Appetizers: By A. Einstein

- The important thing is not to stop questioning. Curiosity has its own reason for existing. One cannot help but be in awe when he contemplates the mysteries of eternity, of life, of the marvelous structure of reality. It is enough if one tries merely to comprehend a little of this mystery every day. Never lose a holy curiosity.
- Reading, after a certain age, diverts the mind too much from its creative pursuits. Any man who reads too much and uses his own brain too little falls into lazy habits of thinking.

Statistical Estimation of Event-Time Distribution

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Some Events of Interest

- Death.
- First publication after PhD graduation.
- Occurrence of tumor.
- Onset of depression.
- Machine/system failure.
- Occurrence of a natural disaster.
- Hospitalization.
- Non-life insurance claim.
- Accident or terrorist attack.
- Onset of economic recession.
- Divorce.

Event Times and Distributions

• T: the time to the occurrence of an event of interest.

- $F(t) = \Pr\{T \le t\}$: the distribution function of *T*.
- $S(t) = \overline{F}(t) = 1 F(t)$: survivor/reliability function.
- Hazard rate/ probability and Cumulative Hazards:

Cont:
$$\lambda(t)dt \approx \Pr\{T \le t + dt | T \ge t\} = \frac{f(t)}{S(t-)}dt$$

Disc:
$$\lambda(t_j) = \Pr\{T = t_j | T \ge t_j\} = \frac{f(t_j)}{S(t_j)}$$

Cumulative:
$$\Lambda(t) = \int_0^t \lambda(w) dw$$
 or $\Lambda(t) = \sum_{t_i \le t} \lambda(t_j)$

Representation/Relationships

• $0 < t_1 < \ldots < t_M = t, \mathcal{M}(t) = \max |t_i - t_{i-1}| = o(1),$

$$S(t) = \Pr\{T > t\} = \prod_{i=1}^{M} \Pr\{T > t_i | T \ge t_{i-1}\}$$

$$\approx \prod_{i=1}^{M} \left[1 - \{\Lambda(t_i) - \Lambda(t_{i-1})\}\right].$$

• S as a product-integral of Λ : When $\mathcal{M}(t) \to 0$,

$$S(t) = \prod_{w \le t} \left[1 - \Lambda(dw) \right]$$

• In general, Λ in terms of $F: \Lambda(t) = \int_0^t \frac{dF(w)}{1-F(w-)}$.

Estimation of *F* and Why?

- Most Basic Problem: Given a sample T_1, T_2, \ldots, T_n from an unknown distribution F, to obtain an estimator \hat{F} of F.
- Why is it important to know how to estimate F?
 - Functionals/parameters $\theta(F)$ of F (e.g., mean, median, variance) can be estimated via $\hat{\theta} = \theta(\hat{F})$.
 - Prediction of time-to-event for new units.
 - Knowledge of population of units or event times.
 - For comparing groups, e.g., thru a statistic

$$Q = \int W(t)d\left[\hat{F}_1(t) - \hat{F}_2(t)\right]$$

where W(t) is some weight function.

Gastroenterology Data: Aalen and Husebye ('91) Migratory Motor Complex (MMC) Times for 19 Subjects



Question: How to estimate the MMC period dist, *F*?

Parametric Approach

 Unknown df F is assumed to belong to some parametric family (e.g., exponential, gamma, Weibull)

 $\mathcal{F} = \{ F(t;\theta) : \theta \in \Theta \subset \Re^p \}$

with functional form of $F(\cdot; \cdot)$ known; θ is unknown.

• Based on data t_1, t_2, \ldots, t_n , θ is estimated by $\hat{\theta}$, say, via maximum likelihood (ML). $\hat{\theta}$ maximizes likelihood

$$L(\theta) = \prod_{i=1}^{n} f(t_i; \theta) = \prod_{i=1}^{n} \lambda(t_i; \theta) \exp\{-\Lambda(t_i; \theta)\}.$$

• The distribution function *F* is estimated by

$$\hat{F}_{pa}(t) = F(t;\hat{\theta}).$$

Parametric Estimation: Asymptotics

• When \mathcal{F} holds, MLE of θ satisfies

$$\hat{\theta} \sim \mathsf{AN}\left(\theta, \frac{1}{n}\mathcal{I}(\theta)^{-1}\right);$$

 $\mathcal{I}(\theta) = \operatorname{Var}\left\{\frac{\partial}{\partial \theta} \log f(T_1; \theta)\right\} = \operatorname{Fisher}$ information.

• Therefore, when \mathcal{F} holds, by δ -method, with

$$\overset{\bullet}{F}(t;\theta) = \frac{\partial}{\partial\theta}F(t;\theta)$$

then

$$\hat{F}_{pa}(t) \sim \mathsf{AN}\left(F(t;\theta), \frac{1}{n} \stackrel{\bullet}{F}(t;\theta)' \mathcal{I}(\theta)^{-1} \stackrel{\bullet}{F}(t;\theta)\right).$$

Nonparametric Approach

- No assumptions are made regarding the family of distributions to which the unknown df F belongs.
- Empirical Distribution Function (EDF):

$$\hat{F}_{np}(t) = \frac{1}{n} \sum_{i=1}^{n} I\{T_i \le t\}$$

- $\hat{F}_{np}(\cdot)$ is a *nonparametric* MLE of *F*.
- Since $I\{T_i \leq t\}, i = 1, 2, ..., n$, are IID Ber(F(t)), by Central Limit Theorem,

$$\hat{F}_{np}(t) \sim AN\left(F(t), \frac{1}{n}F(t)[1-F(t)]\right).$$

An Efficiency Comparison

- Assume that family $\mathcal{F} = \{F(t; \theta) : \theta \in \Theta\}$ holds. Both \hat{F}_{pa} and \hat{F}_{np} are asymptotically unbiased.
- To compare under *F*, we take ratio of asymptotic variances to give the efficiency of parametric estimator over nonparametric estimator.

$$\mathsf{Eff}(\hat{F}_{pa}(t):\hat{F}_{np}(t)) = \frac{F(t;\theta)[1-F(t;\theta)]}{\overset{\bullet}{F}(t;\theta)'\mathcal{I}(\theta)^{-1}\overset{\bullet}{F}(t;\theta)}.$$

• When $\mathcal{F} = \{F(t; \theta) = 1 - \exp\{-\theta t\} : \theta > 0\}$, then

$$\mathsf{Eff}(\hat{F}_{pa}(t):\hat{F}_{np}(t)) = \frac{\exp\{\theta t\} - 1}{(\theta t)^2}$$

Efficiency: Parametric/Nonparametric

Asymptotic efficiency of parametric versus nonparametric estimators under a *correct* negative exponential family model.



Effi of Para Relative to NonPara in Expo Case

Whither Nonparametrics?

- Consider however the case where the negative exponential family is fitted, but it is actually not the correct model. Let us suppose that the gamma family of distributions is the *correct* model.
- Under wrong model, with $\overline{T} = \frac{1}{n} \sum_{i=1}^{n} T_i$ the sample mean, the parametric estimator of *F* is

$$\hat{F}_{pa}(t) = 1 - \exp\{-t/\bar{T}\}.$$

• Under gamma with shape α and scale θ , and since $\overline{T} \sim AN(\alpha/\theta, \alpha/(n\theta^2))$, by δ -method

$$\hat{F}_{pa}(t) \sim \mathsf{AN}\left(1 - \exp\{-\theta t/\alpha\}, \frac{1}{n} \frac{(\theta t)^2}{\alpha} \exp\{-2(\theta t)/\alpha\}\right).$$

Efficiency: Under a Mis-specified Model

Simulated efficiency: parametric over nonparametric under a *mis-specified* exponential family model. *True* Family of Model: Gamma Family



Effi of Para vs NonPara under Misspecified Model

MMC Data: Censoring Aspect

For each unit, red mark is the potential termination time.



Remark: All 19 MMC times completely observed.

Estimation of F: With Censoring

- For *i*th unit, a right-censoring variable C_i with C_1, C_2, \ldots, C_n IID df G.
- Observables are $(Z_i, \delta_i), i = 1, 2, ..., n$ with $Z_i = \min\{T_i, C_i\}$ and $\delta_i = I\{T_i \leq C_i\}$.
- Problem: For observed (Z_i, δ_i) s, to estimate df F or hazard function Λ of the T_i s.
- Nonparametric Approaches:
 - 'Naive' (product-limit)!
 - Nonparametric MLE (Kaplan-Meier).
 - Martingale and method-of-moments.
- Pioneers: Kaplan & Meier; Efron; Nelson; Breslow; Breslow & Crowley; Aalen; Gill.

Product-Limit Estimator

Counting and At-Risk Processes:

$$N(t) = \sum_{i=1}^{n} I\{Z_i \le t; \delta_i = 1\};$$

$$Y(t) = \sum_{i=1}^{n} I\{Z_i \ge t\}$$

• Hazard probability estimate at *t*:

$$\hat{\Lambda}(dt) = \frac{\Delta N(t)}{Y(t)} = \frac{\text{\# of Observed Failures at } t}{\text{\# at-risk at } t}$$

Product-Limit Estimator (PLE):

$$1 - \hat{F}(t) = \hat{S}(t) = \prod_{w \le t} \left[1 - \frac{\Delta N(t)}{Y(t)} \right]$$

Some Properties of PLE

- Nonparametric MLE of *F* (Kaplan-Meier, '58).
- PLE is a step-function which jumps only at observed failure times.
- With censored data, unequal jumps.
- Efron ('67): Possesses self-consistency property.
- Biased for finite n.
- When no censoring and no tied values: $\Delta N(t_{(i)}) = 1$ and $Y(t_{(i)}) = n - i + 1$, so

$$\hat{S}(t_{(i)}) = \prod_{j=1}^{i} \left[1 - \frac{1}{n-j+1} \right] = 1 - \frac{i}{n}.$$

Stochastic Process Approach

• A martingale M is a zero-mean process which models a fair game. With \mathcal{H}_t = history up to t:

 $E\{M(s+t)|\mathcal{H}_t\} = M(t).$

• $M(t) = N(t) - \int_0^t Y(w) \Lambda(dw)$ is a martingale, so with $J(t) = I\{Y(w) > 0\}$ and stochastic integration,

$$E\left\{\int_0^t \frac{J(w)}{Y(w)} dN(w)\right\} = E\left\{\int_0^t J(w)\Lambda(dw)\right\}.$$

• Nelson-Aalen estimator of Λ , and PLE:

$$\hat{\Lambda}(t) = \int_0^t \frac{dN(w)}{Y(w)}, \quad \text{so} \quad \hat{S}(t) = \prod_{w \le t} [1 - \hat{\Lambda}(dw)].$$

Likelihood Process: Hazard-Based

J. Jacod's likelihood:

$$L_t(\Lambda(\cdot)) = \prod_{w \le t} \left[Y(w)\Lambda(dw) \right]^{N(dw)} \left[1 - Y(w)\Lambda(dw) \right]^{1-N(dw)}$$

 \bullet When $\Lambda(\cdot)$ is continuous,

$$L_t(\Lambda(\cdot)) = \left\{ \prod_{w \le t} \left[Y(w) \Lambda(dw) \right]^{N(dw)} \right\} e^{-\int_0^t Y(w) \Lambda(dw)}.$$

• With $\mathcal{T}(t) = \int_0^t Y(w) dw = \mathsf{TTOT}(t)$, for $\lambda(t) = \theta$,

$$L_t(\theta) = \theta^{N(t)} \exp\{-\theta \mathcal{T}(t)\}.$$

Asymptotic Properties

- Proofs uses martingale central limit theorem.
- NAE: $\sqrt{n}[\hat{\Lambda}(t) \Lambda(t)] \Rightarrow Z_1(t)$ with $\{Z_1(t) : t \ge 0\}$ a zero-mean *Gaussian process* with

$$d_1(t) = \operatorname{Var}(Z_1(t)) = \int_0^t \frac{\Lambda(dw)}{S(w)\overline{G}(w-)}.$$

• PLE: $\sqrt{n}[\hat{F}(t) - F(t)] \Rightarrow Z_2(t) \stackrel{st}{=} S(t)Z_1(t)$ so

$$d_2(t) = \operatorname{Var}(Z_2(t)) = S(t)^2 \int_0^t \frac{\Lambda(dw)}{S(w)\bar{G}(w-)}.$$

• If $\overline{G}(w) \equiv 1$ (no censoring), $d_2(t) = F(t)S(t)!$

Gaussian Process: Sample Paths

Brownian Motion Paths



Regression Models

- In many situations we observe covariates: age, blood pressure, race, etc. How to account of them to improve knowledge of time-to-event.
- Modelling approaches:
 - Log-linear models:

 $\log(T) = \beta' \mathbf{x} + \sigma \epsilon.$

The accelerated failure-time model. Error distribution to use? Normal errors not appropriate.

 Hazard-based models: Cox proportional hazards (PH) model; Aalen's additive hazards model.

Cox ('72) PH Model: Single Event

• Conditional on \mathbf{x} , hazard rate of T is:

 $\lambda(t|\mathbf{x}) = \lambda_0(t) \exp\{\beta' \mathbf{x}\}.$

• $\hat{\beta}$ maximizes partial likelihood function of β :

$$L_P(\beta) \equiv \prod_{i=1}^n \prod_{t < \infty} \left[\frac{\exp(\beta' \mathbf{x}_i)}{\sum_{j=1}^n Y_j(t) \exp(\beta' \mathbf{x}_j)} \right]^{\Delta N_i(t)}$$

• Aalen-Breslow semiparametric estimator of $\Lambda_0(\cdot)$:

$$\hat{\Lambda}_0(t) = \int_0^t \frac{\sum_{i=1}^n dN_i(w)}{\sum_{i=1}^n Y_i(w) \exp(\hat{\beta}' \mathbf{x}_i)}.$$

MMC Data: Recurrent Aspect

Aalen and Husebye ('91) Full Data



MMC Data Set

Problem: Estimate inter-event time distribution.

Another Data Set: Bladder Cancer

Bladder Cancer Data Set (Byar, 1980; Wei, Lin, Weissfeld, 1989)



Calendar Time



An observable covariate vector: $\mathbf{X}(s) = (X_1(s), X_2(s), ..., X_q(s))^t$

On Recurrent Event Modelling

- Performed intervention after each event occurrence.
- Accumulating event occurrences. Could have a weakening or strengthening effect.
- Covariates, possibly time-dependent.
- Association of event occurrences per subject.
- Random observation monitoring period.
- Number of events observed is informative.
- Informative right-censoring mechanism because of sum-quota accrual scheme.

Observables: One Subject

- $\mathbf{X}(s) =$ covariate vector, possibly time-dependent
- $T_1, T_2, T_3, \ldots =$ inter-event or gap times
- S_1, S_2, S_3, \ldots = calendar times of event occurrences
- $\tau =$ end of observation period: Assume $\tau \sim G$
- $K = \max\{k : S_k \le \tau\} =$ number of events in $[0, \tau]$
- Z = unobserved frailty variable
- $N^{\dagger}(s) =$ number of events in [0, s]
- $Y^{\dagger}(s) = I\{\tau \ge s\} =$ at-risk indicator at time s
- $\mathbf{F}^{\dagger} = \{\mathcal{F}_{s}^{\dagger} : s \ge 0\} = \text{filtration: information that includes interventions, covariates, etc.}$

Recurrent Event Models: IID Case

• Parametric Models:

• HPP: $T_{i1}, T_{i2}, T_{i3}, \dots$ IID EXP(λ).

• IID Renewal Model: $T_{i1}, T_{i2}, T_{i3}, \dots$ IID F where

 $F \in \mathcal{F} = \{F(\cdot; \theta) : \theta \in \Theta \subset \Re^p\};$

e.g., Weibull family; gamma family; etc.

- Non-Parametric Model: $T_{i1}, T_{i2}, T_{i3}, \ldots$ IID *F* which is some df.
- With Frailty: For each unit *i*, there is an *unobservable* Z_i from some distribution $H(\cdot; \xi)$ and $(T_{i1}, T_{i2}, T_{i3}, ...)$, given Z_i , are IID with survivor function

$$[1 - F(t)]^{Z_i}.$$

Sum-Quota Effect: HPP Model

- T_1, T_2, \dots IID EXP (λ) and $\tau \sim G = EXP(\eta)$.
- $K = \max\{k : \sum_{j=1}^{k} T_j \le \tau\} = \max\{k : S_k \le \tau\}.$
- Given τ and K = k: With $V_1, V_2, \dots, V_k \stackrel{iid}{\sim} UNIF[0, \tau]$, then $(S_1, S_2, \dots, S_k) \stackrel{d}{=} (V_{(1)}, V_{(2)}, \dots, V_{(k)})$.
- Given τ : K is sufficient (completely informative) for λ .
- Given τ and K, (T_1, T_2, \ldots, T_k) and (S_1, S_2, \ldots, S_k) are completely uninformative about λ ;
- Also, $E\{T_{K+1}\} = 1/\theta + 1/(\theta + \eta) > 1/\theta$.
- MLE of λ based on n units:

$$\hat{\lambda} = \frac{K_{\bullet}}{\tau_{\bullet}}$$

More General Models

- References: Therneau and Grambsch ('00) book; Therneau and Hamilton ('97); Cook and Lawless ('01); Also, Kalbfleisch and Prentice, Lawless, Nelson books.
- Time-to-first event: ignores information hence inefficient.
- Wei, Lin Weissfeld (WLW) marginal model: event number used as stratification variable; separate model per stratum.
- Prentice, Williams and Peterson (PWP) conditional method: 'at-risk process' for *j*th event only becomes 1 after the (*j* 1)th event.
- Andersen and Gill (AG) intensity model: 'at-risk process' remains at 1 until unit is censored.

A General Class of Models

• Peña and Hollander (2004) model.

$$\begin{split} N^{\dagger}(s) &= A^{\dagger}(s|Z) + M^{\dagger}(s|Z) \\ M^{\dagger}(s|Z) \in \mathcal{M}_{0}^{2} = \text{sq-int martingales} \\ A^{\dagger}(s|Z) &= \int_{0}^{s} Y^{\dagger}(w) \lambda(w|Z) dw \end{split}$$

• Intensity:

 $\lambda(s|Z) = Z \,\lambda_0[\mathcal{E}(s)] \,\rho[N^{\dagger}(s-);\alpha] \,\psi[\beta^{t}X(s)]$

 This class of models includes as special cases many models in reliability and survival analysis.

Effective Age Process



Effective Age Process, $\mathcal{E}(s)$

- Predictable, observable, nonnegative, dynamically specified, monotone, and differentiable on $[S_{k-1}, S_k)$, $\mathcal{E}(s)$ with $\mathcal{E}'(s) \ge 0$.
- Perfect Intervention: $\mathcal{E}(s) = s S_{N^{\dagger}(s-)}$.
- Imperfect Intervention: $\mathcal{E}(s) = s$.
- Minimal Intervention (Brown & Proschan, '83; Block, Borges & Savits, '85):

$$\mathcal{E}(s) = s - S_{\Gamma_{\eta(s-)}}$$

where, with I_1, I_2, \ldots IID BER(p),

$$\eta(s) = \sum_{i=1}^{N^{\dagger}(s)} I_i$$
 and $\Gamma_k = \min\{j > \Gamma_{k-1} : I_j = 1\}$.

Semi-Parametric Estimation: No Frailty

Observed Data for n Subjects:

$$\{(\mathbf{X}_{i}(s), N_{i}^{\dagger}(s), Y_{i}^{\dagger}(s), \mathcal{E}_{i}(s)): 0 \le s \le s^{*}\}, i = 1, \dots, n$$

 $N_i^{\dagger}(s) = \#$ of events in [0, s] for *i*th unit

 $Y_i^{\dagger}(s) =$ at-risk indicator at s for *i*th unit

with the model for the 'signal' being

$$A_i^{\dagger}(s) = \int_0^s Y_i^{\dagger}(v) \,\rho[N_i^{\dagger}(v-);\alpha] \,\psi[\beta^{\mathsf{t}} \mathbf{X}_i(v)] \,\lambda_0[\mathcal{E}_i(v)] dv$$

where $\lambda_0(\cdot)$ is an unspecified baseline hazard rate function.

Processes and Notations

Calendar/Gap Time Processes:

$$N_i(s,t) = \int_0^s I\{\mathcal{E}_i(v) \le t\} N_i^{\dagger}(dv)$$

$$A_i(s,t) = \int_0^s I\{\mathcal{E}_i(v) \le t\} A_i^{\dagger}(dv)$$

Notational Reductions:

$$\mathcal{E}_{ij-1}(v) \equiv \mathcal{E}_i(v) I_{(S_{ij-1},S_{ij}]}(v) I\{Y_i^{\dagger}(v) > 0\}$$
$$\varphi_{ij-1}(w|\alpha,\beta) \equiv \frac{\rho(j-1;\alpha)\psi\{\beta^{t}\mathbf{X}_i[\mathcal{E}_{ij-1}^{-1}(w)]\}}{\mathcal{E}'_{ij-1}[\mathcal{E}_{ij-1}^{-1}(w)]}$$

Generalized At-Risk Process

$$Y_{i}(s, w | \alpha, \beta) \equiv \sum_{j=1}^{N_{i}^{\dagger}(s-)} I_{(\mathcal{E}_{ij-1}(S_{ij-1}), \mathcal{E}_{ij-1}(S_{ij})]}(w) \varphi_{ij-1}(w | \alpha, \beta) + I_{(\mathcal{E}_{iN_{i}^{\dagger}(s-)}(S_{iN_{i}^{\dagger}(s-)}), \mathcal{E}_{iN_{i}^{\dagger}(s-)}((s \wedge \tau_{i}))]}(w) \varphi_{iN_{i}^{\dagger}(s-)}(w | \alpha, \beta)$$

For IID Renewal Model (PSH, 01) this simplifies to:

$$Y_i(s,w) = \sum_{j=1}^{N_i^{\dagger}(s-)} I\{T_{ij} \ge w\} + I\{(s \land \tau_i) - S_{iN_i^{\dagger}(s-)} \ge w\}$$

Estimation of Λ_0

$$A_i(s,t|\alpha,\beta) = \int_0^t Y_i(s,w|\alpha,\beta)\Lambda_0(dw)$$

$$S_0(s,t|\alpha,\beta) = \sum_{i=1}^n Y_i(s,t|\alpha,\beta)$$

$$J(s,t|\alpha,\beta) = I\{S_0(s,t|\alpha,\beta) > 0\}$$

Generalized Nelson-Aalen 'Estimator':

$$\hat{\Lambda}_0(s,t|\alpha,\beta) = \int_0^t \left\{ \frac{J(s,w|\alpha,\beta)}{S_0(s,w|\alpha,\beta)} \right\} \left\{ \sum_{i=1}^n N_i(s,dw) \right\}$$

Estimation of α and β

Partial Likelihood (PL) Process:

$$L_P(s^*|\alpha,\beta) = \prod_{i=1}^n \prod_{j=1}^{N_i^{\dagger}(s^*)} \left[\frac{\rho(j-1;\alpha)\psi[\beta^{t}\mathbf{X}_i(S_{ij})]}{S_0[s^*, \mathcal{E}_i(S_{ij})|\alpha,\beta]} \right]^{\Delta N_i^{\dagger}(S_{ij})}$$

• PL-MLE: $\hat{\alpha}$ and $\hat{\beta}$ are maximizers of the mapping

$$(\alpha,\beta) \mapsto L_P(s^*|\alpha,\beta)$$

Iterative procedures. Implemented in an R package called gcmrec (Gonzaléz, Slate, Peña '04).

Estimation of \overline{F}_0

• G-NAE of $\Lambda_0(\cdot)$: $\hat{\Lambda}_0(s^*, t) \equiv \hat{\Lambda}_0(s^*, t | \hat{\alpha}, \hat{\beta})$

• G-PLE of $\overline{F}_0(t)$:

$$\hat{\bar{F}}_0(s^*, t) = \prod_{w=0}^t \left[1 - \frac{\sum_{i=1}^n N_i(s^*, dw)}{S_0(s^*, w | \hat{\alpha}, \hat{\beta})} \right]$$

• For IID renewal model with $\mathcal{E}_i(s) = s - S_{iN_i^{\dagger}(s-)}$, $\rho(k; \alpha) = 1$, and $\psi(w) = 1$, the estimator in PSH (2001) obtains.

Sum-Quota Effect: IID Renewal

• Generalized product-limit estimator \hat{F}_0 of common gap-time df F_0 presented in PSH (2001, JASA).

$$\sqrt{n}(\hat{\bar{F}}_0(\cdot) - \bar{F}_0(\cdot)) \Longrightarrow \mathsf{GP}(0, \sigma^2(\cdot))$$

$$\sigma^2(t) = \bar{F}_0(t)^2 \int_0^t \frac{d\Lambda_0(w)}{\bar{F}_0(w)\bar{G}(w-)\left[1+\nu(w)\right]}$$
$$\nu(w) = \frac{1}{\bar{G}(w-)} \int_w^\infty \rho^*(v-w)dG(v)$$

 $\rho^*(\cdot) = \sum_{j=1}^{\infty} F_0^{\star j}(\cdot) = \text{renewal function}$

Semi-Parametric Estimation: With Frailty

• Recall the intensity rate:

 $\lambda_i(s|Z_i, \mathbf{X}_i) = Z_i \,\lambda_0[\mathcal{E}_i(s)] \,\rho[N_i^{\dagger}(s-); \alpha] \,\psi(\beta^{\mathsf{t}} \mathbf{X}_i(s))$

- Frailties Z_1, Z_2, \ldots, Z_n are unobserved and assumed to be IID Gamma(ξ, ξ)
- Unknown parameters: $(\xi, \alpha, \beta, \lambda_0(\cdot))$
- Use of the EM algorithm (Dempster, et al; Nielsen, et al), with frailties as missing observations.
- Estimator of baseline hazard function under no-frailty model plays an important role.
- Details are in Peña, Slate & Gonzalez (2004, JSPI?).

First Application: MMC Data Set

Aalen and Husebye (1991) Data Estimates of distribution of MMC period



Migrating Moto Complex (MMC) Time, in minutes

Second Application: Bladder Data Set

Bladder cancer data pertaining to times to recurrence for n = 85 subjects studied in Wei, Lin and Weissfeld ('89).



Calendar Time

Results and Comparisons

Estimates from Different Methods for Bladder Data

Cova	Para	AG	WLW	PWP	General Model	
			Marginal	Cond*nal	Perfect ^a	Minimal ^b
$\log N(t-)$	α	-	-	-	.98 (.07)	.79
Frailty	ξ	-	-	-	∞	.97
rx	eta_1	47 (.20)	58 (.20)	33 (.21)	32 (.21)	57
Size	β_2	04 (.07)	05 (.07)	01 (.07)	02 (.07)	03
Number	β_3	.18 (.05)	.21 (.05)	.12 (.05)	.14 (.05)	.22

^{*a*}Effective Age is backward recurrence time ($\mathcal{E}(s) = s - S_{N^{\dagger}(s-)}$). ^{*b*}Effective Age is calendar time ($\mathcal{E}(s) = s$).

Estimates of SFs for Two Groups

Blue: Thiotepa Group	Red: Placebo Group
Solid: Perfect Repair	Dashed: Minimal Repair



Concluding Remarks

- Background in the estimation of an event-time distribution under different settings.
- General and flexible model: incorporates aspects of recurrent event modelling.
- Current deficiency: Effective age! paradigm shift in data gathering.
- Further studies: asymptotics; goodness of fit, and validation & diagnostics. (R. Stocker, J. Quiton, R. Strawderman)
- Recurrent event model and longitudinal markers via latent classes. (J. Han, E. Slate)
- Special Topics (Stat 718) Spr 2006 dealing with stochastic process approach to event-time modelling.