Causal Inference for the Comparison of Dynamic Treatment Regimens

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Introduction

- In many chronic disease settings subjects are seen at regular intervals and the treatment that they receive is dependent on their evolving history of time-dependent covariates
- A **dynamic treatment regimen** is a rule (or set of rules) that define how the treatment depends on this history

Goal: Using observational data we wish to estimate and perform inference for survival under multiple dynamic treatment regimens

1. Estimate survival under a single defined treatment regimen
2. Compare survival across multiple treatment regimens

Outline

Motivating Example - Epoetin Dosing Strategies

- Dialysis patients are typically given epoetin (Epo) for the correction of anemia
- At repeated visits, hematocrit (Hct) and other covariates are observed and the dose of epoetin is adjusted accordingly
- Known association between higher Hct and improved quality of life, reduced hospitalizations and reduced mortality [Ofsthun et al., 2003, Jones et al., 2004, Li and Collins, 2004]
- Some evidence that after adjusting for Hct, a higher epoetin dose is associated with higher mortality [Zhang et al., 2004]
- No true consensus as to the best target Hct range

Scientific Goal: Use Medicare data to compare survival under dosing regimens with different target hematocrit ranges

Notation

Observe $i = 1 \ldots N$ individuals at regular intervals $t = 0, 1, 2, \ldots$

- $L_i(t)$ vector of possibly time-varying covariates measured at t
  - here assume $L_{1i}(t)$ is hematocrit
- $V_i = L_i(0)$ is the vector of baseline covariates
- $Z_i(t)$ the treatment/dose of drug prescribed at visit t
- T_i the time from baseline to death
- $D_i(t)$ is an indicator of death in the time period $(t, t+1]$

Use bars to represent history up to and including time t

$$\bar{L}_i(t) = \{L_i(s) : 0 \leq s \leq t\}$$

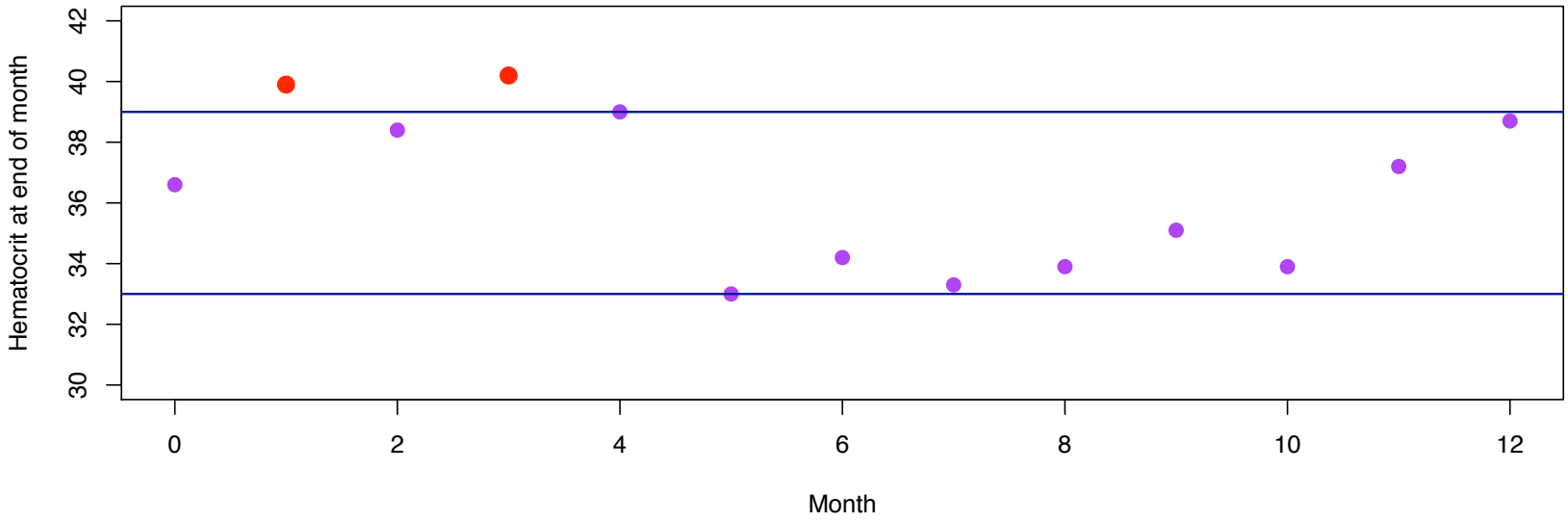
Treatment Regimen Definition

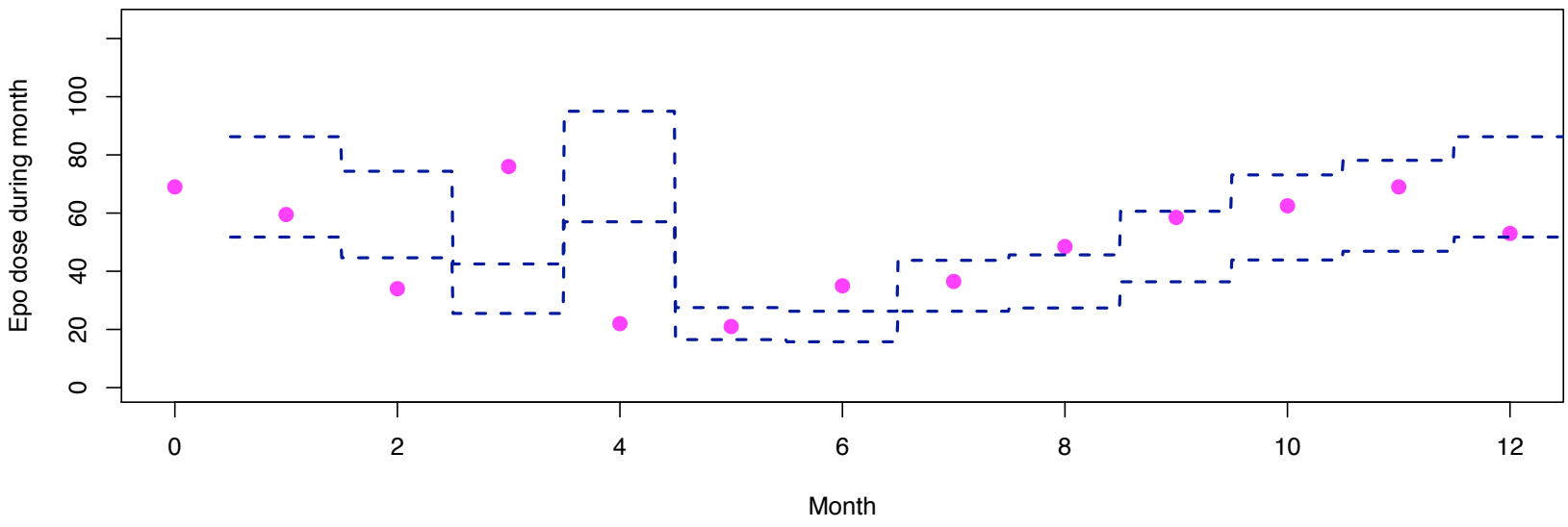
Examine survival under pre-defined treatment regimens $\mathcal{G}$ such as:

$$Z_i(t)|Z_i(t-1), L_{1i}(t) \in \begin{cases} Z_i(t-1) \times (p_1, p_2) & \text{if } L_{1i}(t) > b_2 \\ Z_i(t-1) \times (p_3, p_4) & \text{if } L_{1i}(t) \in [b_1, b_2] \\ Z_i(t-1) \times (p_5, p_6) & \text{if } L_{1i}(t) < b_1 \end{cases}$$

- $[b_1, b_2]$ is the target hematocrit/hemoglobin range
- p's define allowable ranges of multiplicative change in dose
  - for example: $(b_1, b_2) = (33, 39)$; $(p_1, p_2) = (0.5, 0.75)$; $(p_3, p_4) = (0.75, 1.25)$; $(p_5, p_6) = (1.25, 1.5)$

- A regimen $\mathcal{G}$ is fully defined by a set of $(b_1, b_2, p_1, \ldots, p_6)$
- Let $A_{ik}(t)$ be an indicator of subject i's adherence to a regimen $\mathcal{G}_k$ at time t





$$A_{ik} = (1 \quad 1 \quad 1 \quad 0 \quad 1 \quad 1 \quad 0 \quad 1 \quad 0 \quad 1 \quad 1 \quad 1 \quad 1)$$

Motivating Example - Epoetin Dosing Strategies

- CREATE trial: No significant reduction in cardiovascular events for group targeting 13.0-15.0 g/dL vs 10.5-11.5 g/dL
  - i.e. $(b_1, b_2) = (13.0, 15.0)$ for group 1 [Drüeke et al., 2006]
  - Hazard Ratio 0.78; 95% CI, 0.53 to 1.14 0.53 to 1.14;

- March 2007 FDA black box warning advising...

  "physicians to monitor red blood cell levels (hemoglobin) and to adjust the ESA dose to maintain the lowest hemoglobin level needed to avoid the need for blood transfusions."

Existing Statistical Approaches

- G-estimation of Structural Nested Models
  - Most often use an Accelerated Failure Time model for survival under treatment/no treatment
  - ex) effect of prophylaxis therapy for pneumonia on survival in AIDS subjects [Robins et al., 1992]

- Optimal Dynamic Treatment Regimens
  - We are not interested in optimality, regimens are deterministic, would be hard to adjust for flexible adherence [Murphy, 2003, Robins, 2004]

- Marginal Structural Models
  - ex) Cox model comparing regimens for starting HAART when defined at baseline [Hernán et al., 2006]
  - Can be extended to suit our needs

Artificial Censoring

- In reality, most subjects will not be adherent to the treatment regimen under consideration at all times.
- Estimate the survival experience that the cohort of subjects would have had if they had truly been adhered to the regimen
- Proceed by artificially censoring subjects at the first visit in which they are non-adherent to the regimen under consideration

$$C_i(t) = 1 - \mathrm{I}[\bar{A}_i(t) = \bar{1}]$$

- This censoring will almost certainly induce a *selection bias*
  - If having more severe disease (unmeasured) is associated with both poorer survival and lower adherence artificial censoring will overestimate the treatment effect

Inverse Probability Weighting

$$sw_i^{\dagger}(t) = \prod_{k=0}^{t} \frac{P[C_i(k) = 0 | \bar{C}_i(k-1) = 0, V_i = v_i]}{P[C_i(k) = 0 | \bar{C}_i(k-1) = 0, \bar{Z}_i(k) = \bar{z}_i(k), \bar{L}_i(k) = \bar{l}_i(k)]}$$

- The denominator is the probability that a subject is not censored at time t given that he was not censored before time t and his past treatment and covariate history
- Confounders, such as hematocrit/hemoglobin, are included in the weights instead of in the survival model
- Creates a pseudo-population in which the probability of adherence is independent of measured confounders
- Standard (weighted) survival time methods are then used to analyze the data

[Diggle et al., 2002, Hernán et al., 2004, Robins, 1999, Robins et al., 2000, Hernán et al., 2000]

No Unmeasured Confounders

Counterfactual outcomes: $T_{\bar{a}}$ is the time of death a subject would have experiences had he/she received treatment history $\bar{a}$ (possibly *counter-to-the-fact*)

The assumption of **No Unmeasured Confounders** holds if

$$T_{\bar{a}} \coprod A(k) \mid \{\bar{A}(k-1) = \bar{a}(k-1), \bar{L}(k) = \bar{l}(k)\} \qquad \forall\ \bar{a}(k-1), \bar{l}(k)$$

i.e. counterfactual outcome $T_{\bar{a}}$ and treatment received at time k, $A(k)$, are conditionally independent given the observed treatment and covariate history among those alive at visit k

[Hernán et al., 2001, Robins, 1998a, Robins, 1999]

IPW Kaplan-Meier Estimator

- Estimate survival function under a defined treatment regimen
- Pooled logistic regression model for survival weighted by $sw^{\dagger}$

$$\text{logit}[D(t) = 1 | \bar{C}(t) = 0] = \beta_0(t)$$

where $\beta_0(k)$ is a cubic spline.

- The fitted values of $\hat{\beta}_0(k)$ are used to obtain the estimated Kaplan-Meier survival curve through

$$\hat{S}(t) = \prod_{u=1}^{t} (1 - \hat{\beta}_0(u))$$

- Estimator is consistent provided:
  1. weight model is correctly specified
  2. no unmeasured confounders

[Robins and Finkelstein, 2000, Cole and Hernán, 2004]

Analysis for two Defined Treatment Regimens I

Known Regimen Membership

Use IPW to weight the familiar Cox PH model
[Robins et al., 2000, Hernán et al., 2000]

$$\lambda_T(t|G, V) = \lambda_0(t) \exp(\beta_1 G + \beta_2' V)$$

- $\lambda_0(t)$ is an unspecified baseline hazard function
- Let G be an indicator of membership in group 1

- $\exp(\beta_1)$ is the **causal hazard ratio** comparing survival under full adherence to regimen 1 to survival under full adherence to regimen 2

Marginal Structural Cox Proportional Hazard Model

- Fit MSM using a pooled weighted logistic regression model

$$\text{logit}P[D(t) = 1|D(t-1) = 0, G, V] = \beta_0(t) + \beta_1 G + \beta_2' V$$

- IPW induce a within-subject correlation so use robust variance estimate from GEE (conservative)

MSMs will yield consistent estimates under assumptions of

- correctly specified weight model for IPW
- no unmeasured confounders
- correctly specified marginal model for the effect of treatment (regimen) on mortality

Analysis for two Defined Treatment Regimens II

Unknown Regimen Membership

- Subjects may be adherent to one, both or neither regimens at some time points because of:
  - Overlapping target ranges
  - Different target ranges but similar rules outside these ranges

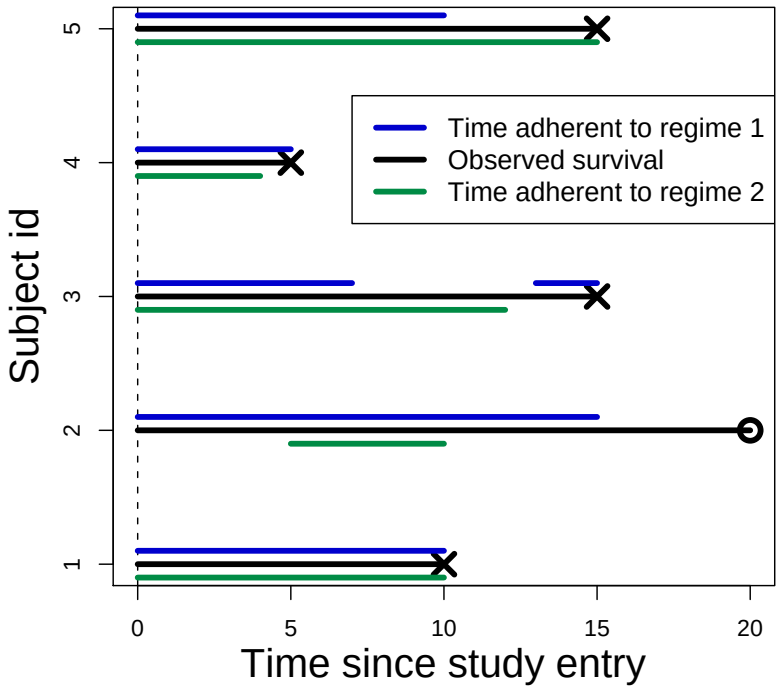
Cloning Methodology

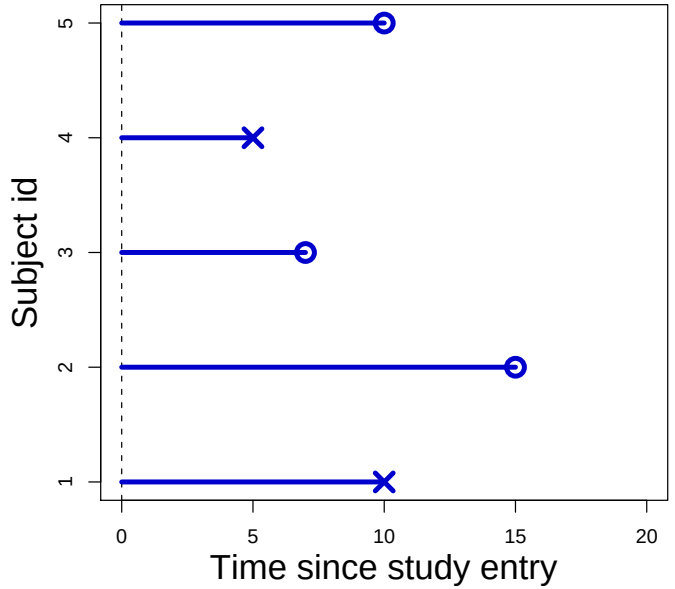
For each subject $i = 1, \ldots, n$, clone $k = 1, 2$ is considered to be following regimen k.

- $A_{ik}(t)$ indicator of subject i's adherence to regimen k at t
- $C_{ik}(t)$ indicator of subject i's artificial censoring to regimen k at time t
- $sw^{\dagger}_{ik}(t)$ IPW weights, $i = 1, \ldots, n$, $k = 1, 2$, $t = 0, 1, 2, \ldots$
- $L_{ik}(t) = L_i(t)$ covariates (identical across clones)

Clone correlation structure:

- Within subject (between clone) correlations:
  - Same event time (if observed & uncensored for both regimens)
  - Depending on regimen similarity possible correlation in weights
- Within clone correlation due to estimation of weights


Time adherent to regime 1
Observed survival
Time adherent to regime 2
Subject id
Time since study entry
0
5
10
15
20
1
2
3
4
5


Subject id
Time since study entry
0
5
10
15
20
1
2
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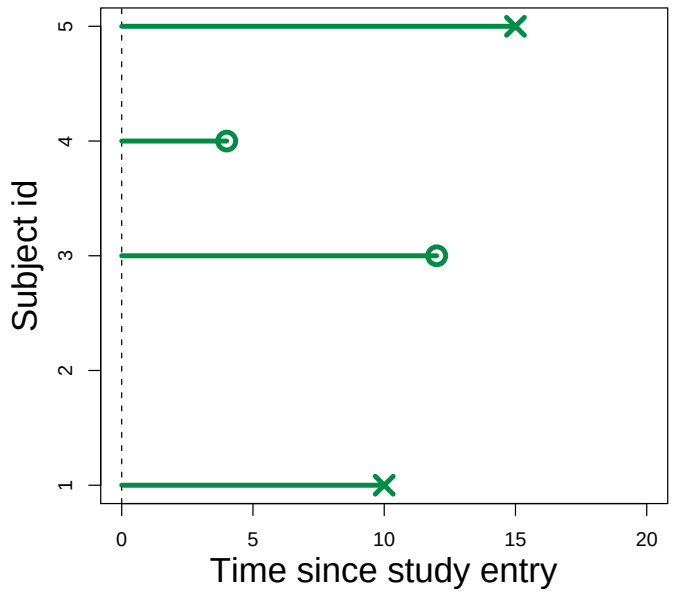
4
5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5

Cloned IPW Weighted Log-Rank Test

- Weighted log-rank test, Xie and Liu [Xie and Liu, 2005]
- Rank tests for matched survival data, Jung [Jung, 1999]

For subjects $i = 1, \ldots, n$ and clones $k = 1, 2$

- $X_{ik} = \min(T_{ik}, C_{ik})$ is the observed event time
- $\Delta_{ik} = I(T_{ik} \leq C_{ik})$ is the event indicator
- $\widehat{sw}^{\dagger}_{ik}(t)$ consistent for true IPW $w_{ik}(t)$
- $d^{w}_{k}(t)$ and $Y^{w}_{k}(t)$ are the weighted numbers of deaths and subjects at risk.

Testing

$$H_0 : \Lambda_1(t) = \Lambda_2(t) \quad \text{for all } 0 \leq t \leq \tau$$
$$H_1 : \Lambda_1(t) \neq \Lambda_2(t) \quad \text{for some } 0 \leq t \leq \tau$$

Cloned IPW Weighted Log-Rank Test

Test statistic:

$$W^* = \frac{1}{\sqrt{n}} \sum_{t=1}^{T} \left\{ d_1^w(t) - Y_i^w(t) \left(\frac{d_1^w(t) + d_2^w(t)}{Y_1^w(t) + Y_2^w(t)} \right) \right\}$$

- Asymptotics of W^* for paired data, Lee, Wei and Ying [Lee et al., 1993]
- Convergence of weighted martingale process, Marzec and Marzec [Marzec and Marzec, 1997]

Under H_0 we have $W^* \rightarrow N(0, \sigma^2)$ and a consistent estimate of $\hat{\sigma}^2$

Cloned Marginal Structural Cox Proportional Hazard Model

- In settings with a large number of small correlated groups of survival observations, estimates from the Cox model are still consistent [Lee et al., 1992]

- Use the usual Cox MSM as before but now treat each clone as an independent observation

$$\lambda_T(t|G_i, V_i) = \lambda_0(t)\exp(\beta_1 G_i + \beta_2' V_i)$$

- Uses GEE weighted logistic model with working independence
- Consistent sandwich covariance estimate
- Estimating the causal hazard ratio for full adherence to regimen 1 versus full adherence to regimen 2

Extensions to Multiple Treatment Regimens

- $G_{ik} = k$ is a clone's regimen assignment ($k = 1, 2, \ldots, K$)
- Consider the following Cox proportional hazard MSMs:

1. **Linear regimen effect**

$$\lambda_T(t|G_{ik}, V_{ik}) = \lambda_0(t)\exp(\beta_1 G_{ik} + \beta_2' V_{ik})$$

   - $\exp(\beta_1)$ = causal HR for a 1 unit increase in regimen number
   - Assumes V effects constant for comparisons of any 2 regimens

2. **Regimen treated as a factor variable**

$$\lambda_T(t|G_{ik}, V_{ik}) = \lambda_0(t)\exp[\beta_1 I_{(G_{ik}=2)} + \ldots + \beta_{K-1} I_{(G_{ik}=K)} + \beta_K' V_{ik}]$$

   - $\exp(\beta_k)$ = causal HR comparing regimen (k+1) with regimen 1
   - Other than the common effect of V, no structure is imposed across the regimens

Extensions to Multiple Treatment Regimens

3. **Linear regimen effect with a log time interaction**

$$\lambda_T(t|G_{ik}, V_{ik}) = \lambda_0(t)\exp(\beta_1 G_{ik} + \beta_2 G_{ik} * \log t + \beta_3' V_{ik})$$

   - $\exp(\beta_1 + \beta_2 \log t)$ = causal HR for a 1 unit increase in regimen number at observation time t.
   - Common linear effect of $\log(t)$ on log HR across all regimens

4. **Regimen treated as a factor with a log time interaction**

$$\lambda_T(t|G_{ik}, V_{ik}) = \lambda_0(t)\exp[\beta_1 I_{(G_{ik}=2)} + \ldots + \beta_{K-1} I_{(G_{ik}=K)} + \gamma_1 \log t * I_{(G_{ik}=2)} + \ldots + \gamma_{K-1} \log t * I_{(G_{ik}=K)} + \beta_K' V_{ik}]$$

   - This model introduces a within regimen effect of time
   - $\exp(\beta_1 + \gamma_1 \log t)$ = causal HR comparing regimen 2 with regimen 1 at observation time t
   - Within each regimen pair the log HR is assumed linear in $\log t$

5. **Spline in regimen number and effect of log time.**

$$\lambda_T(t|G_{ik}, V_{ik}) = \lambda_0(t)\exp[\beta_1(G_{ik}) + \beta_2(G_{ik}) * \log t + \beta_3' V_{ik}]$$

Clones Simulation Study

Goals

- Control the causal structure in the data across clones
- Simulate a minimum amount of data: $\{T_i, \bar{A}_{i1}, \ldots, \bar{A}_{iK}\}$
- Introduce selection bias to be corrected for through IPW

- For each subject $T_i \sim \text{Exponential}(\lambda_k)$, $\bar{A}_{ik} = \bar{1}$
- Cloning is simulated through **coadherence** probabilities:
  - Conditional probability of adherence to regimen j given adherence to regimen k: $p_{j|k} = P[A_{ij}(t) = 1 | A_{ik}(t) = 1]$
  - Assume $p_{j|k} = p_{k|j} = p_{jk} = P[A_{ij} = 1 \ \& \ A_{ik} = 1]$
  - Fix $p_{jj} = 1$, specify $\binom{K}{2}$ coadherence probabilities

Clones Simulation Study

Rate Parameter Selection

- Select rate parameters so that HR persist through cloning

$$\frac{\lambda(t|A_{ik}=1)}{\lambda(t|A_{ij}=1)} = \frac{\lambda_k}{\lambda_j}$$

- For $K = 6$, λ_1, λ_3, λ_6 and p_{jk} and solve using Maple

Introduction of Selective Nonadherence

- Use a Copula model to generate (T_i, X_i)
- Choose conditional (on X_i) probabilities that maintain p_{jk}s
- Subjects with larger X_i (and therefore larger T_i) are more likely to be adherent to regimens with longer mean survival
- Unweighted analyses will overestimate survival for these regimens

Estimated Median Hazard Ratios (HR), Variances (Var) and 95% Confidence Interval (CI) coverages from cloning methodology simulations (500 replications each with $n_k = 2500$)

	Underlying	Complete	Clones, Unweighted			Clones, IPW weighted			
	True HR	Data HR	HR	Var	CI Cov	HR	Var	95% CI	CI Cov
Regimen 2 vs 3	0.91	0.90	0.90	0.023	0.95	0.90	0.024	(0.85, 0.96)	0.93
Regimen 4 vs 3	1.17	1.18	1.34	0.036	0.00	1.16	0.032	(1.10, 1.23)	0.96
Regimen 5 vs 3	1.28	1.29	1.47	0.040	0.00	1.30	0.036	(1.23, 1.38)	0.91

Analysis of USRDS Dataset

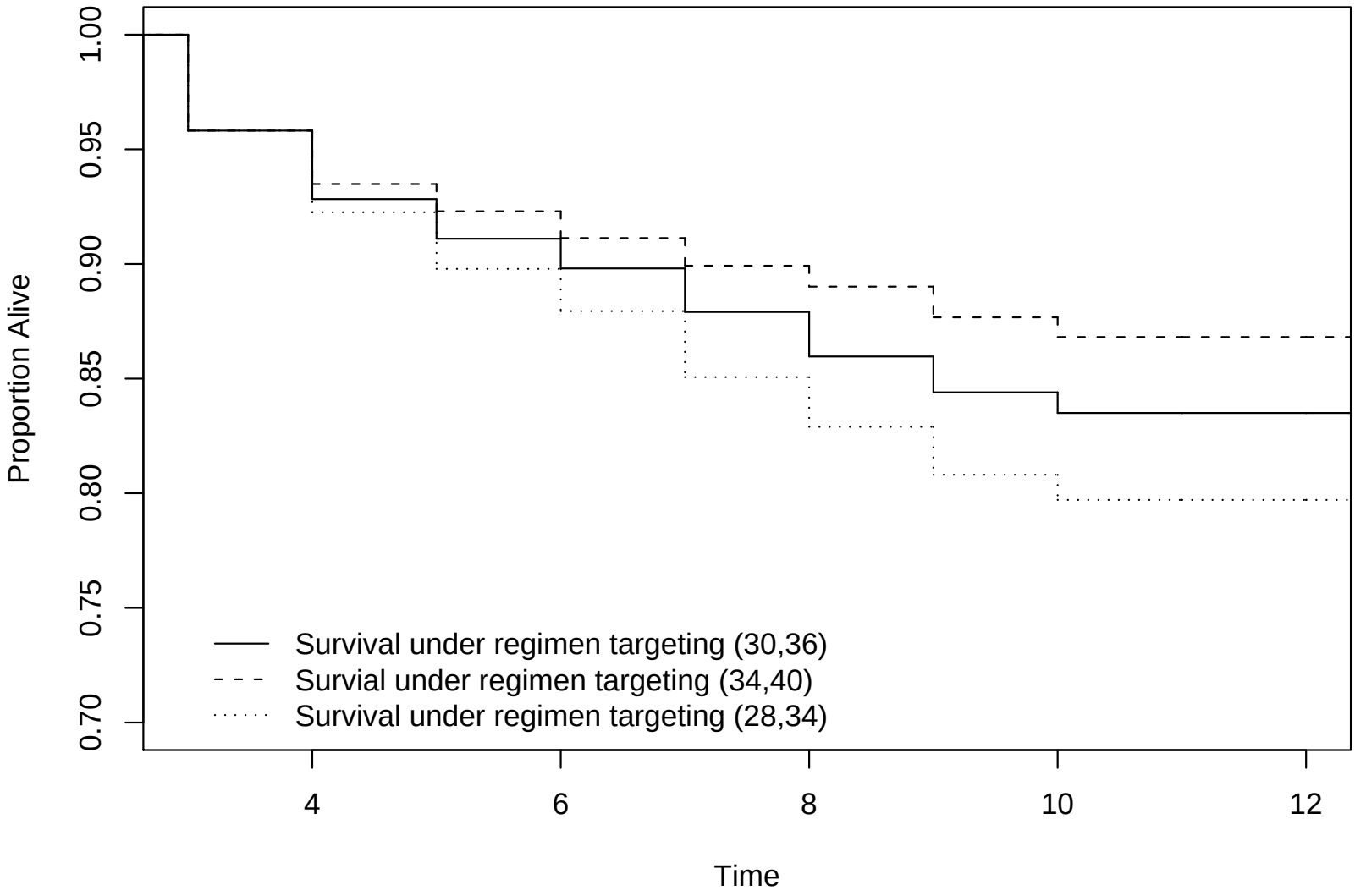
- United States Renal Data System (USRDS) data set based on Medicare claims for ESRD treatment is available for analyses
- Analysis restricted to the year 2003
- Excluded subjects with HIV, AIDS and/or any cancer
- 33,873 adult subjects, 217,474 person-months of observation
- Annual death rate of approximately 15%
- Begin analysis at month 3 with up to 9 months of follow-up per subject

Analysis of USRDS Dataset

- Compare survival under regimen with target $(30, 36)$ to regimens with targets $(x-3, x+3)$, $x = 31, \ldots, 40$

$$Z_i(t)|Z_i(t-1), L_{1i}(t)_1 \in \begin{cases} Z_i(t-1) \times (0, 0.75) & \text{if } L_{1i}(t)] \geq x-3 \\ Z_i(t-1) \times (0.75, 1.25) & \text{if } L_{1i}(t) \in (x-3, x+3) \\ Z_i(t-1) \times (1.25, \infty) & \text{if } L_{1i}(t) \leq x+3 \end{cases}$$

- Weight model adjusted for month, gender, age, race, hypertension, diabetes, current Hct and previous month's Epo dose
- Additional weights calculated for administrative censoring and censoring for loss to follow-up



Kaplan-Meier estimates for USRDS data under three treatment regimens

Analysis of USRDS Dataset

1. **Linear regimen effect**: estimated causal HR for a unit increase in regimen number is 0.985 (0.980, 0.990)

2. **Regimen treated as a factor variable**:

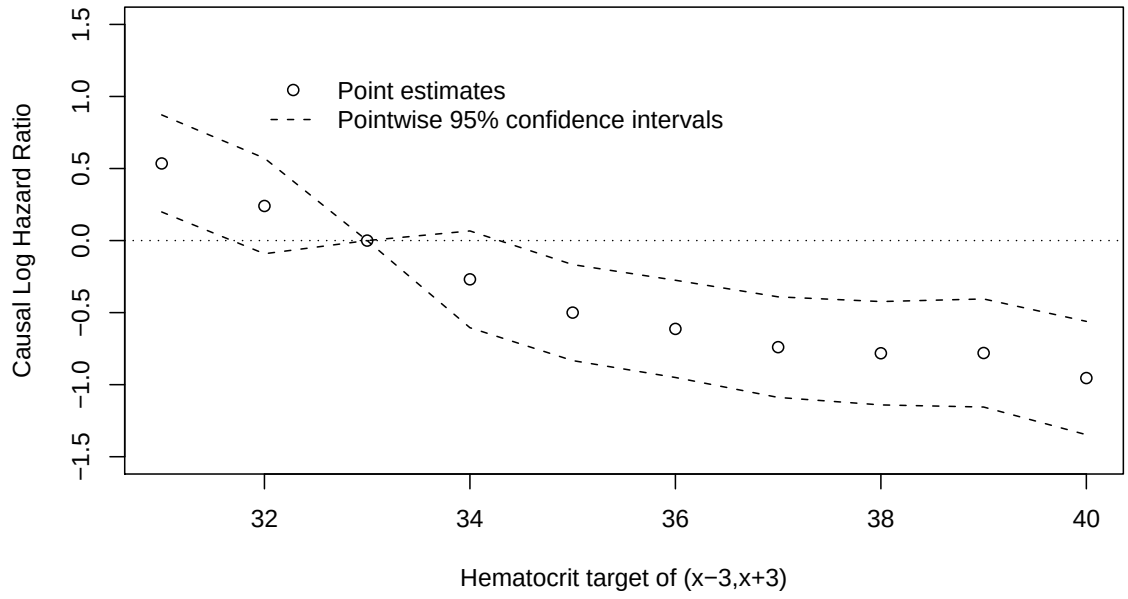
	Hazard Ratio	95% CI
$\mathcal{G}(28,34)$ vs $\mathcal{G}(30,36)$	1.049	(0.984, 1.119)
$\mathcal{G}(29,35)$ vs $\mathcal{G}(30,36)$	1.031	(0.966, 1.099)
$\mathcal{G}(31,37)$ vs $\mathcal{G}(30,36)$	0.978	(0.917, 1.044)
$\mathcal{G}(32,38)$ vs $\mathcal{G}(30,36)$	0.957	(0.897, 1.021)
$\mathcal{G}(33,39)$ vs $\mathcal{G}(30,36)$	0.939	(0.880, 1.002)
$\mathcal{G}(34,40)$ vs $\mathcal{G}(30,36)$	0.921	(0.863, 0.983)
$\mathcal{G}(35,41)$ vs $\mathcal{G}(30,36)$	0.915	(0.857, 0.977)
$\mathcal{G}(36,42)$ vs $\mathcal{G}(30,36)$	0.920	(0.861, 0.982)
$\mathcal{G}(37,43)$ vs $\mathcal{G}(30,36)$	0.930	(0.871, 0.993)

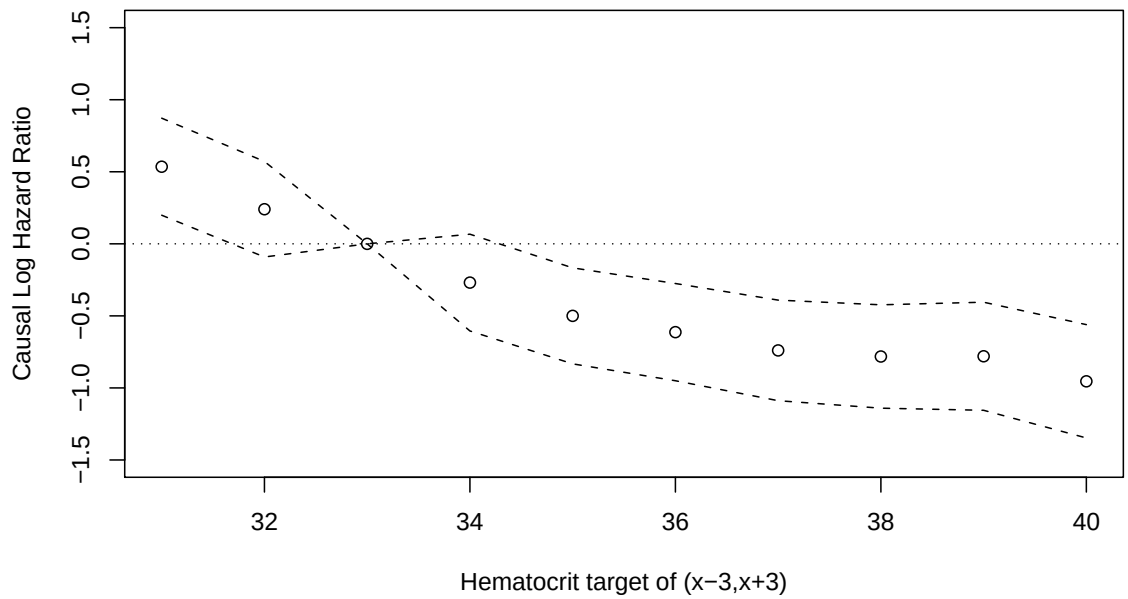
3 Linear regimen effect with a log time interaction

Month	Hazard Ratio	95% CI
3	1.000	(0.994, 1.006)
4	0.950	(0.942, 0.957)
5	0.912	(0.900, 0.925)
6	0.883	(0.866, 0.900)
7	0.859	(0.839, 0.879)
8	0.838	(0.816, 0.862)
9	0.821	(0.796, 0.847)
10	0.805	(0.779, 0.833)
11	0.792	(0.763, 0.821)
12	0.780	(0.749, 0.811)

4 **Regimen treated as a factor variable with a log time interaction**

Plots of causal log hazard ratios at (a) 6 months and (b) 9 months comparing regimen with hematocrit target (x-3, x+3) to regimen with target (30,36)


Point estimates
Pointwise 95% confidence intervals
Causal Log Hazard Ratio
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
32
34
36
38
40
Hematocrit target of (x−3,x+3)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Hematocrit target of (x−3,x+3)

G-estimation

- Alternative method to IPW and MSMs, do not need to artificially censor
- Still makes appropriate adjustment for effect of exposure in the presence of a time-dependent confounder
- Introduced by Robins and coauthors [Robins, 1986, Robins, 1987, Robins et al., 1992, Robins, 1992, Mark and Robins, 1993]

- Full set of observable data: $\{T_i, \bar{L}_i(\tau), \bar{A}_i(\tau)\}$ were L are covariates, A is treatment level and τ is maximum visit time
- Specify a Structural Nested Failure Time Model (SNFTM) linking counterfactual outcomes $T_{\bar{a}}$ to observed outcomes $T_{\bar{A}}$

$$T_{\bar{a}} = H(\psi_0) \qquad \text{where} \qquad H(\psi) \equiv h(T_{\bar{A}}, \bar{L}, \bar{A}, \psi)$$

Conditions for SNFTM: [Robins, 1998b]

1. *Consistency* $T_{\bar{a}} = h(T_{\bar{A}}, \bar{L}, \bar{A}, \psi)$ for all ψ if $\bar{a} = \bar{A}$
2. $T_{\bar{A}} = h(T_{\bar{A}}, \bar{L}, \bar{A}, 0)$ with probability 1 if and only if $\psi_0 = 0$

So $\psi_0 = 0$ represents the null hypothesis of no treatment effect

In survival setting can use an AFT model [Robins et al., 1992]

$$H(\psi) = \int_0^T \exp[\psi A(t)]dt$$

$\exp(-\psi_0)$ is the expansion factor for survival comparing cts treatment ($\bar{a} = (1, 1, \ldots)$) to no treatment ($\bar{a} = (0, 0, \ldots)$)

Alternative Specification of a SNFTM - Shift Functions

Lok et al 2004 parameterize a SNFTM through *shift functions*:

$$\phi[t, \bar{l}(k), \bar{a}(k)] = s^{-1}_{\bar{l}(k),[\bar{a}(k-1),\bar{0}]} \circ s_{\bar{l}(k),[\bar{a}(k),\bar{0}]}(t)$$

where

$$s_{\bar{l}(k),g}(t) = P\{T_g > t | \bar{L}(k) = \bar{l}(k), \bar{A}(k) = \bar{g}[h(k)], T > k\}$$

is the conditional survival function for T_g given the full history up until time k and given survival past time k

$\phi[t, \bar{l}(k), \bar{a}(k)]$ is the time at which the survival proportion given a treatment history of $[\bar{a}(k-1), \bar{0}]$ is the same as that at time t for the history $[\bar{a}(k), \bar{0}]$

Monte Carlo Algorithm for G-Estimation

1. Estimate ψ and test $H_0 : \psi_0 = 0$

   - For any ψ calculate T_0^{ϕ} the counterfactual survival under baseline regimen given shift function ϕ

   $$T_0^{\phi} = \phi[L(0), A(0)] \circ \phi[\bar{L}(1), \bar{A}(1)] \circ \cdots \circ \phi[\bar{L}(T), \bar{A}(T)](T)$$

   - Regress $A(t)$ on $\bar{A}(t-1)$, $\bar{L}(t)$ and T_0^{ϕ}
   - Under *no unmeasured confounders*, θ the regression parameter for T_0^{ϕ} should be zero
   - If $H_0 : \theta = 0$ is rejected the current value of ψ is ruled out
   - $\hat{\psi}$ is the value for which $\hat{\theta} = 0$ and a $(1-\alpha)$ CI is given by the set of ψ's for which H_0 was not rejected

Monte Carlo Algorithm for G-Estimation

2. Estimate survival curve $P(T_g > t)$ for treatment regimen g

- Given $\hat{\psi}$ use Monte Carlo to simulate an independent set of rv with the same distribution as T_g. [Robins et al., 1992]
  - Generate t_v from the empirical dist of $T_0^{\phi(\hat{\psi})}$
  - Draw $l_v(m)$ from $f\{l(m)|\bar{l}(m-1), g[\bar{l}(m-1)], t_v, T > m\}$
  - Continue until $t_{v,g} = \phi^{-1}\{t_v, \bar{l}(m-1), g[\bar{l}(m-1)]\} \leq m$ (i.e. event occurs under g)
- The set $\{t_{v,g}, v = 1, \ldots, V\}$ will have the same distribution as T_g and can, for example, be used to estimate the Kaplan-Meier survival curve

G-Estimation in the Epoetin Dosing Setting

- Shift functions defined with reference to some baseline treatment such as placebo or no treatment
- For $Z(t)$ dose of epoetin some possibilities:

$$\begin{aligned} A(t) &= Z(t) - Z^* & A(t) &= \frac{[Z(t)-Z^*]}{Z^*} \\ A(t) &= Z(t) - Z(0) & A(t) &= \frac{[Z(t)-Z(t-1)]}{Z(t-1)} \\ A(t) &= Z(t) - Z(t-1) & A(t) &= \frac{[Z(t)-Z(0)]}{Z(0)} \end{aligned}$$

- $A(t) = 0$ corresponds to a type of baseline regimen
- Note $A(t) \in (-\infty, \infty)$ and $A(t) > 0$ is an increase in dose

G-Estimation in the Epoetin Dosing Setting

Consider the following deterministic rule

$$Z(t) = g'[\bar{L}(t), \bar{Z}(t-1)] = \begin{cases} (1+q_1) \times Z(t-1) & \text{if } L_1(t) > b_2 \\ (1+q_2) \times Z(t-1) & \text{if } L_1(t) \in [b_1, b_2] \\ (1+q_3) \times Z(t-1) & \text{if } L_1(t) < b_1 \end{cases}$$

and define the treatment regimen g as

$$A(t) = g[\bar{L}(t), \bar{Z}(t-1)] = \frac{g'[\bar{L}(t), \bar{Z}(t-1)] - Z(t-1)}{Z(t-1)}$$

Could use a shift function with exponential term:

$$\exp\{\psi_1 a(k) + \psi_2 a(k) I[I(k) \in (b_1, b_2)] + \psi_3 a(k) I[I(k) > b_2]\}$$

(direct effect of treatment a(t) for a current hematocrit level either below, above or within the target range)

Advantages and Disadvantages

G-estimation

- No artificial censoring (do not need to discard any data)
- Only estimate the survival curve for one regimen at a time
- Specification of blip/shift function not entirely natural
- If ψ is high dimensional the grid search will be computationally complex

IPW/MSM methods

- Resemble and naturally extend standard statistical models (ex causal Cox PH model)
- Direct comparison of regimens through causal hazard ratio
- Can not estimate interactions between treatment and time-varying covariates

Concluding Remarks

- Unique link between treatment regimen definition and adherence
- Three methods provide consistent estimates of survival under a particular regimen
- Provided methodology for comparing regimens when adherence is not known at baseline
  - Allow subjects to contribute information to multiple regimens
  - Consistent estimate of hazard ratio from Cox PH MSM

Future Work

- Loosen the current definition of adherence
  - ex) Artificially censor subjects after they have been non-adherent for two consecutive visits
  - Current methods can be used, changes estimand
- Extend cloning methodology
  - ex) Allow for a single cross-over or non-adherent period
  - After a clone is artificially censored for non-adherence they re-cloned and each new "subclone" is followed once they restart one of the two defined treatment regimens
  - May be justifiable only in a prevalent treatment setting
- Apply g-estimation methodology to the available cohort of USRDS data
- Prediction?

References I

- Cole, S. and Hernán, M. (2004). Adjusted survival curves with inverse probability weights. *Computer Methods and Programs in Biomedicine*, 75(1):45–49.
- Diggle, P., Heagerty, P., Liang, K., and Zeger, S. (2002). *Analysis of Longitudinal Data*. New York: Oxford University Press.
- Drüeke, T., Locatelli, F., Clyne, N., Eckardt, K.-U., Macdougall, I., Tsakiris, D., Burger, H.-U., and Scherhad, A. (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *The New England Journal of Medicine*, 355(20):2071–2084.
- Hernán, M., Brumback, B., and Robins, J. (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*, 11(5):561–570.
- Hernán, M., Brumback, B., and Robins, J. (2001). Marginal structural models to estimate the joint causal effect of nonrandomized treatments. *Journal of the American Statistical Association*, 96(454):440–448.
- Hernán, M., Lanoy, E., Costagliola, D., and Robins, J. (2006). Comparison of dynamic treatment regimes via inverse probability weighting. *Basic & Clinical Pharmacology & Toxicology*, 98(3):237–242.
- Hernán, M., S., H.-D., and Robins, J. (2004). A structural approach to selection bias. *Epidemiology*, 15(5):615–625.
- Jones, M., Ibels, L., Schenkel, B., and Zagari, M. (2004). Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis. *Kidney International*, 65(3):775–767.
- Jung, S. (1999). Rank tests for matched survival data. *Lifetime Data Analysis*, 5(1):67–79.

References II

- Lee, E., Wei, L., and Amato, D. (1992). Cox-type regression analysis for large numbers of small groups of correlated failure time observations.
In Klein, J. and Goel, P., editors, *Survival Analysis: State of the Art*, pages 237–247. Dodrecht: Kluwer Academic Publishers.
- Lee, E., Wei, L., and Ying, Z. (1993). Linear regression analysis for highly stratified failure time data.
Journal of the American Statistical Association, 88(422):557–565.
- Li, S. and Collins, A. (2004). Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients.
Kidney International, 65(3):626–633.
- Lok, J., Gill, R., van der Vaart, A., and Robins, J. (2004). Estimating the causal effect of a time-varying treatment on time-to-event using structural nested failure time models.
Statistica Neerlandica, 58(3):271–295.
- Mark, S. and Robins, J. (1993). Estimating the causal effect of smoking cessation in the presence of confounding factors using a rank preserving structural failure time model.
Statistics in Medicine, 12(17):1605–1628.
- Marzec, L. and Marzec, P. (1997). Generalized martingale-residual processes for goodness-of-fit inference in Cox's type regression models.
The Annals of Statistics, 25(2):683–714.
- Murphy, S. A. (2003). Optimal dynamic treatment regimes.
Journal of the Royal Statistical Society: Series B (Statistical Methodology), 65(2):331–355.
- Ofsthun, N., Labrecque, J., Lacson, E., Keen, M., and Lazarus, J. (2003). The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients.
Kidney International, 63(5):1908–1914.

References III

- Robins, J. (1986). A new approach to causal inference in mortality studies with sustained exposure periods - application to control of the healthy worker survivor effect.
Mathematical Modelling, 7:1393–1512.
- Robins, J. (1987). Errata to"A new approach to causal inference in mortality studies with sustained exposure periods - application to control of the healthy worker survivor effect.".
Computers and Mathematics with Applications, 14(9-12):917–921.
- Robins, J. (1992). Estimation of the time-dependent accelerated failure time model in the presence of confounding factors.
Biometrika, 79(2):321–334.
- Robins, J. (1998a). Marginal structural models.
In *1997 Proceedings of the Section on Bayesian Statistical Science*, pages 1–10. Alexandria, Virginia: American Statistical Association.
- Robins, J. (1998b). Structural nested failure time models.
In Armitage, P. and Colton, T., editors, *The Encyclopedia of Biostatistics*, pages 4372–4389. Chichester, United Kingdom: John Wiley and Sons Ltd.
- Robins, J. (1999). Marginal structural models versus structural nested models as tools for causal inference.
In M.E., H. and D., B., editors, *Statistical Models in Epidemiology: The Environment and Clinical Trials*, pages 95–134. New York: Springer-Verlag.
- Robins, J. (2004). Optimal structural nested models for optimal sequential decisions.
In Lin, D. and Heagerty, P., editors, *Proceedings of the Second Seattle Symposium in Biostatistics: Analysis of Correlated Data*, pages 189—326. Seattle: Springer.
- Robins, J., Blevins, D., Ritter, G., and M., W. (1992). G-estimation of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on the survival of AIDS patients.
Epidemiology, 3(4):319–336.

References IV

- Robins, J. and Finkelstein, D. (2000). Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests.
Biometrics, 56(3):779–788.
- Robins, J., Hernán, M., and Brumback, B. (2000). Marginal structural models and causal inference in epidemiology.
Epidemiology, 11(5):550–560.
- Xie, J. and Liu, C. (2005). Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data.
Statistics in Medicine, 24(20):3089–3110.
- Zhang, Y., Thamer, M., Stefanik, K., Kaufman, J., and Cotter, D. (2004). Epoetin requirements predict mortality in hemodialysis patients.
American Journal of Kidney Diseases, 44(5):866–876.

Cloned IPW Weighted Log-Rank Test

Define weighted at risk and event processes

$$Y_k^w(t) = \sum Y_{ik}^w(t) \quad \text{with} \quad Y_{ik}^w(t) = w_{ik}(t) I(X_{ik} \leq t)$$

$$dN_k^w(t) = \sum dN_{ik}^w(t) \quad \text{with} \quad dN_{ik}^w(t) = w_{ik}(t) dN_{ik}(t)$$

$$= \begin{cases} w_{ik}(X_{ik}) & \text{if } t = X_{ik} \ \& \ \Delta_{ik} = 1 \\ 0 & \text{otherwise} \end{cases}$$

Test statistic:

$$W^* = \sqrt{n} \int_0^\infty H(t) \{ d\hat{\Lambda}_1^w(t) - d\hat{\Lambda}_2^w(t) \}$$

with

$$H(t) = \frac{1}{n} \frac{Y_1^w(t) Y_2^w(t)}{Y_1^w(t) + Y_2^w(t)} \qquad \hat{\Lambda}_k^w(t) = \int_0^t \frac{dN_k^w(s)}{Y_k^w(s)}$$

Coadherence probabilities used to induce selective nonadherence in cloning simulations for subjects generated under original regimen $\tilde{k}$ and cloned under regimen j with baseline covariate X

(a) Regimen $j = 1$ clones

	X		
$\tilde{k}$	0	1	2
1	1	1	1
2	4/6	3/6	2/6
3	3/6	2/6	1/6
4	2/6	1/6	0
5	2/6	1/6	0
6	2/6	1/6	0

(b) Regimen $j = 2$ clones

	X		
$\tilde{k}$	0	1	2
1	4/6	3/6	2/6
2	1	1	1
3	4/6	3/6	2/6
4	3/6	2/6	1/6
5	2/6	1/6	0
6	2/6	1/6	0

(c) Regimen $j = 3$ clones

	X		
$\tilde{k}$	0	1	2
1	3/6	2/6	1/6
2	4/6	3/6	2/6
3	1	1	1
4	4/6	3/6	2/6
5	3/6	2/6	1/6
6	2/6	1/6	0

(d) Regimen $j = 4$ clones

	X		
$\tilde{k}$	0	1	2
1	0	1/6	2/6
2	1/6	2/6	3/6
3	2/6	3/6	4/6
4	1	1	1
5	2/6	3/6	4/6
6	1/6	2/6	3/6

(e) Regimen $j = 5$ clones

	X		
$\tilde{k}$	0	1	2
1	0	1/6	2/6
2	0	1/6	2/6
3	1/6	2/6	3/6
4	2/6	3/6	4/6
5	1	1	1
6	2/6	3/6	4/6

(f) Regimen $j = 6$ clones

	X		
$\tilde{k}$	0	1	2
1	0	1/6	2/6
2	0	1/6	2/6
3	0	1/6	2/6
4	1/6	2/6	3/6
5	2/6	3/6	4/6
6	1	1	1