

Modelling and Analysis of Recurrent Event Data

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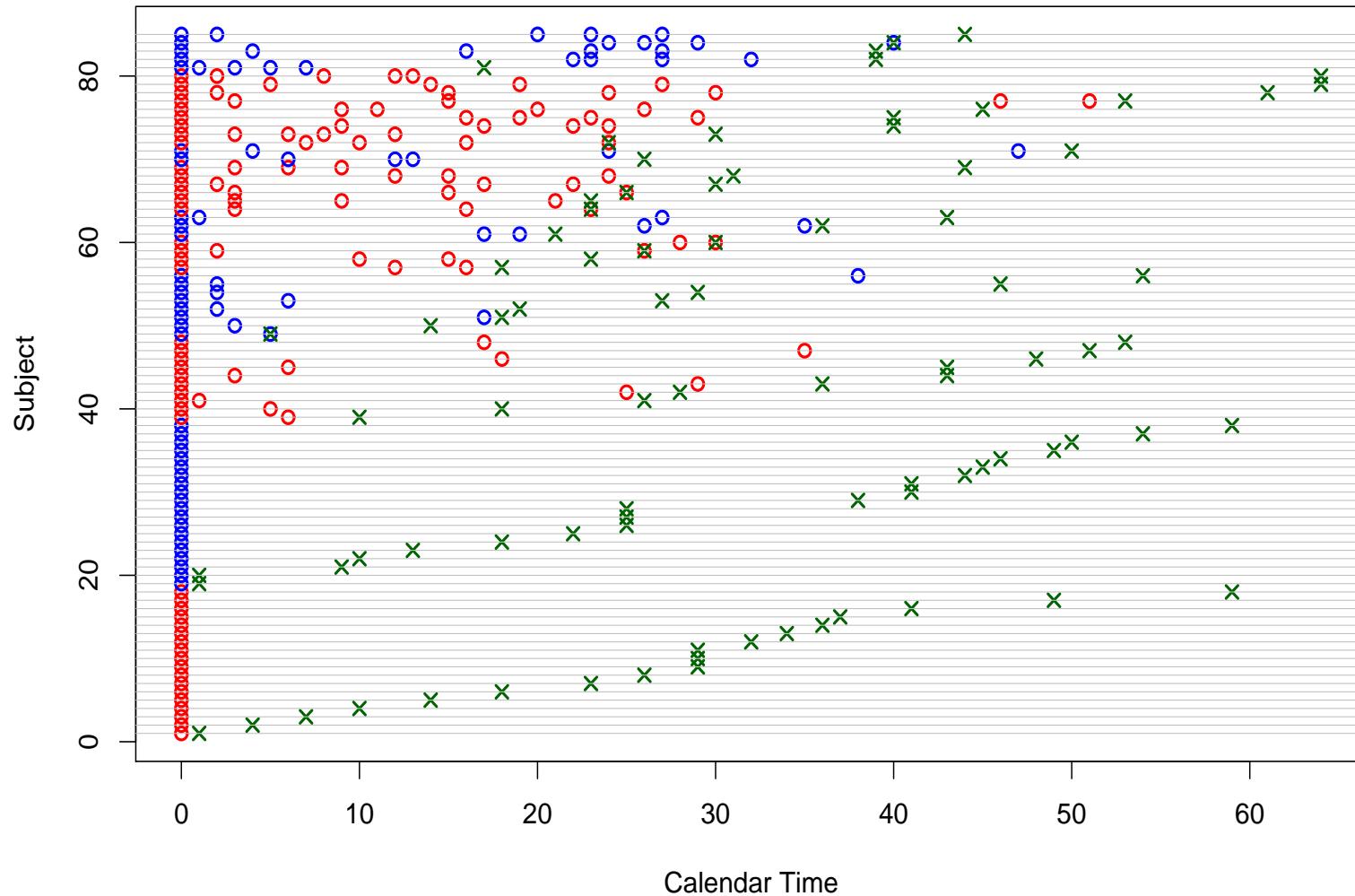
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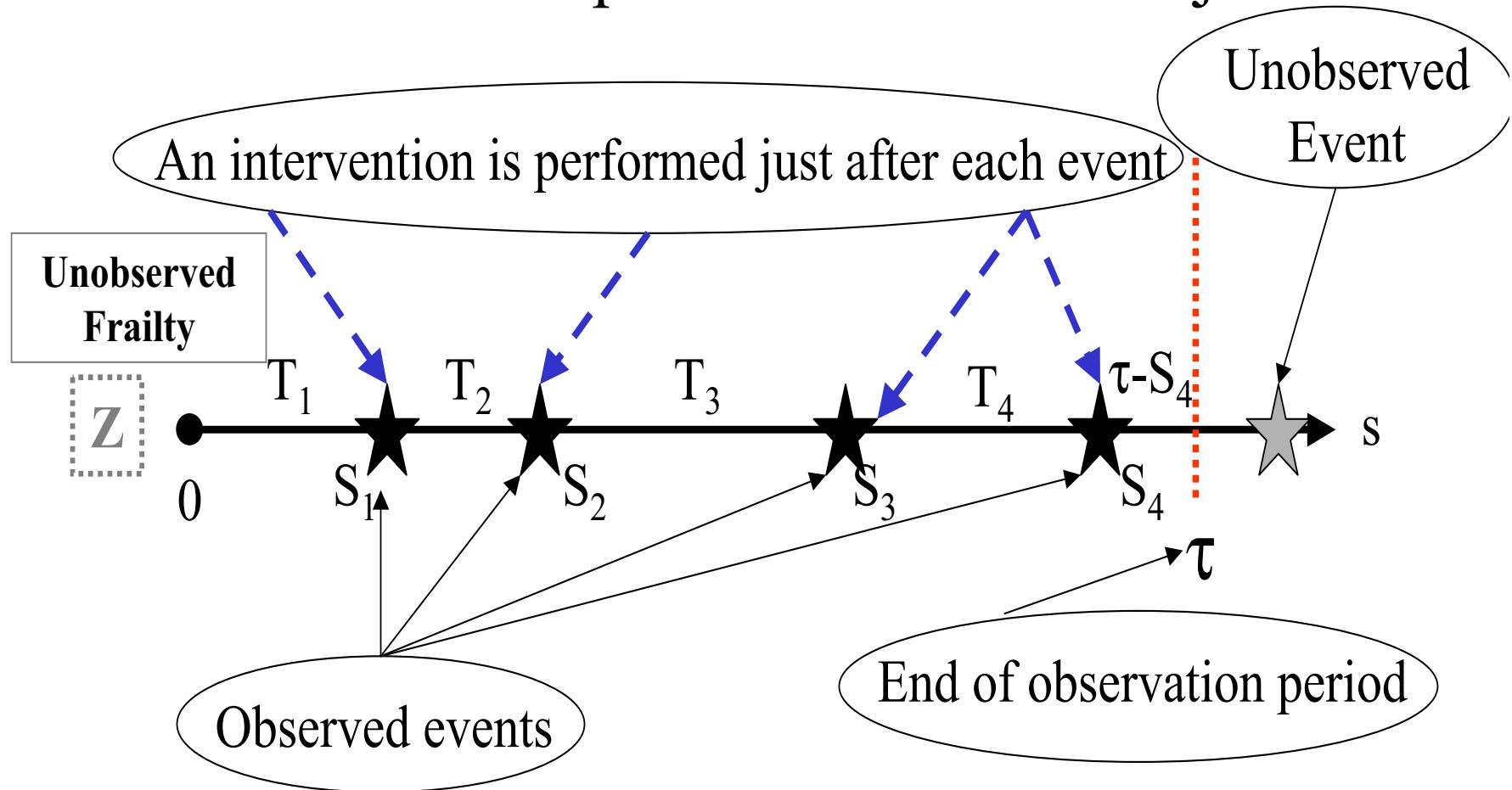
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Bladder Cancer Data (WLW, '89)



A Pictorial Representation: One Subject



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

Random Entities: One Subject

- $\mathbf{X}(s)$ = covariate vector, possibly time-dependent
- T_1, T_2, T_3, \dots = inter-event or gap times
- S_1, S_2, S_3, \dots = calendar times of event occurrences
- τ = end of observation period
- **Accrued History:** $\mathbf{F}^\dagger = \{\mathcal{F}_s^\dagger : s \geq 0\}$
- Z = unobserved frailty variable
- $N^\dagger(s)$ = number of events in $[0, s]$
- $Y^\dagger(s)$ = at-risk indicator at time s

Current Approaches

- In Therneau and Grambsch ('00) book; Therneau and Hamilton ('97); Cook and Lawless ('01)
- **Time-to-first event:** ignores information hence inefficient
- **Wei, Lin Weissfeld (WLW) marginal model:** event number is used as a 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) method:** ‘at-risk process’ remains at 1 until unit is censored

On Recurrent Event Modelling

- Intervention effects after each event occurrence.
- Effects of accumulating event occurrences. Could be weakening or strengthening effect.
- Effects of covariates.
- Associations of event occurrences per subject.
- Random observation monitoring period.
- Number of events informative about stochastic mechanism.
- Informative right-censoring mechanism because of sum-quota accrual scheme.

General Class of Models

- A general and flexible class of models (Peña and Hollander).
- $\{A^\dagger(s|Z) : s \geq 0\}$ is a predictable, nondecreasing process such that given Z and accrued information:

$$\{M^\dagger(s|Z) = N^\dagger(s) - A^\dagger(s|Z) : s \geq 0\}$$

is a zero-mean martingale (a fair game process).
Assume multiplicative form:

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

Intensity Process

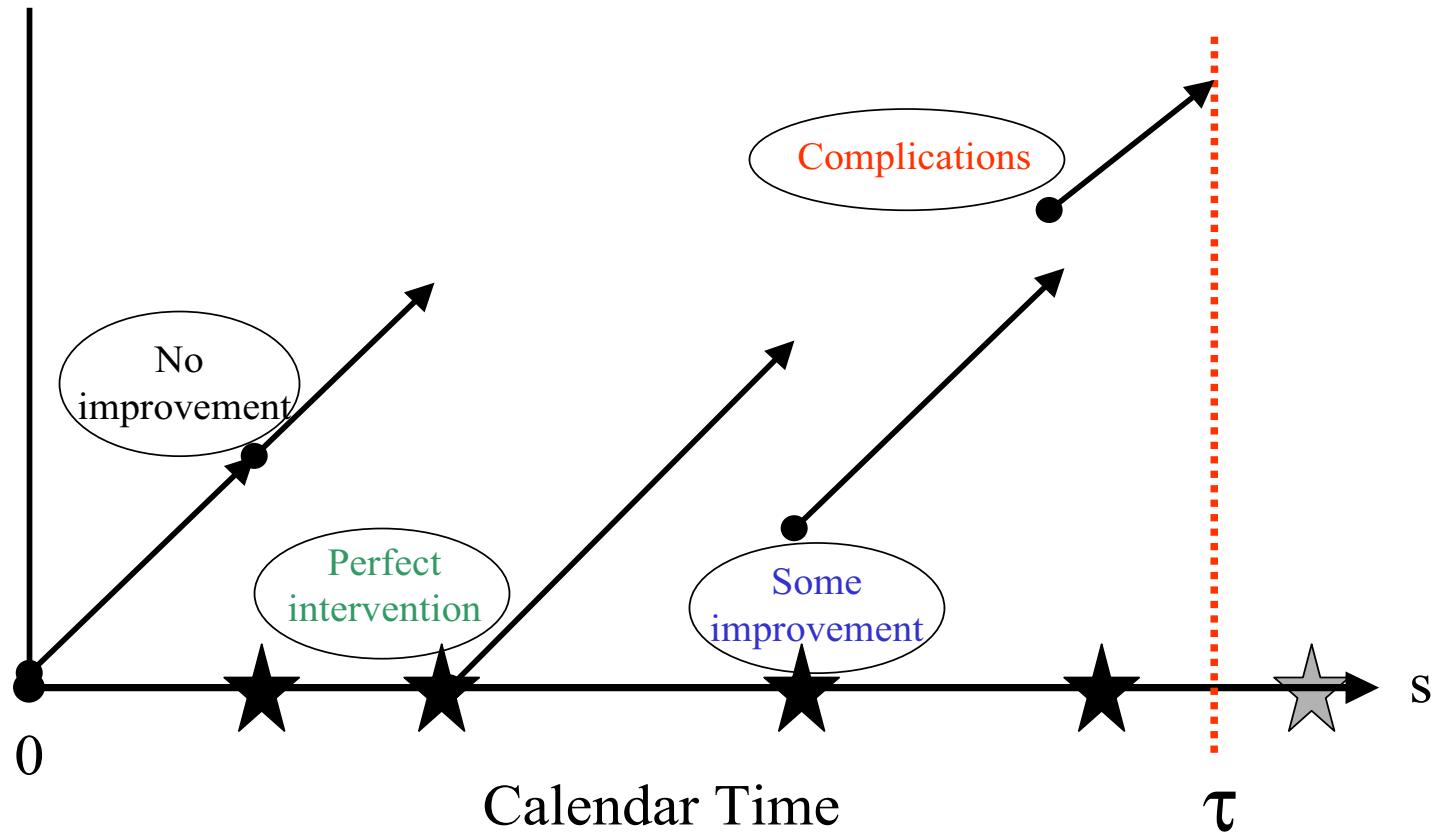
- *Effective Age Process:* $\{\mathcal{E}(s) : 0 \leq s \leq \tau\}$
 - (Dynamically) observed and predictable;
 - $\mathcal{E}(0) = e_0 \geq 0$;
 - $\mathcal{E}(s) \geq 0$ for every s ;
 - On $[S_{k-1}, S_k]$, $\mathcal{E}(s)$ is monotone and differentiable with $\mathcal{E}'(s) \geq 0$.
- Intensity Specification:

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

Effective Age Process

Illustration: Effective Age Process
“Possible Intervention Effects”

Effective
Age, $E(s)$



Possible Effective Ages, $\mathcal{E}(s)$

- ‘Always Perfect Intervention’: (Backward Recurrence Time)

$$\mathcal{E}(s) = s - S_{N^\dagger(s-)}$$

- ‘Always Minimal Intervention’: (Calendar Time)

$$\mathcal{E}(s) = s$$

- Minimal Intervention Model: At each event, a probability of p for a perfect intervention; and a probability of $1 - p$ for a minimal intervention.

Estimation: Without Frailties

- Observed Data:

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

- Compensator:

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

- Martingale:

$$\mathbf{M}^\dagger = \mathbf{N}^\dagger - \mathbf{A}^\dagger = (N_1^\dagger - A_1^\dagger, \dots, N_n^\dagger - A_n^\dagger)$$

Calendar/Gap Time Processes

$$Z_i(s, t) = I\{\mathcal{E}_i(s) \leq t\}, \quad i = 1, \dots, n$$

$$N_i(s, t) = \int_0^s Z_i(v, t) N_i^\dagger(dv)$$

$$A_i(s, t) = \int_0^s Z_i(v, t) A_i^\dagger(dv)$$

$$M_i(s, t) = N_i(s, t) - A_i(s, t) = \int_0^s Z_i(v, t) M_i^\dagger(dv)$$

Generalized At-Risk Process

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

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

$$Y_i(s, w|\alpha, \beta) \equiv \sum_{j=1}^{N_i^\dagger(s-)} I_{(\mathcal{E}_{ij-1}(S_{ij-1}), \mathcal{E}_{ij-1}(S_{ij})]}(w) \varphi_{ij-1}(w|\alpha, \beta)$$
$$+ I_{(\mathcal{E}_{iN_i^\dagger(s-)}(S_{iN_i^\dagger(s-)}), \mathcal{E}_{iN_i^\dagger(s-)}(\min(s, \tau_i))]}(w) \varphi_{iN_i^\dagger(s-)}(w|\alpha, \beta)$$

G-Nelson-Aalen ‘Estimator’

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

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

$$\hat{\Lambda}_0(s, t | \alpha, \beta) = \int_0^t \left\{ \frac{I\{S_0(s, w | \alpha, \beta) > 0\}}{S_0(s, w | \alpha, \beta)} \right\} \left\{ \sum_{i=1}^n N_i(s, dw) \right\}$$

Estimating 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 estimators: $\hat{\alpha}$ and $\hat{\beta}$ are maximizers of

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

G-PLE 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 $\bar{F}_0(t)$:

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

Estimation: With Frailties

- Recall the intensity rate:

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

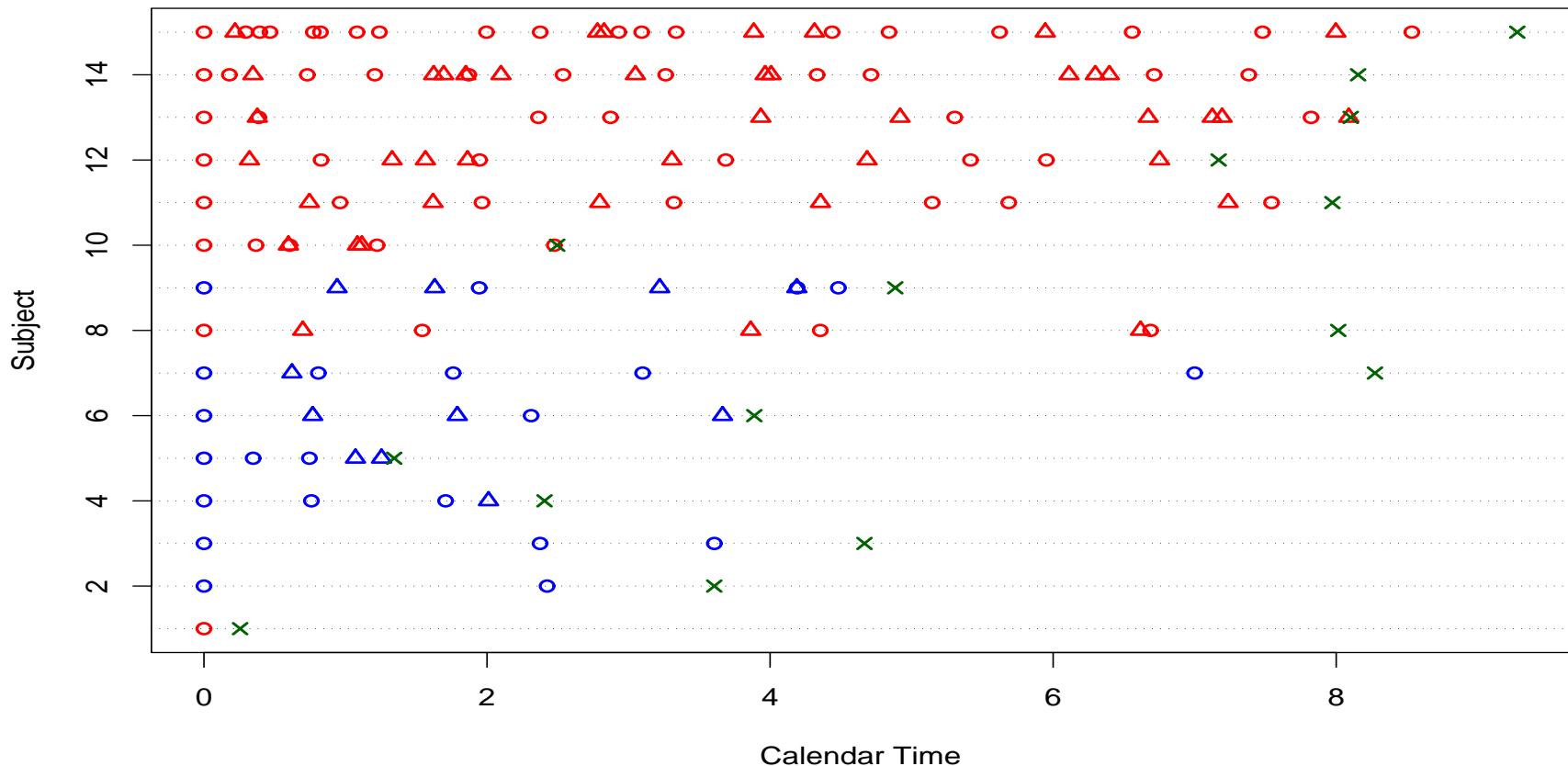
- Frailities Z_1, Z_2, \dots, Z_n are **unobserved** and are IID **Gamma(ξ, ξ)**
- Unknown parameters: $(\xi, \alpha, \beta, \lambda_0(\cdot))$
- Use of the **EM-type** algorithm (Dempster, et al; Nielsen, et al), with frailties as missing observations.

Algorithm

- **Step 0:** (Initialization) Seed values $\hat{\xi}, \hat{\alpha}, \hat{\beta}$; no-frailty estimator $\hat{\Lambda}_0$.
- **Step 1:** (E-step) Compute $\hat{Z}_i = E(Z_i | \text{data}, \hat{\xi}, \hat{\alpha}, \hat{\beta}, \hat{\Lambda}_0)$.
- **Step 2:** (M-step 1) New estimate of $\Lambda_0(\cdot)$. Form: analogous to the no-frailty case with \hat{Z}_i 's.
- **Step 3:** (M-step 2) New estimates of α and β .
- **Step 4:** (M-step 3) New estimate of ξ ; maximize marginal likelihood for ξ .
- **Step 5:** Check for convergence.

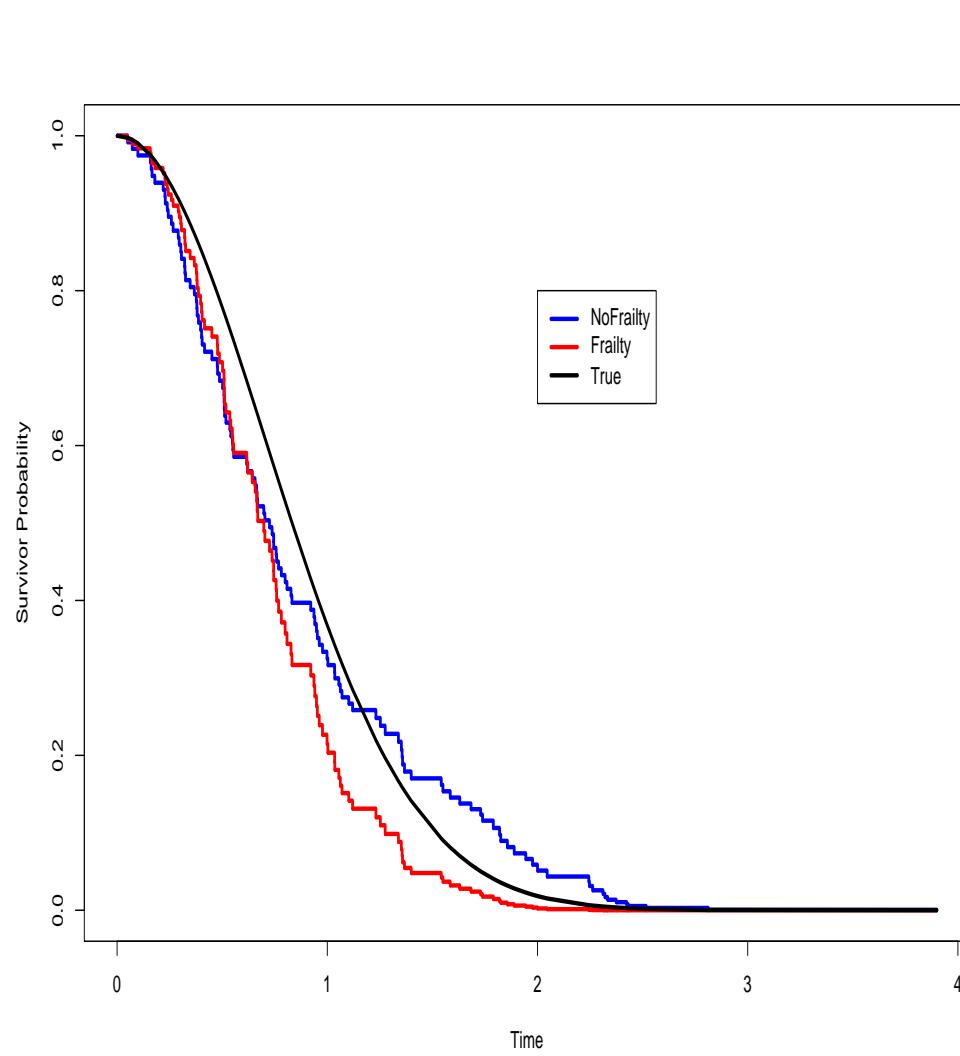
A Simulated Data

Parameters: $n = 15$; $\alpha = 0.90$; $\beta = (1.0, -1.0)$; $X_1 \sim B(.5)$; $X_2 \sim N(0, 1)$; $\xi = 2$; $\tau \sim U(0, 10)$; MI($p = .6$);
Baseline: Weibull(2,1)



Estimates of Parameters

- With Frailty Fit
 - 102 iterations in EM
 - $\hat{\alpha} = .8748$
 - $\hat{\beta} = (1.099, -1.3986)$
 - $\hat{\xi} = 2.1831$
- Without Frailty Fit
 - $\hat{\alpha} = .963$
 - $\hat{\beta} = (0.590, -0.571)$



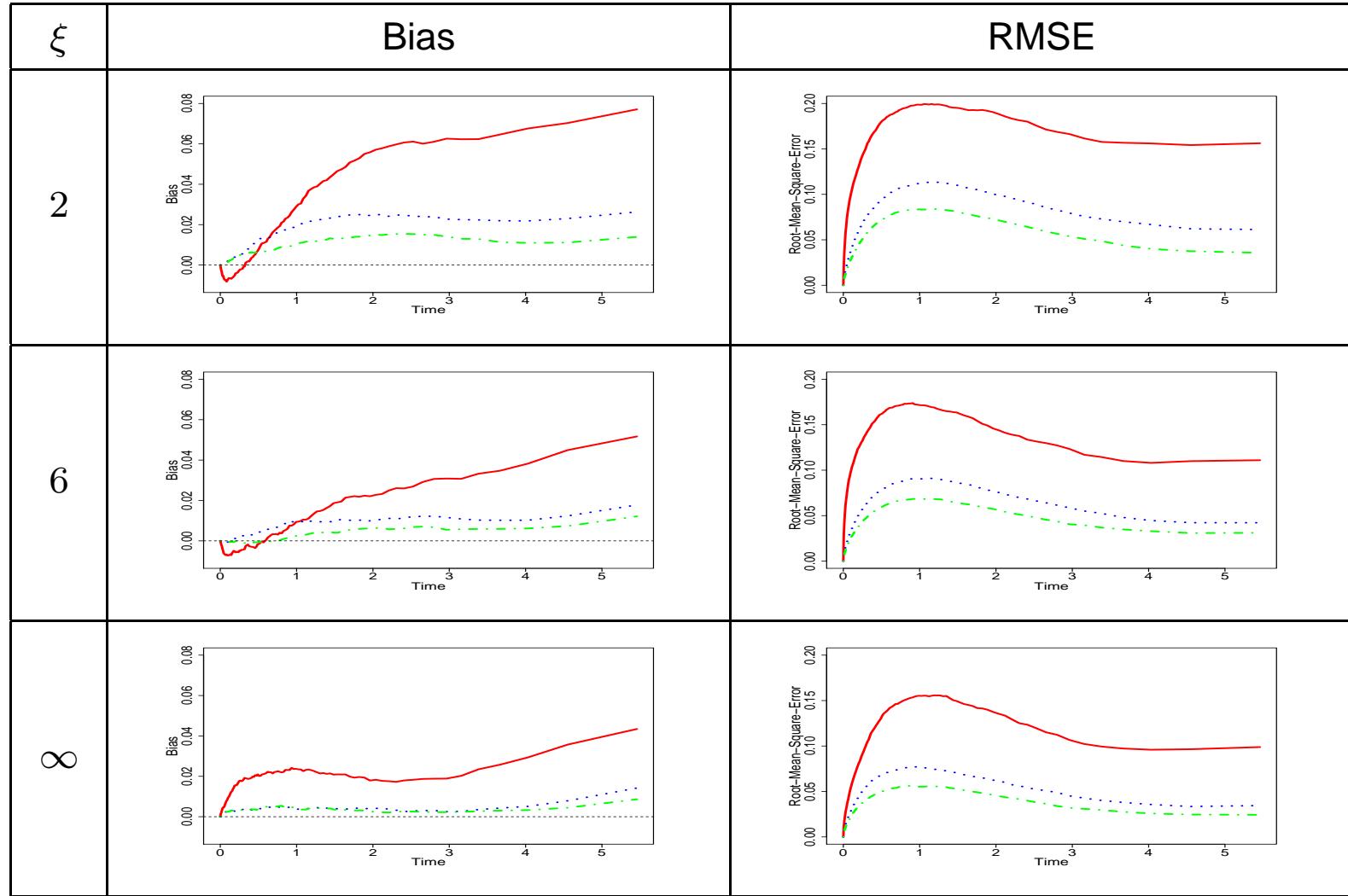
Properties: Simulated

- $\rho(k; \alpha) = \alpha^k$; $\alpha \in \{.9, 1.0, 1.05\}$
- $\psi(u) = \exp(u)$
- $\beta = (1, -1)$; $X_1 \sim \text{Ber}(.5)$; $X_2 \sim \mathbf{N}(0, 1)$
- Baseline: Weibull with shape $\gamma = .9$ and $\gamma = 2$
- Gamma frailty parameter: $\xi \in \{2, 6, \infty\}$; $\eta \equiv \xi/(1 + \xi)$
- Effective Age: Minimal intervention model with $p = .6$
- Sample Size: $n \in \{10, 30, 50\}$
- Censoring: $\tau \sim \text{Uniform}(0, B)$ (approx 10 events/unit)
- Replications/Simulation Set: 1000

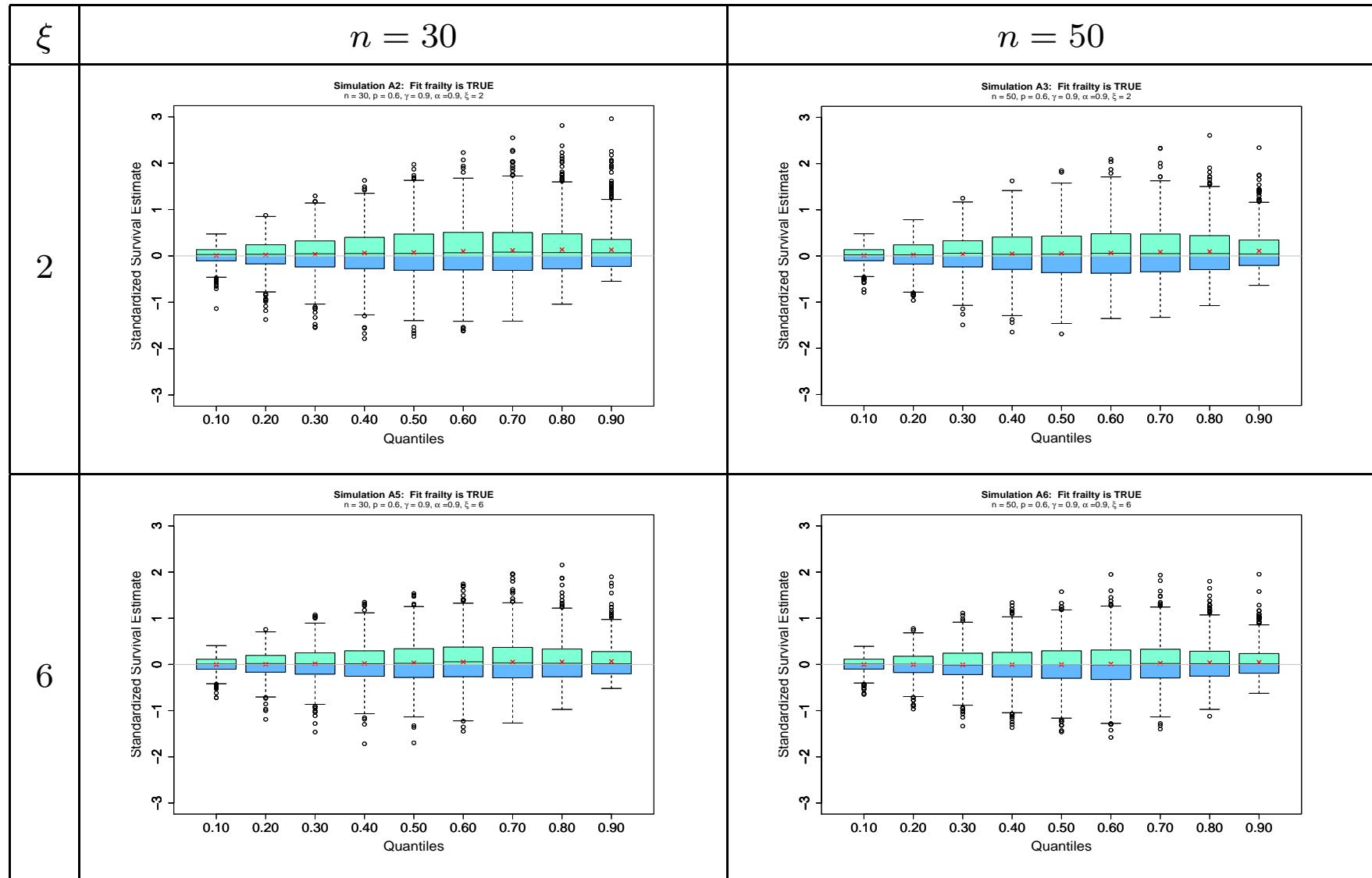
Finite-Dimensional Parameters

TableA	α	γ	ξ	η	n	$\hat{\mu}_{Ev}$	$\hat{\alpha}$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\eta}$
A2.me	0.9	0.9	2	0.67	30	4.1	0.898	1.01	-1.01	0.734
A2.sd							0.031	0.379	0.24	0.124
A3.me	0.9	0.9	2	0.67	50	5.2	0.899	1.02	-1	0.705
A3.sd							0.021	0.287	0.165	0.091
A5.me	0.9	0.9	6	0.86	30	4.3	0.9	0.988	-1.01	0.904
A5.sd							0.030	0.3	0.175	0.085
A6.me	0.9	0.9	6	0.86	50	5.3	0.899	0.998	-1	0.884
A6.sd							0.021	0.221	0.136	0.071
A8.me	0.9	0.9	∞	1	30	4.8	0.893	1.03	-1.03	
A8.sd							0.0247	0.222	0.135	
A9.me	0.9	0.9	∞	1	50	4.4	0.895	1.02	-1.02	
A9.sd							0.018	0.158	0.104	

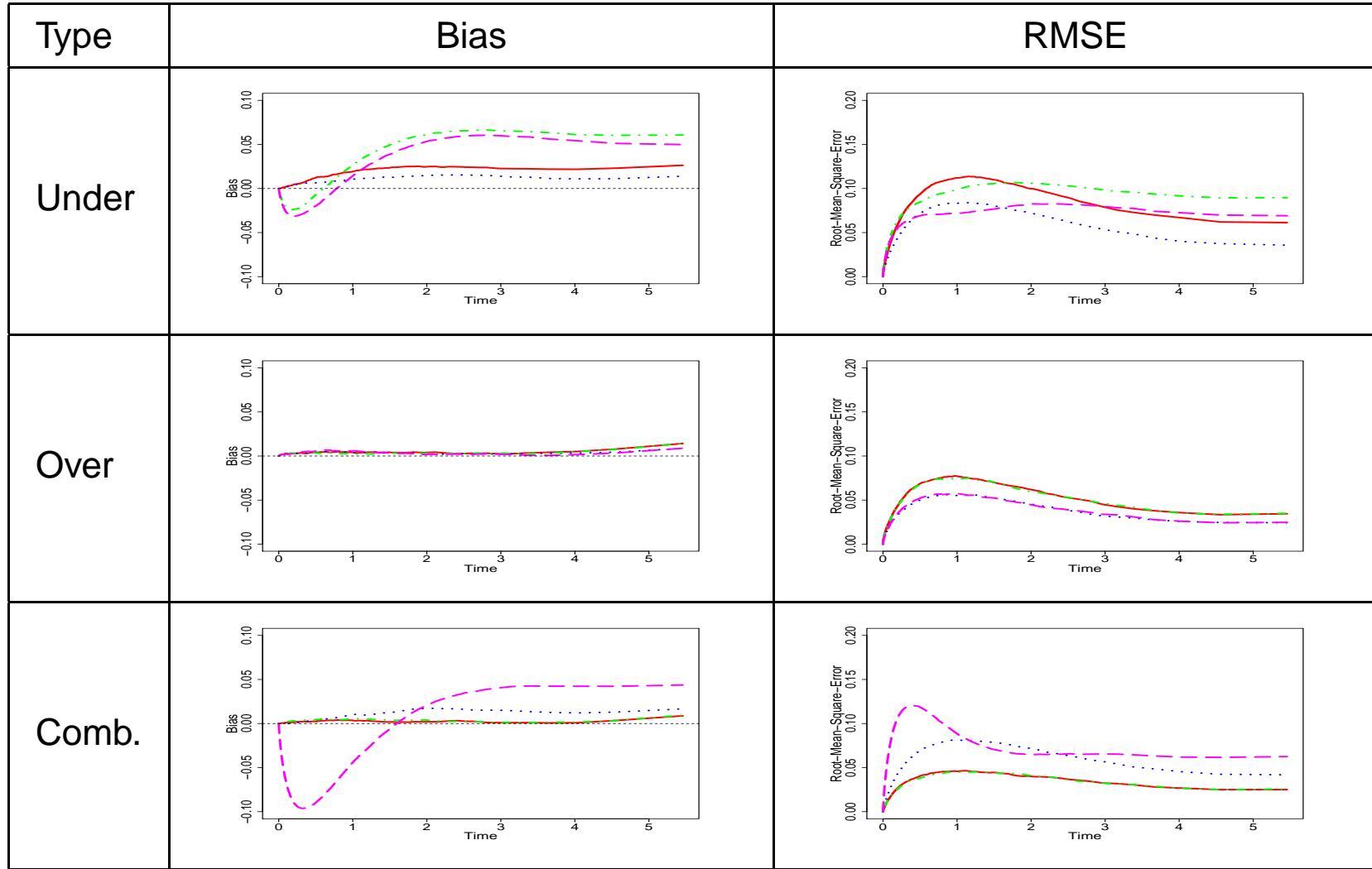
Baseline Survivor Function



Peek Towards Asymptopia

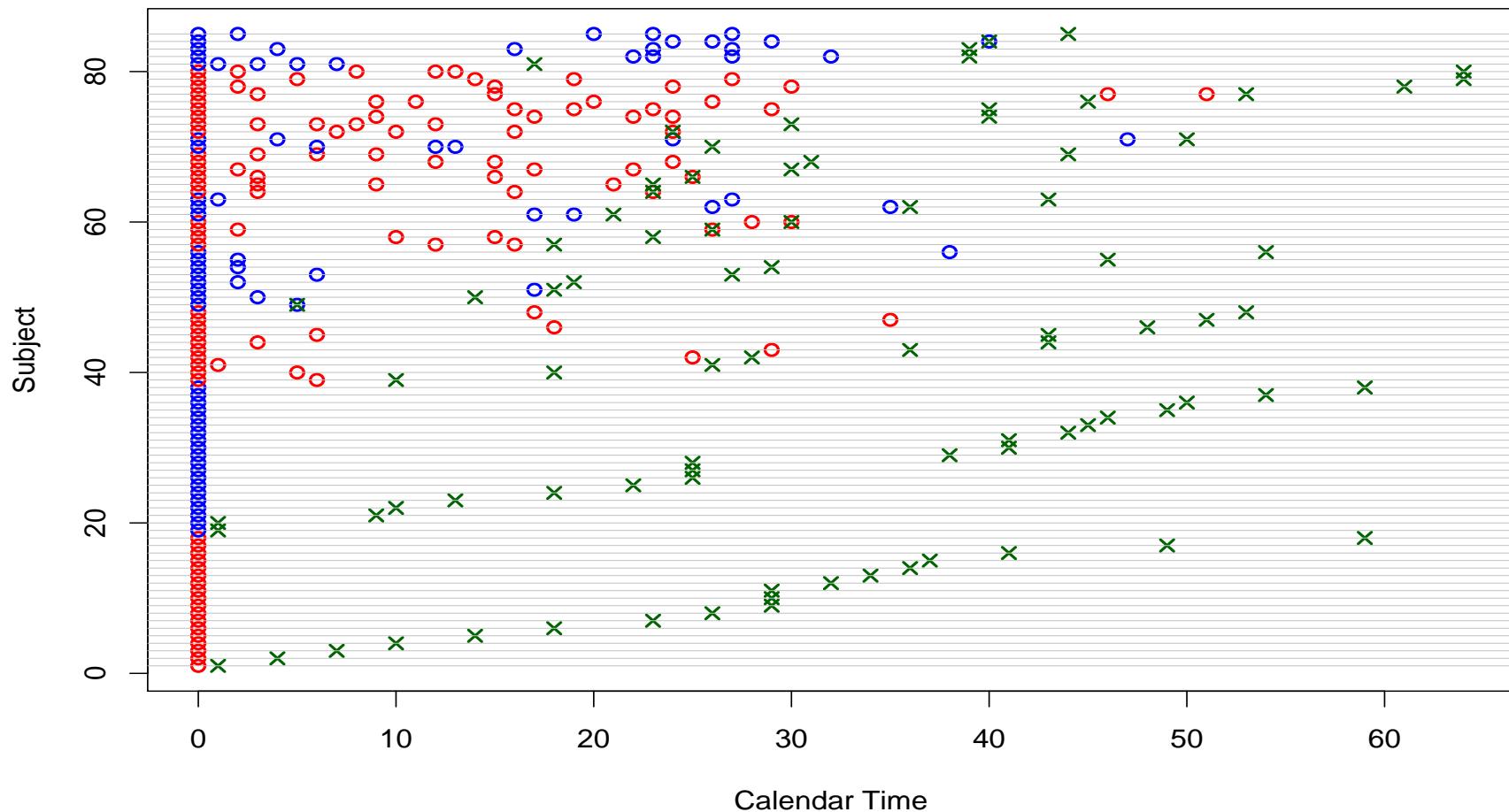


Effect of Mis-specifications



Application: Bladder Data

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



Estimates of Parameters

- X_1 : (1 = placebo; 2 = thiotepa)
- X_2 : size (cm) of largest initial tumor
- X_3 : # of initial tumors
- Effective age: ('always perfect intervention') [also fitted with 'always minimal intervention'].
- Without frailties and 'perfect' intervention:
 - $\hat{\alpha} = 0.98$ (*s.e.* = 0.07);
 - $(\hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3) = (-0.32, -0.02, 0.14)$;
 - s.e.s of $\hat{\beta} = (0.21, 0.07, 0.05)$.
- Fitting model *with* gamma frailties: 13 iterations in EM led to $\hat{\xi} = 5432999$ indicating absence of frailties.

Comparisons with Existing Methods

- Estimates from Different Methods for Bladder Data

Cova	Para	AG	WLW Marginal	PWP Cond*nal	General Model	
					Perfect ^a	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

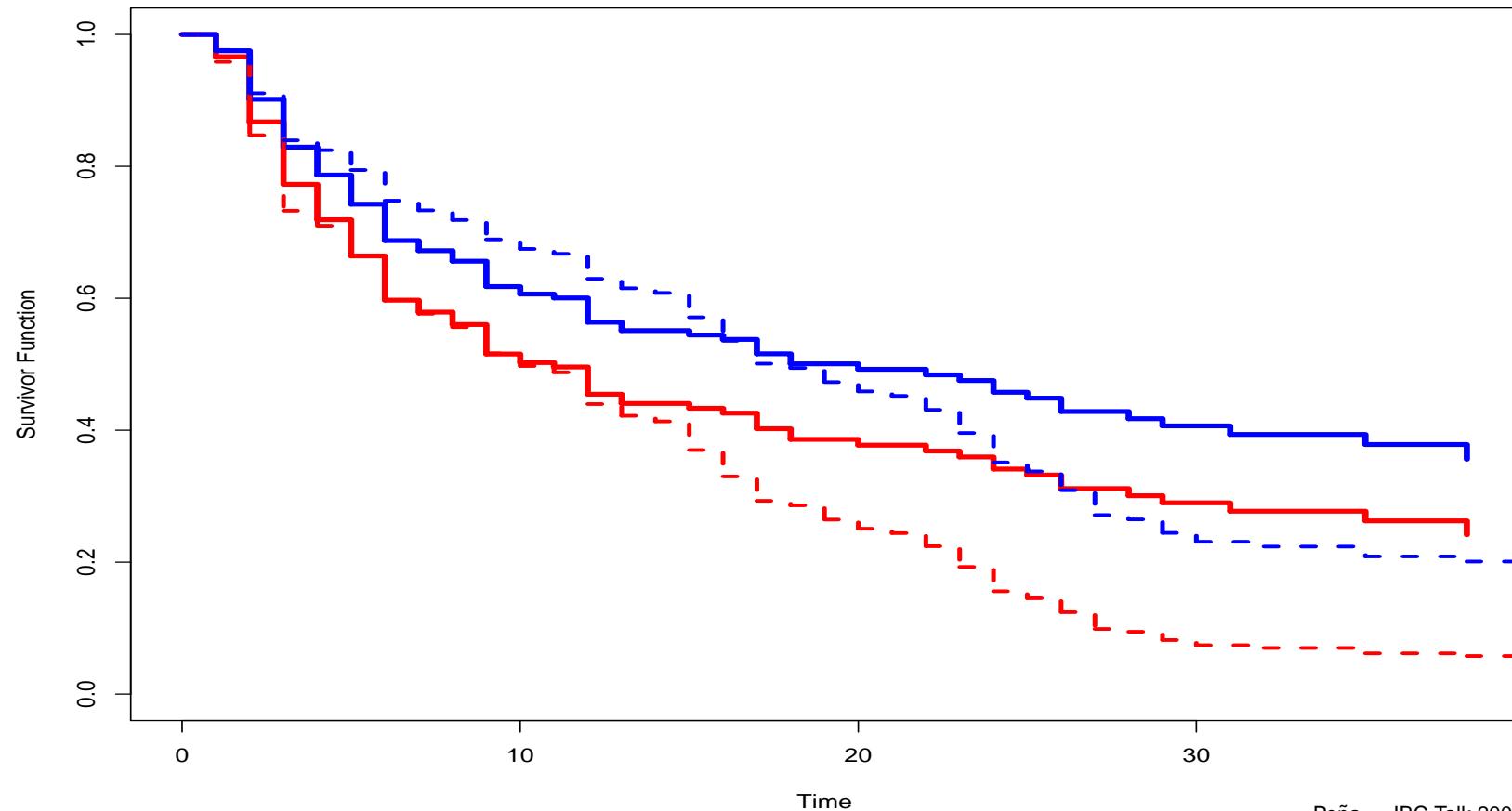
^aEffective Age is backward recurrence time ($\mathcal{E}(s) = s - S_{N^\dagger(s-)}$).

^bEffective Age is calendar time ($\mathcal{E}(s) = s$).

- Frailty **not** needed when ‘always perfect intervention’; crucial when ‘always minimal intervention’.

Estimates of SFs for Two Groups

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



Concluding Remarks

- General and flexible model: incorporates aspects of recurrent event modelling.
- Allows a formal mathematical treatment which could enable reconciliation of different methods.
- Robust analysis of recurrent event data.
- Current deficiency: Need to monitor the effective age!
- Potential: Assess some existing models in light of this larger model.
- Further studies: asymptotics; goodness of fit, and model validation aspects.