Oct - 25

$h(t|X) = h_0(t)\, e^{\beta^T X}$

$h_0(t)$: time-varying

$e^{\beta^T X}$: remains constant over time

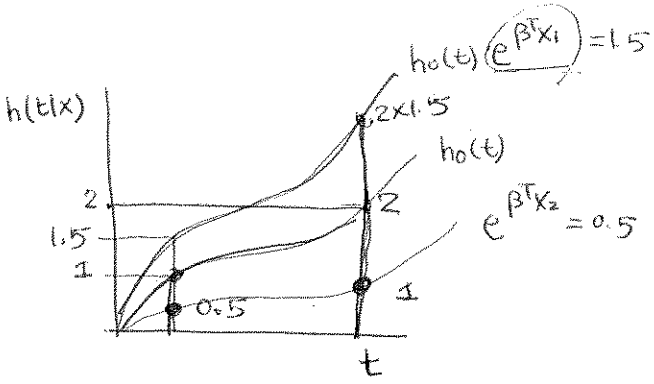
- Two ways to make $e^{\beta^T X}$ vary over time

  $\beta(t)$ small for small t

  $\beta(t)$ large for large t

① time-dependent covariates $\quad X \longrightarrow X(t)$

② covariates have time-dependent effect $\quad \beta \longrightarrow \beta(t)$



$$\frac{h(t|X_1)}{h_0(t)} = e^{\beta^T X_1}$$

$$H(t|X) = \int_0^t h_0(u)\, e^{\beta^T X}\, du = H_0(t)\, e^{\beta^T X}$$

$$e^{\beta^T X_1} < e^{\beta^T X_2} \Rightarrow H(t|X_1) < H(t|X_2) \quad \text{for all } t$$

$$S(t|X_1) = e^{-H(t|X_1)} \qquad S(t|X_2) = e^{-H(t|X_2)}$$

$$\frac{h(t|X_1)}{h(t|X_2)} = \frac{h_0(t)\, e^{\beta^T X_1(t)}}{h_0(t)\, e^{\beta^T X_2(t)}}$$

- ICS Chapter 7 has three examples of joint modeling, AIDS studies (7.1.1), cancer vaccine studies (7.1.2) and health-related quality of life studies (7.1.3)

- We will closely follow the cancer vaccine study example. Also, check Brown and Ibrahim (2003).
  posted

- In cancer vaccine (immunotherapy) trials, vaccinations are given to patients to raise the patient's antibody levels against the tumor cells.

- A successful vaccine activates the patient's immune system against future tumor growth.

  ** time to recurrence of a tumor

  ** Immunologic measures (IgM titre levels) are taken repeatedly during follow-up (believed to be predictive of tumor recurrence).

time-varying covariate

patient's antibody production ↑ (⇒ IgM titre measure) ↑

⇒ body's immune strength ↑

⇒ eradicate and prevent future tumors

Immunoglobulin M (IgM)

From Wikipedia, the free encyclopedia

Immunoglobulin M, or **IgM** for short, is a basic antibody that is produced by B cells. IgM is by far the physically largest antibody in the human circulatory system. It is the first antibody to appear in response to initial exposure to an antigen.[1][2] The spleen, where plasmablasts responsible for antibody production reside, is the major site of specific IgM production.[3][4]

B cell

From Wikipedia, the free encyclopedia

This article is about the immune system cell. For the electrical cell, see Battery (vacuum tube).

B cells, also known as **B lymphocytes**, are a type of white blood cell of the lymphocyte subtype.[1] They function in the humoral immunity component of the adaptive immune system by secreting antibodies.[2] Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines.[1]

In mammals, B cells mature in the bone marrow, which is at the core of most bones.[2] In birds, B cells mature in the bursa of Fabricius, a lymphoid organ. (The "B" from B cells comes from the name of this organ, where it was first discovered by Chang and Glick,[2] and not from bone marrow as commonly believed).

- Examining the association between the antibody measures and survival $\Rightarrow$ Understanding the biological pathways of the disease
- The longitudinal measures may be associated with survival.
- **However**, the antibody measures are prone to measurement error; therefore, the raw data should not be used in a survival analysis.
- Specify the likelihood for the joint model,

$$p(\mathbf{X}, \mathbf{y} \mid \theta) = p(\mathbf{X} \mid \theta) p(\mathbf{y} \mid \mathbf{X}, \theta).$$

where $\mathbf{X}$ and $\mathbf{y}$ are longitudinal measurements and survival times, respectively, and θ denotes all unknown parameters.

- Data (followed the book notation but the notation in the paper is different):
  - ⋆⋆ Longitudinal measurements, x_{ij}, $j = 1, \ldots, m_i$, taken at time t_{ij} from patient i.
  - ⋆⋆ Survival time and censoring indicator for subject i, y_i and ν_i.

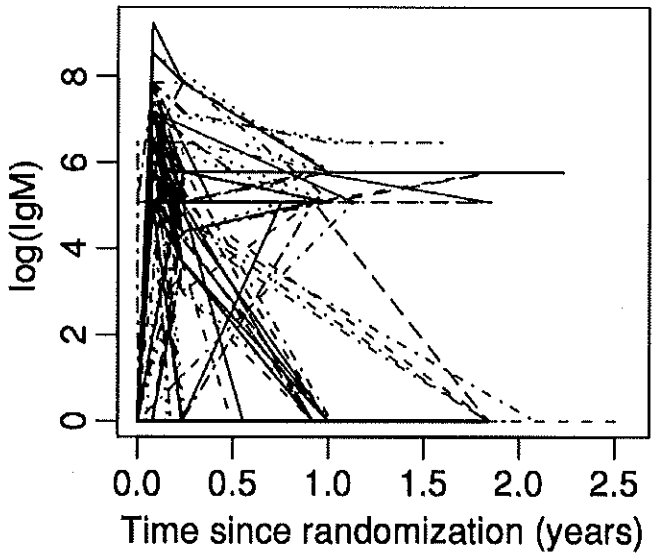


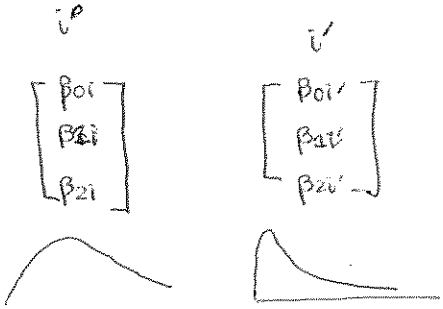
Figure 1. Observed trajectories of IgM for all 224 patients.

- Model for the longitudinal measure x_{ij}, $i = 1, \ldots$ and $j = 1, \ldots, m_i$.

$$x_{ij} = \psi_\beta(t_{ij}) + \epsilon_{ij},$$

where $x_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + \beta_{2i} t_{ij}^2 + \epsilon_{ij}$

  - $\psi_\beta(t)$ is the trajectory function (unknown true covariate).
  - Measurement error, $\epsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2)$
  - The trajectory function $\psi_\beta(t)$ can take on many forms.



- As a specific form, consider a quadratic form by

$$\psi_\beta(t_{ij}) = \beta_{0i} + \beta_{1i} t_{ij} + \beta_{2i} t_{ij}^2$$

  - ⋆⋆ This form can reflect an initial increase in antibody levels in response to cancer vaccine therapy, followed by a decline as the treatment begins to wear off.
  - ⋆⋆ β is indexed by i to allow between-patient variability for longitudinal measurements.

Proportional hazards

$h_0(t) = \gamma \alpha t^{\alpha-1}$ $\Leftrightarrow$ $W_i \sim$ Standard EV

Equi

Standard EV $\Rightarrow$ Weibull

$\log(t_i) = \mu + \tilde{\gamma}\psi_\beta(t) + z'\tilde{\alpha} + \sigma W_i$, $W_i \sim$

- Model for survival y_i, $i = 1, \ldots, n$.

$$h(t \mid X) = h_0(t) \exp\{\gamma \psi_\beta(t) + \mathbf{z}'\alpha\},$$

where

- $h_0(t)$: baseline hazard
- γ: a scale parameter linking the trajectory to the hazard function
- α: a parameter vector linking a vector $\mathbf{z}$ of baseline covariates to the failure time

$\beta_i = \begin{bmatrix} \beta_{0i} \\ \beta_{1i} \\ \beta_{2i} \end{bmatrix}$, γ, α, $h_0(t)$

- For the baseline hazard,
  - ⋆⋆ Construct a finite partition of the time axis, $0 < s_1 < s_2 < \ldots < s_J$ with $s_J > \max(y_i)$.

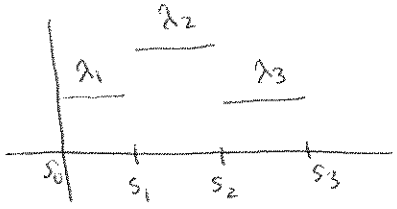
    $\Rightarrow$ we have the J intervals, $(0, s_1]$, $(s_1, s_2]$,..., $(s_{J-1}, s_J]$.
  - ⋆⋆ Assume piecewise constant hazards

$$h_0(t) = \lambda_j, \quad s_{j-1} < t \leq s_j, j = 1, \ldots, J$$

↻ We know

$$f(y_i, \nu_i \mid \mathbf{X}_i) = \{h(y_i \mid \boldsymbol{\theta}, \mathbf{X}_i)\}^{\nu_i} \{\exp(-H(y_i \mid \boldsymbol{\theta}, \mathbf{X}_i))\}$$

where $H(y_i \mid \boldsymbol{\theta}, \mathbf{X}_i)$ is the cumulative hazard.



↻ Find the cumulative hazard!

$$H(y \mid \theta, x) = \int_0^y h_0(u) \cdot e^{\gamma \psi_\beta(u) + z'\alpha} \, du$$

$$= e^{z'\alpha} \int_0^y h_0(u) \, e^{\gamma \psi_\beta(u)} \, du \qquad \begin{matrix} y > s_j, & s_j \\ y < s_j, & y \end{matrix}$$

$$= e^{z'\alpha} \cdot \sum_{j=1}^{J} \lambda_j \, I(y > s_{j-1}) \cdot \int_{s_{j-1}}^{\min(y, s_j)} e^{\gamma \psi_\beta(u)} \, du$$

$= H_{ij}(\beta, \gamma, \lambda)$

no analytic solution w/ $\psi_\beta(u) = \beta_0 + \beta_1 u + \beta_2 u^2$

$\Rightarrow$ numerical integration is needed

$$\delta_{ij} = \begin{cases} 1 & \\ 0 & \end{cases} \qquad y_i \in I_j = (s_{j-1}, s_j]$$

- The joint likelihood

$$\mathcal{L}_i = \prod_{j=1}^{J} \left\{ \lambda_j e^{\gamma \varphi_\beta(y_i) + z_i'\alpha} \right\}^{\nu_i \cdot \delta_{ij}} \exp\left(- e^{z_i'\alpha} \sum_{j=1}^{J} H_{ij}(\beta, \gamma, \lambda) \right)$$

$$\times \frac{1}{(2\pi\sigma^2)^{m_i/2}} \exp\left(- \frac{1}{2\sigma^2} \sum_{j=1}^{m_i} \left(x_{ij} - \varphi_\beta(t_{ij}) \right)^2 \right)$$

- Priors:
  - ⋆⋆ Recall all random parameters $\boldsymbol{\theta} = (\boldsymbol{\beta}, \sigma^2, \gamma, \boldsymbol{\lambda}, \alpha)$.
  - ⋆⋆ Conjugate prior for the underlying hazard, $\lambda_j \overset{indep}{\sim} \text{Gamma}(a_j, b_j), j = 1, \ldots, J$
  - ⋆⋆ Error variance, $\sigma^2 \sim \text{IG}(a, b)$
  - ⋆⋆ Let $\gamma \sim \text{N}(\mu_\gamma, \sigma^2_\gamma)$.
  - ⋆⋆ For the baseline covariate parameter vector, $\alpha \sim \text{N}(\mu_\alpha, \Sigma_\alpha)$.
  - ⋆⋆ To relax the distributional assumption on the $\boldsymbol{\beta}_i$'s, assume

$$\boldsymbol{\beta}_i \overset{iid}{\sim} G, \quad G \sim \text{DP}(MG_0), \quad \text{and} \quad G_0 = \text{N}_3(\boldsymbol{b}_0, V_0),$$

where $\boldsymbol{b}_0 = [b_{00}, b_{01}, b_{02}]' \sim \text{N}_3(\bar{b}_0, W)$ and $V_0 \sim$ Inv-Wishart.

~~$\beta_i \overset{iid}{\sim} N_3(\bar{b}_0, W)$~~

$\beta_i \overset{iid}{\sim} N_3(b_0, V_0)$

$b_0 \sim N_3(\bar{b}_0, W)$

- Posterior inference

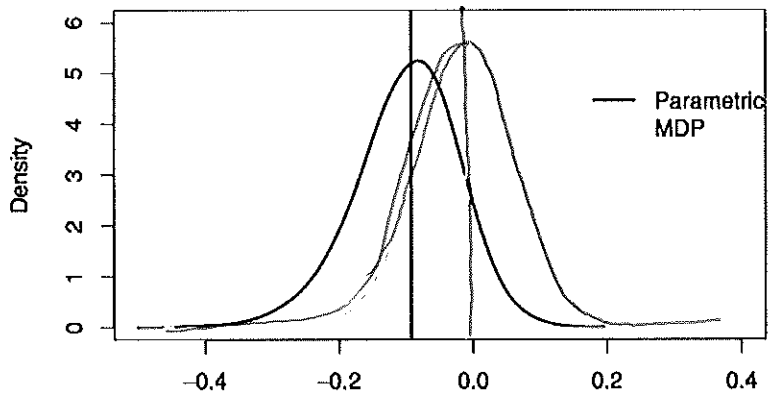


Figure 2. Posterior densities of γ for study E1694 for the MDP model (dashed line) and the parametric model (solid line). The vertical lines represent the posterior medians.

$\beta_{0i} + \beta_{1i} t_{ij} + \beta_{2i} t_{ij}^2$

- Posterior inference

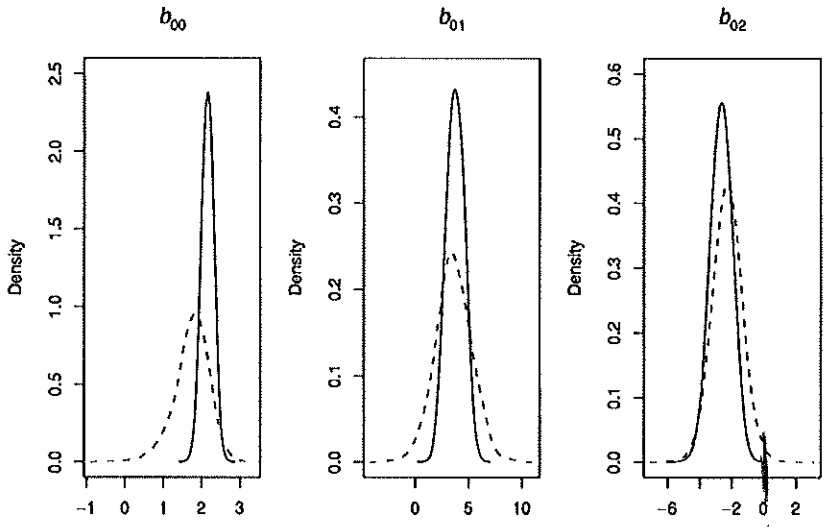


Figure 3. Posterior density estimates of $b_0 = (b_{00}, b_{01}, b_{02})'$ from the MDP model (dashed line) and the parametric model (solid line).

- Posterior inference

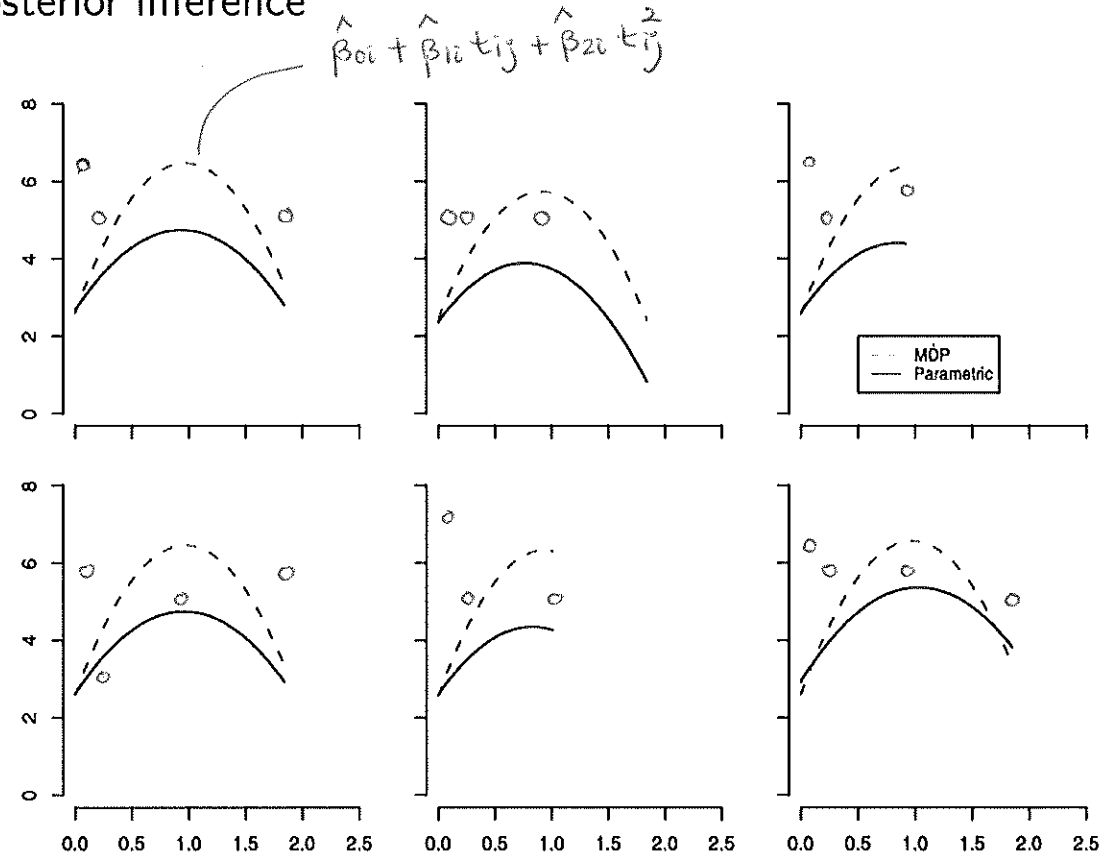


Figure 4. Sample trajectories and their fits with $J = 8$ for 6 patients. The circles represent the observed data.

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

$$\log(h(t \mid x)) = \log(h_0(t)) + \beta^T x$$

♣ One last comment on the regression model (ICS 10.6)

- So far, we have

$$\log(h(t \mid \mathbf{X})) = \beta_0(t) + \sum_{j=1}^{p} x_j \beta_j,$$

where

- $\beta_0(t)$ is the log-baseline hazard function
- β_j, $j = 1, \ldots, p$: parameters which modulate the effects of the explanatory variables.

- Sometimes the proportional hazards assumption is not appropriate.

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

- $h_0(t) = \lambda_j$ if $t \in I_j = (s_{j-1}, s_j]$
- $\beta(t) = \beta_j$ if $t \in I_j \in (s_{j-1}, s_j]$

• Generalize the model to allow the covariate effects to depend on time,

$$\log(h(t \mid \mathbf{X})) = \beta_0(t) + \sum_{j=1}^{p} x_j \beta_j(t).$$

⋆⋆ Many authors have suggested particular forms for the time dependence in $\beta_j(t)$.

↺ One simple example (Gamerman, 1991 and Murray et al, tech. report): Consider the piecewise constant model,

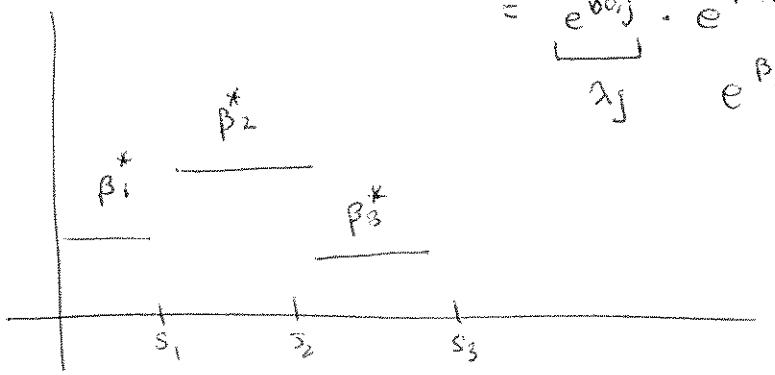
$$h(t \mid \gamma) = \exp(\gamma_j), \quad \text{for } t \in (s_{j-1}, s_j], \quad j = 1, \ldots, J.$$

Extend the model,

$$h(t \mid X, \gamma) = \exp(\gamma_{0,j} + \gamma_{1,j} X)$$

$$= \underbrace{e^{\gamma_{0,j}}}_{\lambda_j} \cdot e^{\gamma_{1,j} X}$$

$$e^{\beta_j X}$$



- The assumption that the covariates effects act additively can be too restrictive, e.g. neural networks (Ripley, 1994).

- Generalize the model to allow the nonadditive covariate effects,

$$\log(h(t \mid \mathbf{X})) = \beta_0(t) + \sum_{j=1}^{p} x_j \psi\Big(\sum_{k \neq j} w_{ij} x_k\Big) \beta_j(t).$$

where

$\star\star$ $\psi(\cdot)$: activation function with $\psi(0) = 1$

$\star\star$ Interesting? Read Chapter 10.6 for more!

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.

- 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 single random factor, Factor A with n levels

$\star\star$ **(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.

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

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

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

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

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

if $i = i'$ & $j \neq j'$ $\quad$ ~~$Cov(y_{ij}, y_{i'j'})$~~

$Cov(y_{ij}, y_{ij'}) = \sigma_\tau^2$

if