PH 252E: Lectures 2 and 3

Time-dependent confounding;
Identification of the joint effects of
multiple interventions

Outline

1. Specify observed data

With censoring, right censoring, missing data

2. Identification

Review – point treatment setting

3. Identification

- Time-dependent confounding
- Sequential Randomization Assumption/ sequential back door criteria
- Longitudinal G computation formula

A roadmap for causal inference

- 1. Specify **Causal Model** representing <u>real</u> background knowledge
- 2. Specify Causal Question
- 3. Specify Observed Data and link to causal model
- **4. Identify**: Knowledge + data sufficient?
- 5. Commit to an **estimand** as close to question as possible, and a **statistical model** representing real knowledge.
- 6. Estimate
- 7. Interpret Results

Quick Notation/Concept Review

- Observed data? Its distribution?
- Link to SCM?
- Statistical Model?

Linking the Observed Data to the SCM

- Defining the statistical estimation problem requires specifying the link between endogenous variables X and the observed data O
 - In other words, we specify how the observed data were generated by the data generating system encoded in our SCM
- Often, O=X
 - le endogenous variables in SCM correspond to observed variables O
 - Ex: point treatment: O=(W,A,Y)

Linking the Observed Data to the SCM

- We observe a sample of size n of the random variable O
 - We will work with independent samples
 - The framework is not restricted to this
- We assume our observed data were generated by sampling n times from the data generating system specified in our causal model
- This gives us n i.i.d. copies $O_1, O_2, ..., O_n$ drawn from true probability distribution P_0

The Statistical Model

- The structural causal model $\mathcal{M}^{\mathcal{F}}$ (which tells us the set of possible distributions for U,X) implies a model (set of possible distributions) for O
- We refer to this set of possible distributions as the statistical model ${\mathcal M}$
- The true distribution P_0 of O is an element of \mathcal{M}

The Statistical Model

- Often, a model that respects the limits of our knowledge puts no restrictions on the set of allowed distributions for O
- In this case our statistical model is nonparametric
- We need to respect this fact when we frame the statistical estimation problem

Specifying the Observed Data: Longitudinal data

Basic longitudinal observed data structure

$$O = (L(1), A(1), L(2), A(2), ..., L(K), L(K+1))$$

= $(\bar{A}(K), \bar{L}(K+1)) \sim P_0 \in \mathcal{M}$

- With survival data and additional right censoring: Observe data drawn up till the minimum of end of follow up (K+1), censoring, or "failure" (ie event of interest occurs)
 - For notational convenience, much literature defines data after failure or censoring as equal to last observed value

A roadmap for causal inference

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- 4. Identify: Knowledge + data sufficient?
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Quick Notation/Concept Review

- Target Causal Parameter?
 - General notation
 - Function of what distribution?
- What do we mean (in causal context) by identification?
- Target Statistical parameter (estimand)?
 - General notation
 - Function of what distribution?
- Identification of ATE in point treatment context (assumptions and estimand)?

Review: Identifiability

- Are the assumptions in our model sufficient to express our target causal quantity $(\Psi^F(P_{U,X}))$ as a parameter of the distribution P_0 of the observed data $(\Psi(P_0))$?
 - Distribution P_0 of O implied by distribution $P_{U,X}$: $P_0=P(P_{U,X})$
 - Need to show that $\Psi^{F}(P_{U,X})=\Psi(P(P_{U,X}))$ for all $P_{U,X}$ in $\mathcal{M}^{\mathcal{F}}$
- Focus here on one identifiability result:
 - "G-computation formula"
- Holds under
 - Randomization assumption
 - Backdoor criterion

Recap: Identifiability for point treatment

- SCM $\mathcal{M}^{\mathcal{F}}$:
 - $-X=(W,A,Y); U=(U_W,U_A,U_Y)^P_U$
 - No exclusion restrictions or independence assumptions
- Observe: $O=(W,A,Y)^P_0$
- Statistical model ${\mathcal M}$ is non-parametric
- Target Causal parameter: $\Psi^F(P_{U,X}) = E_{U,X}(Y_1 Y_0)$
- Can we write $\Psi^F(P_{U,X})$ as a parameter Ψ of P_0 ?

$$\Psi:\mathcal{M}
ightarrow\mathbb{R}$$

Identifiability of Point Treatment Effects under the Randomization Assumption

Randomization Assumption (RA):

$$Y_a \perp A|W$$

Identifiability Result

$$P_0(Y = y|A = a, W = w) = P_{U,X}(Y_a = y|A = a, W = w)$$

By definition of counterfactuals

$$= P_{U,X}(Y_a = y|W = w)$$

Under the randomization assumption

Identifiability of Point Treatment Effects under the Randomization Assumption

• If the Randomization Assumption $Y_a \perp A|W$ holds then:

$$E_{U,X}(Y_a|W=w) = E_0(Y|A=a, W=w)$$

This gives us the G-computation formula

$$E_{U,X}(Y_a) = \sum_w E_0(Y|A=a,W=w)P_0(W=w)$$

$$\Psi^{\mathsf{F}}(\mathsf{P}_{\mathsf{U},\mathsf{X}})$$

$$\Psi(\mathsf{P}_0)\text{: "estimand"}$$

Recall: Positivity Assumption

- Need E(Y|A=a,W=w) to be well-defined
- In non-parametric model, each treatment of interest must occur with some positive probability for each possible covariate history
- Let $g_0(a|W)$ denote $P_0(A=a|W)$
- Positivity assumption:

$$g_0(a|W) > 0$$
- a.e.

Backdoor criterion

- Plausibility of the randomization assumption can be hard to assess.
 - What variables to include in W? Are they sufficient?
- Alternative: Graphical criteria for establishing whether a given adjustment set is sufficient
 - If W satisfies backdoor criterion, the effect of A on Y is identified via the G-computation formula

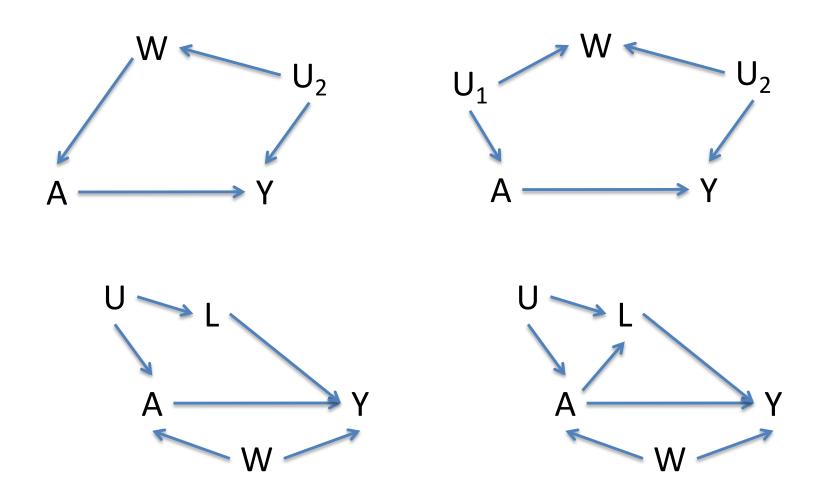
$$E_{U,X}(Y_a) = \sum_{w} E_0(Y|A = a, W = w)P_0(W = w)$$
 $\Psi^{\mathsf{F}}(\mathsf{P}_{\mathsf{U},\mathsf{X}})$
 $\Psi(\mathsf{P}_0)$

Back-door criterion

- A set of variables W satisfies the back door criterion with respect to (A,Y) if
 - 1. No node in W is a descendent of A
 - Motivation:
 - 1. Avoid blocking the path of interest
 - 2. Avoid introducing spurious sources of dependence
 - 2. W blocks all "backdoor" paths from A to Y
 - Backdoor path= path with arrow into A
 - Motivation: Block all sources of spurious association between A and Y

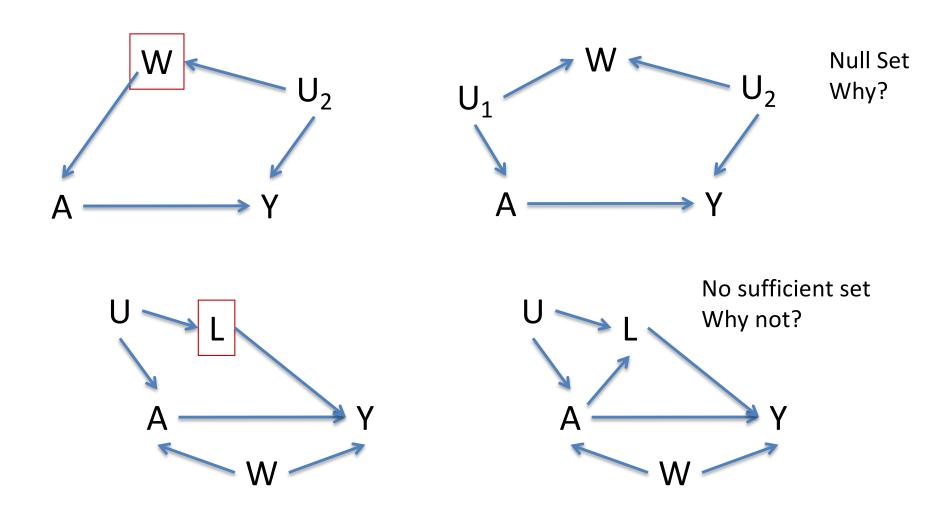
Quick Practice: Backdoor Criteria

Back door criteria holds for effect of A on Y conditional on what?



Quick Practice: Backdoor Criteria

Back door criteria holds for effect of A on Y conditional on what?



Backdoor criterion

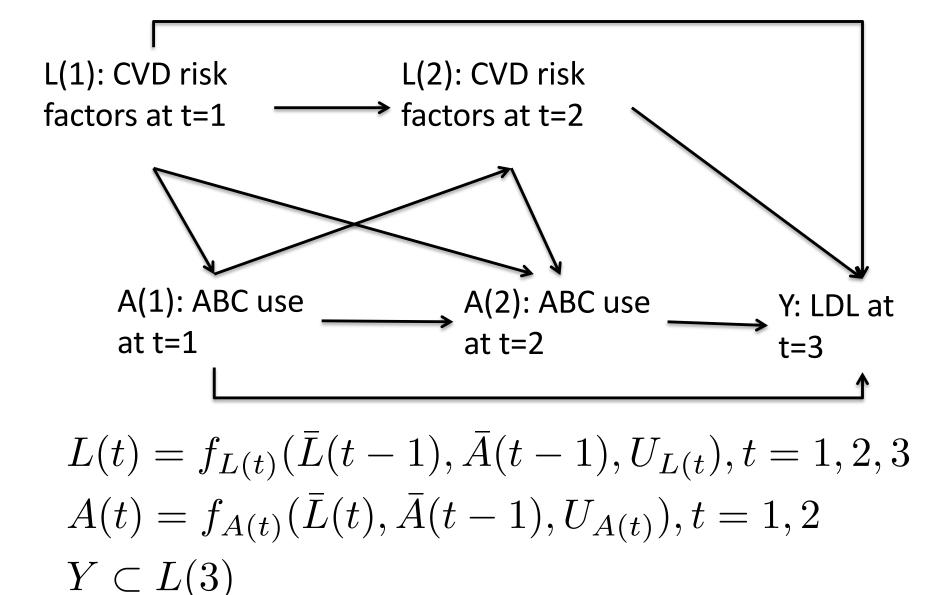
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$$E_{U,X}(Y_a) = \sum_{w} E_0(Y|A = a, W = w)P_0(W = w)$$
 $\Psi^{\mathsf{F}}(\mathsf{P}_{\mathsf{U},\mathsf{X}})$
 $\Psi(\mathsf{P}_0)$

Identifiability for longitudinal exposures

- What causal assumptions are sufficient for our target longitudinal causal parameter to be identified as a parameter of the observed data distribution?
- Back to our simplified example for illustration
 - Effect of Abacavir use at t=1 and t=2 on LDL at t=3
 - Measure CVD risk factors at t=1 and t=2
 - Assume no deaths, censoring, or missing data

Abacavir Example: SCM/Graph



Abacavir Example: Target Parameter and Observed Data

- Target causal parameter: $E_{U,X}(Y_{ar{a}=1}-Y_{ar{a}=0})$
- Observed data: n i.i.d. copies of $O = (L(1), A(1), L(2), A(2), Y) \sim P_0$
- Under what conditions can we write our target causal parameter as a parameter of the observed data distribution?
- We need to move beyond the simple back door criterion....

How are longitudinal parameters different?

 Our previous identifiability result relied on conditioning on some set of covariates W that were sufficient to block all back door paths from our intervention A to our outcome Y

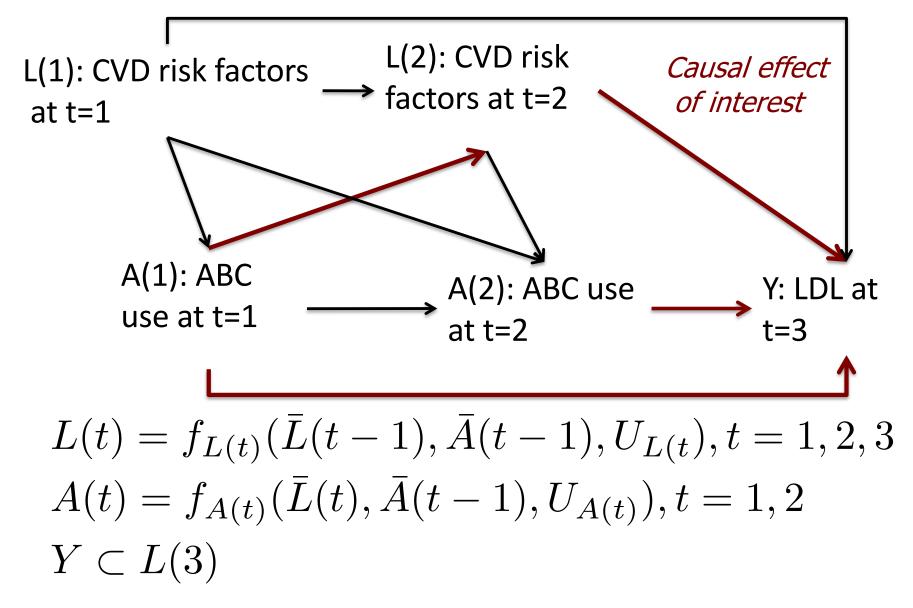
We could <u>not</u> condition on descendents of A

How are longitudinal parameters different?

 When we are interested in intervening on multiple nodes, we are often in a situation where no one set of covariates that meet the back door criterion for all intervention nodes simultaneously exists

 However, the distribution of counterfactuals indexed by interventions on these multiple nodes may still be identified...

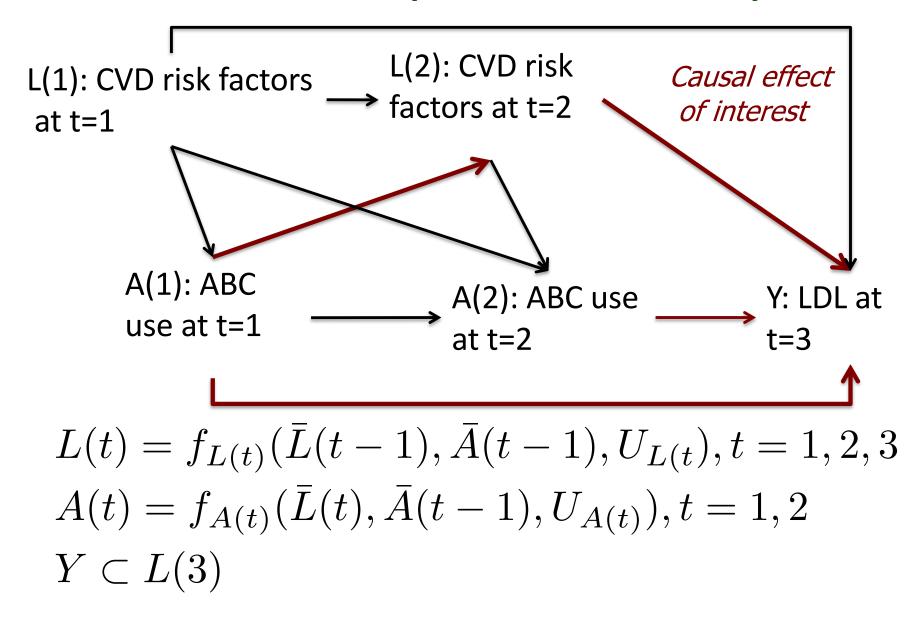
ABC Example: SCM/Graph



Is $E(Y_{11} - Y_{00})$ identified using the standard (point treatment) back door criterion?

- We need to find a single set of variables that
 - 1. Are non-descendents of (A(1),A(2)) and
 - 2. Block all back door paths from (A(1),A(2)) to Y...

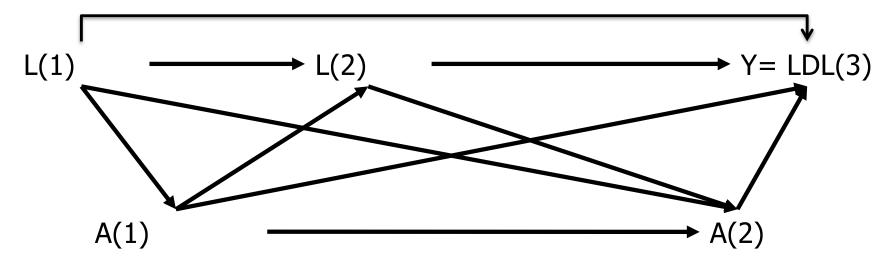
ABC Example: SCM/Graph



 Option #1: Does L(1) satisfy backdoor criterion for Effect A(1) and A(2) on Y?

$$E(Y_{11}) \stackrel{?}{=}$$

$$\sum_{l(1)} E(Y|A(1) = 1, A(2) = 1, L(1))P(L(1) = l(1))$$

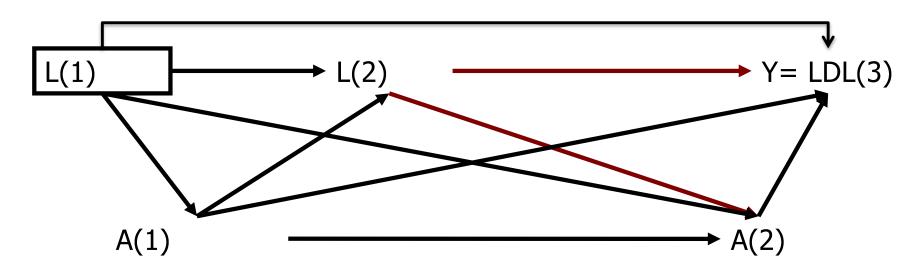


$$E(Y_{11})$$

$$\sum_{l(1)} E(Y|A(1) = 1, A(2) = 1, L(1))P(L(1) = l(1))$$

Why not?

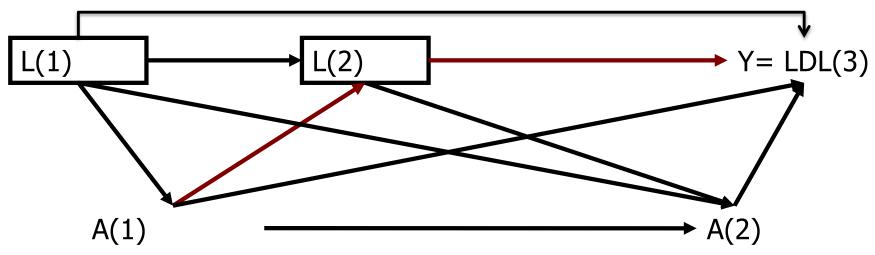
Unblocked backdoor path



 Option #2: Does (L(1),L(2)) satisfy backdoor criterion for Effect A(1) and A(2) on Y?

$$E(Y_{11}) \stackrel{?}{=} \\ \sum_{\bar{l}} E(Y|A(1) = 1, A(2) = 1, \bar{L} = \bar{l}) P(\bar{L} = \bar{l}) \\ \text{L(1)} \\ \xrightarrow{A(1)} P(\bar{L} = \bar{l}) \\ \xrightarrow{A(2)} P(\bar{L} = \bar{l}) \\ \xrightarrow$$

$$E(Y_{11})$$
 $= \sum_{\bar{l}} E(Y|A(1) = 1, A(2) = 1, \bar{L} = \bar{l})P(\bar{L} = \bar{l})$



- Intuition: losing the effect of A(1) on Y via L(2)
 - Point treatment identifiability result takes expectation with respect to the wrong distribution of covariates L

Even if A does not affect Y via L(2), we may have a problem

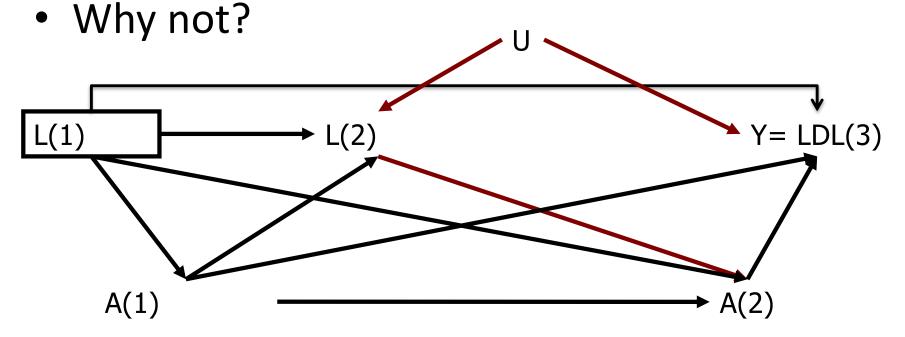
• if L(2) is a confounder for A(2) and affected by A(1)...

$$E(Y_{11}) \stackrel{?}{=} \sum_{l(1)} E(Y|A(1) = 1, A(2) = 1, L(1))P(L(1) = l(1))$$

$$E(Y_{11})$$

$$\sum_{l(1)} E(Y|A(1) = 1, A(2) = 1, L(1))P(L(1) = l(1))$$

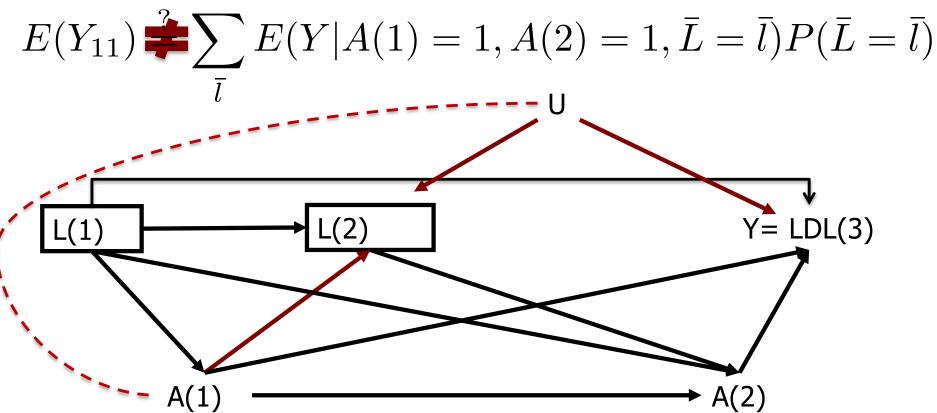
Unblocked backdoor path



• Option #2:

$$E(Y_{11}) \stackrel{?}{=} \\ \sum_{\bar{l}} E(Y|A(1) = 1, A(2) = 1, \bar{L} = \bar{l}) P(\bar{L} = \bar{l}) \\ \text{L(1)} \\ \xrightarrow{\text{A(1)}} \text{L(2)} \\ \xrightarrow{\text{A(2)}} \text{L(2)}$$

Why does the point treatment G-computation formula break down?



- Conditioning on collider creating new confounding
 - Point treatment identifiability result takes expectation with respect to the wrong distribution of covariates

The Dilemma of Time –Dependent Confounding

- No subset of covariates for which the simple back door criterion holds
 - We need L(2) to block the back door path from A(2) to Y
 - But L(2) is a descendent of A(1)
- Is our target parameter really unidentified?

 Not necessarily! But we do need a new identifiability assumption -> new estimand

How can we modify the point treatment G-computation formula?

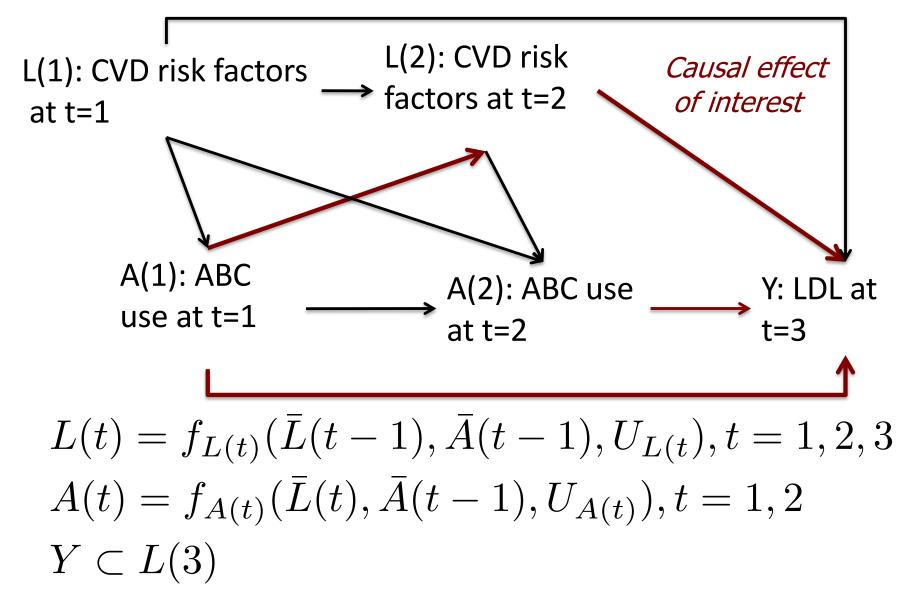
Point treatment identifiability result takes
 expectation over the wrong distribution of L(2)

$$\sum_{\bar{l}} E(Y|A(1) = 1, A(2) = 1, \bar{L} = \bar{l}) P(\bar{L} = \bar{l})$$

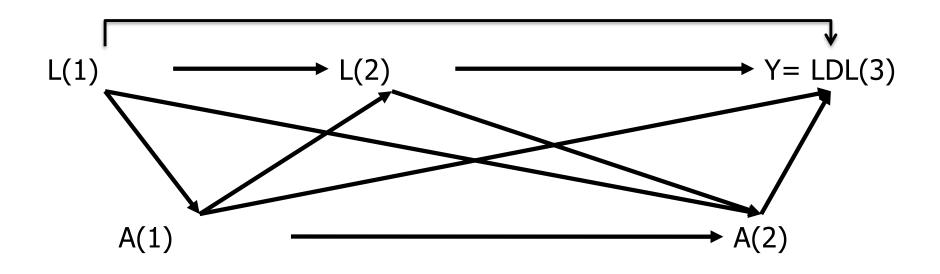
Distribution of CVD risk factors under "non-intervened on" SCM

 Instead: that expectation with respect to the distribution of covariates (L(1),L(2)) under intervention to set A(1)=1,A(2)=1

ABC Example: SCM/Graph



Example: Longitudinal G-computation Formula



$$E(Y_{11}) = \sum_{l(1), l(2)} \left(\begin{array}{c} E(Y|A(1) = 1, A(2) = 1, L(1) = l(1), L(2) = l(2)) \times \\ P(L(2) = l(2)|A(1) = 1, L(1) = l(1)) \times P(L(1) = l(1)) \end{array} \right)$$

Distribution of CVD risk factors under post-intervention SCM

Longitudinal G computation Formula

$$E(Y_{\bar{a}}) = \sum_{\bar{l}} E(Y|\bar{A}(K)) = \bar{a}(K), \bar{L}(K) = \bar{l}(K)) \times$$

$$\prod_{t=1}^{K} P(L(t) = l(t) | \bar{A}(t-1) = \bar{a}(t-1), \bar{L}(t-1) = \bar{l}(t-1))$$

Distribution of covariates under post-intervention SCM

Key insight: we don't need to adjust for everything all at once

- Instead, we can think of simulating our data sequentially from our set of structural equations
- This lets us consider the problem of identifiability sequentially
 - For each A(t) in sequence, ask if its effect on Y can be identified by conditioning on some subset of the observed past.

Identifiability for the effects of multiple interventions

- What do we need for identifiability in this case?
- Intuition: Sequentially Randomized Trial
 - If at each time point we could randomize A(t) within strata of (some subset of) covariates and treatment observed up until then
 - Then, at each time point the effect of A(t) on future nodes would be identified
 - We know we measured enough of the past to estimate the effect of intervening on that node
 - We could then estimate the effect of setting each A(t) sequentially

Identifiability for multiple interventions

Sequential Randomization Assumption

$$Y_{\bar{a}} \perp A(t)|\bar{L}(t), \bar{A}(t-1) = \bar{a}(t-1), t = 1, ..., K$$

- If A(t) is randomly assigned at each time point, given the observed past, this will hold
- This is sometimes called a sequentially randomized trial or sequential multiple assignment randomized trial (SMART)
- Counterpart to the Randomization Assumption for a single intervention

$$Y_a \perp A|W$$

A graphical criterion for identifiability

- For the single time point case, the back door criterion:
- 1. Allowed us to evaluate if our target parameter was identified by the G computation formula
- 2. Helped us to decide what to condition on
 - What to include in "W"
 - Recall- not always a good idea to include all pretreatment variables...
- Is there an equivalent criterion for target parameters with multiple interventions?

Identifying the effects of interventions on multiple nodes

 The <u>sequential back door criterion</u> (counterpart to the back door criterion for a single intervention node):

For each intervention node A(t), every "intervention avoiding" backdoor path from A(t) to Y must be blocked by some subset of non-descendents of A(t)

 Intervention avoiding= path with no arrows into a future "A" node (i.e. a intervention node after A(t))

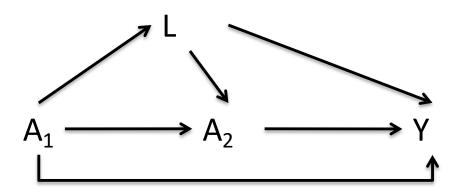
Sequential Back Door Criterion

- Essentially we just want to apply the usual back door criterion, for each intervention node A(t) in series:
 - We are looking for set of covariates (+ past treatment) that will block all back door paths from A(t) to the outcome
 - 2. These covariates cannot be descendents of A(t)
 - Same justification: Want to remove any sources of association between each A(t) and the outcome other than those that we are interested in

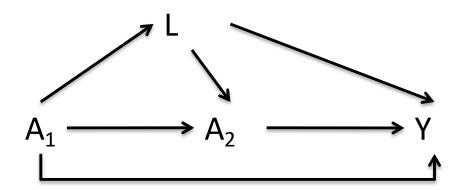
Sequential Back door Criterion

- Just the standard back door criterion applied to each intervention node is sequence <u>except</u>
- Now it is OK if there is an unblocked back door path that goes through a future intervention node
- Why?
 - Any paths through future A nodes will already be blocked because we are intervening to set those nodes
 - We don't need to worry about blocking them

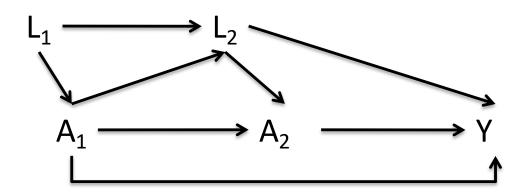
- Target: E(Y_{a1a2})
- Sequential back door holds?
 - For A₁ given what?
 - For A₂ given what?



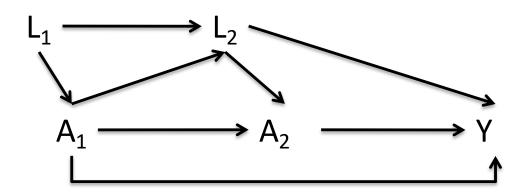
- Target: $E(Y_{a1a2})$
- Sequential back door holds?
 - For A₁ given what? nothing
 - For A₂ given what? **A1,L**



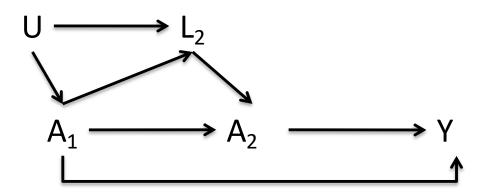
- Target: E(Y_{a1a2})
- Sequential back door holds?
 - For A₁ given what?
 - For A₂ given what?



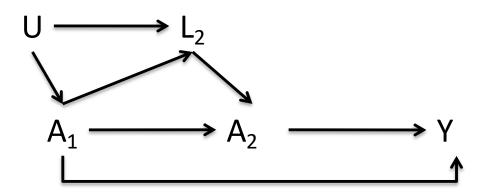
- Target: E(Y_{a1a2})
- Sequential back door holds?
 - For A₁ given what? L1
 - For A₂ given what? A1, L2



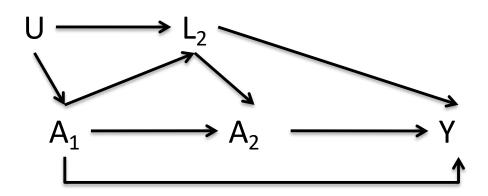
- Target: $E(Y_{a1a2})$
- Sequential back door holds?
 - For A₁ given what?
 - For A₂ given what?



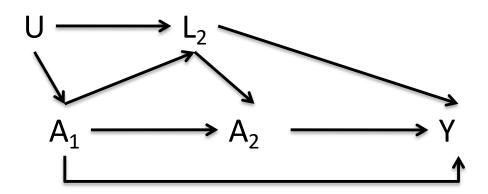
- Target: E(Y_{a1a2})
- Sequential back door holds?
 - For A₁ given what? Nothing
 - For A₂ given what? A1
 - Unconfounded



- Target: E(Y_{a1a2})
- Sequential back door holds?
 - For A₁ given what?
 - For A₂ given what?



- Target: E(Y_{a1a2})
- Sequential back door holds?
 - For A₁ given what? No sufficient set
 - For A₂ given what? **A1, L2**



Identifiability Result

Under the Sequential Randomization
 Assumption (or if full measured history sufficient to satisfy the sequential back door criterion):

 $\Psi(P_{U,X})$: Causal Parameter of Interest

$$\frac{P(Y_{\bar{a}} = y)}{\sum_{\bar{l}} \left(\begin{array}{c} P(Y = y | \bar{A} = \bar{a}, \bar{L} = \bar{l}) \times \\ \prod_{t=1}^{K} P\left(L(t) = l(t) | \bar{A}(t-1) = \bar{a}(t-1), \bar{L}(t-1) = \bar{l}(t-1) \right) \end{array} \right)}$$

$\Psi(P_0)$: Target statistical parameter/estimand

Generalization of point treatment G-computation formula
 Proof Pearl Causality p. 123 (or Robins 1986 using counterfactual framework)

Positivity Assumption

 Analogous to point treatment case, need some positive probability of following regime of interest at each time point regardless of covariate history

$$g_0(A(t) = a(t)|\bar{A}(t-1) = \bar{a}(t-1), \bar{L}(t)) > 0, t = 1, ..., K,$$
- a.e.

 $\Psi(P_{U,X})$: Causal Parameter of Interest

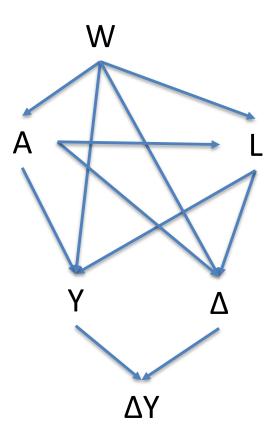
$$P(Y_{\bar{a}} = y) = \sum_{\bar{l}} \begin{pmatrix} P(Y = y | \bar{A} = \bar{a}, \bar{L} = \bar{l}) \times \\ \prod_{t=1}^{K} P(L(t) = l(t) | \bar{A}(t-1) = \bar{a}(t-1), \bar{L}(t-1) = \bar{l}(t-1)) \end{pmatrix}$$

 $\Psi(P_0)$: Target statistical parameter/estimand

Identification- Back to missing data

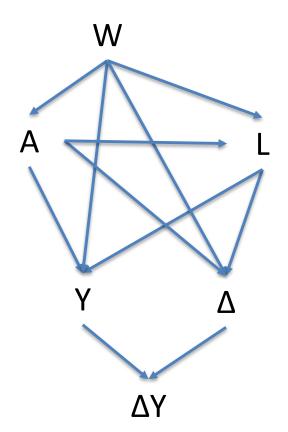
Missing outcome- One Approach

- Endogenous variables:
 X={W, A,L, Δ, Y, ΔΥ}
 - W=baseline CHD risk factors
 - A=ABC use
 - L= post-baseline risk factors
 - $-\Delta$ = Indicator LDL is measured
 - Y= true LDL cholesterol
 - (not always observed)
 - ΔY= Observed LDL
- Observed Data?



Missing outcome- One Approach

- Endogenous variables:
 X={W, A, L, Δ, Y, ΔΥ}
 - W=baseline CHD risk factors
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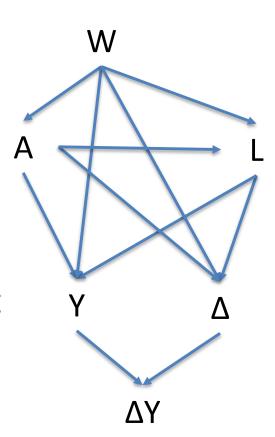


- Observed Data: n iid copies of O=(W,A,L,Δ,ΔY)~P₀
- Target Causal Parameter: E(Y_a)
- Identified? Under what assumptions? Estimand?

- Target Causal Parameter: E(Y_a)
- Identification
 - Is W sufficient to satisfy backdoor criteria for effect of A on Y?

$$E(Y_a) = E_W E(Y|A = a, W)?$$

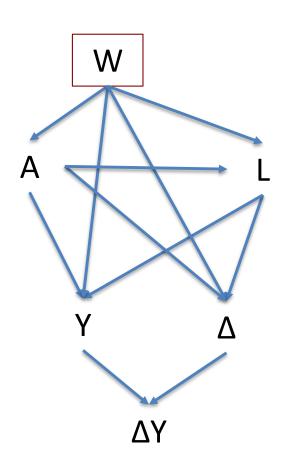
– What is wrong with this approach? Are we done?



- Target Causal Parameter: E(Y_a)
- Identification
 - Is W sufficient to satisfy backdoor criteria for effect of A on Y? Yes

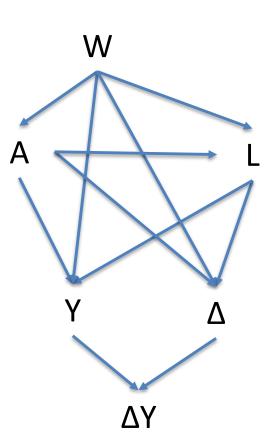
$$E(Y_a) = E_W E(Y|A=a,W)?$$

- What is wrong with this approach?
 - RHS a function of P_0 ? NO



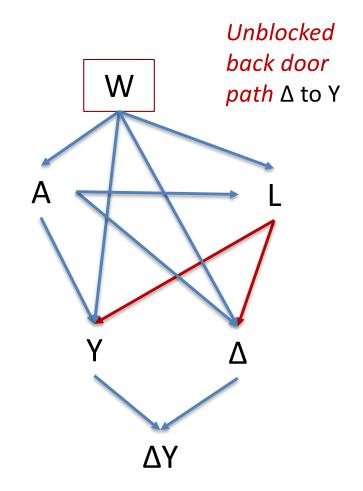
- Target Causal Parameter: E(Y_a)
- Identification
 - Intervene on A and Δ
 - Point treatment G-comp adjusting for W?
 - Is W sufficient to satisfy backdoor criteria for both interventions Y?
 - Why or why not?

$$E(Y_a) = E(Y_{a,\delta=1}) = E_W E(Y|A=a, \Delta=1, W)$$
?



- Target Causal Parameter: E(Y_a)
- Identification
 - Intervene on A and Δ
 - Point treatment G-comp adjusting for W?
 - Is W sufficient to satisfy backdoor criteria for both interventions Y? NO
 - Why or why not?

$$E(Y_a) = E(Y_{a,\delta=1}) = E_W E(Y|A=a, \Delta=1, W)$$
?



Target Causal Parameter:

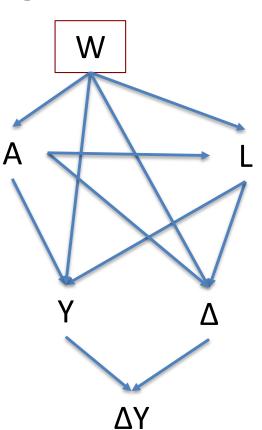
$$E(Y_a) = E(Y_{a,\delta=1})$$

 Sequential Randomization Assumption:

$$Y_{a,\delta=1} \perp A|W$$

$$Y_{a,\delta=1} \perp \Delta|A = a, W, L$$





W

Target Causal Parameter:

$$E(Y_a) = E(Y_{a,\delta=1})$$

 Sequential Randomization Assumption:

$$Y_{a,\delta=1} \perp A|W$$

$$Y_{a,\delta=1} \perp \Delta | A = a, W, L$$



$$E(Y_{a,\delta=1}) = \sum_{w,l} E(Y|A = a, \Delta = 1, W = w, L = l)P(L = l|A = a, W = w)P(W = w)$$
₆₈

Target Causal Parameter:

$$E(Y_a) = E(Y_{a,\delta=1})$$

Estimand:

$$E(Y_{a,\delta=1}) = \sum_{w,l} E(Y|A = a, \Delta = 1, W = w, L = l)P(L = l|A = a, W = w)P(W = w)$$

- RHS a function of PO?
- Positivity assumption?

Estimand:

$$E(Y_{a,\delta=1}) = \sum_{w,l} E(Y|A = a, \Delta = 1, W = w, L = l)P(L = l|A = a, W = w)P(W = w)$$

- RHS a function of P_0 ? **yes**
- Positivity assumption:

$$P(A = a|W) > 0$$

 $P(\Delta = 1|A = a, W, L) > 0$

– Example where it might not hold?

Summary (1)

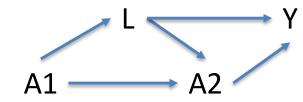
- Key concept: "time dependent confounding"
 - Simple back door criteria/Randomization assumption and corresponding point treatment G computation formula may fail for target parameters indexed by interventions on multiple nodes
 - In particular if there is a variable affected by one intervention node but needed to control for confounding (block backdoor paths to outcome) for another
 - Parameters that may seem to be "point treatment" may still have this problem
 - Ex: missing data

Summary (2)

- In setting of time-dependent confounding need
- 1. New identification assumptions:
 - Sequential randomization assumption/backdoor criteria
- 2. New estimands: Longitudinal G-comp formula
 - Point treatment G comp formula is a special case
- 3. New estimators: Coming up next!

Longitudinal-G comp formula (Simple Example)

- SCM & Observed data:
 - O=X=(A1,L,A2,Y)



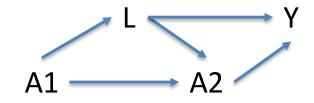
- All Us independent
- Target Causal Parameter: E(Y₁₁)
- Why can't we just Identify E(Y₁₁) as follows?

$$E(Y_{11}) = E(E(Y_{11}|L))$$

= $E(E(Y|A1 = 1, L, A2 = 1))$

Longitudinal-G comp formula (Simple Example)

- SCM & Observed data:
 - O=X=(A1,L,A2,Y)



- All Us independent
- Target Causal Parameter: E(Y₁₁)
- Why can't we write $\mathcal{E}(Y_{11}) = E(E(Y_{11}|L))$

$$EE(Y|A1 = 1, L, A2 = 1))$$

• Problem: $E(Y|A1 = 1, L, A2 = 1) \neq E(Y_{11}|L)$

$$E(Y|A1=1,L,A2=1) = E(Y_{11}|A1=1,L_1,A2=1)$$
 Definition of c.f.
$$= E(Y_{11}|L_1)$$
 $Y_{11}\perp (A1,A2) \mid L_1$

Proof: Longitudinal-G comp formula (Simple Example)

- SCM & Observed data:
 - O=X=(A1,L,A2,Y)

- All Us independent
- Target Causal Parameter: E(Y₁₁)

$$\begin{split} E(Y_{11}) &= E[E(Y_{11}|A1)] \quad \text{iterated expectation} \\ &= E[E(Y_{11}|A1=1)] \quad \text{Y}_{11} \bot \text{A1} \\ &= E\{E[E(Y_{11}|A1=1,L,A2)|A1=1]\} \quad \text{iterated expectation} \\ &= E\{E[E(Y_{11}|A1=1,L,A2=1)|A1=1]\} \quad \text{Y}_{11} \bot \text{A2} \mid \text{A1=1,L} \\ &= E\{E[E(Y|A1=1,L,A2=1)|A1=1]\} \quad \text{Definition of c.f.} \\ &= \sum E(Y|A1=1,L,A2=1)P(L=l|A1=1) \quad \text{Definition} \end{split}$$