Modeling and Analysis of Recurrent Event Data

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Historical Perspective: Random Censorship Model (RCM)

$$T_1, T_2, \ldots, T_n \overset{IID}{\sim} F$$

$$C_1, C_2, \ldots, C_n \overset{IID}{\sim} G$$

$$F \quad \text{and} \quad G \quad \text{not related}$$

$$\{T_i\} \perp \{C_i\}$$

Random Observables:

$$(Z_1, \delta_1), (Z_2, \delta_2), \ldots, (Z_n, \delta_n)$$

$$Z_i = T_i \wedge C_i \quad \text{and} \quad \delta_i = I\{T_i \leq C_i\}$$

Goal: To make inference on the distribution F or the hazard $\Lambda = \int dF/\bar{F}_-$, or functionals (mean, median, etc.).

Nonparametric Inference

$$F \in \mathcal{F} = \text{space of continuous distributions}$$

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

$$N(s) = \sum_i I\{Z_i \leq s; \delta_i = 1\} \quad \text{and} \quad Y(s) = \sum_i I\{Z_i \geq s\}$$

$$\textbf{NAE:} \quad \hat{\Lambda} = \int \frac{dN}{Y} \quad \text{and} \quad \textbf{PLE:} \quad \hat{\bar{F}} = \prod \left[1 - \frac{dN}{Y}\right]$$

Properties of $\hat{\Lambda}$ and $\hat{F}$ well-known, e.g., biased; consistent; and when normalized, weakly convergent to Gaussian processes.

$$\text{Avar}(\hat{\bar{F}}(t)) = \frac{1}{n}\bar{F}(t)^2 \int_0^t \frac{dF(s)}{\bar{F}(s)^2 \bar{G}(s)}$$

An Informative RCM

- Koziol-Green (KG) Model (1976):

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

- Lehmann-type alternatives
- Proportional hazards:

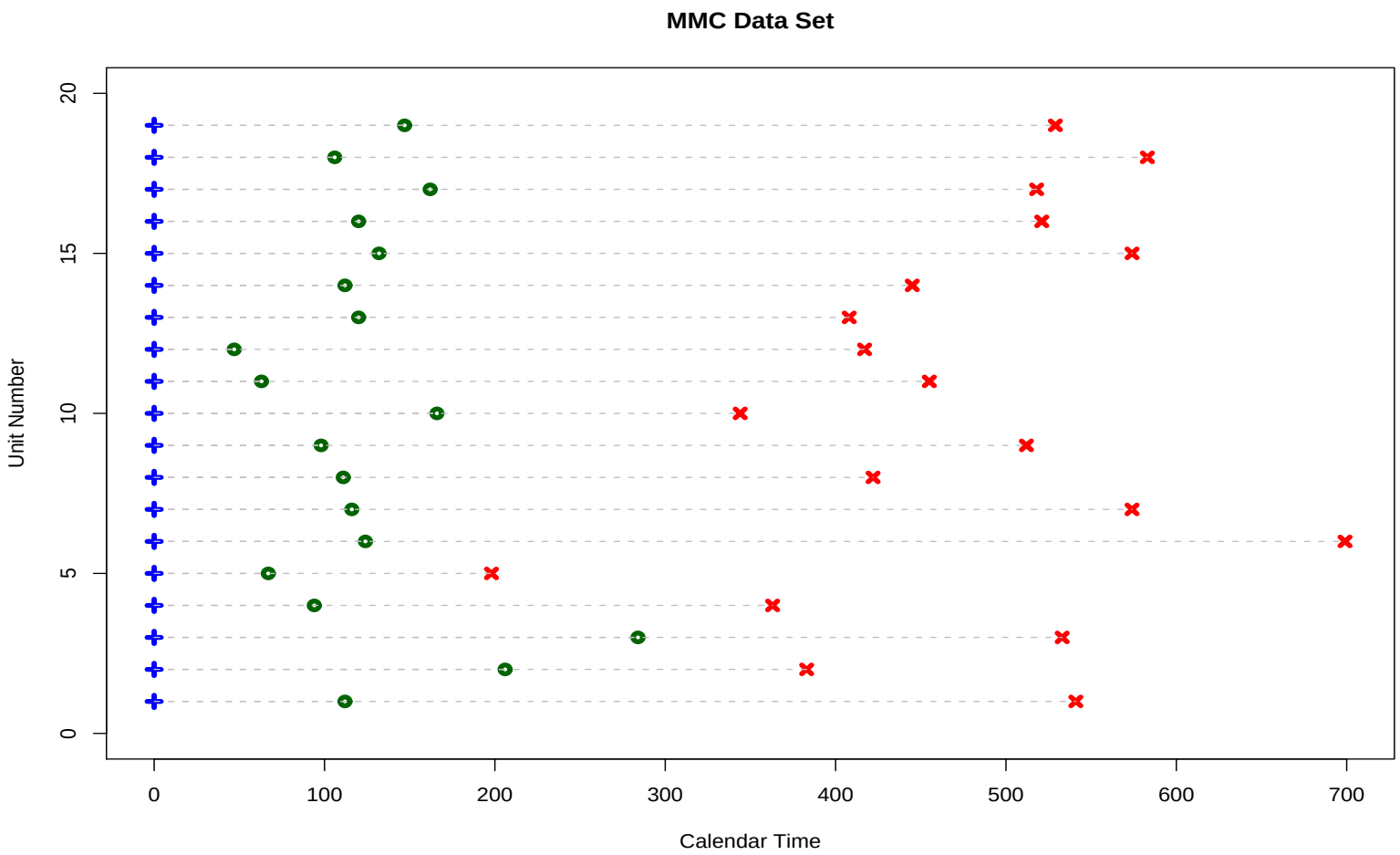
$$\Lambda_G = \beta \Lambda_F$$

- $Z_i = \min(T_i, C_i) \sim \bar{F}^{\beta+1}$
- $\delta_i = I\{T_i \leq C_i\} \sim \text{BER}(1/(\beta+1))$
- An important characterizing property:

$$Z_i \perp \delta_i$$

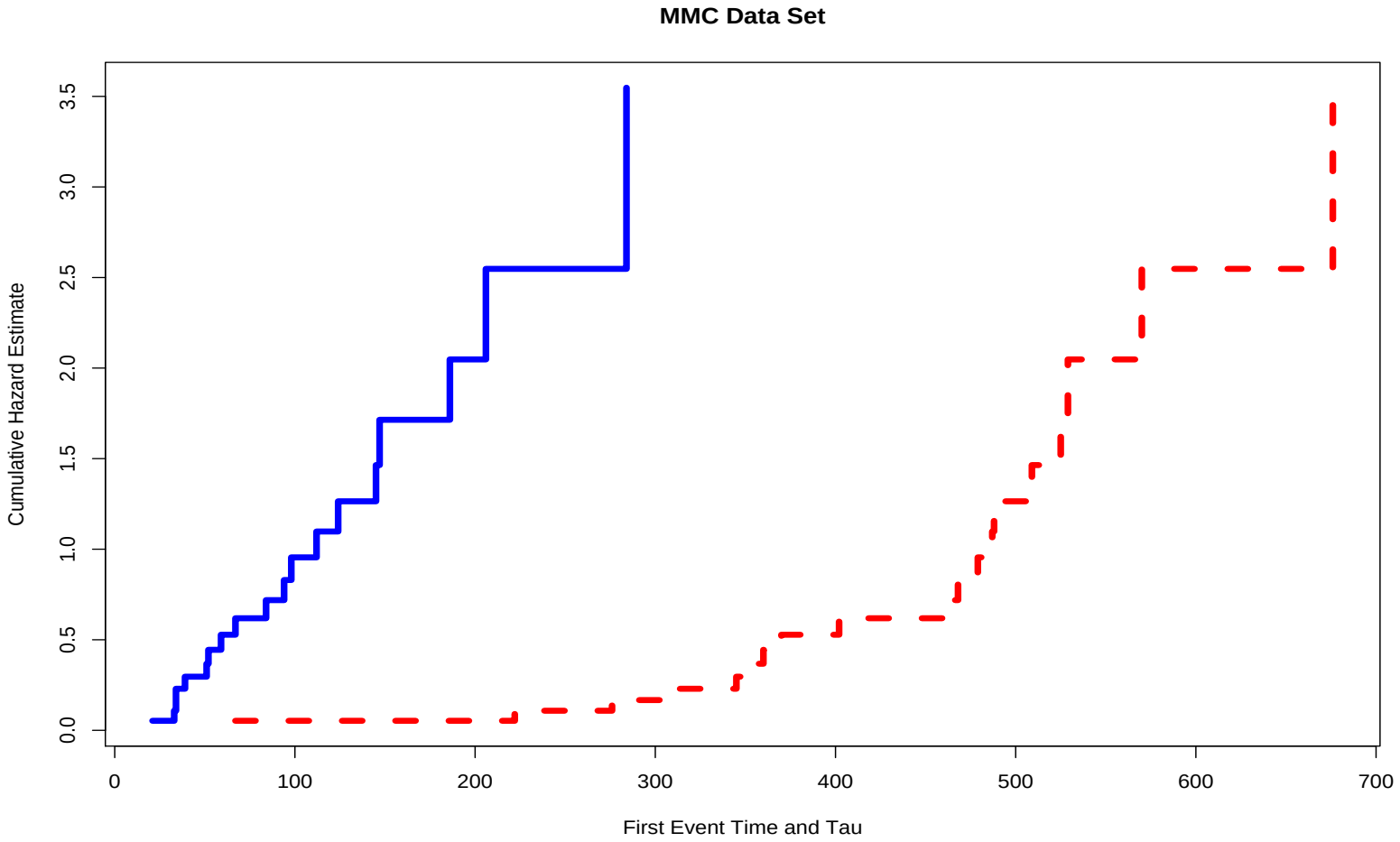
MMC Data: First Event Times and Tau's

Migratory Motor Complex (MMC) data set from Aalen and Husebye, Stat Med, 1991.



MMC Data: Hazard Estimates

KG model holds if and only if $\Lambda_\tau \propto \Lambda_{T_1}$



KG Model's Utility

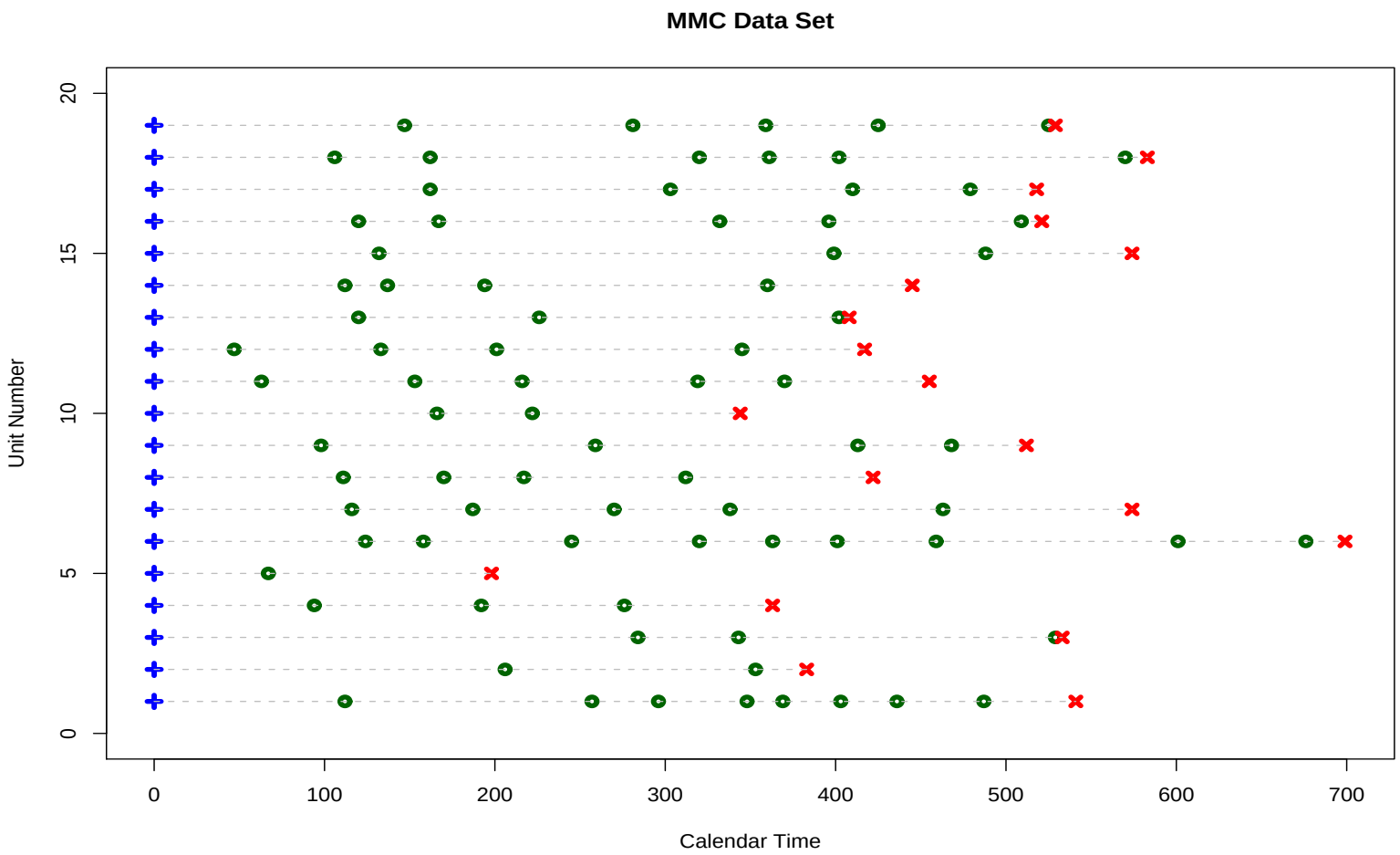
- Chen, Hollander and Langberg (JASA, 1982): exploited independence between Z_i and δ_i to obtain the exact bias, variance, and MSE functions of PLE. Comparisons with asymptotic results.
- Cheng and Lin (1987): exploited semiparametric nature of KG model to obtain a more efficient estimator of F compared to the PLE.
- Hollander and Peña (1988): obtained better confidence bands for F under KG model.
- Csorgo & Faraway (1998): KG model not practically viable, but serves as a mathematical specimen (a lá yeast) for examining exact properties of procedures and for providing pinpoint assessment of efficiency losses/gains.

Recurrent Events: Some Examples

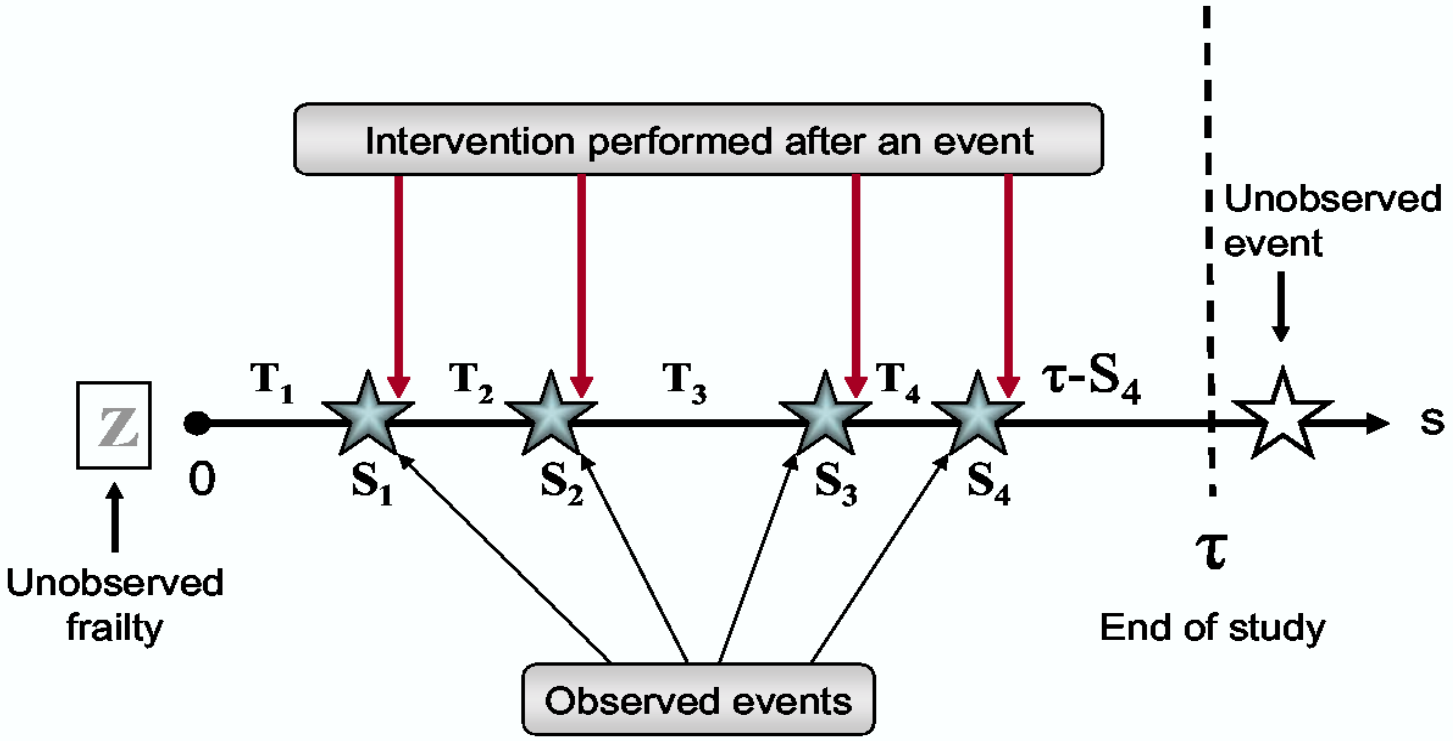
- admission to hospital due to chronic disease
- tumor re-occurrence
- migraine attacks
- alcohol or drug (eg cocaine) addiction
- machine failure or discovery of a bug in a software
- commission of a criminal act by a delinquent minor!
- major disagreements between a couple
- non-life insurance claim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

Full MMC Data: With Recurrences

$n = 19$ subjects; event = end of migratory motor complex cycle; random length of monitoring period per subject.



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:

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

- **Basic Observable:** $(K, \tau, T_1, T_2, \ldots, T_K, \tau - S_K)$
- always a right-censored observation.
- dependent and informative censoring.
- effects of covariates, frailties, interventions after each event, and accumulation of events.

Simplest Model: One Subject

- $T_1, T_2, \ldots \overset{IID}{\sim} F$: (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
- Peña, Strawderman and Hollander (JASA, 01): nonparametric estimation of F.

Nonparametric Estimation of F

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

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

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

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

Main Asymptotic Result

kth Convolution: $$F^{\star(k)}(t) = \Pr\left\{\sum_{j=1}^{k} T_j \leq t\right\}$$

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

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

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

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

Extending KG Model: Recurrent Setting

- *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

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

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

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

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

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

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

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

Transformed Processes

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

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

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

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

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:

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

Is It A Legitimate Profile Likelihood?

- Let $\mathfrak{C}$ be the space of all cumulative hazard functions defined on $[0, \infty)$.

Theorem

Let $L(s^*; \Lambda, \beta)$ be the full likelihood function given by

$$L = \left\{ \prod_{i=1}^{n} \prod_{v=0}^{s^*} \left[Y_i^{\dagger}(v) \lambda[R_i(v)] dv \right]^{\Delta N_i^{\dagger}(v)} [Y_i^{\tau}(v) \beta \lambda(v) dv]^{\Delta N_i^{\tau}(v)} \right\}$$
$$\exp\left\{ -\sum_{i=1}^{n} \left[\int_0^{s^*} Y_i^{\dagger}(v) \lambda[R_i(v)] dv + \int_0^{s^*} Y_i^{\tau}(v) \beta \lambda(v) dv \right] \right\}.$$

then

$$L_P(s^*; \beta) = \max_{\Lambda \in \mathfrak{C}} L(s^*; \Lambda, \beta).$$

Estimators of Λ and $\bar{F}$

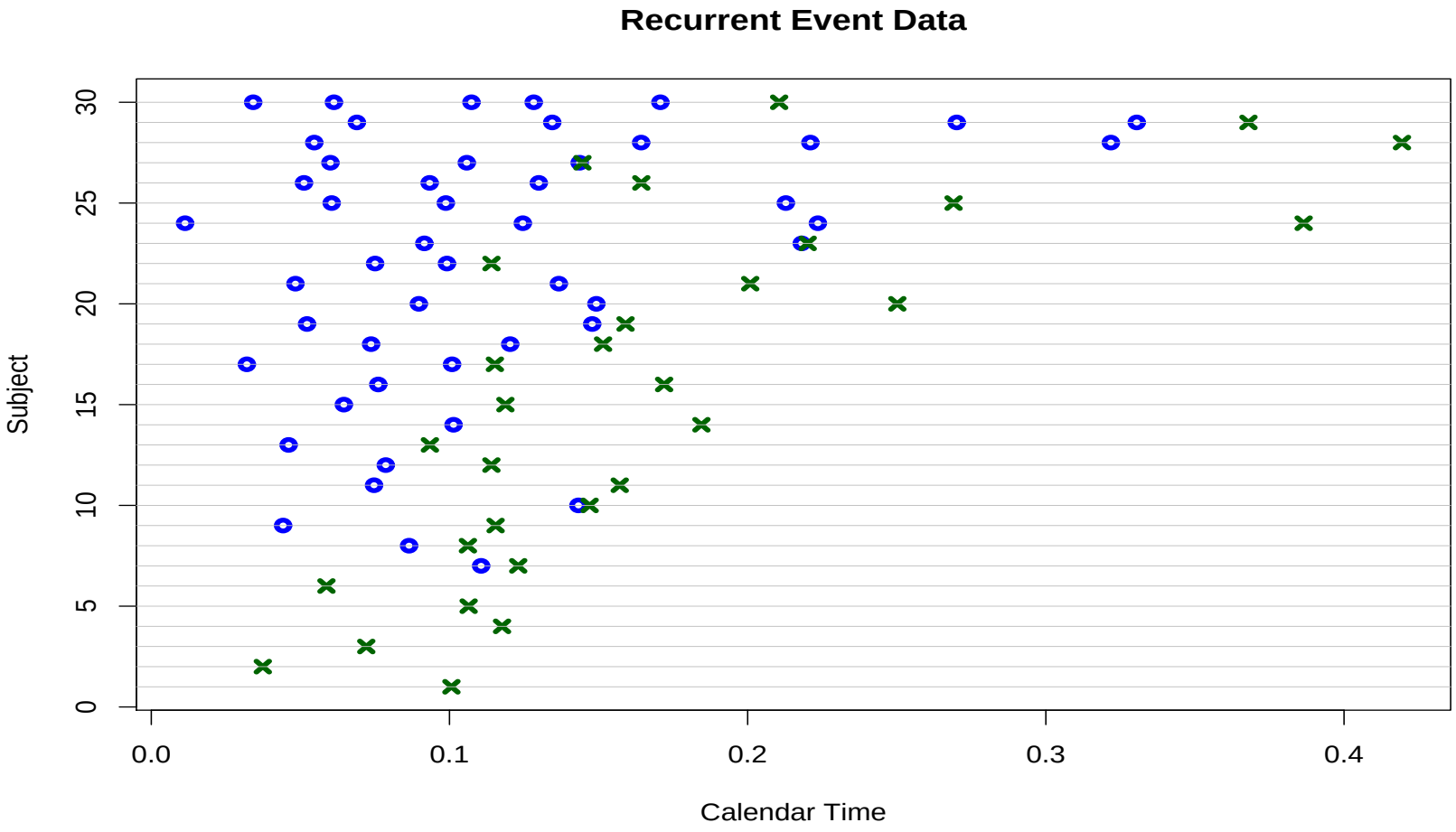
Estimator of Λ:

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

Estimator of $\bar{F}$:

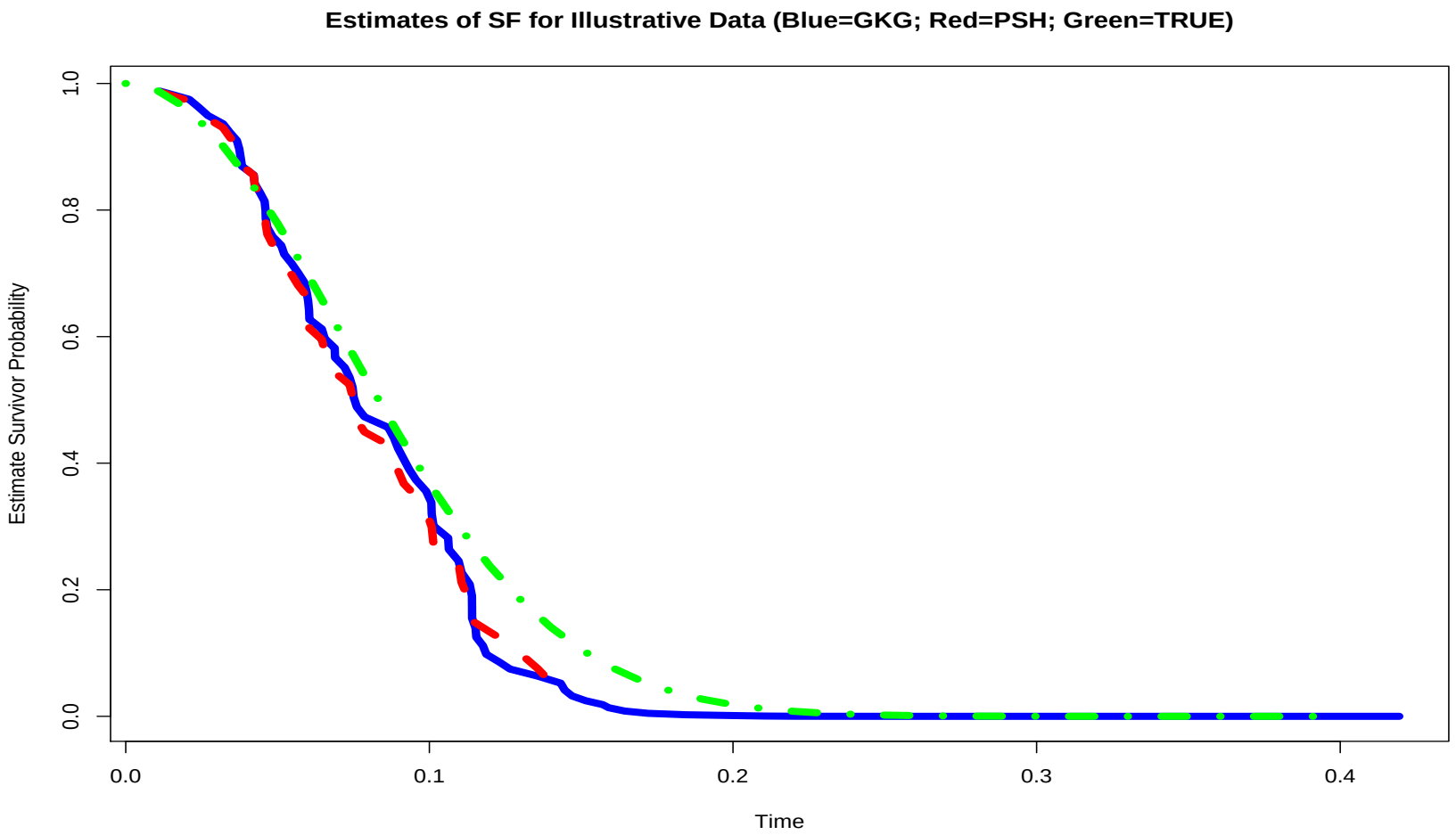
$$\hat{\bar{F}}(s^*, t) = \hat{\bar{F}}(s^*, t|\hat{\beta}) = \prod_{w=0}^{t} \left\{ 1 - \frac{N(s^*, dw) + N^\tau(dw)}{Y(s^*, w) + \hat{\beta} Y^\tau(w)} \right\}$$

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, less than or equal to unity, as is to be expected.

Case of Exponential F: β_0 Known

Theorem

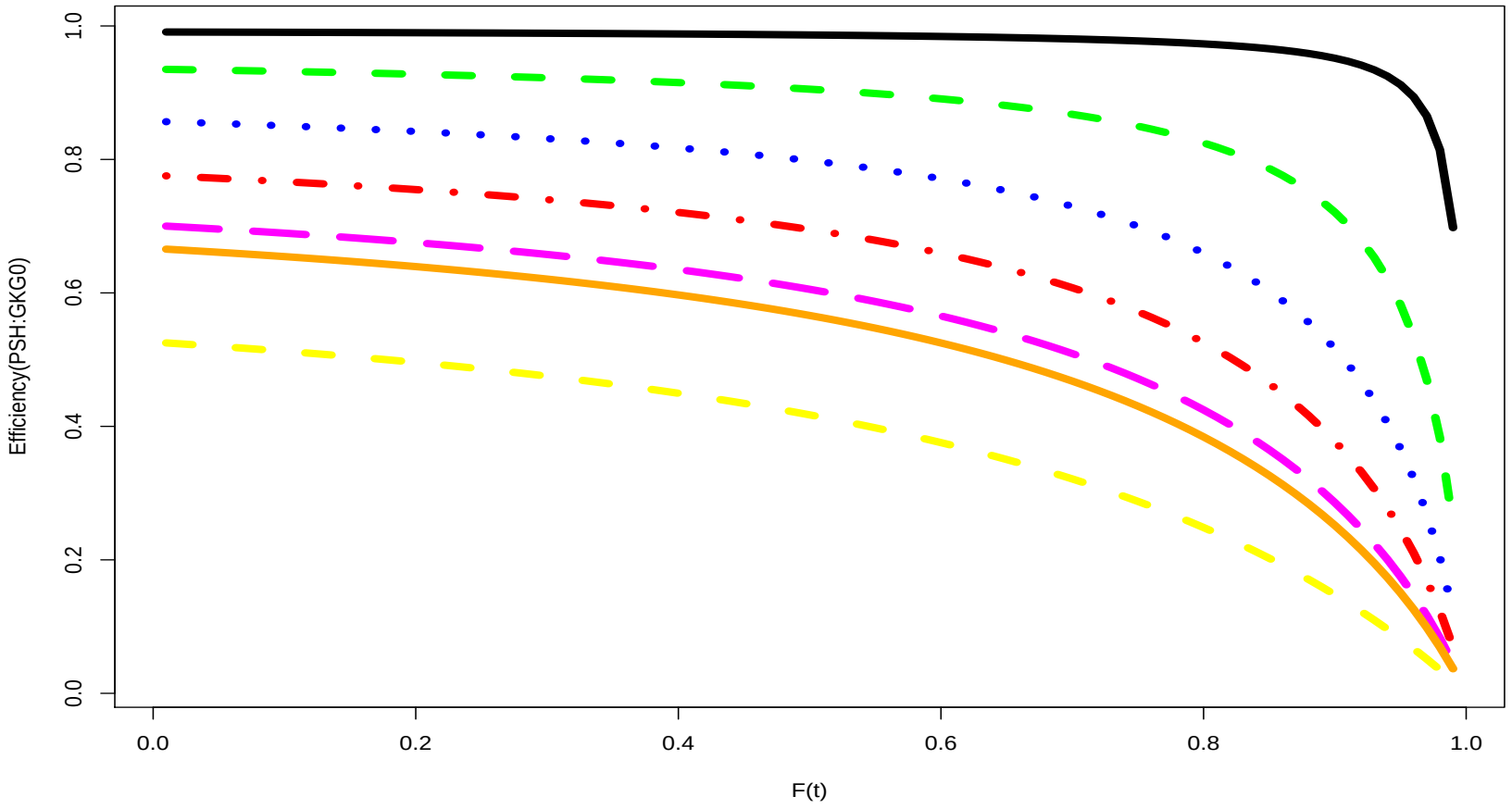
If $\bar{F}_0(t) = \exp\{-\theta_0 t\}$ *for* $t \geq 0$ *and* $s^* \to \infty$, *then*

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

Also, $\forall t \geq 0$,

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

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

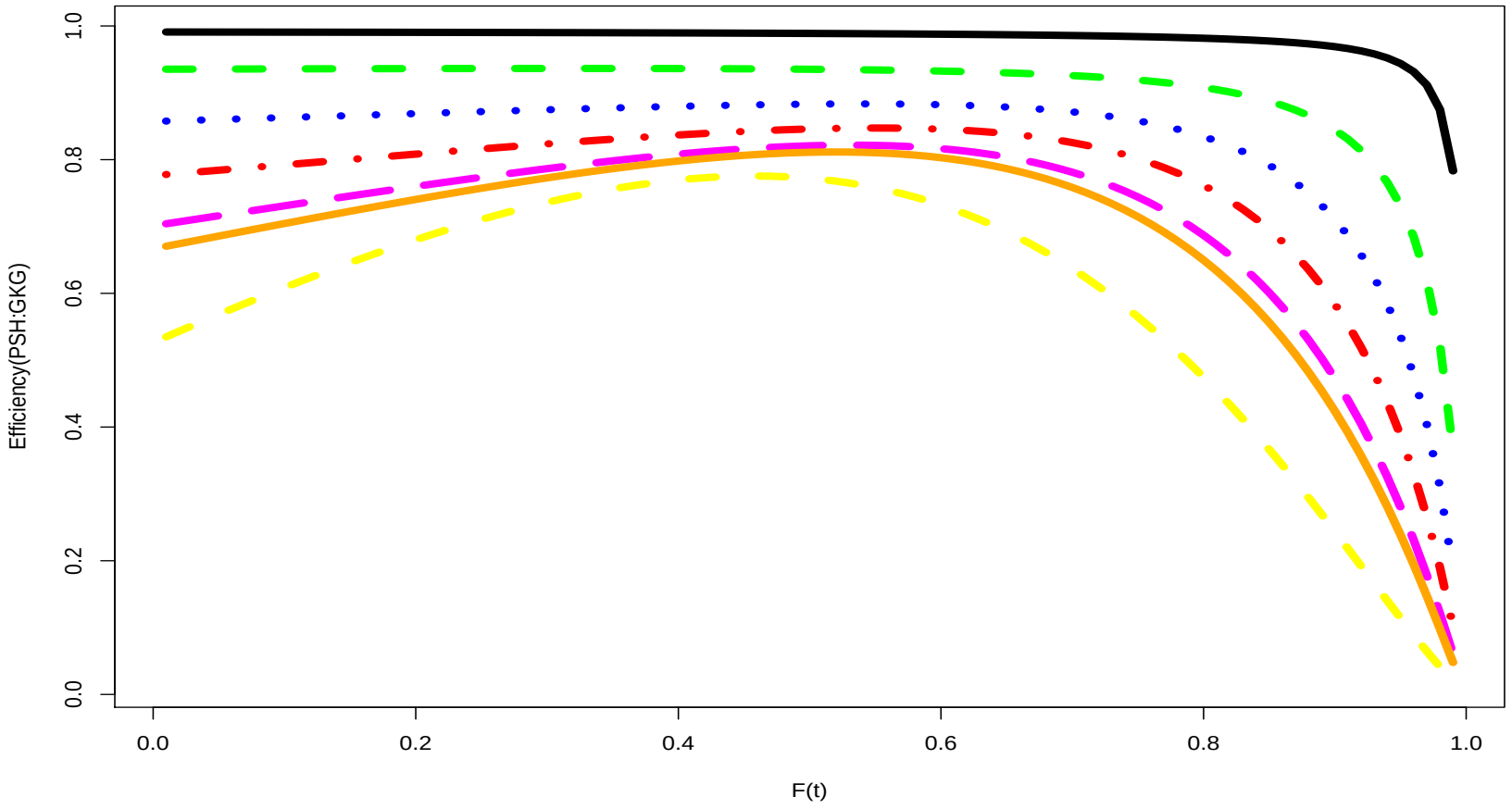
Under the GKG model, for all $(\bar{F}_0, \beta_0)$ with $\beta_0 > 0$, $\tilde{\bar{F}}(s^*, t)$ is asymptotically dominated by $\hat{\bar{F}}(s^*, t)$ in the sense that

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

Proof.

Neat application of Cauchy-Schwartz Inequality. □

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



Assessing Asymptotic Approximations under Exponential

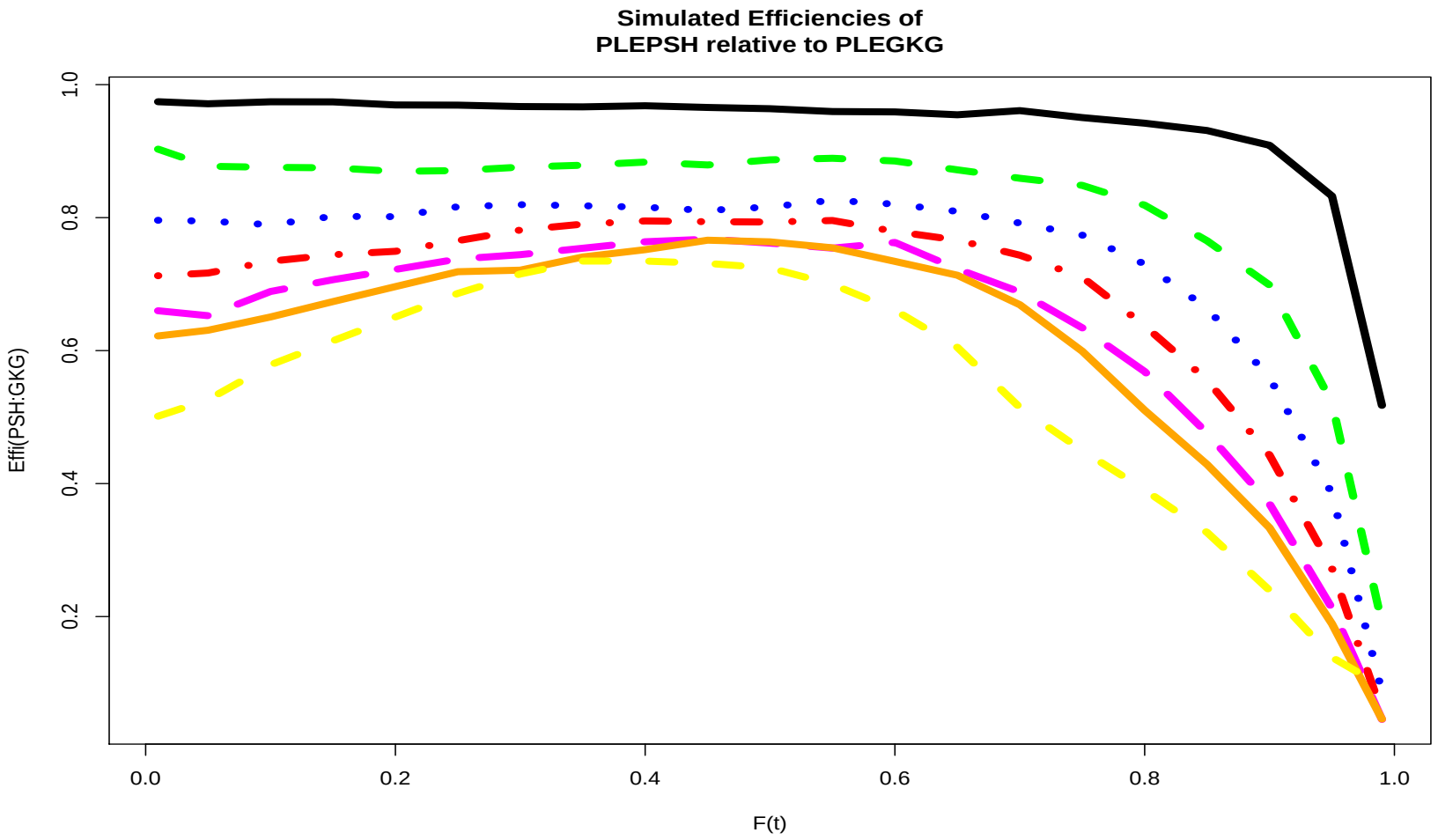
	$n = 50$			$n = 100$		
β_0	Mean	SE	ASE	Mean	SE	ASE
0.1	.1014	.0245	.0234	.1005	.0169	.0165
0.3	.3048	.0624	.0596	.3018	.0430	.0422
0.5	.5119	.1038	.0983	.5045	.0708	.0695
0.7	.7176	.1518	.1406	.7075	.1032	.0994
0.9	.9213	.1964	.1864	.9093	.1356	.1318
1.0	1.0294	.2298	.2107	1.0172	.1579	.1490
1.5	1.5615	.3963	.3445	1.5316	.2572	.2436

- Mean: mean of the simulated values of $\hat{\beta}$.
- SE: standard error of the simulated values of $\hat{\beta}$.
- ASE: asymptotic standard error obtained from earlier formula.
- 10000 replications were performed.

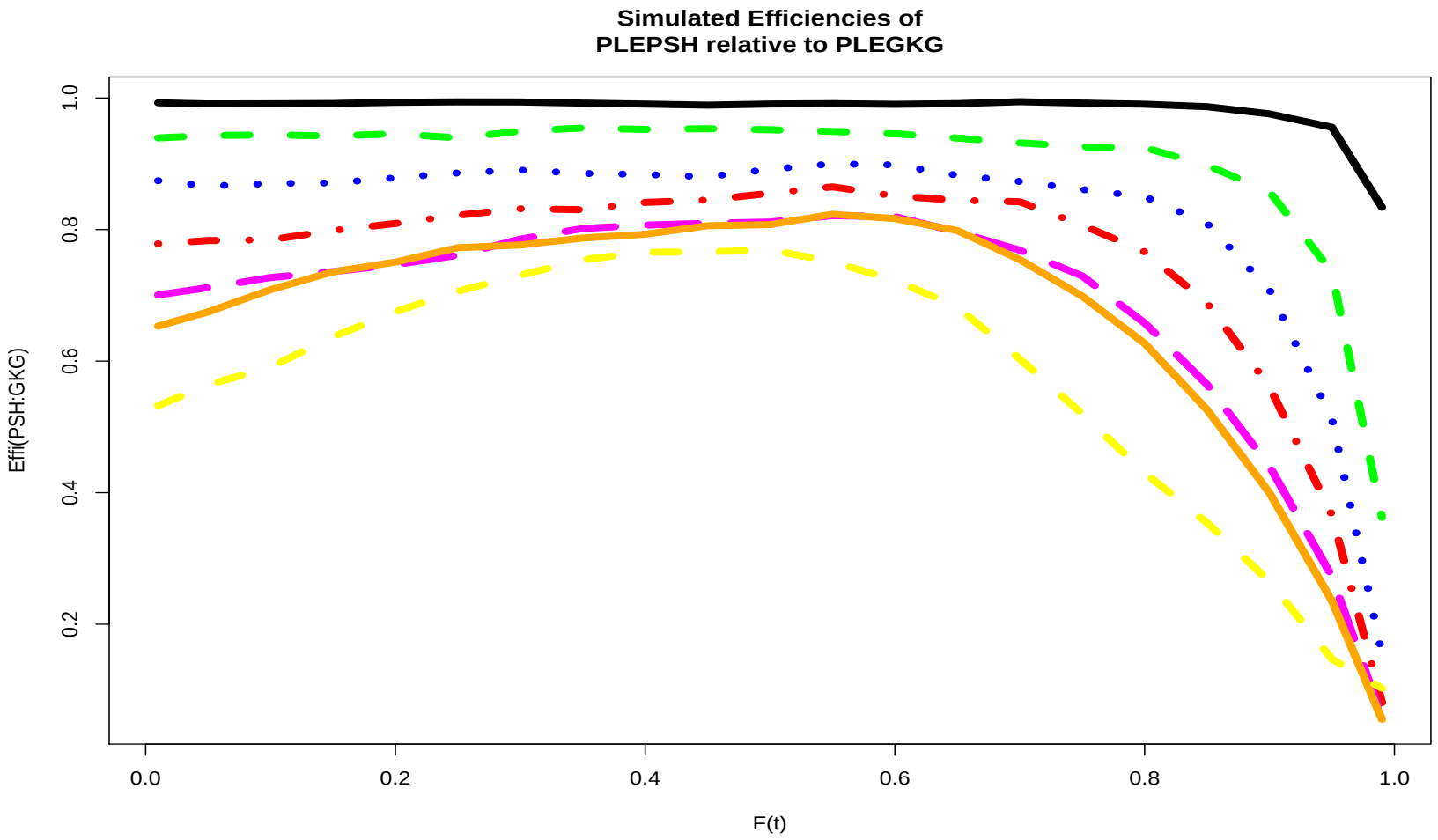
Simulations under Weibull F: $\hat{\beta}$ Results

	$n = 30, \alpha = 2$		$n = 50, \alpha = 2$		$n = 30, \alpha = .9$		$n = 50, \alpha = .9$	
β_0	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0.1	.10	.03	.10	.02	.10	.03	.10	.02
0.3	.31	.09	.30	.07	.30	.07	.30	.06
0.5	.52	.16	.51	.12	.51	.13	.50	.10
0.7	.73	.23	.72	.17	.72	.20	.71	.14
0.9	.95	.32	.92	.23	.94	.26	.92	.19
1.0	1.06	.36	1.03	.26	1.04	.30	1.03	.22
1.5	1.64	.63	1.58	.43	1.60	.55	1.56	.38

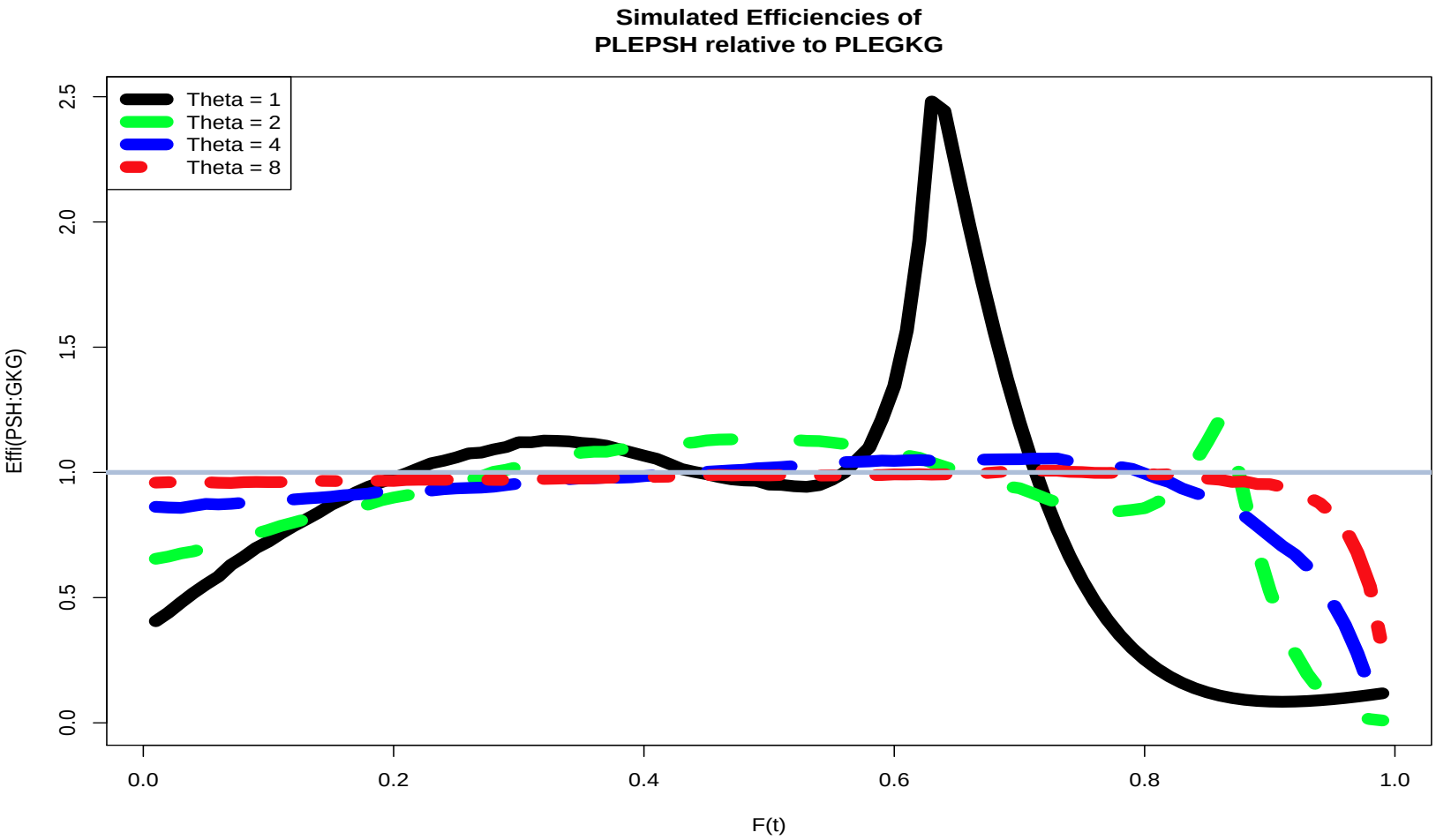
Simulated Rel Eff of $\tilde{\tilde{F}} : \hat{\hat{F}}$ under a Weibull F with $\alpha = 2$



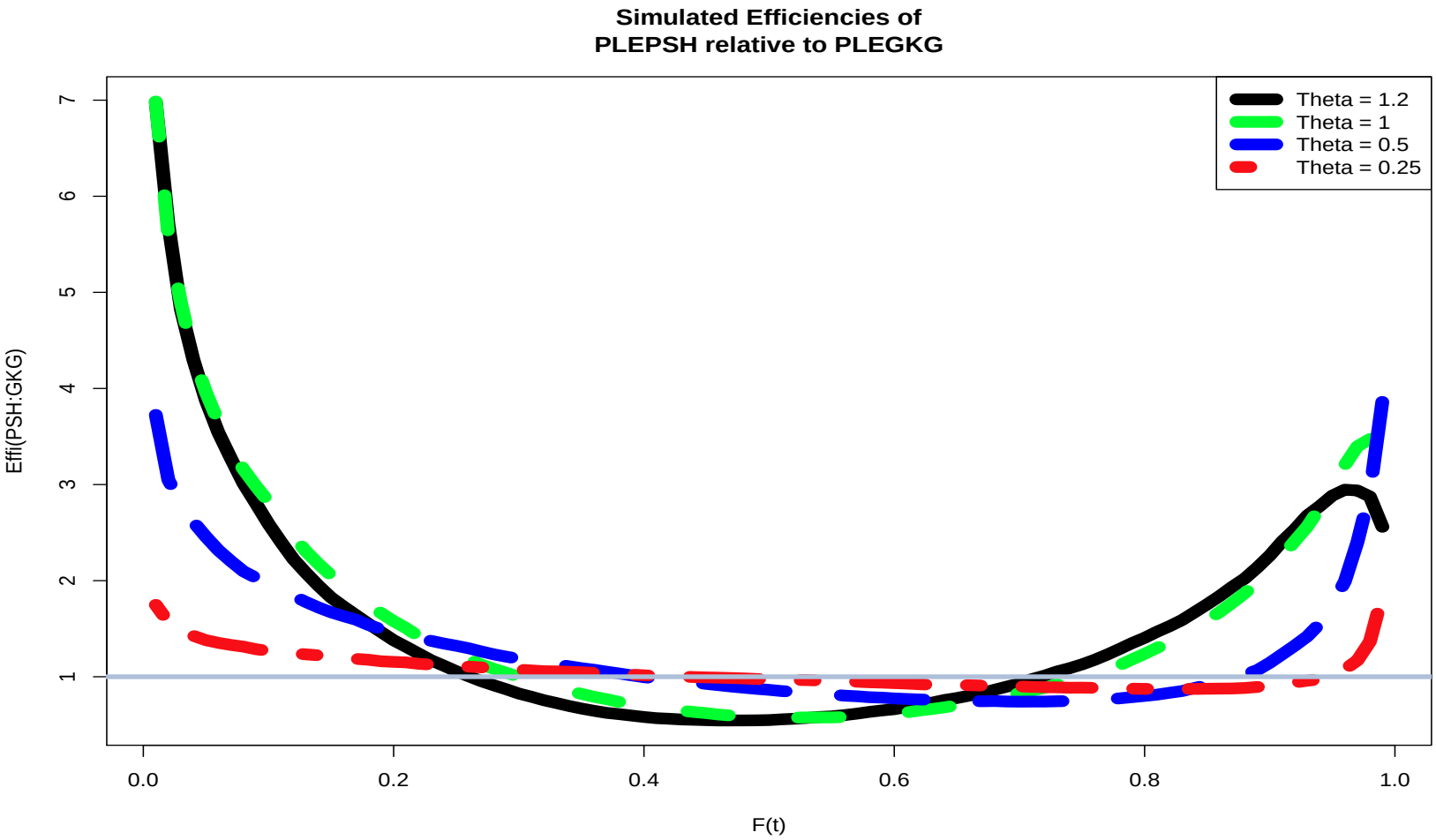
Simulated Rel Eff of $\tilde{\tilde{F}}$: $\hat{\hat{F}}$ under a Weibull F with $\alpha = 0.9$



Mis-Specified Model: F_0 is Exp(1) and G_0 is Uniform$[0, \theta]$



Mis-Specified Model: F_0 is Weibull$(2, 1)$ and G_0 is Exp(θ)

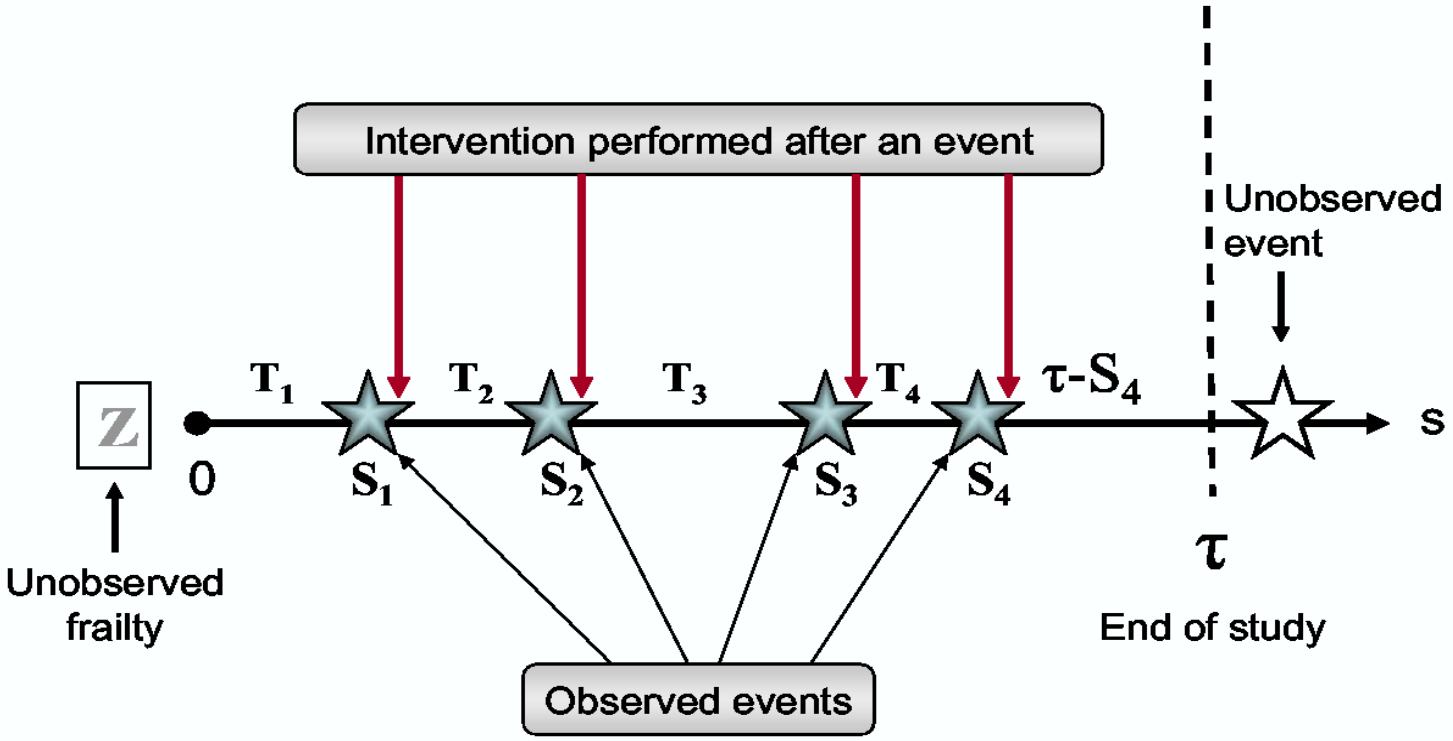


Briefly: On More General Recurrent Event Models

Must be able to model the following:

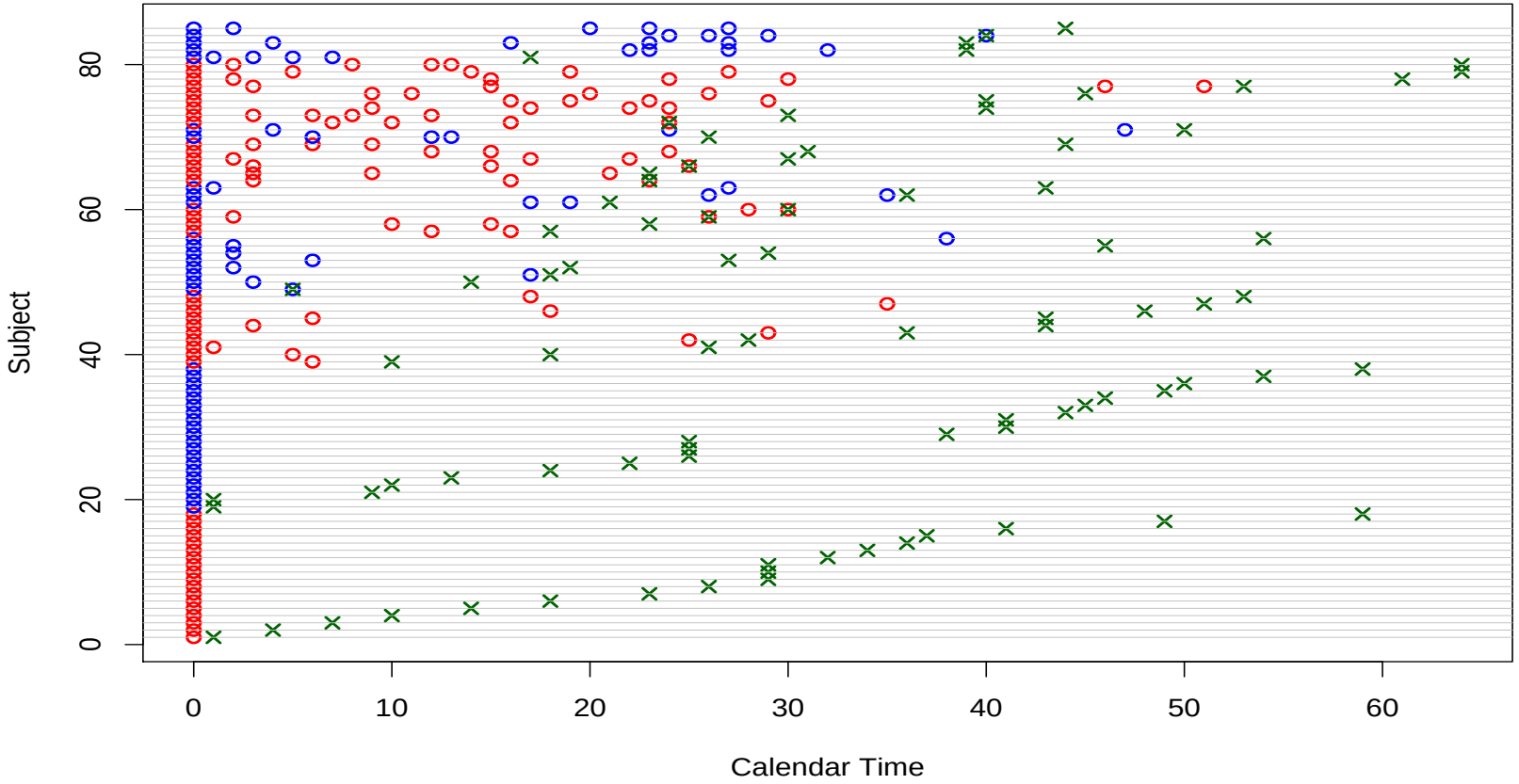
- comparing treatment groups.
- effect of covariates or regressor variables.
- effect of interventions after each event.
- effect of accumulating event occurrences.
- modeling association of inter-event times within a unit or subject.

Recall: Data Accrual for One Subject



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

Bladder Cancer Data Set: Groups [control (red), thiotepa (blue)]; Covariates; in WLW (89)



A General Class of Dynamic Recurrent Event Models

$$P\{dN_i^\dagger(s) = 1 | \mathfrak{F}_{s-}, Z_i\} = Z_i \lambda_0[\mathcal{E}_i(s)] \rho[(s, N_i^\dagger(s-)); \alpha] \psi[X_i(s)\beta] ds$$

- $\lambda_0(\cdot)$: baseline hazard rate function; nonparametric.
- $\mathcal{E}_i(\cdot)$: predictable effective (real) age process; effect of interventions.
  - $\mathcal{E}_i(s) = s$: minimal intervention.
  - $\mathcal{E}_i(s) = s - S_{iN_i^\dagger(s-)}$: perfect intervention.
- $\rho(\cdot, \cdot; \alpha)$: known function; effect of event occurrences.
- $\psi(\cdot)$: known link function; effect of covariate X_i.
- Z_i: unobserved frailty variable; distribution $H(\cdot; \eta)$.
- Model Parameters: $(\lambda_0(\cdot), \alpha, \beta, \eta)$.

Some Inferential Aspects for General Model

- Peña and Hollander (2004): proposed and discussed model, especially its generality.
- Peña, Slate and Gonzalez (2007): semiparametric estimation of model parameters.
- Stocker and Peña (2007): parametric estimation of model parameters.
- Peña (2012?): asymptotic properties of the estimators of semiparametric estimators of model parameters.
- Other inference methods: goodness-of-fit; group comparisons; model validation; estimating parameters in effective age process; Bayesian Approach.
- Challenge: need to gather effective age or real age of subjects/units/components in real studies.

Some Concluding Thoughts

- Revisited RCM with one event and Koziol-Green (KG) model.
- Revisited nonparametric estimation of inter-event distribution with recurrent event data.
- Extended KG model to recurrent event settings.
- Semiparametric estimation under this GKG recurrent event model.
- Examined properties of estimators under GKG structure.
- Efficiency losses of fully nonparametric estimator relative to GKG-based estimator.
- How about a Bayesian Approach to Inference?
- Touched on general dynamic models for recurrent event data.

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