Marginal Structural Models
for Investigating Long-Term Effectiveness of a Time-Dependent Treatment: An Application to Multiple Sclerosis

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Outline

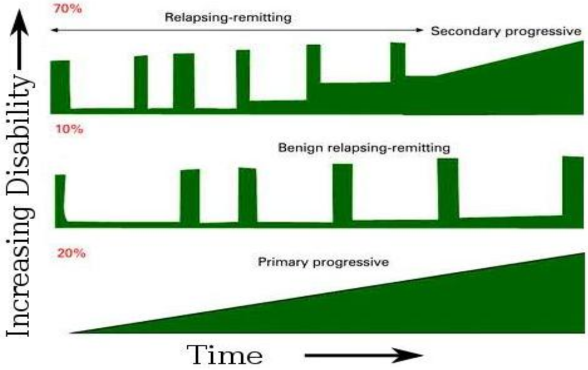
1. Data & Background
2. Marginal Structural Cox
3. Sensitivity Analysis
4. Reference and Discussion

Multiple Sclerosis >

Multiple sclerosis (MS) disease:

1. associated with damage of nerve cells
2. Leads to "disability" in advanced stage
3. Disability is attributed to
    - incomplete recovery of a relapse
    - deterioration of functional ability over time

Multiple Sclerosis > Relapses and Progression



From "The Bare Essentials Multiple sclerosis" by A. Coles (2009) Pract. Neurol.

Disability measured by "Expanded Disability Status Scale" (EDSS)

Research Problem >

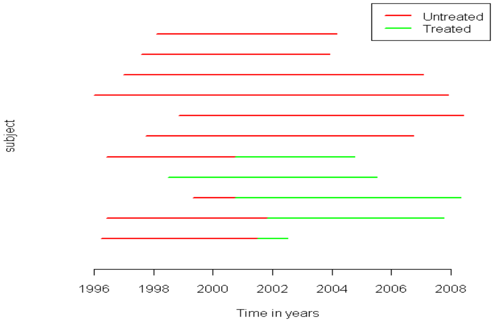
Outcome: Reaching a milestone in disability progression scale (time to sustained EDSS 6)
Treatment: Use of β-interferons (3 kinds)

We want to see whether these treatments have any **beneficial effect** on the patients or not.

Treatment effect estimation >

- **Randomized clinical trial** would be preferred to estimate causal effect.
- Given that this is a **life-long disease**, clinical trials are less practical, highly selective, expensive.
- Under **conditional exchangeability** assumption based on the confounders, we can try to estimate it from **observational data**.

Data >



775 patients are selected with **similar eligibility criteria** (registered in BC MS clinics).

Analysis >

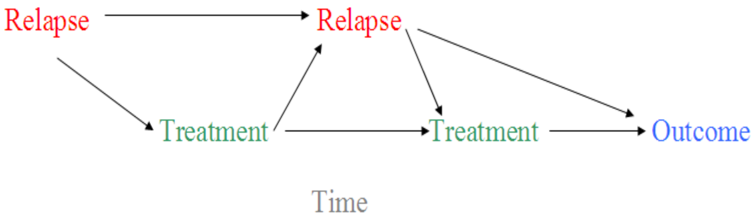
Time-dependent Cox:

$$\lambda_{T_{\bar{a}}}(t|V) = \lambda_0 \exp\left(\beta_1 a(t) + \beta_2 V + \beta_3 L(t)\right)$$

1. T = Outcome (Time to EDSS 6)
2. a(t) = Treatment at t (β-interferons)
3. L(t) = Time-dependent covariates at t (relapse)
4. V = Baseline covariates (gender, age, disease duration, EDSS)

Data for each time interval.

Causal graph >



Relapse is both **confounder** and **mediator** variable in the causal structure.
We need to adjust for confounder, but adjusting for a mediator variable will introduce bias (**over-adjustment/block path**) in the analysis using standard tools [Hernán et al., 2004].

Estimating Exposure Probability >

Past treatment $a(t-1)$, baseline covariate V and time-dependent confounders $L(t)$ are used in a logistic regression model (best subset by AIC) to estimate the IPTW weights:

1. for treated, the estimate is predicted probability $\hat{p}$ and
2. for untreated, it is 1 - $\hat{p}$

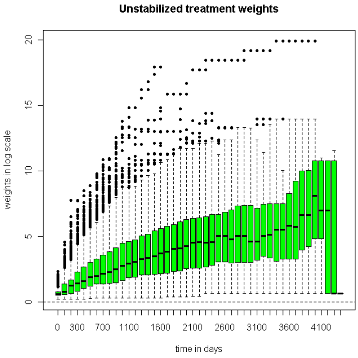
$$W(t) = \prod_{j=1}^{t} \frac{1}{Pr(A(j) = a(j)|\bar{A}(j-1) = \bar{a}(j-1), \bar{L}(j) = \bar{l}(j))}$$

$$SW(t) = \prod_{j=1}^{t} \frac{Pr(A(j) = a(j)|\bar{A}(j-1) = \bar{a}(j-1), V = v)}{Pr(A(j) = a(j)|\bar{A}(j-1) = \bar{a}(j-1), \bar{L}(j) = \bar{l}(j))}$$

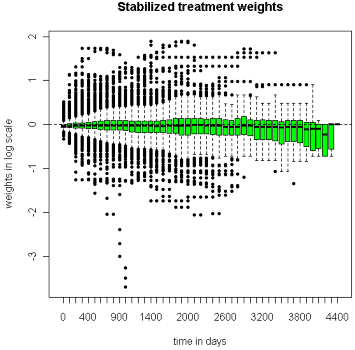
Similarly for censoring weights [Hernán et al., 2000; Robins et al., 2000].

Treatment weights >

$W(t)$

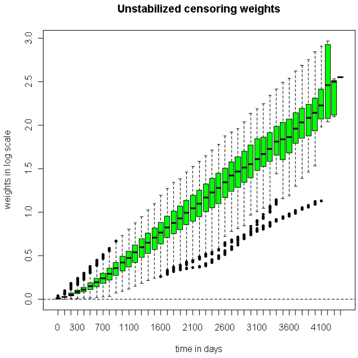


$SW(t)$

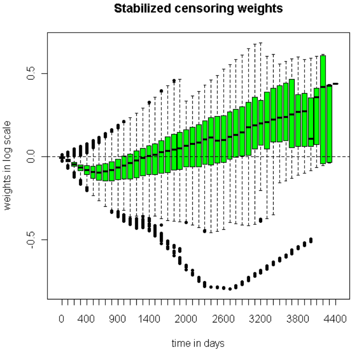


Censoring weights >

$W^{\dagger}(t)$

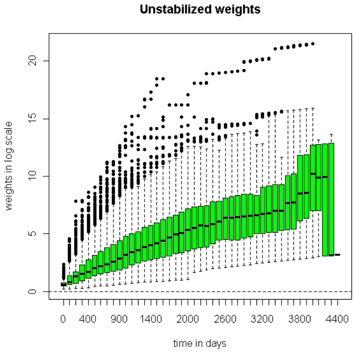


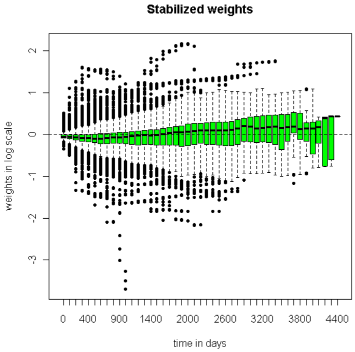
$SW^{\dagger}(t)$



Weights >

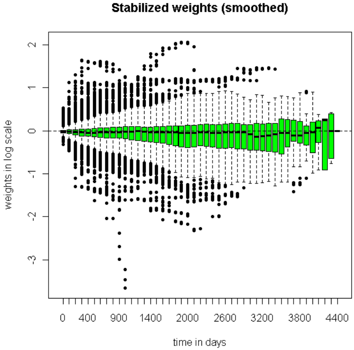
$$w(t) = W(t) \times W^{\dagger}(t) \qquad sw(t) = SW(t) \times SW^{\dagger}(t)$$





Smoothed weights >

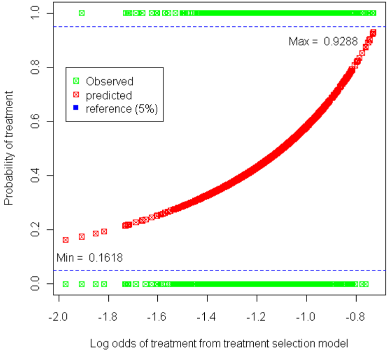
$$w_i^{(n)}(t) = \frac{w_i(t)N(t)}{\sum_{i \in R(t)} w_i(t)}$$ [Xiao et al., 2010]



Maximum inverse weight is 8 for creating pseudo-population

Experimental Treatment Assumption >

Mortimer et al. [2005]

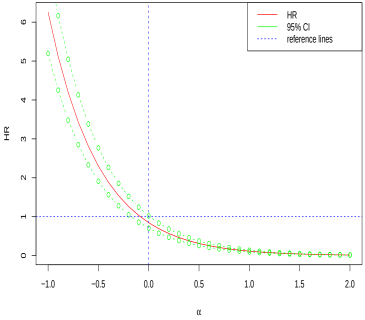


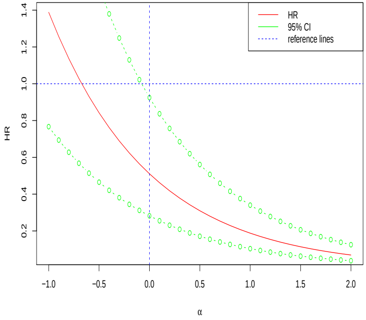
Avonex 46, Rebif 198, Betaseron 156, No drug 303, Switch 72

Unmeasured confounder >

Functions of treatment status $a(t)$ [Klungsøyr et al., 2009]

$\alpha\left(2a(t) - 1\right)$ $\alpha a(t)$

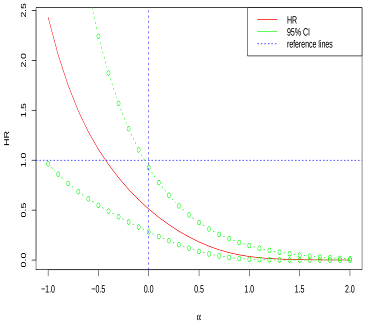




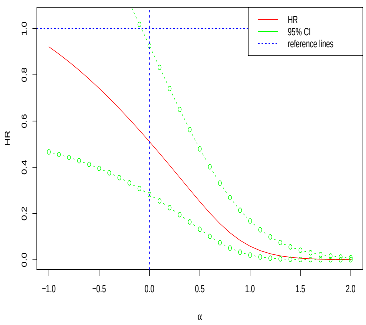
Unmeasured confounder >

Functions of treatment $a(t)$ & time-dependent covariate $l_1(t)$:

$$\alpha\big(2a(t)-1\big)l_1(t)$$



$$\alpha a(t) l_1(t)$$



Further Assumptions to be Checked>

- **Conditional exchangeability** or sequential randomization: $Y_{\bar{a}}(t) \coprod A(t) | A(t-1), L(t)$
- **Consistency**: for every subject with $A = a$, $Y_a = Y$ (observed)
- **Time ordering**: $a(t)$ happens before $Y_a(t)$
- **No model misspecification**

Bibliographic Notes

- MS literature: Tremlett et al. [2010]
- MSM theory: Robins [1999] Hernán et al. [2000] Robins et al. [2000] Hernán et al. [2004]
- MSM sensitivity: Brumback et al. [2004] Mortimer et al. [2005] Klungsøyr et al. [2009]
- MSM computational: Xiao et al. [2010] van der Wal [2011] Bryan et al. [2004]

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Thank You!

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