Comparative effectiveness of dynamic treatment regimes

An application of the parametric g-formula

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What is comparative effectiveness research (CER)?

- "The **generation and synthesis of evidence that compares the benefits and harms** of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care"
  - IOM 2009

- Comparative effectiveness or comparative safety

What is the purpose of CER?

- "To assist consumers, clinicians, purchasers, and policy makers **to make informed decisions** that will improve health care at both the individual and population levels"
  - IOM 2009

- To help decision-makers

CER is about causal inference

- "The **generation and synthesis of evidence** that compares the benefits and harms…"
- "**to make informed decisions** that will improve health…"

- In other words, CER is about comparing the effects of well-defined interventions or strategies to answer policy, public health, and clinical questions

3 requirements for CER

1. A relevant, well-defined question
   - A key prerequisite
2. High-quality data
   - Appropriate for the question above
3. Valid statistical methods
   - To be applied to the high-quality data to answer the well-defined question

CER **questions** are becoming increasingly complex

- En epidemiology, clinical medicine, comparative effectiveness research…
- Often not about the average treatment effect of a non-time-varying treatment
- Often involving dynamic strategies or regimes
  - i.e., treatment strategies that depend on the individual's evolving covariates

Example: antiretroviral therapy (ART) for HIV-infected patients

- RCTs have been successful in showing that assignment to combined ART is best
- However, key questions still unanswered
  - what to start
  - when to start
  - when to switch
  - when to monitor
- Dozens of relevant strategies with potentially very wide variation in effectiveness

Examples of complex questions involving dynamic regimes

- When to start treatment?
  - What would be the 5-year mortality risk when cART is initiated within 6 months of either an AIDS diagnosis or CD4 cell count first dropping below 500 cells/mm^3
  - Below 350?
  - Within 3 months?
  - Within 6 months of CD4 first dropping below 500 and viral load above 1000?

Examples of complex questions involving dynamic regimes

- When to change treatment?
  - What would be the 5-year mortality risk when the cART regime is switched within 6 months of immunologic failure?
  - What if we wait until viral load is greater than 1000? Until CD4<350?
- When to monitor treated patients?
  - Should we measure viral load every 3, 6, 12 months? Before/After treatment?

CER questions are complex because clinical decisions are

- Classical RCTs, however, provide **simple** information
  - Typically an intention-to-treat analysis will say that assignment to A is better than assignment to B
- That's fine for one-time treatments
  - e.g., surgery, a one-dose vaccination, CABG
- But what about long-term clinical strategies?
  - e.g., therapeutics for chronic diseases with no cure (diabetes, HIV disease, chronic kidney disease, cardiovascular disease…)

One option: RCTs

- Design RCTs that compare the effectiveness of explicitly defined clinical **strategies** on clinically relevant outcomes over a clinically relevant (i.e., long) period
- An example of strategy would be
  - start treatment A within 3 months of the CD4 cell count first dropping below 500 or of an AIDS diagnosis, whichever occurs first; switch to treatment B within 3 months of the viral load going over 1000 or immediately if toxicity occurs, unless the patient is pregnant or has a liver disorder, in which case switch to treatment C; if C fails then…

CER and personalized medicine

- Complex clinical strategies need to be compared if we get serious about comparative effectiveness research for individualized treatment decisions

- But once we get this serious, RCTs suddenly look less attractive…

Less attractive RCTs

- Adherence to complex strategies over a long period may be low
  - intention-to-treat analysis → a black box if common deviations from protocol
  - as treated analyses: time-varying confounding like in observational studies
- Long follow-up → drop-out
  - an intention-to-treat analysis not even possible
  - selection bias like in observational studies

- For a discussion on RCTs for CER, see Hernán and Hernández-Díaz. *Clinical Trials* 2012.

The next best option

- **Use observational data to emulate an RCT**

- Need prospective collection of data on time-varying data on treatments, outcomes, and confounders
- Not all data sources include this information
  - Therefore not all data sources can be used

Enter observational registries and electronic medical records

- These data sources are our best chance to compare effectiveness of clinical strategies in a timely way in unselected populations
- They include prospective data on time-varying treatments, outcomes, and confounders
  - RCTs do not typically collect this information
- They can be used to emulate trials without baseline randomization

Observational data for CER are becoming increasingly complex

- Increasingly high-dimensional
- Longitudinal studies with time-varying treatments and confounders
- Measurement of treatment and confounders may occur at subject-specific (random) times

Examples of complex longitudinal data

- Large populations followed for long periods with frequent measurement of treatments, outcomes, and confounders
  - At prespecified intervals: e.g., the Nurses' Health Study, MACS/WIHS
  - At random intervals: e.g., clinical cohorts like the HIV-CAUSAL Collaboration, USRDS claims, electronic medical records

Many methods originally developed for less complex questions

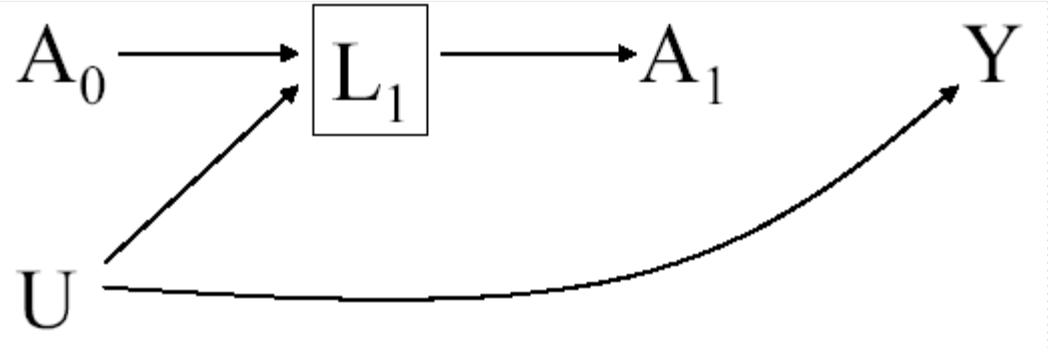
- Conventional regression
  - Bias if confounders affected by previous treatment
- Propensity score matching
  - For time-varying treatments?
- Instrumental variable estimation
  - Who are the compliers when treatment is given every month? And the never takers?
- Principal stratification
  - How are principal strata defined?

G-methods

- Robins, 1986 and onwards
- "G" stands for "Generalized" causal comparisons
  - Including the contrast of dynamic regimes in the presence of time-varying confounders

- G-formula (Robins 1986)
- g-estimation of structural nested models (Robins 1989)
- inverse probability weighting of marginal structural models (Robins 1998)

Aside: Time-varying confounders "affected" by exposure



A_t: Antiretroviral therapy (0: no, 1: yes) at time *t*
Y: Viral load (1 if detectable, 0: otherwise)
L: CD4 count (0: high, 1: low)
U: True immunosupression level

(Unknown to data analyst: No effect of A_t on Y)

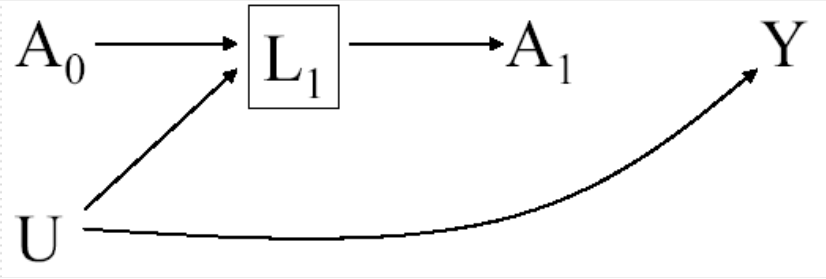
Aside: Stratification to compute the causal effect of A

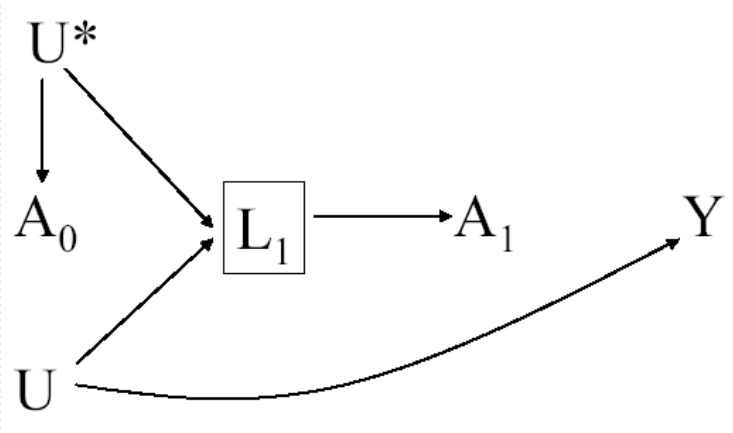
- Is the conditional risk ratio equal to the causal risk ratio (i.e., one)?
  - $\Pr[Y=1|A=2, L_1=l] / \Pr[Y=1|A=0, L_1=l]$
- NO
- Conditioning on L_1
  - eliminates confounding (blocks the back-door path) for one component of A, i.e., A_1
  - creates selection bias for the other component of A, i.e., A_0
  - As long as one component of A is associated with Y, A is associated with Y

Aside:
To stratify or not to stratify…

- Not stratifying is bad because there is confounding
- Stratifying is bad because stratification eliminates confounding at the cost of introducing selection bias
- Because the confounder for part of the exposure is affected by another part of the exposure

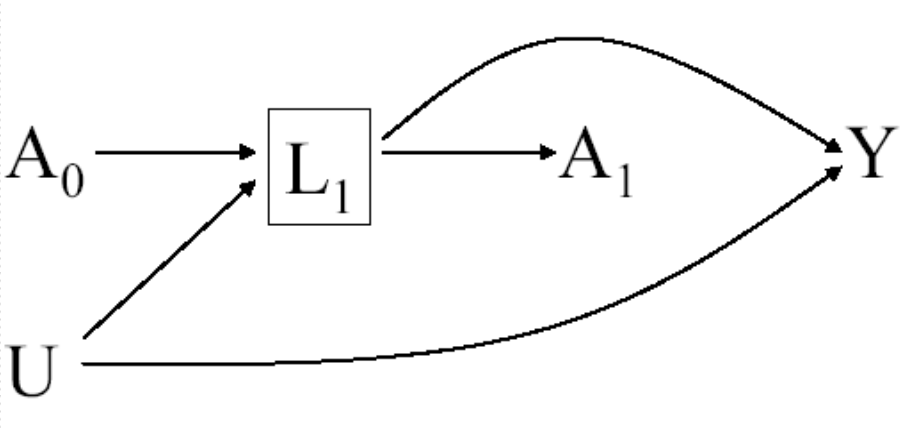
Aside:
More generally





- Bias if either the confounder is affected by the exposure or shares a common cause with it
- Bias even if the confounder is not on the causal pathway from exposure to outcome

What if the confounder is on the causal pathway?



- Conditioning on the confounder not only creates selection bias but also prevents identification of the total effect of exposure
  - In general, stratification by intermediate variables to identify direct effects is dangerous

In summary

- Methods that estimate association measure ignoring data on L_1
  - Association measure does not have a causal interpretation if there is confounding by L_1
- Methods that estimate association measure within levels of L_1
  - Association measure does not have a causal interpretation if L_1 affected by exposure (or a cause of the exposure)
- Need for other methods

G-formula, IP weighting, G-estimation

- Appropriately adjust for confounding when time-dependent confounders are affected by exposure (or by causes of exposure)
- For example, in IP weighting adjustment is achieved by eliminating the arrow from confounder to subsequent exposure (in the pseudo-population)
  - Not by conditioning on the confounder

Identifying assumptions

- Exchangeability
  - Sequential ignorability, no unmeasured confounding
- Positivity
  - Experimental treatment assumption
- Well-defined interventions

✓ See Robins and Hernán (2008)

- Estimation of the causal effects of time-varying exposures. In: *Longitudinal Data Analysis*. Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, eds.

The g-formula

- aka the g-computation algorithm formula (Robins 1986)
- Later rediscovered by computer scientists (Pearl et al)

- Under its assumptions, the g-formula can be used to estimate any average causal effect
- Not *a* causal method but *the* causal method

The g-formula

- Solution to causal inference from complex longitudinal data?
- Well, there is no “solution” to causal inference from observational data
  - Unmeasured confounding always a possibility
    - Lack of exchangeability given the measured covariates
  - The g-formula adjusts appropriately for time-varying measured confounding
    - Like IP weighting, unlike conventional methods

The g-formula

- Nonparametric method!!
  - Need to estimate the conditional distribution of outcome, confounders…
  - For longitudinal data and/or continuous covariates it requires essentially infinite data and computing time
  - Not a trivial problem…
    - More later
- Let's describe the g-formula for the "when to start" question

Data and notation (I)

- Time k measured in months
  - $k=0,1,2\ldots 150$
- A_k
  - indicator of treatment initiation before end of month k
- V
  - vector of variables measured at or before $k=0$
  - sex, geographic origin, mode of transmission, race, cohort, calendar year years since HIV diagnosis, age

Data and notation (II)

- L_k
  - vector of time-varying variables during period k
  - indicators for measurement of viral load ($L_{1,k}$) and CD4 ($L_{2,k}$), most recently measured viral load ($L_{3,k}$) and CD4 ($L_{4,k}$), AIDS diagnosis ($L_{5,k}$)
- Y_{k+1}
  - indicator of death by end of month $k+1$
- C_{k+1}
  - indicator of censoring by end of month $k+1$

Dynamic regimes of interest

- "start cART when CD4 cell count first drops below x or there is a diagnosis of an AIDS-defining illness, whichever happens first"
  - Regimes indexed by x
- Formalization:

Let $g_k(\bar{a}_{k-1}, \bar{l}_k) = 1$ if either

1. $g_{k-1}(\bar{a}_{k-2}, \bar{l}_{k-1}) = 0$ and $l_{4,k} < x$ or $l_{5,k} = 1$ or
2. $g_{k-1}(\bar{a}_{k-2}, \bar{l}_{k-1}) = 1$

and let $g_k(\bar{a}_{k-1}, \bar{l}_k) = 0$ otherwise for $k \geq 0$.

Estimand of interest

$\Pr[Y^x_{k+1} = 1]$

- counterfactual risk of death by month $k+1$ for $k=0,\ldots,60$ under treatment regime x
  - and with censoring by loss to follow-up abolished
- The g-formula expresses this counterfactual risk in terms of only the observed data distribution
  - Under the identifying assumptions

The g-formula for $\Pr[Y^{x}_{k+1} = 1]$

$$\sum_{\bar{l}_k} \sum_{j=0}^{k} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, \bar{A}_j = \bar{a}_j, \bar{Y}_j = \bar{C}_{j+1} = 0) \times$$

$$\prod_{s=0}^{j} \{ \Pr(Y_s = 0 | \bar{L}_{s-1} = \bar{l}_{s-1}, \bar{A}_{s-1} = \bar{a}_{s-1}, \bar{Y}_{s-1} = \bar{C}_s = 0) \times$$

$$f(l_s | \bar{l}_{s-1}, \bar{a}_{s-1}, \bar{Y}_s = \bar{C}_s = 0) \}$$

- General form of epidemiologic standardization for time-varying treatments and confounders

Two nontrivial problems

1. Need to estimate the entire likelihood
   - Nonparametric estimation is out of the question
     - except marginal distribution of baseline covariates *V* can be empirically estimated
   - Parametric estimation perceived as too dangerous
2. Need to compute a huge integral
   - Approximated via Monte Carlo simulation

Should we consider parametric estimation of the g-formula?

- A big chunk of Robins et al's careers devoted to semiparametric methods
  - IP weighting of MSMs, g-estimation of SNMs
- Model misspecification viewed as particularly bad for longitudinal data
  - Can lead to propagation of errors
- Now we are talking about going fully parametric? Really?
  - Well, you never know until you try

Parametric vs. semiparametric

- IP weighting of dynamic MSMs
  - Model for treatment initiation
  - Structural model to smooth over regimes
  - Cain et al. *Int J Biostat* 2010.

- Parametric g-formula
  - Parametric models for every single density in the likelihood of the observed data
  - Young et al. *Stat Biosci* 2011, Westreich et al. *Stats Med* 2012.

Implementation of parametric g-formula

- 3 steps
  1. Parametric modeling to estimate factors of the g-formula
  2. Monte Carlo simulation to approximate the integral
  3. Computation of risk
     - Nonparametric bootstrap for variance estimation
  - Technical details, including on random dynamic regimes, in Young et al. *Stat Biosci* 2011

- Publicly available SAS macro
  - http://www.hsph.harvard.edu/causal

Step 1: Parametric modeling of conditional densities

1. Fit models for the conditional densities of the covariates

$$f(l_s|\bar{l}_{s-1}, \bar{a}_{s-1}, \bar{Y}_s = \bar{C}_s = 0)$$

   - e.g., logistic for discrete, log-linear for continuous
   - Use empirical distribution for baseline covariates

2. Fit a logistic model for the conditional density of the outcome

$$\Pr[Y_{k+1} = 1|\bar{L}_k = \bar{l}_k, \bar{A}_k = \bar{a}_k, \bar{Y}_k = \bar{C}_{k+1} = 0]$$

Step 2: Monte Carlo simulation under regime x

For $k = 0, \ldots, K$ and $v = 1, \ldots, n$:

1. If $k = 0$ set $l_{0,v}$ to the observed values for subject v. Otherwise if $k > 0$
   (a) Set $l_{1,k,v} = 1$ if $\sum_{s=1}^{12} l_{1,k-s,v} = 0$ and $k \geq 12$. Otherwise, draw $l_{1,k,v}$ from the probability function estimated in step I.1.a based on previously drawn covariates $\bar{l}_{k-1,v}$ and assigned treatment $\bar{a}_{k-1,v}$ under x (see step II.2).
   (b) Set $l_{2,k,v} = l_{2,k-1,v}$ if $l_{1,k,v} = 0$. Otherwise, draw $l_{2,k,v}$ from the density function estimated in step I.1.b based on previously drawn covariates $\bar{l}_{k-1,v}$ and assigned treatment $\bar{a}_{k-1,v}$ under x.
   (c) Set $l_{3,k,v} = 1$ if $\sum_{s=1}^{12} l_{3,k-s,v} = 0$ and $k \geq 12$. Otherwise, draw $l_{3,k,v}$ from the probability function estimated in step I.1.c based on previously drawn covariates $l_{2,k,v}$, $l_{1,k,v}$, $\bar{l}_{k-1,v}$ and assigned treatment $\bar{a}_{k-1,v}$ under x.

Step 2: Monte Carlo simulation under regime x

(d) Set $l_{4,k,v} = l_{4,k-1,v}$ if $l_{3,k,v} = 0$. Otherwise, draw $l_{4,k,v}$ from the density function estimated in step I.1.d based on previously drawn covariates $l_{2,k,v}$, $l_{1,k,v}$, $\bar{l}_{k-1,v}$ and assigned treatment $\bar{a}_{k-1,v}$ under x.

(e) Set $l_{5,k,v} = 1$ if $l_{5,k-1,v} = 1$. Otherwise, draw $l_{5,k,v}$ from the probability function estimated in step I.1.e based on previously drawn covariates $\bar{l}_{4,k,v}$, $\bar{l}_{3,k,v}$, $\bar{l}_{2,k,v}$, $\bar{l}_{1,k,v}$, and assigned treatment $\bar{a}_{k-1,v}$ under x

2. Assign the treatment $a_{k,v}$ under x. Specifically,

   Set $a_{-1,v} = 0$.

Step 3: Computation of risk under regime x

- For k=0, 1,…K, estimate the g-formula as

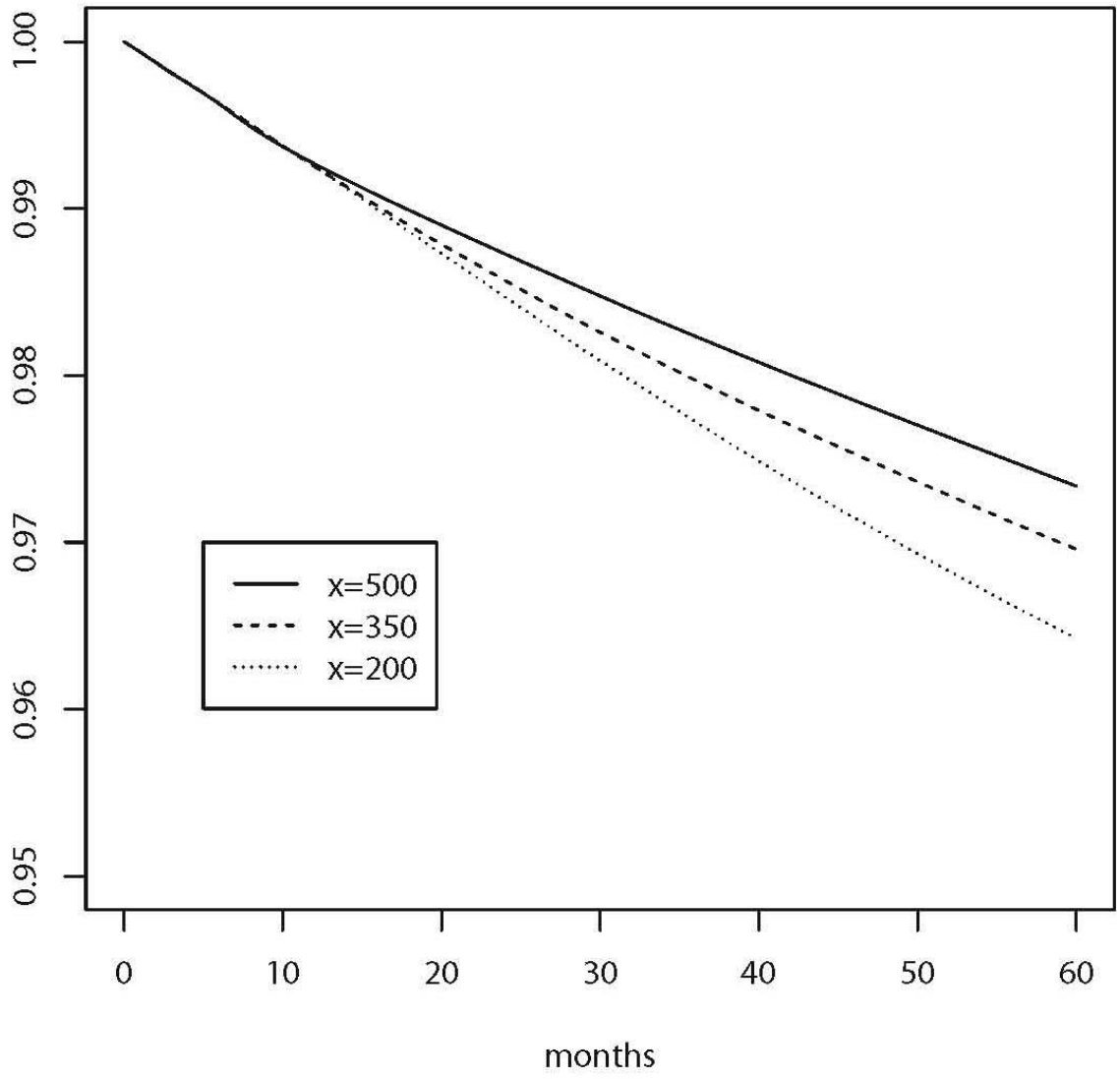
$$\frac{1}{n}\sum_{v=1}^{n}\sum_{j=0}^{k}\hat{\Pr}[Y_{j+1}=1|\bar{L}_j=\bar{l}_{j,v},\bar{A}_j=\bar{a}_{j,v},\bar{Y}_j=\bar{C}_{j+1}=0]\times$$

$$\prod_{s=0}^{j}\{1-\hat{\Pr}[Y_s=1|\bar{L}_{s-1}=\bar{l}_{s-1,v},\bar{A}_{s-1}=\bar{a}_{s-1,v},\bar{Y}_{s-1}=\bar{C}_s=0]\}$$

Point estimates and 95% CIs

x	*Risk (%)*	*Risk Ratio*
500	2.65 (2.15, 3.43)	1.00 (ref)
450	2.77 (2.28, 3.47)	1.05 (0.99, 1.09)
400	2.92 (2.43, 3.55)	1.10 (0.99, 1.18)
350	3.06 (2.59, 3.67)	1.16 (1.00, 1.29)
300	3.22 (2.73, 3.81)	1.22 (1.02, 1.41)
250	3.44 (2.87, 4.07)	1.30 (1.03, 1.55)
200	3.65 (3.01, 4.44)	1.38 (1.05, 1.71)

Survival under 3 dynamic regimes



Stability of results

- Results did not materially change under different modeling strategies
  - functional forms for continuous variables, e.g., polynomial, restricted cubic splines
  - inclusion of “interaction” terms
  - modeling of measurement process
- More formal model selection and goodness of fit tests are ongoing

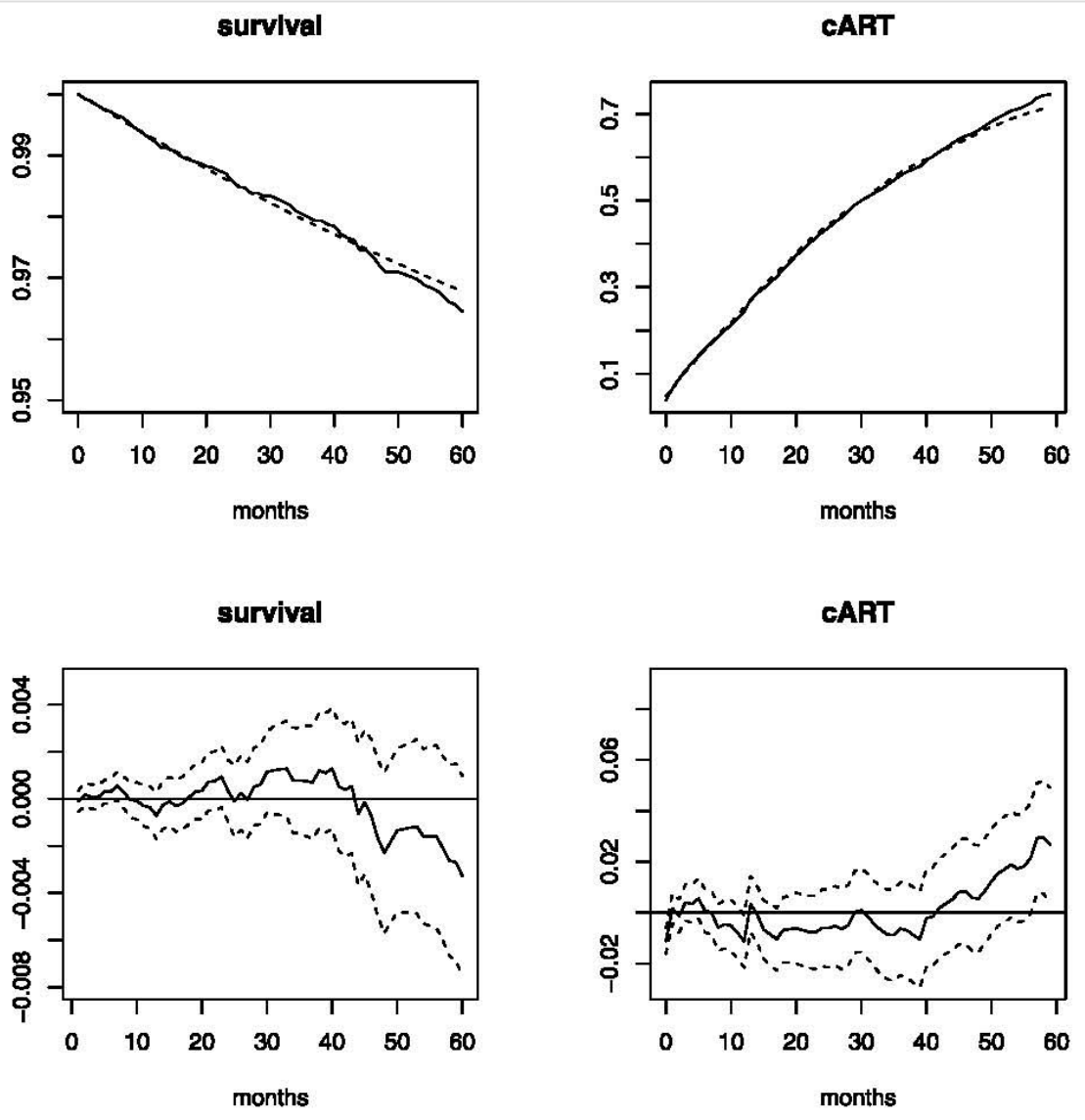
The “natural course”

- One necessary condition is that our approach predicts the observed data correctly

- That is, we need to be able to predict what would had happened under no treatment intervention

Natural course

- Observed vs. predicted
  - Top: absolute
  - Bottom: difference (95% CI)



Natural course

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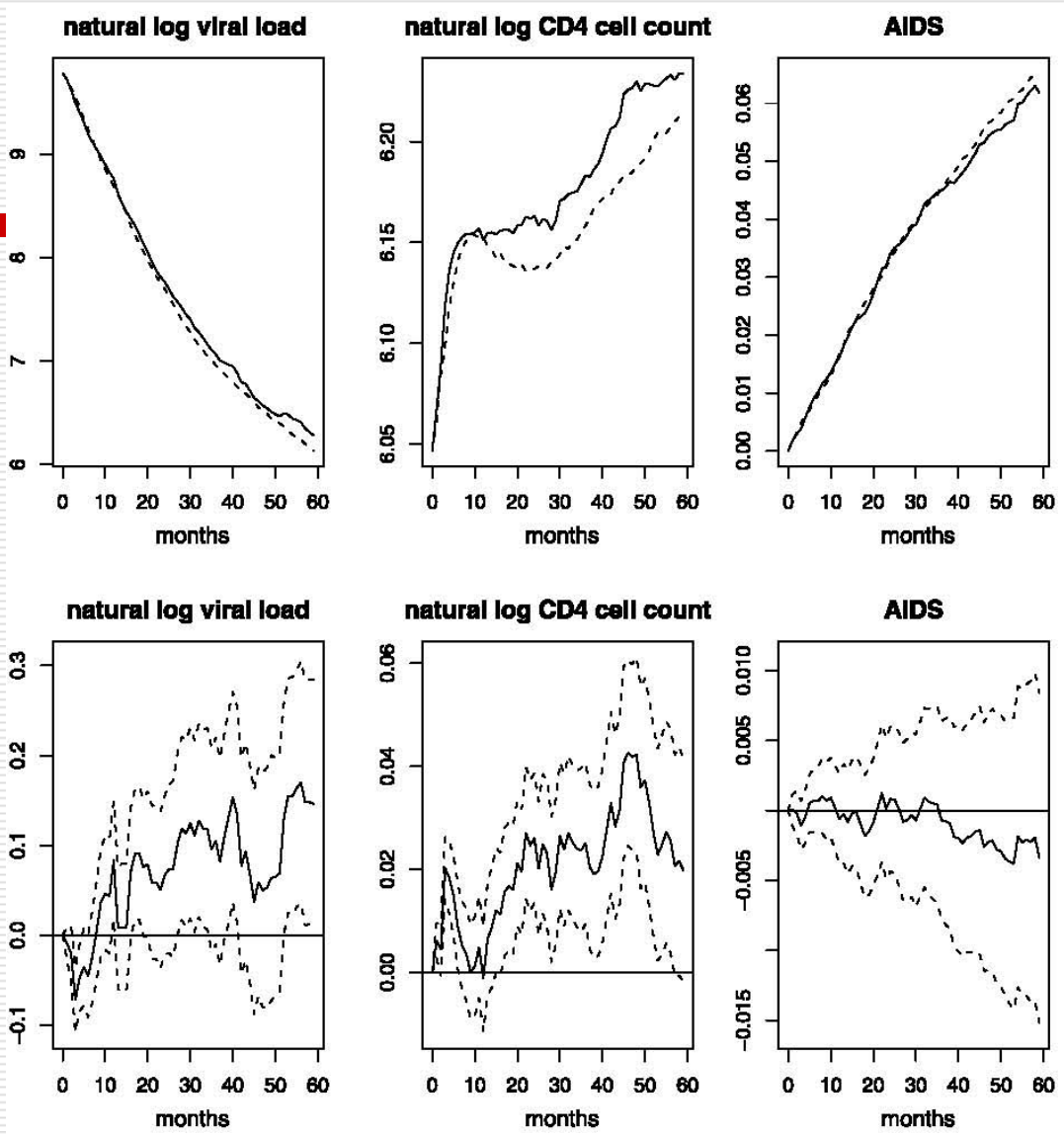

Conclusions (I)

- Parametric estimation more efficient than semiparametric estimation, duh!
  - Compared with IP weighted estimates in Cain et al. *Annals of Internal Medicine* 2011
- Parametric g-formula is more flexible than any of the other g-methods
  - and is computationally tractable

Conclusions (II)

- Most shockingly, so far the parametric g-formula yields reasonable/stable estimates
  - More applications coming
  - Weight loss and diabetes, fish and heart disease…

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