obtained the log-likelihood for gap times with replace

$$T_{ij}$$
 by  $S_{ij}$  and  $\int_{T_{i(j-1)}}^{T_{ij}}$  by  $\int_{0}^{S_{ij}}$ 

in expression of log-likelihood.