Modeling and Non- and Semi-Parametric Inference with Recurrent Event Data

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Some (Recurrent) Events

- Submission of a manuscript for publication.
- Occurrence of tumor.
- Onset of depression.
- Patient hospitalization.
- Machine/system failure.
- Occurrence of a natural disaster.
- Non-life insurance claim.
- Change in job.
- Onset of economic recession.
- At least a 200 points decrease in the DJIA.
- Marital disagreement.

Event Times and Distributions

- T : the time to the occurrence of an event of interest.
- $F(t) = \Pr\{T \leq t\}$: the distribution function of T.
- $S(t) = \bar{F}(t) = 1 - F(t)$: survivor/reliability function.
- Hazard rate/ probability and Cumulative Hazards:

$$\text{Cont:} \quad \lambda(t)dt \approx \Pr\{T \leq t + dt | T \geq t\} = \frac{f(t)}{S(t-)}dt$$

$$\text{Disc:} \quad \lambda(t_j) = \Pr\{T = t_j | T \geq t_j\} = \frac{f(t_j)}{S(t_j-)}$$

$$\text{Cumulative:} \quad \Lambda(t) = \int_0^t \lambda(w)dw \quad \text{or} \quad \Lambda(t) = \sum_{t_j \leq t} \lambda(t_j)$$

Representation/Relationships

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

$$S(t) = \Pr\{T > t\} = \prod_{i=1}^{M} \Pr\{T > t_i | T \geq t_{i-1}\}$$
$$\approx \prod_{i=1}^{M} [1 - \{\Lambda(t_i) - \Lambda(t_{i-1})\}] \, .$$

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

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

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

Estimation of F and Why?

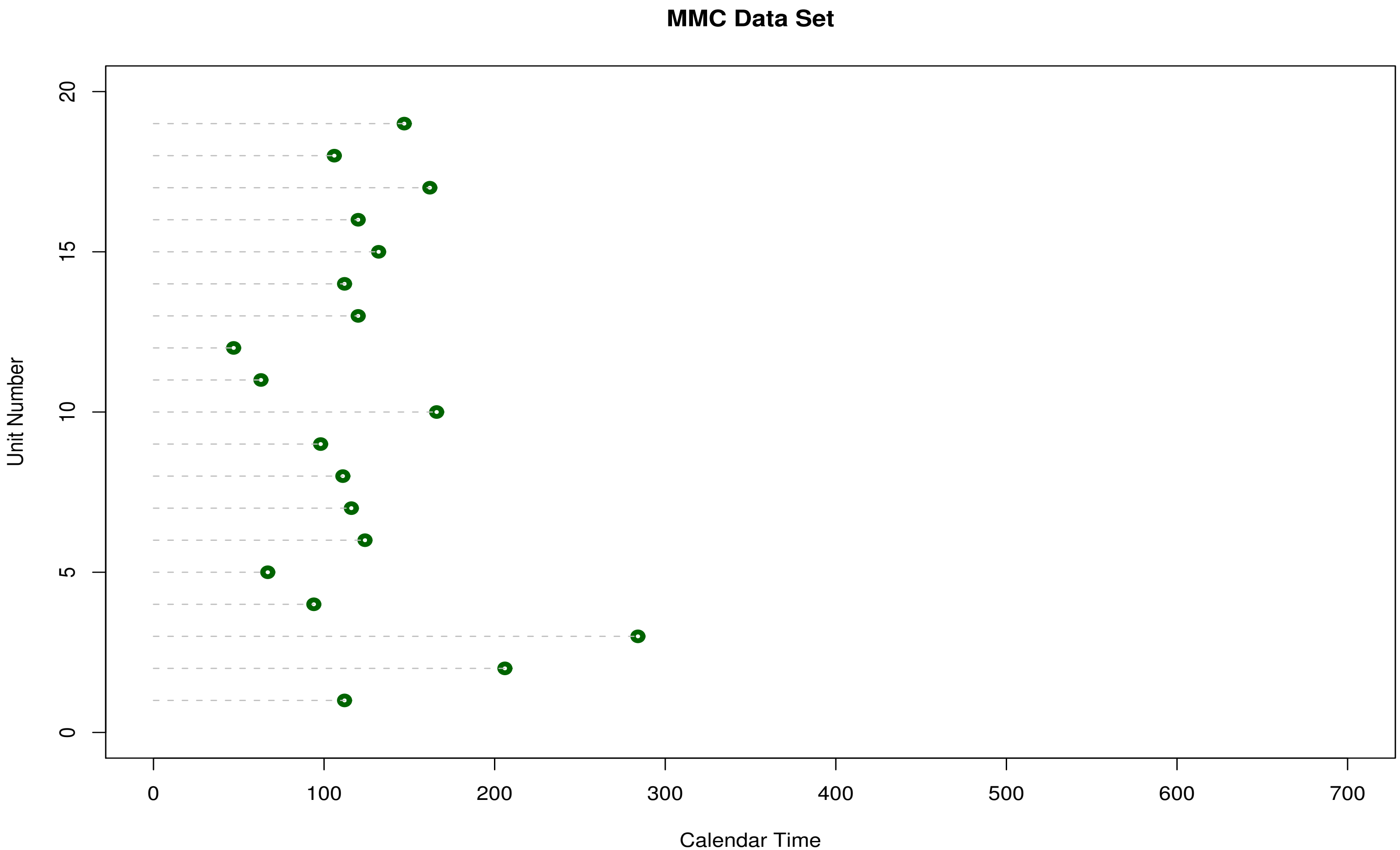
- Most Basic Problem: Given a sample $T_1, T_2, \ldots, T_n$ from an unknown distribution F, to obtain an estimator $\hat{F}$ of F.
- Why is it important to know how to estimate F?
  - Functionals/parameters $\theta(F)$ of F (e.g., mean, median, variance) can be estimated via $\hat{\theta} = \theta(\hat{F})$.
  - 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

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

- DF F estimated by: $\hat{F}_{pa}(t) = F(t;\hat{\theta})$.

Parametric Estimation: Asymptotics

- *When $\mathcal{F}$ holds*, MLE of θ satisfies

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

$$\mathcal{I}(\theta) = \text{Var}\{\tfrac{\partial}{\partial\theta}\log f(T_1;\theta)\} = \text{Fisher information.}$$

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

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

then

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

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 $I\{T_i \le t\}, i = 1, 2, \ldots, n,$ 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 $\mathcal{F}$, we take ratio of asymptotic variances to give the efficiency of parametric estimator over nonparametric estimator.

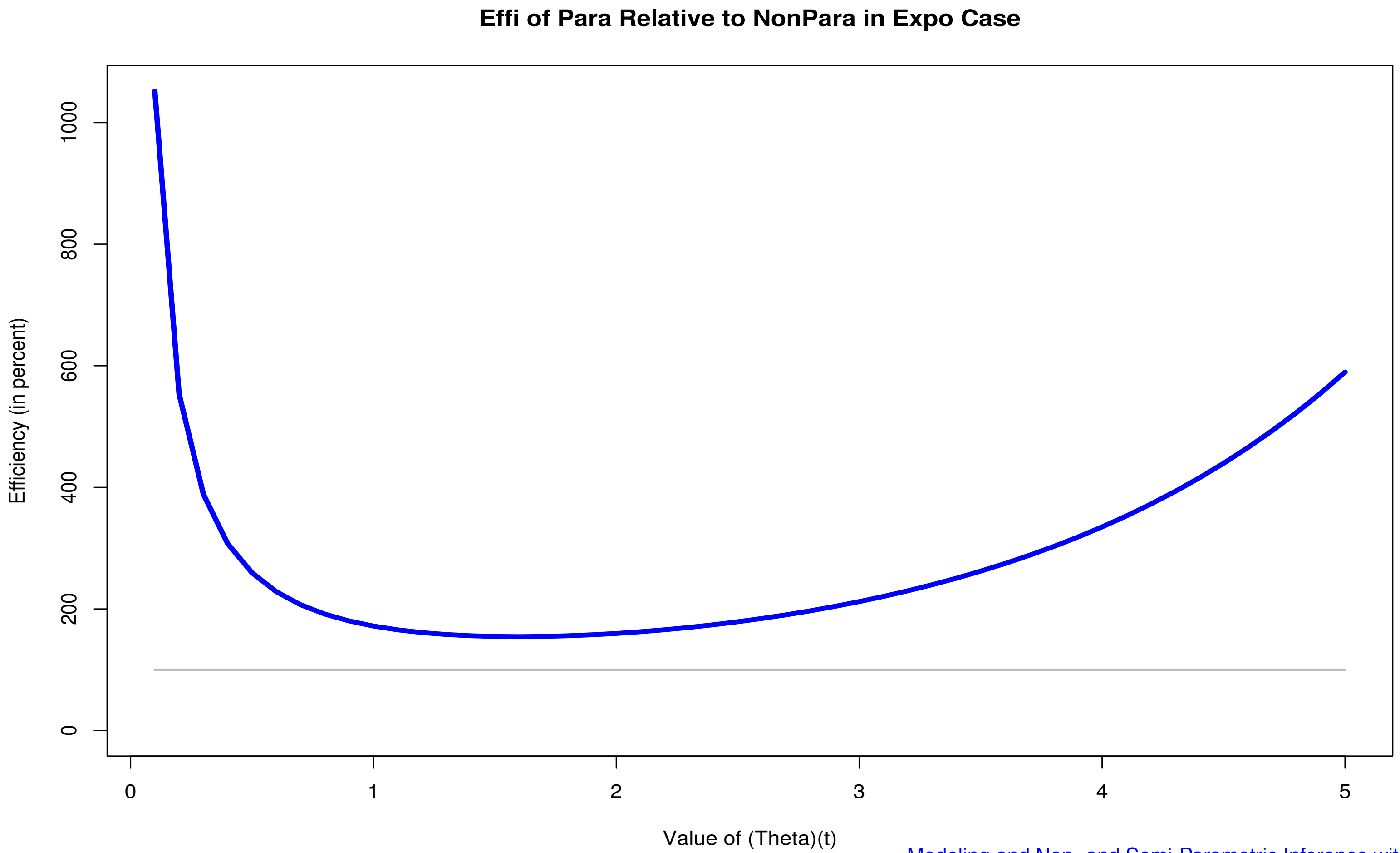
$$\text{Eff}(\hat{F}_{pa}(t) : \hat{F}_{np}(t)) = \frac{F(t;\theta)[1 - F(t;\theta)]}{\dot{F}(t;\theta)' \mathcal{I}(\theta)^{-1} \dot{F}(t;\theta)}.$$

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

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

Efficiency: Parametric/Nonparametric

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



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 $\bar{T} = \frac{1}{n}\sum_{i=1}^{n} T_i$ the sample mean, the parametric estimator of F is

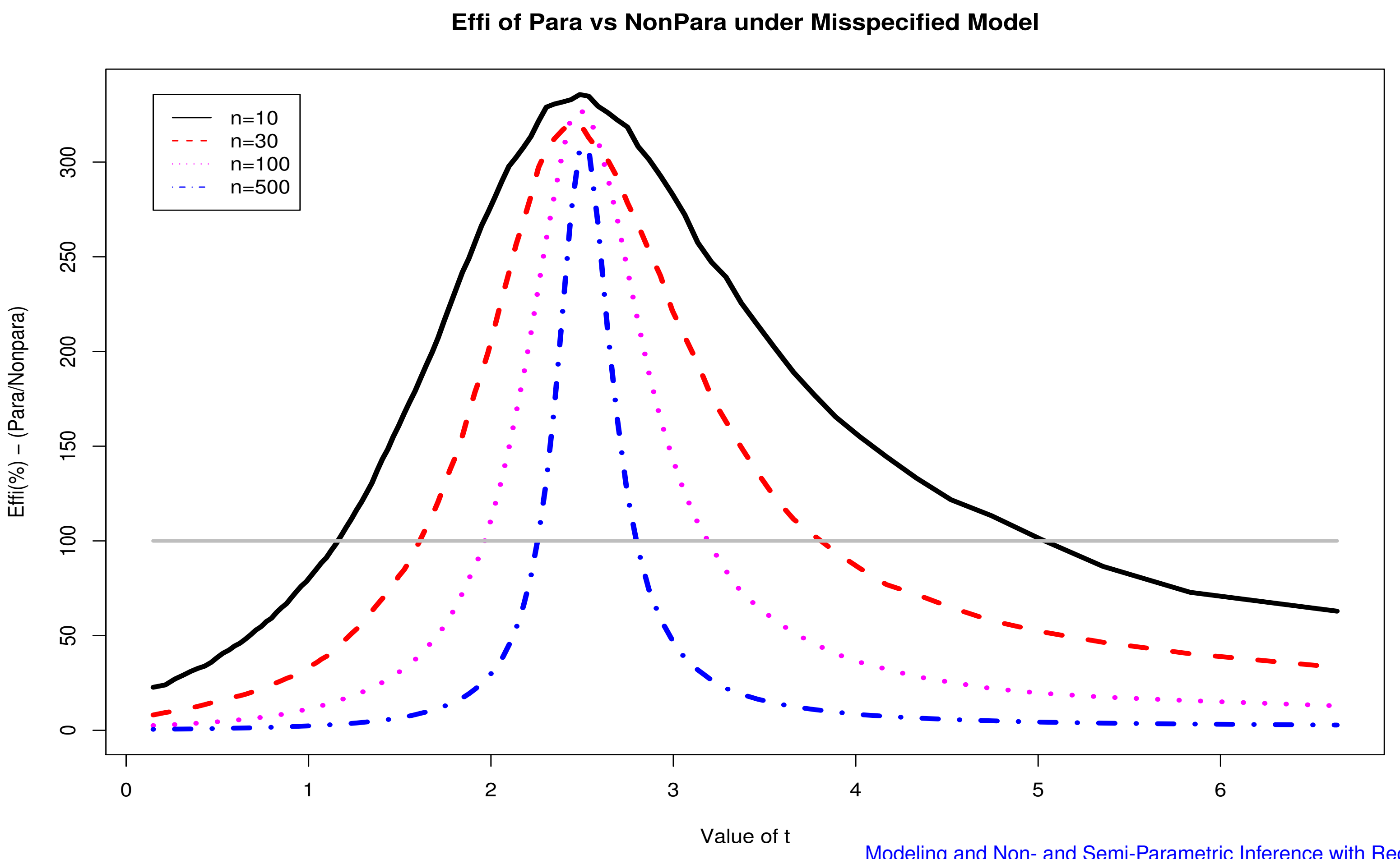
$$\hat{F}_{pa}(t) = 1 - \exp\{-t/\bar{T}\}.$$

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

$$\hat{F}_{pa}(t) \sim \text{AN}\left(1 - \exp\left\{-\frac{\theta t}{\alpha}\right\}, \frac{1}{n}\frac{(\theta t)^2}{\alpha^3}\exp\left\{-\frac{2(\theta t)}{\alpha}\right\}\right).$$

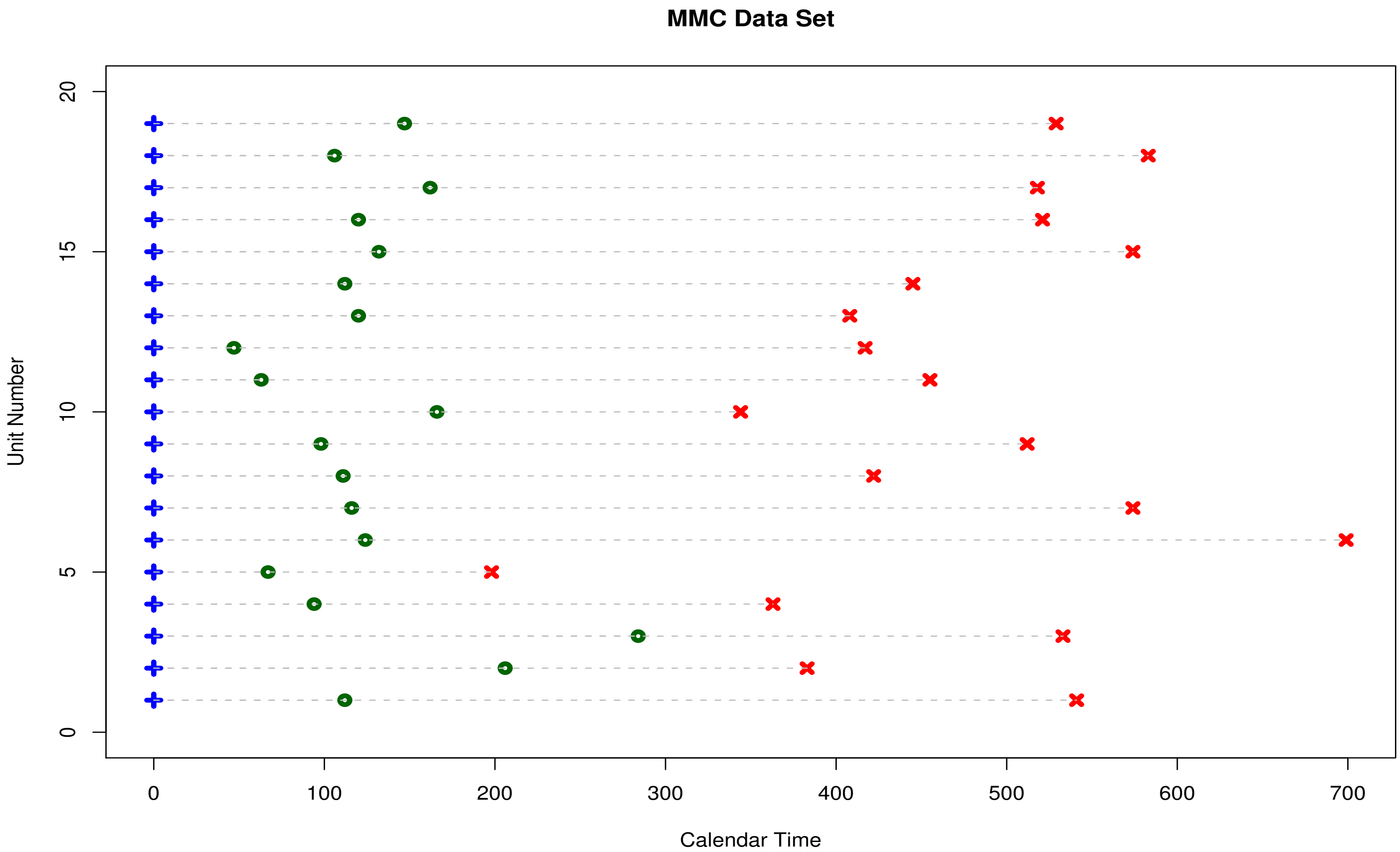
Efficiency: Under a Mis-specified Model

Simulated Effi: MSE(Non-Parametric)/MSE(Parametric) under a *mis-specified* exponential family model. *True* Family of Model: Gamma Family



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 ith unit, a right-censoring variable C_i with $C_1, C_2, \ldots, C_n$ IID df G.
- Observables are $(Z_i, \delta_i), i = 1, 2, \ldots, n$ 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_is.
- Nonparametric Approaches:
    - 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:

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

- 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):

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

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 $J(t) = I\{Y(t) > 0\}$ 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:

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

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

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

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

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

Asymptotic Properties

- NAE: $\sqrt{n}[\hat{\Lambda}(t) - \Lambda(t)] \Rightarrow Z_1(t)$ with $\{Z_1(t) : t \geq 0\}$ a zero-mean *Gaussian process* with

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

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

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

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

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 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:

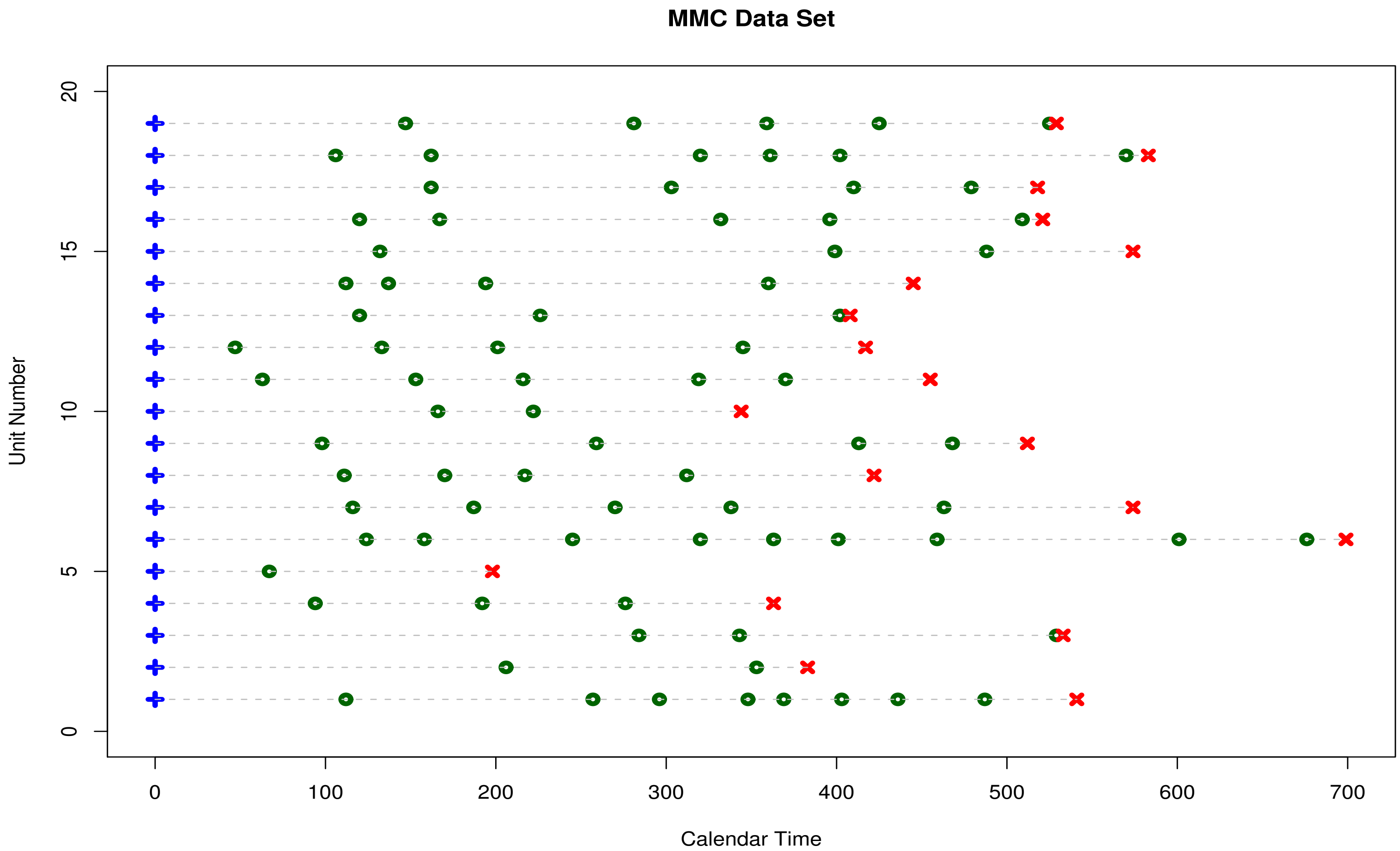
$$L_P(\beta) \equiv \prod_{i=1}^{n}\prod_{t<\infty}\left[\frac{\exp(\beta'\mathbf{x}_i)}{\sum_{j=1}^{n} Y_j(t)\exp(\beta'\mathbf{x}_j)}\right]^{\Delta N_i(t)}.$$

- 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

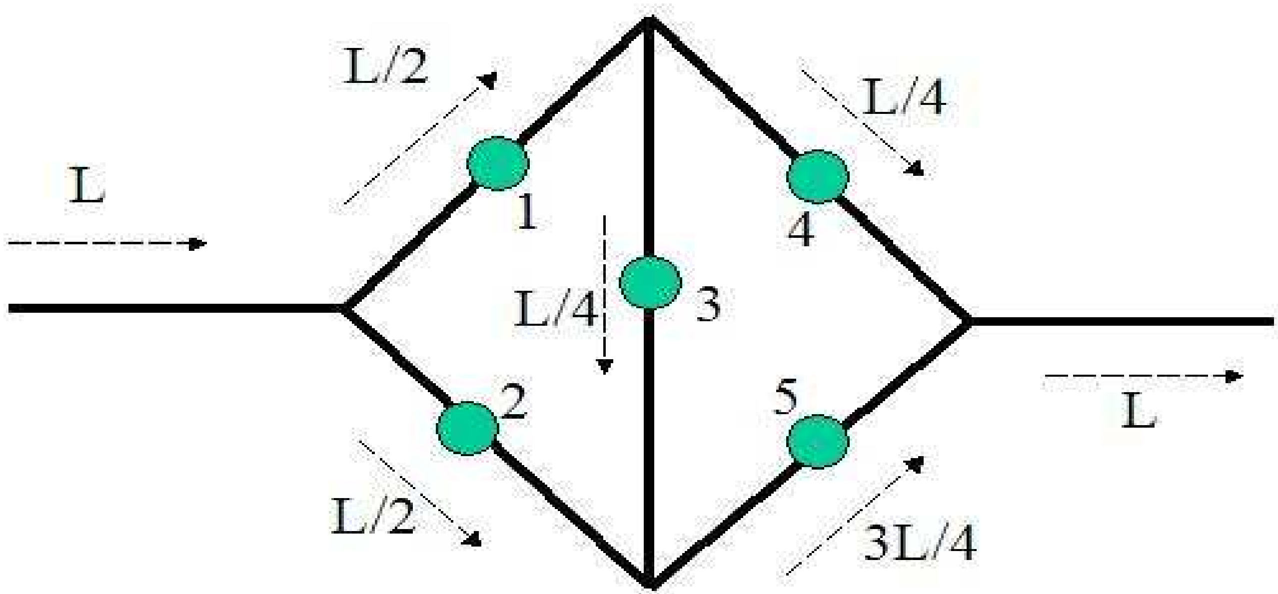


Problem: Estimate inter-event time distribution.

Recurrent Events: In Complex Systems

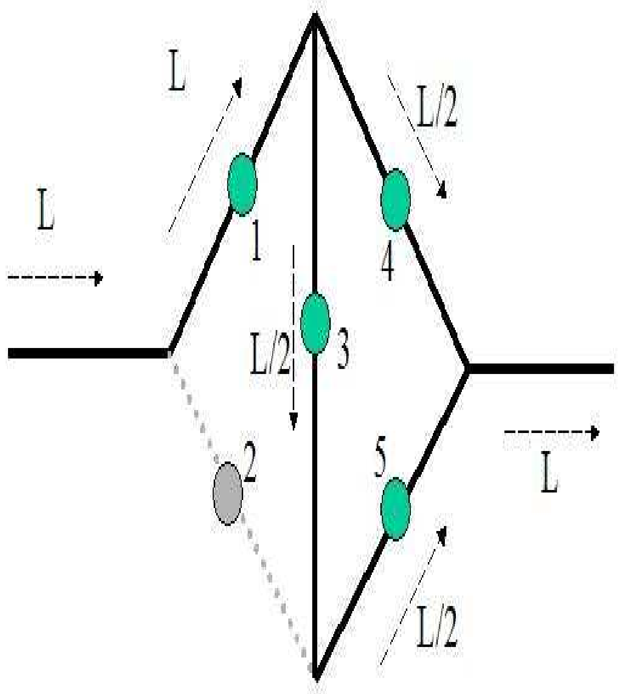
A Reliability Bridge Structure

$$\phi(x_1, x_2, x_3, x_4, x_5) = x_1 x_3 x_5 \vee x_2 x_3 x_4 \vee x_1 x_4 \vee x_2 x_5$$

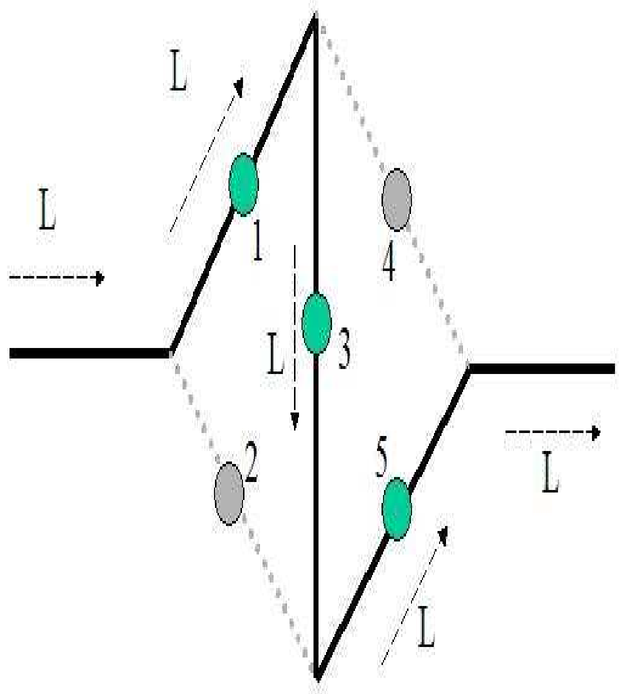


System’s Dynamic Evolution

After Component 2 Has Failed: Series-Parallel



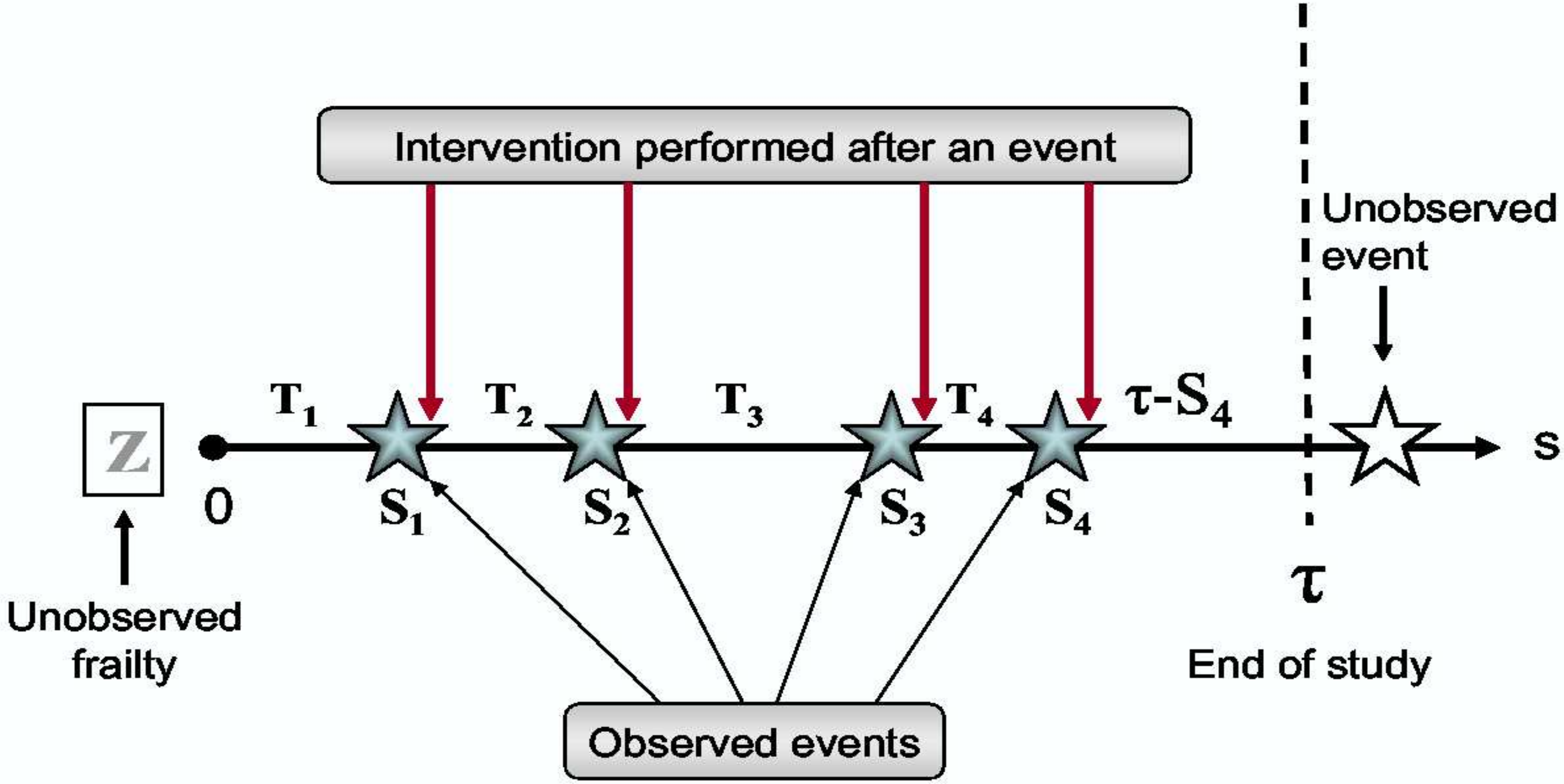
After Components 2 and 4 Have Failed: Series



Points to Ponder in Modeling

- System fails under certain component failure configurations (called cut sets).
- Recurrent event of interest are the successive component failure occurrences.
- Component failures dynamically change effective structure function. Originally a bridge system; then after #2 fails, it is a series-parallel system; then after #2 and #4 fail, it is a series system.
- Component failures change component loads (essence of load-sharing system).
- System failure time may right-censor some component failure times.

Representation: One Subject



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

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 $\tau \sim G$
- $K = \max\{k : S_k \leq \tau\} =$ number of events in $[0, \tau]$
- $Z =$ unobserved frailty variable
- $N^\dagger(s) =$ number of events in $[0, s]$
- $Y^\dagger(s) = I\{\tau \geq s\} =$ at-risk indicator at time s
- $\mathbf{F}^\dagger = \{\mathcal{F}_s^\dagger : s \geq 0\} =$ filtration: information that includes interventions, covariates, etc.

Aspect of Sum-Quota Accrual

Remark: A unique feature of recurrent event modeling is the sum-quota constraint that arises due to a fixed or random observation window. Failure to recognize this in the statistical analysis leads to erroneous conclusions.

$$K = \max\left\{k : \sum_{j=1}^{k} T_j \leq \tau\right\}$$

$(T_1, T_2, \ldots, T_K)$ satisfies $\displaystyle\sum_{j=1}^{K} T_j \leq \tau < \sum_{j=1}^{K+1} T_j$.

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

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

A General Class of Full Models

- Peña and Hollander (2004) model.

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

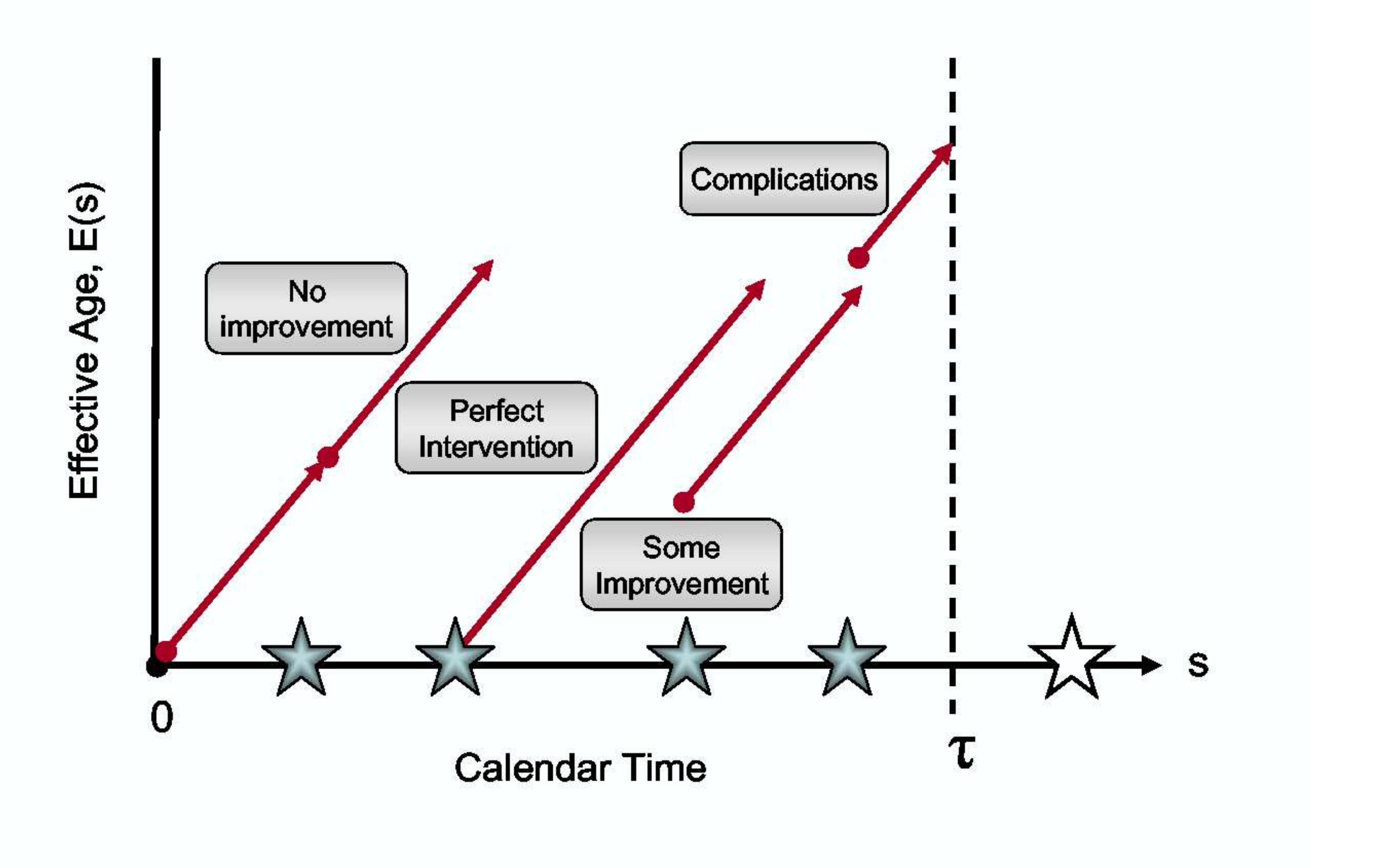
$$M^\dagger(s|Z) \in \mathcal{M}_0^2 = \text{sq-int martingales}$$

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

- Intensity Process:

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

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),

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

Semi-Parametric Estimation: No Frailty

Observed Data for n Subjects:

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

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

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

with the model for the 'signal' being

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

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:

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

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

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:

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

- 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 estimator in PSH (2001) obtains.

Sum-Quota Effect: IID Renewal

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

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

$$\sigma^2(t) = \bar{F}(t)^2 \int_0^t \frac{d\Lambda(w)}{\bar{F}(w)\bar{G}(w-)\left[1 + \nu(w)\right]}$$

$$\nu(w) = \frac{1}{\bar{G}(w-)} \int_w^\infty \rho^*(v - w) dG(v)$$

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

Semi-Parametric Estimation: With Frailty

- Recall the intensity rate:

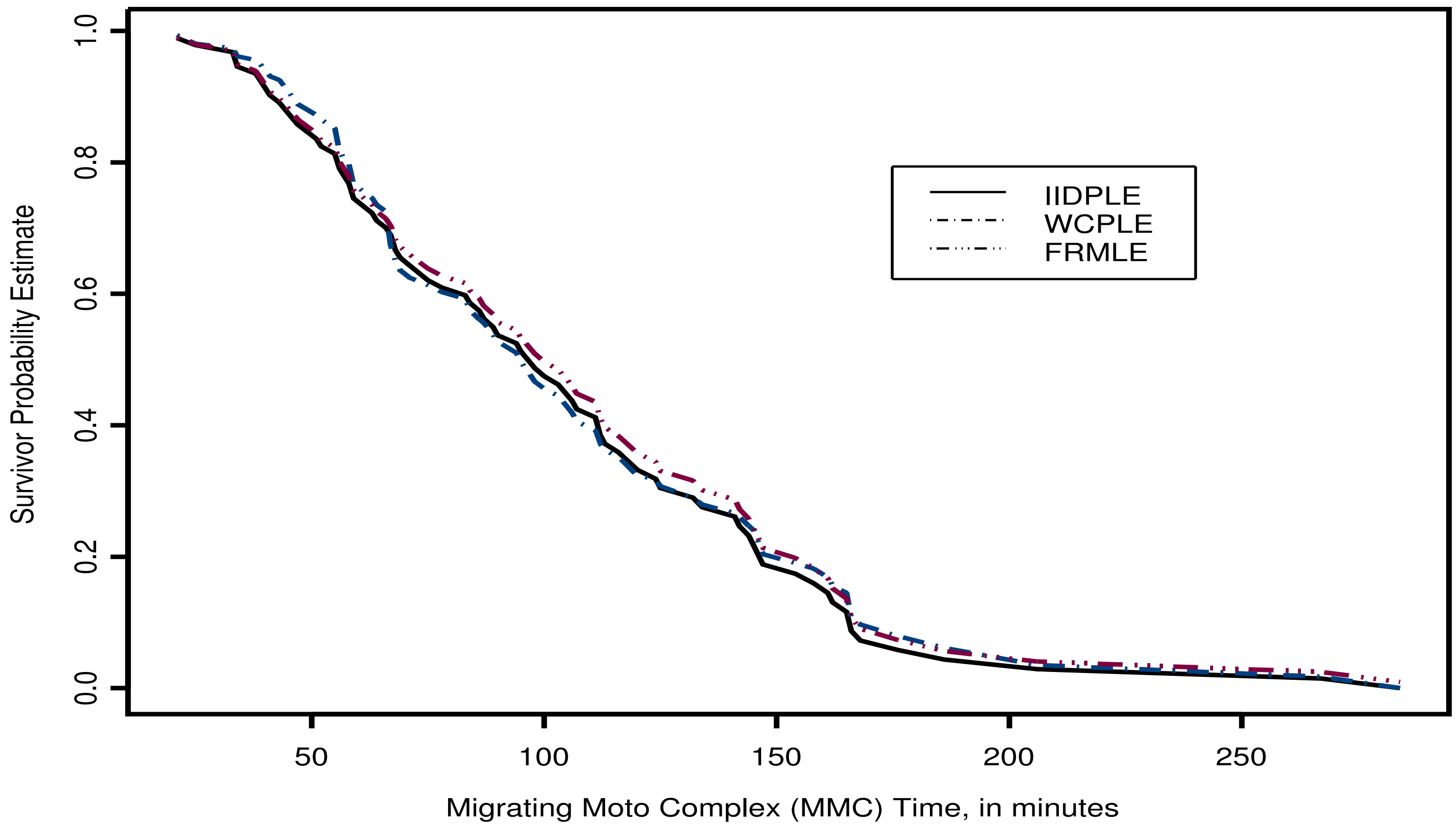
$$\lambda_i(s|Z_i, \mathbf{X}_i) = Z_i \, \lambda_0[\mathcal{E}_i(s)] \, \rho[N_i^\dagger(s-); \alpha] \, \psi(\beta^{\mathtt{t}} \mathbf{X}_i(s))$$

- 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 in Peña, Slate & Gonzalez (*JSPI*, 2007).

First Application: MMC Data Set

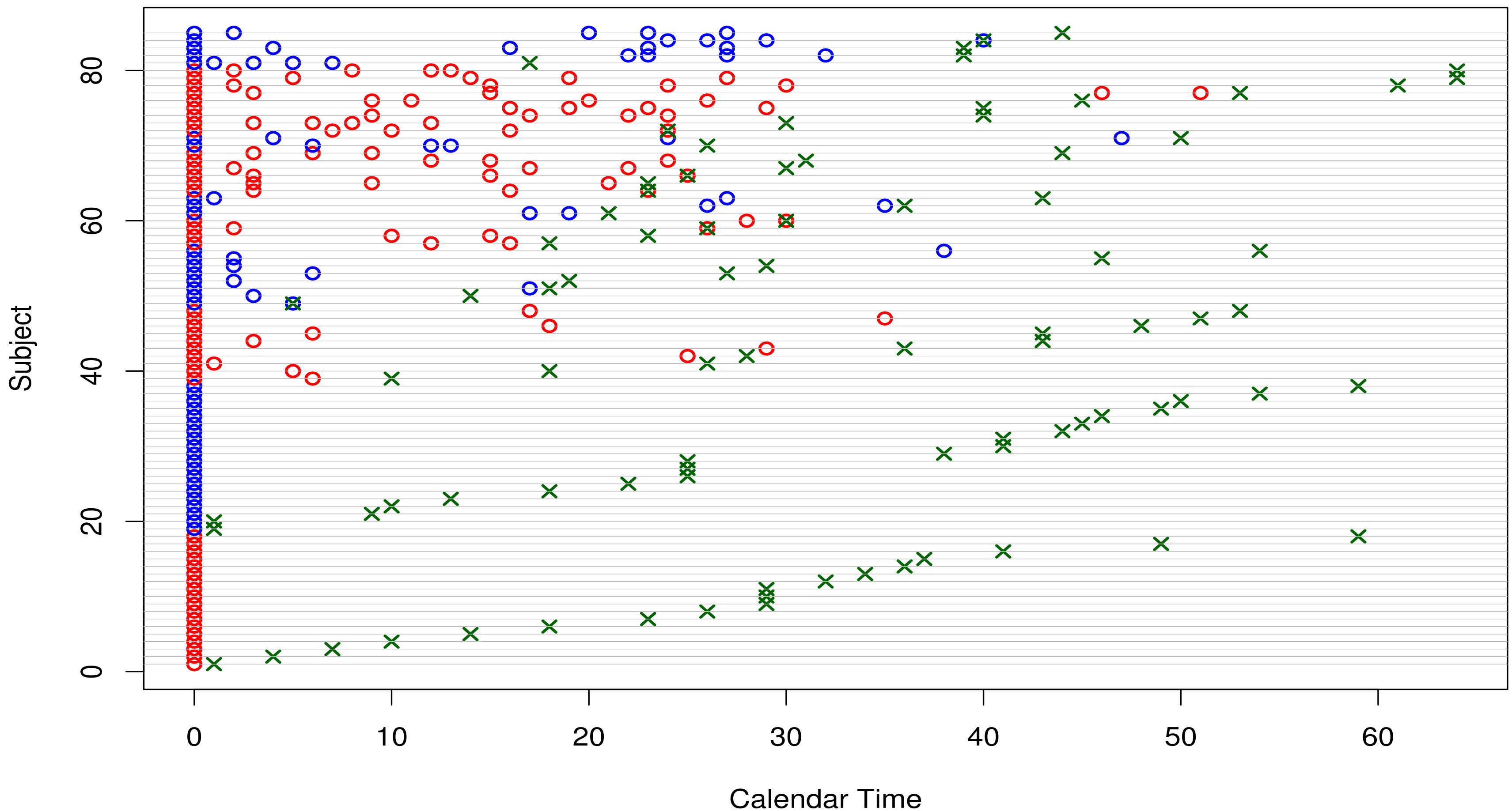
Aalen and Husebye (1991) Data

Estimates of distribution of MMC period



Second 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 Minimal[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 ($\mathcal{E}(s) = s$).

On Asymptotic Properties

- Asymptotics under the no-frailty models.
- Difficulty: $\Lambda_0(\cdot)$ has $\mathcal{E}(s)$ as argument in the model; whereas, interest is usually on $\Lambda_0(t)$.
- No martingale structure in gap-time axis. MCLT not directly applicable.
- Under regularity conditions: consistency and joint weak convergence to Gaussian processes of standardized $(\hat{\alpha}, \hat{\beta})$ and $\hat{\Lambda}_0(s^*, \cdot)$.
- Results extend those in Andersen and Gill (AoS 82) regarding Cox PHM, though proofs different.
- Research on the asymptotics for the model with frailty *in progress.*

Asymptotics: Master Theorem

- $\{\mathbf{H}_i\}$ a sequence defined on $[0, s^*] \times [0, t^*]$.
- $M_i(s,t) = \int_0^s I\{\mathcal{E}_i(v) \le t\} M_i^\dagger(dv)$.
- $Y_i(s,t)$ - generalized at-risk process.
- Under some regularity conditions, and if

$$\frac{1}{n} \sum_{i=1}^{n} \mathbf{H}_i^{\otimes 2}(s^*, \cdot) Y_i(s^*, \cdot) \xrightarrow{upr} \mathbf{v}(s^*, \cdot),$$

- then, with $\Sigma(s^*, t) = \int_0^t \mathbf{v}(s^*, w) \Lambda_0(dw)$,

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \int_0^{\cdot} \mathbf{H}_i(s^*, w) M_i(s^*, dw) \Longrightarrow \mathbf{GP}(0, \Sigma(s^*, \cdot)).$$

Relevant Empirical Measures

- Simplified model (one unit):

$$\Pr\{dN_i^\dagger(v) = 1 | \mathcal{F}_{s-}\} = Y_i^\dagger(v)\lambda_0[\mathcal{E}_i(v)]\Xi_i(v;\eta)dv.$$

- *Conditional* PM $Q(s^*, w; \eta)$ on $\{1, 2, \ldots, N^\dagger(s^*-) + 1\}$:

$$Q(\{j\}; s^*, w; \eta) = \frac{\varphi_{j-1}(w;\eta) I\{\mathcal{E}(S_{j-1}) < w \leq \mathcal{E}(S_j)\}}{Y(s^*, w)}$$

with $S_{N^\dagger(s^*-)+1} = \min(s^*, \tau)$.

- *Conditional* PM $P(s^*, w; \eta)$ on $\{1, 2, \ldots, n\}$:

$$P(\{i\}; s^*, w; \eta) = \frac{Y_i(s^*, w; \eta)}{n\mathbb{P}Y(s^*, w; \eta)}.$$

Empirical Means & Variances

$$\mathbb{P}f(\mathbf{D}) = \frac{1}{n}\sum_{i=1}^{n} f(\mathbf{D}_i)$$

$$\mathbb{E}_{Q(s^*,w;\eta)}g(J) = \sum_{j=1}^{N^\dagger(s^*-)+1} g(j)Q(\{j\}; s^*, w; \eta)$$

$$\mathbb{V}_{Q(s^*,w;\eta)}g(J) = \mathbb{E}_{Q(s^*,w;\eta)}[g^2(J)] - (\mathbb{E}_{Q(s^*,w;\eta)}g(J))^2$$

$$\mathbb{E}_{P(s^*,w;\eta)}g(I) = \sum_{i=1}^{n} g(i)P(\{i\}; s^*, w; \eta)$$

$$\mathbb{V}_{P(s^*,w;\eta)}g(I) = \mathbb{E}_{Q(s^*,w;\eta)}[g^2(I)] - (\mathbb{E}_{Q(s^*,w;\eta)}g(I))^2$$

Relevant Limit Functions

- $s_0(s^*, w; \eta, \Lambda_0) =$ plim $\mathbb{P}Y(s^*, w; \eta)$.
- Partial Likelihood Information Limit:

$$\mathcal{I}_p(s^*, t; \eta, \Lambda_0) = \text{plim}$$
$$\int_0^t \left\{ \left[\mathbb{E}_{P(s^*,w;\eta)} \mathbb{V}_{Q(s^*,w;\eta)} \left(\nabla_\eta \log \Xi_I(\mathcal{E}_{IJ-1}^{-1}(w); \eta) \right) + \right.\right.$$
$$\left.\left. \mathbb{V}_{P(s^*,w;\eta)} \mathbb{E}_{Q(s^*,w;\eta)} \left(\nabla_\eta \log \Xi_I(\mathcal{E}_{IJ-1}^{-1}(w); \eta) \right) \right] \right\} \times$$
$$s_0(s^*, w; \eta, \Lambda_0)\ \Lambda_0(dw).$$

- With $\mathbf{e}(s^*, w; \eta, \Lambda_0) =$ plim $\frac{\mathbb{P}\nabla_\eta Y(s^*,w;\eta)}{\mathbb{P}Y(s^*,w;\eta)}$, let

$$A(s^*, t; \eta, \Lambda_0) = \int_0^t \mathbf{e}(s^*, w; \eta, \Lambda_0)\Lambda_0(dw).$$

Weak Convergence Results

As $n \to \infty$ and under certain regularity conditions:

$$\sqrt{n}(\hat{\eta}(s^*, t^*) - \eta) \Rightarrow N(0, \mathcal{I}_p(s^*, t^*; \eta, \Lambda_0)^{-1})$$

$$\sqrt{n}(\hat{\Lambda}_0(s^*, \cdot) - \Lambda_0(\cdot)) \Rightarrow GP(0, \Gamma(s^*, \cdot; \eta, \Lambda_0))$$

where the limiting variance function is given by

$$\begin{aligned}\Gamma(s^*, t; \eta, \Lambda_0) &= \int_0^t \frac{\Lambda_0(dw)}{s_0(s^*, w; \eta)} \\ &+ \quad A(s^*, t; \eta, \Lambda_0)\mathcal{I}_p(s^*, t^*; \eta, \Lambda_0)^{-1} A(s^*, t; \eta, \Lambda_0)^{\mathtt{t}}.\end{aligned}$$

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 ($k = 1, 2, \ldots, k_0$):

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

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

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

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

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 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

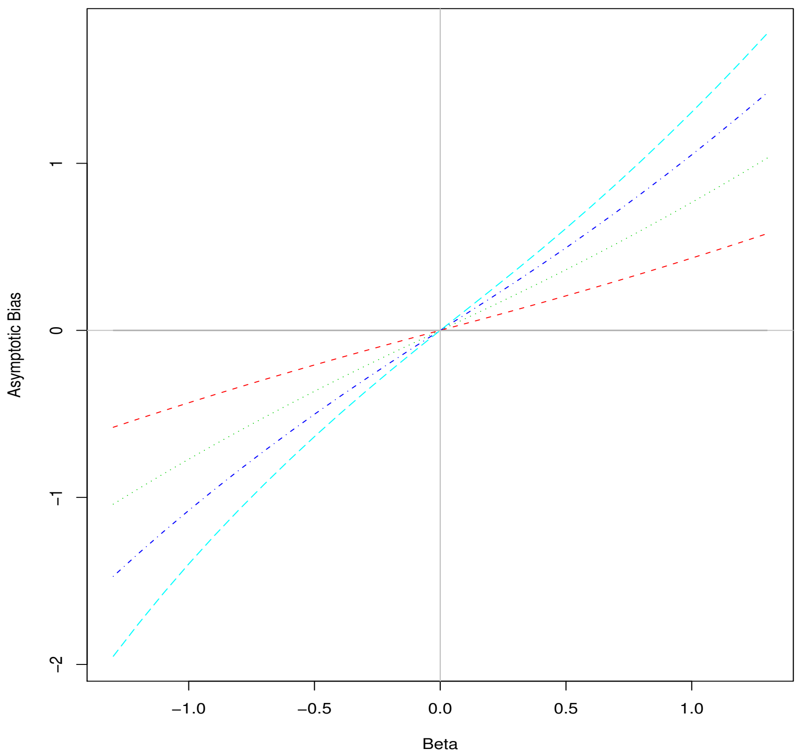
$$e_k^{WLW}(v;\theta,\beta,\beta^*) = \frac{E(Xe^{\beta^* X}\bar{\mathcal{G}}_k(v\theta e^{\beta X}))}{E(e^{\beta^* X}\bar{\mathcal{G}}_k(v\theta e^{\beta X}))}$$

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

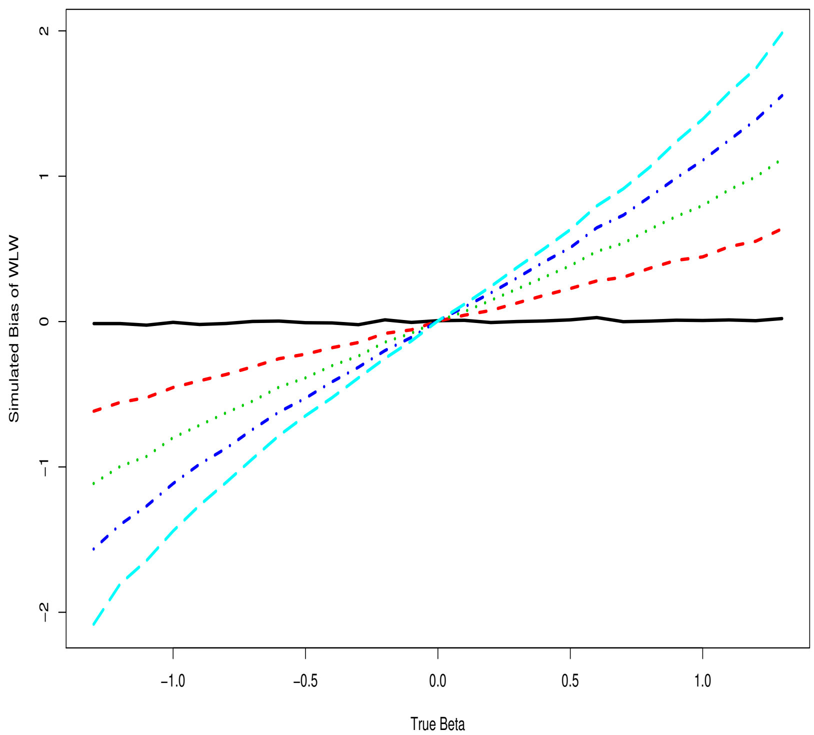
Bias Plots for WLW Estimator

Colors pertain to value of k, the Event Position
$k = 1$: Black; $k = 2$: Red; $k = 3$: Green; $k = 4$: DarkBlue;
$k = 5$: LightBlue

Theoretical



Simulated



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 $k = 1, 2, \ldots$.
- $\hat{\beta}_k^{PWP}$ are **asymptotically unbiased** for β for each k (at least in this HPP model)!
- Theoretical result consistent with observed results from simulation studies and D. Oakes' observation.

Concluding Remarks

- Recurrent events prevalent in many scientific areas.
- Dynamic models: accommodate unique aspects of recurrent data.
- Inference for dynamic models need to be examined at a deeper level.
- *Current limitation:* keeping track of effective age. Current data schemes ignore this.
- GOF and residual analysis (Quiton's dissertation).
- General studies on marginal modeling approaches!
- *Dynamic recurrent event modeling*, a challenge and a fertile research area.

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