Developments in Recurrent Event Modeling & Analysis

Edsel A. Peña
(E-Mail: pena@stat.sc.edu)

University of South Carolina
Columbia, South Carolina 29208 USA

INSA-Département Génie Mathématique et Modélisation
Toulouse, France
January 20, 2014

Outline of Talk

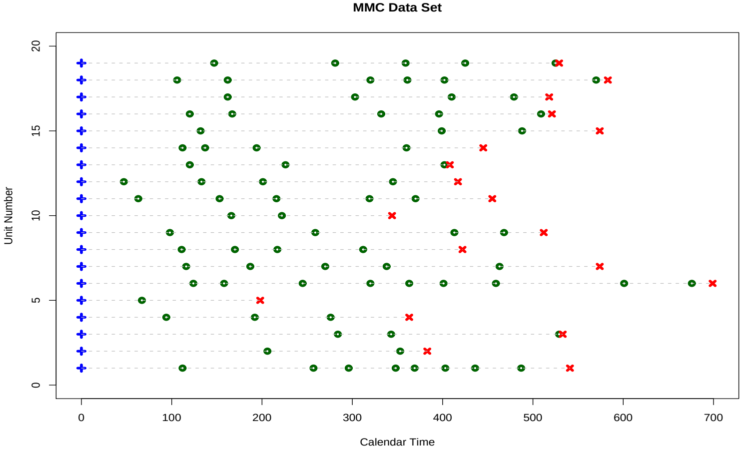
- Recurrent events
- Aspects of Data Accrual
- IID Recurrent Event Model
- Efficiency Aspects: Extending KG Model
- Regression Models for Recurrent Events
- Cox-type and a General Dynamic Recurrent Event Model
- Inference for General Model
- Marginal Modeling Approaches: Some Issues
- Recurrent Competing Risks Settings
- Other Current Research Problems
- Concluding Remarks

Recurrent Events: Some Examples

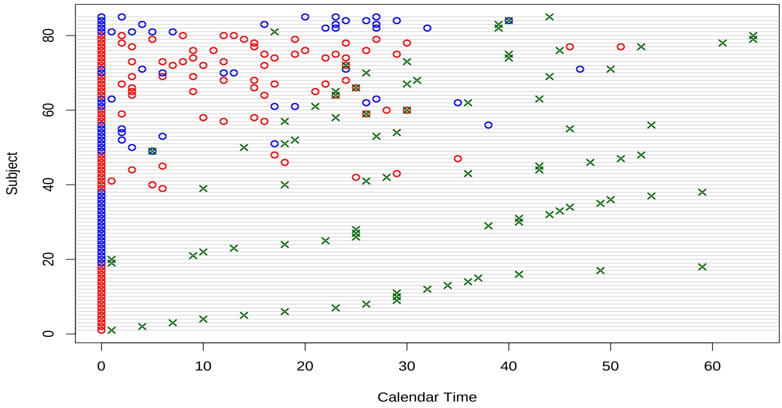
- In Reliability & Engineering Settings:
  - machine or equipment failure
  - discovery of a bug in a software or computer crashing
  - cracks in highways
- In Biomedical Settings:
  - admission to hospital due to chronic disease
  - tumor re-occurrence
  - migraine attacks
  - alcohol or drug (eg cocaine) addiction
- In Other Settings:
  - commission of a criminal act by a delinquent minor!
  - major disagreements between a couple
  - non-life insurance claim
  - drop of ≥ 200 points in DJIA during trading day
  - publication of a research paper by a professor

Migratory Motor Complex (MMC) Data

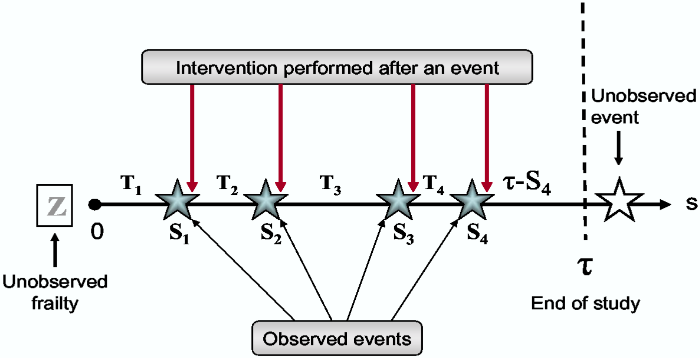
Data set from Aalen and Husebye ('91) with $n = 19$ subjects.



Bladder Cancer Data Set [Wei, Lin, Weissfeld, '89]



Data Accrual: One Subject



Covariate vector: $\mathbf{X}(s) = (X_1(s), \ldots, X_q(s))$

Some Aspects in Recurrent Data

- random monitoring length (τ).
- random # of events (K) and sum-quota constraint:

$$K = \max\left\{k : \sum_{j=1}^{k} T_j \le \tau\right\} \text{ with } \sum_{j=1}^{K} T_j \le \tau < \sum_{j=1}^{K+1} T_j$$

- **Basic Observable:** $(K, \tau, T_1, T_2, \ldots, T_K, \tau - S_K)$
- always a right-censored observation.
- dependent and informative censoring.
- size-biased sampling: gap-time censored tends to be stochastically longer.
- effects of covariates, frailties, interventions after each event, and accumulation of events.

Recurrent Event Models: IID Case

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

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

Simplest Model: One Subject

- $T_1, T_2, \ldots \stackrel{IID}{\sim} F$: (renewal model)
- 'perfect interventions' after each event
- $\tau \sim G$
- F and G not related
- no covariates (X)
- no frailties (Z)
- F could be parametric or nonparametric.
- Relevant Functions:

$$\bar{F} = 1 - F; \quad \Lambda = -\log \bar{F}; \quad \lambda = \Lambda'; \quad \bar{F} = \exp(-\Lambda)$$

$$\lambda(t)dt \approx P\{T \in (t, t+dt] | T \geq t\}$$

- Product-Integral Representation:

$$\bar{F}(t) = \prod_{v=0}^{t} [1 - \Lambda(dv)]$$

Nonparametric Estimation of F

Some Results from Peña, Strawderman and Hollander (JASA, 01):

$$N(t) = \sum_{i=1}^{n} \sum_{j=1}^{K_i} I\{T_{ij} \le t\}$$

$$Y(t) = \sum_{i=1}^{n} \left\{ \sum_{j=1}^{K_i} I\{T_{ij} \ge t\} + I\{\tau_i - S_{iK_i} \ge t\} \right\}$$

$$\textbf{GNAE}: \quad \tilde{\Lambda}(t) = \int_0^t \frac{dN(w)}{Y(w)}$$

$$\textbf{GPLE}: \quad \tilde{\bar{F}}(t) = \prod_0^t \left[1 - \frac{dN(w)}{Y(w)} \right]$$

Main Asymptotic Result

$$k\textbf{th Convolution:} \quad F^{\star(k)}(t) = \Pr\left\{\sum_{j=1}^{k} T_j \le t\right\}$$

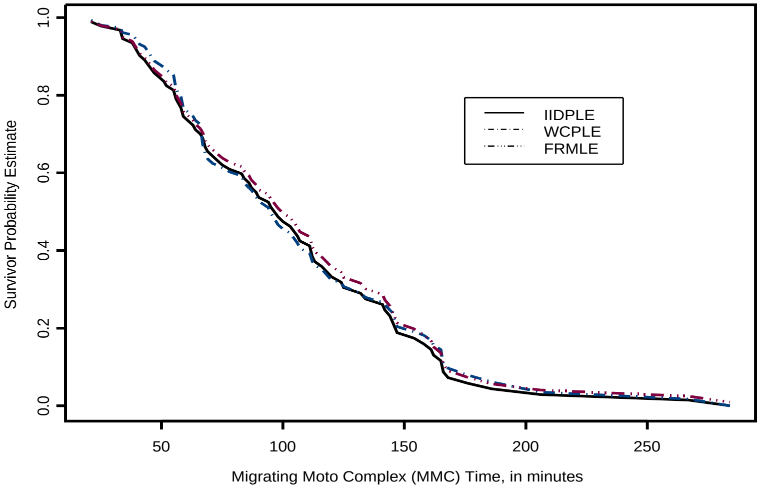
$$\textbf{Renewal Function:} \quad \rho(t) = \sum_{k=1}^{\infty} F^{\star(k)}(t)$$

$$\nu(t) = \frac{1}{\bar{G}(t)} \int_t^{\infty} \rho(w-t)dG(w)$$

$$\sigma^2(t) = \bar{F}(t)^2 \int_0^t \frac{dF(w)}{\bar{F}(w)^2 \bar{G}(w)[1+\nu(w)]}$$

Theorem (JASA, 01): $\sqrt{n}(\tilde{\bar{F}}(t) - F(t)) \Rightarrow \mathrm{GP}(0, \sigma^2(t))$

Survivor Function Estimate for MMC Data



Extending KG Model in Recurrent Setting [in JNS, '12]

- *Wanted:* a tractable model with monitoring time informative about F.
- Potential to refine analysis of efficiency gains/losses.
- Idea: Why not simply generalize the KG model for the RCM.
- **Generalized KG Model** (GKG) for Recurrent Events:

$$\exists \beta > 0, \quad \bar{G}(t) = \bar{F}(t)^{\beta}$$

with β unknown, and F the common inter-event time distribution function.

- Remark: τ may also represent system failure/death, while the recurrent event could be shocks to the system.
- Remark: Association (within unit) could be modeled through a frailty.

Estimation Issues and Some Questions

- How to semiparametrically estimate β, Λ, and $\bar{F}$?
- Parametric estimation in Adekpedjou, Peña, and Quiton (2010, JSPI).
- How much efficiency loss is incurred when the informative monitoring model structure is ignored?
- How much penalty is incurred with Single-event analysis relative to Recurrent-event analysis?
- In particular, what is the efficiency loss for estimating F when using the nonparametric estimator in PSH (2001) relative to the semiparametric estimator that exploits the informative monitoring structure?

Basic Processes

$$S_{ij} = \sum_{k=1}^{j} T_{ik}$$

$$N_i^\dagger(s) = \sum_{j=1}^{\infty} I\{S_{ij} \le s\}$$

$$Y_i^\dagger(s) = I\{\tau_i \ge s\}$$

$$R_i(s) = s - S_{iN_i^\dagger(s-)} = \text{backward recurrence time}$$

$$A_i^\dagger(s) = \int_0^s Y_i^\dagger(v)\lambda[R_i(v)]dv$$

$$N_i^\tau(s) = I\{\tau_i \le s\}$$

$$Y_i^\tau(s) = I\{\tau_i \ge s\}$$

Transformed Processes

$$Z_i(s,t) = I\{R_i(s) \le t\}$$

$$N_i(s,t) = \int_0^s Z_i(v,t) N_i^\dagger(dv) = \sum_{j=1}^{N_i^\dagger(s))} I\{T_{ij} \le t\}$$

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

$$A_i(s,t) = \int_0^s Z_i(v,t) A_i^\dagger(dv) = \int_0^t Y_i(s,w)\lambda(w)dw$$

$\{M_i(v,t) = N_i(v,t) - A_i(v,t) : v \ge 0\}$ are martingales.

Aggregated Processes

$$N(s,t) = \sum_{i=1}^{n} N_i(s,t)$$

$$Y(s,t) = \sum_{i=1}^{n} Y_i(s,t)$$

$$A(s,t) = \sum_{i=1}^{n} A_i(s,t)$$

$$N^{\tau}(s) = \sum_{i=1}^{n} N_i^{\tau}(s)$$

$$Y^{\tau}(s) = \sum_{i=1}^{n} Y_i^{\tau}(s)$$

First, Assume β Known

Via Method-of-Moments Approach, 'estimator' of Λ:

$$\hat{\Lambda}(s, t|\beta) = \int_0^t \left\{ \frac{N(s, dw) + N^\tau(dw)}{Y(s, w) + \beta Y^\tau(w)} \right\}$$

Using product-integral representation of $\bar{F}$ in terms of Λ, 'estimator' of $\bar{F}$:

$$\hat{\bar{F}}(s, t|\beta) = \prod_{w=0}^{t} \left\{ 1 - \frac{N(s, dw) + N^\tau(dw)}{Y(s, w) + \beta Y^\tau(w)} \right\}$$

Estimating β: Profile Likelihood MLE

Profile Likelihood:

$$L_P(s^*;\beta) = \beta^{N^\tau(s^*)} \times \prod_{i=1}^{n} \left\{ \left[\prod_{v=0}^{s^*} \left\{ \frac{1}{Y(s^*,v) + \beta Y^\tau(v)} \right\}^{N_i^\tau(\Delta v)} \right] \times \left[\prod_{v=0}^{s^*} \left\{ \frac{1}{Y(s^*,v) + \beta Y^\tau(v)} \right\}^{N_i(s^*,\Delta v)} \right] \right\}$$

Estimator of β:

$$\hat{\beta} = \arg\max_{\beta} L_P(s^*;\beta)$$

Computational Aspect: in `R`, we used `optimize` to get good seed for the Newton-Raphson iteration.

Estimators of Λ and $\bar{F}$

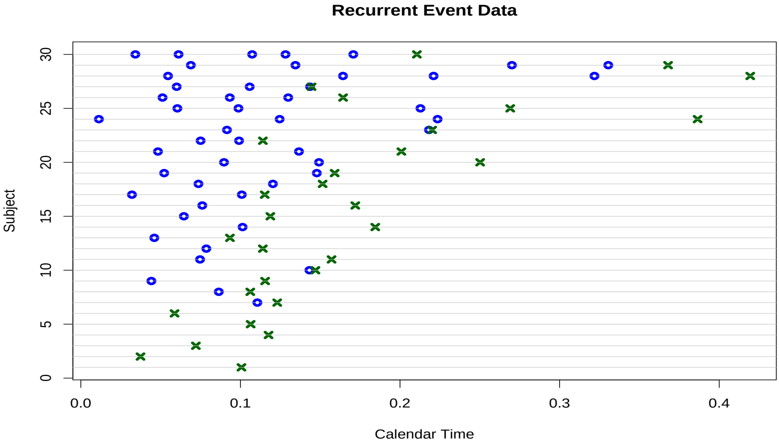
Estimator of Λ:

$$\hat{\Lambda}(s^*, t) = \hat{\Lambda}(s^*, t|\hat{\beta}) = \int_0^t \left\{ \frac{N(s^*, dw) + N^\tau(dw)}{Y(s^*, w) + \hat{\beta} Y^\tau(w)} \right\}$$

Estimator of $\bar{F}$:

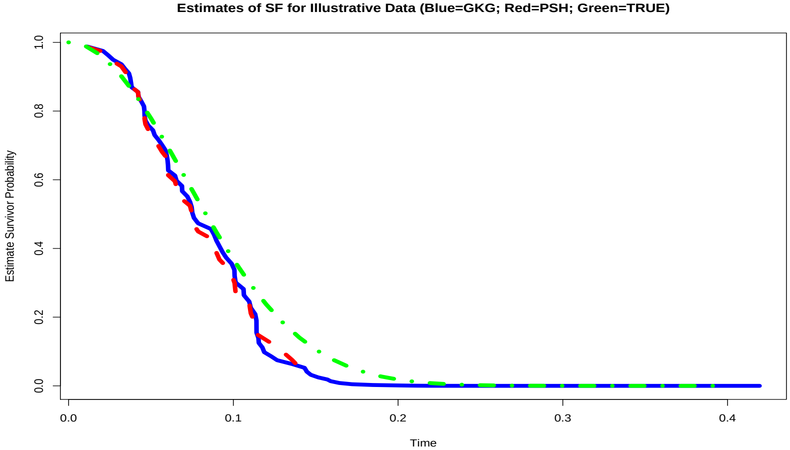
$$\hat{\bar{F}}(s^*, t) = \hat{\bar{F}}(s^*, t|\hat{\beta}) = \prod_{w=0}^{t} \left\{ 1 - \frac{N(s^*, dw) + N^\tau(dw)}{Y(s^*, w) + \hat{\beta} Y^\tau(w)} \right\}$$

Illustrative Data ($n = 30$): GKG[Wei(2,.1), $\beta = .2$]



Estimates of β and $\bar{F}$

$$\hat{\beta} = .2331$$



Properties of Estimators

$$G_s(w) = G(w)I\{w < s\} + I\{w \geq s\}$$

$$\mathbb{E}\{Y_1(s,t)\} \equiv y(s,t) = \bar{F}(t)\bar{G}_s(t) + \bar{F}(t)\int_t^\infty \rho(w-t)dG_s(w)$$

$$\mathbb{E}\{Y_1^\tau(t)\} \equiv y^\tau(t) = \bar{F}(t)^\beta$$

$$\text{True Values} = (F_0, \Lambda_0, \beta_0)$$

$$y_0(s,t) = y(s,t;\Lambda_0,\beta_0)$$

$$y_0^\tau(s) = y^\tau(s;\Lambda_0,\beta_0)$$

Existence, Consistency, Normality

Theorem

There is a sequence of $\hat{\beta}$ that is consistent, and $\hat{\Lambda}(s^*, \cdot)$ and $\hat{\bar{F}}(s^*, \cdot)$ are both uniformly strongly consistent.

Theorem

As $n \to \infty$, we have

$$\sqrt{n}(\hat{\beta} - \beta_0) \Rightarrow N(0, [\mathcal{I}_P(s^*; \Lambda_0, \beta_0)]^{-1})$$

with

$$\mathcal{I}_P(s^*; \Lambda_0, \beta_0) = \frac{1}{\beta_0} \int_0^{s^*} \frac{y_0^{\tau}(v) y_0(s^*, v)}{y_0(s^*, v) + \beta_0 y_0^{\tau}(v)} \lambda_0(v) dv.$$

Weak Convergence of $\hat{\Lambda}(s^*, \cdot)$

Theorem

As $n \to \infty$, $\{\sqrt{n}[\hat{\Lambda}(s^*, t) - \Lambda_0(t)] : t \in [0, t^*]\}$ converges weakly to a zero-mean Gaussian process with variance function

$$\sigma^2_{\hat{\Lambda}}(s^*, t) = \int_0^t \frac{\Lambda_0(dv)}{y_0(s^*, v) + \beta_0 y_0^{\tau}(v)} +$$

$$\left[\int_0^{s^*} \frac{y_0(s^*, v) y_0^{\tau}(v)}{\beta_0[y_0(s^*, v) + \beta_0 y_0^{\tau}(v)]} \Lambda_0(dv)\right]^{-1} \times$$

$$\left[\int_0^t \frac{y_0^{\tau}(v)}{y_0(s^*, v) + \beta_0 y_0^{\tau}(v)} \Lambda_0(dv)\right]^2.$$

Remark: The last product term is the effect of estimating β. It inflates the asymptotic variance.

Weak Convergence of $\hat{\bar{F}}(s^*, \cdot)$ and $\tilde{\bar{F}}(s^*, \cdot)$

Corollary

As $n \to \infty$, $\{\sqrt{n}[\hat{\bar{F}}(s^*, t) - \bar{F}_0(t)] : t \in [0, t^*]\}$ *converges weakly to a zero-mean Gaussian process whose variance function is*

$$\sigma^2_{\hat{\bar{F}}}(s^*, t) = \bar{F}_0(t)^2 \sigma^2_{\hat{\Lambda}}(s^*, t) \equiv \bar{F}_0(t)^2 \sigma^2_{\tilde{\Lambda}}(s^*, t).$$

Recall/Compare!

Theorem (PSH, 2001)

As $n \to \infty$, $\{\sqrt{n}[\tilde{\bar{F}}(s^*, t) - \bar{F}_0(t)] : t \in [0, t^*]\}$ *converges weakly to a zero-mean Gaussian process whose variance function is*

$$\sigma^2_{\tilde{\bar{F}}}(s^*, t) = \bar{F}_0(t)^2 \int_0^t \frac{\Lambda_0(dv)}{y_0(s^*, v)}.$$

Asymptotic Relative Efficiency: β_0 Known

If we know β_0:

$$ARE\{\tilde{\bar{F}}(s^*, t) : \hat{\bar{F}}(s^*, t|\beta_0)\} =$$
$$\left\{\int_0^t \frac{\Lambda_0(dw)}{y_0(s^*, w)}\right\}^{-1} \times$$
$$\left\{\int_0^t \frac{\Lambda_0(dw)}{y_0(s^*, w) + \beta_0 y_0^\tau(w)}\right\}$$

Clearly, this could not exceed unity, as is to be expected.

Case of Exponential F: β_0 Known

Theorem

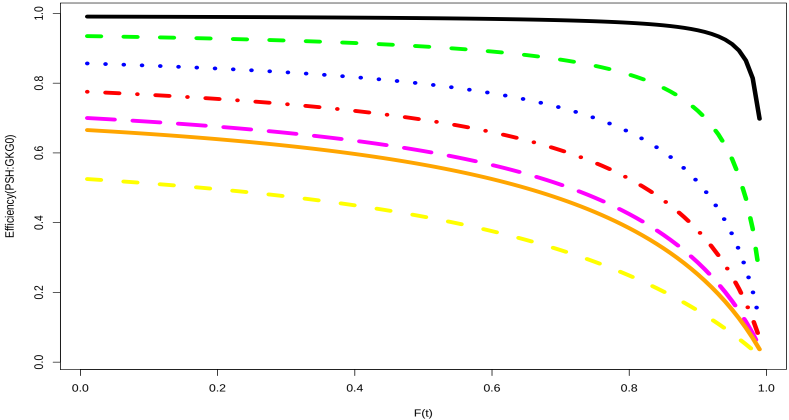
If $\bar{F}_0(t) = \exp\{-\theta_0 t\}$ *for* $t \geq 0$ *and* $s^* \to \infty$, *then*

$$ARE\{\tilde{\hat{F}}(\infty, t) : \hat{\hat{F}}(\infty, t|\beta_0)\} = \left\{\int_{\bar{F}_0(t)}^{1} \frac{du}{(1+\beta_0)u^{2+\beta_0}}\right\}^{-1} \times \left\{\int_{\bar{F}_0(t)}^{1} \frac{du}{(1+\beta_0)u^{2+\beta_0} + \beta_0^2 u^{1+\beta_0}}\right\}.$$

Also, $\forall t \geq 0$,

$$ARE\{\tilde{\hat{F}}(\infty, t) : \hat{\hat{F}}(\infty, t; \beta_0)\} \leq \frac{1+\beta_0}{1+\beta_0+\beta_0^2}.$$

ARE-Plots; $\beta_0 \in \{.1, .3, .5, .7, .9, 1.0, 1.5\}$ Known; $F = Exponential$



Case of β_0 Unknown

- As to be expected, if β_0 is known, then the estimator exploiting the GKG structure is more efficient.
- Question: Does this dominance hold true still if β_0 is now estimated?

Theorem

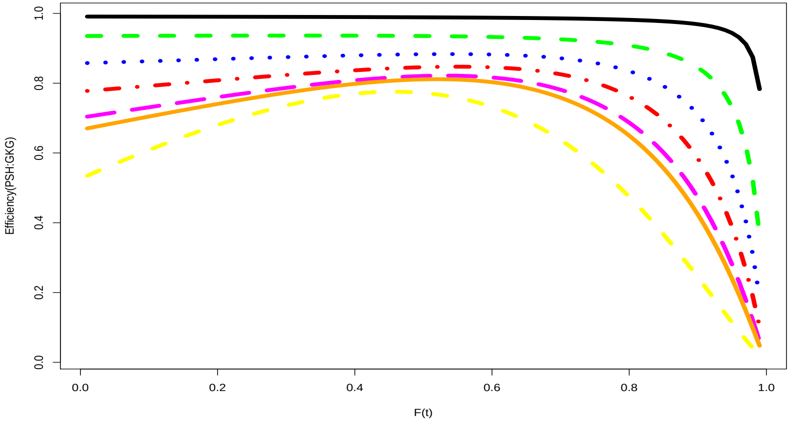
Under the GKG model, for all $(\bar{F}_0, \beta_0)$ with $\beta_0 > 0$, $\tilde{\bar{F}}(s^*, t)$ is asymptotically dominated by $\hat{\bar{F}}(s^*, t)$ in the sense that

$$ARE(\tilde{\bar{F}}(s^*, t) : \hat{\bar{F}}(s^*, t)) \leq 1.$$

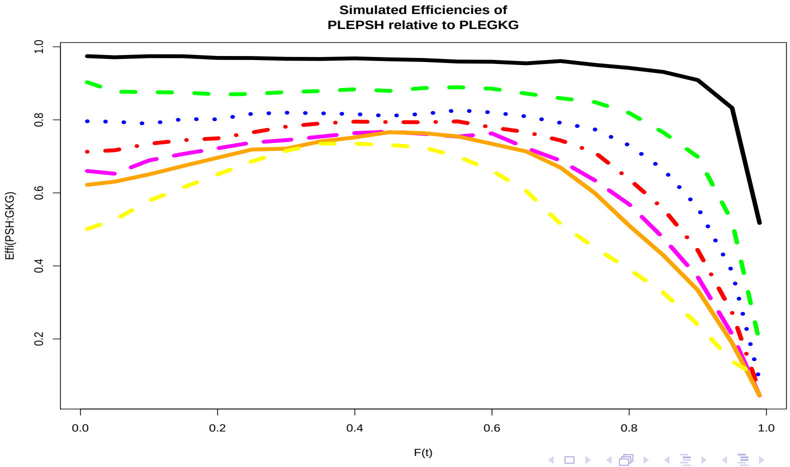
Proof.

Proof uses a neat application of Cauchy-Schwartz Inequality. □

ARE-Plots; $\beta_0 \in \{.1, .3, .5, .7, .9, 1.0, 1.5\}$ Unknown; $F = Exponential$



Simulated $RE(\tilde{\tilde{F}} : \hat{\hat{F}})$ under a Weibull F with $\alpha = 2$; $\beta_0 \in \{.1, .3, .5, .7, .9, 1.0, 1.5\}$ but Unknown



Regression Models

- **Covariates:** temperature, degree of usage, stress level, age, blood pressure, race, etc.
- How to account of covariates 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 $\Lambda_0(\cdot)$:

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

A General Class of *Full* Models

- Peña and Hollander (2004) model.

$$N^\dagger(s) = A^\dagger(s|Z) + M^\dagger(s|Z)$$

$$M^\dagger(s|Z) \in \mathcal{M}_0^2 = \text{sq-int martingales}$$

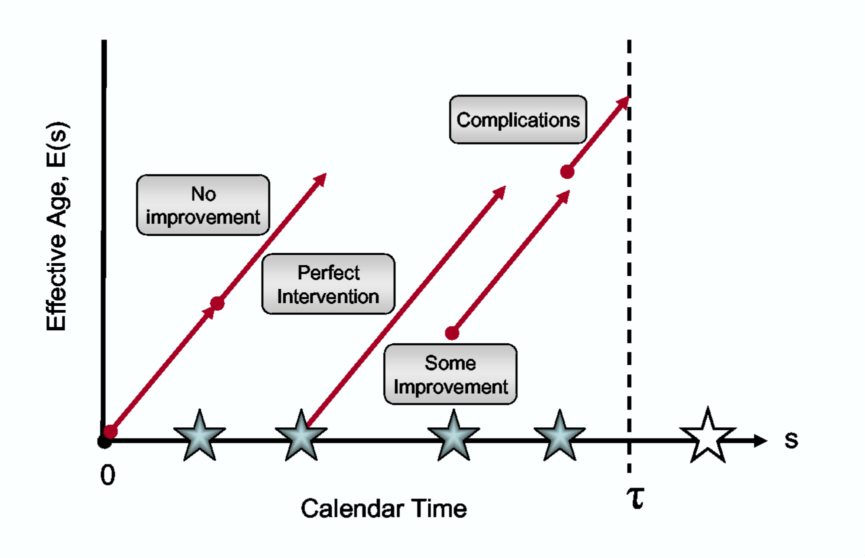
$$A^\dagger(s|Z) = \int_0^s Y^\dagger(w)\lambda(w|Z)dw$$

- Intensity Process:

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

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

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



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

- PERFECT Intervention: $\mathcal{E}(s) = s - S_{N^\dagger(s-)}$.
- IMPERFECT Intervention: $\mathcal{E}(s) = s$.
- MINIMAL Intervention (BP '83; BBS '85):

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

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

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

Remark: Perfect repairs at times when coin lands head; Imperfect repairs at the times when coin lands tails!

Semi-Parametric Estimation: No Frailty

Observed Data for n Subjects:

$$\{(\mathbf{X}_i(s), N_i^\dagger(s), Y_i^\dagger(s), \mathcal{E}_i(s)) : \; 0 \le s \le s^*\}, i = 1, \ldots, n$$

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

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

with the model for the 'signal' being

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

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:

$$\mathcal{E}_{ij-1}(v) \equiv \mathcal{E}_i(v) I_{(S_{ij-1}, S_{ij}]}(v) I\{Y_i^{\dagger}(v) > 0\}$$

$$\varphi_{ij-1}(w|\alpha,\beta) \equiv \frac{\rho(j-1;\alpha)\psi\{\beta^{\mathrm{t}}\mathbf{X}_i[\mathcal{E}_{ij-1}^{-1}(w)]\}}{\mathcal{E}'_{ij-1}[\mathcal{E}_{ij-1}^{-1}(w)]}$$

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:

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

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 $\bar{F}_0$

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

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

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

Asymptotics: General Model without Frailty [Peña, '14]

$$\eta \equiv (\alpha, \beta)^{\mathtt{T}}$$

$$\sqrt{n}(\hat{\eta}_n - \eta^0) \xrightarrow{d} N\left(0, \Sigma(s^*, t^*)^{-1}\right).$$

$$W_n(s^*, \cdot) = \sqrt{n}\left[\hat{\Lambda}_0^{(n)}(s^*, \cdot) - \Lambda_0^0(\cdot)\right] \Rightarrow GP[0, C(s^*, \cdot, \cdot)];$$

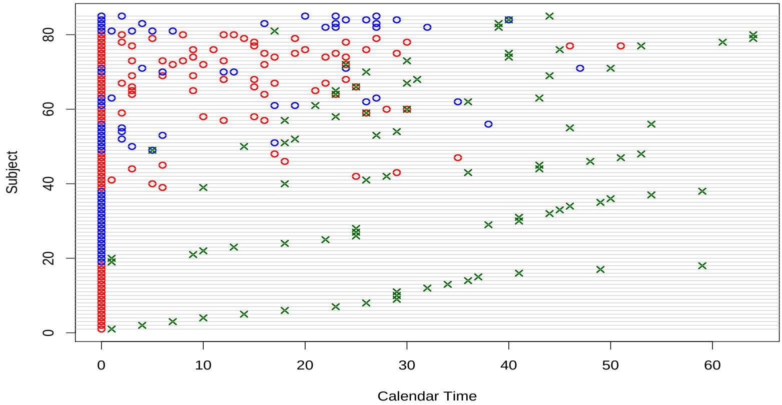
$$C(s^*, t_1, t_2) = \int_0^{\min(t_1, t_2)} \frac{\Lambda_0^0(dw)}{S^{(0)}(s^*, w)} + b(s^*, t_1)^{\mathtt{t}}\{\Sigma(s^*, t^*)\}^{-1} b(s^*, t_2);$$

$$b(s^*, t) = \int_0^t q^{(1)}(s^*, w)\Lambda_0^0(dw).$$

Remark: Extends Andersen-Gill (AoS, '82) results.

An Application: Bladder Data Set

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



Results and Comparisons

- Estimates from Different Methods for Bladder Data

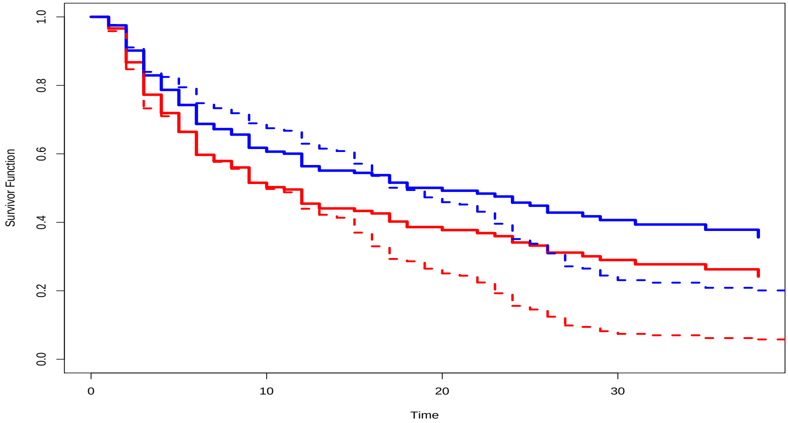
Cova	Para	AG	WLW Marginal	PWP Cond*nal	General Model Perfect[a]	General Model Imperfect[b]
$\log N(t-)$	α	-	-	-	.98 (.07)	.79
Frailty	ξ	-	-	-	∞	.97
rx	β_1	-.47 (.20)	**-.58 (.20)**	**-.33 (.21)**	**-.32 (.21)**	**-.57**
Size	β_2	-.04 (.07)	**-.05 (.07)**	**-.01 (.07)**	**-.02 (.07)**	**-.03**
Number	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 ($\mathcal{E}(s) = s$).

Details: In Peña, Slate, and Gonzalez (JSPI, '07), including for model with frailties.

Estimates of Survivor Functions @ Mean of Covariates

Under Perfect and Imperfect Repair Effective Ages



Some Comments on Marginal Modeling: WLW and PWP

- k_0 specified (usually the maximum value of the observed Ks).
- Assume a Cox PH-type model for each S_k, $k = 1, \ldots, k_0$.
- Counting Processes ($k = 1, 2, \ldots, k_0$):

$$N_k(s) = I\{S_k \le s; S_k \le \tau\}$$

- At-Risk Processes ($k = 1, 2, \ldots, k_0$):

$$Y_k^{WLW}(s) = I\{S_k \ge s; \tau \ge s\}$$

$$Y_k^{PWP}(s) = I\{S_{k-1} < s \le S_k; \tau \ge s\}$$

Working Model Specifications

- **WLW Model**

$$\left\{ N_k(s) - \int_0^s Y_k^{WLW}(v)\lambda_{0k}^{WLW}(v)\exp\{\beta_k^{WLW} X(v)\} dv \right\}$$

- **PWP Model**

$$\left\{ N_k(s) - \int_0^s Y_k^{PWP}(v)\lambda_{0k}^{PWP}(v)\exp\{\beta_k^{PWP} X(v)\} dv \right\}$$

- are *assumed* to be zero-mean martingales (in s).

Parameter Estimation

- See Therneau & Grambsch's book *Modeling Survival Data: Extending the Cox Model*.
- $\hat{\beta}_k^{WLW}$ and $\hat{\beta}_k^{PWP}$ obtained via partial likelihood (Cox (72) and Andersen and Gill (82)).
- Overall β-estimate:

$$\hat{\beta}^{WLW} = \sum_{k=1}^{k_0} \hat{c}_k \hat{\beta}_k^{WLW};$$

  c_ks being 'optimal' weights. See WLW paper.
- $\hat{\Lambda}_{0k}^{WLW}(\cdot)$ and $\hat{\Lambda}_{0k}^{PWP}(\cdot)$: Aalen-Breslow-Nelson type estimators.

Two Relevant Questions

- **Question 1:** When one assumes marginal models for S_ks that are of the Cox PH-type, does there exist a *full model* that *actually induces* such PH-type marginal models?

  Answer: YES, by a very nice paper by Nang and Ying (Biometrika:2001). BUT, the joint model obtained is rather 'limited'.

- **Question 2:** If one *assumes* Cox PH-type marginal models for the S_ks (or T_ks), but the *true* full model does not induce such PH-type marginal models *[which may usually be the case in practice]*, what are the *consequences*?

Case of the HPP Model

- *True Full Model:* for a unit with covariate $X = x$, events occur according to an HPP model with rate:

$$\lambda(t|x) = \theta \exp(\beta x).$$

- For this unit, inter-event times $T_k, k = 1, 2, \ldots$ are IID exponential with mean time $1/\lambda(t|x)$.
- Assume also that $X \sim BER(p)$ and $\mu_\tau = E(\tau)$.
- Main goal is to infer about the regression coefficient β which relates the covariate X to the event occurrences.

Full Model Analysis

- $\hat{\beta}$ solves
$$\frac{\sum X_i K_i}{\sum K_i} = \frac{\sum \tau_i X_i \exp(\beta X_i)}{\sum \tau_i \exp(\beta X_i)}.$$
- $\hat{\beta}$ does not directly depend on the S_{ij}s. Why?
- **Sufficiency:** (K_i, τ_i)s contain all information on (θ, β).

$$(S_{i1}, S_{i2}, \ldots, S_{iK_i}) | (K_i, \tau_i) \stackrel{d}{=} \tau_i (U_{(1)}, U_{(2)}, \ldots, U_{(K_i)}).$$

- Asymptotics:

$$\hat{\beta} \sim AN\left(\beta, \frac{1}{n} \frac{(1-p) + pe^{\beta}}{\mu_\tau \theta [(1-p) + pe^{\beta}]}\right).$$

Some Questions

- Under WLW or the PWP: how are β_k^{WLW} and β_k^{PWP} related to θ and β?
- Impact of event position k?
- Are we *ignoring* that K_is are informative? Why not also put a marginal model on the K_is?
- Are we violating the *Sufficiency Principle*?
- Results simulation-based: Therneau & Grambsch book ('01) and Metcalfe & Thompson (SMMR, '07).
- Comment by D. Oakes that PWP estimates *less biased* than WLW estimates.

Properties of $\hat{\beta}_k^{WLW}$

- Let $\hat{\beta}_k^{WLW}$ be the partial likelihood MLE of β based on at-risk process $Y_k^{WLW}(v)$.
- **Question:** Does $\hat{\beta}_k^{WLW}$ converge to β?
- $g_k(w) = w^{k-1}e^{-w}/\Gamma(k)$: standard gamma pdf.
- $\bar{\mathcal{G}}_k(v) = \int_v^\infty g_k(w)dw$: standard gamma survivor function.
- $\bar{G}(\cdot)$: survivor function of τ.
- $E(\cdot)$: denotes expectation wrt X.

Limit Value (LV) of $\hat{\beta}_k^{WLW}$

- **Limit Value** $\beta_k^* = \beta_k^*(\theta, \beta)$ of $\hat{\beta}_k^{WLW}$: solution in β^* of

$$\int_0^\infty E(X\theta e^{\beta X} g_k(v\theta e^{\beta X}))\bar{G}(v)dv =$$

$$\int_0^\infty e_k^{WLW}(v; \theta, \beta, \beta^*) E(\theta e^{\beta X} g_k(v\theta e^{\beta X}))\bar{G}(v)dv$$

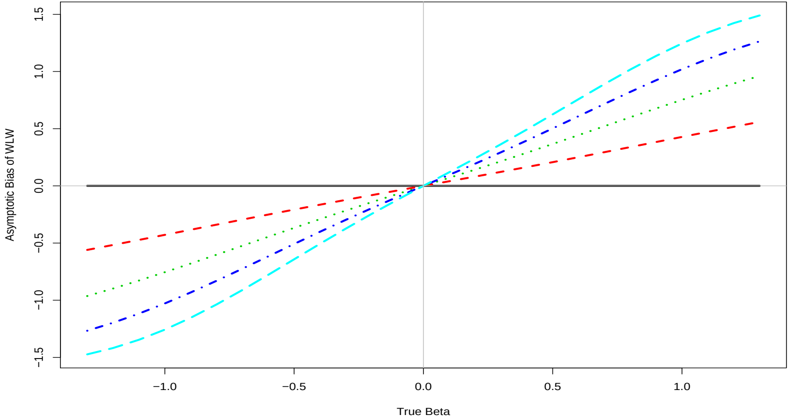
where

$$e_k^{WLW}(v; \theta, \beta, \beta^*) = \frac{E(Xe^{\beta^* X}\bar{\mathcal{G}}_k(v\theta e^{\beta X}))}{E(e^{\beta^* X}\bar{\mathcal{G}}_k(v\theta e^{\beta X}))}$$

- Asymptotic Bias of $\hat{\beta}_k^{WLW} = \beta_k^* - \beta$

Theoretical Bias of $\hat{\beta}_k^{WLW}$ WLW Estimators

Plots are for $k = 1(BLACK), 2, 3, 4, 5(LIGHTBLUE)$.



On PWP Estimators

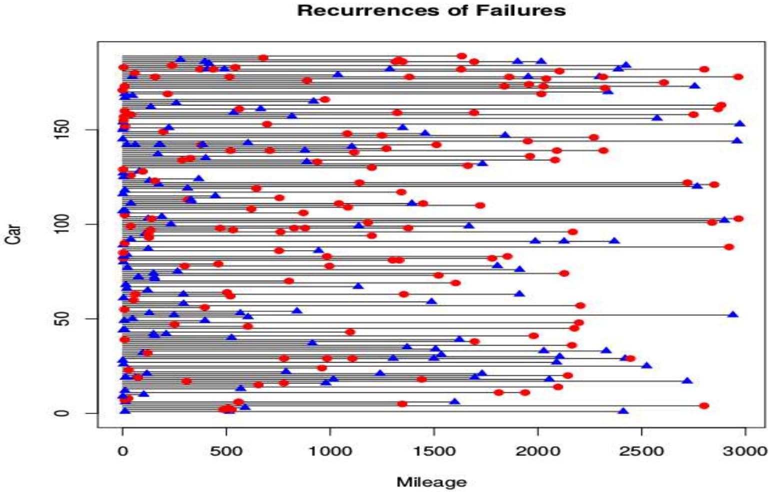
- Main Difference Between WLW and PWP:

$$E(Y_k^{WLW}(v)|X) = \bar{G}(v)\bar{\mathcal{G}}_k(v\theta \exp(\beta X));$$

$$E(Y_k^{PWP}(v)|X) = \bar{G}(v)\frac{g_k(v\theta \exp(\beta X))}{\theta \exp(\beta X)}.$$

- Leads to: $u_k^{PWP}(s; \theta, \beta) = 0$ for $k = 1, 2, \ldots$.
- Remark: The u_k's are corresponding score functions.
- $\hat{\beta}_k^{PWP}$ are **asymptotically unbiased** for β for each k (at least in this HPP model)!
- Theoretical result consistent with observed results from simulation studies and explains D. Oakes' observation.

A Car Warranty Data with Two Competing Causes of Failures



Current Research Problems I

- Recurrent events.
- Competing risks.
- Longitudinal markers.
- Terminal event.
- Problem: How to Jointly Model all these aspects.
- Question: How to exploit competing recurrent events and marker data to inform about the terminal event?
- Question: Is it worth keeping track of the marker and/or competing recurrent events when interest is on the terminal event?

Current Research Problems II

- Reliability systems: composed of several components or subsystems.
- Coherent structure function: mathematical representation of how components/subsystems constitute system.
- Components/subsystems possibly stochastically dependent.
- System-modeling and analysis through component-modeling and analysis.
- Possible recurrences at component-level and/or changing structure function as components fail.
- Dynamic reliability models, in particular, load-sharing models.
- Relevant for maintenance of engineering and reliability systems.

Concluding Remarks

- Recurrent events prevalent in many areas.
- Dynamic models: accommodate unique aspects.
- More research in inference for dynamic models; e.g., theoretical properties for model with frailties.
- Caution: informative aspects of model.
- Beware: marginal modeling approaches.
- *Current limitation:* tracking effective age. Feasible with electronic and mechanical systems.
- Efficiency gains using data from the event recurrences, which may be competing.
- Other problems: markers, terminal events, coherent system analysis.
- *Dynamic recurrent event modeling*: challenging and still fertile!

Acknowledgments

- Jean-Yves Dauxois and INSA for the invitation to attend workshop.
- Co-Workers [* = former or current students]:
  - A. Adekpedjou*
  - A. McLain*
  - JR Gonzalez*
  - M. Hollander
  - P. Liu*
  - J. Quiton*
  - E. Slate
  - R. Stocker*
  - R. Strawderman
  - L. Taylor*
- Research supports from US National Science Foundation (NSF) and US National Institutes of Health (NIH).