On Dynamic Recurrent Event Modeling and Analysis

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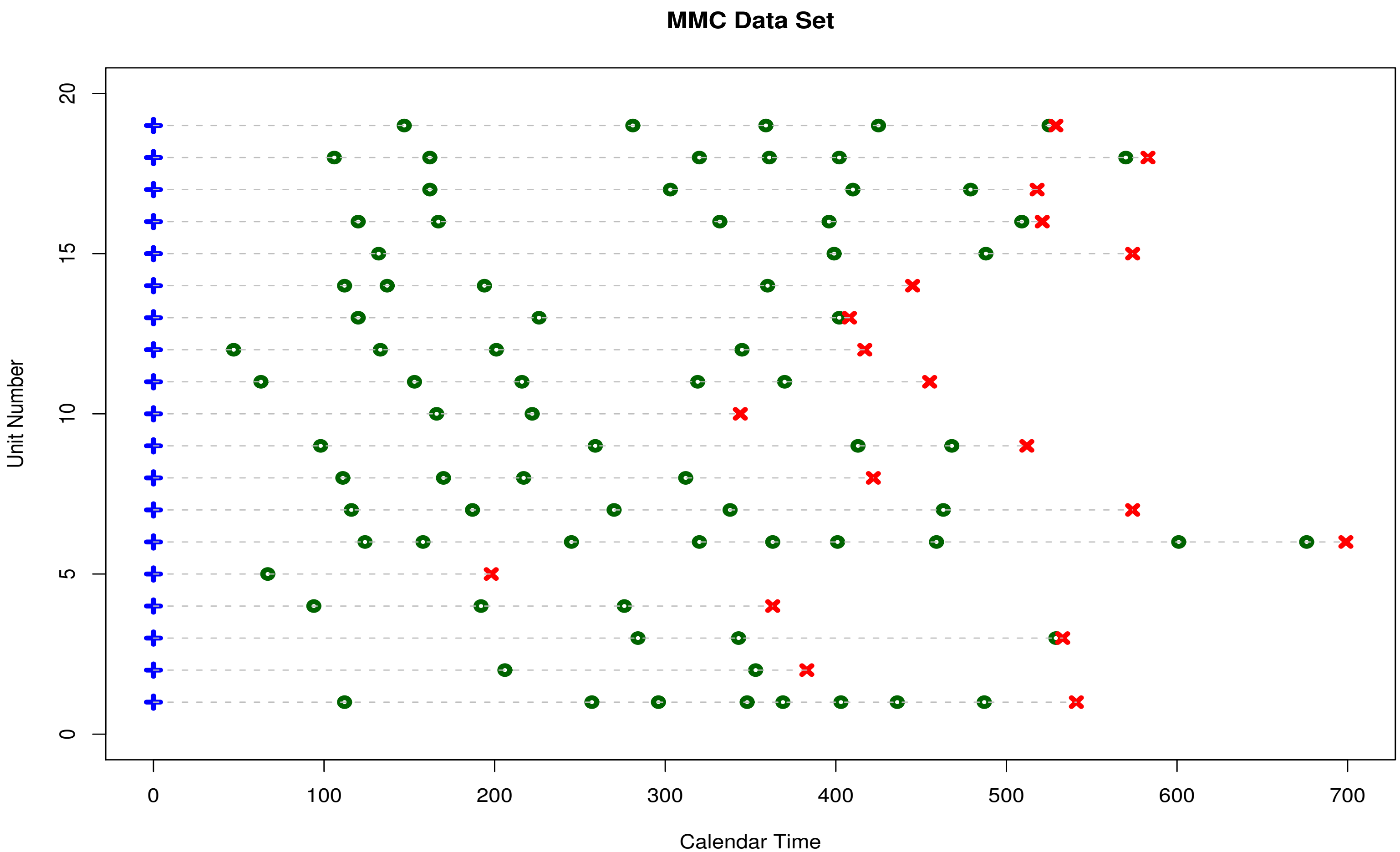
Recurrent Phenomena

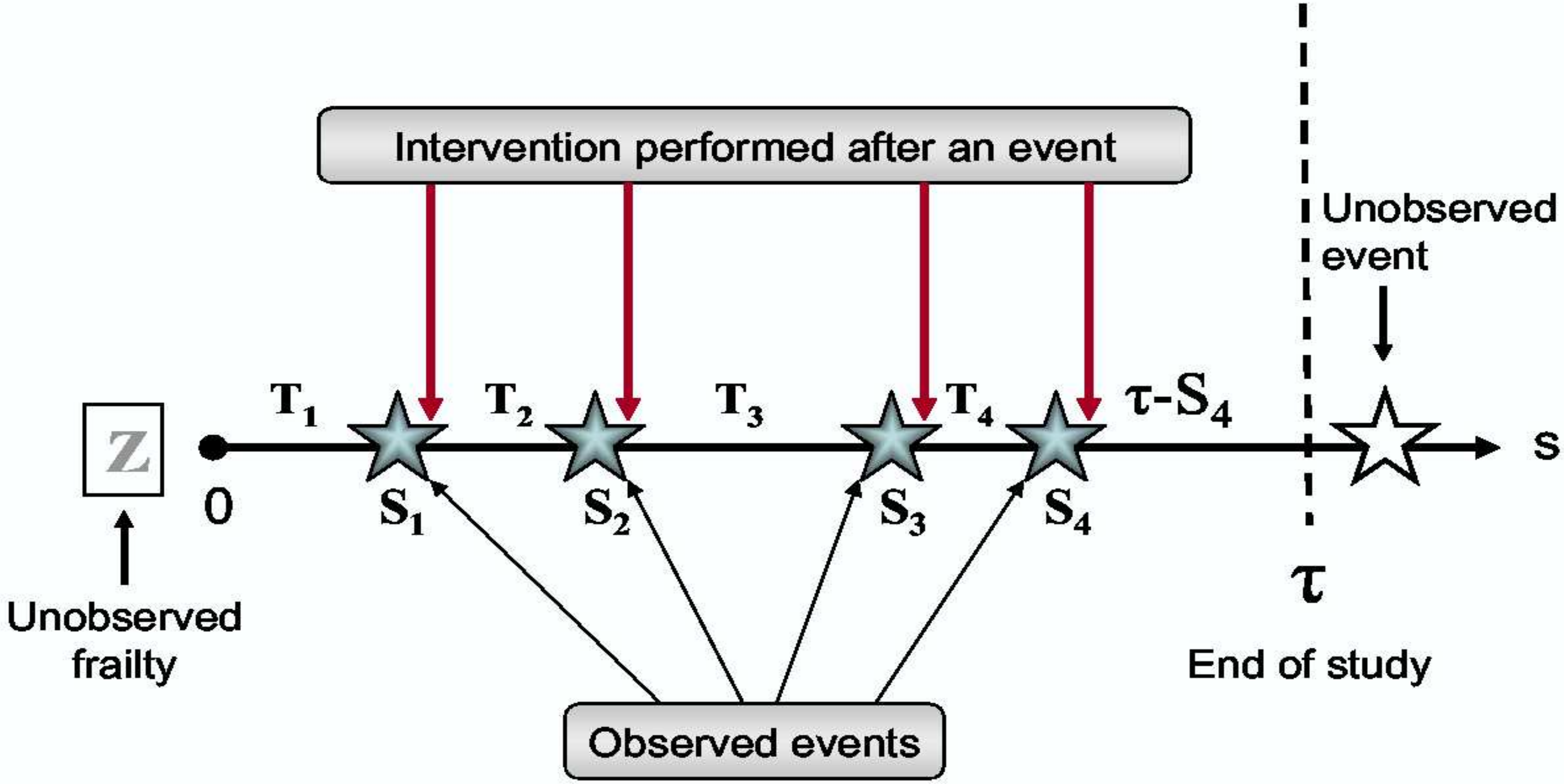
- Hospitalization due to a chronic disease.
- Drug/alcohol abuse
- Occurrence of migraine headaches.
- Onset of depression.
- Episodes of epileptic seizures.
- Non-fatal heart attacks.
- Software crashes and subsystem failures.
- Non-life insurance claims.
- In sociology: serious marital disagreements.
- Publication of a research paper or book.

Motivating Data Set: MMC Data Set

Migratory Motor Complex (MMC) Times for 19 Subjects
(Aalen and Husebye, 1991)



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
- τ = end of observation period.
- $K = \max\{k : S_k \leq \tau\}$ = 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 $\displaystyle\sum_{j=1}^{K} T_j \leq \tau < \sum_{j=1}^{K+1} T_j$.

General Class of Dynamic Models

- Peña and Hollander (2004) model.

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

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

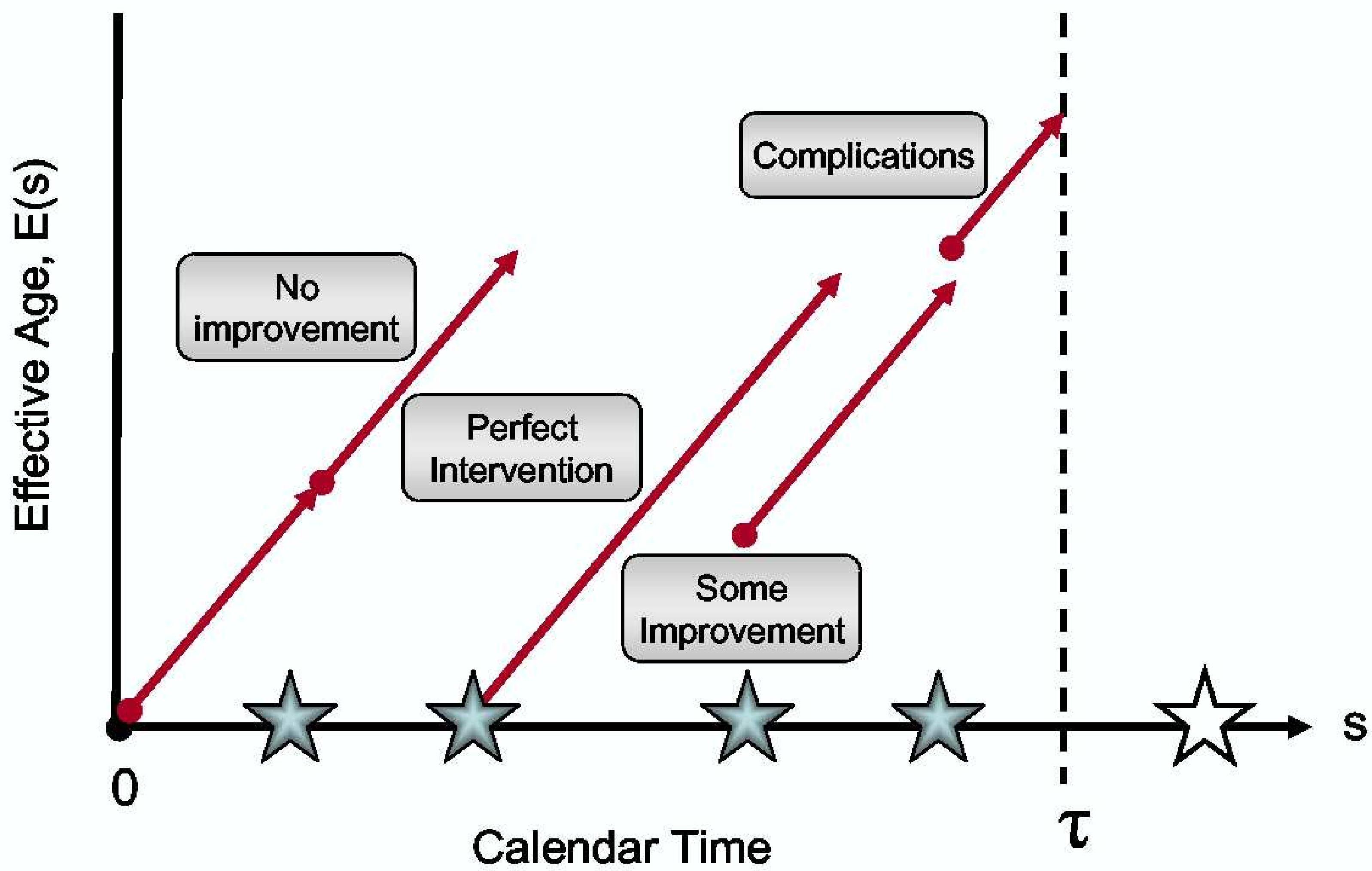
$$A^\dagger(s|Z) = \int_0^s Y^\dagger(w)\lambda(w|Z)dw$$

- Intensity Rate Process:

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

- Class includes as special cases many models in reliability and survival analysis.

Effective Age Process



Some Effective Age Processes

- 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),

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

Semi-Parametric Estimation: No Frailty

Observed Data for n Subjects:

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

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

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

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

Baseline gap-time distribution associated with $\lambda_0(\cdot)$ will be denoted by $\bar{F}_0$.

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:

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

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

Change-of-Variable Transformations

$$\int_0^s H(s,\mathcal{E}(v))I\{\mathcal{E}_i(v)\le t\}N^\dagger(dv) = \int_0^t H(s,w)N(s,dw);$$

$$\int_0^s H(s,\mathcal{E}(v))I\{\mathcal{E}_i(v)\le t\}A^\dagger(dv) = \int_0^t H(s,w)Y(s,w)\Lambda_0(dw);$$

$$Y(s,w) = \sum_{j=1}^{N^\dagger(s-)} I_{(\mathcal{E}_{j-1}(S_{j-1}),\ \mathcal{E}_{j-1}(S_j)]}(w)\ \varphi_{j-1}(w) +$$

$$I_{(\mathcal{E}_{N^\dagger(s-)}(S_{N^\dagger(s-)}),\ \mathcal{E}_{N^\dagger(s-)}((s\wedge\tau))]}(w)\ \varphi_{N_i^\dagger(s-)}(w|\alpha,\beta);$$

$$\int_0^s H(s,\mathcal{E}(v))I\{\mathcal{E}_i(v)\le t\}M^\dagger(dv) = \int_0^t H(s,w)M(s,dw).$$

Generalized At-Risk Processes

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

$$I_{(\mathcal{E}_{iN_i^\dagger(s-)}(S_{iN_i^\dagger(s-)}),\, \mathcal{E}_{iN_i^\dagger(s-)}((s\wedge\tau_i))]}(w)\ \varphi_{iN_i^\dagger(s-)}(w|\alpha, \beta)$$

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:

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

- 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.

Semi-Parametric Estimation: With Frailty

- Recall the intensity rate:

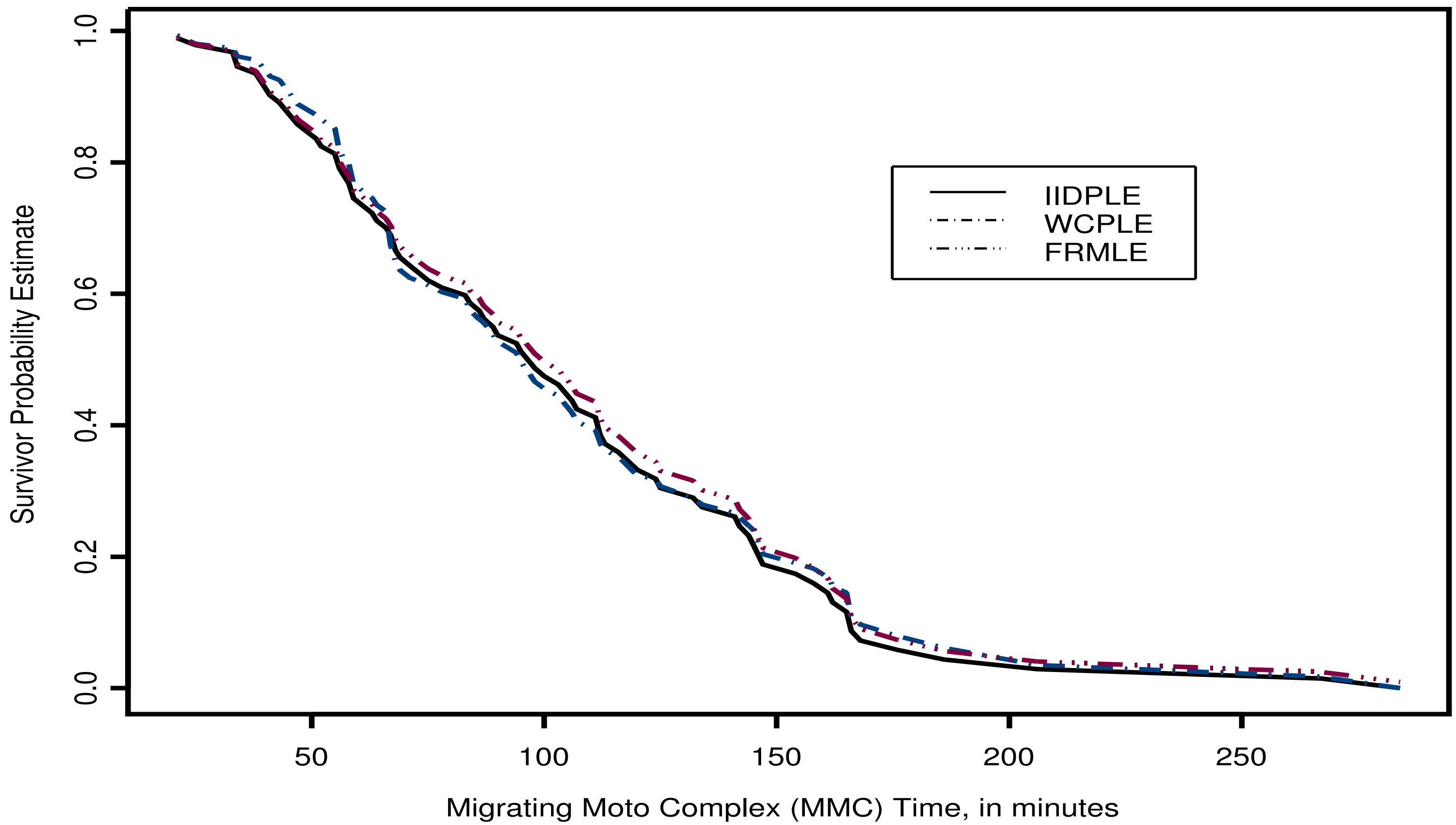
$$\lambda_i(s|Z_i, \mathbf{X}_i) = Z_i\,\lambda_0[\mathcal{E}_i(s)]\,\rho[N_i^\dagger(s-);\alpha]\,\psi(\beta^{\mathtt{t}}\mathbf{X}_i(s))$$

- 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*, to appear).

An Application: MMC Data Set

Aalen and Husebye (1991) Data

Estimates of distribution of MMC period



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 $[0, s^*] \times [0, t^*]$.
- $M_i(s,t) = \int_0^s I\{\mathcal{E}_i(v) \leq t\} M_i^\dagger(dv)$.
- $Y_i(s,t)$ - 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 $\{1, 2, \ldots, n\}$:

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

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

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

Concluding Remarks

- Many aspects of the general dynamic recurrent event model still under investigation.
- Asymptotics for the model with frailty.
- Testing hypothesis procedures.
- Goodness-of-fit and residual analysis.
- Its practical relevance still needs exploring, e.g., could the effective age process be determined appropriately in practice.
- Comparisons with marginal-based models (PWP, WLW).
- *Dynamic recurrent event modeling* remains a challenge and is a fertile area for research.