How to estimate beta-interferon treatment effectiveness in MS using some fancy modelling

Ehsan Karim
Department of Statistics, UBC

Pharmacoepidemiology in MS Research Group (PiMS),
Brain Research Centre conference centre,
UBC Hospital, Vancouver

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Outline

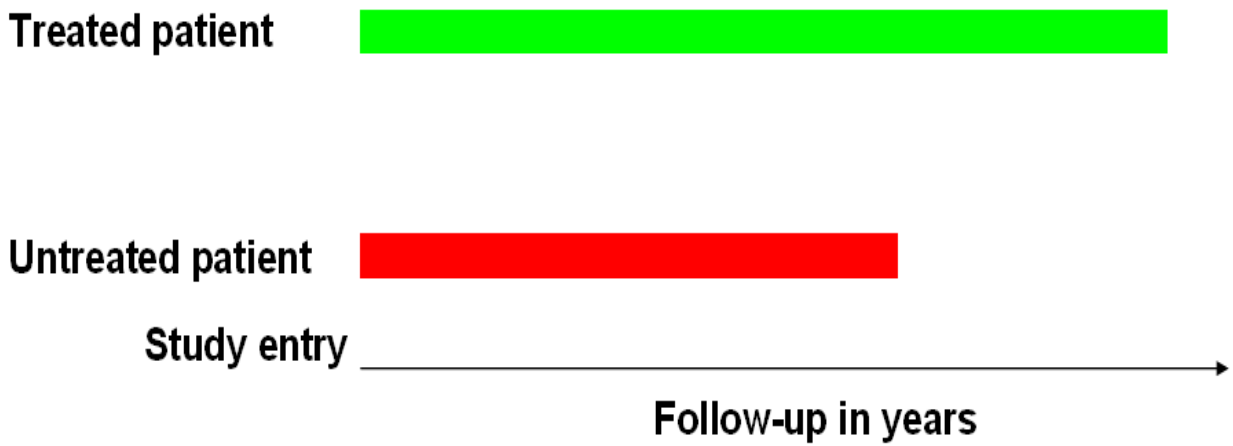
1. Why modelling
2. Why fancy modelling
3. A rough sketch
4. Take home message

Why modelling > Objective

- **Outcome**: Reaching a milestone in disability progression (time to sustained EDSS 6)
- **Treatment**: Use of β-interferons (3 kinds)
- **Objective**: Treatments have any long-term beneficial effect?

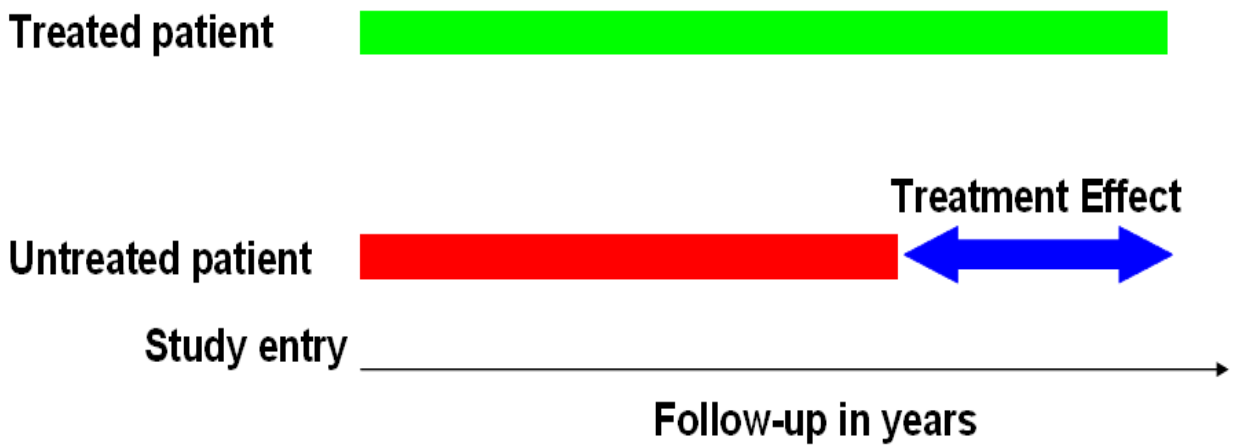
Randomized controlled trial or **observational** study?

Why modelling > Treatment Effect



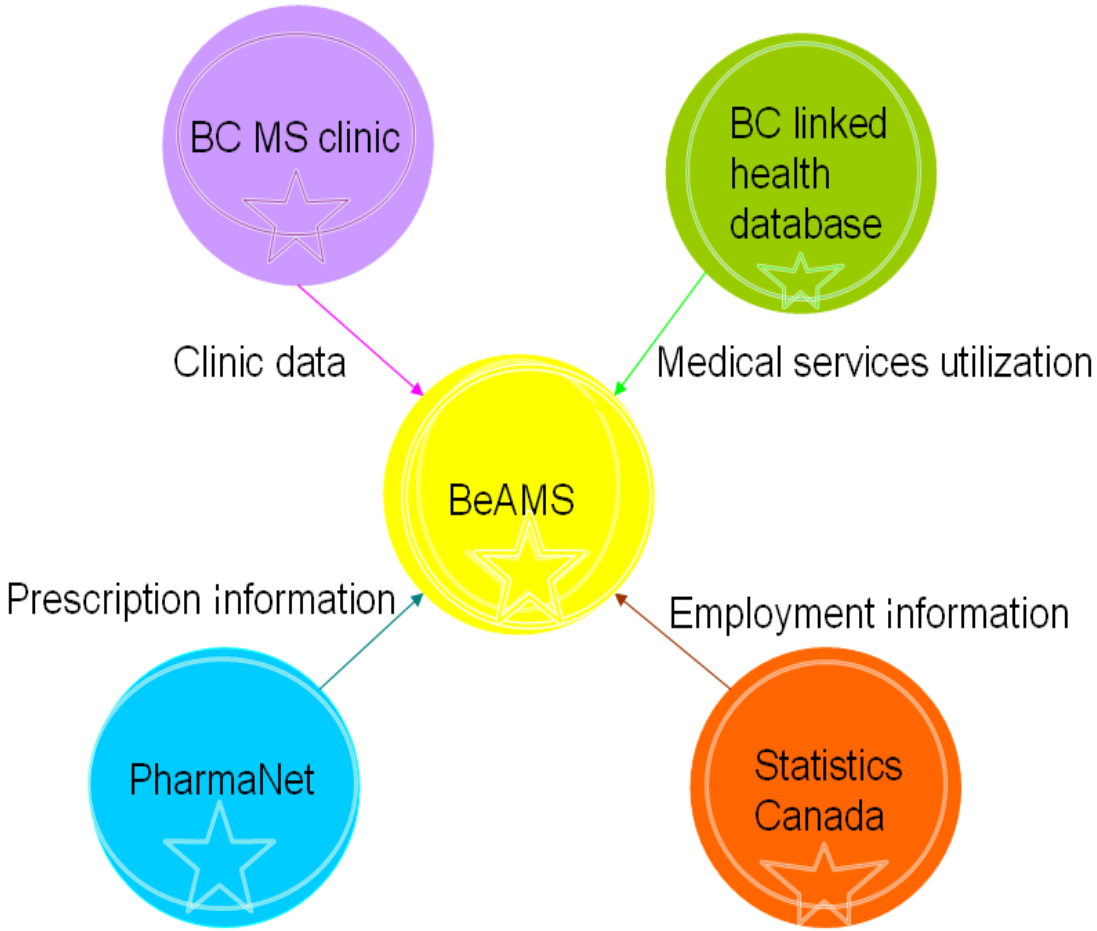
Treatment Effect from ideal situation

Why modelling > Treatment Effect



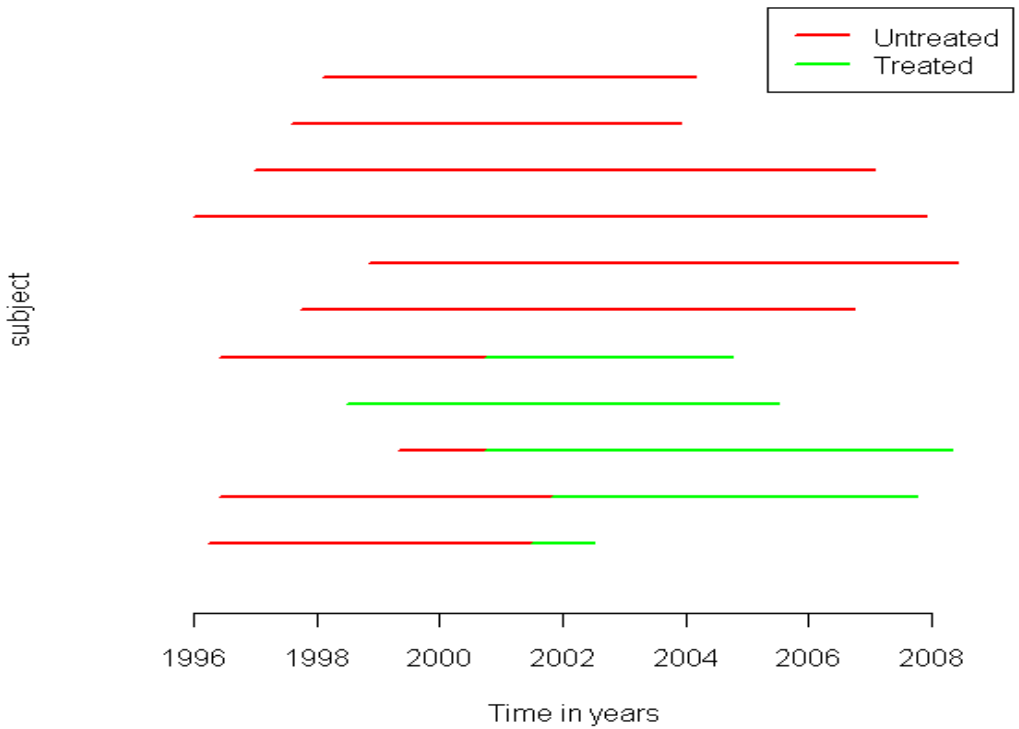
Treatment Effect from ideal situation: KM / Cox PH model?

Why modelling > Less than ideal situation



Baseline covariates: Gender, Age, Disease duration
Time-varying covariates: Relapse, EDSS scores

Why modelling > Observational data



Patients are selected with **similar eligibility criteria**.

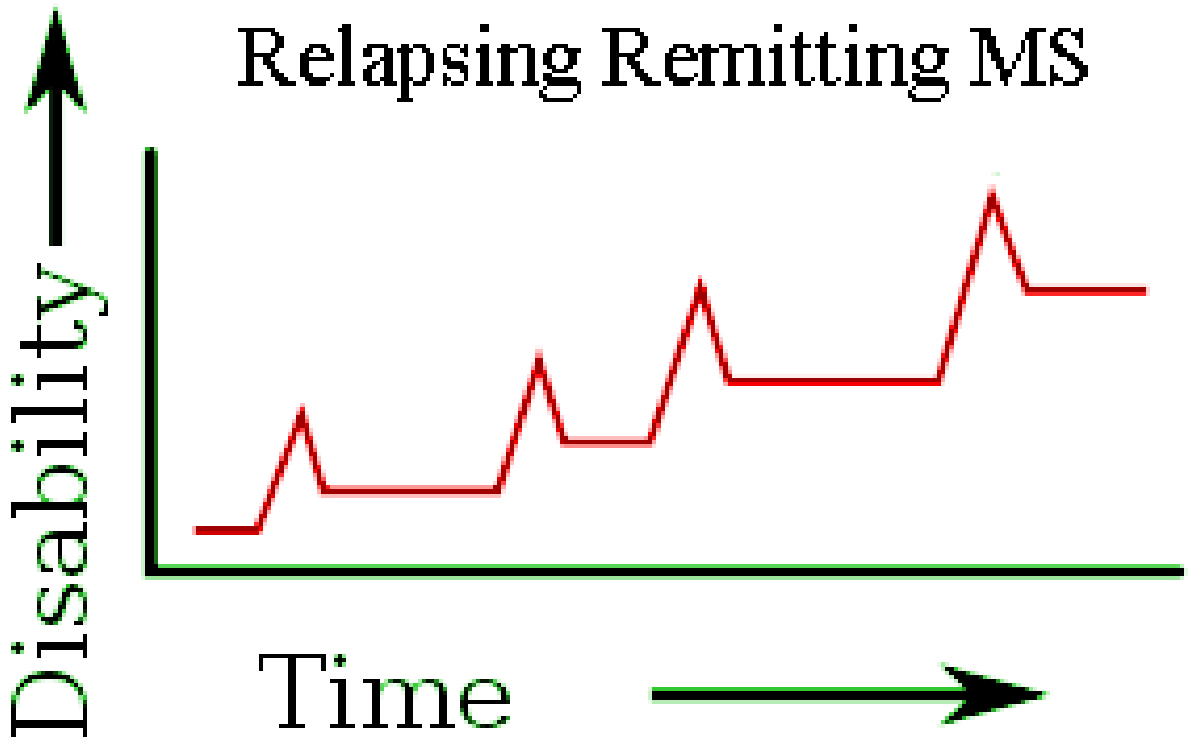
Why modelling > Standard analysis tool

Time-dependent (treatment) Cox Model:

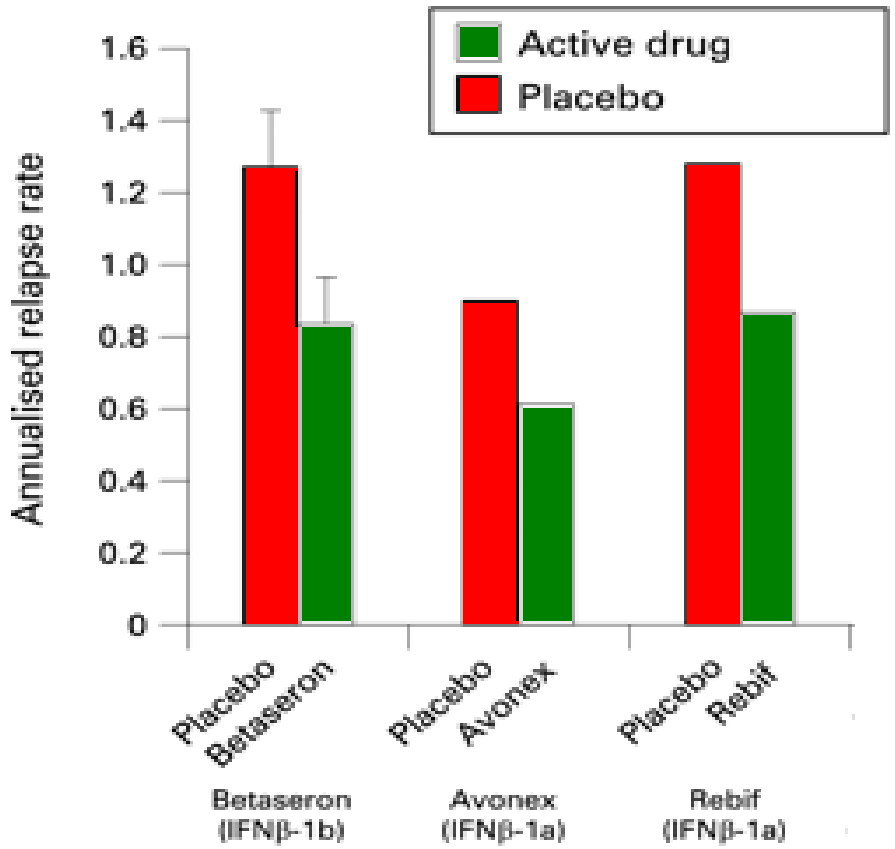
$$\lambda_{T_{\bar{a}}}(t|V) = \lambda_0 \times \exp\big(\beta_1 a(t) + \beta_2 V + \beta_3 L\big)$$

Hazard	Hazard at baseline	Treatment at time t	Baseline covariates	more covariates?
			(1)Gender, (2)Age, (3)Disease duration	(4)Relapse, (5)EDSS score

Why modelling > Why time dependent covariate

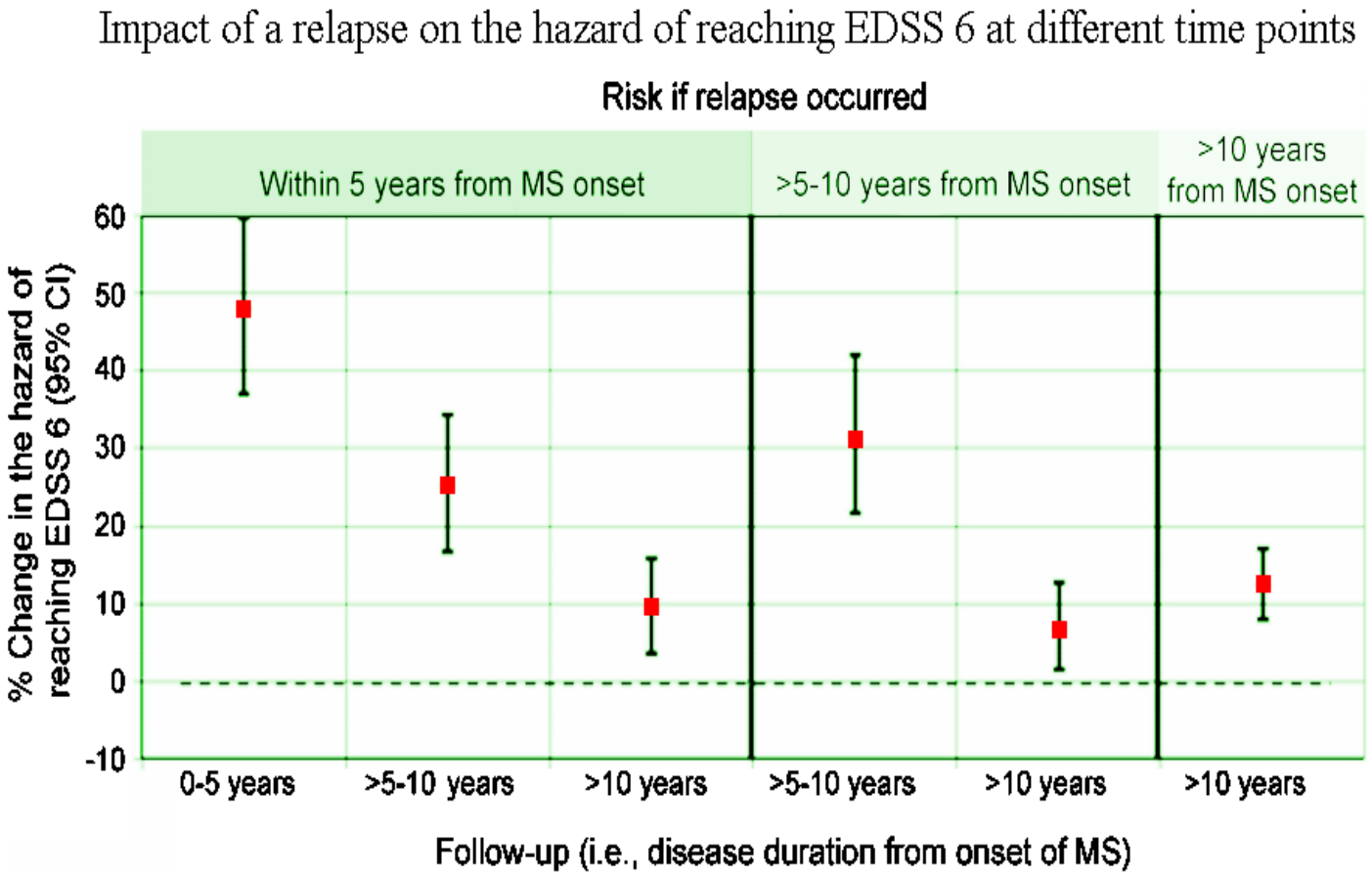


Why modelling > Why time dependent covariate



[Coles, 2009]

Why modelling > Why time dependent covariate



[Tremlett et al., 2009]

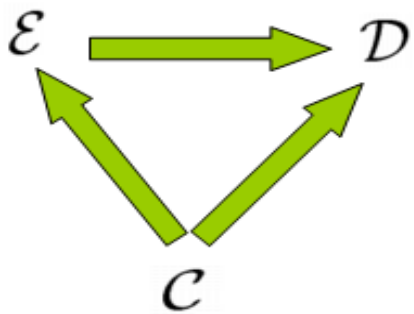
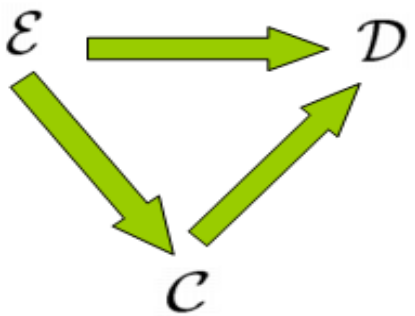
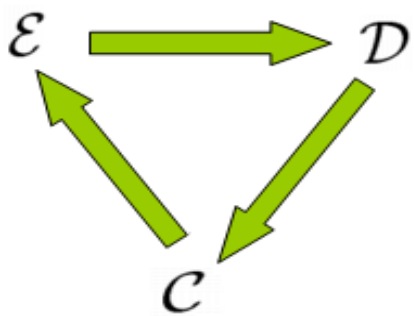
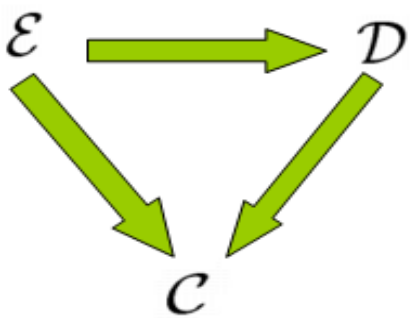
Why modelling > Extended Cox-model?

Time-dependent Cox Proportional Hazards Model:

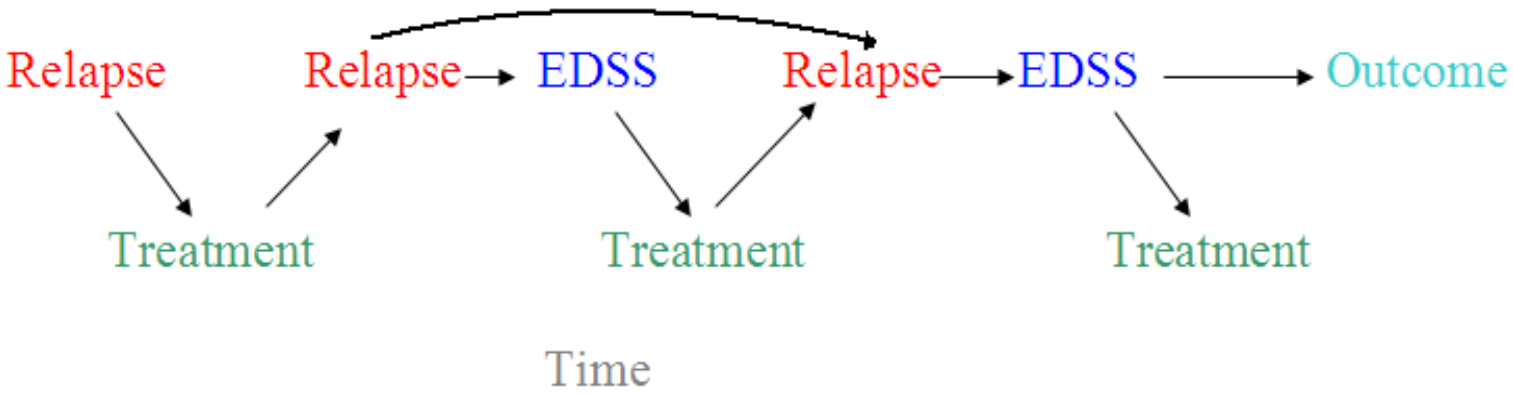
$$\lambda_{T_{\bar{a}}}(t|V) = \lambda_0 \times \exp\big(\beta_1 a(t) + \beta_2 V + \beta_3 L(t)\big)$$

Hazard	Hazard at baseline	Treatment at time t	Baseline covariates	Time-dependent covariates
			(1)Gender, (2)Age, (3)Disease duration	(1)Relapse, (2)EDSS score

Why fancy modelling > Causal Graphs

Common Cause	Mediator
	
Cases itself	**Collider**
	

Why fancy modelling > Over-Adjustment



- Relapse is both **confounder** and **mediator** variable.
- Need to adjust for confounder, but adjusting for a mediator variable will **over-adjust/block causal path** [Hernán et al., 2004].

A rough sketch >

Treatment Selection Model: $A(j) \sim \bar{A}(j-1), V, \bar{L}(j)$

Weight Model:

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

A rough sketch >

MSM Cox:

$$\lambda_{T_{\bar{a}}}(t|V) = \lambda_0 \times \exp\big(\beta_1 a(t) + \beta_2 V\big)$$

Hazard	Hazard at baseline	Treatment at time t	Baseline covariates
			(1)Gender, (2)Age, (3)Disease duration

with weights $SW(t)$ (adjusting for time-dependent covariates) [Robins, 1999; Hernán et al., 2000; Robins et al., 2000].

Still need to check the assumptions behind this model.

Take home message >

Need to be very cautious while

- analyzing and
- interpreting results

from **observational** data,

especially while dealing with *time-dependent* variables.

References

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Thank You!

Contact e-mail: ehsan@stat.ubc.ca