# A new model for joint analysis of an event process and associated longitudinal outcome

Elizabeth H. Slate and Edsel A. Peña

Dept. of Biometry and Epidemiology, Medical University of SC

Department of Statistics, University of South Carolina

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# Motivation

A recurrent event process has an associated longitudinal outcome.

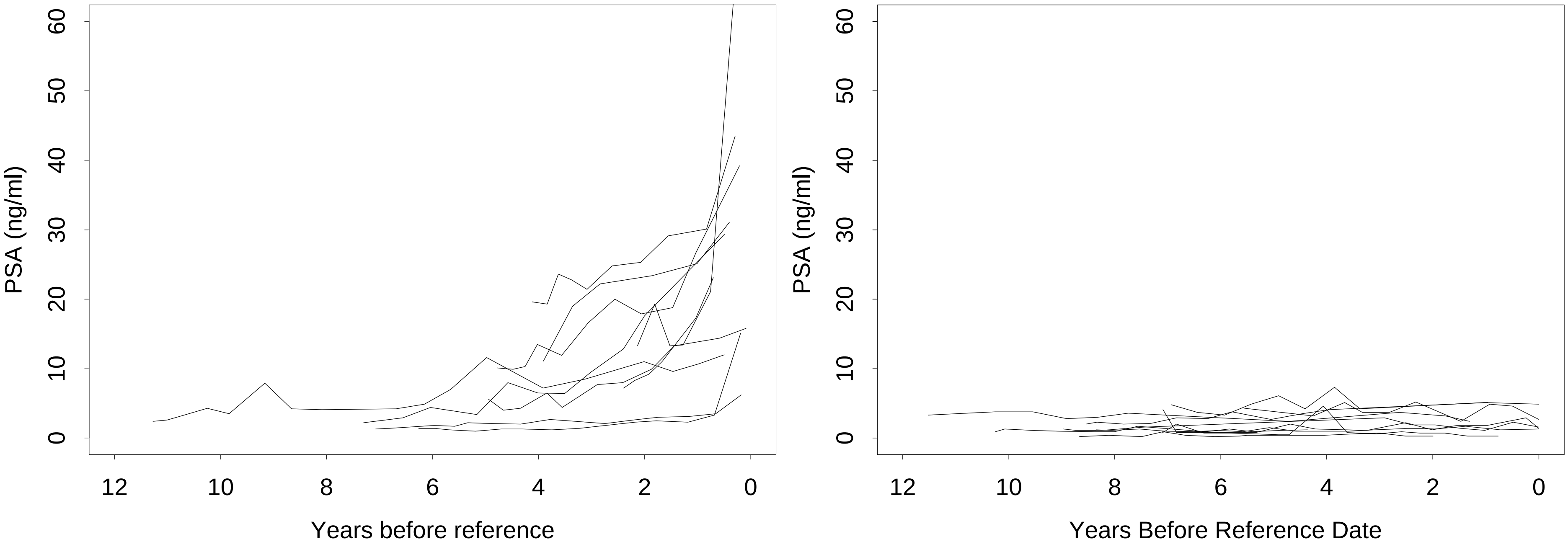
- Longitudinal outcome (marker)
  - a series of measurements for each individual
  - need to accommodate serial correlation, irregular observation times
- Recurrent event outcome
  - each individual may experience multiple events
  - need to accommodate censoring, correlation among inter-event times

# Example Scenarios

| Marker | Event |
| --- | --- |
| PSA | PCa (single event) |
| Cholesterol level | MI |
| LVH | Heart failure |
| Angina | MI |
| Stress level | Arrhythmia |
| Air pollution | Asthma hospitalizations |
| Plasma level of new drug | disease-related events |
| “Chatter” | Terrorist attacks |

# Examples – NPCT PSA Data

Select PCa Cases | Select Non-PCa Cases




Clark, *et al.*, *JAMA*, 1996; Slate and Clark, 1999.

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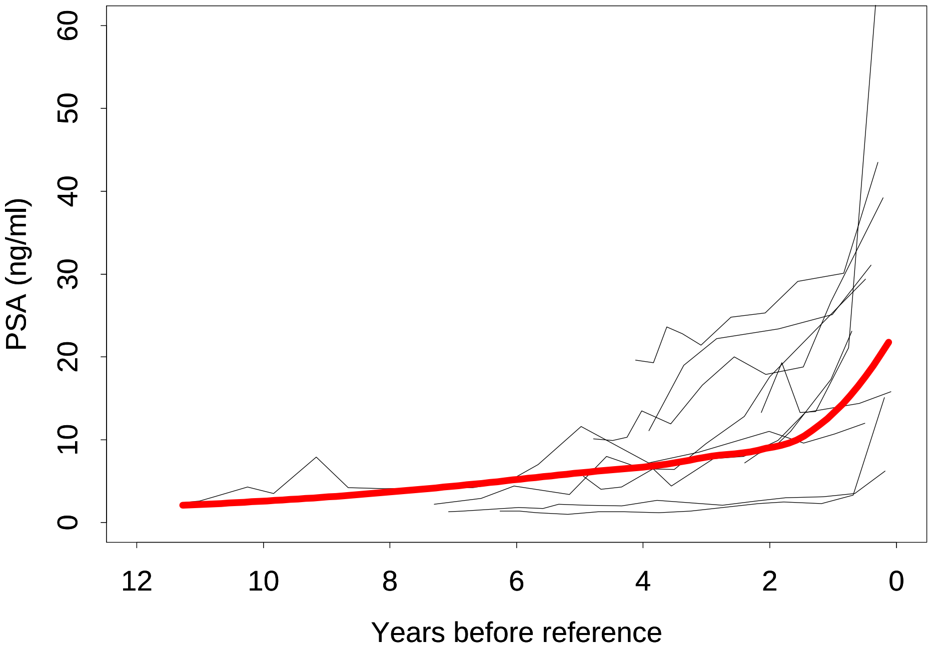
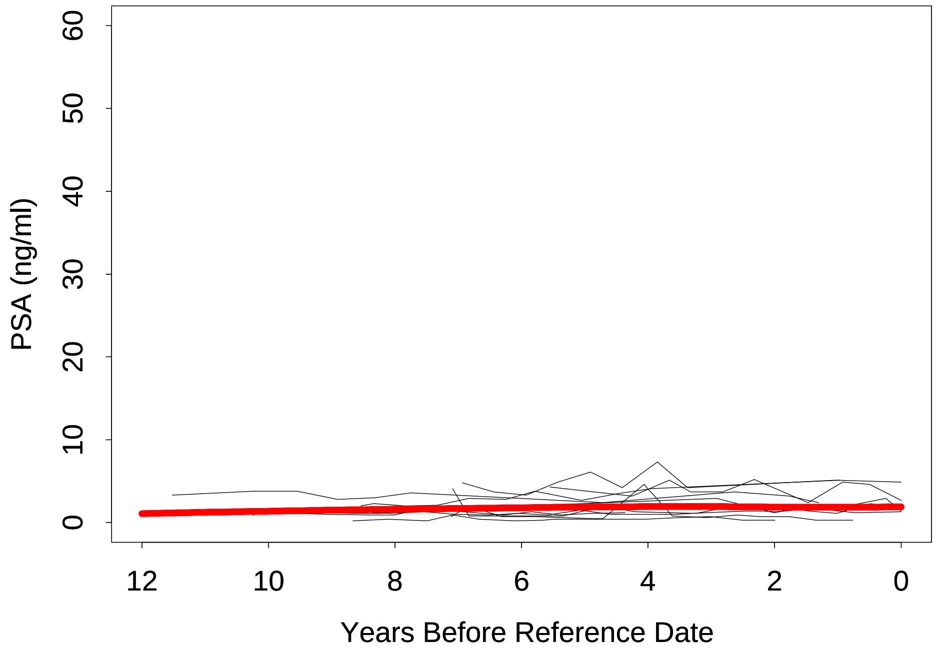



Select Non-PCa Cases

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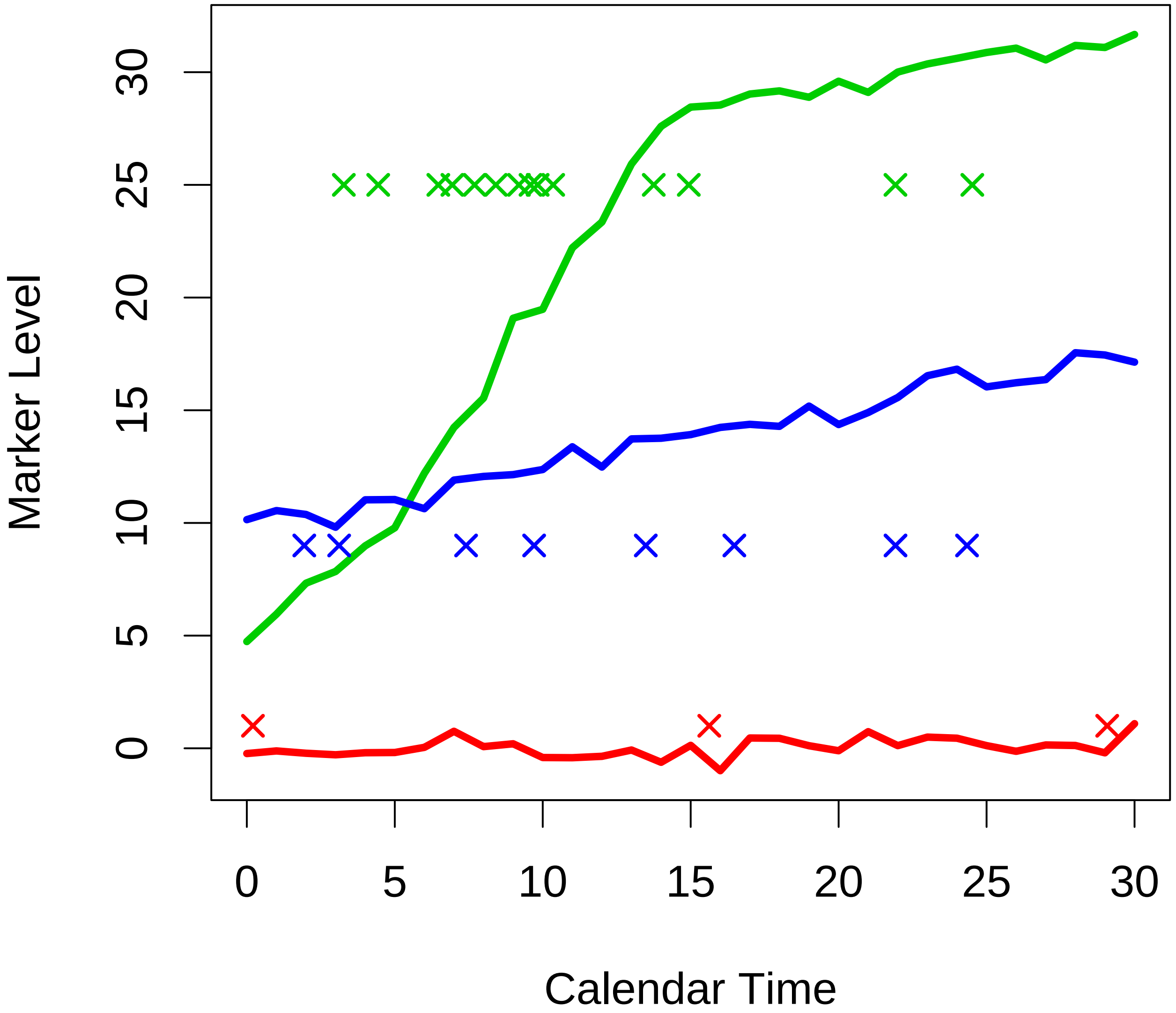
# Schematic – Recurrent Event



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- What is the effect of action following the occurrence of an event?
- Does the marker aid in prediction of events?
- Is the occurrence of an event predictive for the marker?
- Is the association between the marker and event process the same for all individuals?

# Modeling Approaches

- Event Process | Marker
  - Marker as (time-dependent) covariate for event process.
  - Predict events given marker history.
- Marker | Event Process
  - Event occurrence times as covariate for marker process.
  - Characterize marker evolution for different event patterns.
- Focus here: (Marker, Event Process) modeling event process and longitudinal marker as *joint* outcomes.

# Benefits of modeling jointly

- Fitted model provides a concise description of the data available.
- Context for evaluating the association between the marker and event process.
- Model provides a means for incorporating the information from the longitudinal marker for predicting the event process; and vice versa.
- Given multiple markers, can aid selection of marker that is most informative (predictive) about the event process.

# Approaches to joint modeling

- [Event | Marker] [Marker] (measurement error model)
  *e.g.*, CD4 counts and progression to AIDS
  - Tsiatis, DeGruttola and Wulfsohn (1995)
  - Faucett and Thomas (1996)
  - Shi, Taylor and Muñoz (1996)
  - Wulfsohn and Tsiatis (1997)
  - Law, Taylor and Sandler (2002)

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- [Marker | Event] [Event]
  *e.g.*, Pawitan and Self (1993) in AIDS context
- Latent Variables to simplify dependence
  - Shared random effects
    *e.g.*, DeGruttola and Tu (1994), Schluchter (1992)
  - Latent processes
    *e.g.*, Xu and Zeger (2001), Henderson, Diggle and Dobson (2000)
  - Latent classes
    Lin *et al.* (2002)

# Latent variable joint modeling

Marker $\mathbf{Y}_i(t)$ observed at times $t_{i1}, t_{i2}, \ldots, t_{im_i}$

Event Time $T_i$ single event

- Shared random effects

$$[\mathbf{Y}_i, T_i] = \int [\mathbf{Y}_i \mid \mathbf{b}_i][T_i \mid \mathbf{b}_i][\mathbf{b}_i]\, d\mathbf{b}_i$$

- Latent processes

$$[\mathbf{Y}_i(t), T_i] = \int [\mathbf{Y}_i(t) \mid \eta_i(t)][T_i \mid \eta_i(t)][\eta_i(t)]\, d\eta_i(t)$$

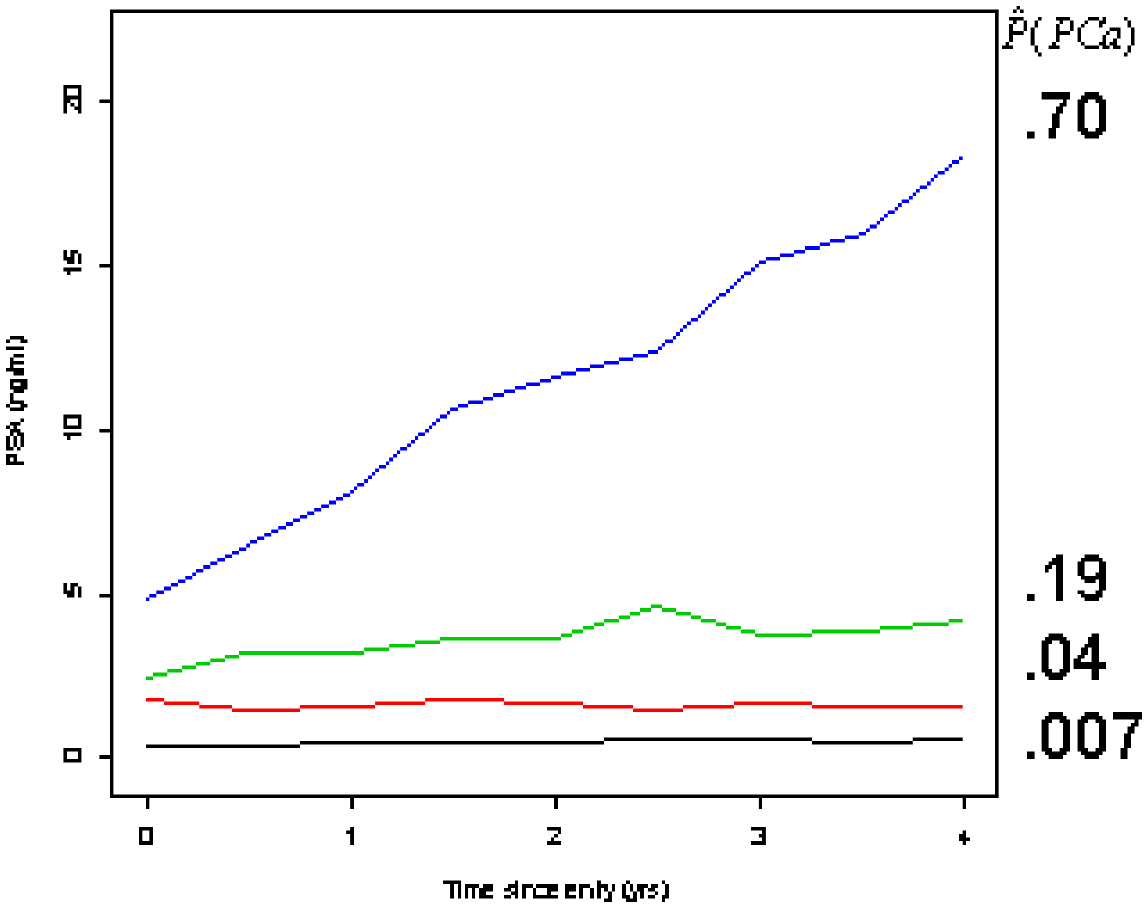
- Latent classes

$$[\mathbf{Y}_i, T_i] = \sum_{k=1}^{K} [\mathbf{Y}_i \mid \mathbf{c}_{ik}][T_i \mid \mathbf{c}_{ik}][\mathbf{c}_{ik}]$$

# Advantages of latent classes

- Conditional independence simplifies modeling the association.
- Association can be distinct for each class – “protects” against potential misspecification in other approaches.
- Captures subpopulation structure – distinct patterns for the joint responses.

# Flexibility of latent class approach



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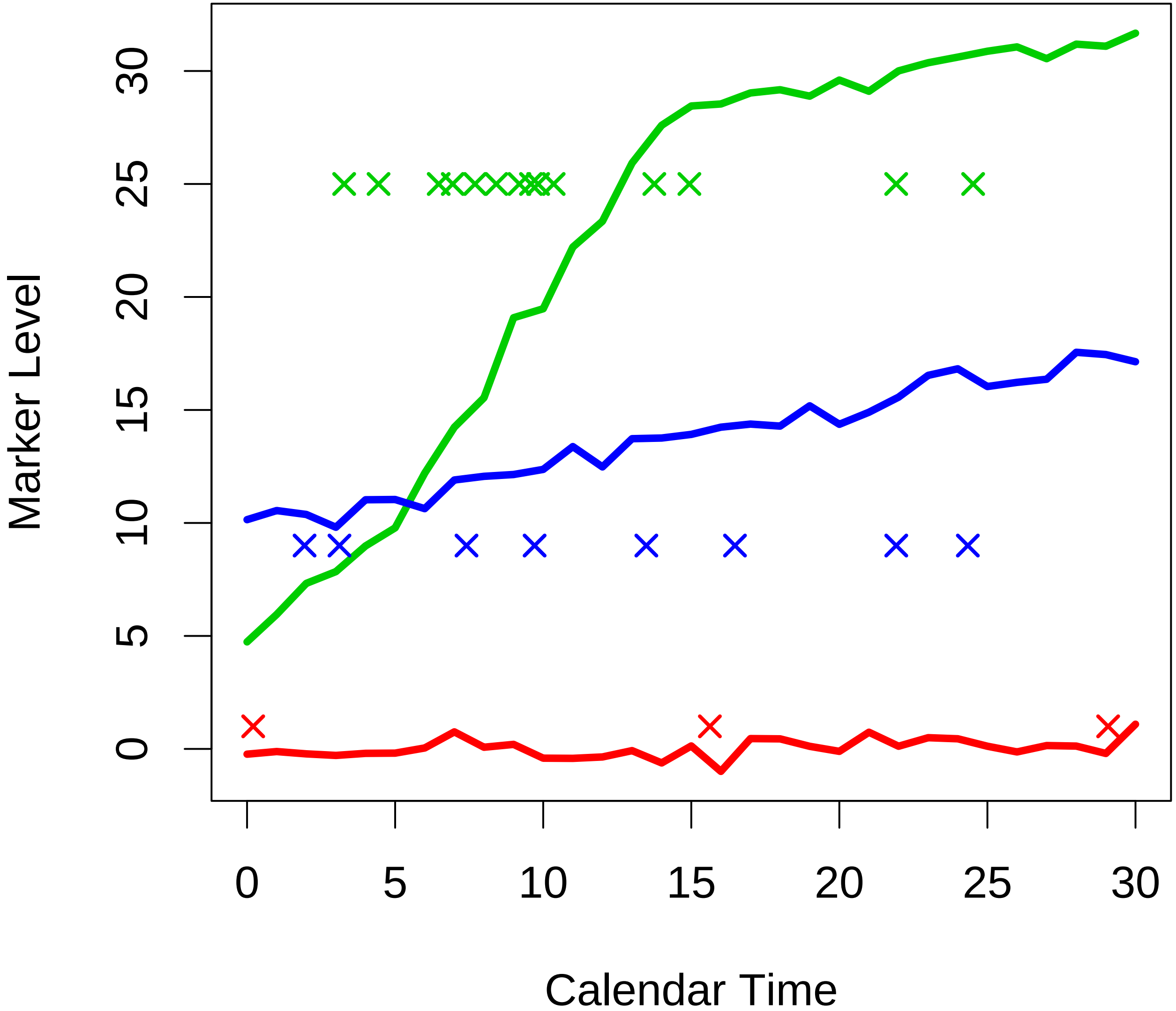


# Single event model: PSA–PCa Lin *et al.*, *JASA*, 2

$\mathbf{Y}_i = \ln(\text{PSA}_i + 1)$, $T_i =$ PCa diagnosis time

$$[\mathbf{Y}_i, T_i] = \sum_{k=1}^{K} [\mathbf{Y}_i \mid \mathbf{c}_{ik}][T_i \mid \mathbf{c}_{ik}][\mathbf{c}_{ik}]$$

Latent class membership: Multinomial logit with covariates $\nu_i$

$$\Pr(c_{ik} = 1) \propto \exp(\nu_i^T \eta_k)$$

Longitudinal marker: Linear with subject- and class-specific effects; covariates $U_i$, $V_i$, $W_i$

$$E(\mathbf{Y}_i \mid b_i, c_{ik} = 1) = U_i\beta + V_i b_i + W_i M_k + \epsilon_i$$

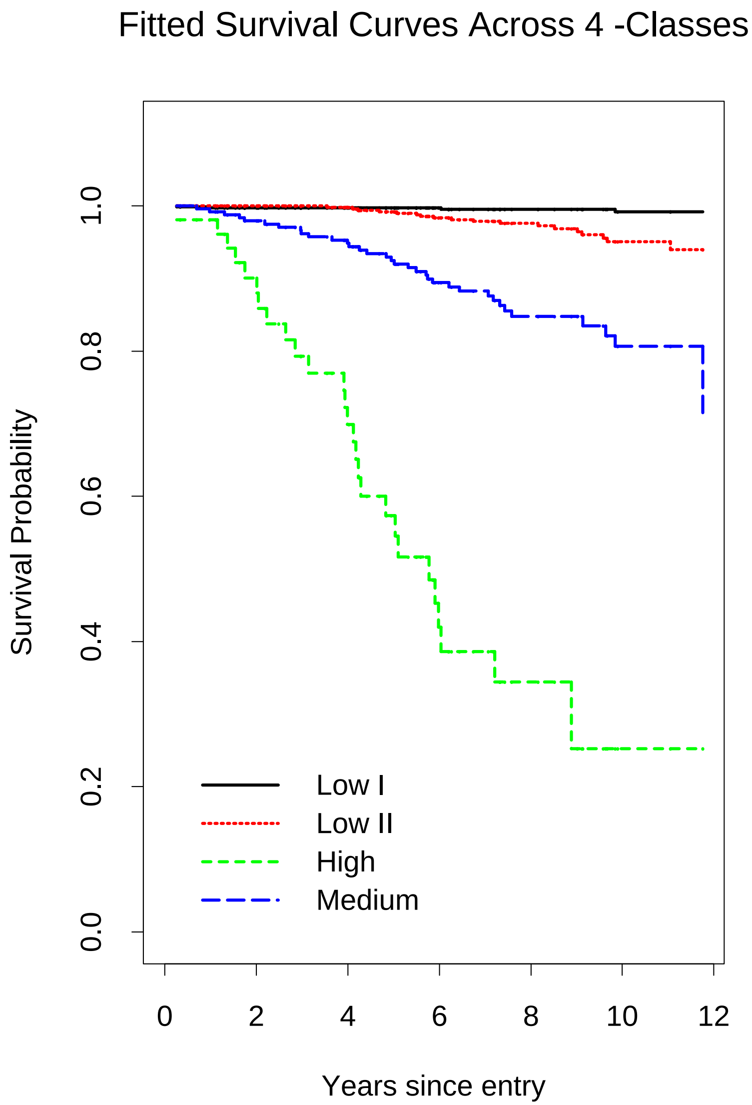
Hazard: Cox model with class-specific baseline, frailty ($Z_i$); covariates $X_i$

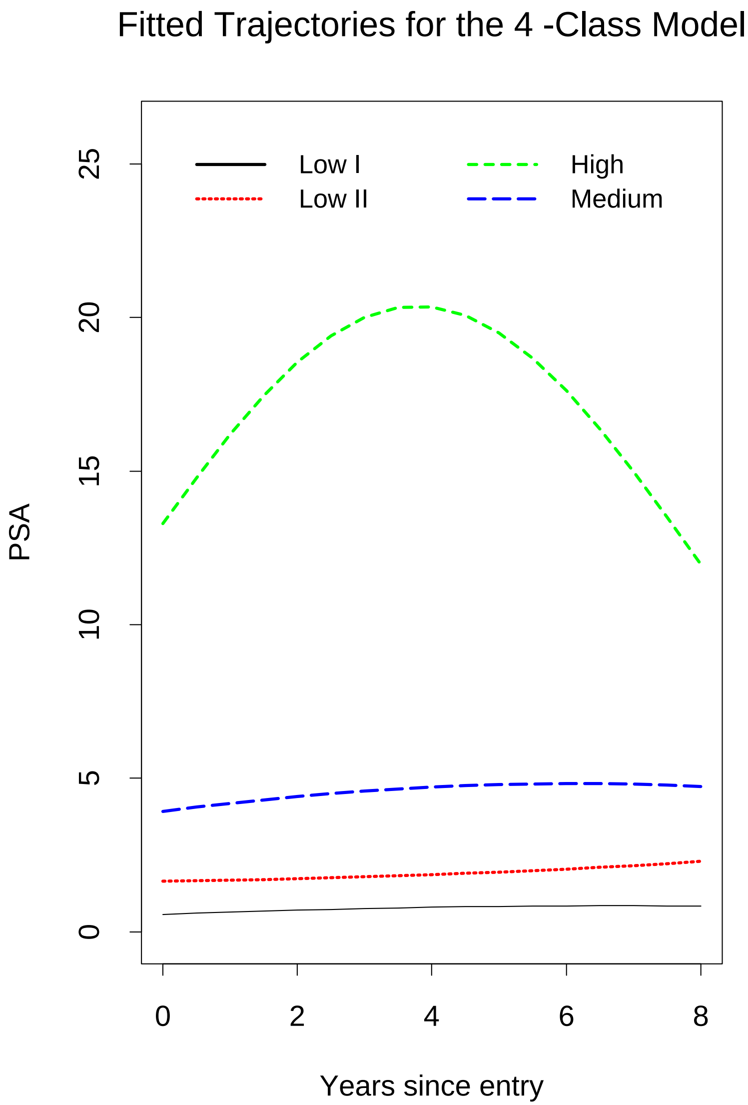
$$Z_i R_i(t) \lambda_k(t) \exp(\gamma^T X_i)$$

# Estimation

- For fixed number of latent classes $K$, use EM algorithm.
  - Complete data: $(\mathbf{Y}_i, \min\{T_i, \tau_i\}, \delta_i, b_i, Z_i, \mathbf{c}_i)$
  - Missing data: $(b_i, Z_i, \mathbf{c}_i)$
- Select number of latent classes!
  We used $BIC = \log L_k - \frac{1}{2}(Npar_k) \log n$

# PSA–PCa results: $K = 4$



# Proposed Extension

In the latent class structure, replace the single event survival model by the general class of recurrent event models of Peña and Hollander (2003).

$$[\mathbf{Y}_i, (N_i, R_i)] = \sum_{k=1}^{K} [\mathbf{Y}_i \mid \mathbf{c}_{ik}][(N_i, R_i) \mid \mathbf{c}_{ik}][\mathbf{c}_{ik}]$$

- Latent class membership:

$$\Pr(c_{ik} = 1) \propto \exp(\nu_i^T \eta_k)$$

- Longitudinal marker:

$$E(\mathbf{Y}_i \mid b_i, c_{ik} = 1) = U_i\beta + V_i b_i + W_i M_k + \epsilon_i$$

- Recurrent event process:

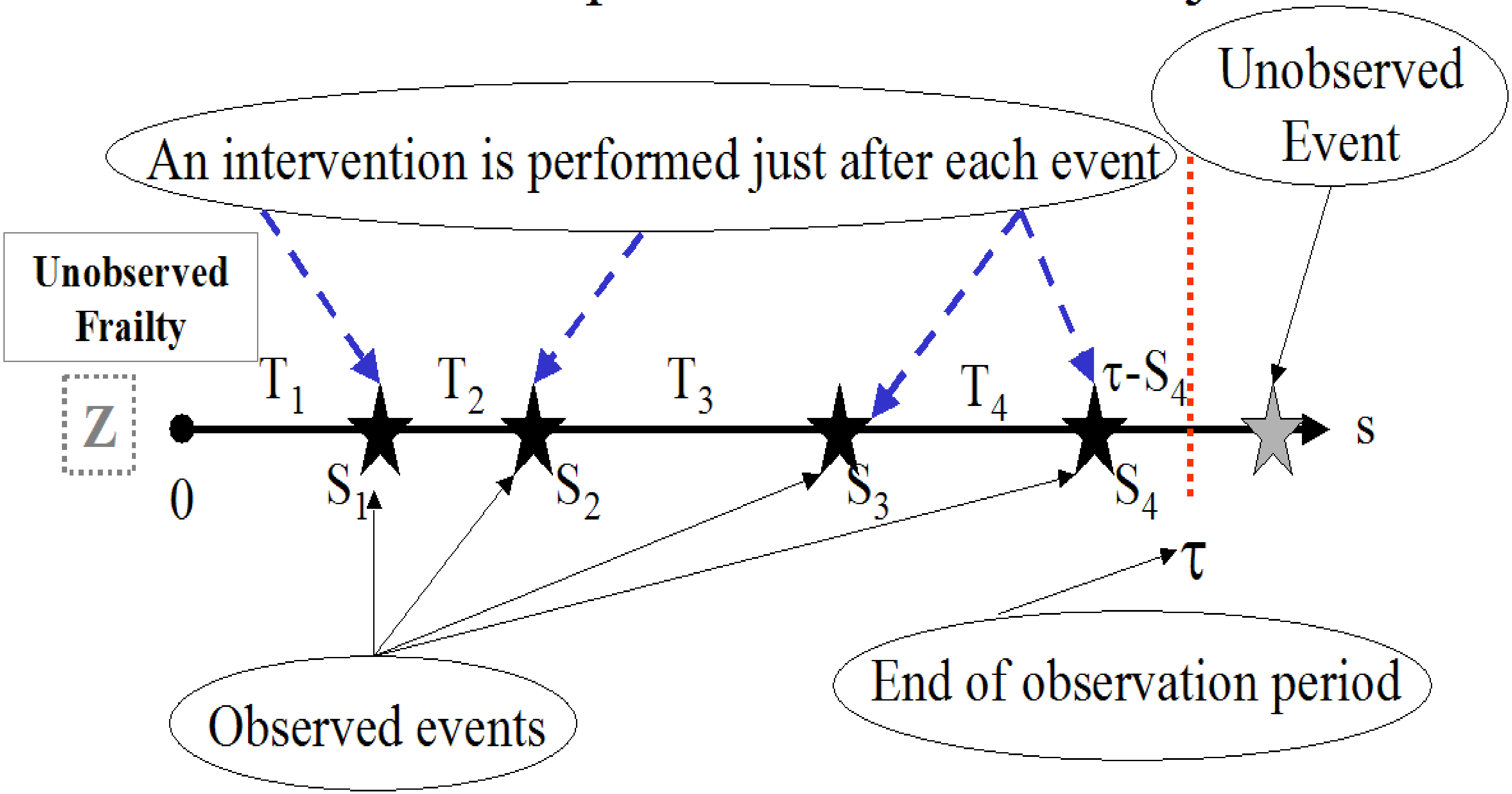
  Peña and Hollander (2003)...

# Recurrent event model **Peña & Hollander, 2003**

Accommodate:

- Effects of intervention following event occurrence.
- Effects of accumulating event occurrences (weakening/strengthening).
- Covariates.
- Random observation time.
- Informativeness of number of events observed.

# A Pictorial Representation: One Subject




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

# Intensity Process (details Saturday)

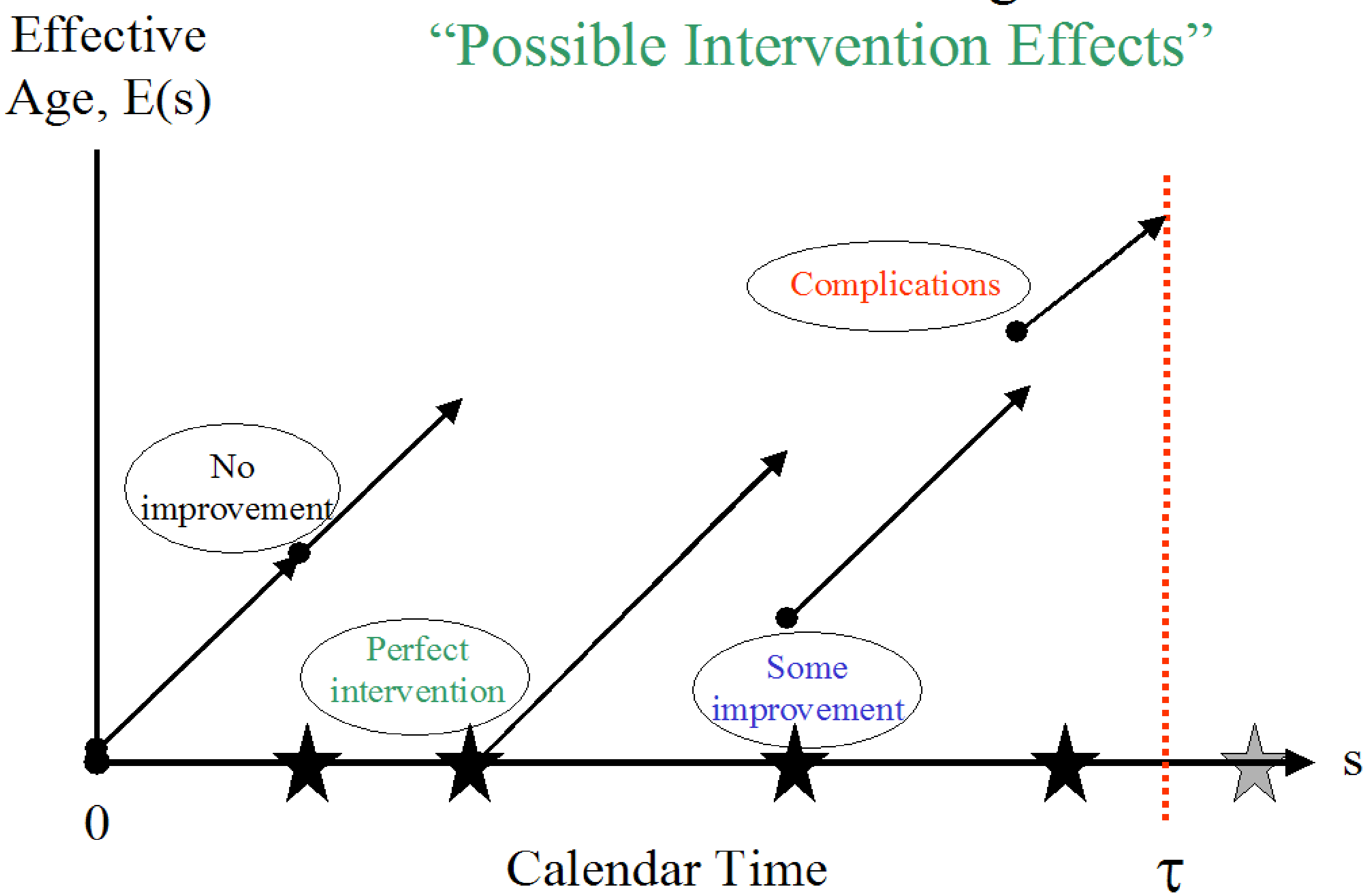
For subject $i$ in latent class $k$:

$$\lambda(s|Z_i, c_{ik} = 1) = Z_i \; \lambda_{0k}[\mathcal{E}_i(s)] \; \rho[N_i(s-); \alpha_k] \; \psi[X_i(s)\gamma_k]$$

where

- $\lambda_{0k}(\cdot) =$ unknown baseline hazard rate function for class $k$.
- $\mathcal{E}_i(s) =$ effective age of the subject at calendar time $s$. **Idea:** performed intervention changes the effective age of the subject acting on the baseline hazard rate.
- $\rho(\cdot; \alpha_k) =$ a positive function on $\{0, 1, 2, \ldots\}$ with $\rho(0; \alpha_k) = 1$ and with unknown parameter $\alpha_k$, depending on the class.
- $\psi(\cdot) =$ positive link function containing the effect of covariates $X_i$; $\gamma_k$ are unknown. *e.g.*, $\psi(X_i \, \gamma_k) = \exp(X_i \, \gamma_k)$.
- $Z_i =$ unobservable frailty. Induces associations among subject's inter-event times. Class dependent...?

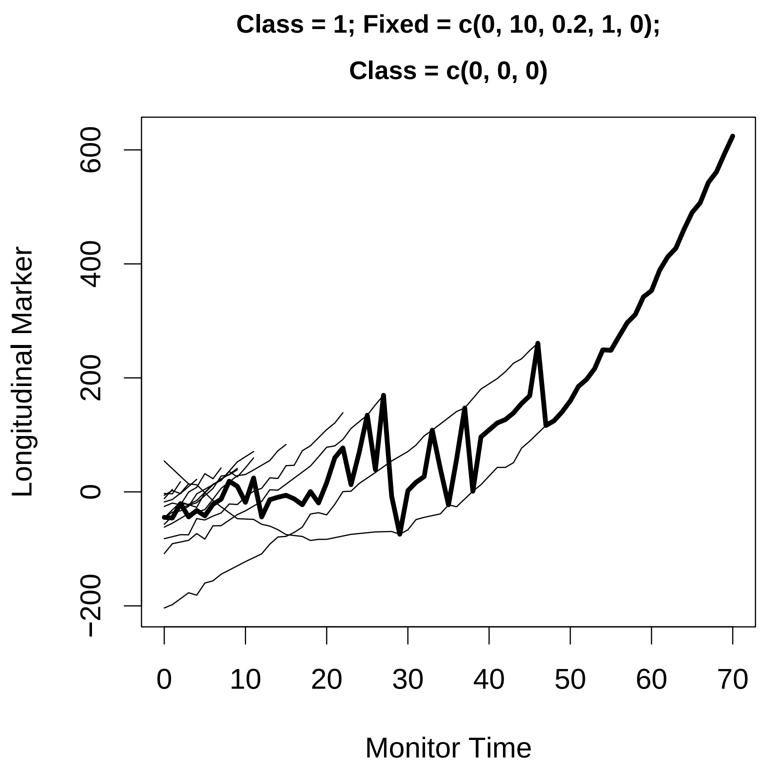
# Illustration: Effective Age Process
## “Possible Intervention Effects”

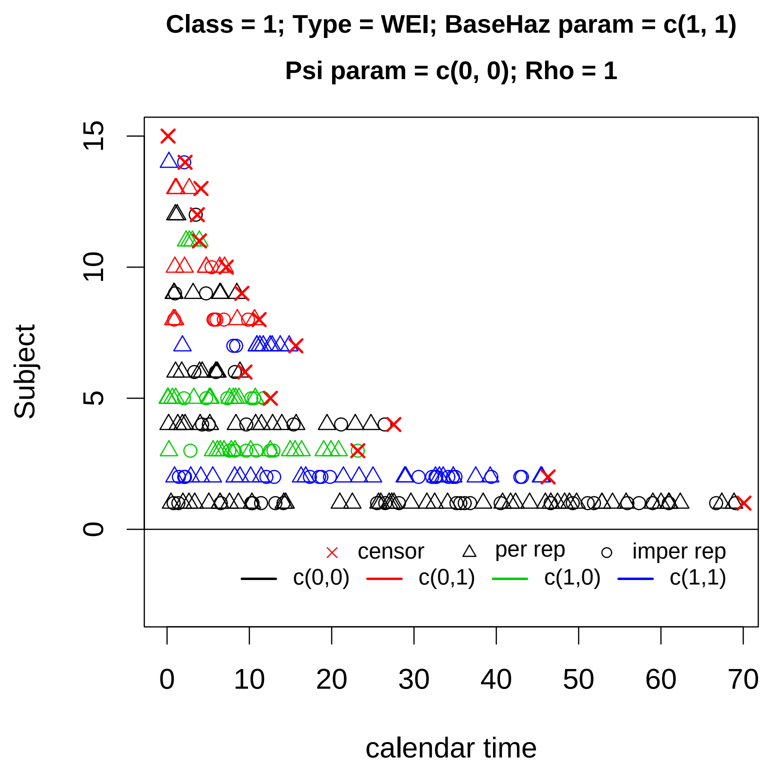


# Illustration

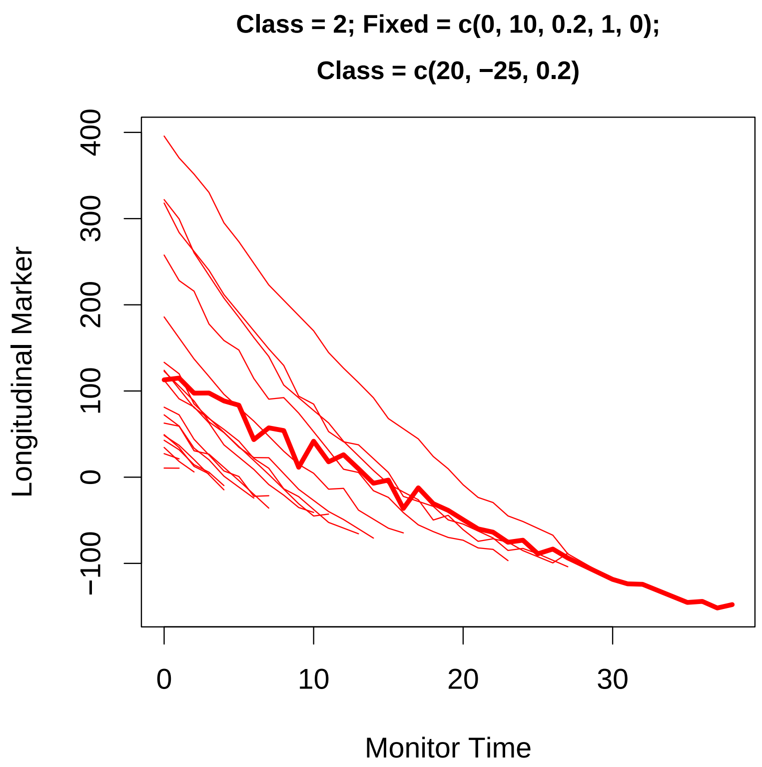
- $K = 3$ latent classes. Class membership based on bivariate binary covariate $\nu_i$
- Longitudinal marker covariates:
  - Fixed effects: $U_i =$ intercept, time, time$^2$, binary $\nu_i$
  - Random effects: $V_i =$ intercept, time, time$^2$
  - Class effects: $W_i =$ intercept, time, time$^2$
- Recurrent event process:
  - $\lambda_{0k}$: Weibull, params $(1, 1)$, $(2, 1)$, $(0.5, 1)$
  - $\rho(m) = {\alpha_k}^m$, $\alpha_1 = 1$, $\alpha_2 = 0.95$, $\alpha_3 = 1.02$
  - $\psi(X_i\,\gamma_k) = \exp(X_i\gamma_k)$, $X_i = \nu_i$, $\gamma_k \in \mathcal{R}^2$ class dependent
  - $\mathcal{E}(\cdot)$: $\Pr($perfect repair$) = 0.6$
  - No frailty

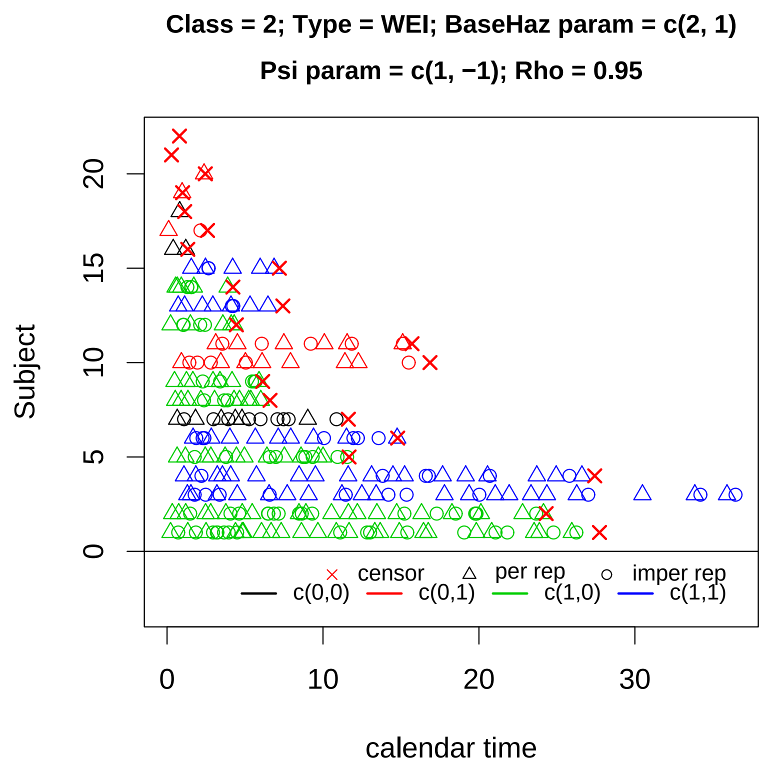
# Illustration – Class 1



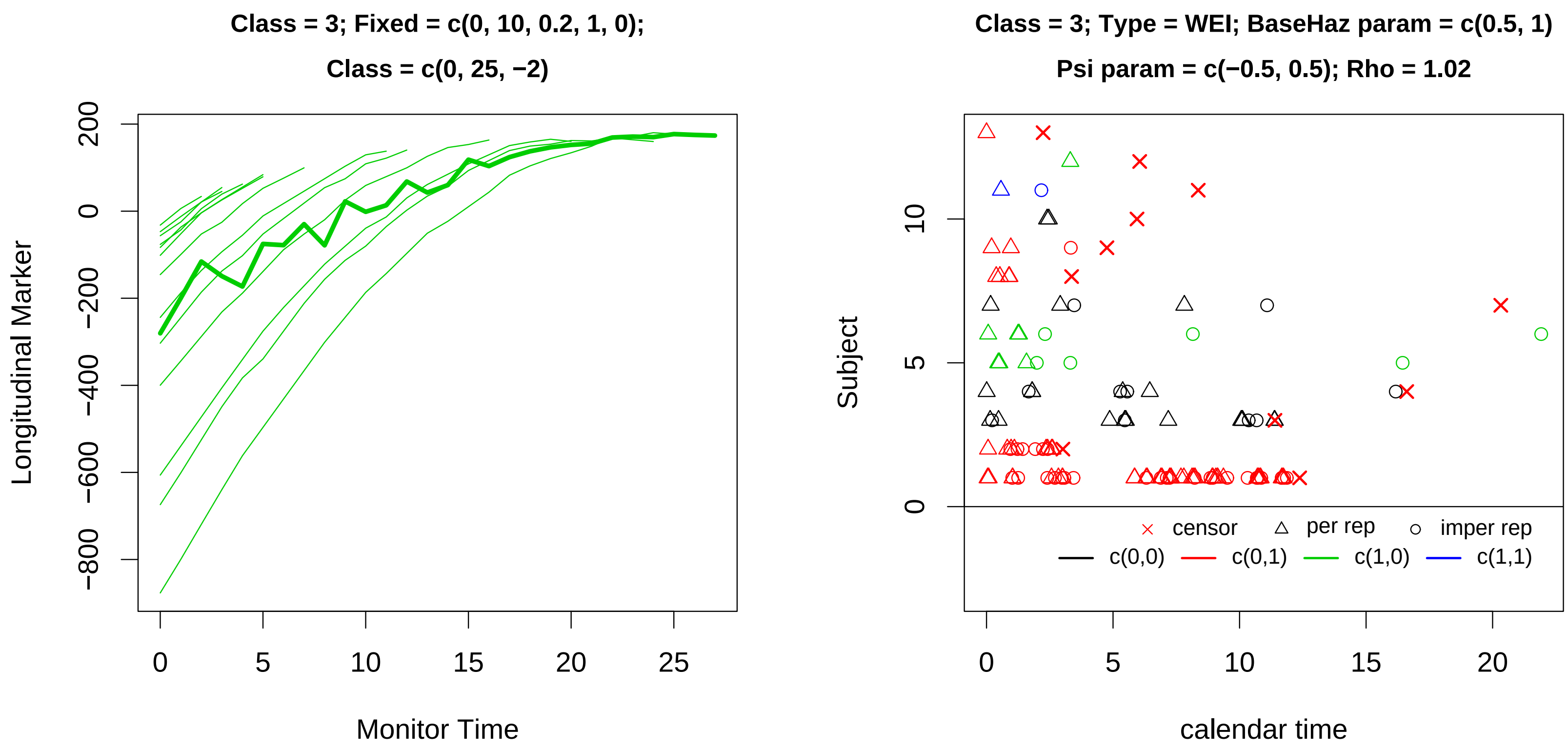



# Illustration – Class 2



# Illustration – Class 3



# Estimation

- Maximum likelihood – EM algorithm (Dempster, Laird and Rubin, 1977)
  - Complete data: $(\mathbf{Y}_i, \{(N_i(s), R_i(s)), s \leq \tau_i\}, b_i, Z_i, \mathbf{c}_i)$
  - Missing data: $(b_i, Z_i, \mathbf{c}_i)$
- Number of latent classes.
  - AIC, BIC
  - Bayesian model averaging
- In progress...

# Diagnostics

- Conditional independence of $\mathbf{Y}_i$ and $\{(N_i(s), R_i(s)), s \leq \tau_i\}$
  Build upon ideas of generating pseudo class membership
  - Bandeen-Roche *et al*. (1997)
  - Lin *et al*. (2002)
- Residual diagnostics
  - Survival-type residuals *e.g.* (Lin *et al.*, 2002)
  - Build on current work in growth mixture modeling: B. Muthén, C. Hendricks Brown, C-P. Wang

# Extensions

Many!

- Effect of event occurrence (and subsequent intervention) on longitudinal marker.
- Multiple markers (Lin *et al.* 2002).
- Partially observable classes (cure-rate models) (Law *et al.*, 2002; Ibrahim *et al.*)