AMS 276
Lecture 5: Frailty Models

Fall 2016

- A frailty model is a **random effects model** for time variables.
- Random effects? Consider one-factor random effects model

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}, \quad i = 1, \ldots, n, \text{ and } j = 1, \ldots, m_i$$

e.g.: An experiment is designed to study the maternal ability of mice using litter weights of ten-day old litters. There are four mothers, each of which has six litters. $4 \times 6 = 24$

- y_{ij}: the weight of j-th litter corresponding to the i-th mouse, $i = 1, \ldots, n\,(= 4)$ and $j = 1, \ldots, m\,(= 6)$.
- μ: an overall mean effect $m_i = 6$ for all i
- τ_i: the effect due to the i-th mouse
- ϵ_{ij}: unobserved errors

- Consider one-factor random effects model

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}, \quad i = 1, \ldots, n, \text{ and } j = 1, \ldots, m$$

$\star\star$ (a) Maternal ability (τ_i) is certainly variable across parents.
(b) It is unlikely that the experimenter is interested in these four specific female mice.

$\Rightarrow$ Consider these mice to be a random sample from a very large population of mice, and τ_i is a random effect.

$\star\star$ μ is a constant.

$\star\star$ Both τ_i and ϵ_{ij} are random.

$\mu_i = \mu + \tau_i$

$\mu_i \overset{iid}{\sim} N(\mu, \sigma_\tau^2)$

$y_{ij} \overset{iid}{\sim} N(\mu_i, \sigma_\epsilon^2)$

- Consider one-factor random effects model

$$y_{ij} = \mu + \tau_i + \epsilon_{ij}, \quad i = 1, \ldots, n, \text{ and } j = 1, \ldots, m$$

w/o τ_i, $Var(y_{ij}) = \sigma_\epsilon^2$ — My $\hat{\sigma}_\epsilon^2 \approx$ true σ_ϵ^2 + true σ_τ^2

** A single random factor, Factor A with n levels

** **(Assumption)** Factor A has a large number of possible levels and n of these population levels is chosen at random for investigation. $\Rightarrow \tau_i$ is a random effect.

** $\tau_i \overset{iid}{\sim} N(0, \sigma_\tau^2)$, independent of ϵ_{ij}.

** $\epsilon_{ij} \overset{iid}{\sim} N(0, \sigma_\epsilon^2)$.

** The intra-class correlation, $\rho = \sigma_\tau^2/(\sigma_\tau^2 + \sigma_\epsilon^2)$.

$$\frac{Cov(y_{ij}, y_{ij'})}{\sqrt{Var(y_{ij})}\sqrt{Var(y_{ij'})}} = \frac{\sigma_\tau^2}{\sigma_\tau^2 + \sigma_\epsilon^2}$$

$Cov(y_{ij}, y_{i'j'})$

if $i = i'$ & $j = j'$ $\quad Var(y_{ij}) = \sigma_\tau^2 + \sigma_\epsilon^2 = Var(\mu + \tau_i + \epsilon_{ij})$

$= Var(\tau_i + \epsilon_{ij})$

$= Var(\tau_i) + Var(\epsilon_{ij})$

$= \sigma_\tau^2 + \sigma_\epsilon^2$

if $i = i'$ & $j \neq j'$ $\quad Cov(y_{ij}, y_{ij'}) = \sigma_\tau^2$

$= Cov(\mu + \tau_i + \epsilon_{ij}, \mu + \tau_i + \epsilon_{ij'})$

$= Cov(\tau_i + \epsilon_{ij}, \tau_i + \epsilon_{ij'})$

$= Var(\tau_i) = \sigma_\tau^2$

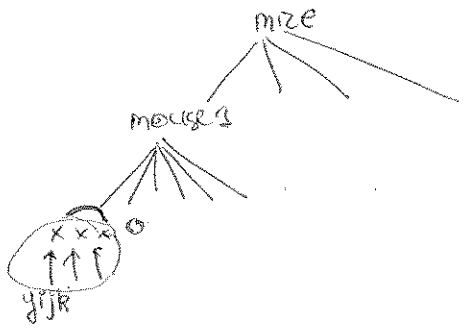
if $i \neq i'$

$Cov(y_{ij}, y_{i'j'}) = 0$

- "fixed" effects and "random effects" (taken from BDA page 391)

  The terms 'fixed' and 'random' come from the non-Bayesian statistical tradition and are somewhat confusing in a Bayesian context where all unknown parameters are treated as 'random.'
  ....

- Maybe helpful:
  `https://www2.stat.duke.edu/courses/Fall08/sta290/Lectures/randomeffects/randomeffects.pdf`



• So far we have assumed that the survival times of distinct individuals are independent of each other.

• This assumption may not be valid in some settings

e.g. a sample of siblings or litter mates, a sample of married couples.

$\Rightarrow$ It is so natural to assume that there is *some association* within a group of survival times in the sample.

$\Rightarrow$ How?

• ICS Chapter 4 & KM Chapter 13

- The hazard function for each individual may depend on
  - **Covariates**: known and measurable
  - **Frailty**:
    - unknown and unobservable random effects shared by subjects within a subgroup (cluster) $\Rightarrow$ can't explain
    - The frailty represents *the total effect on survival of the covariates not measured.* $\Rightarrow$ account for unobserved heterogeneity
    - Explicitly account for the extra variance associated with unmeasured risk factor.
    - Ignoring these effects $\Rightarrow$ Overdispersion and inconsistent estimate of β

- Frailties may be individual-specific ("individual frailty") and group-specific ("shared frailty").

- A common approach for the frailty model is a *common random effect* that acts *multiplicatively on the hazard rates* of all subgroup members.

w/o Frailty

$$h(y_{ij} \mid x_{ij}) = h_0(y_{ij})\, e^{\beta' x_{ij}} \times w_i$$

w_i

♣ Proportional Hazards Model with Frailty

- The conditional hazard function of y_{ij} is assumed to be

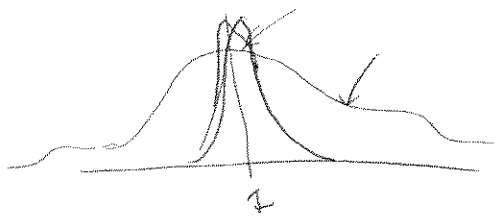
$$h(y \mid w_i, \mathbf{X}_{ij}) = h_0(y) w_i \exp(\mathbf{X}_{ij}' \beta).$$

- ⋆⋆ y_{ij}: the survival time for the j^{th} subject in the i^{th} cluster, $i = 1, \ldots, n$ and $j = 1, \ldots, m_i$ (m_i can be 1 for all i).
- ⋆⋆ $N = \sum_{i=1}^{n} m_i$: the total number of subjects
- ⋆⋆ w_i: unobserved frailty random variable for the i^{th} cluster
- ⋆⋆ β: $p \times 1$ vector of unknown regression coefficients
- ⋆⋆ $h_0(\cdot)$: unknown baseline hazard function *common* to every subject
- ⋆⋆ $\mathbf{X}_{ij}$: $p \times 1$ covariate vector for the j^{th} subject in the i^{th} cluster, and may be time dependent.

$h_0(y \mid w_i, x_{ij}) = h_0(y)\, w_i\, e^{x_{ij}'\beta}$

$w_i' = c \cdot w_i$

$h_0'(y) = \frac{1}{c} h_0(y)$



$h(y \mid w_i, x_{ij}) = h_0(y) \times 1 \times e^{x_{ij}'\beta}$

$u_i = 0 \Rightarrow w_i = 1$

- The baseline hazard function: remain unspecified as before.
- The distribution of the frailty: need to specify

$w_i > 0 \in \mathbb{R}^+$

$u_i \in \mathbb{R}$

$w_i = e^{u_i} \Leftrightarrow u_i = \log w_i$

- The conditional hazard function of y_{ij} is

$$h(y \mid w_i, \mathbf{X}_{ij}) = h_0(y) w_i \exp(\mathbf{X}_{ij}'\beta) = h_0(y) \exp(u_i + \mathbf{X}_{ij}'\beta).$$

$\star\star$ $u_i \overset{iid}{\sim} \mathrm{N}(0, \sigma^2)$ (similar to $\tau_i \overset{iid}{\sim} \mathrm{N}(0, \sigma_\tau^2)$ in the linear model)

Note: $\sigma^2 = 0 \Rightarrow$ the basic proportional hazards model

$\star\star$ w_i: iid sample from a distribution with mean 1 and some unknown variance. e.g. gamma, log-normal, inverse Gaussian...

$\in \mathbb{R}^+$

For cluster i, we have m_i individuals. y_{ij}, ν_{ij}, x_{ij}, ω_i $\quad j = 1, \dots, m_i$

$\mathbf{y}_i$, $\boldsymbol{\nu}_i$: m_i-dim vectors; $\mathbf{x}_i$: $m_i \times p$ matrix

$$\Rightarrow \quad f(\mathbf{y}_i, \boldsymbol{\nu}_i \mid \mathbf{x}_i, \omega_i, \beta) = \prod_{j=1}^{m_i} \left(h(y_{ij} \mid x_{ij}, \omega_i, \beta) \right)^{\nu_i} \times \exp\left(- H(y_{ij} \mid x_{ij}, \omega_i, \beta) \right)$$

$f(y) = h(y) S(y)$

$S(y) = e^{-H(y)}$

$$= \prod_{j=1}^{m_i} \left(h_0(y_{ij}) \, \omega_i \, e^{x_{ij}'\beta} \right)^{\nu_i} \; \circledast \; \exp\left(- H_0(y_{ij}) \, \omega_i \, e^{x_{ij}'\beta} \right)$$

$$\Rightarrow \quad f(y_i, \nu_i \mid x_i, \beta) = \int f(y_i, \nu_i \mid \omega_i, x_i, \beta) \, f(\omega_i \mid x_i, \beta) \, d\omega_i$$

$f(y_i, \nu_i, \omega_i \mid x_i, \beta)$

$$= \int \circledast \times \frac{(\kappa^{-1})^{\kappa^{-1}}}{\Gamma(\kappa^{-1})} \, \omega_i^{\kappa^{-1}-1} \exp(-\kappa^{-1}\omega_i) \, d\omega_i$$

$$= \prod_{j=1}^{m_i} \underbrace{\left(h_0(y_{ij}) \, e^{x_{ij}'\beta} \right)^{\nu_{ij}}}_{\alpha \gamma y^{\alpha-1}} \frac{(\kappa^{-1})^{\kappa^{-1}}}{\Gamma(\kappa^{-1})} \cdot \frac{\Gamma\left(\sum_{j=1}^{m_i} \nu_{ij} + \kappa^{-1} \right)}{\left(\underbrace{\sum_{j=1}^{m_i} H_0(y_{ij}) \, e^{x_{ij}'\beta}}_{\gamma y^{\alpha}} + \kappa^{-1} \right)^{\sum \nu_{ij} + \kappa^{-1}}}$$

$$\Rightarrow \quad f(y, \nu \mid x, \beta) = \prod_{i=1}^{m} f(y_i, \nu_i \mid x_i, \beta)$$

θ^{-1} $\quad E(w_i) = \frac{\kappa^{-1}}{\kappa^{-1}} = 1$

$\circlearrowleft$ Consider $\quad w_i \overset{iid}{\sim} \text{Gamma}(\kappa^{-1}, \kappa^{-1}) \quad \text{Var}(w_i) = \kappa$

- $\star\star$ For identifiability, we set the mean of the frailty distribution to be unity.
- $\star\star$ $\text{Var}(w_i) = \kappa$, so

  larger values of $\kappa \Rightarrow$ greater heterogeneity among clusters
- $\star\star$ Clusters with a larger value of the frailty (i.e., larger w_i) will experience the event at earlier times than clusters with smaller w_i.

$\circlearrowleft$ Use an E-M algorithm and obtain estimates.

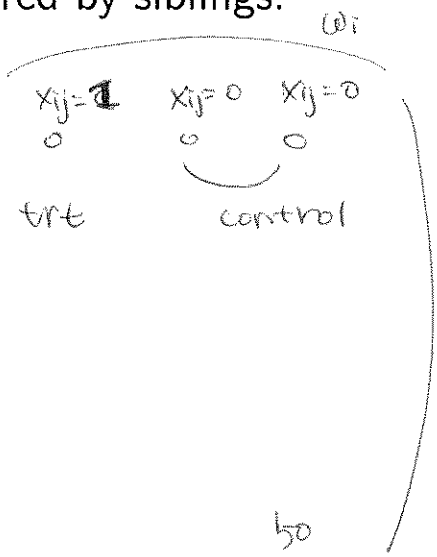
KM 13.3

Their θ = our κ

* [Example: K-M 13.1 (page 429)]

Mantel et al. (1977) reports the results of a litter-matched study of the tumorigenesis of a drug.

- ** Rats are taken from fifty distinct litters.
- ** One rat of the litter was randomly selected and given the drug.
- ** For each litter, two rats were selected as controls and were given a placebo.
- ** All mice were females.
- ** **Questions:** Associations between litter mates in their times to development of tumors may be due to common genetic backgrounds shared by siblings.



$*$ [Example: K-M 13.1 (page 429)] We use the proportional hazards model with gamma frailties;

$$h(y \mid w_i, X_{ij}) = h_0(y) w_i \exp(\beta X_{ij})$$

where X_{ij}, $i = 1, \ldots, 50$ and $j = 1, 2, 3$ is the indicator of treatment and w_i is shared frailty for litter i.

```
> library(KMsurv)  # To get the datasets in K-M
> library(survival) # R functions
>
> data(rats)
>
> rats_f <- rats[rats$sex=="f",]
> coxph.fit.frailty <- coxph(Surv(time, status) ~ as.factor(rx)
+ frailty(litter), data=rats_f)
```

$*$ We use the proportional hazards model with gamma frailties ($w_i \overset{iid}{\sim} \text{Gamma}(\kappa^{-1}, \kappa^{-1})$).

```
> coxph.fit.frailty <- coxph(Surv(time, status) ~ as.factor(rx)
+ frailty(litter), data=rats_f)
> coxph.fit.frailty
Call:
coxph(formula = Surv(time, status) ~ as.factor(rx) + frailty(litter),
    data = rats_f)

                     coef se(coef)    se2  Chisq   DF      p
as.factor(rx)1   0.914    0.323  0.319  8.012  1.0  0.0046
frailty(litter)                       17.692 14.4  0.2443

Iterations: 6 outer, 24 Newton-Raphson
     Variance of random effect= 0.499  I-likelihood = -180.8
Degrees of freedom for terms=  1.0 14.4
Likelihood ratio test=37.6  on 15.4 df, p=0.00124  n= 150
```

$**$ $\hat{\kappa} = 0.499$.

Hb. $k = 0 \Rightarrow$ no heter- —

$**$ No significant random effects based on its p-value (usually not a primary interest).

* We use the proportional hazards model with gamma frailties (fixed $\kappa = \theta = 1$).

```
> coxph.fit.frailty.1 <- coxph(Surv(time, status) ~ as.factor(rx)
+ frailty(litter, theta=1), data=rats_f)
> coxph.fit.frailty.1
Call:
coxph(formula = Surv(time, status) ~ as.factor(rx) + frailty(litter,
    theta = 1), data = rats_f)

                          coef se(coef)    se2  Chisq   DF      p
as.factor(rx)1           0.927    0.328  0.322  7.994  1.0 0.0047
frailty(litter, theta = 1                      27.496 22.7 0.2238

Iterations: 1 outer, 6 Newton-Raphson
     Variance of random effect= 1   I-likelihood = -181.3
Degrees of freedom for terms=  1.0 22.7
Likelihood ratio test=51.2  on 23.7 df, p=0.000878  n= 150
```

** κ is fixed at 1.

* We use the proportional hazards model with log-normal frailties ($\log(w_i) \overset{iid}{\sim} N(0, \sigma^2)$).

** We can choose "gamma"(default), "gaussian" or "t" distribution for frailties.

```
> coxph.fit.frailty.2 <- coxph(Surv(time, status) ~ as.factor(rx)
+ frailty(litter, distribution="gaussian"), data=rats_f)
> coxph.fit.frailty.2
Call:
coxph(formula = Surv(time, status) ~ as.factor(rx) + frailty(litter,
    distribution = "gaussian"), data = rats_f)

                           coef se(coef)    se2  Chisq   DF      p
as.factor(rx)1            0.913    0.323  0.319  8.011  1.0 0.0046
frailty(litter, distribut                        15.567 11.9 0.2056

Iterations: 6 outer, 21 Newton-Raphson
     Variance of random effect= 0.412
Degrees of freedom for terms=  1.0 11.9
Likelihood ratio test=35.3  on 12.9 df, p=0.000711  n= 150
```

** $\hat{\sigma}^2 = 0.412$.

** No significant random effects based on its p-value.

* [Example: K-M 13.1 (page 429)] We use the proportional hazards model **without** frailties.

```
> coxph.fit <- coxph(Surv(time, status) ~ as.factor(rx), method="breslow",
data=rats_f)
> coxph.fit
Call:
coxph(formula = Surv(time, status) ~ as.factor(rx), data = rats_f,
    method = "breslow")


                 coef exp(coef) se(coef)    z      p
as.factor(rx)1 0.898     2.455    0.317 2.83 0.0047

Likelihood ratio test=7.87  on 1 df, p=0.00503
n= 150, number of events= 40
```

$$S(t) = e^{-H(t)}$$

$$H(t) = -\log(S(t))$$

$$h(t) = -\frac{d \log S(t)}{dt}$$

$$h(y \mid x_{ij}, \beta, \omega_i) = h_0(y)\, \omega_i\, e^{x_{ij}'\beta}$$

$$h(y \mid x_{ij}, \beta)$$

- The conditional survival function (conditional on w_i):

$$S(t \mid \omega, x) = \exp\left(-\int_0^t h_0(u)\, \omega\, e^{x'\beta}\, du \right)$$

$$= \exp\left(-H_0(t)\, \omega\, e^{x'\beta} \right)$$

- The marginal survival function (marginalized over w_i):

$$S(t \mid x) = \int_0^\infty \underbrace{\exp\left(-H_0(t) \cdot \omega e^{x'\beta} \right)}_{S(t \mid \omega, x)} \cdot \underbrace{\frac{(k^{-1})^{k^{-1}}}{\Gamma(k^{-1})}\, \omega^{k^{-1}-1}\, e^{-k^{-1}\omega}}_{f(\omega)}\, d\omega$$

$$= \frac{(k^{-1})^{k^{-1}}}{\Gamma(k^{-1})} \cdot \frac{\Gamma(k^{-1})}{(k^{-1} + H_0(t)\, e^{x'\beta})^{k^{-1}}}$$

$$= \frac{(k^{-1})^{k^{-1}}}{(k^{-1} + H_0(t)\, e^{x'\beta})^{k^{-1}}}$$

- The marginal hazard function:

$$\Rightarrow h(t \mid X) = \frac{h_0(t)\, e^{X'\beta}}{1 + K\, H_0(t)\, e^{X'\beta}}$$

as $K \to 0$ ($\Leftrightarrow \mathrm{Var}(\omega_i) \to 0$)

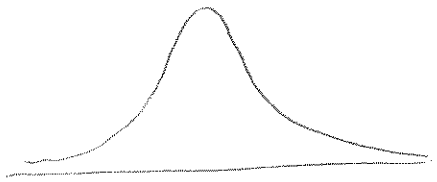
$$h(t \mid X) \longrightarrow h_0(t)\, e^{X'\beta}$$

$$\frac{h(t \mid X)}{h_0(t)} = e^{X\beta}$$

* Recall that the ratio of conditional hazards is a constant.

* Observe that the marginal relationship between the hazard and covariates *no longer* follows the proportional hazards model!

$f(x) \propto e^{-\frac{(x-\mu)^2}{2\sigma^2}}$



- *Alternative distribution for w_i:* Positive Stable Frailties (ICS 4.1.4)

ICS $\alpha \in (0, 2)$

⋆⋆ $w_i \overset{iid}{\sim} \underline{\text{PS}}(\alpha)$ with Laplace transform

$$\mathrm{E}(\exp(-sw)) = \exp(-s^{\alpha}),$$

for $0 < \alpha < 1$.

no closed form expression for the density function

⋆⋆ Infinite mean & no moments exist.

⋆⋆ The marginal survival function.

$$S(t \mid x) = \int_0^{\infty} \exp\left(-H_0(t)\, \omega\, e^{x'\beta}\right) p(\omega)\, d\omega$$

$$= E\left(\exp\left(-\underbrace{H_0(t)\, e^{x'\beta}}_{s} \cdot \omega\right)\right)$$

$$= \exp\left(-\left(H_0(t)\, e^{x'\beta}\right)^{\alpha}\right)$$

$S(t) = e^{-H(t)}$

$\star\star$ The marginal cumulative hazard function.

$$H(t \mid x) = -\log(S(t \mid x))$$

$$= H_0^{\alpha}(t)\, e^{\alpha x'\beta}$$

Basic: $h(t \mid x) = h_0(t)\, e^{x\beta}$

$$\frac{h(t \mid x)}{h_0(t)} = e^{x\beta}$$

$\star\star$ The marginal hazard function.

$$h(t \mid x) = \alpha\, H_0^{\alpha-1}(t)\, h_0(t)\, e^{\alpha x'\beta}$$

$$\boxed{e^{\alpha x'\beta}}$$

$\Rightarrow$ marginal hazards are also proportional.

$\star\star$ Interpretation of α: the attenuation of β in the marginal hazard.

$\in (0, 1)$

$\star\star$ The marginal hazards are also proportional!

$\star\star$ The computation is not so simple. Please check ICS 4.1.4.

♣ Bayesian Proportional Hazards Model with Frailty

$$h(y \mid w_i, \mathbf{X}_{ij}) = h_0(y) w_i \exp(\mathbf{X}'_{ij}\beta).$$

- The baseline hazard function e.g.
  - ⋆⋆ Weibull baseline hazard (parametric)
  - ⋆⋆ A gamma process prior on the cumulative baseline hazard
  - ⋆⋆ Piecewise exponential baseline hazards...
- The distribution of the frailty

e.g. gamma, log-normal, inverse Gaussian...

- *Example 1:* Weibull Model with Gamma Frailty (ICS 4.1.1)

$\Leftrightarrow$ The Weibull for the baseline hazard and gamma for frailties!

- Observed data: $\mathcal{D}_{obs} = (\mathbf{y} = \{y_{ij}\}, \boldsymbol{\nu} = \{\nu_{ij}\}, \mathbf{X} = \{\mathbf{X}_{ij}\})$, $i = 1, \ldots, n$ (clusters) and $j = 1, \ldots, m_i$ (subjects)

- Complete data: $\mathcal{D} = (\mathbf{y}, \boldsymbol{\nu}, \mathbf{X}, \underline{\mathbf{w}})$

- The Weibull baseline hazard function:

$$h_0(y) = \underline{\gamma \alpha y^{\alpha - 1}},$$

where (γ, α) are the parameters of the Weibull distribution.

- The conditional hazard function becomes

$$h(y_{ij} \mid \mathbf{X}_{ij}, w_i) = h_0(y_{ij}) w_i \exp(\mathbf{X}_{ij}'\beta) = \gamma\alpha y_{ij}^{\alpha-1} w_i \theta_{ij},$$

where $\theta_{ij} = \exp(\mathbf{X}_{ij}'\beta)$.

- $w_i \overset{iid}{\sim} \text{Gamma}(\kappa^{-1}, \kappa^{-1})$.
- The observed data likelihood can be obtained by integrating out w_i, but the likelihood becomes too complicate. So, we condition on w_i (as we imputed y for subjects with censored time).
- We need to specify priors for β, α, γ and $\eta = \kappa^{-1}$.

  e.g. $\beta \sim \text{N}_p$, $\alpha \sim$ Gamma, $\gamma \sim$ Gamma and $\eta \sim \pi(\cdot)$.

  * This approach is also called the multiplicative Weibull model formulation.

- The complete data likelihood is given by

$$\mathcal{L}(\beta, \gamma, \alpha, \eta | \mathcal{D}) = \prod_{i=1}^{n} \prod_{j=1}^{m_i} (\gamma \alpha y_{ij}^{\alpha-1} w_i \theta_{ij})^{\nu_{ij}} \exp\{-\gamma y_{ij}^{\alpha} \theta_{ij} w_i\}.$$

$$\pi(\omega, \gamma, \alpha, \beta, \eta \mid D) \propto \mathcal{L}(\beta, \gamma, \alpha, \eta \mid D) \times \pi(\omega \mid \eta^{K-1}) \pi(\eta) \times \pi(\beta) \pi(\gamma) \pi(\alpha)$$

- What to draw through MCMC?

$$\mathbf{w}, \boldsymbol{\beta}, \gamma, \alpha, \eta$$

The full conditionals;

- w_i
- $\boldsymbol{\beta} \sim \pi(\boldsymbol{\beta})$
- $\gamma \sim \pi(\gamma)$
- $\alpha \sim \pi(\alpha)$
- $\eta = \kappa^{-1}$

- (ICS Example 4.3) Kidney Infection Data:
  - From 38 kidney patients using portable dialysis equipment.
  - Recorded the times of infection from tie time of insertion of the catheter (thin plastic tube) for first and second infections.

    " A nephrostomy tube is a catheter (thin plastic tube) that is inserted through your skin and into your kidney. The nephrostomy tube is placed to drain urine from your kidney into a collecting bag outside your body. You may need one tube for each kidney." from Googling
  - After the occurrence or censoring of the first infection, sufficient time was allowed for the infection to be cured before the second insertion was allowed.
  - Covariates: Sex, age and disease types

Fall 16 – AMS276 Project 1

Due: Tuesday November 15.

The project is to reproduce part of results given in ICS Example 4.3 (page 109). We consider the kidney infection data given in Example 1.4. Please read Example 1.4 and the paper by McGilchrist and Aisbett (1991) (posted on our course website) for detailed description of the data. The data text file is separately posted.

We consider the shared frailty model;

$$h(y_{ij} \mid w_i, \boldsymbol{x}_{ij}) = h_0(y_{ij}) w_i \exp(\boldsymbol{x}_{ij}'\boldsymbol{\beta}).$$

We include two covariates ($p = 2$): age of the patient at the time of each infection and sex of the patient. We consider the following two models for $h_0(t)$;

- **Model II** Fit the Weibull baseline hazard with multiplicative gamma frailties. That is, we assume the Weibull baseline hazard function

  $$h_0(y_{ij}) = \gamma\alpha y_{ij}^{\alpha-1},$$

  where (γ, α) are the parameters of the Weibull distribution. We use the gamma frailty model, $w_i \overset{iid}{\sim} \text{Gamma}(\kappa^{-1}, \kappa^{-1})$. Priors for $\eta = \kappa^{-1}$, $\boldsymbol{\beta}$, γ and α are specified as follows;

  $$\eta \sim \text{Gamma}(\phi_1, \phi_2), \quad \boldsymbol{\beta} \sim \text{N}_2(\bar{\boldsymbol{\beta}}, \Sigma), \quad \gamma \sim \text{Gamma}(\rho_1, \rho_2), \text{ and } \alpha \sim \text{Gamma}(a_1, a_2).$$

  (The book has a typo in line 1 below eq (4.1.13). κ should be κ^{-1}.)

  The hyperparameter values used in Example 4.3 are $\phi_1 = \phi_2 = 0.001$, $\bar{\boldsymbol{\beta}} = \mathbf{0}$, $\Sigma = \text{diag}(10^3, 2)$, $\rho_1 = \rho_2 = 0.001$, $a_1 = a_2 = 0.001$.

  (There is another typo in line 6 of paragraph 2. ".... For Models II (not III) and IV ....").

  The posterior is estimated and summarized in Tables 4.3 and 4.4. In Table 4.4, there is μ in the first column. That is γ under Model II (i.e., their posterior mean estimate of γ is 0.016).

1. Derive the full conditionals and implement the model. Check mixing of your MCMC chain and provide some evidence of showing good convergence.

   (There is a typo in full conditional derivation in 4.1.1. Please derive the full conditionals carefully.)

2. Summarize your posterior and compare to the results given in the tables. You can also check with my results that will be illustrated in class.

3. Interpret your posterior estimates.

4. Fit a comparable frequentiest model and compare the inferences.

Table 1
Recurrence data and frailty estimates

Patient number	Recurrence times	Event types	Age	Sex	Disease type	Frailty estimate
1	8, 16	1, 1	28	1	3	2.3
2	23, 13	1, 0	48	2	0	1.9
3	22, 28	1, 1	32	1	3	1.2
4	447, 318	1, 1	31–32	2	3	.5
5	30, 12	1, 1	10	1	3	1.5
6	24, 245	1, 1	16–17	2	3	1.1
7	7, 9	1, 1	51	1	0	3.0
8	511, 30	1, 1	55–56	2	0	.5
9	53, 196	1, 1	69	2	1	.7
10	15, 154	1, 1	51–52	1	0	.4
11	7, 333	1, 1	44	2	1	.6
12	141, 8	1, 0	34	2	3	1.2
13	96, 38	1, 1	35	2	1	1.4
14	149, 70	0, 0	42	2	1	.4
15	536, 25	1, 0	17	2	3	.4
16	17, 4	1, 0	60	1	1	1.1
17	185, 177	1, 1	60	2	3	.8
18	292, 114	1, 1	43–44	2	3	.8
19	22, 159	0, 0	53	2	0	.5
20	15, 108	1, 0	44	2	3	1.3
21	152, 562	1, 1	46–47	1	2	.2
22	402, 24	1, 0	30	2	3	.6
23	13, 66	1, 1	62–63	2	1	1.7
24	39, 46	1, 0	42–43	2	1	1.0
25	12, 40	1, 1	43	1	1	.7
26	113, 201	0, 1	57–58	2	1	.5
27	132, 156	1, 1	10	2	0	1.1
28	34, 30	1, 1	52	2	1	1.8
29	2, 25	1, 1	53	1	0	1.5
30	130, 26	1, 1	54	2	0	1.5
31	27, 58	1, 1	56	2	1	1.7
32	5, 43	0, 1	50–51	2	1	1.3
33	152, 30	1, 1	57	2	2	2.9
34	190, 5	1, 0	44–45	2	0	.7
35	119, 8	1, 1	22	2	3	2.2
36	54, 16	0, 0	42	2	3	.7
37	6, 78	0, 1	52	2	2	2.1
38	63, 8	1, 0	60	1	2	1.2

gence occurs. Estimates of β together with standard errors are:

Variable	*Age*	*Sex*	*GN*	*AN*	*PKD*
Regression coefficient estimate	.0063	−1.7947	.2062	.4099	−1.2961
Standard error	.0134	.4337	.4840	.4937	.7120

Estimates of frailties are listed in the last column of Table 1.

The estimate of σ^2 is .3821. In general, the effect of the prior distribution on frailty terms is to shrink estimates toward the origin, thereby biasing the estimate of σ^2. Nevertheless the frailty estimates given in Table 1 appear very reasonable. The only regression coefficient that is significantly large compared to its standard error is that of the sex variable, indicating a lower infection rate for female patients.